

## Overview

### Useful For

Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of autoinflammatory syndromes and related disorders

Establishing a diagnosis of autoinflammatory disease, and in some cases guiding management and allowing for surveillance of disease features

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

### Genetics Test Information

This test includes next-generation sequencing and supplemental Sanger sequencing to evaluate for the genes listed on the panel.

### Highlights

This test uses next-generation sequencing to test for variants in the *CARD14*, *IL10RA*, *IL10RB*, *IL1RN*, *IL36RN*, *ISG15*, *LPIN2*, *MEFV*, *MVK*, *NLRP12*, *NLRP3 (CIAS1)*, *NOD2 (CARD15)*, *PLCG2*, *PSMB8*, *PSTPIP1 (CD2BP1)*, *RBCK1 (HOIL1)*, *SH3BP2*, and *TNFRSF1A* genes.

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

### Reflex Tests

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

### 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 \(Spanish\)](#)
- [Blood Spot Collection Instructions](#)

### Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Supplemental Sanger Sequencing

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**NY State Available**

Yes

**Specimen****Specimen Type**

Varies

**Advisory Information**

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. Include physician name and phone number with specimen.

**Specimen Required**

**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)/Refrigerated

**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.

**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

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will be assessed under FIBR / Fibroblast Culture. An additional 4 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:** 100mcL (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**

**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)

**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**

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

## Clinical and Interpretive

### Clinical Information

Autoinflammatory disorders include several monogenic defects associated with abnormal activation of the innate immune system leading to clinically evident inflammation and high levels of acute-phase reactants. These disorders typically present in childhood, often manifesting with unexplained fevers. While these features can mimic infections or hematological neoplasias, the inflammatory lesions are non-neoplastic and sterile. While periodic fever adenitis pharyngitis aphthous ulcer (PFAPA) syndrome (aphthous stomatitis, pharyngitis, and adenitis), systemic juvenile idiopathic arthritis (sJIA), adult-onset Still disease, and Behcet disease overlap phenotypically with autoinflammatory conditions, a genetic cause of these disorders has not been identified and, therefore, they are not included on this panel. Several of the autoinflammatory conditions represented on this panel are responsive to IL-1 blocking therapies; therefore, determining the underlying genetic cause may help guide treatment decisions.

Monogenic autoinflammatory conditions include the periodic fever syndromes (ie, familial Mediterranean fever, cryopyrinopathy-associated periodic syndrome, Muckle-Wells syndrome, familial cold autoinflammatory syndrome, neonatal onset multisystem inflammatory disease or chronic infantile neurologic cutaneous and articular syndrome, tumor necrosis factor [TNF] receptor-associated periodic syndrome, hyper IgD syndrome/Mevalonate kinase deficiency), diseases with pyogenic lesions (ie, deficiency of IL-1 receptor antagonist [DIRA]; pyogenic arthritis, pyoderma gangrenosum and acne [PAPA]; Majeed syndrome), diseases with granulomatous lesions (ie, Blau syndrome), diseases with psoriasis (ie, deficiency of interleukin 36-receptor antagonist [DITRA]); diseases with panniculitis-induced lipodystrophy (JMP syndrome, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome [CANDLE], Nakajo-Nishimura syndrome [NNS], proteasome-associated autoinflammatory syndromes [PRAAS]). DITRA and CARD14-mediated psoriasis (CAMPS) both present with pustular skin lesions and early-onset inflammatory bowel disease (IBD). See Table 1 for a summary of genes included in this panel, associated diseases, and the mode of inheritance.

NOD2-associated autoinflammatory disease (NAID), also known as Yao syndrome, is a newly-described clinical entity characterized by recurrent fever, dermatitis, and inflammatory arthritis along with GI symptoms in a majority of the patients. Variants in *NOD2* have been associated with NAID; however, the variants that have been implicated to date are common variants that confer risk for development of the disorder and are not diagnostic. These common variants are not included in the report for this panel; however, a list of all common variants identified is available by request.

While several of the autoinflammatory conditions, including those without a known genetic basis, are responsive to interleukin-1 (IL-1) blocking therapies, PRAAS, CANDLE, DITRA, and CAMPS are not responsive to IL-1 blockade. Anakinra, Riloncept, and Canakinumab are several examples of medications that target IL-1.

The NOD-like receptors (NLRs), which include 23 family members in humans, are an integral part of the innate immune system. NLRs are involved in the formation of the inflammasome, of which the NLRP3 (NALP3) inflammasome is most relevant to human disease and is responsible for activation of the proinflammatory cytokine IL-1 beta.

#### Table 1. Genes included in the Autoinflammatory Gene Panel (listed in alphabetical order)

GENE SYMBOL (ALIAS)	PROTEIN	OMIM	INCIDENCE	INHERITANCE	PHENOTYPE DISORDER
<i>CARD14</i>	Caspase recruitment domain-containing protein 14 isoform 1	607211	Rare	AD	Pityriasis rubra pilaris, psoriasis 2 (CAMPS)
<i>IL10RA</i>	Interleukin-10 receptor subunit alpha precursor	146933	Rare	AR	Very early onset inflammatory bowel disease 28 (VEOIBD)
<i>IL10RB</i>	Interleukin-10 receptor subunit beta precursor	123889	Rare	AR	Very early onset inflammatory bowel disease 25 (VEOIBD)
<i>IL1RN</i>	Interleukin-1 receptor antagonist protein isoform 2	147679	Rare	AR	Deficiency of interleukin 1 receptor antagonist (DIRA)
<i>IL36RN</i>	Interleukin-36 receptor antagonist protein	605507	Rare	AR	Pustular psoriasis 14,  deficiency of IL36 receptor antagonist (DITRA)
<i>ISG15</i>	Ubiquitin-like protein ISG15 precursor	147571	Rare	AR	Immunodeficiency 38 A
<i>LPIN2</i>	Phosphatidate phosphatase LPIN2	605519	Primarily identified in Arab ethnicities	AR	Majeed syndrome
<i>MEFV</i>	Pyrin isoform 1	608107	Primarily identified in Armenian, Arab, Turkish, Italian, and Jewish ethnicities	AR (most), AD (rarely)	Familial Mediterranean fever (FMF)



<i>MVK</i>	Mevalonate kinase isoform a	251170	Primarily identified in Caucasians of western European ancestry	AR/AD	Hyperimmunoglobulinemia D syndrome (HIDS), Mevalonate kinase-associated periodic fever syndrome, Mevalonic aciduria, Porokeratosis 3, multiple types (AD)
<i>NLRP12 (NALP12)</i>	NACHT, leucine rich repeat (LRR) and PYD domains-containing protein 12 isoform 2	609648	Rare	AD	Familial cold autoinflammatory syndrome 2 (FCAS2)
<i>NLRP3 (NALP3) (CIAS1)</i>	NACHT, LRR, and PYD domains-containing protein 3 isoform a	606416	Primarily identified in Caucasians of western European ancestry	AD	Familial cold autoinflammatory syndrome 1 (FCAS1), Muckle-Wells syndrome; Neonatal onset multisystem inflammatory disease (NOMID)/chronic infantile neurological cutaneous and articular syndrome (CINCA)
<i>NOD2 (CARD15)</i>	Nucleotide-binding oligomerization domain-containing protein 2 isoform 1	605956	Rare	AD	Blau syndrome, Early-onset Sarcoidosis, Inflammatory bowel disease 1  Pediatric granulomatous arthritis (PGA)



<i>PLCG2</i>	1-Phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-2	600220	Rare	AD	PLC gamma 2-associated antibody deficiency and immune dysregulation (PLAID), autoinflammation and PLC gamma 2-associated antibody deficiency and immune dysregulation (APLAID)
<i>PSMB8</i>	Proteasome subunit beta type-8 isoform E2 precursor	177046	Rare	AR	CANDLE (chronic atypical neutrophilic dermatitis with lipodystrophy); JMP (joint contractures, muscular atrophy, microcytic anemia, and panniculitis-induced lipodystrophy); PRASS (proteasome-associated auto-inflammatory syndrome); JASL (Japanese autoinflammatory syndrome with lipodystrophy)
<i>PSTPIP1</i> ( <i>CD2BP1</i> )	Proline-serine-threonine phosphatase-interacting protein 1	606347	Rare	AD	Pyogenic sterile arthritis pyoderma gangrenosum acne (PAPA)

<i>RBCK1 (HOIL1)</i>	RanBP-type and C3HC4-type zinc finger-containing protein 1 isoform 2	610924	Rare	AR	Polyglucosan body myopathy 1 with or without immunodeficiency ;  chronic autoinflammation, invasive bacterial infections, muscle amylopectinosis
<i>SH3BP2</i>	SH3 domain-binding protein 2 isoform a	602104	Rare	AD	Cherubism, autoinflammatory bone disease
<i>TNFRSF1A</i>	Tumor necrosis factor receptor superfamily member 1A precursor	191190	Primarily identified in Caucasians of western European ancestry	AD	Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)

AD=autosomal dominant AR=autosomal recessive XL=X-linked

## 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 one 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.

If testing was performed because of a family history of autoinflammatory disease, it is important 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 polymorphisms 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 pathogenic variants 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.

A list including benign, likely benign, and high minor allele frequency (>1%) risk-associated variants detected is available from the lab upon request after results are received.

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. Ozen S, Bilginer T: A clinical guide to autoinflammatory diseases: FMF and next of kin. *Nature Rev. Rheumatol.* 2014;10:135-147
2. Canna SW, Goldbach-Mansky R: New monogenic autoinflammatory diseases-a clinical overview. *Semin Immunopathol* 2015;37:387-394
3. Henderson C, Goldbach-Mansky R: Monogenic IL-1-mediated autoinflammatory and immunodeficiency syndromes: finding the right balance in response to danger signals. *Clin Immunol* 2010;135:210-222
4. Caso F, Galozzi P, Costa L, et al: Autoinflammatory granulomatous diseases: from Blau syndrome and early-onset sarcoidosis to NOD2-mediated disease and Crohn's disease. *RMD Open* 2015;1:e000097
5. Stern SM, Ferguson PJ: Autoinflammatory bone diseases. *Rheum Dis Clin North Am* 2013;39:735-749
6. Martinon F, Aksentijevich I: New Players driving inflammation in monogenic autoinflammatory diseases. *Nat Rev Rheumatol* 2015;11:11-20
7. Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes. *Annu Rev Med* 2014;65:223-244
8. Picard C, Gaspar HB, Al-Herz W, Bousfina A, et al: International Union of Immunological Societies: 2017 Primary Immunodeficiency Disease Committee Report on Inborn Errors of Immunity, *J Clin Immunol* 2018;38:96-128

#### 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. 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. (Unpublished Mayo method)

The following genes are evaluated in this multi-gene panel:

*CARD14, IL10RA, IL10RB, IL1RN, IL36RN, ISG15, LPIN2, MEFV, MVK, NLRP12, NLRP3 (CIAS1), NOD2 (CARD15), PLCG2, PSMB8, PSTPIP1 (CD2BP1), RBCK1 (HOIL1), SH3BP2, TNFRSF1A*

## PDF Report

No

## Day(s) and Time(s) Test Performed

Monday; Varies

## Analytic Time

4 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

Test ID	Test Order Name	Order LOINC Value
AUTOP	Autoinflammatory PID Gene Panel	In Process



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Result ID	Test Result Name	Result LOINC Value
BA3878	Gene(s) Evaluated	48018-6
BA3879	Result Summary	50397-9
BA3880	Result Details	82939-0
BA3881	Interpretation	69047-9
BA3882	Additional Information	48767-8
BA3883	Method	49549-9
BA3884	Disclaimer	62364-5
BA3885	Reviewed by	18771-6