MAYO CLINIC LABORATORIES

Test Definition: GCT

Galactosemia Reflex, Blood

Overview

Useful For

Preferred test for diagnosis, carrier detection, and determination of genotype of galactose-1-phosphate uridyltransferase deficiency, the most common cause of galactosemia

Differentiating Duarte variant galactosemia from classic galactosemia

Confirming results of newborn screening programs

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
GALZ	Galactosemia, Full Gene Analysis	Yes	No
CULFB	Fibroblast Culture for Genetic Test	Yes	No
CULAF	Amniotic Fluid Culture/Genetic Test	Yes	No
MATCC	Maternal Cell Contamination, B	Yes	No

Genetics Test Information

Preferred test to evaluate for possible diagnosis of galactosemia, routine carrier screening, and follow-up of abnormal newborn screening results. Comprehensive reflex test begins with quantitative galactose-1-phosphate uridyltransferase (GALT) enzyme analysis. If quantitative GALT enzyme value is less than 24.5 nmol/h/mg of hemoglobin, full gene sequencing of the *GALT* gene is performed.

Testing Algorithm

Testing begins with galactose-1-phosphate uridyltransferase (GALT) enzyme analysis. If GALT activity is greater than or equal to 24.5 nmol/h/mg of hemoglobin, testing is complete. No molecular test will be performed. If GALT activity is less than 24.5 nmol/h/mg of hemoglobin, galactosemia full gene sequencing will be performed at an additional charge.

For more information see Galactosemia Testing Algorithm

Special Instructions

- Informed Consent for Genetic Testing
- Galactosemia Testing Algorithm
- Informed Consent for Genetic Testing (Spanish)
- Galactosemia-Related Test List

Method Name

Enzyme Reaction followed by Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS)

NY State Available
Yes

Specimen

Specimen Type
Whole Blood EDTA

Ordering Guidance
This test is appropriate for the diagnosis of, and routine carrier screening for, galactose-1-phosphate uridyltransferase deficiency.

This assay is **not appropriate** for monitoring dietary compliance. For dietary monitoring, order GAL1P / Galactose-1-Phosphate, Erythrocytes.

Necessary Information
Patient's age is required.

Specimen Required
Multiple whole blood tests for galactosemia can be performed on one specimen. Prioritize order of testing when submitting specimens. For a list of tests that can be ordered together, see Galactosemia-Related Test List.

Container/Tube:
Preferred: Lavender top (EDTA)
Acceptable: Green top (sodium heparin) or yellow top (ACD)
Specimen Volume: 5 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot**.

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. If not ordering electronically, complete, print, and send an Biochemical Genetics Test Request (T798) with the specimen.

Specimen Minimum Volume
2 mL

Reject Due To

Gross hemolysis	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole Blood EDTA	Refrigerated (preferred)	28 days	
	Ambient	14 days	

Clinical & Interpretive

Clinical Information

Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 4 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase (GALT), galactokinase, uridine diphosphate galactose-4-epimerase, and galactose mutarotase. GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life-threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death.

Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and motor function abnormalities. Female patients with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births.

Galactose-1-phosphate (Gal1P) accumulates in the erythrocytes of patients with galactosemia. The quantitative measurement of Gal1P is useful for monitoring compliance with dietary therapy. Gal1P is thought to be the causative factor for development of liver disease in these patients. Because of this, patients should maintain low levels and be monitored on a regular basis.

Duarte-variant galactosemia (compound heterozygosity for the Duarte variant, N314D, and a classic variant) is generally associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Previously, it was unknown whether children with Duarte-variant galactosemia were at an increased risk for adverse developmental outcomes due to milk exposure and were often treated with a low galactose diet during infancy. More recently, the outcomes data suggest a lack of evidence for developmental complications due to milk exposure, therefore treatment recommendations remain controversial. The Los Angeles variant, which consists of N314D and a second genetic variant, L218L, is associated with higher levels of GALT enzyme activity than the Duarte-variant allele.

Newborn screening for galactosemia is performed in all 50 US states, though the method by which potentially affected individuals are detected varies from state to state and may include the measurement of total galactose (galactose and Gal1P) and/or determining the activity of the GALT enzyme. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If enzyme level is less than 24.5 nmol/h/mg of hemoglobin, sequencing of the *GALT* gene is performed.

For more information see Galactosemia Testing Algorithm.

Reference Values

> or =24.5 nmol/h/mg of hemoglobin

Interpretation

The laboratory provides an interpretation of the results, including galactose-1-phosphate uridyltransferase enzyme activity and genotype, if necessary. This interpretation provides an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional testing.

In any specimen where enzyme activity is less than 24.5 nmol/h/mg of hemoglobin *GALT* full gene sequencing will be performed. For testing algorithm and more information, see Galactosemia Testing Algorithm.

The *GALT* gene maps to chromosome 9p13. Several disease-causing variants are common in patients with classic galactosemia (G/G genotype). The most frequently observed is the Q188R classic variant. This alteration accounts for 60% to 70% of classic galactosemia alleles. The S135L variant is the most frequently observed in African Americans 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 classical galactosemia. The 5-kilobase deletion is common in individuals of Ashkenazi Jewish descent. The Duarte variant (N314D and -119_-116delGTCA) is observed in 5% of the general US population.

Cautions

This assay will not reliably detect deletions-insertions (delins) of 40 or more base pairs (bp), including Alu insertions, long interspersed elements (LINES), and short interspersed elements (SINES). The bioinformatics software pipeline is verified to detect 95% of deletions up to 75 bp and insertions up to 47 bp.

Additionally, low-level mosaic variants may not be detected.

This test is not designed 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.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in the interpretation of results may occur if information given is inaccurate or incomplete.

Many disorders may present with symptoms similar to those associated with galactosemia. Therefore, biochemical testing is performed to establish the diagnosis of galactosemia prior to DNA analysis.

Clinical Reference

1. Berry GT. Classic galactosemia and clinical variant galactosemia. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated March 11, 2021. Accessed September 10, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1518/
2. Walter JH, Fridovich-Keil JL. Galactosemia. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. Eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed September 10, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=%20225081023

3. Carlock G, Fischer ST, Lynch ME, et al. Developmental outcomes in Duarte galactosemia. Pediatrics. 2019;143(1):e20182516. doi:10.1542/peds.2018-2516

Performance

Method Description

Galactose-1-Phosphate Uridyltransferase Enzyme Analysis:
An aqueous mixture containing water, uridine diphosphate (UDP)-glucose, (13)C2-labeled galactose-1-phosphate, and UDP-N-acetylglucosamine (internal standard) is added to hemolysate aliquot. The mixture is then vortexed briefly and incubated.

After incubation, the reaction is quenched, extracted, and centrifuged. The top layer is transferred to a 96-well plate and then injected onto a liquid chromatography tandem mass spectrometry (LC-MS/MS). The ratio of the extracted peak area of (13)C2 labeled UDP-galactose to its internal standard UDP-N-acetylglucosamine as determined by LC-MS/MS is used to calculate the concentration of product analyte in the sample. The concentration of the product is then normalized using the calculated hemoglobin concentration to determine the patient's enzyme level in nmol/h/mg of hemoglobin.(Unpublished Mayo method)

GALT Full Gene Sequencing:
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 *GALT* gene. NGS and/or a polymerase chain reaction (PCR)-based quantitative method is performed to test for the presence of deletions and duplications in the *GALT* gene.

There may be regions of *GALT* that cannot be effectively amplified for sequencing or deletion and duplication analysis because of technical limitations of the assay, including regions of homology, high guanine-cytosine content, and repetitive sequences. Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

PCR-based methods and/or Sanger sequencing is used to confirm variants detected by NGS when appropriate.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Monday, Wednesday, Friday

Report Available

4 to 7 days

Specimen Retention Time

2 months

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

82775
81406 (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
GCT	Galactosemia Reflex, B	24082-0

Result ID	Test Result Name	Result LOINC® Value
8333	Gal-1-P Uridyltransferase, RBC	24082-0
2296	Interpretation (GALT)	59462-2
58115	Reviewed By	18771-6