

Overview

Useful For

Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hyper-IgE syndrome (HIES)

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

Identifying variants within genes known to be associated with HIES, allowing for predictive testing of at-risk family members and/or determination of targeted management (anticipatory guidance, management changes, specific therapies)

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 21 genes associated with hyper-IgE syndrome: *AIRE*, *CARD11*, *CARD9*, *CARMIL2*, *DOCK8*, *ERBIN*, *IL6R*, *IL6ST*, *IL17RA*, *IL17RC*, *IL17F*, *PGM3*, *SPINK5*, *STAT1*, *STAT3*, *TGFBR1*, *TGFBR2*, *TRAF3IP2*, *TYK2*, *WAS*, and *ZNF341*. See [Targeted Genes and Methodology Details for Hyper-IgE Syndrome Gene Panel](#) and Method Description for additional details.

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

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](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)
- [Targeted Genes and Methodology Details for Hyper-IgE Syndrome Gene Panel](#)
- [Inborn Errors of Immunity, Autoimmunity, and Autoinflammatory Disease Patient Information](#)

Method Name

Sequence Capture and Targeted Next-Generation Sequencing (NGS)

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 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, Tissue. 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. [Molecular Genetics: Congenital Inherited Diseases Patient Information](#) (T521)
3. [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

Hyper IgE syndrome (HIES) is characterized by an increased susceptibility to infection (particularly recurrent skin and pulmonary infections), eczema, and elevated serum IgE. There is variable expression among individuals and additional features may be present, including vascular, skeletal, and connective tissue pathology. While the incidence of HIES is estimated to be between 1:100,000 to 1,000,000 at birth, this may be an underestimate due to incomplete penetrance.

Dominant negative variants in *STAT3* were first identified as the genetic cause of HIES, which was referred to as Job syndrome. Now additional genes have been identified, and cases due to *STAT3* variants are referred to as STAT3-HIES. Infection in STAT3-HIES is often due to *Staphylococcus aureus* and *Candida* species. While HIES may be inherited in an autosomal dominant pattern, many cases are *de novo*.

Genetic variants in additional genes have been identified that result in HIES. ZNF341 (zinc finger protein 341) deficiency results in an autosomal recessive form of HIES, also known as AR-HIES. Partial deficiency of interleukin (IL) 6 signal transducer (IL6ST) has been reported in both autosomal recessive and autosomal dominant forms of HIES, while complete IL6ST deficiency is typically fatal in utero or early in the neonatal period. Additionally, variants in *PGM3*, *CARD11*, and other genes have been identified as causes of HIES. Furthermore, other distinct immunodeficiency disorders or other conditions may have overlapping features with HIES (eg, elevated IgE or severe infection), making the diagnosis challenging. While the phenotypes of disorders leading to elevated IgE and predisposition to infection are often similar, the therapeutic options and treatment strategies differ.

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**Reference Values**

An interpretive report will be provided

**Interpretation**

All detected variants are evaluated according to American College of Medical Genetics and Genomics (ACMG) 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 to 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. Refer to the [Targeted Genes and Methodology Details for Hyper-IgE Syndrome Gene Panel](#) for the most up to date list of genes included in this test. For detailed

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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 health care 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.<sup>(1)</sup> 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 judgment.

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; ACMG Laboratory Quality Assurance Committee: 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 May;17(5):405-424
2. Tsilifis C, Freeman AF, Gennery AR: STAT3 Hyper-IgE syndrome-an update and unanswered questions. *J Clin Immunol*. 2021 Jul;41(5):864-880
3. Asano T, Khourieh J, Zhang P, et al: Human STAT3 variants underlie autosomal dominant hyper-IgE syndrome by negative dominance. *J Exp Med*. 2021 Aug 2;218(8):e20202592. doi: 10.1084/jem.20202592
4. Hsu AP, Davis J, Puck JM, Holland SM, Freeman AF: STAT3 hyper IgE syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. *GeneReviews*. [Internet] University of Washington, Seattle; 2010. Updated March 26, 2020. Accessed January 23, 2023. Available at [www.ncbi.nlm.nih.gov/books/NBK25507/](http://www.ncbi.nlm.nih.gov/books/NBK25507/)
5. 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 Oct;42(7):1473-1507. doi: 10.1007/s10875-022-01289-3

## 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.(Unpublished Mayo method)

See [Targeted Genes and Methodology Details for Hyper-IgE Syndrome Gene Panel](#) for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered.

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

Genes analyzed: *AIRE, CARD11, CARD9, CARMIL2, DOCK8, ERBIN, IL6R, IL6ST, IL17RA, IL17RC, IL17F, PGM3, SPINK5, STAT1, STAT3, TGFB1, TGFB2, TRAF3IP2, TYK2, WAS, ZNF341*

### 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

Mayo Clinic Laboratories - Rochester Main Campus

## 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
HIESG	Hyper-IgE Syndrome Gene Panel	103740-7

Result ID	Test Result Name	Result LOINC® Value
619817	Test Description	62364-5
619818	Specimen	31208-2
619819	Source	31208-2
619820	Result Summary	50397-9
619821	Result	82939-0
619822	Interpretation	69047-9
619823	Additional Results	82939-0
619824	Resources	99622-3
619825	Additional Information	48767-8
619826	Method	85069-3
619827	Genes Analyzed	82939-0
619828	Disclaimer	62364-5
619829	Released By	18771-6