

Overview

Useful For

Identifying variants in individuals who test negative for the common variants and who have a biochemical diagnosis of galactosemia or galactose-1-phosphate uridylyltransferase activity levels indicative of carrier status

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 1 gene associated with galactosemia: *GALT*.

[Identification of a pathogenic variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for galactosemia.](#)

Additional first tier testing may be considered/recommended. For more information see [Galactosemia Testing Algorithm](#)

Testing Algorithm

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

See [Galactosemia Testing Algorithm](#).

Special Instructions

- [Molecular Genetics: Biochemical Disorders Patient Information](#)
- [Informed Consent for Genetic Testing](#)
- [Galactosemia Testing Algorithm](#)
- [Blood Spot Collection Card-Spanish Instructions](#)
- [Blood Spot Collection Card-Chinese Instructions](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)
- [Blood Spot Collection Instructions](#)

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

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 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.

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 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. 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)

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

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

Classic galactosemia is an autosomal recessive disorder of galactose metabolism caused by variants in the galactose-1-phosphate uridylyltransferase (*GALT*) gene. The complete or near complete deficiency of the *GALT* enzyme is life threatening. If left untreated, complications include liver failure, sepsis, intellectual disability, and death. Galactosemia is treated by a galactose-free diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, children with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. The prevalence of classic galactosemia is approximately 1 in 30,000.

Duarte variant galactosemia (compound heterozygosity for the Duarte variant, N314D and a classic variant) is generally associated with higher levels of *GALT* activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Typically, individuals with Duarte variant galactosemia have a milder phenotype but are often treated with a low galactose diet during infancy. The LA variant, consisting of N314D and a second change, L218L, is associated with higher levels of *GALT* activity than the Duarte variant alone.

Newborn screening, which identifies potentially affected individuals by measuring total galactose (galactose and galactose-1-phosphate) or determining the activity of the *GALT* enzyme, varies from state to state. The diagnosis of galactosemia is established by follow-up quantitative measurement of *GALT* activity. If enzyme activity levels are indicative of carrier or affected status, molecular testing for common *GALT* variants may be performed. If 1 or both disease-causing variants are not detected by targeted variant analysis and biochemical testing has confirmed the diagnosis of galactosemia, sequencing of the *GALT* gene is available to identify private variants.

The *GALT* gene maps to 9p13 and more than 180 variants have been identified. Several disease-causing variants are common in patients with classic galactosemia (G/G genotype). The most frequently observed is the Q188R variant, which accounts for 60% to 70% of classic galactosemia alleles. The S135L variant is the most frequently observed variant in the African American population and accounts for approximately 50% of the altered alleles in this population. The K285N variant is common in those of eastern European descent and accounts for 25% to 40% of the alleles in this population. The L195P variant is observed in 5% to 7% of classic galactosemia. The Duarte variant (N314D) is found in 5% of the general United States population.

The above variants, plus the LA variant, are included in GCT / Galactosemia Reflex, Blood, which is the preferred test for the diagnosis of galactosemia or for follow-up to positive newborn screening results. These variants are also included in GAL14 / Galactosemia Gene Analysis (14-Variant Panel), Varies. Full sequencing of the *GALT* gene can be useful for the

identification of variants when 1 or no variants are found with these tests in an individual with demonstrated GALT activity deficiency. Full sequencing of the *GALT* gene identifies over 95% of the sequence variants in the coding region and splice junctions. See [Galactosemia Testing Algorithm](#) in Special Instructions for additional information.

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.

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. 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. Elsas LJ 2nd, Lai K: The molecular biology of galactosemia. *Genet Med.* 1998 Nov-Dec;1(1):40-48
3. Novelli G, Reichardt JK: Molecular basis of disorders of human galactose metabolism: past, present, and future. *Mol Genet Metab.* 2000 Sep-Oct;71(1-2):62-65
4. Bosch AM, Ijlst L, Oostheim W, et al: Identification of novel variants in classical galactosemia. *Hum Mutat.* 2005 May;25(5):502
5. Welling L, Bernstein LE, Berry GT: et al: International clinical guideline for the management of classical galactosemia; diagnosis, treatment, and follow-up. *J Inher Metab Dis.* 2017 Mar;40(2):171-176

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 gene 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 gene 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.

The reference transcript for *GALT* gene is NM_000155.4. Reference transcript numbers may be updated due to transcript re-versioning. Always refer to the final patient report for gene transcript information referenced at the time of testing. Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria. (Unpublished Mayo method)

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; Blood spots/Saliva: 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. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81406
88233-Tissue culture, skin, solid tissue biopsy (if appropriate)
88240-Cryopreservation (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
GALZ	Galactosemia, Full Gene Analysis	76037-1

Result ID	Test Result Name	Result LOINC® Value
608596	Test Description	62364-5
608597	Specimen	31208-2
608598	Source	31208-2
608599	Result Summary	50397-9
608600	Result	82939-0
608601	Interpretation	69047-9
608602	Resources	99622-3
608603	Additional Information	48767-8
608604	Method	85069-3
608605	Genes Analyzed	48018-6
608606	Disclaimer	62364-5
608607	Released By	18771-6