MAYO CLINIC LABORATORIES

Test Definition: AGABS

Alpha-Galactosidase, Blood Spot

Overview

Useful For

Diagnosis of Fabry disease in male patients using blood spot specimens

Verifying abnormal serum alpha-galactosidase results in male patients with a clinical presentation suggestive of Fabry disease

Follow-up to an abnormal newborn screen for Fabry disease

This test is **not useful for** patients undergoing a workup for a meat or meat-derived product allergy.

Genetics Test Information

This test provides diagnostic testing for male patients with positive newborn screen results, positive family history, or clinical signs and symptoms suspicious for Fabry disease.

Testing Algorithm

This test provides diagnostic testing for male patients with positive newborn screen results, positive family history, or clinical signs and symptoms suspicious for Fabry disease.

Testing Algorithm

The following algorithms are available:

-Fabry Disease Diagnostic Testing Algorithm

-Fabry Disease: Newborn Screen-Positive Follow-up

For more information, see Newborn Screening Act Sheet Fabry Disease: Decreased Alpha-Galactosidase A

Special Instructions

- Informed Consent for Genetic Testing
- Fabry Disease Diagnostic Testing Algorithm
- Fabry Disease: Newborn Screen-Positive Follow-up
- Biochemical Genetics Patient Information
- Blood Spot Collection Card-Spanish Instructions
- Newborn Screening Act Sheet Fabry Disease: Decreased Alpha-Galactosidase A
- Blood Spot Collection Card-Chinese Instructions
- Informed Consent for Genetic Testing (Spanish)
- Blood Spot Collection Instructions

Method Name

Fluorometric Enzyme Assay

NY State Available

Yes

Specimen

Specimen Type
Whole blood

Ordering Guidance
If testing needed for assessment of meat or meat-derived product allergy, order either ALGAL / Galactose-Alpha-1,3-Galactose (Alpha-Gal), IgE, Serum or APGAL / Galactose-Alpha-1,3-Galactose (Alpha-Gal) Mammalian Meat Allergy Profile, Serum.

Carrier detection using enzyme levels is unreliable for female patients as results may be within the normal values. Order FABRZ / Fabry Disease, Full Gene Analysis, Varies for testing carrier status.

Additional Testing Requirements
Additional studies including molecular genetic analysis of the *GLA* gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) are recommended to detect carriers.

Necessary Information
Provide a reason for testing with each specimen.

Specimen Required
Supplies: Card-Blood Spot Collection (Filter Paper) (T493)
Container/Tube:
Preferred: Blood spot collection card
Acceptable: PerkinElmer 226 (formerly Ahlstrom 226) filter paper and Whatman Protein Saver 903 paper
Specimen Volume: 2 blood spots
Collection Instructions:
1. Do not use device or capillary tube containing EDTA to collect specimen.
2. 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.
3. Let blood dry on the filter paper at ambient temperature in a horizontal position for a minimum of 3 hours.
4. Do not expose specimen to heat or direct sunlight.
5. Do not stack wet specimens.
6. Keep specimen dry.
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)

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. Biochemical Genetics Patient Information (T602)

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

Specimen Minimum Volume

1 Blood spot

Reject Due To

Shows serum rings Multiple layers	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole blood	Ambient (preferred)	90 days	FILTER PAPER
	Frozen	90 days	FILTER PAPER
	Refrigerated	90 days	FILTER PAPER

Clinical & Interpretive

Clinical Information

Fabry disease is an X-linked lysosomal storage disorder resulting from deficient activity of the enzyme alpha-galactosidase A (alpha-Gal A) and the subsequent deposition of glycosylsphingolipids in tissues throughout the body, in particular, the kidney, heart, and brain. Variants within the *GLA* gene cause Fabry disease with severity and symptom onset dependent on the amount of residual enzyme activity. The classic form of Fabry disease occurs in male patients who have less than 1% alpha-Gal A activity. Symptoms usually appear in childhood or adolescence and can include acroparesthesias (burning pain in the extremities), gastrointestinal issues, multiple angiokeratomas, reduced or absent sweating, corneal opacity, and proteinuria. In addition, progressive renal involvement leading to kidney failure (formerly end-stage renal disease) typically occurs in adulthood, followed by cardiovascular and cerebrovascular disease. The estimated incidence varies from 1 in 3000 infants detected via newborn screening to 1 in 10,000 male patients diagnosed after onset of symptoms.

Measurement of alpha-Gal A in blood spots, leukocytes (AGAW / Alpha-Galactosidase, Leukocytes), or serum (AGAS / Alpha-Galactosidase, Serum) can reliably diagnose classic or variant Fabry disease in males. Male patients with residual alpha-Gal A activity greater than 1% may present with 1 of 3 variant forms of Fabry disease with onset of symptoms later in life: a kidney variant associated with kidney failure but without the pain or skin lesions; a cardiac variant typically presenting in the sixth to eighth decade with left ventricular hypertrophy, cardiomyopathy and arrhythmia, and proteinuria, but without kidney failure; and a cerebrovascular variant presenting as stroke or transient ischemic attack. The variant forms of Fabry disease may be underdiagnosed. Molecular genetic analysis of the *GLA* gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) allows for confirmation of a diagnosis of classic of variant Fabry disease in affected male patients with reduced alpha-Gal A activity.

Female patients who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely

affected. Measurement of alpha-Gal A activity is not generally useful for identifying carriers of Fabry disease, as many of these individuals will have normal levels. Therefore, molecular genetic analysis of the *GLA* gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) is recommended as the most appropriate diagnostic test to detect asymptomatic or symptomatic female carriers.

The biomarkers globotriaosylsphingosine (LGB3S / Globotriaosylsphingosine, Serum) and ceramide trihexosides (CTSU / Ceramide Trihexosides and Sulfatides, Random, Urine) may be elevated in patients with Fabry disease and can also be used in follow up of absent or reduced alpha-Gal A activity in both male and female patients.

Unless irreversible damage has already occurred, treatment with enzyme replacement therapy has led to significant clinical improvement in affected individuals. In addition, some (adult) patients may be candidates for an oral chaperone therapy. For this reason, early diagnosis and treatment are desirable, and in a few US states early detection of Fabry disease through newborn screening has been implemented.

Molecular genetic testing is the recommended diagnostic test for female patients

Reference Values

Males: > or =1.2 nmol/mL/hour
Females: > or =2.8 nmol/mL/hour
An interpretive report will be provided.

Interpretation

In male patients, results less than 1.2 nmol/mL/hour in properly submitted specimens are consistent with Fabry disease. Normal results (> or =1.2 nmol/mL/hour) are not consistent with Fabry disease.

In female patients, normal results (> or =2.8 nmol/mL/hour) in properly submitted specimens are typically not consistent with carrier status for Fabry disease; however, enzyme analysis, in general, is not sufficiently sensitive to detect all carriers. Because a carrier range has not been established in females, molecular genetic analysis of the *GLA* gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) should be considered when alpha-galactosidase A activity is less than 2.9 nmol/mL/hour, or if clinically indicated.

Pseudodeficiency results in low measured alpha-galactosidase A activity but is not consistent with Fabry disease; FABRZ / Fabry Disease, Full Gene Analysis, Varies should be performed to resolve the clinical question.

For more information see Fabry Disease Diagnostic Testing Algorithm.

Cautions

Individuals with pseudodeficiency alleles can show reduced alpha-galactosidase A enzyme activity with this assay.

Clinical Reference

1. Desnick RJ, Ioannou YA, Eng CM. Alpha-galactosidase A deficiency: Fabry disease. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed November 7, 2023. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225546984
2. Matern D, Gavrilov D, Oglesbee D, Raymond K, Rinaldo P, Tortorelli S. Newborn screening for lysosomal storage disorders. Semin Perinatol. 2015;39(3):206-216
3. Mehta A, Hughes DA: Fabry Disease. In: Pagon RA, Adam MP, Ardinger HH, et al: eds. GeneReviews [Internet].

University of Washington, Seattle; 2002. Updated March 9, 2023. Accessed November 7, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1292/

4. Laney DA, Bennett RL, Clarke V, et al. Fabry disease practice guidelines: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2013;22(5):555-564

Performance

Method Description

Whole blood is collected on grade 903 (Whatman) filter paper. A one-eighth inch (3-mm) disk is punched out of the dried blood spot into a 96-well plate. An elution liquid/inhibitor, *N*-acetyl-D-galactosamine, and 4-methylumbelliferyl-alpha-D-galactopyranoside in citrate-phosphate buffer as the substrate are added. After the incubation period, the liquid from the plate is manually transferred to a second 96-well plate. Stop buffer (150 mM EDTA) is added to all wells. A set of calibration standards are added to every plate and are derived from 4-methylumbelliferone (4-MU) that is serially diluted manually in the plate with the highest calibrator being equivalent to an enzyme activity of 12.2 nmol/mL/hour. The plate is then read on the spectrofluorometer. Fluorescence readings for duplicate wells are averaged and the average fluorescence is used to calculate the enzyme activity result.(Poeppl AG, Murray GJ, Medin JA. Enhanced filter paper enzyme assay for high-throughput population screening for Fabry disease. Anal Biochem. 2005;337(1):161-163; Cowan T, Pasquali M. Laboratory Investigations of Inborn Errors of Metabolism. In: Sarafoglou K, Hoffman GF, Roth KS eds. Pediatric Endocrinology and Inborn Errors of Metabolism. 2nd ed. McGraw-Hill; 2017:1139-1158)

PDF Report

No

Day(s) Performed

Thursday

Report Available

8 to 15 days

Specimen Retention Time

1 year

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 Definition: AGABS

Alpha-Galactosidase, Blood Spot

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

82657

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
AGABS	Alpha-Galactosidase, BS	55908-8

Result ID	Test Result Name	Result LOINC® Value
50883	Specimen	31208-2
50884	Specimen ID	57723-9
50885	Source	31208-2
50886	Order Date	82785-7
50887	Reason For Referral	42349-1
50888	Method	85069-3
50889	Alpha-Galactosidase, BS	55908-8
50890	Interpretation	59462-2
50891	Amendment	48767-8
50892	Reviewed By	18771-6
50893	Release Date	82772-5