MAYO CLINIC LABORATORIES

Test Definition: BCELL

B-Cell and Antibody Deficiency Gene Panel, Varies

Overview

Useful For

Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of an inherited primary B-cell disorder or humoral immunodeficiency

Establishing a diagnosis of a primary B-cell disorder or humoral immunodeficiency, 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 primary B-cell disorders or humoral immunodeficiencies, 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 61 genes associated with inherited B-cell disorders and humoral immunodeficiency: *ADA, ADA2, AICDA, ATP6AP1, BLNK, BTK, CARD11, CD19, CD27, CD40, CD40LG, CD70, CD79A, CD79B, CD81, CDCA7, CTLA4, CR2, CXCR4, DCLRE1C, DNMT3B, GATA2, ICOS, IGHM, IGLL1, IKBKG, IKZF1, IKZF3, IL21, IL21R, IRF2BP2, KDM6A, KMT2A, KMT2D, LIG1, LRBA, MOGS, MS4A1, NFKB1, NFKB2, PIK3CD, PIK3R1, PLCG2, PRKCD, RAC2, RAG1, RAG2, RNF168, SEC61A1, SH2D1A, SH3KBP1, SLC39A7, TCF3, TNFRSF13B, TNFRSF13C, TNFSF12, TNFSF13, TOP2B, TRNT1, UNG,* and *XIAP.* See Targeted Genes and Methodology Details for B-Cell and Antibody Deficiency 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 inherited B-cell disorders and humoral immunodeficiency.

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)
- Combined Immunodeficiency, Severe Combined Immunodeficiency, and B-Cell/Antibody Deficiency Patient Information
- Targeted Genes and Methodology Details for B-Cell and Antibody Deficiency 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. Combined Immunodeficiency, Severe Combined Immunodeficiency, and B-Cell/Antibody Deficiency 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

Primary B-cell disorders and humoral immunodeficiencies are characterized by an insufficient number of B cells or the impaired functioning or differentiation of B cells. B-cell disorders account for approximately half to two-thirds of all genetic primary immunodeficiency disorders (PIDD). They may result in a decrease or dysfunction of one or more isotypes of immunoglobulin, leading to increased susceptibility to infection, particularly bacterial infections, such as sinopulmonary infections, gastrointestinal infections, otitis, skin infections, and conjunctivitis. In the absence of infection, patients may be asymptomatic and, thus, difficult to diagnose. In addition, primary B-cell disorders may result in lymphoproliferative disorders or be associated with autoimmune (AI) manifestations, including AI cytopenias, AI endocrine disorders, and AI enteropathy.

PIDD that are primarily antibody deficiencies fall into four main categories:

1. Agammaglobulinemias, which are characterized by severe reduction in all serum immunoglobulin isotypes with profoundly decreased or absent B cells
2. Common variable immunodeficiency (CVID)-like diseases that are characterized by severe reduction in at least two serum immunoglobulin isotypes with normal or low number of B cells
3. Hyper-IgM syndromes, which are characterized by severe reduction in serum IgG and IgA with normal or elevated IgM and normal numbers of B cells
4. A mixed group of isotype, light chain, or functional antibody deficiencies generally with normal numbers of B cells
In addition, there are several PIDD that also have an associated T-cell or other cellular immunodeficiency as well as B-cell defects.

Agammaglobulinemia typically presents in the first few years of life with recurrent bacterial infections, a severe life-threatening bacterial infection (ie, meningitis, sepsis), and decreased lymphoid tissue (ie, small adenoids, tonsils, and lymph nodes in X-linked agammaglobulinemia, due to Bruton tyrosine kinase [*BTK*] gene variants). Inheritance can be either X-linked (eg, due to variants in *BTK*), autosomal dominant (eg, *TCF3*, *TOP2B*), or autosomal recessive (eg, *IGHM*, *CD79A*, *CD79B*, *IGLL1*, *BLNK*, and *PIK3R1*).

Common variable immunodeficiency (CVID) is the most common adult humoral immunodeficiency disorder with an incidence of approximately 1:10,000 to 1:50,000. CVID may present with frequent and unusual infections during early childhood, adolescence, or adulthood. As per current diagnostic criteria, CVID is not considered in children younger than 4 years of age. In addition, a significant proportion of patients may have autoimmune or inflammatory manifestations, enlarged lymphoid tissues, granulomas, and an increased susceptibility to cancer. These patients typically have normal numbers of B cells (<5% of CVID patients have <1% B cells, which is due to early B-cell defects) but have impaired terminal differentiation, resulting in decreased levels of IgG and IgA, with or without a decrease in IgM. Over two-thirds of patients have quantitative defects in switched memory B cells. Some patients may also have quantitative and functional T-cell defects or natural killer (NK) cell deficiency. Patients with decreased naive T-cell numbers are considered to have late-onset combined immunodeficiency. Genetic variants have been identified in several genes, including *ICOS*, *TNFRSF13B* (*TACI*), *CD19*, *TNFRSF13C* (*BAFFR*), *MS4A1* (*CD20*), *CR2* (*CD21*), *CD81*, *LRBA*, *NFKB2*, and *IKZF1* (*IKAROS*) in a subset of CVID patients. However, most of these patients have unknown genetic defects and may have oligogenic or polygenic causes of disease.

Hyper IgM syndrome is characterized by an inability to switch from the production of IgM-type antibodies to IgG, IgA, or IgE isotypes. The condition is most often caused by variants in *CD40LG*, but variants in other genes (eg, *CD40*, *AICDA*, *PI3KCD*, *UNG*) have also been reported to cause disease. Patients with CD40L and CD40 deficiency tend to present with severe opportunistic infections more reminiscent of a cellular immunodeficiency and, therefore, may also be considered as combined immunodeficiencies.

Selective antibody deficiencies may occur when a patient is either lacking a specific immunoglobulin isotype (eg, selective IgA deficiency or IgG deficiency) or a specific vaccine antibody response (impaired pneumococcal polysaccharide responsiveness). Selective deficiencies may be due to variants in genes encoding immunoglobulin heavy or light chains. Selective IgA deficiency (sIgAD) is the most common PIDD with an incidence of 1:200 to 1:1000, depending on the cohort studied. Most patients with sIgAD are asymptomatic though some may have frequent infections. There is also a higher incidence of celiac disease in this group. Most patients with selective antibody deficiencies are treated if they have frequent infections in addition to impaired vaccine antibody responses. Some patients with sIgAD may have autoantibodies to IgA.

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 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. 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 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.(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. 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
3. Smith T, Cunningham-Rundles C. Primary B-cell immunodeficiencies. Hum Immunol. 2019;80(6):351-362. doi:10.1016/j.humimm.2018.10.015
4. Peng XP, Caballero-Oteyza A, Grimbacher B. Common variable immunodeficiency: more pathways than roads to Rome. Annu Rev Pathol. 2023;18:283-310. doi:10.1146/annurev-pathmechdis-031521-024229
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8. Jhamnani RD, Nunes-Santos CJ, Bergerson J, Rosenzweig SD. Class-switch recombination (CSR)/dyper-IgM (HIGM) syndromes and phosphoinositide 3-kinase (PI3K) defects. Front Immunol. 2018;9:2172. doi:10.3389/fimmu.2018.02172
9. de la Morena MT. Clinical phenotypes of hyper-IgM syndromes. J Allergy Clin Immunol Pract. 2016;4(6):1023-1036. doi:10.1016/j.jaip.2016.09.013
10. Yazdani R, Fekrvand S, Shahkarami S, et al. The hyper IgM syndromes: Epidemiology, pathogenesis, clinical manifestations, diagnosis and management. Clin Immunol. 2019;198:19-30. doi:10.1016/j.clim.2018.11.007
11. Bousfiha A, Moundir A, Tangye SG, et al. The 2022 update of IUIS phenotypical classification for human inborn errors of immunity. J Clin Immunol. 2022;42(7):1508-1520. doi:10.1007/s10875-022-01352-z

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), 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 B-Cell and Antibody Deficiency 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:
ADA, ADA2, AICDA, ATP6AP1, BLNK, BTK, CARD11, CD19, CD27, CD40, CD40LG, CD70, CD79A, CD79B, CD81, CDCA7, CTLA4, CR2, CXCR4, DCLRE1C, DNMT3B, GATA2, ICOS, IGHM, IGLL1, IKBKG, IKZF1, IKZF3, IL21, IL21R, IRF2BP2, KDM6A, KMT2A, KMT2D, LIG1, LRBA, MOGS, MS4A1, NFKB1, NFKB2, PIK3CD, PIK3R1, PLCG2, PRKCD, RAC2, RAG1, RAG2, RNF168, SEC61A1, SH2D1A, SH3KBP1, SLC39A7, TCF3, TNFRSF13B, TNFRSF13C, TNFSF12, TNFSF13, TOP2B, TRNT1, UNG, and *XIAP.*

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
BCELL	Bcell/Antibody Deficiency GenePanel	97565-6

Result ID	Test Result Name	Result LOINC® Value
620107	Test Description	62364-5
620108	Specimen	31208-2
620109	Source	31208-2
620110	Result Summary	50397-9
620111	Result	82939-0
620112	Interpretation	69047-9
620113	Additional Results	82939-0
620114	Resources	99622-3
620115	Additional Information	48767-8
620116	Method	85069-3
620117	Genes Analyzed	82939-0
620118	Disclaimer	62364-5

620119	Released By	18771-6