MAYO CLINIC LABORATORIES

Test Definition: AUTOG

Autoinflammatory Disorders Gene Panel, Varies

Overview

Useful For

Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of an inherited autoinflammatory disorder

Establishing a diagnosis of a monogenic autoinflammatory disorder, allowing for appropriate management and surveillance for disease features based on the gene or variant involved

Identifying variants within genes known to be associated with monogenic autoinflammatory disorders, allowing for predictive testing of at-risk family members

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CULFB	Fibroblast Culture for Genetic Test	Yes	No

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 117 genes associated with autoinflammatory disorders: *ACP5, ADA, ADA2, ADAM17, ADAR, AIRE, ALPI, AP3B1, AP3D1, ARPC1B, ASAH1, C1QA, C1QB, C1QC, C1R, C1S, C2, CARD11, CARD14, CASP10, CASP8, CD3G, CD40LG, CD48, CD55, CDC42, COPA, CTLA4, DDX58, DNASE1, DNASE1L3, DNASE2, DOCK8, FADD, FOXP3, GATA2, HAVCR2, ICOS, IFIH1, IKBKG, IL10, IL10RA, IL10RB, IL1RN, IL2RA, IL2RB, IL2RG, IL36RN, ISG15, ITCH, ITGB2, ITK, JAK1, LACC1, LIG4, LPIN2, LRBA, LSM11, LYN, LYST, MEFV, MVK, NLRC4, NLRP1, NLRP12, NLRP3, NOD2, OAS1, OTULIN, PIK3CD, PIK3R1, PLCG2, POLA1, POMP, PRF1, PRKCD, PSMA3, PSMB10, PSMB4, PSMB8, PSMB9, PSMG2, PSTPIP1, RAB27A, RBCK1, RIPK1, RNASEH2A, RNASEH2B, RNASEH2C, RNF31, RNU7-1, SAMD9L, SAMHD1, SH2D1A, SH3BP2, SKIV2L, SLC29A3, SLC37A4, STAT1, STAT2, STAT3, STIM1, STING1, STX11, STXBP2, TLR7, TNFAIP3, TNFRSF1A, TPP2, TREX1, TRNT1, UNC13D, USP18, WAS, WDR1, XIAP,* and *ZAP70*. See Targeted Genes and Methodology Details for Autoinflammatory Disorders Gene Panel for details regarding the targeted gene regions evaluated by this test.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for a heritable form of autoinflammatory disease.

Testing Algorithm

For skin biopsy or cultured fibroblast specimens, fibroblast culture 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
- Blood Spot Collection Card-Chinese Instructions

- Informed Consent for Genetic Testing (Spanish)
- Blood Spot Collection Instructions
- Inborn Errors of Immunity, Autoimmunity, and Autoinflammatory Disease Patient Information
- Targeted Genes and Methodology Details for Autoinflammatory Disorders Gene Panel

Method Name
Sequence Capture and Amplicon-Based Next-Generation Sequencing (NGS)/Quantitative Real-Time Polymerase Chain Reaction (qPCR) and Sanger Sequencing as needed.

NY State Available
Yes

Specimen

Specimen Type
Varies

Ordering Guidance
Targeted testing for familial variants (also called site-specific or known variants testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

Shipping Instructions
Specimen preferred to arrive within 96 hours of collection.

Specimen Required
Patient Preparation: A previous bone marrow transplant from an allogenic donor 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:

Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Any anticoagulant
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**
Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated

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 CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

Specimen Type: Cultured fibroblasts
Container/Tube: T-25 flask
Specimen Volume: 2 Flasks
Collection Instructions: Submit confluent cultured fibroblast cells from a skin biopsy from another laboratory. Cultured cells from a prenatal specimen will not be accepted.
Specimen Stability Information: Ambient (preferred)/Refrigerated (<24 hours)
Additional Information: A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

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. Inborn Errors of Immunity, Autoimmunity and Autoinflammatory Disease Patient Information

Specimen Minimum Volume

Blood: 1 mL; Skin biopsy or cultured fibroblasts: See Specimen Required

Reject Due To

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

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

Systemic autoinflammatory disorders result from dysregulation of the innate immune system and are characterized by a hyperinflammatory state with elevated acute phase reactants. These disorders may present at any age, but symptoms often begin in childhood with unexplained fever that may be accompanied by a rash. While these features can mimic infections or hematological neoplasias, the inflammatory lesions are noncancerous and sterile. Additional features may be present and highly variable, depending on the organ or organs impacted by cytokine amplification loops and sterile

inflammation. Symptoms may involve the gastrointestinal (GI) tract (eg, serositis, abdominal pain, early-onset inflammatory bowel disease), bone, eyes (eg, uveitis), musculoskeletal system (eg, arthritis and arthralgias), central nervous system (eg, meningitis), or other tissues. Some autoinflammatory disorders are also associated with an increased risk of developing AA amyloidosis. These disorders include familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), cryopyrin-associated autoinflammatory syndrome (CAPS), and hyper-IgD syndrome/mevalonate kinase deficiency (HIDS/MKD).

Autoinflammatory disorders are classified by molecular pathogenesis or clinical features. Pathophysiologic classification is based on the pathway or cytokine that drives disease, such as interleukin (IL)-1, interferon, nuclear factor kappa B, and IL-18. Disease classification based on clinical features often focuses on skin involvement or fever duration and frequency. Age of onset, triggers, and additional organ system involvement are also used to classify these disorders and aid clinical diagnosis.

The genetic basis of many heritable autoinflammatory disorders has been identified. Autoinflammatory disorders may be inherited in an autosomal recessive, autosomal dominant, or X-linked manner. Disease-causing variants may also arise *de novo*. The inheritance pattern appears more complicated for some disorders. For example, FMF is typically inherited in an autosomal recessive manner. However, some affected individuals appear to have only one disease-causing alteration. For other autoinflammatory disorders, cases of digenic and oligogenic inheritance have also been described. Inheritance may also be multifactorial, requiring an environmental component along with low-penetrance variants. One example is Yao syndrome, a recently described clinical entity characterized by recurrent fever, dermatitis, inflammatory arthritis, and GI symptoms in most affected individuals. While some variants in *NOD2* have been reported in association with Yao syndrome, they are relatively common among the general population. They may confer an increased risk for developing Yao syndrome but are not diagnostic and appear insufficient to cause disease by themselves. Some disorders such as PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis) syndrome, systemic juvenile idiopathic arthritis, adult-onset Still disease, and Behcet disease have significant phenotypic overlap with monogenic autoinflammatory conditions, but a genetic cause of these disorders has not been identified.

Finally, several examples of post-zygotic (mosaic or somatic) genetic alterations causing autoinflammatory disorders have been described. While it may be possible to identify mosaic variants, this test is primarily intended for the identification of germline variants and the diagnosis of inherited monogenic autoinflammatory disorders.

Determining the underlying genetic cause of an autoinflammatory condition may help guide treatment decisions. For example, colchicine is an effective therapy for many patients with FMF, but some patients may not respond. Instead, these individuals, and others affected by a subset of autoinflammatory disorders, may respond to IL-1 blocking therapies. Anakinra, rilonacept, and canakinumab are several examples of medications that target IL-1. However, another subset of autoinflammatory disorders is not responsive to IL-1 blockade, such as proteasome-associated autoinflammatory syndromes (PRAAS), CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy), deficiency of IL-36 receptor antagonist, and CAMPS (CARD14-mediated psoriasis). Medications that target other components of the IL-1 pathway are under development. In addition, medications that target other pathways (eg, anti-tumor necrosis factor, anti-IL-6, and JAK-inhibitors) have demonstrated efficacy in some patients.

Reference Values

An interpretive report will be provided.

Interpretation

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

Cautions

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

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:
This analysis targets single and multi-exon deletions/duplications; however, in some instances, single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

This test is not designed to detect low levels of mosaicism or differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent non-leukoreduced blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants**:**
Currently, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

Variant Evaluation:
Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(1) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

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 periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgement.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424
2. Hashkes PJ, Laxer RM, Simon A. Textbook of Autoinflammation. Springer Nature; 2019
3. Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42(7):1473-1507
4. Rood JE, Behrens EM. Inherited autoinflammatory syndromes. Annu Rev Pathol. 2022;17:227-249
5. Gutierrez MJ, Lapidus SK. Systemic autoinflammatory diseases. Rheum Dis Clin North Am. 2022;48(1):371-395
6. Broderick L, Hoffman HM. IL-1 and autoinflammatory disease: biology, pathogenesis and therapeutic targeting. Nat Rev Rheumatol. 2022;18(8):448-463

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in

coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletions/insertions (delins) less than 40 base pairs (bp), and above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. See Targeted Genes and Methodology Details for Autoinflammatory Disorders Gene Panel for details regarding the targeted gene regions identified by this test.(Unpublished Mayo method)

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Genes analyzed:
ACP5, ADA, ADA2, ADAM17, ADAR, AIRE, ALPI, AP3B1, AP3D1, ARPC1B, ASAH1, C1QA, C1QB, C1QC, C1R, C1S, C2, CARD11, CARD14, CASP10, CASP8, CD3G, CD40LG, CD48, CD55, CDC42, COPA, CTLA4, DDX58, DNASE1, DNASE1L3, DNASE2, DOCK8, FADD, FOXP3, GATA2, HAVCR2, ICOS, IFIH1, IKBKG, IL10, IL10RA, IL10RB, IL1RN, IL2RA, IL2RB, IL2RG, IL36RN, ISG15, ITCH, ITGB2, ITK, JAK1, LACC1, LIG4, LPIN2, LRBA, LSM11, LYN, LYST, MEFV, MVK, NLRC4, NLRP1, NLRP12, NLRP3, NOD2, OAS1, OTULIN, PIK3CD, PIK3R1, PLCG2, POLA1, POMP, PRF1, PRKCD, PSMA3, PSMB10, PSMB4, PSMB8, PSMB9, PSMG2, PSTPIP1, RAB27A, RBCK1, RIPK1, RNASEH2A, RNASEH2B, RNASEH2C, RNF31, RNU7-1, SAMD9L, SAMHD1, SH2D1A, SH3BP2, SKIV2L, SLC29A3, SLC37A4, STAT1, STAT2, STAT3, STIM1, STING1, STX11, STXBP2, TLR7, TNFAIP3, TNFRSF1A, TPP2, TREX1, TRNT1, UNC13D, USP18, WAS, WDR1, XIAP, and *ZAP70*

PDF Report
Supplemental

Day(s) Performed
Varies

Report Available
28 to 42 days

Specimen Retention Time
Whole blood: 2 weeks (if available); Extracted DNA: 3 months; Cultured fibroblasts, skin biopsy: 1 month

Performing Laboratory Location
Rochester

Fees & 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 account representative. 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. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81443
88233-Tissue culture, skin, solid tissue biopsy (if appropriate)
88240-Cryopreservation (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
AUTOG	Autoinflammatory Gene Panel	In Process

Result ID	Test Result Name	Result LOINC® Value
620093	Test Description	62364-5
620094	Specimen	31208-2
620095	Source	31208-2
620096	Result Summary	50397-9
620097	Result	82939-0
620098	Interpretation	69047-9
620099	Additional Results	82939-0
620100	Resources	99622-3
620101	Additional Information	48767-8
620102	Method	85069-3
620103	Genes Analyzed	82939-0
620104	Disclaimer	62364-5
620105	Released By	18771-6