Glucose 6-Phosphate Dehydrogenase (G6PD) Deficiency Fact Sheet for Providers

New York State Mandate:
Newborn screening is mandated in New York State by Public Health Law, sections 2500-a and 2500-f. In 2022 the statute was amended to add G6PD Deficiency to the list of newborn screening conditions in New York. While G6PD deficiency was not added to the panel of conditions screened by the Newborn Screening Program through testing of dried blood spots, this regulatory amendment mandates that newborns be given a diagnostic test for G6PD deficiency if they:

- Present with hemolytic anemia
- Present with hemolytic jaundice
- Present with early-onset increasing neonatal jaundice persisting beyond the first week of life (bilirubin level greater than the 40th %ile for age in hours)
- Are admitted to the hospital for jaundice following discharge
- Have a familial, racial, or ethnic risk of G6PD deficiency (African, Asian, Mediterranean or Middle Eastern ancestry)

Newborns who meet any one of the above clinical criteria should be tested for G6PD deficiency using a quantitative test.

What is G6PD Deficiency?

G6PD deficiency is an inborn error of metabolism that causes increased susceptibility to erythrocyte damage and hemolysis during periods of oxidative stress. G6PD is an essential housekeeping enzyme in all body cells and is responsible for mitigating oxidative damage from reactive oxygen species (ROS). The role and physiology of erythrocytes make them particularly vulnerable to oxidative damage.

Epidemiology

Of the known human enzymopathies, G6PD deficiency is the most common, affecting 400-500 million people worldwide. Prevalence varies greatly between different populations, with the highest prevalence found in those with African, Mediterranean, Asian, or Middle Eastern ancestry. Researchers speculate that its distribution is related to a proposed protective effect against malaria. It is important to ascertain accurate family history and ancestry/origins of your patients because the law requires diagnostic testing be offered to these high-risk populations.

Signs and Symptoms of G6PD Deficiency

Many individuals with G6PD deficiency will remain asymptomatic during their lifetime. However, symptoms may be induced by exposure to certain foods, medications, or infections. Fava beans and anti-malarial medications are among the most common triggers.

In newborns, G6PD deficiency may present as neonatal hyperbilirubinemia, acute hemolytic anemia (AHA), and/or chronic nonspherocytic hemolytic anemia (CNSHA). Newborns with G6PD deficiency have a two-fold increased risk for neonatal hyperbilirubinemia. These levels may be severe enough to lead to neurological sequelae such as bilirubin encephalopathy and kernicterus. Symptoms may include poor feeding, vomiting, lethargy, extreme sleepiness, and hypotonia. AHA following a trigger can vary in severity, ranging from mild (and possibly undiagnosed) to severe and life-threatening. Signs and symptoms may include pallor, jaundice, rapid heart rate, dark urine, splenomegaly, fever, fatigue, shortness of breath, and abdominal pain. In rare cases (<10/million), affected individuals may present with unprovoked chronic hemolytic anemia, or CNSHA.

Genetics of G6PD Deficiency

G6PD deficiency is caused by pathogenic variants in the *G6PD* gene on the X chromosome. Hemizygous males and homozygous females experience G6PD deficiency. Heterozygous females may also have G6PD deficiency with varying degrees of enzyme activity and disease severity because of variable X-inactivation. Due to the X-linked inheritance pattern, affected males will pass their pathogenic variant to each of their daughters, and none of their sons. Female carriers have a 50% risk to pass this condition to both daughters and sons. Approximately one half of known *G6PD* variants are benign, and some genotype-phenotype correlations have been identified. *De novo* variants have been documented.

Diagnosis and Laboratory Testing of G6PD Deficiency in Newborns

Test Method	Notes	NYS-Permitted Labs Performing Test
Quantitative enzyme analysis	• Standard method for diagnosis • Detects low, intermediate, and normal G6PD activity in blood • False negatives possible when done following a hemolytic attack, blood transfusion within the last 6 weeks, or in presence of high reticulocyte count	Quest Diagnostics ARUP Laboratories Mayo Clinic Laboratories
Qualitative enzyme analysis	• Should not be ordered • Only detects severe deficiency	
Gene sequencing	• Gold standard • Can detect female carriers • May detect variants of unknown clinical consequence • Blood transfusion within last 6 weeks can cause inaccurate results • Results may take 1-2 weeks	Mayo Clinic Laboratories

Enzyme activity among females is highly variable and may be increased compared to males but still abnormally low. To reduce misdiagnoses, it is recommended that females undergo combined quantitative enzyme activity testing and genetic testing.

Management/Treatment for G6PD Deficiency

Any neonate identified with G6PD deficiency should be referred to the appropriate specialists (Hematology and/or Genetics) for further workup and familial genetic counseling.

The primary treatment for G6PD deficiency is the avoidance of oxidative stressors. On rare occasions anemia may be severe enough to warrant blood transfusion. Folic acid and iron may be useful during hemolysis. However, G6PD deficiency is typically asymptomatic and the associated hemolysis is short-term.

G6PD Resources

Baby's First Test: https://www.babysfirsttest.org/newborn-screening/conditions/glucose-6-phosphate-dehydrogenase-deficiency

G6PD Deficiency Association: https://www.g6pd.org/

Diagnosis and Management of G6PD Deficiency: https://www.aafp.org/afp/2005/1001/p1277.html

G6PD Newborn screening: https://newbornscreening.hrsa.gov/conditions/glucose-6-phosphate-dehydrogenase-deficiency

GARD: https://rarediseases.info.nih.gov/diseases/6520/glucose-6-phosphate-dehydrogenase-deficiency/

G6PD Deficiency Foundation: https://g6pddf.org/

NORD: https://rarediseases.org/rare-diseases/glucose-6-phosphate-dehydrogenase-deficiency/

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