G6PD Pharmacogenomics Competency
A.L. is a 27-year-old male who had a G6PD enzyme activity test ordered as part of a workup for G6PD deficiency. He received one unit of red blood cells (RBC) transfusion two weeks ago.

How do RBC transfusions usually affect the G6PD activity value?

a) Falsely increase the G6PD activity value
b) Falsely decrease the G6PD activity value
c) Only platelet transfusions affect the G6PD activity value
Which of the following G6PD phenotypes can only be assigned to individuals with two X-chromosomes?

a) G6PD normal
b) G6PD deficiency
c) G6PD variable
A G6PD deficient patient is prescribed sulfamethoxazole. Which of the following therapeutic recommendations is most appropriate based on the G6PD phenotype and drug-specific risk?

a) Dispense sulfamethoxazole; no reason to avoid a low-to-no risk drug
b) Substitute a different antimicrobial; avoid use of high-risk drugs
c) Use caution and close monitoring when dispensing sulfamethoxazole, a medium-risk drug
d) Enzyme activity must be measured before dispensing sulfamethoxazole
Objectives

• Upon completion of this competency, participants should be able to:
  – Assign the G6PD phenotype based on a patient’s $G6PD$ genotype
  – Make therapeutic recommendations based on a patient’s G6PD test result
A 14-year-old male with newly diagnosed T-cell acute lymphoblastic lymphoma is suspected to be G6PD deficient. At the time of diagnosis, he is at high-risk of developing tumor lysis syndrome (serum uric acid 8.6 mg/dL).

His primary care team ordered two doses of rasburicase (24 hours apart).

The patient's hemoglobin dropped from 16.3 to 5.9 g/dL in 48 hours.

One year after initial presentation, G6PD activity testing revealed a G6PD deficiency.
What is G6PD?
**G6PD Gene**

- **G6PD** is a gene located on the X-chromosome.
  - Biological males have one X-chromosome
    - Only one copy (allele) of the **G6PD** gene
  - Biological females have two X-chromosomes
    - Two copies (alleles) of the **G6PD** gene

- Certain genetic variations in the **G6PD** gene cause a person to have decreased G6PD enzyme activity
**G6PD Deficiency Prevalence**

- Common enzyme deficiency, estimated 400 million people affected worldwide
- Highest prevalence in Sub-Saharan African countries, East Asia and the Mediterranean.

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence Estimate Total Population (95% CI)</th>
<th>Prevalence Estimate Males (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>7.5% (7.1-7.9)</td>
<td>8.5% (7.9-9.1)</td>
</tr>
<tr>
<td>Middle East</td>
<td>6% (5.7-6.4)</td>
<td>7.2% (6.6-7.7)</td>
</tr>
<tr>
<td>Asia</td>
<td>4.7% (4.4-4.9)</td>
<td>5.2% (4.7-5.6)</td>
</tr>
<tr>
<td>Europe</td>
<td>3.9% (3.5-4.2)</td>
<td>3.8% (2.9-4.7)</td>
</tr>
<tr>
<td>Americas</td>
<td>3.4% (3.0-3.8)</td>
<td>5.2% (4.7-5.8)</td>
</tr>
<tr>
<td>Pacific</td>
<td>2.9% (2.4-3.4)</td>
<td>3.4% (2.7-4.1)</td>
</tr>
</tbody>
</table>

CI: Confidence interval

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G6PD is the primary enzyme that protects RBCs from oxidative stress.

G6PD enzymes convert NADP⁺ to NADPH

Hexokinase:
Glucose → Glucose-6-phosphate

ATP → ADP

G6PD:
Glucose-6-phosphate → 6-phosphogluconate

NADP⁺ → NADPH

Glutathione reductase:

GSSG → GSH

ATP: Adenosine triphosphate
ADP: Adenosine diphosphate
GSSG: Glutathione disulfide
GSH: Glutathione
NADPH: Nicotinic adenine dinucleotide phosphate

What happens in G6PD deficiency?

G6PD enzyme converts NADP⁺ to NADPH
(primary protection mechanism of erythrocytes from oxidative stress)

- Hexokinase: Glucose → Glucose-6-phosphate
- G6PD: Glucose-6-phosphate → 6-phosphogluconate
- Glutathione reductase: NADPH → NADP⁺
- Certain medications can generate reactive oxygen species, causing oxidative stress on cells

What happens G6PD deficiency?

G6PD enzymes convert NADP⁺ to NADPH (only protection mechanism of erythrocytes from oxidative stress)

Hexokinase

Glucose → Glucose-6-phosphate

ATP → ADP

G6PD

Glucose-6-phosphate → 6-phosphogluconate

NADP⁺ → NADPH

Glutathione reductase

NADPH

GSSG → GSH

Certain medications can generate reactive oxygen species, causing oxidative stress on cells

G6PD-deficient erythrocytes have reduced NADPH production → defective in handling oxidative stress → drug-induced lysis → patients at higher risk for hemolytic anemia

**GOAL:** Know the patient’s G6PD status prior to prescribing a medication that can cause hemolytic anemia in cases of G6PD deficiency.
G6PD Allele Variants
G6PD Enzyme Activity Test

- G6PD enzyme activity tests have been considered the “gold standard” for assigning G6PD phenotype.
- Common interfering factors with the spectrophotometric method include:

<table>
<thead>
<tr>
<th>Clinical/Laboratory Parameter</th>
<th>Potential Interference on G6PD Activity Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical anemia (hemoglobin &lt;7 g/dL)</td>
<td>↓</td>
</tr>
<tr>
<td>pRBC transfusion (&lt;60 days)</td>
<td>↑</td>
</tr>
<tr>
<td>Reticulocytosis</td>
<td>↑</td>
</tr>
<tr>
<td>Leukocytosis (&gt;100 x 10³ cells/mm³)</td>
<td>↑</td>
</tr>
</tbody>
</table>

pRBC: packed red blood cell

• *G6PD* variants are classified based on the median residual enzyme activity expressed as a percentage of normal activity

<table>
<thead>
<tr>
<th>Class</th>
<th>Median G6PD Activity</th>
<th>Risk of Hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt;10%</td>
<td>Chronic, untriggered</td>
</tr>
<tr>
<td>II</td>
<td>&lt;12%</td>
<td>Triggered</td>
</tr>
<tr>
<td>III</td>
<td>10-60%</td>
<td>Triggered</td>
</tr>
<tr>
<td>IV</td>
<td>60-150%</td>
<td>No</td>
</tr>
</tbody>
</table>

*WHO classification of *G6PD* variants (prior to 2022)*

The WHO updated their treatment classification of *G6PD* variants in 2022

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<th>Risk of Hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&lt;20%</td>
<td>Chronic (CNSHA)</td>
</tr>
<tr>
<td>B</td>
<td>&lt;45%</td>
<td>Acute, triggered</td>
</tr>
<tr>
<td>C</td>
<td>60–150%</td>
<td>No hemolysis</td>
</tr>
<tr>
<td>U</td>
<td>Any</td>
<td>Uncertain clinical significance</td>
</tr>
</tbody>
</table>

CNSHA: Chronic non-spherocytic hemolytic anemia
Assigning G6PD phenotypes
The assignment of G6PD phenotype is based on one (people with one X-chromosome) or two (people with two X-chromosomes) $G6PD$ allele(s) that the patient carries.

There are three G6PD phenotypes:
- Normal
- Deficient
- Variable
Normal G6PD Phenotype

• People with a normal G6PD phenotype have normal G6PD enzyme function
  • Biological males with one non-deficient allele (B allele)
  • Biological females with two non-deficient alleles
• Example genotypes:
  • A/null, A/B
• Approximately 92% of the world’s population has a normal G6PD phenotype

People with a G6PD deficiency phenotype have decreased G6PD enzyme function

- Biological males with one deficient allele
- Biological females with two deficient alleles

Example genotypes:
- A-, A-/A-
- Approximately 4% of the world’s population is predicted to be G6PD deficient

Note: The estimated frequency of G6PD deficiency with CNSHA is less than 10 per million population; therefore, limited data is available for this phenotype.
Variable G6PD Phenotype

• Assigned to individuals with two X-chromosomes carrying one deficient allele and one non-deficient allele

• Example genotypes:
  • A-/B, A-/A

• G6PD enzyme activity falls somewhere on the range of normal to deficient and cannot be predicted from the genotype alone

• In order to assign a G6PD phenotype, G6PD enzyme activity should be performed
  — Note: G6PD enzyme activity can change over a person’s lifetime for those with a variable G6PD phenotype

The exact percent of each phenotype group varies by race and ethnicity.

https://cpicpgx.org/guidelines/guideline-for-rasburicase-and-g6pd/ Accessed 08/29/2022
G6PD Phenotype-based Recommendations
Patients who are G6PD deficient are at high risk of developing hemolytic anemia when exposed to certain medications or fava beans.

### Medications that should be AVOIDED in patients with G6PD deficiency

<table>
<thead>
<tr>
<th>Medication</th>
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<tbody>
<tr>
<td>Dapsone</td>
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<tr>
<td>Methylene blue</td>
</tr>
<tr>
<td>Pegloticase</td>
</tr>
<tr>
<td>Primaquine – standard dose (0.25-0.5 mg/kg daily for 14 days)</td>
</tr>
<tr>
<td>Rasburicase</td>
</tr>
<tr>
<td>Tafenoquine</td>
</tr>
<tr>
<td>Toluidine blue</td>
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### Medications that should be used with CAUTION in patients with G6PD deficiency

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<tbody>
<tr>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>Primaquine – medium dose (0.75 mg/kg or 45 mg once weekly for 8 weeks)</td>
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For More Information…

• For more information about G6PD and high-risk medications visit the CPIC guideline at https://cpicpgx.org/gene/g6pd/

• For more information about the St. Jude implementation efforts for G6PD visit www.stjude.org/G6PD
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Correct Answer: A
Question #2

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Correct Answer: C
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Correct Answer: A
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