Overview

Useful For

Genetic test for individuals at high risk for G6PD deficiency (for initial or time-sensitive screening for G6PD deficiency, refer to phenotyping enzyme assay G6PD / Glucose-6-Phosphate Dehydrogenase [G-6-PD], Quantitative, Erythrocytes)

Aiding in the diagnosis of glucose-6-phosphate dehydrogenase (G6PD) deficiency

Determining G6PD deficiency status in individuals with inconclusive or unexpected phenotyping results

Differentiation of heterozygous females with skewed X-inactivation from homozygous and compound heterozygous females

Definitive diagnosis of carrier status in females

Evaluation of neonates (particularly males) with unexplained jaundice

Identifying individuals at risk of drug-induced acute hemolytic anemia (AHA) related to G6PD deficiency

Genetics Test Information

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a very common X-linked condition, impacting about 400 million people worldwide. Both males and females may be impacted due to how common G6PD deficiency is in the population.

Several medications, including rasburicase, methylene blue and dapsone, result in acute hemolytic anemia (AHA) when taken by individuals with G6PD deficiency.

FDA labeling and Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines recommend that G6PD testing be undertaken in high-risk populations before prescribing drugs known to cause AHA. Knowing a patient's genotype is generally sufficient to avoid contraindicated drugs, but follow-up with the phenotyping enzyme assay may be necessary to clarify results in some cases.

This test involves full gene sequencing of all exons and intron/exon boundaries of the G6PD gene. A comprehensive interpretation will be provided including congenital and pharmacogenomic implications of results. Testing should be considered before prescribing medication associated with hemolysis in individuals with G6PD deficiency.

Testing Algorithm

The following algorithms are available in Special Instructions:

- G6PD Genotyping Algorithm for Therapeutic Drug Recommendations
- Newborn Screen Follow-up for Glucose-6-Phosphate Dehydrogenase (G-6-PD) Deficiency

For more information, see Newborn Screening Act Sheet Glucose-6-Phosphate Dehydrogenase Deficiency in Special Instructions.

Special Instructions

- Informed Consent for Genetic Testing
- Multiple Saliva Genotype Tests
Method Name
Polymerase Chain Reaction (PCR) Followed by DNA Sequence Analysis

NY State Available
Yes

Specimen

Specimen Type
Varies

 Necessary Information
1. Patient's sex is required.

2. Include physician name and phone number with the specimen.

Specimen Required
Submit only 1 of the following specimens:

Specimen Type: Whole blood

Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)

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

Specimen Type: Saliva

Supplies: DNA Saliva Collection Kit (T651)

Container/Tube: Oragene DNA Self-Collection Kit (T651: fees apply)

Specimen Volume: Full tube
Collection Instructions:

1. Fill tube to line.

2. Send specimen in original container per kit instructions.

**Specimen Stability Information:** Ambient

**Specimen Type:** DNA

**Container/Tube:** 2 mL screw top tube

**Specimen Volume:** 100 mcL (microliters)

Collection Instructions:

1. The preferred volume is 100 mcL at a concentration of 250 ng/mcL.

2. Include concentration and volume on tube.

**Specimen Stability Information:** Frozen (preferred)/Ambient/Refrigerated

**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. If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:

   - Benign Hematology Test Request (T755)
   - Pharmacogenomics Test Request (T797)
   - Therapeutics Test Request (T831)

**Specimen Minimum Volume**

Blood: 0.45 mL
Saliva: Full tube of saliva

**Reject Due To**

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

**Specimen Stability Information**

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<thead>
<tr>
<th>Specimen Type</th>
<th>Temperature</th>
<th>Time</th>
<th>Special Container</th>
</tr>
</thead>
<tbody>
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Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzymopathy with about 400 million people affected worldwide. It is most commonly found in populations where Plasmodium falciparum malaria is (or was) endemic, but G6PD deficiency may be present in any population.

G6PD converts glucose-6-phosphate to 6-phosphoglyconolactone in the first step of the pentose phosphate pathway (PPP), this reaction also produces nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) from nicotinamide adenine dinucleotide phosphate (NADP). NADPH, through subsequent enzymatic reactions, protects erythrocytes from damage by detoxifying hydrogen peroxide and other sources of oxidative stress.

G6PD is encoded by the gene G6PD, which lies on the X-chromosome. G6PD deficiency is inherited in an X-linked recessive manner; therefore, males are more commonly affected than females, but due to the high prevalence of G6PD deficiency, homozygous and compound heterozygous females are not uncommon. A large number of G6PD pathogenic variants have been discovered. These variants are subdivided into a class system based on definitions from the World Health Organization (WHO).

Table 1. G6PD variant WHO class and associated G6PD deficiency phenotype

<table>
<thead>
<tr>
<th>WHO class</th>
<th>Associated Clinical Presentation</th>
<th>G6PD activity</th>
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<tbody>
<tr>
<td>I</td>
<td>Chronic nonspherocytic hemolytic anemia (CNSHA)</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>II</td>
<td>Asymptomatic unless challenged</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>III</td>
<td>Asymptomatic unless challenged</td>
<td>10%-60%</td>
</tr>
<tr>
<td>IV</td>
<td>None</td>
<td>Normal</td>
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With the exception of those with chronic nonspherocytic hemolytic anemia (CNSHA), individuals with G6PD deficiency are typically asymptomatic until they are challenged with an exogenous factor such as a drug, infection, or fava beans. The exogenous factor can trigger acute hemolytic anemia (AHA) in individuals with G6PD deficiency. The severity of AHA is highly variable, ranging from mild to life-threatening and can be fatal. Therefore, determining the G6PD deficiency status is recommended on the FDA label of several drugs either proven or suspected to cause AHA in patients with G6PD deficiency. For a list of drugs known to cause AHA in individuals with G6PD deficiency, see Pharmacogenomic Associations Tables in Special Instructions.

Preemptive genotyping allows for the identification of patients at risk for an adverse reaction to drugs known to cause AHA in those with G6PD deficiency. In most cases, genotyping provides sufficient information to avoid the use of contraindicated drugs. In some cases, including heterozygous females, the phenotyping assay is necessary to determine if such drugs should be avoided. Skewed X-inactivation in heterozygous females has been reported to result in G6PD deficiency, but the phenotyping assay is necessary to determine G6PD activity level. For more information regarding the need for G6PD enzyme activity follow-up testing to this genotyping assay, refer to the G6PD Genotyping Algorithm for Therapeutic Drug Recommendations in Special Instructions.

Reference Values
An interpretive report will be provided.
**Interpretation**

All detected alterations will be evaluated according to the latest American College of Medical Genetics recommendations.(1) Variants will be classified based on known, predicted, or possible effect on gene pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Cautions**

Patients who have received a heterologous blood transfusion within the preceding 6 weeks, or who have received an allogeneic blood or marrow transplant, can have inaccurate genetic test results due to the presence of both donor and recipient DNA.

For patients who have been transfused within the preceding 6 weeks, the enzyme assay G6PD / Glucose-6-Phosphate Dehydrogenase (G-6-PD), Quantitative, Erythrocytes will also be affected, so it is not an appropriate alternative test.

Patients who have received an allogeneic blood or marrow transplant would be expected to convert G6PD status to that of donor. However, if the patient’s transplant was partially successful or if there is a relapse of an underlying hematologic malignancy, a mixture of donor and recipient genotype may be seen on genetic analysis. The enzyme assay can be run after transplantation: order G6PD / Glucose-6-Phosphate Dehydrogenase (G-6-PD), Quantitative, Erythrocytes.

Rare variants exist that could lead to false-negative or false-positive results. Other variants in the primer binding regions can affect the testing, and ultimately, the genotype assessment made.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Large deletions or rearrangements are not detected by this assay.

Sometimes a genetic alteration of unknown significance may be identified. In this case, testing of appropriate family members may be useful to determine pathogenicity of the alteration.

This test is not designed to provide specific dosing or drug selection recommendations and is to be used as an aid to clinical decision making only. Drug-label guidance should be used when dosing patients with medications regardless of the predicted phenotype.

Skewed X-inactivation in heterozygous females has been reported to result in G6PD deficiency, but the phenotyping assay is necessary to determine G6PD activity level and assign G6PD deficiency status in these cases.

**Clinical Reference**


4. OMIM 305900 Glucose-6-phosphate dehydrogenase. Available at www.omim.org/entry/305900

Performance

Method Description
Genomic DNA is extracted from whole blood. The \textit{G6PD} gene is amplified by PCR. The PCR products are then purified and sequenced in both directions using fluorescent dye-terminator chemistry. Sequencing products are separated on an automated sequencer and trace files analyzed for variations in the exons and intron/exon boundaries of all exons using mutation detection software and visual inspection. Mutation nomenclature is based on GenBank accession number NM_001042351.2 using human genome assembly GRCh37 (hg19).(Unpublished Mayo method)

PDF Report
No

Day(s) and Time(s) Test Performed
Monday, Wednesday

Analytic Time
3 days (Not reported on Saturday or Sunday)

Maximum Laboratory Time
7 days

Specimen Retention Time
Whole Blood or saliva: 2 weeks; Extracted DNA: 2 months

Performing Laboratory Location
Rochester

Fees and 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 Regional Manager. 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 U.S. Food and Drug Administration.

CPT Code Information
81249

LOINC® Information

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<td>G6PD Full Gene Sequencing</td>
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