Test Definition: IBDGP

IBD PID Gene Panel

Overview

Useful For

Genetic testing for patients with very early onset inflammatory bowel disease (IBD), early onset IBD, or IBD refractory to treatment

Identifying variants in genes known to be associated with monogenic 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 familial variant analysis (FMTT). See Ordering Guidance section (Specimen tab) for more details.

This test **is not useful for** establishing a diagnosis of typical polygenic IBD or for differentiating between Crohn's disease and ulcerative colitis.

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, 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.

Prior Authorization is available for this assay.

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

Highlights

Identification of a pathogenic variant may assist with prognosis, clinical management, familial screening, and genetic counseling. This is **not** a serological test and is **not intended** to establish a diagnosis of typical polygenic inflammatory bowel disease (IBD) or to differentiate between Crohn's disease and ulcerative colitis.

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
FIBR	Fibroblast Culture	Yes	No
CRYOB	Cryopreserve for Biochem Studies	No	No

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

Ordering Guidance

This test is **not** a serological screening test for inflammatory bowel disease (IBD) and does not differentiate between Crohn disease, ulcerative colitis, or other inflammatory bowel conditions. This test **should not be used** as an adjunct test to establish a diagnosis of IBD. For serology testing to distinguish between ulcerative colitis and Crohn disease, order IBDP2 / Inflammatory Bowel Disease Serology Panel, Serum.

This panel has limited utility in patients who present with IBD in adulthood and respond well to conventional therapy.

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on

this panel. See FMTT / Familial Mutation, Targeted Testing, Varies.

Necessary Information

1. Primary Immunodeficiency (PID) Panel Prior Authorization Ordering Instructions is required. Submit the required form with the specimen.

2. Primary Immunodeficiencies Patient Information (T791) is strongly recommended, but not required, to be filled out and sent with the specimen. This information aids in providing a more thorough interpretation of test results. Ordering providers are strongly encouraged to complete the form and send it with the specimen.

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.

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

Acceptable:

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, PerkinElmer 226 (formerly Ahlstrom 226) filter paper, or Blood Spot Collection Card

Specimen Volume: 2 to 5 Blood spots on collection card

Collection Instructions:

1. An alternative blood collection option for a patient older than1 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.

Specimen Stability Information: Ambient (preferred)/Refrigerated

Additional Information:

1. For collection instructions, see Blood Spot Collection Instructions.

2. For collection instructions in Spanish, see Blood Spot Collection Card-Spanish Instructions (T777).

3. For collection instructions in Chinese, see Blood Spot Collection Card-Chinese Instructions (T800).

Specimen Type: Peripheral blood mononuclear cells (PBMC)

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

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

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

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.

Specimen Volume: 4-mm punch

Specimen Stability Information: Refrigerated (preferred)/Ambient

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

Specimen Type: Extracted 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:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

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

3. Primary Immunodeficiencies Patient Information (T791)

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

Reject Due To

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

Specimen Minimum Volume

Whole blood: 1 mL

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies (preferred)		

Clinical & Interpretive

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 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.

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

1. Uhlig HH, Schwerd T, Koletzko S, et al: The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology. 2014 Nov;147(5):990-1007

2. Uhlig HH, Schwerd T: From Genes to Mechanisms: The expanding spectrum of monogenic disorders associated with inflammatory bowel disease. Inflamm Bowel Dis. 2016 Jan;22(1):202-212

3. Kelsen JR, Baldassano RN, Artis D, Sonnenberg GF: Maintaining intestinal health: the genetics and immunology of very early-onset inflammatory bowel disease. Cell Mol Gastroenterol Hepatol. 2015 Sep 1;1(5):462-476

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)

Genes analyzed: *ADA, ADAM17, AICDA, BTK, CD3G, CD40LG, CTLA4, CYBA, CYBB, DCLRE1C*, *DKC1, 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

Specimen Retention Time

Extracted DNA: 2 months

Performing Laboratory Location

Rochester

Fees & Codes

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 US Food and Drug Administration.

CPT Code Information

81443

Prior Auhtorization

Insurance preauthorization is available for this testing; forms are available.

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.

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
IBDGP	IBD PID Gene Panel	In Process

Result ID	Reporting Name	LOINC®
BA3894	Gene(s) Evaluated	48018-6
BA3895	Result Summary	50397-9
BA3896	Result Details	82939-0
BA3897	Interpretation	69047-9
BA3898	Additional Information	48767-8
BA3899	Method	85069-3
BA3900	Disclaimer	62364-5
BA3901	Reviewed by	18771-6