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## Overview

### Useful For

Genetic test for individuals at high risk for glucose-6-phosphate dehydrogenase (G6PD) deficiency

Aiding in the diagnosis of 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 are available in Special Instructions:

[-G6PD Genotyping Algorithm for Therapeutic Drug Recommendations](#)

[-Newborn Screen Follow-up for Glucose-6-Phosphate Dehydrogenase \(G6PD\) Deficiency](#)

[-Newborn Screening Act Sheet Glucose-6-Phosphate Dehydrogenase Deficiency](#)

### Special Instructions

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- [Informed Consent for Genetic Testing](#)
  - [Pharmacogenomic Associations Tables](#)
  - [G6PD Genotyping Algorithm for Therapeutic Drug Recommendations](#)
  - [Newborn Screening Act Sheet Glucose-6-Phosphate Dehydrogenase Deficiency](#)
  - [Newborn Screen Follow-up for Glucose-6-Phosphate Dehydrogenase \(G6PD\) Deficiency](#)
  - [Informed Consent for Genetic Testing \(Spanish\)](#)

**Method Name**

Polymerase Chain Reaction (PCR) followed by DNA Sequence Analysis

**NY State Available**

Yes

**Specimen****Specimen Type**

Varies

**Ordering Guidance**

For initial or time-sensitive screening for glucose-6-phosphate dehydrogenase deficiency, order G6PD1 / Glucose 6-Phosphate Dehydrogenase Enzyme Activity, Blood.

**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) 9 days/Refrigerated 30 days

**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

**Specimen Type:** Extracted DNA

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

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

**Collection Instructions:**

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

-[Therapeutics Test Request](#) (T831)

## Specimen Minimum Volume

Blood: 0.45 mL

Saliva: 1 swab

## 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

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

WHO class	Associated Clinical Presentation	G6PD activity
I	Chronic nonspherocytic hemolytic anemia (CNSHA)	<10%
II	Asymptomatic unless challenged	<10%
III	Asymptomatic unless challenged	10%-60%
IV	None	Normal

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 Food and Drug Administration 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 and Genomics 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.

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For patients who have been transfused within the preceding 6 weeks, the enzyme assay G6PD1 / Glucose-6-Phosphate Dehydrogenase Enzyme Activity, Blood 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 G6PD1 / Glucose 6-Phosphate Dehydrogenase Enzyme Activity, Blood.

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

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;(17):105-423
2. Cappellini MD, Fiorelli G: Glucose-6-phosphate dehydrogenase deficiency. *Lancet.* 2008;371:64-67
3. Luzzatto L, Seneca E: G6PD deficiency: a classic example of pharmacogenetics with on-going clinical implications. *Br J Haematol.* 2014;164:469-480
4. OMIM: 305900 Glucose-6-phosphate dehydrogenase. Johns Hopkins University; 1987. Updated August 5, 2019. Accessed December 4, 2020. Available at [www.omim.org/entry/305900](http://www.omim.org/entry/305900)
5. Relling MV, McDonagh EM, Chang T, et al: Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for rasburicase therapy in the context of G6PD deficiency genotype. *Clin Pharmacol Ther.* 2014 Aug;96(2):169-174

### Performance

### Method Description

Genomic DNA is extracted from whole blood. The *G6PD* gene is amplified by polymerase chain reaction (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 variant detection software and visual inspection. Variant nomenclature is based on GenBank accession number NM\_001042351.2 using human genome assembly GRCh37 (hg19). (Unpublished Mayo method)

**PDF Report**

No

**Day(s) Performed**

Monday, Wednesday

**Report Available**

3 to 7 days

**Specimen Retention Time**

Whole Blood or saliva: 2 weeks; Extracted DNA: 2 months

**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**

81249

**LOINC® Information**

Test ID	Test Order Name	Order LOINC® Value
G6PDB	G6PD Full Gene Sequencing	94231-8

Result ID	Test Result Name	Result LOINC® Value
37847	Phenotype	47998-0
37848	Interpretation	69047-9
38194	Additional Information	48767-8
37851	Reviewed By	18771-6

## Test Definition: G6PDB

Glucose-6-Phosphate Dehydrogenase (G6PD)

Full Gene Sequencing, Varies

48399	Result Details	82939-0
37850	Method	85069-3
37902	Disclaimer	62364-5