G6PD Pharmacogenomics Competency

Updated on 08/2022

Question #1

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a) Falsely increase the G6PD activity value

b) Falsely decrease the G6PD activity value

c) Only platelet transfusions affect the G6PD activity value

Question #2

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

Question #3

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

Patient Case

- 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

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

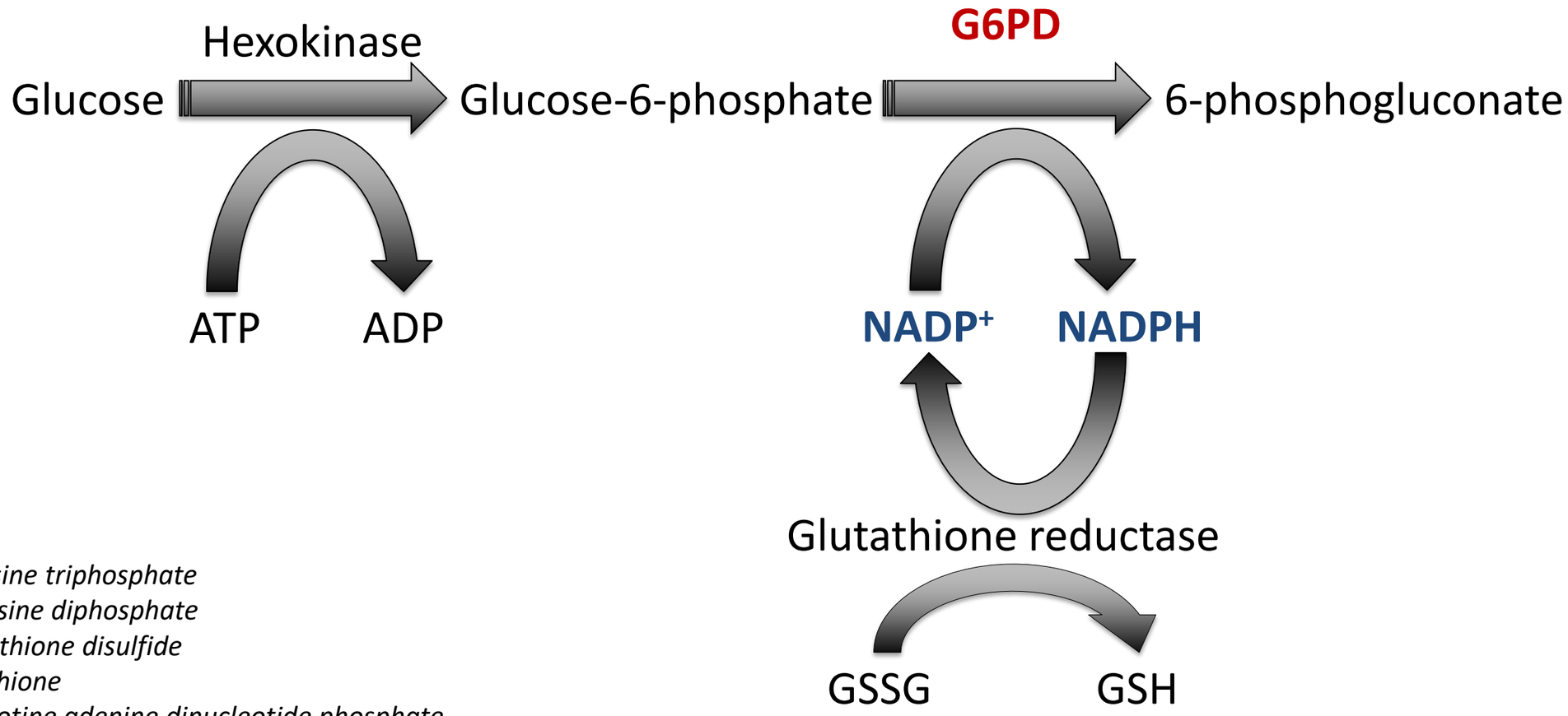
CI: Confidence interval

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

Nkhoma ET, *et al. Blood Cells Mol Dis*. 2009;42:267-278.

G6PD is the primary enzyme that protects RBCs from oxidative stress

G6PD enzymes convert **NADP⁺** to **NADPH**

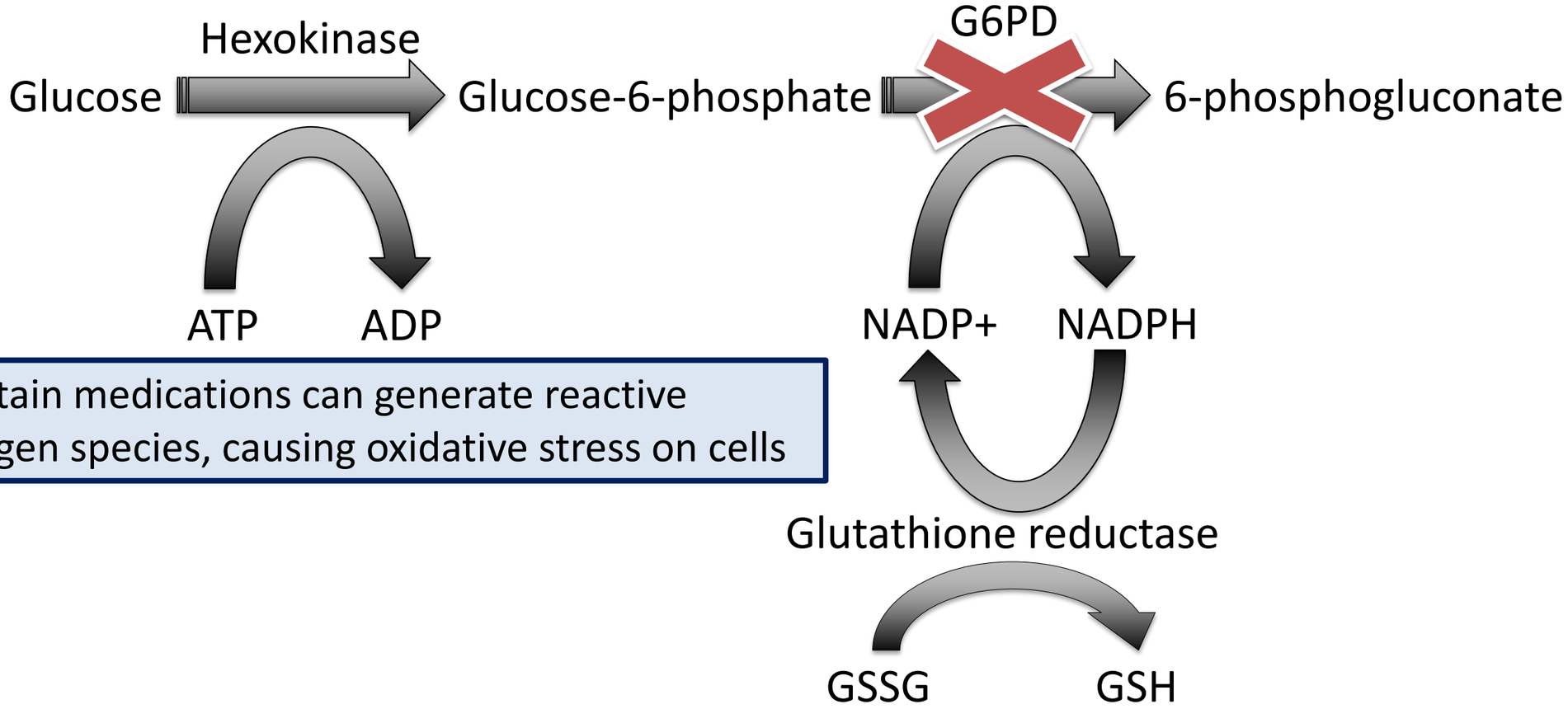


ATP: Adenosine triphosphate
ADP: Adenosine diphosphate
GSSG: Glutathione disulfide
GSH: Glutathione
NAPDH: Nicotine adenine dinucleotide phosphate

World Health Organization. Technical consultation to review the classification of G6PD. Accessed 08/2022.

What happens in G6PD deficiency?

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



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

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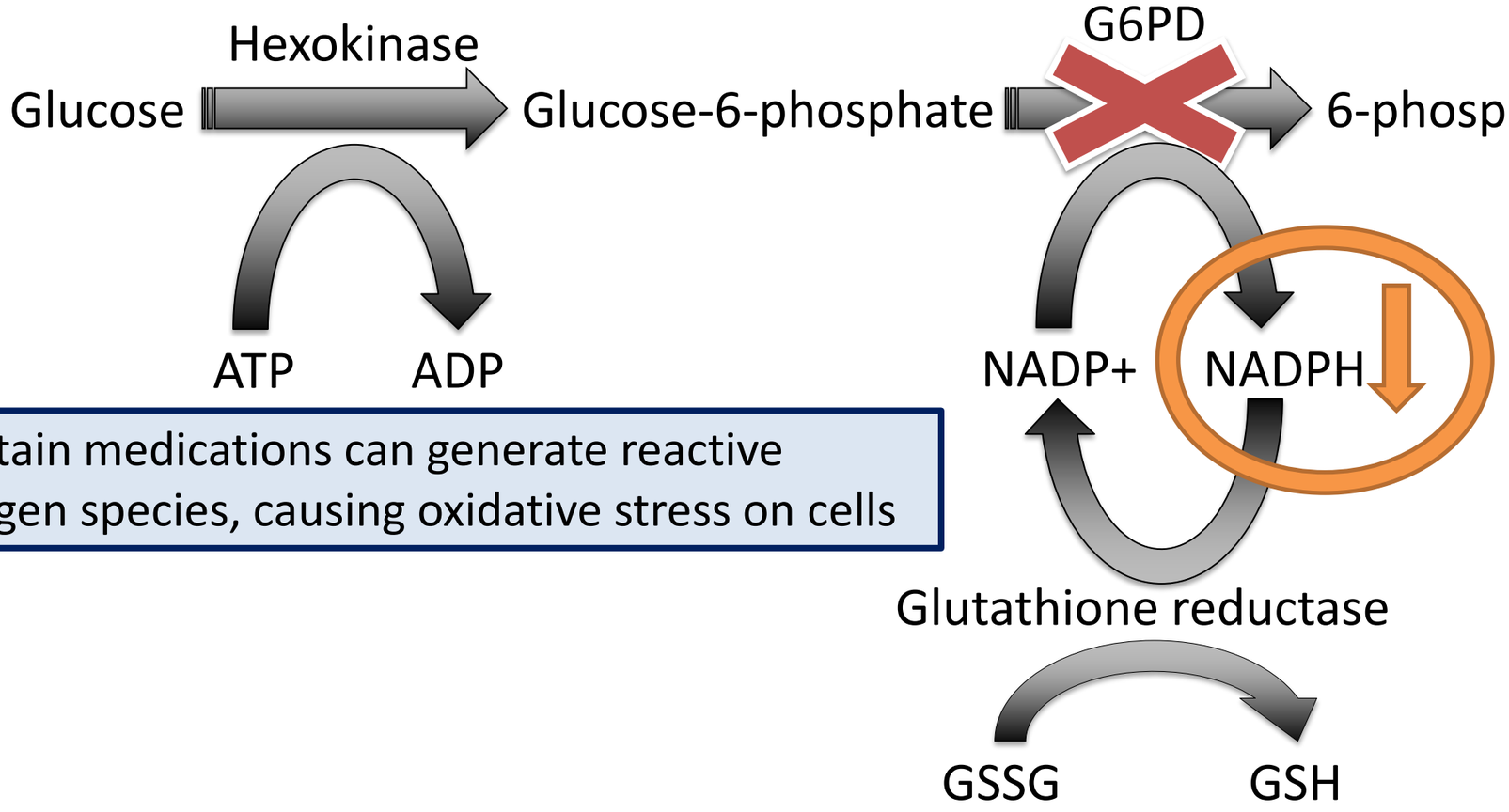
What happens G6PD deficiency?

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



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

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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:

Clinical/Laboratory Parameter	Potential Interference on G6PD Activity Value
Critical anemia (hemoglobin <7 g/dL)	↓
pRBC transfusion (<60 days)	↑
Reticulocytosis	↑
Leukocytosis (>100 x 10^3 cells/mm^3)	↑

pRBC: packed red blood cell

G6PD Alleles – WHO Classification

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

WHO classification of *G6PD* variants (prior to 2022)		
Class	**Median G6PD Activity**	**Risk of Hemolysis**
I	<10%	Chronic, untriggered
II	<12%	Triggered
III	10-60%	Triggered
IV	60-150%	No

G6PD Alleles – WHO Classification (2022)

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

WHO classification of *G6PD* variants (2022 classification)		
Class	**Median G6PD Activity**	**Risk of Hemolysis**
A	<20%	Chronic (CNSHA)
B	<45%	Acute, triggered
C	60–150%	No hemolysis
U	Any	Uncertain clinical significance

CNSHA: Chronic non-spherocytic hemolytic anemia

World Health Organization. Technical consultation to review the classification of G6PD. Accessed 08/2022.

Assigning G6PD phenotypes

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

G6PD Deficiency

- 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.

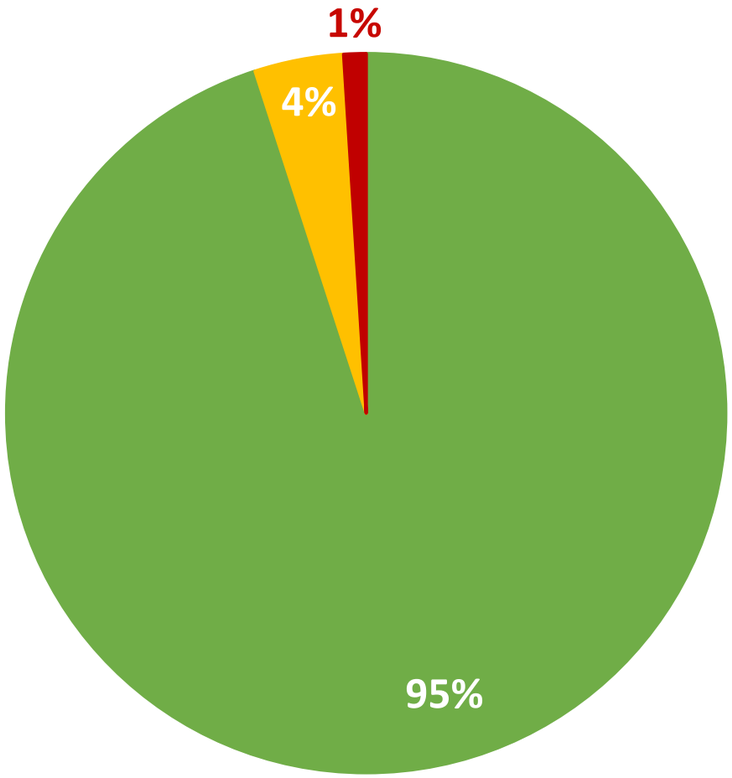
Variable G6PD Phenotype

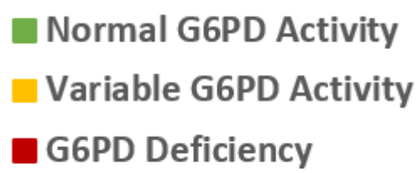
- Assigned to individuals with two X-chromosomes carrying one deficient allele and one non-deficient allele
- Example genotypes:
    - *A-/B, A-/A*

- 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

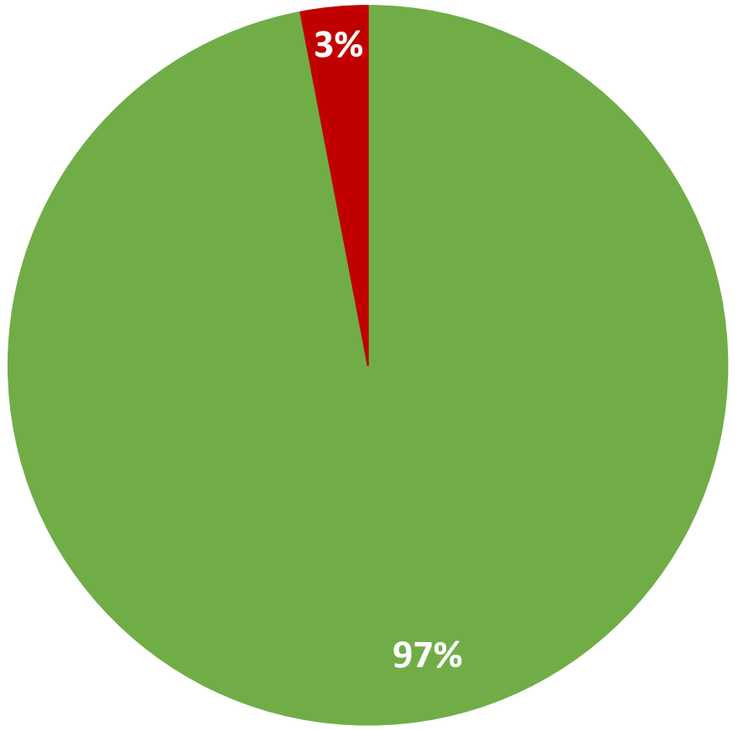
G6PD Phenotype Frequencies

Biological Females





Biological Males



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

G6PD Phenotype-based Recommendations

G6PD Therapeutic 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
Dapsone
Methylene blue
Pegloticase
Primaquine – standard dose (0.25-0.5 mg/kg daily for 14 days)
Rasburicase
Tafenoquine
Toluidine blue

Medications that should be used with CAUTION in patients with G6PD deficiency
Nitrofurantoin
Primaquine – medium dose (0.75 mg/kg or 45 mg once weekly for 8 weeks)

https://cpicpgx.org/guidelines/guideline-for-rasburicase-and-g6pd/ Accessed 08/29/2022

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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