Overview

Useful For

Identifying variants in genes known to be associated with monogenic inflammatory bowel disease (IBD) or IBD-like conditions. Identification may allow for development of a specific treatment and surveillance plan for these patients based on the molecular alteration identified, and predictive testing of at-risk family members.

Diagnosis of monogenic IBD or IBD-like conditions among patients with early onset or very-early onset IBD, or who are refractory to conventional therapy.

Ascertaining carrier status of family members of individuals diagnosed with early onset IBD for genetic counseling purposes. If a family member has already tested positive for a variant in a gene on this panel, order known variant analysis (KVAR). See Advisory Information section (Specimen tab) for more details.

Genetics Test Information

This test uses next-generation sequencing to test for variants in the ADA, ADAM17, AICDA, BTK, CD3G, CD40LG, CTLA4, CYBA, CYBB, DCLRE1C (Artemis), DKC1, DOCK8, FOXP3, G6PC3, ICOS, IKBKG, IL10, IL10RA, IL10RB, IL21, IL21R, IL2RA, IL2RG, ITGB2, LG4, LRBA, MEFV, MVK, NCF2, NCF4, NLRC4, PIK3CD, PIK3R1, PLCG2, RAG1, RAG2, RTEL1, SH2D1A, SKIV2L, SLC37A4, STAT1, STAT3, STIM1, STXBP2, TNFAIP3, TTC37, TTC7A, WAS, WIPF1, XIAP and ZAP70 genes.

Prior Authorization is available for this assay; see Special Instructions.

Highlights

Identification of a pathogenic variant may assist with prognosis, clinical management, familial screening, and genetic counseling.

Reflex Tests

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<th>Reporting Name</th>
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<th>Always Performed</th>
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<tbody>
<tr>
<td>FIBR</td>
<td>Fibroblast Culture</td>
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<td>No</td>
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<tr>
<td>CRYOB</td>
<td>Cryopreserve for Biochem Studies</td>
<td>No</td>
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</table>

Testing Algorithm

For skin biopsy or cultured fibroblast specimens, fibroblast culture and cryopreservation testing will be performed at an additional charge. If viable cells are not obtained, the client will be notified.

Special Instructions

- Informed Consent for Genetic Testing
- Blood Spot Collection Card-Spanish Instructions
- Primary Immunodeficiencies Patient Information
- Blood Spot Collection Card-Chinese Instructions
- Informed Consent for Genetic Testing (Spanish)
- Primary Immunodeficiency (PID) Panel Prior Authorization Ordering Instructions
- Blood Spot Collection Instructions
Method Name
Custom Sequence Capture and Targeted Next-Generation Sequencing Followed by Polymerase Chain Reaction (PCR) and Supplemental Sanger Sequencing

NY State Available
Yes

Specimen

Specimen Type
Varies

Advisory Information
For adjunctive testing designed to differentiate between Crohn's disease and ulcerative colitis, order IBDP / Inflammatory Bowel Disease Serology Panel, Serum.

If chronic granulomatous disease (CGD) is suspected, consider also ordering DHR / Dihydrorhodamine (DHR) Flow Cytometric Test, Blood.

This panel has limited utility in patients who present with inflammatory bowel disease (IBD) in adulthood and respond well to conventional therapy.

Targeted testing for familial variants (also called site-specific or known mutation testing) is available for the genes on this panel. See:

- KVAR1 / Known Variant Analysis-1 Variant, Varies
- KVAR2 / Known Variant Analysis-2 Variants, Varies
- KVAR3 / Known Variant Analysis-3+ Variants, Varies

Call 800-533-1710 to confirm the appropriate test for targeted testing.

Necessary Information
1. Primary Immunodeficiencies Patient Information (T791) is required. See Special Instructions.

Note: Testing may proceed without the Patient Information however it aids in providing a more thorough interpretation. Ordering physicians are strongly encouraged to fill out the form.

2. Primary Immunodeficiency (PID) Panel Prior Authorization Ordering Instructions is required. See Special Instructions.

3. Include physician name and phone number with specimen.

Specimen Required
Patient Preparation: A previous bone marrow transplant from an allogenic donor or a recent (ie, <6 weeks from time of sample collection) heterologous blood transfusion will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Prior Authorization is available for this test. Submit the required form with the specimen.
Submit only 1 of the following specimens:

Preferred:

**Specimen Type:** Whole blood

**Container/Tube:** Lavender top (EDTA)

**Specimen Volume:** 3 mL

**Collection Instructions:**

1. Invert several times to mix blood.
2. Send specimen in original tube.

**Specimen Stability Information:** Ambient (preferred) 4 days/Refrigerated 14 days

**Specimen Type:** Blood spot

**Supplies:** Card-Blood Spot Collection Filter Paper (T493)

**Container/Tube:**

**Preferred:** Collection card (Whatman Protein Saver 903 Paper)

**Acceptable:** Whatman FTA Classic paper, Ahlstrom 226 filter paper, or Blood Spot Collection Card (T493)

**Specimen Volume:** 2 to 5 blood spots on collection card

**Collection Instructions:**

1. An alternative blood collection option for a patient <1 year of age is finger stick.
2. Let blood dry on the filter paper at ambient temperature in a horizontal position for 3 hours.
3. Do not expose specimen to heat or direct sunlight.
4. Do not stack wet specimens.
5. Keep specimen dry.

**Additional Information:**

1. For collection instructions, see [Blood Spot Collection Instructions](#) in Special Instructions.
2. For collection instructions in Spanish, see [Blood Spot Collection Card-Spanish Instructions](#) (T777) in Special Instructions.
3. For collection instructions in Chinese, see [Blood Spot Collection Card-Chinese Instructions](#) (T800) in Special Instructions.
Instructions.

**Specimen Stability Information:** Ambient (preferred)/Refrigerated

**Specimen Type:** Peripheral blood mononuclear cells (PBMCs)

**Container/Tube:** Cell pellet

**Collection Instructions:** Send as a suspension in freezing medium or cell pellet frozen on dry ice.

**Specimen Stability Information:** Frozen

**Specimen Type:** Cultured fibroblasts

**Container/Tube:** T-75 or T-25 flask

**Specimen Volume:** 1 Full T-75 or 2 full T-25 flasks

**Additional Information:** Indicate the tests to be performed on the fibroblast culture cells. A separate culture charge will be assessed under FIBR / Fibroblast Culture. An additional 3 weeks is required to culture fibroblasts before genetic testing can occur.

**Specimen Stability Information:** Ambient (preferred)/Refrigerated <24 hours

**Specimen Type:** Skin biopsy

**Supplies:** Fibroblast Biopsy Transport Media (T115)

**Container/Tube:** Sterile container with any standard cell culture media (eg, minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin. Tubes of culture media can be supplied upon request (Eagle's minimum essential medium with 1% penicillin and streptomycin [T115]).

**Specimen Volume:** 4-mm punch

**Additional Information:** A separate culture charge will be assessed under FIBR / Fibroblast Culture. An additional 4 weeks is required to culture fibroblasts before genetic testing can occur.

**Specimen Stability Information:** Refrigerated (preferred)/Ambient

**Specimen Type:** DNA

**Container/Tube:** 2 mL screw top tube

**Specimen Volume:** 100 mcL (microliters)

**Collection Instructions:**

1. The preferred volume is 100 mcL at a concentration of 250 ng/mcL

2. Include concentration and volume on tube.
Specimen Stability Information: Frozen (preferred)/Ambient/Refrigerated

Forms
1. New York Clients-Informed consent is required. Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:
   - Informed Consent for Genetic Testing (T576)
   - Informed Consent for Genetic Testing-Spanish (T826)

2. If not ordering electronically, complete, print, and send a Gastroenterology and Hepatology Client Test Request (T728) with the specimen.


Specimen Minimum Volume
Whole blood: 1 mL

Reject Due To
All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

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Clinical and Interprete

Clinical Information
Inflammatory bowel disease (IBD) is a term used to encompass disorders involving chronic intestinal inflammation. These conditions are typically classified as either Crohn’s disease or ulcerative colitis based on clinical features, colonoscopy findings, histologic changes, and the anatomical distribution of disease; however, in some cases, overlapping features are noted. Over the past few decades, the incidence of inflammatory bowel disease has been rapidly increasing in both children and adults. Common symptoms include: diarrhea, abdominal pain, fatigue, and unintentional weight loss. The majority of IBD is thought to be either polygenic or multifactorial. In these susceptible individuals, an environmental component appears to trigger disease manifestation. However, in rare cases, IBD or IBD-like intestinal inflammation can be attributed to disease-causing variants in a single gene (monogenic inheritance) which results in a highly penetrant condition.

Monogenic IBD typically presents at a very young age (often <6 years of age at onset of symptoms) compared to polygenic IBD (peak at 20-40 years of age), although the incidence of polygenic IBD in young patients is increasing and conversely some patients with milder forms of monogenic IBD may not present until later. Individuals with polygenic or monogenic IBD may also have other family members affected with IBD (a positive family history). In many cases, patients with a monogenic form of IBD may not respond well to conventional treatment modalities and may have a related primary immunodeficiency. Identification of the genetic cause of disease in these individuals is important as it may change the treatment plan for these individuals. Depending on the genetic cause, targeted therapies or allogeneic hematopoietic stem cell transplantation may be beneficial. Therefore, identification of these
conditions is important as it can guide treatment, including medical therapy, surgery, or stem cell transplant, and may reduce the high morbidity and mortality associated with these conditions.

**Reference Values**

An interpretive report will be provided.

**Interpretation**

Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Cautions**

**Clinical Correlations:**

Some individuals who have involvement of 1 or more of the genes on the panel may have a variant that is not identified by the methods performed (eg, promoter variants, deep intronic variants). The absence of a variant, therefore, does not eliminate the possibility of disease.

Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

For predictive testing of asymptomatic individuals, it is often useful to first test an affected family member. Identification of a pathogenic variant in an affected individual allows for more informative testing of at-risk individuals.

**Technical Limitations:**

Next-generation sequencing may not detect all types of genetic variants. The variant detection software has lower detection efficiency for insertion/deletion variants as compared to single nucleotide variants. Therefore, small deletions and insertions greater than 8 nucleotides in length may not be detected by this test. Copy number variations (CNV) are not currently reported for any of the genes on this panel. Additionally, rare variants may be present that could lead to false-negative or false-positive results. In some cases, DNA variants of undetermined significance may be identified. If results do not match clinical findings, consider alternative methods for analyzing these genes, such as Sanger sequencing or large deletion/duplication analysis.

If the patient has had an allogeneic blood or bone marrow transplant or a recent (ie, <6 weeks from time of sample collection) heterologous blood transfusion, results may be inaccurate due to the presence of donor DNA. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

**Reclassification of Variants-Policy:**

At this time, it is not standard practice for the laboratory to systematically review likely deleterious alterations or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time. Consultation with a healthcare provider, or team of healthcare providers, with expertise in genetics and primary immunodeficiencies, is recommended for interpretation of this result.
Contact the laboratory if additional information is required regarding the transcript or human genome assembly used for the analysis of this patient's results.

Clinical Reference


Performance

Method Description

Next-generation sequencing (NGS) is performed using an Illumina instrument with paired-end reads. The DNA is prepared for NGS using a custom Agilent SureSelect Target Enrichment System. Data is analyzed with a bioinformatics software pipeline for sequence variants. Supplemental Sanger sequencing may be performed occasionally in regions where NGS is insufficient for data capture or not specific enough to correctly identify a variant. Sanger sequencing may also be used for confirmatory testing (Unpublished Mayo method).

The following genes are evaluated in this multigene panel:

ADA, ADAM17, AICDA, BTK, CD3G, CD40LG, CTLA4, CYBA, CYBB, DCLRE1C, DKG1, DOCK8, FOXP3, G6PC3, ICOS, IKBKG, IL10, IL10RA, IL10RB, IL21, IL21R, IL2RA, IL2RG, ITGB2, LIG4, LRBA, MEFV, MVK, NCF2, NCF4, NLRC4, PIK3CD, PIK3R1, PLCG2, RAG1, RAG2, RTEL1, SH2D1A, SKIV2L, SLC37A4, STAT1, STAT3, STIM1, STXBP2, TNFAIP3, TTC37, TTC7A, WAS, WIPF1, XIAP and ZAP70 genes.

PDF Report

No

Day(s) and Time(s) Test Performed

Monday

Analytic Time

2 weeks

Maximum Laboratory Time

8 weeks

Specimen Retention Time

Extracted DNA: 2 months

Performing Laboratory Location

Rochester

Fees and Codes

Fees
• Authorized users can sign in to Test Prices for detailed fee information.
• Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
• Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information
81443

LOINC® Information

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Prior Authorization
Insurance preauthorization is available for this testing; forms are available in Special Instructions.

Patient financial assistance may be available to those who qualify. Patients who receive a bill from Mayo Clinic Laboratories will receive information on eligibility and how to apply.