Test Definition: CDGGP

Congenital Disorders of Glycosylation Gene Panel, Varies

Overview

Useful For

Establishing a molecular diagnosis for patients with congenital disorders of glycosylation

Identifying variants within genes known to be associated with congenital disorders of glycosylation, 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 141 genes associated with congenital disorders of glycosylation: *ALDOB*, *ALDOC*, *ALG1*, *ALG11*, *ALG12*, *ALG13*, *ALG14*, *ALG2*, *ALG3*, *ALG5*, *ALG6*, *ALG8*, *ALG9*, *ARCN1*, *ARV1*, *ATP6AP1*, *ATP6V0A2*, *B3GALNT2*, *B3GALT6*, *B3GAT3*, *B3GLCT*, *B4GALNT1*, *B4GALT1*, *B4GALT7*, *B4GAT1*, *C1GALT1C1*, *CCDC115*, *CHST14* ,*CHST3*, *CHST6*, *CHST8*, *CHSY1*, *COG1*,*COG2*, *COG4*, *COG5*, *COG6*, *COG7*, *COG8*, *DDOST*, *DHDDS*, *DOLK*, *DPAGT1*, *DPM1*, *DPM2*, *DPM3*, *DSE*, *EOGT*, *EXT1*, *EXT2*, *FKRP*, *FKTN*, *FCSK*, *FUT8*, *G6PC3*, *GALE*, *GALK1*, *GALNT2*, *GALNT3*, *GALT*, *GET4*, *GFM1*,*GFPT1*, *GMPPA*, *GMPPB*, *GNE*, *GNPTAB*, *GOLIM4*, *GORASP2*, *CRPPA*, *LARGE1*, *LFNG*, *MAGT1*, *MAN1B1*, *MAN2B2*, *MBTPS1*, *MGAT1*, *MGAT2*, *MOGS*, *MPDU1*, *MPI*, *MPV17*, *NGLY1*, *NUS1*, *PAPSS2*, *PGAP2*, *PGAP3*, *PGM1*, *PGM2*, *PGM3*, *PIGA*, *PIGL*, *PIGM*, *PIGN*, *PIGO*, *PIGT*, *PIGV*, *PIGW*, *PMM1*, *PMM2*, *POFUT1*, *POGLUT1*, *POMGNT1*, *POMGNT2*, *POMK*, *POMT1*, *POMT2*, *PRKCSH*, *RFT1*, *RXYLT1*, *SEC23A*, *SEC23B*, *SEC63*, *SLC10A7*, *SLC26A2*, *SLC35A1*, *SLC35A2*, *SLC35A3*, *SLC35C1*, *SLC35D1*, *SLC37A4*, *SLC39A8*, *SRD5A3*, *SSR3*, *SSR4*, *ST3GAL3*, *ST3GAL5*, *STT3A*, *STT3B*, *STXBP1*, *SYP*, *TF*, *TMEM165*, *TMEM199*, *TRAPPC9*, *TRAPPC11*, *TRIP11*, *TSTA3*, *TUSC3*, *VMA21*, and *XYLT1*. See Targeted Genes and Methodology Details for Congenital Disorders of Glycosylation Gene Panel and Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for congenital disorders of glycosylation.

Testing Algorithm

For skin biopsy and cultured fibroblast specimens, fibroblast culture will be added at an additional charge. If viable cells are not obtained, the client will be notified.

For more information see:
-Lysosomal Disorders Diagnostic Algorithm, Part 2
-Congenital Disorders of Glycosylation: Screening Algorithm.

Special Instructions

- Molecular Genetics: Biochemical Disorders Patient Information

- Informed Consent for Genetic Testing
- Blood Spot Collection Card-Spanish Instructions
- Blood Spot Collection Card-Chinese Instructions
- Informed Consent for Genetic Testing (Spanish)
- Lysosomal Disorders Diagnostic Algorithm, Part 2
- Blood Spot Collection Instructions
- Targeted Genes and Methodology Details for Congenital Disorders of Glycosylation Gene Panel
- Congenital Disorders of Glycosylation: Screening Algorithm

Method Name

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

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

The recommended first-tier test to screen for congenital disorders of glycosylation (CDG) is a biochemical test that analyzes transferrin and apolipoprotein CIII; order CDG / Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum.

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

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 14 days

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 (Eagle's minimum essential medium 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 fibroblast
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.

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 (formerly Ahlstrom 226) filter paper, or blood spot collection card
Specimen Volume: 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 Dried Blood Spot Samples.
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. Due to lower concentration of DNA yielded from blood spot, it is possible that additional specimen may be required to complete testing.
2. For collection instructions, see Blood Spot Collection Instructions.
3. For collection instructions in Spanish, see Blood Spot Collection Card-Spanish Instructions (T777).
4. For collection instructions in Chinese, see Blood Spot Collection Card-Chinese Instructions (T800).

SALIVA:
Patient Preparation: Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.
Preferred: 1 OGD-675 Saliva Collection Container
Acceptable: 2 ORAcollect OCD-100 Swabs
Transport: Ambient (preferred) 30 days/Refrigerated 30 days
Additional Information:
1. Saliva is acceptable but not recommended. Multiple extractions will be required to obtain sufficient 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 saliva, it is possible that additional specimen may be required to complete testing.

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: Biochemical Disorders Patient Information (T527)
3. If not ordering electronically, complete, print, and send a Biochemical Genetics Test Request (T798) with the specimen.

Specimen Minimum Volume
Blood: 1 mL; Blood spots: 2 spots; Skin biopsy, cultured fibroblasts, or saliva: 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
Congenital disorders of glycosylation (CDG), formerly known as carbohydrate-deficient glycoprotein syndrome, are a group of disorders affecting several steps of the pathway involved in the glycosylation of proteins. CDG are classified into 5 groups. CDG types I and II will have abnormal biochemical findings detected by serum transferrin and serum total N-glycan analyses (see CDG / Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum). In the other 3 groups these analyses will be normal.

CDG type I disorders are characterized by defects in the assembly or transfer of the dolichol-linked glycan, while CDG type II includes defects of the glycan moiety processing.

The third group includes disorders of glycosylphosphatidyl inositol anchor protein glycosylation. If clinically suspected, a flow cytometry analysis could facilitate the diagnostic workup.

The fourth group involves disorders of O-mannosylation, a process that takes place predominantly in the muscle and brain tissues.

The fifth group involves deglycosylation defects (eg, NAGLY1-CDG). The urine oligosaccharide profile by matrix-assisted laser desorption/ionization time-of-flight/time-of-flight mass spectrometer (MALDI-TOF/TOF-MS) may be abnormal and facilitate the diagnostic workup.

CDG typically present as multisystemic disorders with a broad range of clinical features including developmental delay, hypotonia, abnormal magnetic resonance imaging findings, skin manifestations, and coagulopathy. There is considerable variation in the severity of this group of diseases, ranging from hydrops fetalis to a mild presentation in adults. Almost all types of CDG are autosomal recessive in inheritance, but some are X-linked.

The broad clinical spectrum and genetic heterogeneity of CDG make a comprehensive panel a helpful tool in establishing a diagnosis for patients with suggestive clinical features.

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations 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 at least one 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 the 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.

Deletion/duplication events that extend past the genes included on the panel may occur. In these instances, genes included in the ordered test are provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. However, copy number variants for genes not listed in the Method Description are typically not reported or interpreted for haploinsufficiency/triplosensitivity. CMACB / Chromosomal Microarray, Congenital, Blood; WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies; or WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies is recommended for a full interpretation of deletions/duplications predicted to extend past the genes included on the panel.

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 the Congenital Disorder of Glycosylation Gene Panel for the most up to date list of genes included in this test. 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 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:
At this time, 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.

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.

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 May;17(5):405-424
2. Freeze HH, Chong JX, Bamshad MJ, Ng BG: Solving glycosylation disorders: fundamental approaches reveal complicated pathways. Am J Hum Genet. 2014;94(2):161-175
3. Krasnewich D: Human glycosylation disorders. Cancer Biomark. 2014 Jan;14(1):3-16

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 (PCR)-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 the Congenital Disorder of Glycosylation Gene Panel for details regarding the targeted genes analyzed and the specific gene regions not routinely covered.(Unpublished Mayo method)

Genes analyzed: *ALDOB*, *ALDOC*, *ALG1*, *ALG11*, *ALG12*, *ALG13*, *ALG14*, *ALG2*, *ALG3*, *ALG5*, *ALG6*, *ALG8*, *ALG9*, *ARCN1*, *ARV1*, *ATP6AP1*, *ATP6V0A2*, *B3GALNT2*, *B3GALT6*, *B3GAT3*, *B3GLCT*, *B4GALNT1*, *B4GALT1*, *B4GALT7*, *B4GAT1*, *C1GALT1C1*, *CCDC115*, *CHST14* ,*CHST3*, *CHST6*, *CHST8*, *CHSY1*, *COG1*,*COG2*, *COG4*, *COG5*, *COG6*, *COG7*, *COG8*, *DDOST*, *DHDDS*, *DOLK*, *DPAGT1*, *DPM1*, *DPM2*, *DPM3*, *DSE*, *EOGT*, *EXT1*, *EXT2*, *FKRP*, *FKTN*, *FCSK*, *FUT8*, *G6PC3*, *GALE*, *GALK1*, *GALNT2*, *GALNT3*, *GALT*, *GET4*, *GFM1*,*GFPT1*, *GMPPA*, *GMPPB*, *GNE*, *GNPTAB*, *GOLIM4*, *GORASP2*, *CRPPA*, *LARGE1*, *LFNG*, *MAGT1*, *MAN1B1*, *MAN2B2*, *MBTPS1*, *MGAT1*, *MGAT2*, *MOGS*, *MPDU1*, *MPI*, *MPV17*, *NGLY1*, *NUS1*, *PAPSS2*, *PGAP2*, *PGAP3*, *PGM1*, *PGM2*, *PGM3*, *PIGA*, *PIGL*, *PIGM*, *PIGN*, *PIGO*, *PIGT*, *PIGV*, *PIGW*, *PMM1*, *PMM2*, *POFUT1*, *POGLUT1*, *POMGNT1*, *POMGNT2*, *POMK*, *POMT1*, *POMT2*, *PRKCSH*, *RFT1*, *RXYLT1*, *SEC23A*, *SEC23B*, *SEC63*, *SLC10A7*, *SLC26A2*, *SLC35A1*, *SLC35A2*, *SLC35A3*, *SLC35C1*, *SLC35D1*, *SLC37A4*, *SLC39A8*, *SRD5A3*, *SSR3*, *SSR4*, *ST3GAL3*, *ST3GAL5*, *STT3A*, *STT3B*, *STXBP1*, *SYP*, *TF*, *TMEM165*, *TMEM199*, *TRAPPC9*, *TRAPPC11*, *TRIP11*, *TSTA3*, *TUSC3*, *VMA21*,and *XYLT1.*

PDF Report
No

Day(s) Performed
Varies

Report Available
28 to 42 days

Specimen Retention Time
Whole blood: 2 weeks (if available); Extracted DNA: 3 months; Blood spots/Saliva: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
CDGGP	CDG Gene Panel	105346-1

Result ID	Test Result Name	Result LOINC® Value
608524	Test Description	62364-5
608525	Specimen	31208-2
608527	Result Summary	50397-9
608528	Result	82939-0
608529	Interpretation	69047-9

608530	Resources	99622-3
608531	Additional Information	48767-8
608532	Method	85069-3
608533	Genes Analyzed	48018-6
608534	Disclaimer	62364-5
608535	Released By	18771-6
608526	Source	31208-2