MAYO CLINIC LABORATORIES

Test Definition: GSDGP

Glycogen Storage Disease Gene Panel

Overview

Useful For

Follow up of abnormal biochemical results consistent with glycogen storage disease (GSD)

Establishing a molecular diagnosis for patients with GSD

Identifying variants within genes known to be associated with GSD allowing for predictive testing of at-risk family members

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 28 genes associated with glycogen storage disease: *AGL, ALDOA, ENO3, EPM2A, FBP1, G6PC, GAA, GBE1, GYG1, GYS1, GYS2, LAMP2, LDHA, NHLRC1, PFKM, PGAM2, PGK1, PGM1, PHKA1, PHKA2, PHKB, PHKG2, PRKAG2, PYGL, PYGM, RBCK1, SLC2A2, SLC37A4*. See Targeted Genes and Methodology Details for Glycogen Storage Disease Gene Panel in Special Instructions and Method Description for additional details.

Identification of a pathogenic variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for glycogen storage disease.

Additional first-tier testing may be considered/recommended. For more information see Ordering Guidance.

Testing Algorithm

If skin biopsy is received, fibroblast culture and cryopreservation for biochemical studies will be added at an additional charge.

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)
- Blood Spot Collection Instructions
- Targeted Genes and Methodology Details for Glycogen Storage Disease Gene Panel

Reflex Tests

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

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 biochemical testing, including glucose monitoring, triglycerides, uric acid level, creatine kinase, liver function tests, and complete blood cell count, may be helpful in establishing a diagnosis.

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

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 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.

Specimen Volume: 4-mm punch

Specimen Stability Information: Refrigerated (preferred)/Ambient

Additional Information: A separate culture charge will be assessed under FIBR / Fibroblast Culture, Tissue. An additional 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 FIBR / Fibroblast Culture, Tissue. An additional 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 of age is finger stick. See Dried Blood Spot Collection Tutorial for how to collect blood spots.

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. For collection instructions, see Blood Spot Collection Instructions.

2. For collection instructions in Spanish, see Blood Spot Collection Card-Spanish Instructions (T777).

3. For collection instructions in Chinese, see Blood Spot Collection Card-Chinese Instructions (T800).

4. Due to lower concentration of DNA yielded from blood spot, it is possible that additional specimen may be required to complete testing.

Specimen Type: Saliva

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

Supplies: Saliva Swab Collection Kit (T786)

Specimen Volume: 1 Swab

Collection Instructions: Collect and send specimen per kit instructions.

Specimen Stability Information: Ambient 30 days

Additional Information: 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 in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing (Spanish) (T826)

2. Molecular Genetics: Biochemical Disorders Patient Information (T527) in Special Instructions

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Minimum Volume

See Specimen Required

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies (preferred)		

Clinical & Interpretive

Clinical Information

Glycogen storage diseases (GSD) are a group of inherited metabolic conditions caused by deficiency of enzymes responsible for glycogen metabolism, resulting in abnormal storage of glycogen in the liver and various muscles. There are over 15 different GSD that vary in symptoms and severity, dependent on the enzyme deficiency, although liver and muscle are the most commonly affected areas.

Generally, GSD can be divided into 2 categories, those with hepatic involvement and those with neuromuscular involvement. Some GSD result in single tissue disease, while others affect multiple organs. Clinical features may include hepatomegaly, hypoglycemia, muscle cramps, exercise intolerance, and progressive fatigue and weakness. Preliminary biochemical testing may be helpful in making a diagnosis (ie, glucose monitoring, triglycerides, uric acid level, creatine

kinase, liver function tests, and complete blood cell count).

This test involves sequencing of 26 genes related to various GSD.

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations 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 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 Laboratory 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 47bp. Insertions/deletions (indels) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller indels.

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 Glycogen Storage Disease Gene Panel in Special Instructions 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 heterologous 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 health care 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 is 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. Chen YT, Kishani PS, Koeberl D: Glycogen storage disease. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Diseases. McGraw-Hill Education; 2019. Accessed October 28, 2020. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225080698&bookid=2709&Resultclick=2

3. Hicks J, Wartchow, E, Mierau G: Glycogen storage diseases: A brief review and update on clinical features, genetic abnormalities, pathologic features, and treatment. Ultrastruct Pathol. 2011;35(5):183-196

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing is 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 pathogenic 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 insertions/deletions (indels) 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. See Targeted Genes and Methodology Details for Glycogen Storage Disease Gene Panel for details regarding the targeted 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 Glycogen Storage Disease Gene Panel in Special Instructions for details regarding the specific gene regions not routinely covered.(Unpublished Mayo method)

Genes analyzed: *AGL*, *ALDOA*, *ENO3*, *EPM2A*, *FBP1*, *G6PC*, *GAA*, *GBE1*, *GYG1*, *GYS1*, *GYS2*, *LAMP2*, *LDHA*, *NHLRC1*, *PFKM*, *PGAM2*, *PGK1*, *PGM1*, *PHKA1*, *PHKA2*, *PHKB*, *PHKG2*, *PRKAG2*, *PYGL*, *PYGM*, *RBCK1*, *SLC2A2*, *SLC37A4*

PDF Report
Supplemental

Specimen Retention Time
Whole Blood: 2 weeks (if available); Extracted DNA: 3 months; Blood spots/Saliva:1 month

Performing Laboratory Location
Rochester

Fees & Codes

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 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
GSDGP	Glycogen Storage Disease Gene Panel	In Process

Result ID	Reporting Name	LOINC®
608548	Test Description	62364-5
608549	Specimen	31208-2

608550	Source	31208-2
608551	Result Summary	50397-9
608552	Result	82939-0
608553	Interpretation	69047-9
608554	Resources	99622-3
608555	Additional Information	48767-8
608556	Method	85069-3
608557	Genes Analyzed	48018-6
608558	Disclaimer	62364-5
608559	Released By	18771-6