Overview

Useful For
Confirmation of a diagnosis of classic or variant Fabry disease in affected males with reduced alpha-galactosidase A enzyme activity

Carrier or diagnostic testing for asymptomatic or symptomatic females, respectively

Testing Algorithm
The following algorithms are available in Special Instructions:

- Fabry Disease: Newborn Screen-Positive Follow-up
- Fabry Disease Diagnostic Testing Algorithm

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

Special Instructions
- Molecular Genetics: Biochemical Disorders Patient Information
- Informed Consent for Genetic Testing
- Fabry Disease Diagnostic Testing Algorithm
- Fabry Disease: Newborn Screen-Positive Follow-up
- 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
Polymerase Chain Reaction (PCR) followed by DNA Sequencing

NY State Available
Yes

Specimen

Specimen Type
Varies

Advisory Information
The recommended first-tier test for males with suspected Fabry disease is alpha-galactosidase A enzyme activity in blood or serum. Order either AGAW / Alpha-galactosidase, Leukocytes or AGAS / Alpha-galactosidase, Serum.

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
Submit only 1 of the following specimens:

Preferred:

Specimen Type: Whole blood

Container/Tube:

Preferred: Lavender top (EDTA) tube or yellow top (ACD) tube

Acceptable: Any anticoagulant

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.
2. Send specimen in original tube.

Specimen Stability Information: Ambient (preferred)/Refrigerated

Acceptable:

Specimen Type: Blood spot

Supplies: Card - Blood Spot Collection (Filter Paper) (T493)

Container/Tube:

Preferred: Collection card (Whatman Protein Saver 903 Paper)

Acceptable: Ahlstrom 226 filter paper, or Blood Spot Collection Card

Specimen Volume: 2 to 5 Blood spots on collection card

Collection Instructions:

1. An alternative blood collection option for a patient older than 1 year of age is finger stick.
2. Let blood dry on the filter paper at ambient temperature in a horizontal position for 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
Test Definition: FABRZ
Fabry Disease Full Gene Analysis

Additional Information:

1. For collection instructions, see Blood Spot Collection Instructions in Special Instructions.

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

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

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.

3. If not ordering electronically, complete, print, and send an Inborn Errors of Metabolism Test Request (T798) with the specimen.

Specimen Minimum Volume

Blood: 1 mL
Blood Spots: 5 punches-3 mm diameter

Reject Due To

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

Specimen Stability Information

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Temperature</th>
<th>Time</th>
<th>Special Container</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varies</td>
<td>Varies</td>
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</table>

Clinical and Interpretive

Clinical Information

Fabry disease is an X-linked recessive disorder with an incidence of approximately 1 in 50,000 males. Symptoms result from a deficiency of the enzyme alpha-galactosidase A (alpha-Gal A). Reduced alpha-Gal A activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues.

Severity and onset of symptoms are dependent on the residual alpha-Gal A activity. Males with less than 1% alpha-Gal A activity have the classic form of Fabry disease. Symptoms can appear in childhood or adolescence and usually include acroparesthesias (pain crises), multiple angioeratomas, reduced or absent sweating, and corneal opacity. By middle age, most patients develop renal insufficiency leading to end-stage renal disease, as well as cardiac and cerebrovascular disease. Males with greater than 1% alpha-Gal A activity may present with a variant form of Fabry disease. The renal variant generally has onset of symptoms in the third decade. The most prominent feature in this form is renal insufficiency and, ultimately, end-stage renal disease. Individuals with the renal variant may or may not...
have other symptoms of classic Fabry disease. Individuals with the cardiac variant are often asymptomatic until they present with cardiac findings such as cardiomyopathy or mitral insufficiency later in life. The cardiac variant is not associated with renal failure.

Female carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severe. Measurement of alpha-Gal A activity is not generally useful for identifying carriers of Fabry disease, as many of these individuals have normal levels of alpha-Gal A.

Alterations in the \textit{GLA} gene result in deficiency of alpha-Gal A. Most of the alterations identified to date are family specific. Full sequencing of the \textit{GLA} gene identifies over 98% of the sequence variants in the coding region and splice junctions. In addition, this assay detects the intron 4 alteration common in the Taiwanese population.\(^{(1)}\)

The recommended first-tier test for males with suspected Fabry disease is biochemical testing that measures alpha-galactosidase enzyme activity in blood or serum: \textit{AGAW / Alpha-galactosidase, Leukocytes} or \textit{AGAS / Alpha-galactosidase, Serum}. Additionally, testing for the glycosphingolipid, globotriaosylsphingosine (LGl3) may aid in further clarifying disease status in both males and females with suspected Fabry disease (\textit{LGB3 / Globotriaosylsphingosine, Serum}). Individuals with decreased or absent enzyme activity and elevated LGl3 are more likely to have an identifiable alterations in the \textit{GLA} gene by molecular genetic testing. However, enzymatic testing alone is not reliable to detect female carriers.

The following algorithms are available in Special Instructions:

- \textit{Fabry Disease: Newborn Screen-Positive Follow-up algorithm}
- \textit{Fabry Disease Diagnostic Testing Algorithm}

\textbf{Reference Values}

An interpretive report will be provided.

\textbf{Interpretation}

All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations.\(^{(2)}\) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

\textbf{Cautions}

A small percentage of individuals who are carriers or have a diagnosis of Fabry disease may have a variant that is not identified by this method (eg, large genomic deletions, promoter alterations). The absence of a variant, therefore, does not eliminate the possibility of positive carrier status or the diagnosis of Fabry disease. For carrier testing, it is important to first document the presence of a \textit{GLA} gene variant in an affected family member.

In some cases, DNA alterations of undetermined significance may be identified.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical and biochemical findings, additional testing should be considered.

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

\textbf{Clinical Reference}


### Performance

<table>
<thead>
<tr>
<th>Method Description</th>
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<tbody>
<tr>
<td>Bidirectional sequence analysis is performed to test for the presence of a sequence variant in all coding regions and intron/exon boundaries of the GLA gene. (Unpublished Mayo method)</td>
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<table>
<thead>
<tr>
<th>PDF Report</th>
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<tbody>
<tr>
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<table>
<thead>
<tr>
<th>Day(s) and Time(s) Test Performed</th>
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<td>Performed weekly, Varies</td>
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<table>
<thead>
<tr>
<th>Analytic Time</th>
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<tr>
<td>14 days</td>
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<table>
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<th>Maximum Laboratory Time</th>
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<tr>
<td>20 days</td>
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<table>
<thead>
<tr>
<th>Specimen Retention Time</th>
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<tr>
<td>Whole Blood: 2 weeks (if available); Extracted DNA: 3 months</td>
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<table>
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<tr>
<th>Performing Laboratory Location</th>
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<tbody>
<tr>
<td>Rochester</td>
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### Fees and Codes

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<th>Fees</th>
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<tr>
<td>- Authorized users can sign in to Test Prices for detailed fee information.</td>
</tr>
<tr>
<td>- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.</td>
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<tr>
<td>- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.</td>
</tr>
</tbody>
</table>

### 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 U.S. Food and Drug Administration.

### CPT Code Information

81405-GLA (galactosidase, alpha) (eg, Fabry disease), full gene sequence

### LOINC® Information
### Test Definition: FABRZ

Fabry Disease Full Gene Analysis

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<th>Test Order Name</th>
<th>Order LOINC Value</th>
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<tbody>
<tr>
<td>FABRZ</td>
<td>Fabry Disease Full Gene Analysis</td>
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<table>
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<td>Result Summary</td>
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<td>53895</td>
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