

### 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
CULAF	Amniotic Fluid Culture/Genetic Test	Yes	No
_STR1	Comp Analysis using STR (Bill only)	No, (Bill only)	No
_STR2	Add'l comp analysis w/STR (Bill Only)	No, (Bill only)	No
CULFB	Fibroblast Culture for Genetic Test	Yes	No
MATCC	Maternal Cell Contamination, B	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, TGFB1, TGFB2, 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

##### Skin biopsy or cultured fibroblast specimens:

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.

##### Cord blood:

For cord blood specimens that have an accompanying maternal blood specimen, maternal cell contamination studies

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will be performed at an additional charge.

**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**

Upon request and after initial testing is complete, WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies may be added to this test. To obtain more information about this option or add WESPR testing, call 800-533-1710.

Customization of this panel and single gene analysis for any gene present on this panel are available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies. To modify this panel via CGPH, use the Inborn Errors of Immunity/Bone Marrow Failure/Telomeropathy/Pulmonary Fibrosis/Very Early Onset IBD/Pancreatitis disease state for step 1 on the [Custom Gene Ordering Tool](#).

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.

**Specimen Required**

**Patient Preparation:** A previous hematopoietic stem cell transplant from an allogenic donor will interfere with testing. For information about testing patients who have received a hematopoietic stem cell transplant, call 800-533-1710.

**Submit only 1 of the following specimens:**

**Specimen Type:** Whole blood

**Container/Tube:** Lavender top (EDTA) or yellow top (ACD)

**Specimen Volume:** 3 mL

**Collection Instructions:**

1. Invert several times to mix blood.

2. Send whole blood specimen in original tube. **Do not aliquot.**
3. Whole blood collected postnatal from an umbilical cord is also acceptable. See Additional Information

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

**Additional Information:**

1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.
2. To ensure minimum volume and concentration of DNA are met, the requested volume must be submitted. Testing may be canceled if DNA requirements are inadequate.
3. For postnatal umbilical cord whole blood specimens, maternal cell contamination studies are recommended to ensure test results reflect that of the patient tested. A maternal blood specimen is required to complete maternal cell contamination studies. Order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on both the cord blood and maternal blood specimens under separate order numbers.

**Specimen Type:** Saliva

**Patient Preparation:** Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.

**Supplies:**

DNA Saliva Kit High Yield (T1007)

Saliva Swab Collection Kit (T786)

**Container/Tube:**

**Preferred:** High-yield DNA saliva kit

**Acceptable:** Saliva swab

**Specimen Volume:** 1 Tube if using T1007 or 2 swabs if using T786

**Collection Instructions:** Collect and send specimen per kit instructions.

**Specimen Stability Information:** Ambient (preferred) 30 days/Refrigerated 30 days

**Additional Information:** Saliva specimens are acceptable but not recommended. Due to lower quantity/quality of DNA yielded from saliva, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.

**Specimen Type:** Blood spot

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

**Container/Tube:**

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

**Acceptable:** PerkinElmer 226 filter paper or blood spot collection card

**Specimen Volume:** 2 to 5 Blood spots

**Collection Instructions:**

1. An alternative blood collection option for a patient older than 1 year is a fingerstick. For detailed instructions, see [How to Collect a Dried Blood Spot Sample](#).
2. Let blood dry on the filter paper at ambient temperature in a horizontal position for a minimum of 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. Blood spot specimens are acceptable but not recommended. Multiple extractions will be required to obtain sufficient

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yield for supplemental analysis, and there is significant risk for test failure due to insufficient DNA.

2. Due to lower concentration of DNA yielded from blood spot, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.

3. For collection instructions, see [Blood Spot Collection Instructions](#)

4. For collection instructions in Spanish, see [Blood Spot Collection Card-Spanish Instructions](#) (T777)

5. For collection instructions in Chinese, see [Blood Spot Collection Card-Chinese Instructions](#) (T800)

**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:** Ambient (preferred) <24 hours/Refrigerated <24 hours

**Additional Information:**

1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.

2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks are required to culture fibroblasts before genetic testing can occur.

**Specimen Type:** Cultured fibroblasts

**Source:** Skin or tissue

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

**Specimen Volume:** 2 Flasks

**Collection Instructions:** Submit confluent cultured fibroblast cells from a skin or tissue biopsy. Cultured cells from a prenatal specimen will not be accepted.

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

**Additional Information:**

1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.

2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks are required to culture fibroblasts before genetic testing can occur.

**Specimen Type:** Extracted DNA

**Container/Tube:**

**Preferred:** Screw Cap Micro Tube, 2 mL with skirted conical base

**Acceptable:** Matrix tube, 1 mL

**Collection Instructions:**

1. The preferred volume is at least 100 µL at a concentration of 75 ng/µL.

2. Include concentration and volume on tube.

**Specimen Stability Information:** Frozen (preferred) 1 year/Ambient/Refrigerated

**Additional Information:** DNA must be extracted in a CLIA-certified laboratory or equivalent and must be extracted from a specimen type listed as acceptable for this test (including applicable anticoagulants). Our laboratory has experience with Chemagic, Puregene, Autopure, MagnaPure, and EZ1 extraction platforms and cannot guarantee that all extraction methods are compatible with this test. If testing fails, one repeat will be attempted, and if unsuccessful, the test will be

reported as failed and a charge will be applied. If applicable, specific gene regions that were unable to be interrogated due to DNA quality will be noted in the report.

### 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

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.

**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;17(5):405-424
2. Tsilifis C, Freeman AF, Gennery AR. STAT3 Hyper-IgE syndrome-an update and unanswered questions. *J Clin Immunol.* 2021;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;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 November 18, 2025. 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;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, TGFBR1, TGFBR2, TRAF3IP2, TYK2, WAS, ZNF341*

**PDF Report**

Supplemental

**Day(s) Performed**

Varies

**Report Available**

14 to 21 days

**Specimen Retention Time**

Whole blood: 28 days (if available); Extracted DNA: 3 months, Saliva: 30 days (if available); Blood spots: 1 year (if available)

**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