Clinical Pharmacogenetics Implementation Consortium Guideline for Medication Use in the Context of *G6PD* Genotype

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Status:
Still in author review

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G6PD CPIC guideline highlights:

- Greater number of drugs (n=47) than other guidelines
  - Classify drugs as low-to-no risk, medium-risk, high-risk, or no recommendations
  - Broad but shallow evidence base
- Many alleles:
  - nomenclature
  - Legacy WHO system for allele functionality
- More commonly tested by phenotype than genotype in “clinic”
- Only actionable Pgx gene on X chromosome
  - “easy” to haplotype
  - Incidental findings

G6PD

- Evidence review: evidence showing a drug's association with hemolytic anemia in G6PD deficiency
  - high, moderate, weak, or no evidence
- For those drugs undergoing evidence review, assignment of drug to risk category
  - high-risk, medium-risk, low-to-no risk
- Assignment of Strength to prescribing recommendations
  - Strong, moderate, optional, vs no recommendation

Which drugs?

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Rasburicase Therapy in the Context of *G6PD* Deficiency Genotype

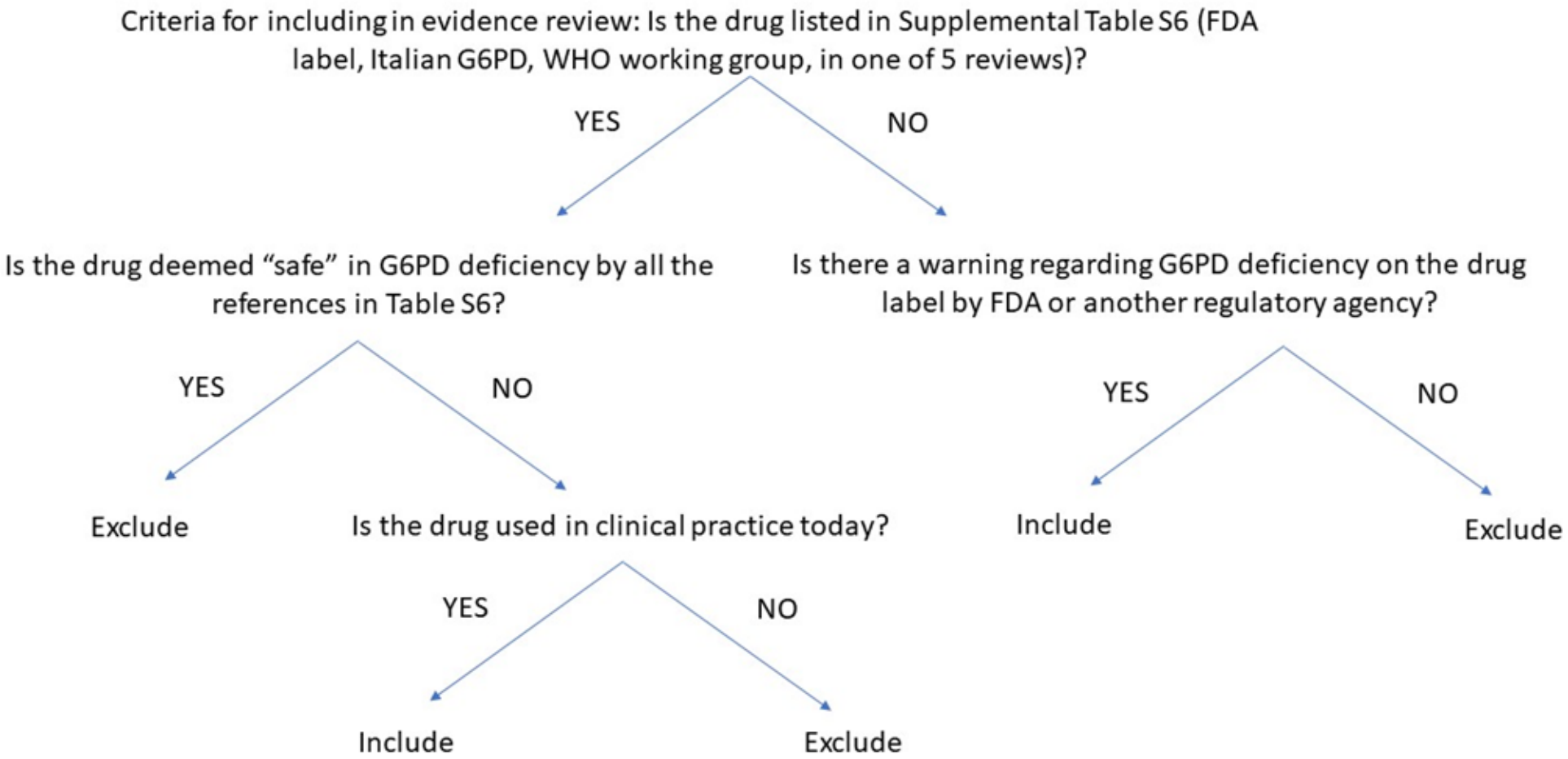
MV Relling[1], EM McDonagh[2], T Chang[3], KE Caudle[1], HL McLeod[4], CE Haidar[1], T Klein[2] and L Luzzatto[5]

> 80 drugs and chemicals

Supplemental Table S6. Drug and compound safety reviews for G6PD deficient patients

Drug/ compound	FDA Drug Label Information[a]	Italian G6PD Deficiency Association www.g6pd.org[b]	WHO Working Group, 1989 (10)	Beutler *et al*, 1994 (1)	Cappellini *et al*, 2008 (3)	Elyassi *et al*, 2008 (26)	(4)	Luzzatto & Poggi, Chapter 17: G6PD Deficiency (Nathan and Oski's Hematology of Infancy and Childhood) (14)
Acalypha indica extract					Possible association with hemolysis in G6PD deficient patients.			
Acetanilide (acetanilid)		Risk level: high, for Medit., Asian.		Should be avoided by G6PD deficient patients.	Definite association with hemolysis in G6PD deficient patients.	Unsafe for Class 1, 2, 3.		Definite risk of hemolysis
Acetylphenylhydrazine (2'-phenylacetohydrazide)		Risk level: high, for all.	Should be avoided by all G6PD deficient					
Acetylphenylhydrazine (2'-phenylacetohydrazide)		Risk level: high, for all.	Should be avoided by all G6PD deficient patients.					

Started with > 80 drugs & chemicals; included 47 in literature review; 32 classified as high, med, or low-to-no risk (15 drugs did not even have a single case report)



Drugs that underwent evidence review for AHA in setting of G6PD deficiency

4-aminosalicylic acid	glyburide	pegloticase	tafenoquine
aspirin	hydroxychloroquine	phenazopyridine	tolbutamide
Chloramphenicol	mafenide	primaquine	toluidine blue
Chloroquine	mepacrine	probenecid	tolazamide
chlorpropamide	mesalazine	Quinine	trametinib
Ciprofloxacin	methylene blue	rasburicase	vitamin C
dabrafenib	moxifloxacin	Sodium nitrite	vitamin K
dapsone	nalidixic acid	sulfacetamide	
dimercaprol	nicorandil	sulfadiazine	
doxorubicin	nitrofural	sulfadimidine	
furazolidone	nitrofurantoin	sulfamethoxazole	
gliclazide	norfloxacin	sulfanilamide	
glimepiride	ofloxacin	sulfasalazine	
glipizide		sulfisoxazole	

Sulfonylurea
Sulfa antimicrobial

From CPIC SOP

Score the evidence

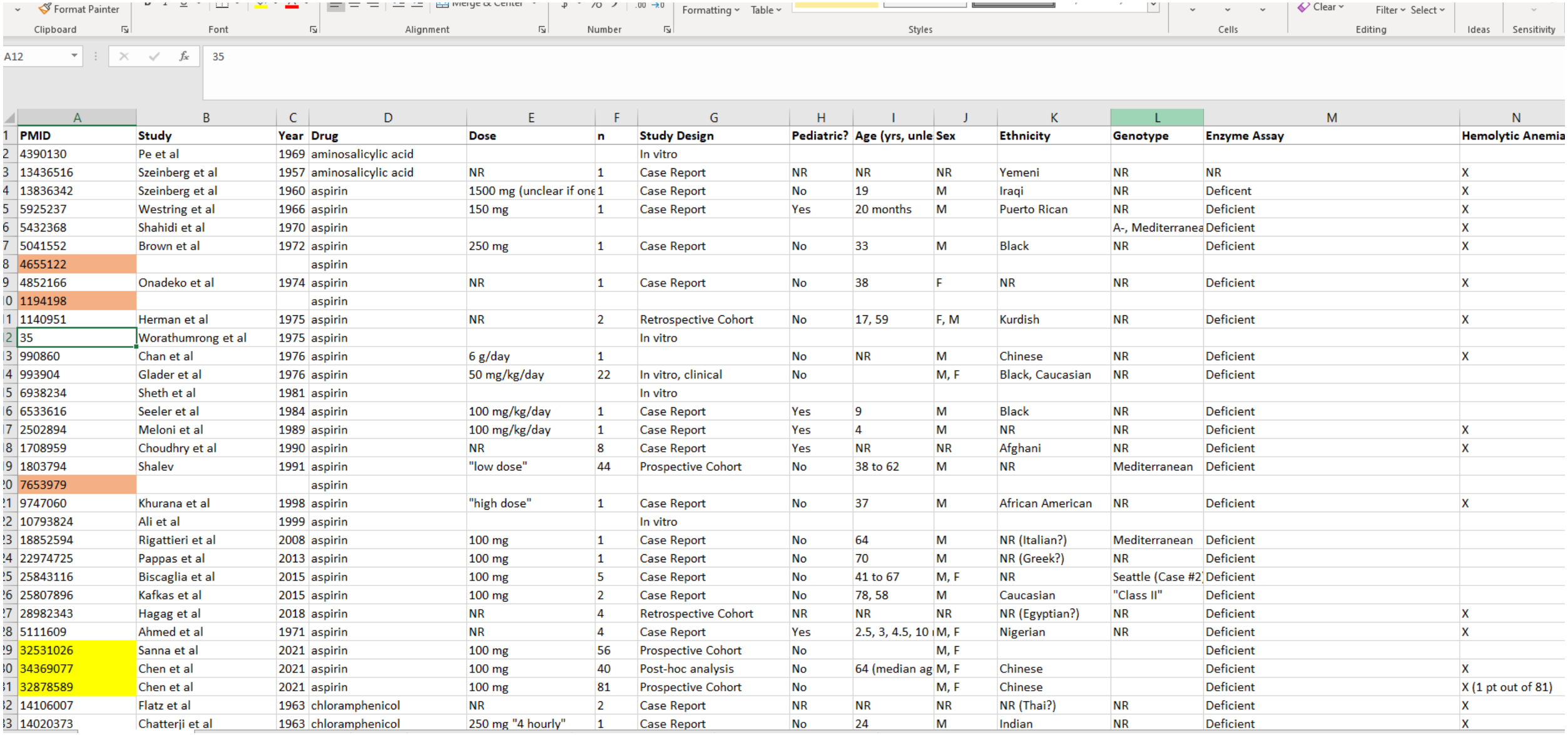
Initially, three or more authors will independently evaluate the literature. These authors will be responsible for presenting studies and recommending a level of evidence for each major finding to all guideline authors on a series of conference calls. All authors will be responsible for reviewing the evidence prior to a conference call and all authors will discuss and decide on the final score during these conference calls. Interim evidence tables will be circulated to the entire author group after each call; any disagreements with assignment of evidence will need to be sent in writing by 10 days after each summation. Re-addressing review of previous evidence summations on future calls will not take place unless circumstances are extraordinary, so all authors are required to review and declare their disagreements in real time.

Publications supporting a major finding should be grouped together and scored based on all the evidence that supports that major finding using the following criteria:

- High: Evidence includes consistent results from well-designed, well-conducted studies.
- Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.
- Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information

Valdes, R., Payne, D.A. & Linder, M.W. Laboratory analysis and application of pharmacogenetics to clinical practice. (Washington, DC, NACB, 2010).

Reviewed hundreds of papers for drug associations with AHA in G6PD deficiency



PMID	Study	Year	Drug	Dose	n	Study Design	Pediatric?	Age (yrs, unle	Sex	Ethnicity	Genotype	Enzyme Assay	Hemolytic Anemia
4390130	Pe et al	1969	aminosalicylic acid			In vitro							
13436516	Szeinberg et al	1957	aminosalicylic acid	NR	1	Case Report	NR	NR	NR	Yemeni	NR	NR	X
13836342	Szeinberg et al	1960	aspirin	1500 mg (unclear if one	1	Case Report	No	19	M	Iraqi	NR	Deficent	X
5925237	Westring et al	1966	aspirin	150 mg	1	Case Report	Yes	20 months	M	Puerto Rican	NR	Deficient	X
5432368	Shahidi et al	1970	aspirin								A-, Mediterranea	Deficient	X
5041552	Brown et al	1972	aspirin	250 mg	1	Case Report	No	33	M	Black	NR	Deficient	X
4655122			aspirin										
4852166	Onadeko et al	1974	aspirin	NR	1	Case Report	No	38	F	NR	NR	Deficient	X
1194198			aspirin										
1140951	Herman et al	1975	aspirin	NR	2	Retrospective Cohort	No	17, 59	F, M	Kurdish	NR	Deficient	X
35	Worathumrong et al	1975	aspirin			In vitro							
990860	Chan et al	1976	aspirin	6 g/day	1		No	NR	M	Chinese	NR	Deficient	X
993904	Glader et al	1976	aspirin	50 mg/kg/day	22	In vitro, clinical	No		M, F	Black, Caucasian	NR	Deficient	
6938234	Sheth et al	1981	aspirin			In vitro							
6533616	Seeler et al	1984	aspirin	100 mg/kg/day	1	Case Report	Yes	9	M	Black	NR	Deficient	
2502894	Meloni et al	1989	aspirin	100 mg/kg/day	1	Case Report	Yes	4	M	NR	NR	Deficient	X
1708959	Choudhry et al	1990	aspirin	NR	8	Case Report	Yes	NR	NR	Afghani	NR	Deficient	X
1803794	Shalev	1991	aspirin	"low dose"	44	Prospective Cohort	No	38 to 62	M	NR	Mediterranean	Deficient	
7653979			aspirin										
9747060	Khurana et al	1998	aspirin	"high dose"	1	Case Report	No	37	M	African American	NR	Deficient	X
10793824	Ali et al	1999	aspirin			In vitro							
18852594	Rigattieri et al	2008	aspirin	100 mg	1	Case Report	No	64	M	NR (Italian?)	Mediterranean	Deficient	
22974725	Pappas et al	2013	aspirin	100 mg	1	Case Report	No	70	M	NR (Greek?)	NR	Deficient	
25843116	Biscaglia et al	2015	aspirin	100 mg	5	Case Report	No	41 to 67	M, F	NR	Seattle (Case #2	Deficient	
25807896	Kafkas et al	2015	aspirin	100 mg	2	Case Report	No	78, 58	M	Caucasian	"Class II"	Deficient	
28982343	Hagag et al	2018	aspirin	NR	4	Retrospective Cohort	NR	NR	NR	NR (Egyptian?)	NR	Deficient	X
5111609	Ahmed et al	1971	aspirin	NR	4	Case Report	Yes	2.5, 3, 4.5, 10	M, F	Nigerian	NR	Deficient	X
32531026	Sanna et al	2021	aspirin	100 mg	56	Prospective Cohort	No		M, F			Deficient	
34369077	Chen et al	2021	aspirin	100 mg	40	Post-hoc analysis	No	64 (median ag	M, F	Chinese		Deficient	X
32878589	Chen et al	2021	aspirin	100 mg	81	Prospective Cohort	No		M, F	Chinese		Deficient	X (1 pt out of 81)
14106007	Flatz et al	1963	chloramphenicol	NR	2	Case Report	NR	NR	NR	NR (Thai?)	NR	Deficient	X
14020373	Chatterji et al	1963	chloramphenicol	250 mg "4 hourly"	1	Case Report	No	24	M	Indian	NR	Deficient	X

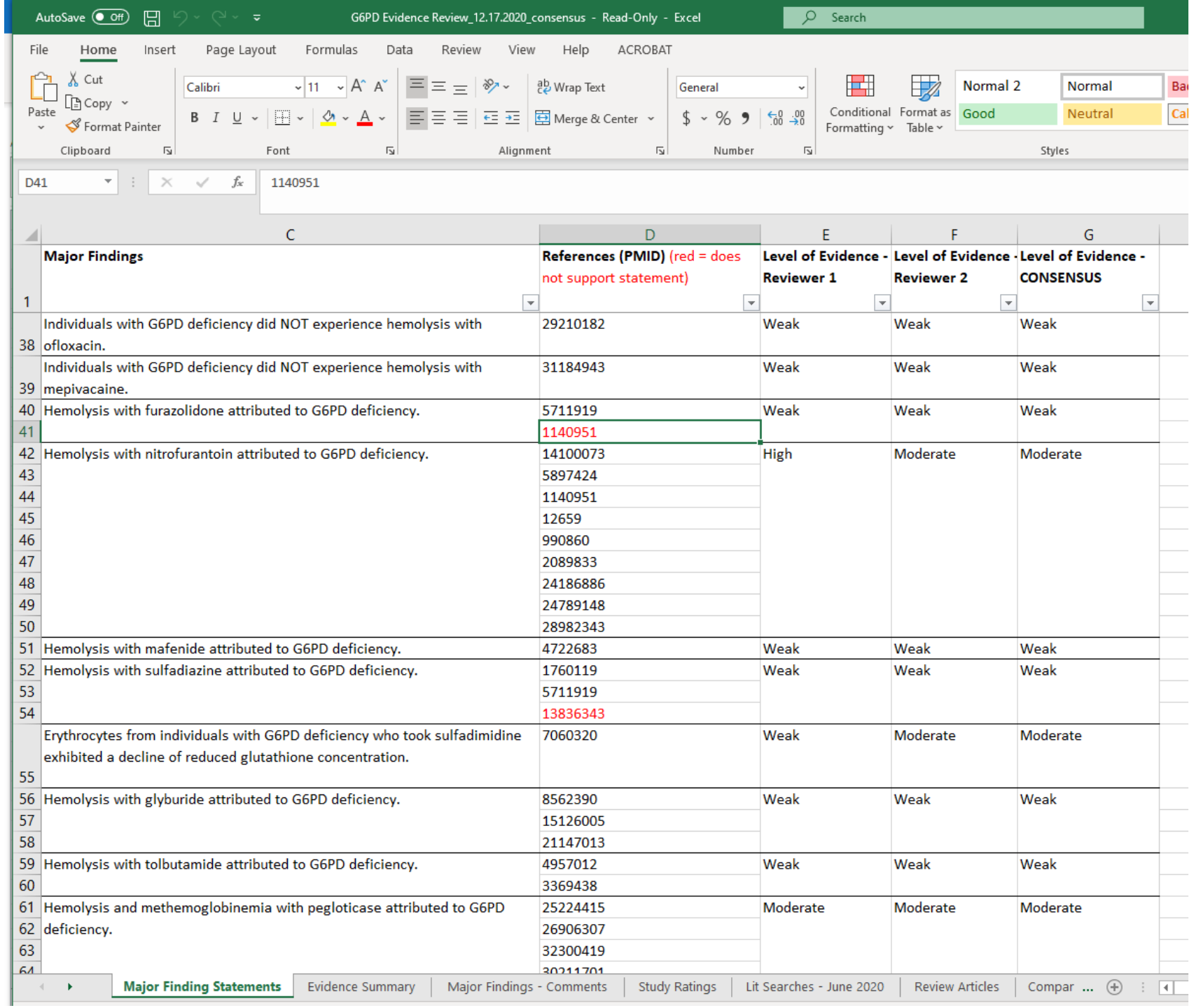
Assigning evidence level for association of drug with G6PD deficiency-associated hemolysis

High evidence	Moderate evidence	Weak evidence
• Good quality studies supporting G6PD involvement with control groups; OR • Case reports with strong biological mechanism (e.g., production of H_20_2), especially if drug rarely used; AND • No convincing contradictory data	• Medium quality studies supporting G6PD involvement with control group; OR • Case reports with plausible mechanism; AND • Little to no convincing contradictory data	• Case reports or *in vitro* evidence only, especially for commonly used drugs; OR • Studies that refute G6PD involvement with no convincing supportive studies; AND • No convincing mechanistic data

Assigning evidence level for lack of association of drug with G6PD deficiency-associated hemolysis

High evidence	Moderate evidence	Weak evidence
• Good quality studies supporting lack of G6PD involvement with control groups; AND • No convincing contradictory data	• Medium quality studies supporting lack of G6PD involvement with control group; AND • Little to no convincing contradictory data	• Weak/flawed studies supporting lack of G6PD involvement; OR • Case reports or in vitro evidence only, especially for commonly used drugs

Worksheet for evidence review for current guideline: evidence linking hemolysis with drug use in G6PD deficiency



G6PD Evidence Review_12.17.2020_consensus - Read-Only - Excel

D41: 1140951

	C	D	E	F	G
1	**Major Findings**	**References (PMID)** (red = does not support statement)	**Level of Evidence - Reviewer 1**	**Level of Evidence - Reviewer 2**	**Level of Evidence - CONSENSUS**
38	Individuals with G6PD deficiency did NOT experience hemolysis with ofloxacin.	29210182	Weak	Weak	Weak
39	Individuals with G6PD deficiency did NOT experience hemolysis with mepivacaine.	31184943	Weak	Weak	Weak
40	Hemolysis with furazolidone attributed to G6PD deficiency.	5711919	Weak	Weak	Weak
41		1140951			
42	Hemolysis with nitrofurantoin attributed to G6PD deficiency.	14100073	High	Moderate	Moderate
43		5897424			
44		1140951			
45		12659			
46		990860			
47		2089833			
48		24186886			
49		24789148			
50		28982343			
51	Hemolysis with mafenide attributed to G6PD deficiency.	4722683	Weak	Weak	Weak
52	Hemolysis with sulfadiazine attributed to G6PD deficiency.	1760119	Weak	Weak	Weak
53		5711919			
54		13836343			
55	Erythrocytes from individuals with G6PD deficiency who took sulfadimidine exhibited a decline of reduced glutathione concentration.	7060320	Weak	Moderate	Moderate
56	Hemolysis with glyburide attributed to G6PD deficiency.	8562390	Weak	Weak	Weak
57		15126005			
58		21147013			
59	Hemolysis with tolbutamide attributed to G6PD deficiency.	4957012	Weak	Weak	Weak
60		3369438			
61	Hemolysis and methemoglobinemia with pegloticase attributed to G6PD	25224415	Moderate	Moderate	Moderate
62	deficiency.	26906307			
63		32300419			
64		30211701			

Major Finding Statements | Evidence Summary | Major Findings - Comments | Study Ratings | Lit Searches - June 2020 | Review Articles | Compar ...

G6PD drugs have been placed into 3 main categories: high risk, medium risk, and low-to-no risk.

- There are separate prescribing tables for those 3 categories, plus separate table for primaquine (dose-dependent)
- Each drug reviewed has a section in either main MS or supplement
- All recommendations apply to children and adults
- We have assigned a strength of prescribing recommendation (strong, moderate, optional) to each drug for its use in G6PD deficiency
- For drugs with no relevant published articles linking that drug to an increased risk of AHA in the setting of G6PD deficiency, there is no recommendation (CPIC Level C)

Assigning risk level for drug-induced hemolysis associated with G6PD deficiency

HIGH RISK MEDICATIONS
Avoid in patients with G6PD deficiency

- High-level evidence + rarely used drug; OR
- Moderate-level evidence + rarely used drug with regulatory warnings for patients with G6PD deficiency; OR
- Moderate-level evidence + strong biological mechanism for risk in patients with G6PD deficiency

MEDIUM RISK MEDICATIONS
Use with caution in patients with G6PD deficiency

- Moderate-level evidence without a strong biological mechanism for risk in patients with G6PD deficiency; OR
- Weak evidence + rarely used drug; OR
- Weak evidence + strong regulatory warnings for patients with G6PD deficiency that may have hindered use in these patients; OR
- Weak evidence + strong biological mechanism for risk in patients with G6PD deficiency

LOW-TO-NO RISK MEDICATIONS
Use without regard to G6PD phenotype

- Weak evidence + commonly used drug; OR
- Weak evidence + mild or inconsistent regulatory warnings for patients with G6PD deficiency

Regulatory agency warnings

- Authors considered current warnings from the U.S. Food and Drug Administration (FDA); European Medicines Agency (EMA); Pharmaceuticals and Medical Devices Agency, Japan (PMDA), and Heath Canada (Santé Canada) (HCSC)
- Strong regulatory warnings were those that indicated that the drug was “contraindicated” or should be “avoided” in patients with G6PD deficiency; language that indicated drugs should be used with “caution” was not considered strong.
- Inconsistent regulatory warnings were considered to be those that were present for some but not all of these four agencies.
- Many such warnings predate the modern drug development era.

TABLE S3. SUMMARY OF SELECT REGULATORY AGENCY WARNINGS FOR MEDICATION USE IN PATIENTS WITH G6PD DEFICIENCY

	United States Food and Drug Administration (FDA)	European Medicines Agency (EMA)	Pharmaceuticals and Medical Devices Agency - Japan (PMDA)	Health Canada (Santé Canada) (HCSC)
4-aminosalicylic acid	n/a	n/a	n/a	n/a
aspirin	n/a	n/a	n/a	n/a
chloramphenicol	n/a	n/a	n/a	n/a
chloroquine	CAUTION	n/a	n/a	n/a
chlorpropamide	CAUTION	n/a	n/a	CAUTION
ciprofloxacin	n/a	n/a	n/a	n/a
dabrafenib	CAUTION	n/a	n/a	n/a
dapsone	AVOID	n/a	CAUTION	CAUTION
dimercaprol	n/a	n/a	n/a	n/a
doxorubicin	n/a	n/a	n/a	n/a
furazolidone	n/a	n/a	n/a	n/a
gliclazide	n/a	n/a	n/a	n/a
glimepiride	CAUTION	CAUTION	n/a	CAUTION
glipizide	CAUTION	n/a	n/a	n/a
glyburide	CAUTION	AVOID	n/a	CAUTION
hydroxychloroquine	CAUTION	n/a	n/a	n/a
mafenide	CAUTION	n/a	n/a	n/a
mepacrine	n/a	n/a	n/a	n/a
mesalazine	n/a	n/a	n/a	n/a
methylene blue	AVOID	AVOID	CAUTION	n/a
moxifloxacin	n/a	n/a	n/a	n/a
nalidixic acid	CAUTION	n/a	CAUTION	n/a
nicorandil	n/a	n/a	n/a	n/a
nitrofural	n/a	n/a	n/a	n/a
nitrofurantoin	CAUTION	n/a	n/a	CAUTION
norfloxacin	CAUTION	n/a	n/a	CAUTION
ofloxacin	n/a	n/a	n/a	n/a
pegloticase	AVOID	AVOID	n/a	n/a
phenazopyridine	n/a	n/a	n/a	n/a
primaquine	AVOID	n/a	n/a	CAUTION
probenecid	CAUTION	n/a	n/a	n/a
quinine	CAUTION	n/a	n/a	AVOID
rasburicase	AVOID	AVOID	AVOID	AVOID
sodium nitrite	AVOID	n/a	n/a	AVOID
sulfacetamide	n/a	n/a	n/a	n/a
sulfadiazine	CAUTION	n/a	CAUTION	CAUTION
sulfadimidine	n/a	n/a	n/a	n/a
sulfamethoxazole	CAUTION	n/a	AVOID	CAUTION
sulfanilamide	n/a	n/a	n/a	n/a
sulfasalazine	CAUTION	n/a	CAUTION	CAUTION
sulfisoxazole	CAUTION	n/a	n/a	AVOID
tafenoquine	AVOID	n/a	n/a	n/a
tolazamide	CAUTION	n/a	n/a	n/a
tolbutamide	CAUTION	n/a	n/a	CAUTION
toluidine blue	n/a	n/a	n/a	n/a
trametinib	CAUTION	n/a	n/a	n/a
vitamin C	CAUTION	n/a	CAUTION	CAUTION
vitamin K	n/a	n/a	n/a	n/a

- Lack of agreement among agencies
- All FDA “avoids” will be CPIC high-risk
- Some “avoids” by EMA, PMDA, and HCSC will be low-to-no risk by CPIC
- Many “cautions” by all agencies will be low-to-no risk or no recommendation by CPIC

TABLE S3. SUMMARY OF SELECT REGULATORY AGENCY WARNINGS FOR MEDICATION USE IN PATIENTS WITH G6PD DEFICIENCY

	United States Food and Drug Administration (FDA)	European Medicines Agency (EMA)	Pharmaceuticals and Medical Devices Agency - Japan (PMDA)	Health Canada (Santé Canada) (HCSC)
4-aminosalicylic acid	n/a	n/a	n/a	n/a
aspirin	n/a	n/a	n/a	n/a
chloramphenicol	n/a	n/a	n/a	n/a
chloroquine	CAUTION	n/a	n/a	n/a
chlorpropamide	CAUTION	n/a	n/a	CAUTION
ciprofloxacin	n/a	n/a	n/a	n/a
dabrafenib	CAUTION	n/a	n/a	n/a
dapsone	AVOID	n/a	CAUTION	CAUTION
dimercaprol	n/a	n/a	n/a	n/a
doxorubicin	n/a	n/a	n/a	n/a
furazolidone	n/a	n/a	n/a	n/a
gliclazide	n/a	n/a	n/a	n/a
glimepiride	CAUTION	CAUTION	n/a	CAUTION
glipizide	CAUTION	n/a	n/a	n/a
glyburide	CAUTION	AVOID	n/a	CAUTION
hydroxychloroquine	CAUTION	n/a	n/a	n/a
mafenide	CAUTION	n/a	n/a	n/a
mepacrine	n/a	n/a	n/a	n/a
mesalazine	n/a	n/a	n/a	n/a
methylene blue	AVOID	AVOID	CAUTION	n/a
moxifloxacin	n/a	n/a	n/a	n/a
nalidixic acid	CAUTION	n/a	CAUTION	n/a
nicorandil	n/a	n/a	n/a	n/a
nitrofural	n/a	n/a	n/a	n/a

TABLE S3. SUMMARY OF SELECT REGULATORY AGENCY WARNINGS FOR MEDICATION USE IN PATIENTS WITH G6PD DEFICIENCY

	United States Food and Drug Administration (FDA)	European Medicines Agency (EMA)	Pharmaceuticals and Medical Devices Agency - Japan (PMDA)	Health Canada (Santé Canada) (HCSC)
nitrofurantoin	CAUTION	n/a	n/a	CAUTION
norfloxacin	CAUTION	n/a	n/a	CAUTION
ofloxacin	n/a	n/a	n/a	n/a
pegloticase	AVOID	AVOID	n/a	n/a
phenazopyridine	n/a	n/a	n/a	n/a
primaquine	AVOID	n/a	n/a	CAUTION
probenecid	CAUTION	n/a	n/a	n/a
quinine	CAUTION	n/a	n/a	AVOID
rasburicase	AVOID	AVOID	AVOID	AVOID
sodium nitrite	AVOID	n/a	n/a	AVOID
sulfacetamide	n/a	n/a	n/a	n/a
sulfadiazine	CAUTION	n/a	CAUTION	CAUTION
sulfadimidine	n/a	n/a	n/a	n/a
sulfamethoxazole	CAUTION	n/a	AVOID	CAUTION
sulfanilamide	n/a	n/a	n/a	n/a
sulfasalazine	CAUTION	n/a	CAUTION	CAUTION
sulfisoxazole	CAUTION	n/a	n/a	AVOID
tafenoquine	AVOID	n/a	n/a	n/a
tolazamide	CAUTION	n/a	n/a	n/a
tolbutamide	CAUTION	n/a	n/a	CAUTION
toluidine blue	n/a	n/a	n/a	n/a
trametinib	CAUTION	n/a	n/a	n/a
vitamin C	CAUTION	n/a	CAUTION	CAUTION
vitamin K	n/a	n/a	n/a	n/a

Strength of recommendations

from the rating scale for evidence-based recommendations on the use of antiretroviral agents (http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf). Therapeutic recommendations are graded as:

Strong recommendation for the statement**:** "The evidence is high quality and the desirable effects clearly outweigh the undesirable effects."

Moderate recommendation for the statement: "There is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional recommendation for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.

No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time

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Clinical Pharmacogenetics Implementation Consortium

Table 2. Drug-specific risk level and associated strength of recommendation for patients with G6PD deficiency for 47 drugs

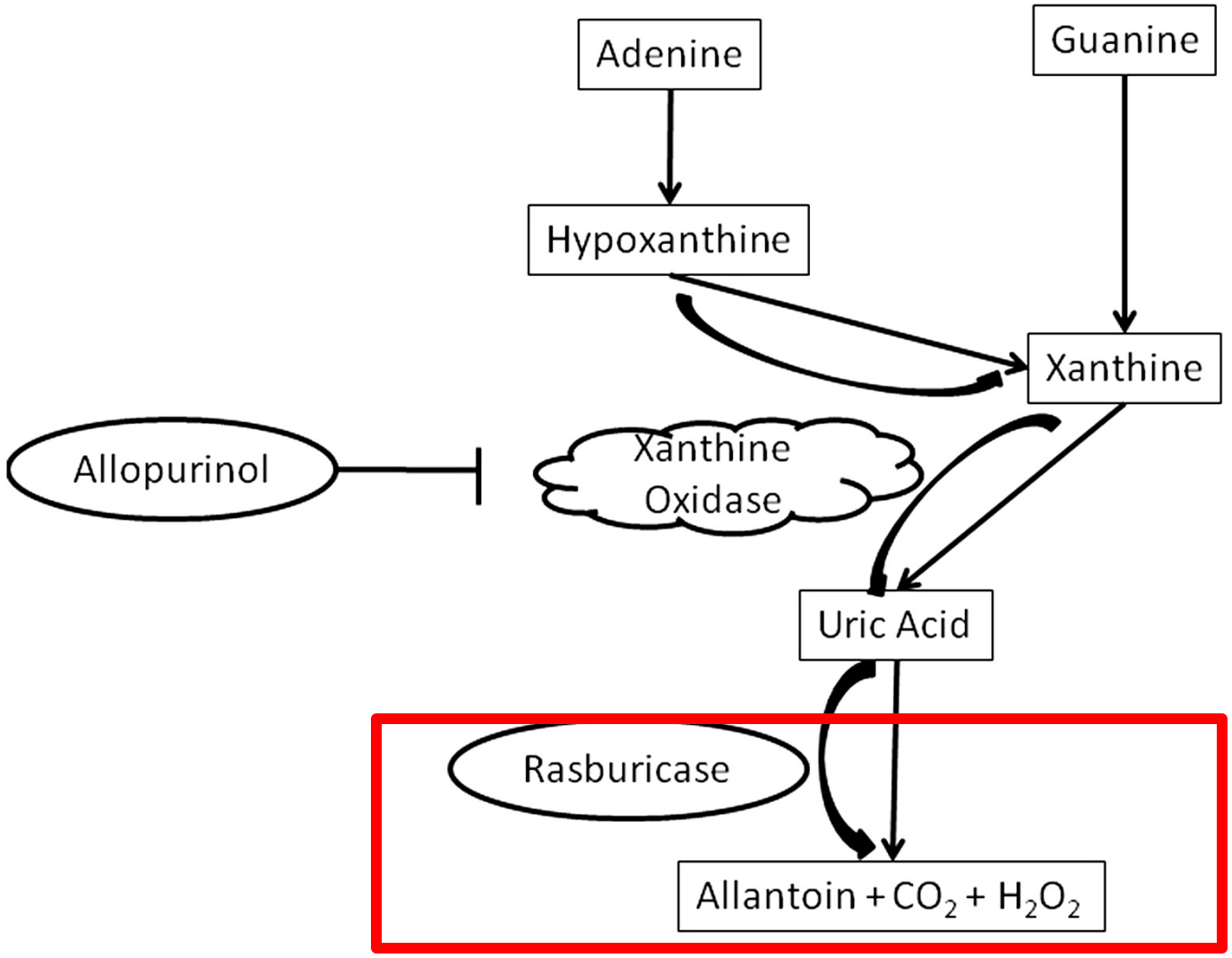
Drug	Risk	Classification of Recommendation
dapsone	High	Strong
methylene blue	High	Moderate
pegloticase	High	Strong
primaquine – standard dose	High	Strong
rasburicase	High	Strong
tafenoquine	High	Strong
toluidine blue	High	Moderate[a]
nitrofurantoin	Medium	Optional
primaquine – low dose (0.75 mg/kg or 45 mg once weekly for 8 weeks) for *Plasmodium vivax* malaria	Medium	Strong
4-aminosalicylic acid	Low-to-no	Optional
aspirin ≤ 1 g/day	Low-to-no	Moderate
chloramphenicol	Low-to-no	Moderate
chloroquine	Low-to-no	Moderate
ciprofloxacin	Low-to-no	Optional
dimercaprol	Low-to-no	Optional
doxorubicin	Low-to-no	Optional
furazolidone	Low-to-no	Optional
glyburide	Low-to-no	Optional
hydroxychloroquine	Low-to-no	Moderate
mafenide	Low-to-no	Optional
nalidixic acid	Low-to-no	Optional
norfloxacin	Low-to-no	Optional
ofloxacin	Low-to-no	Optional
phenazopyridine	Low-to-no	Optional
primaquine – single low dose (0.25 mg/kg) for *Plasmodium falciparum* malaria	Low-to-no	Strong
quinine	Low-to-no	Optional
sulfadiazine	Low-to-no	Optional
sulfadimidine	Low-to-no	Optional
sulfamethoxazole/trimethoprim	Low-to-no	Optional
sulfanilamide	Low-to-no	Optional
sulfasalazine	Low-to-no	Optional
sulfisoxazole	Low-to-no	Optional
tolbutamide	Low-to-no	Optional
vitamin C	Low-to-no	Moderate
vitamin K	Low-to-no	Moderate
aspirin > 1 g/day	n/a	No recommendation
chlorpropamide	n/a	No recommendation
dabrafenib	n/a	No recommendation
gliclazide	n/a	No recommendation
glimepiride	n/a	No recommendation
glipizide	n/a	No recommendation
mepacrine	n/a	No recommendation
mesalazine	n/a	No recommendation
moxifloxacin	n/a	No recommendation
nicorandil	n/a	No recommendation
nitrofural	n/a	No recommendation
probenecid	n/a	No recommendation
sodium nitrite	n/a	No recommendation
sulfacetamide	n/a	No recommendation
tolazamide	n/a	No recommendation
trametinib	n/a	No recommendation

examples

Assigning risk level for rasburicase/pegloticase--Strong

HIGH RISK MEDICATIONS *Avoid in patients with G6PD deficiency*	MEDIUM RISK MEDICATIONS *Use with caution in patients with G6PD deficiency*	LOW-TO-NO RISK MEDICATIONS *Use without regard to G6PD phenotype*
• High-level evidence + rarely used drug; OR • Moderate-level evidence + rarely used drug with regulatory warnings for patients with G6PD deficiency; OR • Moderate-level evidence + strong biological mechanism for risk in patients with G6PD deficiency	• Moderate-level evidence without a strong biological mechanism for risk in patients with G6PD deficiency; OR • Weak evidence + rarely used drug; OR • Weak evidence + strong regulatory warnings for patients with G6PD deficiency that may have hindered use in these patients; OR • Weak evidence + strong biological mechanism for risk in patients with G6PD deficiency	• Weak evidence + commonly used drug; OR • Weak evidence + mild or inconsistent regulatory warnings for patients with G6PD deficiency

Rasburicase (and it pegylated formulation, pegloticase) lowers uric acid by forming allantoin and hydrogen peroxide



Assigning risk level for sulfamethoxazole--optional

HIGH RISK MEDICATIONS
Avoid in patients with G6PD deficiency

- High-level evidence + rarely used drug; OR
- Moderate-level evidence + rarely used drug with regulatory warnings for patients with G6PD deficiency; OR
- Moderate-level evidence + strong biological mechanism for risk in patients with G6PD deficiency

MEDIUM RISK MEDICATIONS
Use with caution in patients with G6PD deficiency

- Moderate-level evidence without a strong biological mechanism for risk in patients with G6PD deficiency; OR
- Weak evidence + rarely used drug; OR
- Weak evidence + strong regulatory warnings for patients with G6PD deficiency that may have hindered use in these patients; OR
- Weak evidence + strong biological mechanism for risk in patients with G6PD deficiency

LOW-TO-NO RISK MEDICATIONS
Use without regard to G6PD phenotype

- Weak evidence + commonly used drug; OR
- Weak evidence + mild or inconsistent regulatory warnings for patients with G6PD deficiency

Sulfamethoxazole: weak evidence (case reports), plus conflicting evidence (some negative studies with controls), plus inconsistent regulatory warnings

	A	B	C	D	E	G	H	I	J	K	L	M	N	O	P	Q
1	Drug	Type of Expe	Major Findings	References (PM	Level of Evi	Risk	Strength o	FDA Labeling	EMA Labe	Japan Label	Canada Lab	Swiss Labe	WHO -1989	WHO - 20	Usage info	
179	Sulfamethoxazole	Clinical	Hemolysis with sulfamethoxazole attributed to G6PD deficiency.	5061461	Weak	Low-to-no	Optional	Caution - In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related (see CLINICAL PHARMACOLOGY and DOSAGE AND	n/a	Caution	Caution	Caution	n/a	Definite F	Int Pham; WHO essent; Top 300 (clincalc)	
180				4116253												
181				4818663												
182				990860												
183				2498187												
184				10157546												
185				18349424												
186				20065266												
187				20732351												
188				25713697												
189				28982343												
190				46571												
191				3495027												
192				16388034												
193				32648956												

Sulfamethoxazole evidence review

- Case reports of AHA with no controls: 4116253 Owusu et al 1972; 2498187 Calabro et al 1989; 20065266 Chisholm-Burns et al 2010; 25713697 Perdigones et al 2014; 5061461 Allen et al 1972
- Single pt SAFETY reports (TMP/SMZ without AHA): 32648956 Lu et al 2020; 10157546 Reinke et al 1995; 16388034 Hui et al 2006
- Strongest study: 28982343 Hagag et al 2018:
  - 1000 pts with G6PD deficiency and anemia, 4 of whom had received TMP/SMZ (included no controls of TMP/SMZ without G6PD deficiency)

REVIEWS OF INFECTIOUS DISEASES • VOL. 9, SUPPLEMENT 2 • MARCH-APRIL 1987

Use of Trimethoprim-Sulfamethoxazole in a Glucose-6-Phosphate Dehydrogenase–Deficient Population

Norman Markowitz and Louis D. Saravolatz

From the University of Michigan Medical School and the Division of Infectious Diseases and Hospital Epidemiology, Henry Ford Hospital, Detroit, Michigan

Double blind randomized trial of TMP/SMZ 320/1600 mg IV q12h vs vanco 1 g IV q 12 h
Half of pts were G6PD deficient

Results: no TMP/SMX pt developed AHA; only 1 vanco pt developed AHA; no differences in Hb

Table 1. Demographic characteristics and hematologic parameters of patients receiving trimethoprim-sulfamethoxazole (TMP-SMZ) or vancomycin.

Group*	Mean age (years)	No. of patients		Mean G-6-PD level (U/g of Hgb)	Mean Hgb level before therapy (g/dl)	Mean Hgb level after therapy (g/dl)	Mean duration of therapy (days)
		Male/female	Black/white				
A (TMP-SMZ ↓)	30.4	11/9	19/1	6.8	11.2	10.9	15.6
B (vancomycin ↓)	33.3	14/11	24/1	6.7	11.7	11.5	15.9
C (TMP-SMZ ↑)	32.9	9/15	22/2	17.1	11.7	11.6	13.6
D (vancomycin ↑)	30.1	15/16	29/2	17.3	11.7	11.8	20.7

NOTE. G-6-PD = glucose-6-phosphate dehydrogenase; Hgb = hemoglobin.

* A G-6-PD level of <11.9 U/g of Hgb is indicated by a downward arrow, and a G-6-PD level of ≥11.9 U/g of Hgb is indicated by an upward arrow.

Table 3. Demographic characteristics and hematologic parameters of patients with severe glucose-6-phosphate dehydrogenase deficiency (<4.5 U/g of hemoglobin [Hgb]) treated with trimethoprim-sulfamethoxazole (TMP-SMZ) or vancomycin.

Group	No. of patients		Mean Hgb level before therapy (g/dl)	Mean Hgb level after therapy (g/dl)	Mean duration of therapy (days)
	Male/female	Black/white			
A (TMP-SMZ)	5/2	7/0	11.1	10.8	17.0
B (vancomycin)	8/2	10/0	12.3	11.7	11.8

Assigning risk level for Nitrofurantoin--optional

HIGH RISK MEDICATIONS
Avoid in patients with G6PD deficiency

- High-level evidence + rarely used drug; OR
- Moderate-level evidence + rarely used drug with regulatory warnings for patients with G6PD deficiency; OR
- Moderate-level evidence + strong biological mechanism for risk in patients with G6PD deficiency

MEDIUM RISK MEDICATIONS
Use with caution in patients with G6PD deficiency

- Moderate-level evidence without a strong biological mechanism for risk in patients with G6PD deficiency; OR
- Weak evidence + rarely used drug; OR
- Weak evidence + strong regulatory warnings for patients with G6PD deficiency that may have hindered use in these patients; OR
- Weak evidence + strong biological mechanism for risk in patients with G6PD deficiency

LOW-TO-NO RISK MEDICATIONS
Use without regard to G6PD phenotype

- Weak evidence + commonly used drug; OR
- Weak evidence + mild or inconsistent regulatory warnings for patients with G6PD deficiency

Nitrofurantoin: moderate evidence (case reports plus one study with controls and one supportive *ex vivo* study of RBCs)—optional because evidence is barely moderate and drug is extremely widely used

1	Drug	Type of Expe	Major Findings	References (PM	Level of Evi	Risk	Strength o	FDA Labeling	EMA Labe	Japan Label	Canada Lab	Swiss Labe	WHO -1989	WHO - 20	Usage info
49	Nitrofurantoin	Clinical	Hemolysis with nitrofurantoin attributed to G6PD deficiency.	14100073	Moderate	Medium	Optional	Caution - Cases o			Caution	Caution (breastfeeding)	Avoid	Definite F	common; WHO essential list
50				5897424											
51				1140951											
52				12659											
53				990860											
54				2089833											
55				24186886											
56				24789148											
57				28982343											

REVIEW ARTICLE

Drug Saf 2010; 33
0114-5916/10/0009-07

Medications and Glucose-6-Phosphate Dehydrogenase Deficiency

An Evidence-Based Review

Ilan Youngster,[1] *Lidia Arcavi,*[2] *Renata Schechmaster,*[2] *Yulia Akayzen,*[3] *Hen Popliski,*[3] *Janna Shimonov,*[3] *Svetlana Beig*[3] and *Matitiahu Berkovitch*[1]

Table II. Commonly used drugs that should be avoided in patients with glucose-6-phosphate dehydrogenase d

	CPIC group
Dapsone	High
Methylthioninium chloride (methylene blue)	High
Nitrofurantoin	Medium
Phenazopyridine	Low to no
Primaquine	High (dose-dep)
Rasburicase	High
Tolonium chloride (toluidine blue)	High

(plus tafenoquine = CPIC high)

Table III. Drugs that were considered unsafe by at least one source, but according to our review can probably be given safely in normal therapeutic doses to glucose-6-phosphate dehydrogenase-deficient patients

Paracetamol (acetaminophen)
Aspirin (acetylsalicylic acid)
Aminophenazone
Antipyrine
Ascorbic acid (vitamin C)
Chloramphenicol
Chloroquine
Ciprofloxacin
Dipyrone (metamizole)
Succimer (dimercaptosuccinic acid)
Furazolidone
Glibenclamide (glyburide)
Isoniazid
Isosorbide dinitrate
Norfloxacin
Nalidixic acid
Mepacrine
Quinine
Sulfacetamide
Sulfanilamide
Sulfasalazine
Sulfisoxazole
Thiazosulfone
Cotrimoxazole (trimethoprim/sulfamethoxazole)

Genes-Drugs

CPIC assigns CPIC levels to genes/drugs with (1) PharmGKB Clinical Annotation Levels of Evidence of 1A, 1B, 2A and 2B, or (2) a PharmGKB PGx level for FDA-approved drug labels of "actionable pgx", "genetic testing recommended", or "genetic testing required", or (3) based on nomination to CPIC for consideration.

The levels (A, B, C, and D) assigned are subject to change; only those gene/drug pairs that have been the subject of guidelines have had sufficient in-depth review of evidence to provide definitive CPIC level assignments.

Need to update gene/drug pair page

49	G6PD	rasburicase	Guideline	A	1A	Testing required	24:78:749
58	G6PD	tafenoquine		A		Testing required	
82	G6PD	chloramphenicol		B	3		
83	G6PD	chlorpropamide		B		Actionable PGx	
84	G6PD	ciprofloxacin		B	4		
87	G6PD	dapsone		B	1B	Actionable PGx	
91	G6PD	dimercaprol		B	3		
96	G6PD	erythromycin		B			
98	G6PD	glibenclamide		B	3	Actionable PGx	
99	G6PD	glimepiride		B		Actionable PGx	
100	G6PD	glipizide		B		Actionable PGx	
101	G6PD	hydroxychloroquine		B		Actionable PGx	
105	G6PD	levofloxacin		B			
106	G6PD	mafenide		B		Actionable PGx	
107	G6PD	mefloquine		B	3		
108	G6PD	mesalazine		B			
110	G6PD	methylene blue		B	3	Actionable PGx	
112	G6PD	moxifloxacin		B			
114	G6PD	nalidixic acid		B		Actionable PGx	
116	G6PD	nitrofurantoin		B	3	Actionable PGx	
117	G6PD	norfloxacin		B		Actionable PGx	
120	G6PD	peglotícase		B	3	Testing required	
121	G6PD	phenazopyridine		B	3		
125	G6PD	primaquine		B	3	Testing required	

116	G6PD	nitrofurantoin	B	3	Actionable PGx
117	G6PD	norfloxacin	B		Actionable PGx
120	G6PD	peglotícase	B	3	Testing required
121	G6PD	phenazopyridine	B	3	
125	G6PD	primaquine	B	3	Testing required
126	G6PD	probenecid	B		Actionable PGx
129	G6PD	quinine	B		Actionable PGx
135	G6PD	sodium nitrite	B		Actionable PGx
136	G6PD	sulfacetamide	B		
137	G6PD	sulfasalazine	B		Actionable PGx
138	G6PD	sulfamethoxazole / trimethoprim	B	3	Actionable PGx
139	G6PD	sulfasalazine	B	4	Actionable PGx
140	G6PD	sulfisoxazole	B		
156	G6PD	dabrafenib	B/C		Actionable PGx
161	G6PD	lidocaine	B/C		
170	G6PD	chloroquine	C	3	Actionable PGx
245	G6PD	vitamin c	C		

G6PD guideline prescribing recommendations

Tables in main manuscript are generic for high, med, low risk drug (+ primaquine) but all alert language is drug-specific

Table 1. Assignment of predicted G6PD phenotype based on genotype

Predicted phenotype	**Genotype[a]**	**Examples of *G6PD* genotypes[b]**
Normal	A person with one X chromosome carrying a non-deficient (class IV) allele	B, Sao Boria, IV
	A person carrying two non-deficient (class IV) alleles	B/B, B/Sao Boria, IV/IV
Deficient	A person with one X chromosome carrying a deficient (class II-III) allele	A-, Orissa, Kalyan-Kerala, Mediterranean, Canton, Chatham, II, III
	A person carying two deficient (class II-III) alleles	A-/A-, A-/Orissa, Orissa/ Kalyan-Kerala, Mediterranean/ Mediterranean, Chatham /Mediterranean, Canton/ Viangchan, II/II, II/III, III/III
Deficient with CNSHA	A person with one X chromosome carrying a deficient (class I) allele	Bangkok, Villeurbanne, I
	A person carrying two deficient (class I) alleles	Bangkok/Bangkok, Bangkok/Villeurbanne, I/I
Variable[c]	A person carrying one non-deficient (class IV) allele and one deficient (class I-III) allele	B /Bangkok, B/Mediterranean, B/A-, IV/I, IV/II, IV/III

CNSHA, chronic non-spherocytic hemolytic anemia; G6PD, glucose-6-phosphate dehydrogenase; WHO, World Health Organization

[a]WHO classifications from (8), other details from (13). Class I alleles are extremely rare; the distinction between class II and III alleles is not clear. Almost all patients will carry class II, III, or IV alleles.

[b]Due to the large number of *G6PD* alleles, many other genotypes may be possible besides those given as examples here; see the **G6PD Allele Definition Table** (5, 6) for a more comprehensive list of alleles and **G6PD Allele Functionality Table** (5, 6) for their assigned function (WHO

Meeting report of the technical consultation to review the classification of glucose-6-phosphate dehydrogenase (G6PD)

25 & 27 January 2022, virtual meeting

18 March 2022 | Meeting report

Download (603.6 kB)

Overview

WHO convened a panel of temporary advisors in January 2022 to review the current classification of glucose-6-phosphate dehydrogenase (G6PD) and recommend changes where needed. Individuals affected by G6PD deficiency can develop acute haemolytic anaemia after exposure to 8-aminoquinolines tafenoquine and primaquine, the only available medicines that are effective against the hypnozoite stage of *Plasmodium vivax*. The deliberations of the meeting were informed by a literature review commissioned by WHO to examine G6PD activity for variants currently classified in Classes II and III, and by the presentation of an interim analysis of an individual patient meta-analysis of G6PD activity among genetic variants.

WHO TEAM

Global Malaria Programme, Malaria Policy Advisory Group

NUMBER OF PAGES

20

REFERENCE NUMBERS

WHO REFERENCE NUMBER: WHO/UCN/GMP/MPAG/2022.01

G6PD classification	Level of residual enzyme activity (% of normal)
Class I (Severe enzyme deficiency with CNSHA)	<10% with CNSHA
Class II (Severe)	<10%
Class III (Moderate to mild)	10–60%
Class IV (Very mild or no enzyme deficiency)	60–150%
Class V (Increased enzyme activity)	more than twice normal

Revised classification

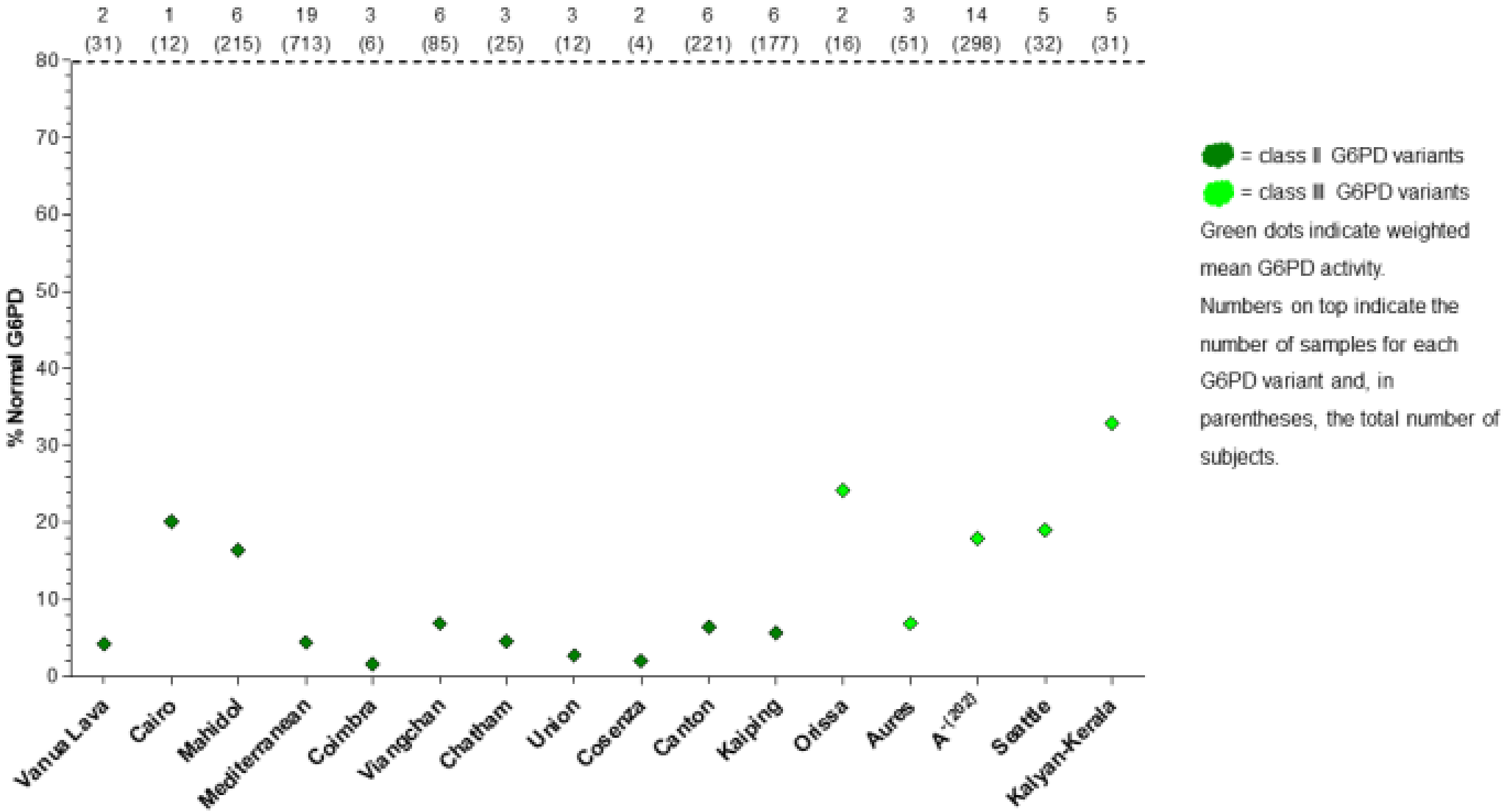
In future, G6PD variants should be classified based on the median residual enzyme activity in male hemizygous individuals for each variant expressed as percentage of normal activity as follows:

WHO classification of G6PD variants in homozygous and hemizygous individuals		
Class	**Median of G6PD Activity**	**Haemolysis**
A	<20%	Chronic (CNSHA)
B	<45%	Acute, triggered
C	60–150%	No haemolysis
U	Any	Uncertain clinical significance

It should be made clear in all publications that this system is strictly for classifying genetic variants of G6PD and applies primarily to hemi/homozygous individuals carrying a particular mutation. It should not be used to classify individual patients.

https://www.who.int/publications/m/item/WHO-UCN-GMP-MPAG-2022.01

Fig. 1. Weighted mean G6PD activity for variants identified in Nannelli et al. *(9)*



https://www.who.int/publications/m/item/WHO-UCN-GMP-MPAG-2022.01

AutoSave Off | G6PD_allele_definition_table - Read-Only - Excel | Search | Relling, Mary

File Home Insert Page Layout Formulas Data Review View Help ACROBAT | Share | Comments

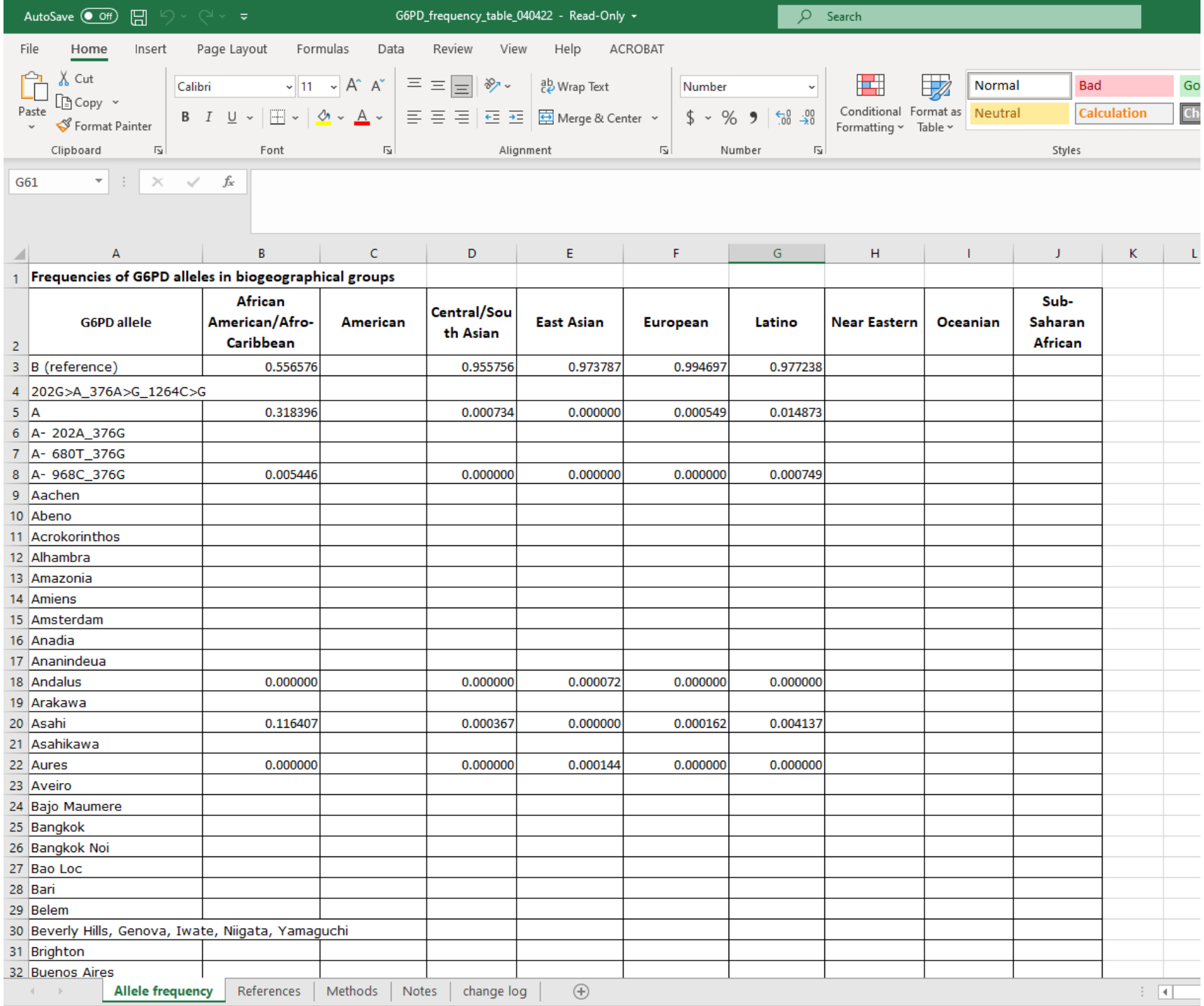
Paste | Cut | Copy | Format Painter | Clipboard | Verdana | 10 | Font | Wrap Text | Merge & Center | Alignment | General | Number | Conditional Formatting | Format as Table | Normal | Bad | Good | Neutral | Calculation | Check Cell | Styles | Insert | Delete | Format | Cells | AutoSum | Fill | Clear | Sort & Filter | Find & Select | Editing | Analyze Data | Analysis | Sensitivity | Sensitivity

Neutral

G20

	A	B	C	D	E	F	G	H	I	J	K
1	GENE:G6PD										
2	NM_001042351.2	c.25C>T	c.34G>T	c.40G>A	c.95A>G	c.99A>G	c.103_105delATC	c.110T>C	c.130G>A	c.131C>G	c.143T>C
3	Effect on protein (c)	p.R9W	p.V12L	p.G14R	p.H32R	p.I33M	p.I35del	p.M37T	p.A44T	p.A44G	p.I48T
4	Position at NC_000023.11 (Homo sapiens chromosome X, GRCh38.p2)	g.154546131G>A	g.154546122C>A	g.154546116C>T	g.154546061T>C	g.154546057T>C	g.154546051_154546053delGAT	g.154546046A>G	g.154536169C>T	g.154536168G>C	g.154536156A>G
5	Position at NG_009015.2 (G6PD RefSeqGene; reverse relative to chromosome)	g.6442C>T	g.6451G>T	g.6457G>A	g.6512A>G	g.6516A>G	g.6520_6522delATC	g.6527T>C	g.16404G>A	g.16405C>G	g.16417T>C
6	rsID				rs137852340		rs137852338			rs78478128	rs76645461
7	G6PD variant										
8	B (wildtype)	G	C	C	T	T	GAT	A	C	G	A
9	202G>A_376A>G_1264C>G										
10	A										
11	A- 202A_376G										
12	A- 680T_376G										
13	A- 968C_376G										
14	Aachen										
15	Abeno										
16	Acrokorinthos										
17	Alhambra										
18	Amazonia										
19	Amiens										
20	Amsterdam										
21	Anadia										
22	Ananindeua										
23	Andalus										
24	Arakawa										
25	Asahi										
26	Asahikawa										
27	Aures										G
28	Aveiro										
29	Bajo Maumere										
30	Bangkok										
31	Bangkok Noi										
32	Bao Loc										
33	Bari										
34	Belem										
35	Beverly Hills, Genova, Iwate, Niigata, Yamaguchi										
36	Brighton										
37	Buenos Aires										
38	Cairo										

Alleles | Notes | Change log



Frequencies of G6PD alleles in biogeographical groups

G6PD allele	African American/Afro-Caribbean	American	Central/South Asian	East Asian	European	Latino	Near Eastern	Oceanian	Sub-Saharan African
B (reference)	0.556576		0.955756	0.973787	0.994697	0.977238			
202G>A_376A>G_1264C>G									
A	0.318396		0.000734	0.000000	0.000549	0.014873			
A- 202A_376G									
A- 680T_376G									
A- 968C_376G	0.005446		0.000000	0.000000	0.000000	0.000749			
Aachen									
Abeno									
Acrokorinthos									
Alhambra									
Amazonia									
Amiens									
Amsterdam									
Anadia									
Ananindeua									
Andalus	0.000000		0.000000	0.000072	0.000000	0.000000			
Arakawa									
Asahi	0.116407		0.000367	0.000000	0.000162	0.004137			
Asahikawa									
Aures	0.000000		0.000000	0.000144	0.000000	0.000000			
Aveiro									
Bajo Maumere									
Bangkok									
Bangkok Noi									
Bao Loc									
Bari									
Belem									
Beverly Hills, Genova, Iwate, Niigata, Yamaguchi									
Brighton									
Buenos Aires									

16 G6PD Class I-III variants were observed in American children with ALL (n= 2489 non-whites, 3836 whites) with G6PD sequencing
All but one (D282H) are included on PharmacoScan

AAChange.refGene	WHO_class	final.cat	PharmacoScan	males, white	females (hom), non-white	females (het), non-white	males, non-white	females (hom), non-white	females (het), non-white	non-white	white
p.R454C	II	classI-III	Union,Maewo, Chinese-2, Kalo	2	0	3	0	0	0	0.002009	0
p.V291M	II	classI-III	Viangchan, Jammu	2	0	1	0	0	0	0.001205	0
p.H155D	II	classI-III	Acrokorinthos	0	0	1	0	0	0	0.000402	0
p.R136C	II	classI-III	Valladolid	0	0	1	0	0	0	0.000402	0
p.R439P	II	classI-III	Pawnee	0	0	0	0	0	1	0	0.000261
p.S188F	II	classI-III	Mediterranean, Dallas, Panama, Sassari, Cagliari, Birmingham	0	0	0	1	0	0	0	0.000261
p.V68M	III	classI-III	Asahi, A-	50	3	73	1	1	2	0.050623	0.001043
p.L323P	III	classI-III	A- (968), Betica,Selma, Guantanamo	4	0	6	0	0	0	0.004018	0
p.E156K	III	classI-III	ilesha	1	0	2	0	0	0	0.001205	0
p.E317K	III	classI-III	Kalyan-Kerala, Jamnaga, Rohini	0	0	1	0	0	1	0.000402	0.000261
p.D282H	III	classI-III	Not Interrogated (Seattle, Lodi, Modena, Ferrara II, Athens-like)	0	0	1	1	0	3	0.000402	0.001043
p.L235F	III	classI-III	Nanning	0	0	1	0	0	0	0.000402	0
p.G163S	III	classI-III	Mahidol	1	0	0	0	0	0	0.000402	0
p.L128R	III	classI-III	Salerno Pyrgos	1	0	0	1	0	0	0.000402	0.000261
p.R227Q	III	classI-III	Mexico City	0	0	0	0	0	1	0	0.000261
p.I48T	III	classI-III	Aures	0	0	0	0	0	1	0	0.000261
p.N126D	IV	classIV	A	138	25	131	8	2	8	0.11812	0.004692
p.D350H	IV	classIV	Mirad'Aire	1	0	6	0	0	0	0.002812	0
p.M159I	NA	VUS	Not Interrogated	1	0	1	0	0	1	0.000804	0.000261
p.G316D	NA	VUS	Not Interrogated	0	0	1	0	0	1	0.000402	0.000261
p.D251N	NA	VUS	Not Interrogated	0	0	1	0	0	0	0.000402	0
p.D194E	NA	VUS	Not Interrogated	0	0	1	2	0	3	0.000402	0.001303
p.V303G	NA	VUS	Not Interrogated	0	0	0	0	0	1	0	0.000261

Robinson KM, et al. Pharmacogenomics J. 2019;19(3):305-14.

TABLE S2. ASSOCIATION BETWEEN ALLELIC VARIANTS AND G6PD ACTIVITY AS DEFINED BY THE WORLD HEALTH ORGANIZATION

Functional Status	Allele Classification
Severe enzyme deficiency, <10% normal enzyme activity, with associated chronic non-spherocytic hemolytic anemia	WHO Class I
Severe enzyme deficiency, <10% normal enzyme activity, no chronic non-spherocytic hemolytic anemia	WHO Class II
Moderate to mild deficiency, 10-60% of normal enzyme activity	WHO Class III
Normal activity, 60-150% normal enzyme activity	WHO Class IV

WHO, World Health Organization

References: (2, 106)

Note: A single case of increased activity (a putative "Class V" allele) was previously included but will not be included going forward.

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Rasburicase Therapy in the Context of *G6PD* Deficiency Genotype

MV Relling[1], EM McDonagh[2], T Chang[3], KE Caudle[1], HL McLeod[4], CE Haidar[1], T Klein[2] and L Luzzatto[5]

Table 2 Recommended therapeutic use of rasburicase in relation to G6PD phenotype

G6PD phenotype	Implications for phenotypic measures	Dosing recommendations for rasburicase	Classification of recommendations[a]
Normal[b]	Low or reduced risk of hemolytic anemia	No reason to withhold rasburicase based on G6PD status[b]	Strong
Deficient or deficient with CNSHA	At risk of acute hemolytic anemia	Rasburicase is contraindicated; alternatives include allopurinol[c]	Strong
Variable[b]	Unknown risk of hemolytic anemia	To ascertain that G6PD status is normal, enzyme activity must be measured; alternatives include allopurinol[c]	Moderate

CNSHA, chronic nonspherocytic hemolytic anemia.

[a]Rating scheme described in **Supplementary Material** online (see Strength of Recommendations). [b]A negative or inconclusive genetic test cannot be assumed to indicate normal G6PD phenotype; an enzyme activity test is needed to assign G6PD phenotype in such cases. [c]Allopurinol is associated with severe cutaneous reactions in the rare carriers of the *HLA-B*58:01* allele.[37]

Table 3. Recommended therapeutic use of high risk drugs* in relation to G6PD phenotype

Predicted G6PD phenotype based on genotype	Implications for phenotypic measures	Therapeutic recommendations for high risk drugs	Classification of recommendations[a]	Considerations
Normal	Low risk of acute hemolytic anemia	No reason to avoid a high risk drug based on G6PD status	Strong	
Deficient	High risk of acute hemolytic anemia	Avoid use of high risk drug	See Table 2 for drug specific strength of recommendation	
Deficient with CNSHA	High risk of acute on chronic hemolysis	Avoid use of high risk drug	Strong	Although there are not published data in individuals with the G6PD Deficient with CNSHA phenotype, there is a strong rationale to avoid these drugs based on evidence in G6PD Deficient individuals.
Variable	Variable risk of acute hemolytic anemia	To ascertain G6PD status, enzyme activity must be measured. Drug use should be guided per the recommendations based on the activity-based phenotype.	Moderate	Due to X-linked mosaicism, individuals with more than one X chromosome (e.g., females, individuals with Klinefelter syndrome) and heterozygous for one nondeficient (class IV) and one deficient (class I–III) allele may display a normal or a deficient phenotype; an enzyme activity test is needed to assign G6PD phenotype in such cases.
Indeterminate	Unknown risk of acute hemolytic anemia	To ascertain G6PD status, enzyme activity must be measured. Drug use should be guided per the recommendations based on the activity-based phenotype.	Moderate	

*Drugs are classified as high, medium, or low-to-no risk for acute hemolytic anemia based on evidence review and based on assumptions of normal dosing regimens. Drug-induced hemolysis in G6PD deficiency is generally related to drug dosage (the higher the dose, the more the oxidative stress and the more likely anemia). Drugs that are commonly given at high and low dosages (e.g., primaquine and aspirin) have separate recommendations for high vs. low dosage.

Table 4. Recommended therapeutic use of medium risk drugs* in relation to G6PD phenotype

Predicted G6PD phenotype based on genotype	Implications for phenotypic measures	Therapeutic recommendations for medium risk drugs	Classification of recommendations[a]	Considerations
Normal	Low risk of acute hemolytic anemia	No reason to avoid a medium risk drug based on G6PD status	Strong	
Deficient	Medium risk of acute hemolytic anemia	Use medium risk drug at standard doses with caution with close monitoring for anemia	Drug-dependent	Close monitoring may be more important at higher or more chronic dosage schedules, and in the setting of infection or other oxidative stress including concomitant use of medium and low risk drugs.
Deficient with CNSHA	High risk of acute on chronic hemolysis	Avoid medium risk drugs	Moderate	There are insufficient data in patients with the G6PD Deficient with CNSHA phenotype to rate as "strong," but all medium risk drugs should be avoided in these rare patients due to the underlying pathophysiology that confers high risk for acute on chronic hemolysis.
Variable	Variable risk of acute hemolytic anemia	If deemed necessary to ascertain G6PD status, enzyme activity must be measured. Drug use should be guided per the recommendations based on the activity-based phenotype.	Moderate	Due to X-linked mosaicism, individuals with more than one X chromosome (e.g., females, individuals with Klinefelter syndrome) and heterozygous for one nondeficient (class IV) and one deficient (class I–III) allele may display a normal or a deficient phenotype; an enzyme activity test is needed to assign G6PD phenotype in such cases.
Indeterminate	Unknown risk of acute hemolytic anemia	If deemed necessary to ascertain G6PD status, enzyme activity must be measured. Drug use should be guided per the recommendations based on the activity-based phenotype.	Moderate	

*Drugs are classified as high, medium, or low-to-no risk for acute hemolytic anemia based on evidence review and based on assumptions of normal dosing regimens. Drug-induced hemolysis in G6PD deficiency is generally related to drug dosage (the higher the dose, the more the oxidative stress and the more likely anemia). Drugs that are commonly given at high and low dosages (e.g., primaquine and aspirin) have separate recommendations for high vs. low dosage.

Table 5. Recommended therapeutic use of low-to-no risk drugs* in relation to G6PD phenotype

Predicted G6PD phenotype based on genotype	Implications for phenotypic measures	Therapeutic recommendations for low-to-no risk drugs	Classification of recommendations[a]	Considerations
Normal	Low-to-no risk of acute hemolytic anemia	No reason to avoid a low-to-no risk drug based on G6PD status.	Strong	
Deficient	Low-to-no risk of acute hemolytic anemia	No reason to avoid a low-to-no risk drug based on G6PD status at standard doses.	See Table 2	Although low-to-no risk drugs are not known to cause a higher risk of AHA in G6PD deficient than G6PD normal patients, G6PD deficient patients may be at higher risk of AHA due to oxidative stress from any cause, and closer monitoring may be indicated.
Deficient with CNSHA	High risk of acute on chronic hemolysis	Use all drugs cautiously in this group; if used, close monitoring for anemia is recommended.	Optional	There are insufficient data in patients with the G6PD Deficient with CNSHA phenotype to rate as "moderate," but all drugs should be used cautiously in these rare patients due to the underlying pathophysiology that confers high risk for acute on chronic hemolysis.
Variable	Low-to-no risk of acute hemolytic anemia	No reason to avoid a low-to-no risk drug based on G6PD status at standard doses.	Moderate	Due to X-linked mosaicism, individuals with more than one X chromosome (e.g., females, individuals with Klinefelter syndrome) and heterozygous for one nondeficient (class IV) and one deficient (class I–III) allele may display a normal or a deficient phenotype; an enzyme activity test is needed to assign G6PD phenotype in such cases.
Indeterminate	In the absence of signs and symptoms of CNSHA, low-to-no risk of acute hemolytic anemia	No reason to avoid a low-to-no risk drug based on G6PD status at standard doses.	Moderate	

*Drugs are classified as high, medium, or low-to-no risk for acute hemolytic anemia based on evidence review and based on assumptions of normal dosing regimens. Drug-induced hemolysis in G6PD deficiency is generally related to drug dosage (the higher the dose, the more the oxidative stress and the more likely anemia). Drugs that are commonly given at high and low dosages (e.g., primaquine and aspirin) have separate recommendations for high vs. low dosage.

Table 6. Recommended therapeutic use of primaquine in relation to G6PD phenotype

Predicted G6PD phenotype based on genotype	Implications for phenotypic measures	Therapeutic recommendations	Classification of recommendations[a]	Considerations
Normal	Low risk of acute hemolytic anemia	No reason to avoid primaquine based on G6PD status	Strong	
Deficient	High risk of acute hemolytic anemia with standard anti-relapse treatment of P. vivax or P. ovale of 0.25-0.5 mg/kg daily for 14 days.	Avoid primaquine, except in the following cases where established expert consensus guidelines for the treatment of malaria should be followed: (1) Treating Plasmodium falciparum malaria by using primaquine single dose as a gametocytocide at 0.25 mg/kg x1 dose (WHO)—without need to monitor for hemolysis; and (2) treating Plasmodium vivax or Plasmodium ovale malaria for radical cure of liver-stage infections: 0.75 mg/kg once weekly x8 weeks (WHO) or 45 mg once weekly x8 weeks (CDC) --with close monitoring for hemolysis. If primaquine is used at doses higher or longer than these 2 regimens, monitor very closely for hemolysis.	Strong	Dosing recommendations for primaquine in patients with G6PD deficiency are derived from the malaria treatment guidelines issued by the World Health Organization and the U.S. Centers for Disease Control and Prevention.
Deficient with CNSHA	High risk of acute on chronic hemolysis	Avoid primaquine	Strong	The strength of evidence among patients with the G6PD Deficient phenotype provides strong rationale to also avoid primaquine in the setting of the more severe G6PD Deficient with CNSHA phenotype.
Variable	Variable risk of acute hemolytic anemia	To ascertain G6PD status, enzyme activity must be measured. Drug use should be guided per the recommendations based on the activity-based phenotype.	Moderate	Due to X-linked mosaicism, individuals with more than one X chromosome (e.g., females, individuals with Klinefelter syndrome) and heterozygous for one nondeficient (class IV) and one deficient (class I–III) allele may display a normal or a deficient phenotype; an enzyme activity test is needed to assign G6PD phenotype in such cases.
Indeterminate	Unknown risk of acute hemolytic anemia	To ascertain G6PD status, enzyme activity must be measured. Drug use should be guided per the recommendations based on the activity-based phenotype.	Moderate	

*Drugs are classified as high, medium, or low-to-no risk for acute hemolytic anemia based on evidence review and based on assumptions of normal dosing regimens. Drug-induced hemolysis in G6PD deficiency is generally related to drug dosage (the higher the dose, the more the oxidative stress and the more likely anemia). Drugs that are commonly given at high and low dosages (e.g., primaquine and aspirin) have separate recommendations for high vs. low dosage.

CDS alert language: drug specific

Name	Type	Compressed size	Password ...	Size	Ratio	Date modified
4-aminosalicylic acid_Pre_and_Pos...	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 9:15 AM
aspirin_less_than_1g_Pre_and_Post...	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 9:21 AM
chloramphenicol_Pre_and_Post_Te...	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 9:24 AM
chloroquine_Pre_and_Post_Test_Al...	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 9:24 AM
ciprofloxacin_Pre_and_Post_Test_Al...	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 9:25 AM
dapsone_Pre_and_Post_Test_Alerts	Microsoft Excel Worksheet	138 KB	No	145 KB	5%	1/25/2022 11:18 AM
dimercaprol_Pre_and_Post_Test_Al...	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 9:28 AM
doxorubicin_Pre_and_Post_Test_Al...	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 9:29 AM
furazolidone_Pre_and_Post_Test_Al...	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 9:29 AM
glyburide_Pre_and_Post_Test_Alerts	Microsoft Excel Worksheet	113 KB	No	120 KB	7%	1/25/2022 9:30 AM
hydroxychloroquine _Pre_and_Post...	Microsoft Excel Worksheet	113 KB	No	120 KB	7%	1/25/2022 10:52 AM
mafenide _Pre_and_Post_Test_Alerts	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 10:53 AM
methylene blue_Pre_and_Post_Test...	Microsoft Excel Worksheet	135 KB	No	141 KB	5%	3/25/2022 12:02 PM
nalidixic acid_Pre_and_Post_Test_Al...	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 9:14 AM
nitrofurantoin_Pre_and_Post_Test_...	Microsoft Excel Worksheet	138 KB	No	145 KB	5%	1/25/2022 11:28 AM
norfloxacin _Pre_and_Post_Test_Ale...	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 10:54 AM
ofloxacin _Pre_and_Post_Test_Alerts	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 10:55 AM
pegloticase_Pre_and_Post_Test_Ale...	Microsoft Excel Worksheet	135 KB	No	141 KB	5%	3/25/2022 12:01 PM
phenazopyridine_Pre_and_Post_Tes...	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 10:56 AM
primaquine_Pre_and_Post_Test_Ale...	Microsoft Excel Worksheet	110 KB	No	116 KB	6%	3/25/2022 12:27 PM
quinine_Pre_and_Post_Test_Alerts	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 10:56 AM
rasburicase_Pre_and_Post_Test_Alerts	Microsoft Excel Worksheet	138 KB	No	145 KB	5%	1/25/2022 11:17 AM
sulfadiazine_Pre_and_Post_Test_Ale...	Microsoft Excel Worksheet	113 KB	No	120 KB	7%	1/25/2022 10:57 AM
sulfadimidine_Pre_and_Post_Test_A...	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 10:57 AM
sulfamethoxazole_trimethoprim_Pr...	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 11:02 AM
sulfanilamide_Pre_and_Post_Test_A...	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 10:58 AM
sulfasalazine_Pre_and_Post_Test_Al...	Microsoft Excel Worksheet	113 KB	No	120 KB	7%	1/25/2022 10:59 AM
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tafenoquine_Pre_and_Post_Test_Al...	Microsoft Excel Worksheet	135 KB	No	141 KB	5%	3/25/2022 12:01 PM
tolbutamide_Pre_and_Post_Test_Al...	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 11:00 AM
toluidine blue_Pre_and_Post_Test_...	Microsoft Excel Worksheet	135 KB	No	141 KB	5%	3/25/2022 12:00 PM
vitamin C_Pre_and_Post_Test_Alerts	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 11:00 AM
vitamin K_Pre_and_Post_Test_Alerts	Microsoft Excel Worksheet	113 KB	No	120 KB	6%	1/25/2022 11:01 AM

examples

CDS for rasburicase (high risk drug, strong recommendation)

G6PD Phenotype	**CDS Context, Relative to Genetic Testing**	CDS Alert Text
No G6PD result on file	Pre-test	The patient's G6PD status may be predictive of hemolytic anemia with rasburicase. A G6PD test does not appear to have been ordered for this patient. Consider ordering a G6PD genotype or enzyme activity test. Use of an alternative agent is recommended if the patient is G6PD deficient. Please consult a clinical pharmacist for more information.
G6PD normal	No CDS	n/a
G6PD deficient	Post-test	This patient has a result consistent with G6PD deficiency. Rasburicase is very likely to cause hemolytic anemia in patients with G6PD deficiency and should be avoided. Strongly consider use of an alternative agent. If it is deemed that this medication remains the preferred agent, monitor the patient closely for signs of hemolysis. Please consult a clinical pharmacist for more information.
G6PD deficient with CNSHA	Post-test	This patient has a result consistent with G6PD deficiency with chronic nonspherocytic hemolytic anemia (CNSHA). Rasburicase is very likely to cause hemolytic anemia and worsen any existing anemia and should be avoided. Strongly consider use of an alternative agent. Please consult a clinical pharmacist for more information.
G6PD variable	Post-test	You are attempting to place an order for rasburicase on a patient whose G6PD genotype results in a phenotype assignment of variable G6PD activity (enzyme activity could range from normal to deficient). The patient is at increased risk of developing hemolytic anemia if they are G6PD deficient and rasburicase is prescribed. A test of G6PD enzyme activity may be informative. Please consult a clinical pharmacist for more information.
G6PD indeterminate	Post-test	You are attempting to place an order for rasburicase on a patient whose G6PD genotype does not allow an assignment of G6PD phenotype. The patient is at increased risk of developing hemolytic anemia if they are G6PD deficient and rasburicase is prescribed. A test of G6PD enzyme activity may be informative. Please consult a clinical pharmacist for more information.

CDS for nitrofurantoin (medium risk drug, optional strength)

G6PD Phenotyp	CDS Context,	CDS Alert Text
No G6PD result on file	Pre-test	The patient's G6PD status may be predictive of hemolytic anemia with nitrofurantoin. A G6PD test does not appear to have been ordered for this patient. Consider ordering a *G6PD* genotype or enzyme activity test. Increased monitoring for signs of hemolysis may be recommended if the patient is G6PD deficient. Please consult a clinical pharmacist for more information.
G6PD	No CDS	n/a
G6PD deficient	Post-test	This patient has a result consistent with G6PD deficiency. Use nitrofurantoin with caution and monitor the patient for signs of hemolysis. Please consult a clinical pharmacist for more information.
G6PD deficient with	Post-test	This patient has a result consistent with G6PD deficiency with chronic nonspherocytic hemolytic anemia (CNSHA). Nitrofurantoin may cause hemolytic anemia and worsen any existing anemia and should be avoided. Consider use of an alternative agent. Please consult a clinical pharmacist for more information.
G6PD variable	Post-test	You are attempting to place an order for nitrofurantoin on a patient whose *G6PD* genotype results in a phenotype assignment of variable G6PD activity (enzyme activity could range from normal to deficient). The patient may be at increased risk of developing hemolytic anemia if they are G6PD deficient and nitrofurantoin is prescribed. A test of G6PD enzyme activity may be informative. Please consult a clinical pharmacist for more information.
G6PD indetermi nate	Post-test	You are attempting to place an order for nitrofurantoin on a patient whose *G6PD* genotype does not allow an assignment of G6PD phenotype. The patient may be at increased risk of developing hemolytic anemia if they are G6PD deficient and nitrofurantoin is prescribed. A test of G6PD enzyme activity may be informative. Please consult a clinical pharmacist for more information.

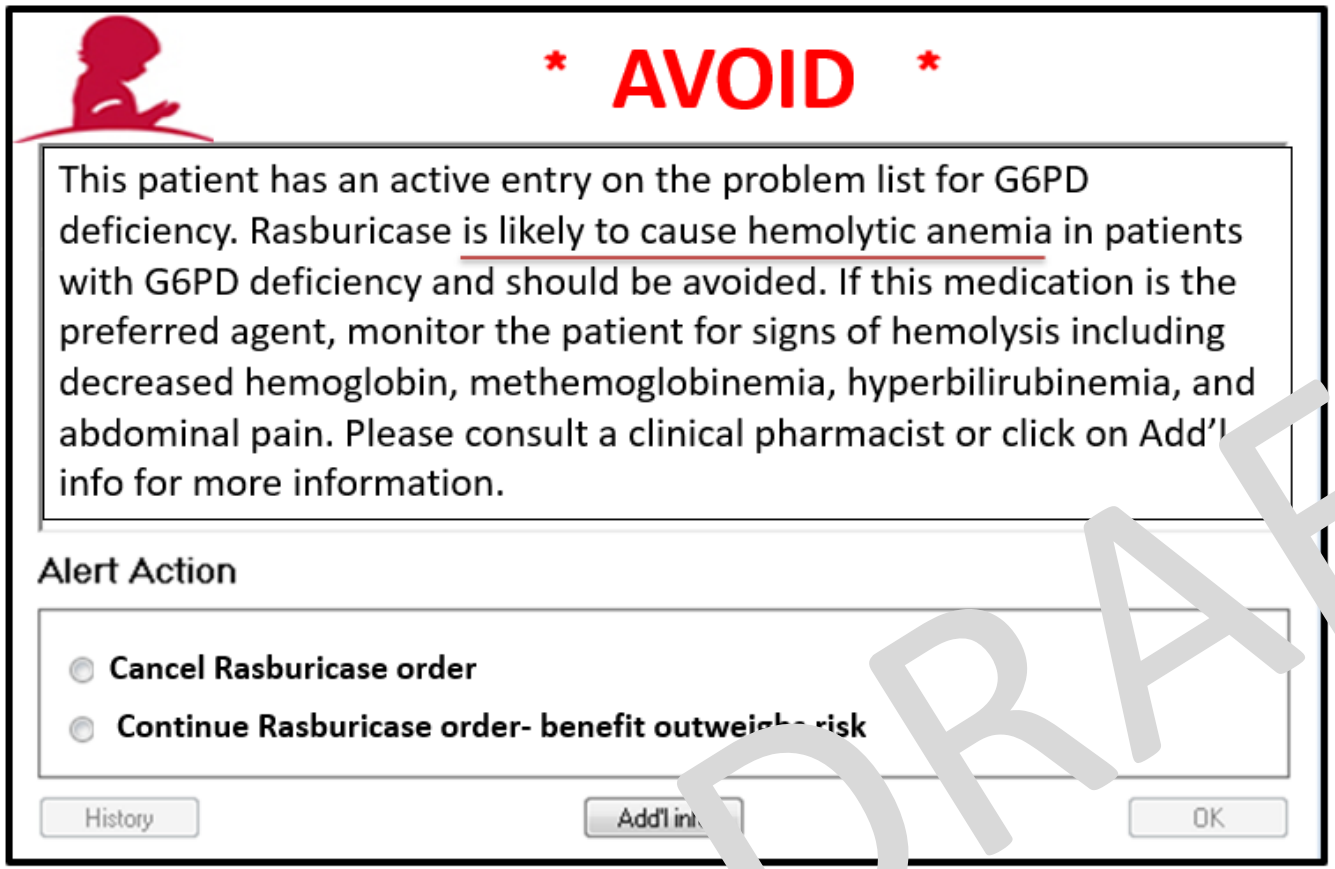
CDS for primaquine (language is dose dependent, all strong recommendations)

G6PD Phenotype	CDS Context, Relative to Genetic Testing	CDS Alert Text
No G6PD result or	No CDS	The patient's G6PD status may be predictive of hemolytic anemia with primaquine, depending on the primaquine dosage regimen. A G6PD test does not appear to have been ordered for this patient. Consider ordering a G6PD genotype or enzyme activity test. Increased monitoring for signs of hemolysis may be recommended if the patient is G6PD deficient, depending on dosage. Please consult a clinical pharmacist for more information.
G6PD normal	No CDS	n/a
G6PD deficient	No CDS	This patient has a result consistent with G6PD deficiency. Avoid primaquine, except in the following cases where established expert consensus guidelines for the treatment of malaria should be followed: (1) Treating Plasmodium falciparum malaria by using primaquine single dose as a gametocytocide at 0.25 mg/kg x1 dose (WHO)—without need to monitor for hemolysis; and (2) treating Plasmodium vivax or Plasmodium ovale malaria for radical cure of liver-stage infections: 0.75 mg/kg once weekly x8 weeks (WHO) or 45 mg once weekly x8 weeks (CDC) --with close monitoring for hemolysis. If primaquine is used at doses higher or longer than these 2 regimens, monitor very closely for hemolysis.
G6PD deficient with CNSHA	Post-test	This patient has a result consistent with G6PD deficiency with chronic nonspherocytic hemolytic anemia (CNSHA). Increased monitoring for worsening of hemolytic anemia may be indicated for patients with G6PD deficiency with CNSHA who receive medications. Please consult a clinical pharmacist for more information.
G6PD variable	No CDS	This patient has a result consistent with G6PD deficiency with chronic nonspherocytic hemolytic anemia (CNSHA). Primaquine is likely to cause hemolytic anemia and worsen any existing anemia and should be avoided. Consider use of an alternative agent or alternative dosage. Please consult a clinical pharmacist for more information.
G6PD indetermina	No CDS	You are attempting to place an order for primaquine on a patient whose G6PD genotype results in a phenotype assignment of variable G6PD activity (enzyme activity could range from normal to deficient). The patient may be at increased risk of developing hemolytic anemia if they are G6PD deficient and primaquine is prescribed, depending on the dose. A test of G6PD enzyme activity may be informative. Please consult a clinical pharmacist for more information.

CDS for sulfamethoxazole, low-to-no risk drug, optional strength

G6PD Phenotype	CDS Context, Relative to Genetic Testing	CDS Alert Text
No G6PD result on file	No CDS	n/a
G6PD normal	No CDS	n/a
G6PD deficient	No CDS	n/a
G6PD deficient with CNSHA	Post-test	This patient has a result consistent with G6PD deficiency with chronic nonspherocytic hemolytic anemia (CNSHA). Increased monitoring for worsening of hemolytic anemia may be indicated for patients with G6PD deficiency with CNSHA who receive medications. Please consult a clinical pharmacist for more information.
G6PD variable	No CDS	n/a
G6PD indeterminate	No CDS	n/a

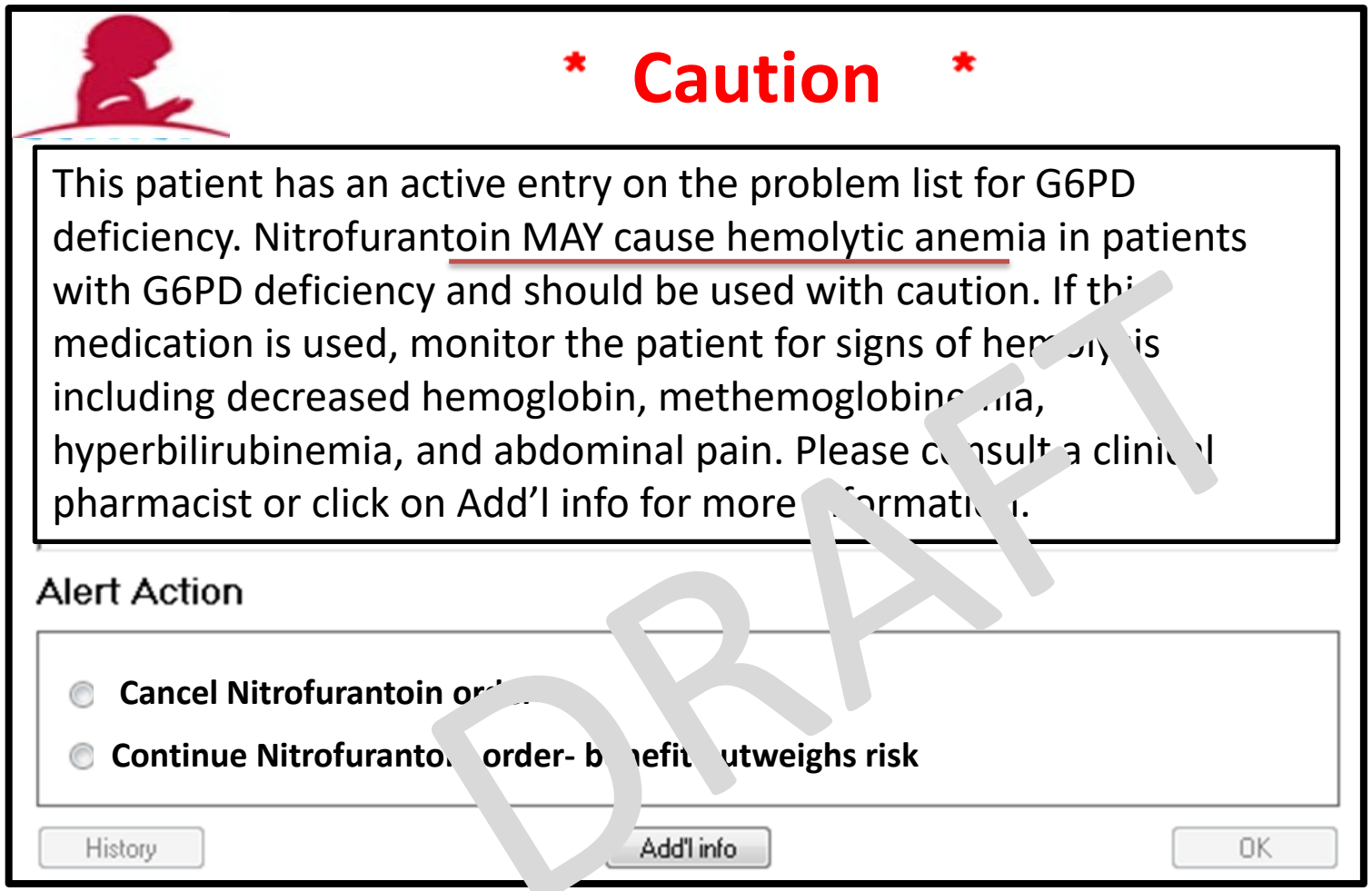
G6PD Deficiency Avoid Alert



Avoid

- Dapsone
- Methylene Blue
- Pegloticase
- Primaquine – std does
- Rasburicase
- Tafenoquine
- Toluidine blue

G6PD Deficiency Caution Alert

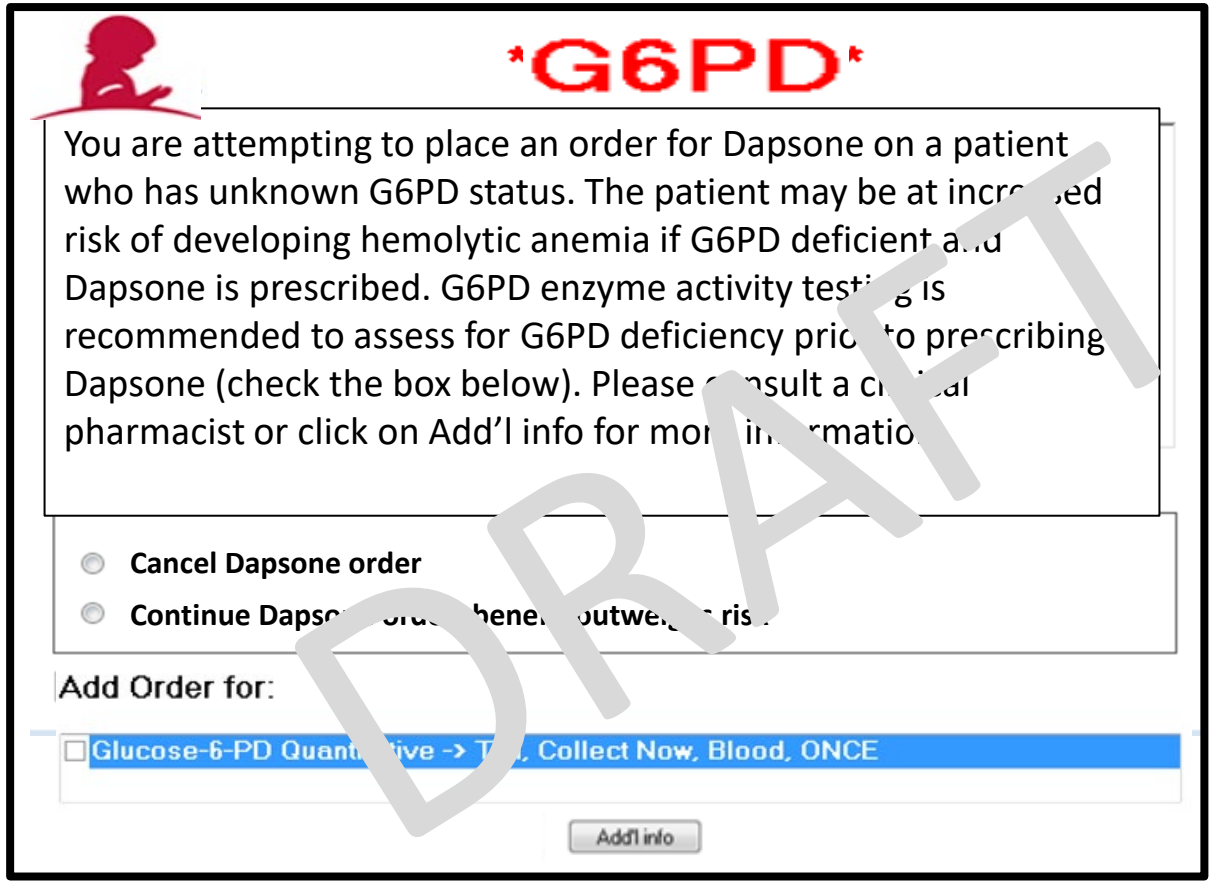


Use with caution

- Nitrofurantoin
- Primaquine—low dose

Pre G6PD Result Alert

- Alert is presented to prescriber when ordering a medication on the Avoid list and patient does not have a *G6PD* genotype or enzyme activity result



Other considerations, incidental findings

- Non-drug triggers: dietary, infections, hyperuricemia, sepsis
- “because the G6PD gene is located on the X chromosome, self-identified males who have a G6PD diplotype indicating the presence of two G6PD alleles may have an inherited sex chromosome disorder such as Klinefelter syndrome. This syndrome occurs in ~1 in 600 persons assigned male at birth, and there are possible medical interventions that may be indicated once that diagnosis is confirmed. Consideration for involvement of genetic counselors and procedures to confirm that diagnosis should be in place for those who routinely test G6PD genotype (51).”

Question slides

Current risk assignments for G6PD drugs; primaquine is dose-dependent

High or Medium risk

dapsone	High-risk	Moderate
methylene blue	High-risk	Moderate
pegloticase	High-risk	Strong
primaquine – standard dose	High-risk	Strong
rasburicase	High-risk	Strong
tafenoquine	High-risk	Strong
toluidine blue	High-risk	Moderate*
nitrofurantoin	Medium-risk	Optional
primaquine – low dose (0.75 mg/kg or 45 mg once weekly for 8 weeks) for Plasmodium vivax malaria	Medium-risk	Strong

Low-to-no risk

4-aminosalicylic acid	Low-to-no risk	Optional
aspirin ≤ 1 g/day	Low-to-no risk	Moderate
chloramphenicol	Low-to-no risk	Moderate
chloroquine	Low-to-no risk	Moderate
ciprofloxacin	Low-to-no risk	Optional
dimercaprol	Low-to-no risk	Optional
doxorubicin	Low-to-no risk	Optional
furazolidone	Low-to-no risk	Optional
glyburide	Low-to-no risk	Optional
hydroxychloroquine	Low-to-no risk	Moderate
mafenide	Low-to-no risk	Optional
nalidixic acid	Low-to-no risk	Optional
norfloxacin	Low-to-no risk	Optional
ofloxacin	Low-to-no risk	Optional
phenazopyridine	Low-to-no risk	Optional
primaquine – single low dose (0.25 mg/kg) for Plasmodium falciparum malaria	Low-to-no risk	Strong
quinine	Low-to-no risk	Optional
sulfadiazine	Low-to-no risk	Optional
sulfadimidine	Low-to-no risk	Optional
sulfamethoxazole	Low-to-no risk	Optional
sulfanilamide	Low-to-no risk	Optional
sulfasalazine	Low-to-no risk	Optional
sulfisoxazole	Low-to-no risk	Optional
tolbutamide	Low-to-no risk	Optional
vitamin C	Low-to-no risk	Moderate
vitamin K	Low-to-no risk	Moderate

No recommendation

aspirin > 1 g/day
chlorpropamide
dabrafenib
gliclazide
glimepiride
glipizide
mepacrine
mesalazine
moxifloxacin
nicorandil
nitrofural
probenecid
sulfacetamide
tolazamide
trametinib

Note: other sulfonylureas, sulfas, and quinolones are low-to-no risk

Current risk assignments for G6PD drugs

High or Medium risk

dapsone	High-risk	Moderate
methylene blue	High-risk	Moderate
pegloticase	High-risk	Strong
primaquine – standard dose	High-risk	Strong
rasburicase	High-risk	Strong
tafenoquine	High-risk	Strong
toluidine blue	High-risk	Moderate*
nitrofurantoin	Medium-risk	Optional
primaquine – low dose (0.75 mg/kg or 45 mg once weekly for 8 weeks) for Plasmodium vivax malaria	Medium-risk	Strong

Low-to-no risk

4-aminosalicylic acid	Low-to-no risk	Optional
aspirin ≤ 1 g/day	Low-to-no risk	Moderate
chloramphenicol	Low-to-no risk	Moderate
chloroquine	Low-to-no risk	Moderate
ciprofloxacin	Low-to-no risk	Optional
dimercaprol	Low-to-no risk	Optional
doxorubicin	Low-to-no risk	Optional
furazolidone	Low-to-no risk	Optional
glyburide	Low-to-no risk	Optional
hydroxychloroquine	Low-to-no risk	Moderate
mafenide	Low-to-no risk	Optional
nalidixic acid	Low-to-no risk	Optional
norfloxacin	Low-to-no risk	Optional
ofloxacin	Low-to-no risk	Optional
phenazopyridine	Low-to-no risk	Optional
primaquine – single low dose (0.25 mg/kg) for Plasmodium falciparum malaria	Low-to-no risk	Strong
quinine	Low-to-no risk	Optional
sulfadiazine	Low-to-no risk	Optional
sulfadimidine	Low-to-no risk	Optional
sulfamethoxazole	Low-to-no risk	Optional
sulfanilamide	Low-to-no risk	Optional
sulfasalazine	Low-to-no risk	Optional
sulfisoxazole	Low-to-no risk	Optional
tolbutamide	Low-to-no risk	Optional
vitamin C	Low-to-no risk	Moderate
vitamin K	Low-to-no risk	Moderate

No recommendation

aspirin > 1 g/day
chlorpropamide
dabrafenib
gliclazide
glimepiride
glipizide
mepacrine
mesalazine
moxifloxacin
nicorandil
nitrofural
probenecid
Sodium nitrite
sulfacetamide
tolazamide
trametinib

Note: other sulfonylureas, sulfas, and quinolones are low-to-no risk

specifications for point-of-care G6PD tests to guide use of 8-aminoquinolines for radical cure of *P. vivax*.

Objectives

i) Revise the most widely used classification of G6PD variants.

ii) Discuss requirements for defining new variants.

iii) Propose new categorization of G6PD for ICD-11, including classification of G6PD variants and clinical manifestations.

References

1. Standardization of procedures for the study of glucose-6-phosphate dehydrogenase, WHO Technical Report Series, no. 366. Geneva: World Health Organization; 1967 (https://apps.who.int/iris/bitstream/handle/10665/40660/WHO_TRS_366.pdf?sequence=1&isAllowed=y).

2. Yoshida A, Beutler E, Motulsky AG. Human glucose-6-phosphate dehydrogenase variants. Bull World Health Organ. 1971;45(2):243–53.

3. Glucose-6-phosphate dehydrogenase deficiency. WHO Working Group. Bull World Health Organ. 1989;67:601–11.

4. Point-of-care G6PD testing to support safe use of primaquine for the treatment of vivax malaria.

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Rasburicase Therapy in the Context of *G6PD* Deficiency Genotype

MV Relling[1], EM McDonagh[2], T Chang[3], KE Caudle[1], HL McLeod[4], CE Haidar[1], T Klein[2] and L Luzzatto[5]

Existing *G6PD* allele frequency table

Supplemental Table S4. Frequencies of *G6PD* variants[1] available with commercial testing in major race/ethnic groups[2]

Allele	WHO Class[3]	dbSNP rsID[4]	cDNA substitution[5]	All			Caucasian			South American			African			Asian		
				Affy Hapmap[6]	EVS[7]	1000 Genomes[8]	Affy Hapmap[6]	EVS[7]	1000 Genomes[8]	Affy Hapmap[6]	EVS[7]	1000 Genomes[8]	Affy Hapmap[6]	EVS[7]	1000 Genomes[8]	Affy Hapmap[6]	EVS[7]	1000 Genomes[8]
A	III-IV	rs1050829	376A>G	N/A	0.113	0.081	0	0.0595	0.005	0.017	N/A	0.036	0.345	0.312	0.324	0	N/A	0
A-	III	rs1050828 rs1050829	202G>A, 376A>G	N/A	0.0425	N/A	N/A	0.0	N/A	N/A	N/A	N/A	N/A	0.117	N/A	N/A	N/A	N/A
Asahi	III	rs1050828	202G>A			0.043			0			0.022			0.17			0
Mediterranean (also known as Dallas, Panama, Sassari)	II	rs5030868	563C>T	N/A	0.0663	N/A	0	0.0743	N/A	0	N/A	N/A	0	0.0522	N/A	0	N/A	N/A
Canton (also known as Taiwan-Hakka, Gifu-like, Agrigento-like)	II	rs72554665	1376G>T (1376G>C is Cosenza variant)	N/A	N/A	T = 0.001	0.0	N/A	0.0	0	N/A	0.0	0	N/A	0.0	0.017	N/A	T = 0.002
Orissa	III	rs78478128	131C>G	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kalyan-Kerala	III	rs137852339	949G>A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Chatham	II	rs5030869	1003G>A	N/A	0.0095	N/A	N/A	0.0149	N/A	N/A	N/A	N/A	N/A	0	N/A	N/A	N/A	N/A

[1]Average allele frequencies are reported, based on the actual numbers of subjects with each allele reported in multiple studies

[2]Grouped according to major race/ethnic groups for studies as defined in Supplemental Table S5

[3]From (13); the phenotype associated with each variant according to WHO classification

[4]National Center for Biotechnology Information dbSNP database. http://www.ncbi.nlm.nih.gov/projects/SNP/

[5]cDNA reference sequence; NM_001042351.1:c., alleles represented are on the negative chromosomal strand. The G6PD gene is on the negative chromosomal strand, alleles on PharmGKB (www.pharmgkb.org) are complemented to the plus chromosomal strand for standardization.

[6]Affymetrix Hapmap database. http://www.affymetrix.com/

[7]National Heart Lung and Blood Institute Exome Variant Server database. http://evs.gs.washington.edu/EVS/

[8]1000 Genomes Project database. http://browser.1000genomes.org/index.html

N/A not available.

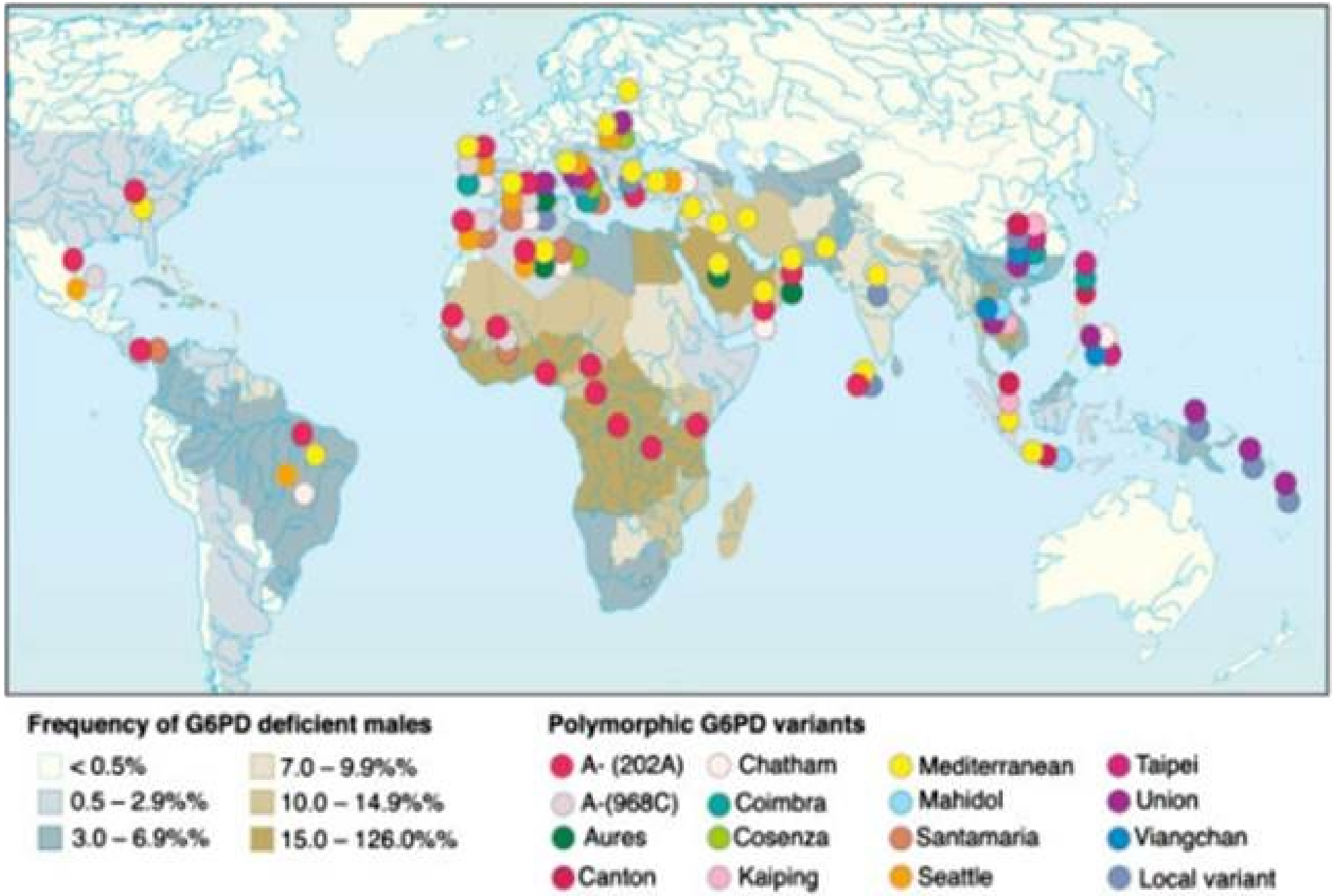
A list of medications to avoid in patients with G6PD deficiency has not been universally adopted

- Mixed evidence has led to different conclusions and recommendations
- Lack of consensus possibly due to
  - –medication risk level
  - –confounding factors
    - Infection

Name	Molecular Formula	Risk Level (note)	For Whom	Note
Glimepiride	$C_{24}H_{34}N_4O_5S$	High	All	
Glipizide	$C_{21}H_{27}N_5O_4S$	High	All	
Glucosulfone (glucosulfone sodium)	$C_{24}H_{34}N_2Na_2O_{18}S_3$	High	All	
Hydroxychloroquine	$C_{18}H_{26}ClN_3O$	High	All	
Ibuprofen	CH3H18O2	Medium	All	
Indigofera Tinctoria	-	Medium	All	
Isobutyl Nitrite	$C_4H_9NO_2$	High	Medit., Asia	
Isoniazid	$C_6H_7N_3O$	Medium	All	
Lawsone Inermis	-	Medium	All	
Levodopa	$C_9H_{11}NO_4$	Medium	All	
Levofloxacin	$C_{18}H_{20}FN_3O_4$	High	Medit., Asia	
Lomefloxacin	$C_{17}H_{19}F_2N_3O_3$	High	All	
Mefloquine	$C_{17}H_{16}F_6N_2O$	High	All	
Menadiol Sodium Sulfate (Vitamin k4 sodium sulfate)	$C_{11}H_8Na_2O_8S_2$	High	All	Note
Menadione (menaphtone)	$C_{11}H_8O_2$	High	All	Note

1 2 3 4 5 6 7 8 9 10 Page size: 15 143 items in 10 pages

G6PD deficiency favism association. https://www.g6pd.org/en/G6PDDeficiency/SafeUnsafe.aspx.



> 190 variants described, but most are very rare

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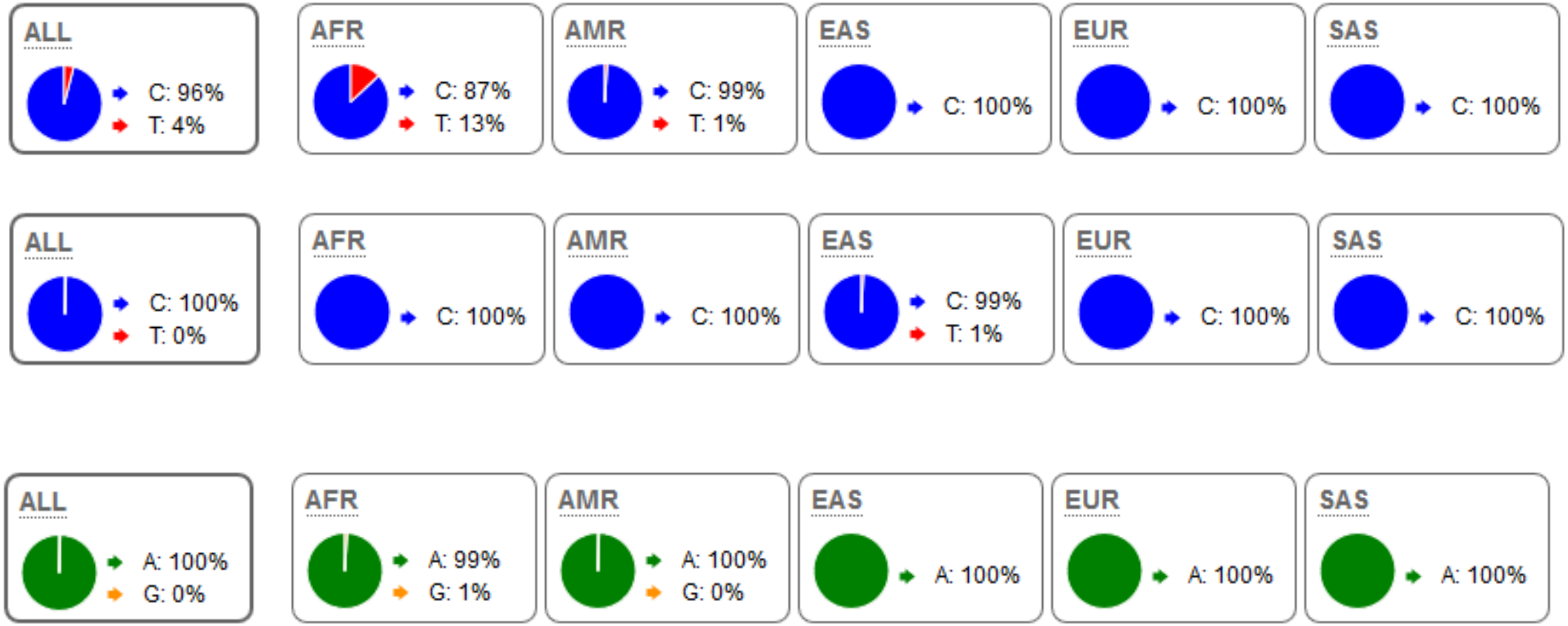

Plus we found one Pawnee variant (< 1 in 100,000 Exac)

Human Molecular Genetics, Vol. 1, No. 3 171–174

Both mutations in G6PD A– are necessary to produce the G6PD deficient phenotype

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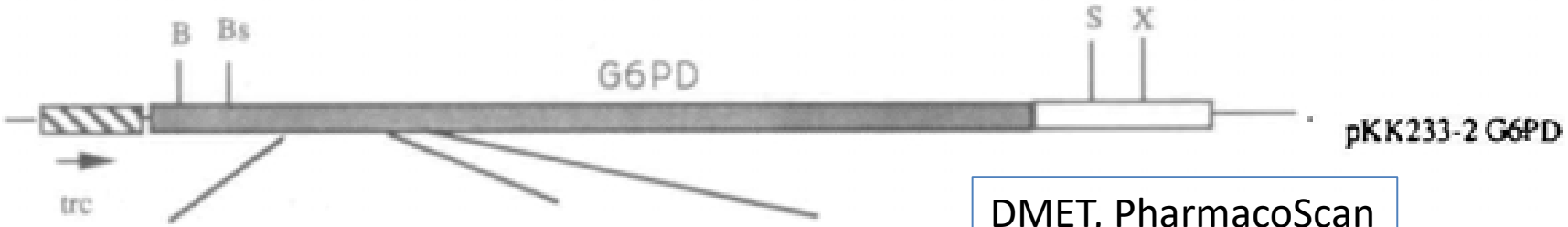
Department of Haematology, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 ONN, UK



DMET, PharmacoScan

68	119	126		
Val	Gln	Asn	B	Wild type
Val	Gln	Asp	A	A; Class IV (normal); MAF .1-.34 African
Met	Gln	Asn	68M	Asahi; Class III (low); rare (Asian)
Met	Gln	Asp	A-	A-; Class III (low); MAF up to 0.24 African
Val	Glu	Asn	119E	
Met	Glu	Asn	119E,68M	

PharmacoScan

Primaquine Phosphate

Oral route

HIV infection - Pneumocystis pneumonia
Malaria, Prevention of relapse; Adjunct
Malaria; Prophylaxis

HIV infection - Pneumocystis pneumonia

1) Guideline Dosage

a) Usual dosage (mild to moderate): 30 mg (base) orally once daily for 21 days in combination with clindamycin 450 mg every 6 hours to 600 mg every 8 hours orally [7]

b) Usual dosage (moderate to severe): 30 mg (base) orally once daily for 21 days in combination with clindamycin 450 mg every 6 hours to 600 mg every 8 hours orally or clindamycin 600 mg every 6 hours to 900 mg every 8 hours IV [7]

See Drug Consult reference: Prevention and Treatment of Pneumocystis Jiroveci Pneumonia (PCP) in HIV-Infected Persons - CDC/NIH/IDSA Guidelines

Malaria, Prevention of relapse; Adjunct

1) Guideline Dosing

a) Dosage: 52.6 mg orally for 14 days; use as an adjunct to an appropriate primary (ie, blood-stage) treatment agent, such as chloroquine, in the treatment of uncomplicated Plasmodium vivax or P ovale malaria [2][1]

b) Alternate dosage: 78.9 mg orally once weekly for 8 weeks for patients who are borderline glucose-6-phosphate dehydrogenase (G6PD) deficient; consultation with an infectious disease specialist is advised if the alternative regimen is used in persons who are G6PD deficient [2][1]

2) FDA Dosing

a) Usual dosage: 26.3 mg orally once daily for 14 days [3].

b) Concomitant medications: Use in combination with a course of chloroquine phosphate [3]

See Drug Consult reference: Malaria -- CDC Recommendations for United States Residents

Malaria; Prophylaxis

1) Prophylaxis For Short-Duration Travel

a) For primary prophylaxis in adults with short-duration travel to areas with primarily Plasmodium vivax malaria, the CDC recommends primaquine phosphate at a dose of 52.6 mg (2 tablets) orally daily beginning 1 to 2 days prior to travel to the malarious area, continued daily at the same time each during the stay in the malarious area, and then for 7 days after departure from the area [12].

2) Presumptive Anti-relapse Therapy

a) For presumptive anti-relapse therapy, the CDC recommends that adults receive a dose of primaquine phosphate 52.6 mg (2 tablets) orally daily for 14 days after departure from the malarious area. Primaquine is given with the primary prophylactic medication. When the primary therapy is chloroquine, doxycycline, or mefloquine, give primaquine during the last 2 weeks of prophylaxis. If the primary agent is atovaquone/proguanil, give primaquine during the final 7 days of atovaquone/proguanil therapy, and then continue primaquine for an additional 7 days. If overlap of primaquine with the primary medication is not possible, primaquine may still be given after primary prophylaxis is complete. Presumptive anti-relapse therapy is not required in persons who received primaquine for primary prophylaxis [12][12].

See Drug Consult reference: Malaria -- CDC Recommendations for United States Residents

GLOBAL MALARIA PROGRAMME

World H
Organiz

Policy brief on single-dose primaquine as a gametocytocide in *Plasmodium falciparum* malaria

January 2015

Need for testing for G6PD deficiency before single low-dose primaquine administration

- Clinically significant haemolysis is not expected to occur in either G6PD-normal or -deficient individuals given a single 15-mg adult dose (0.25 mg base/kg) of primaquine. Therefore, there is no need for systematic testing for G6PD deficiency before administering a single dose of 0.25 mg primaquine base per kg body weight.

Dysoley *et al. BMC Infectious Diseases* (2019) 19:250
https://doi.org/10.1186/s12879-019-3862-1

BMC Infectious Disea

RESEARCH ARTICLE Open Acce

The tolerability of single low dose primaquine in glucose-6-phosphate deficient and normal falciparum-infected Cambodians

Lek Dysoley[1,2], Saorin Kim[3], Sergio Lopes[4], Nimol Khim[3], Steven Bjorges[5], Samphornarann Top[5], Chea Huch[1], Huy Rekol[1], Nelli Westercamp[6], Mark M. Fukuda[7], Jimee Hwang[8], Arantxa Roca-Feltrer[4], Mavuto Mukaka[9,10], Didier Menard[3,11†] and Walter R. Taylor[9,10*†]

0.25 mg base/kg single dose
49 nl pts; 12 deficient
Hb: p = 0.04

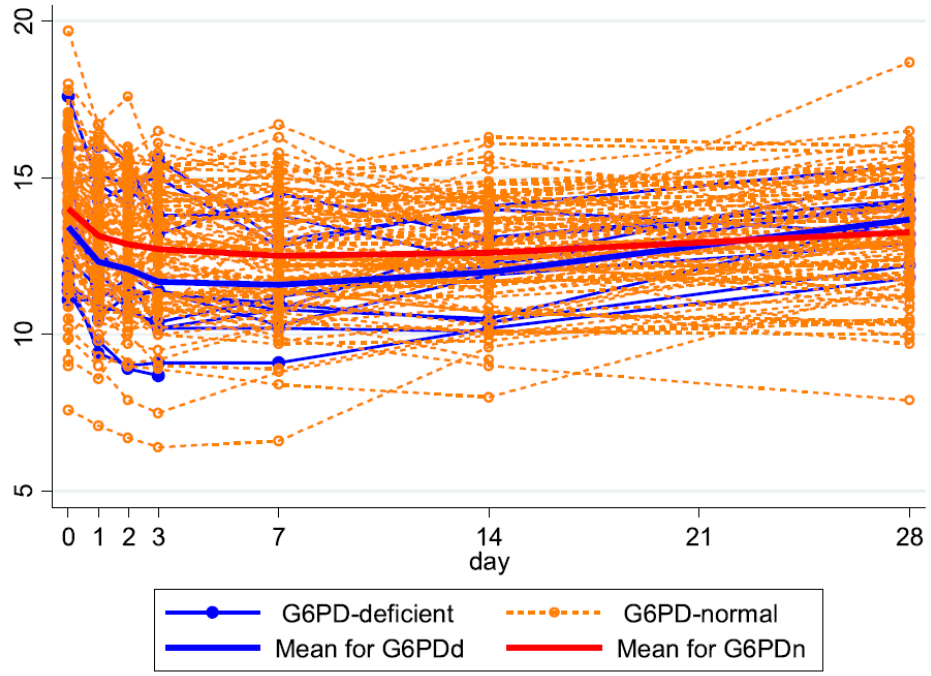
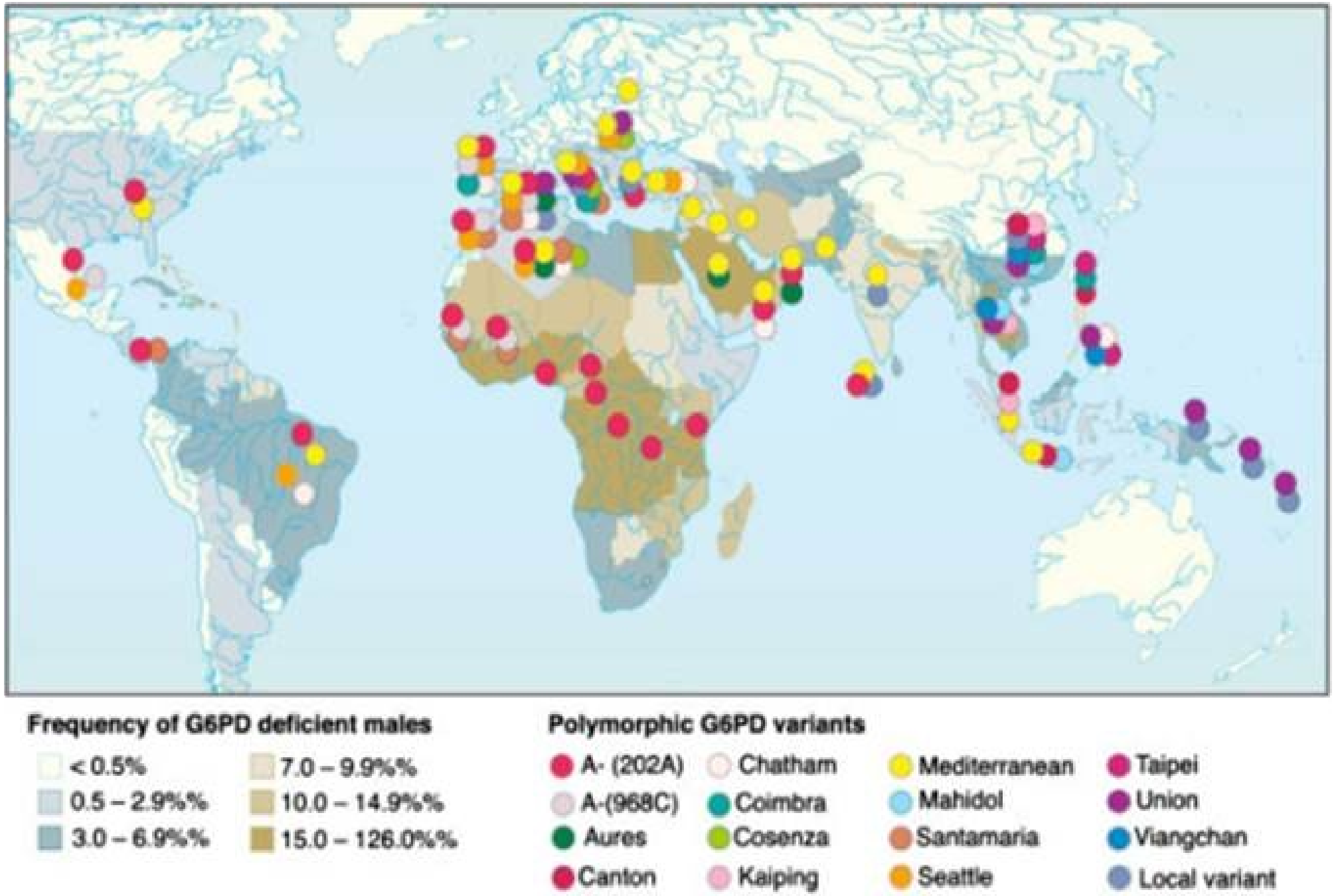


Fig. 3 Haemoglobin dynamics of the HemoCue measured hemoglobin concentrations as a function of glucose-6-phosphate dehydrogenase (G6PD) status

Cochrane Library

Cochrane Database of Systematic Reviews

Primaquine at alternative dosing schedules for preventing relapse in people with *Plasmodium vivax* malaria (Review)



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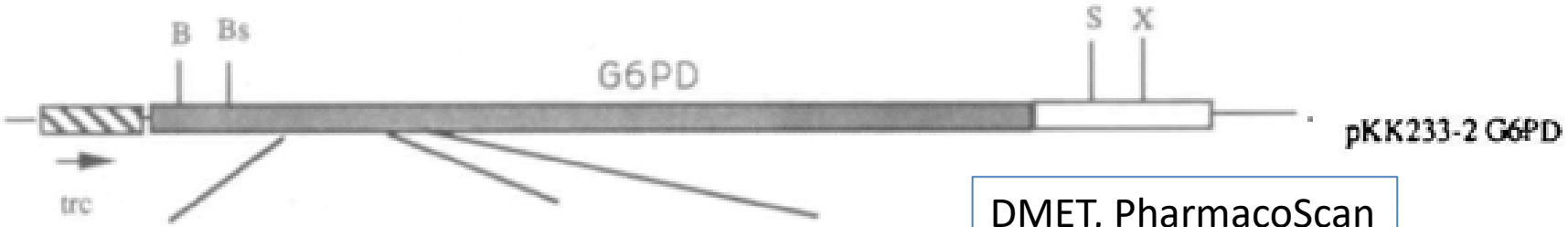

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Met	Gln	Asp	A-	A-; Class III (low); MAF up to 0.24 African
Val	Glu	Asn	119E	
Met	Glu	Asn	119E,68M	

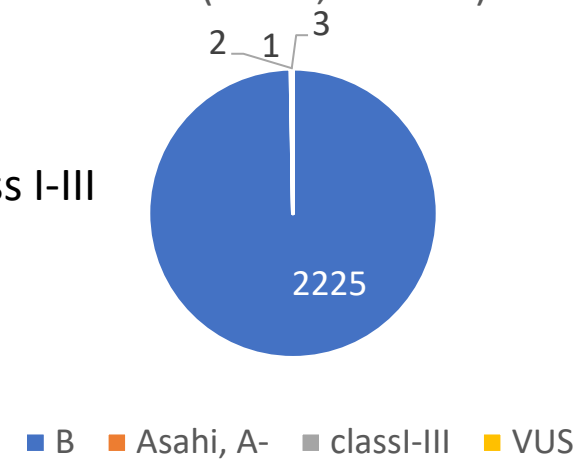
PharmacoScan

G6PD variants based on sequencing (n=6325; 39% non-white): > 83% of variants are A-/Asahi

6.4% of non-whites and <1% of whites have a Class I-III variant

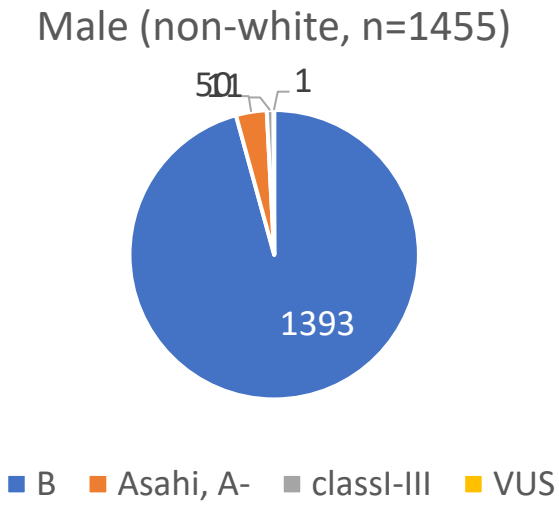
Male (white, n=2231)

1=Asahi/A-
3=other Class I-III
2=VUS



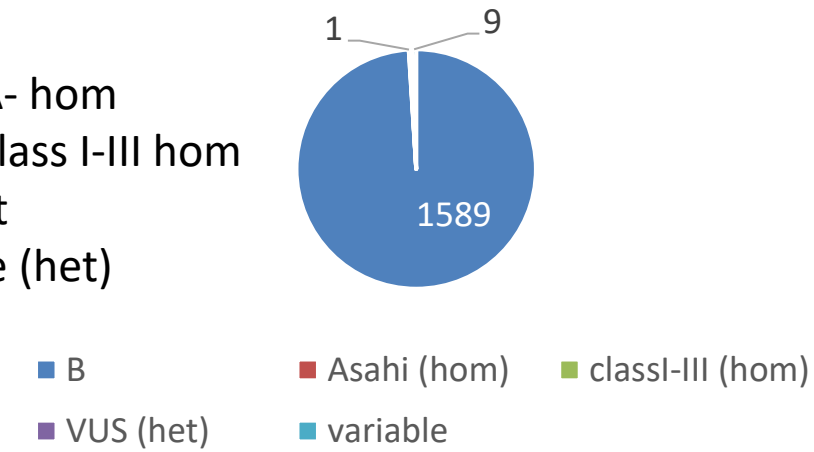
Male (non-white, n=1455)

50=Asahi/A-
11=other Class I-III
1=VUS



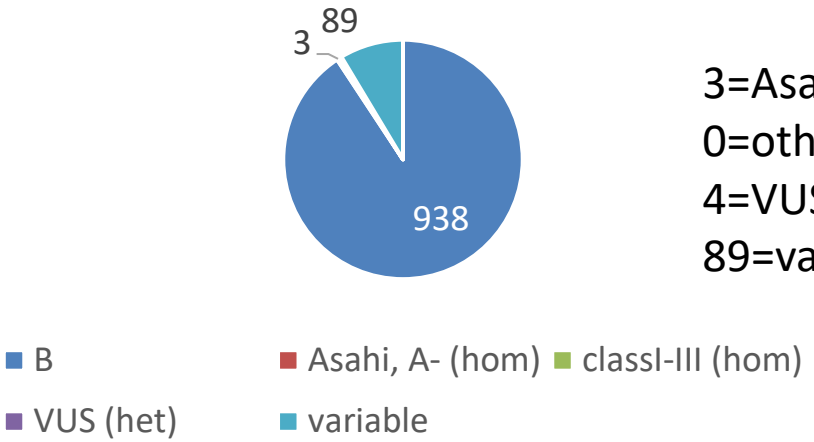
Female (white, n=1599)

1=Asahi/A- hom
0=other Class I-III hom
6=VUS het
9=variable (het)



Female (non-white, n=1030)

3=Asahi/A- hom
0=other Class I-III hom
4=VUS het
89=variable (het, > 90% A-)



Robinson KM, et al. Pharmacogenomics J. 2019;19(3):305-14.

16 G6PD Class I-III variants were observed in American children with ALL (n= 2489 non-whites, 3836 whites) with G6PD sequencing

All but one (D282H) are included on PharmacoScan

AAChange.refGene	WHO_class	final.cat	PharmacoScan	males, white	females (hom), non-white	females (het), non-white	males, non-white	females (hom), non-white	females (het), non-white	non-white	white
p.R454C	II	classI-III	Union,Maewo, Chinese-2, Kalo	2	0	3	0	0	0	0.002009	0
p.V291M	II	classI-III	Viangchan, Jammu	2	0	1	0	0	0	0.001205	0
p.H155D	II	classI-III	Acrokorinthos	0	0	1	0	0	0	0.000402	0
p.R136C	II	classI-III	Valladolid	0	0	1	0	0	0	0.000402	0
p.R439P	II	classI-III	Pawnee	0	0	0	0	0	1	0	0.000261
p.S188F	II	classI-III	Mediterranean, Dallas, Panama, Sassari, Cagliari, Birmingham	0	0	0	1	0	0	0	0.000261
p.V68M	III	classI-III	Asahi, A-	50	3	73	1	1	2	0.050623	0.001043
p.L323P	III	classI-III	A- (968), Betica,Selma, Guantanamo	4	0	6	0	0	0	0.004018	0
p.E156K	III	classI-III	ilesha	1	0	2	0	0	0	0.001205	0
p.E317K	III	classI-III	Kalyan-Kerala, Jamnaga, Rohini	0	0	1	0	0	1	0.000402	0.000261
p.D282H	III	classI-III	Not Interrogated (Seattle, Lodi, Modena, Ferrara II, Athens-like)	0	0	1	1	0	3	0.000402	0.001043
p.L235F	III	classI-III	Nanning	0	0	1	0	0	0	0.000402	0
p.G163S	III	classI-III	Mahidol	1	0	0	0	0	0	0.000402	0
p.L128R	III	classI-III	Salerno Pyrgos	1	0	0	1	0	0	0.000402	0.000261
p.R227Q	III	classI-III	Mexico City	0	0	0	0	0	1	0	0.000261
p.I48T	III	classI-III	Aures	0	0	0	0	0	1	0	0.000261
p.N126D	IV	classIV	A	138	25	131	8	2	8	0.11812	0.004692
p.D350H	IV	classIV	Mirad'Aire	1	0	6	0	0	0	0.002812	0
p.M159I	NA	VUS	Not Interrogated	1	0	1	0	0	1	0.000804	0.000261
p.G316D	NA	VUS	Not Interrogated	0	0	1	0	0	1	0.000402	0.000261
p.D251N	NA	VUS	Not Interrogated	0	0	1	0	0	0	0.000402	0
p.D194E	NA	VUS	Not Interrogated	0	0	1	2	0	3	0.000402	0.001303
p.V303G	NA	VUS	Not Interrogated	0	0	0	0	0	1	0	0.000261

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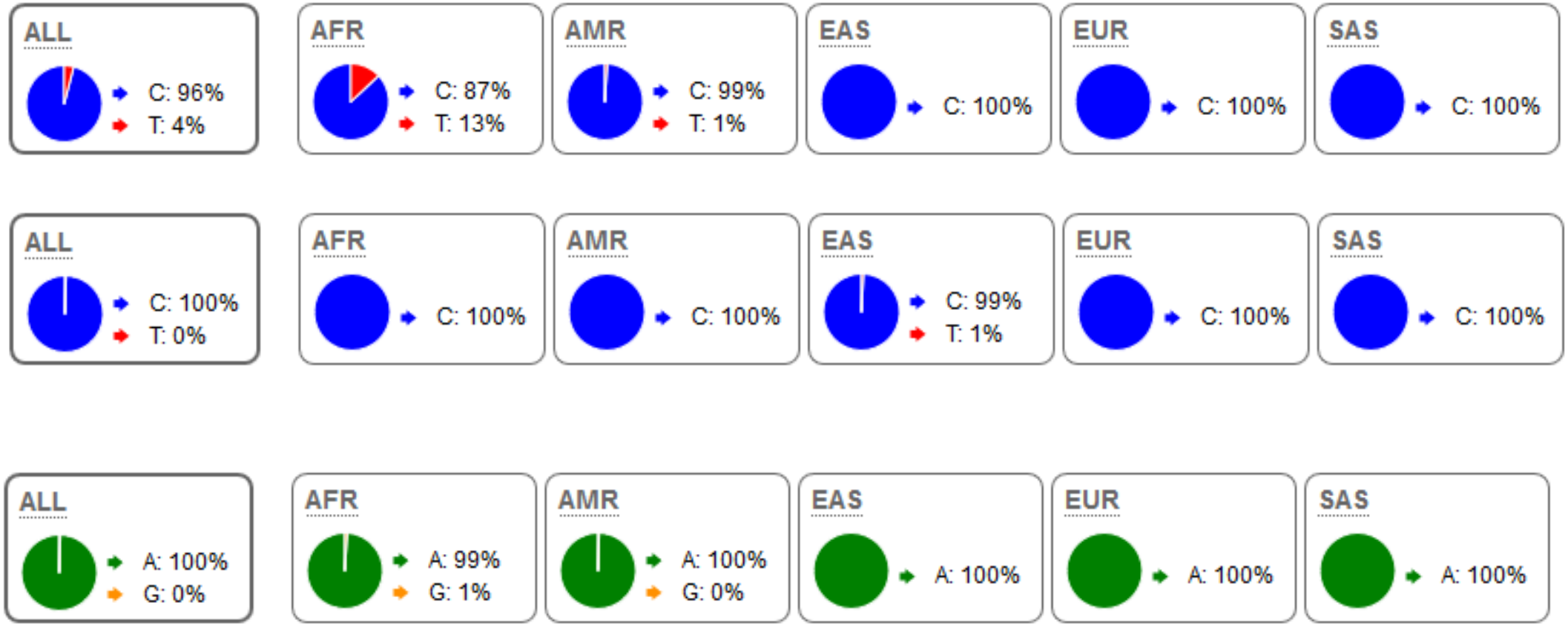


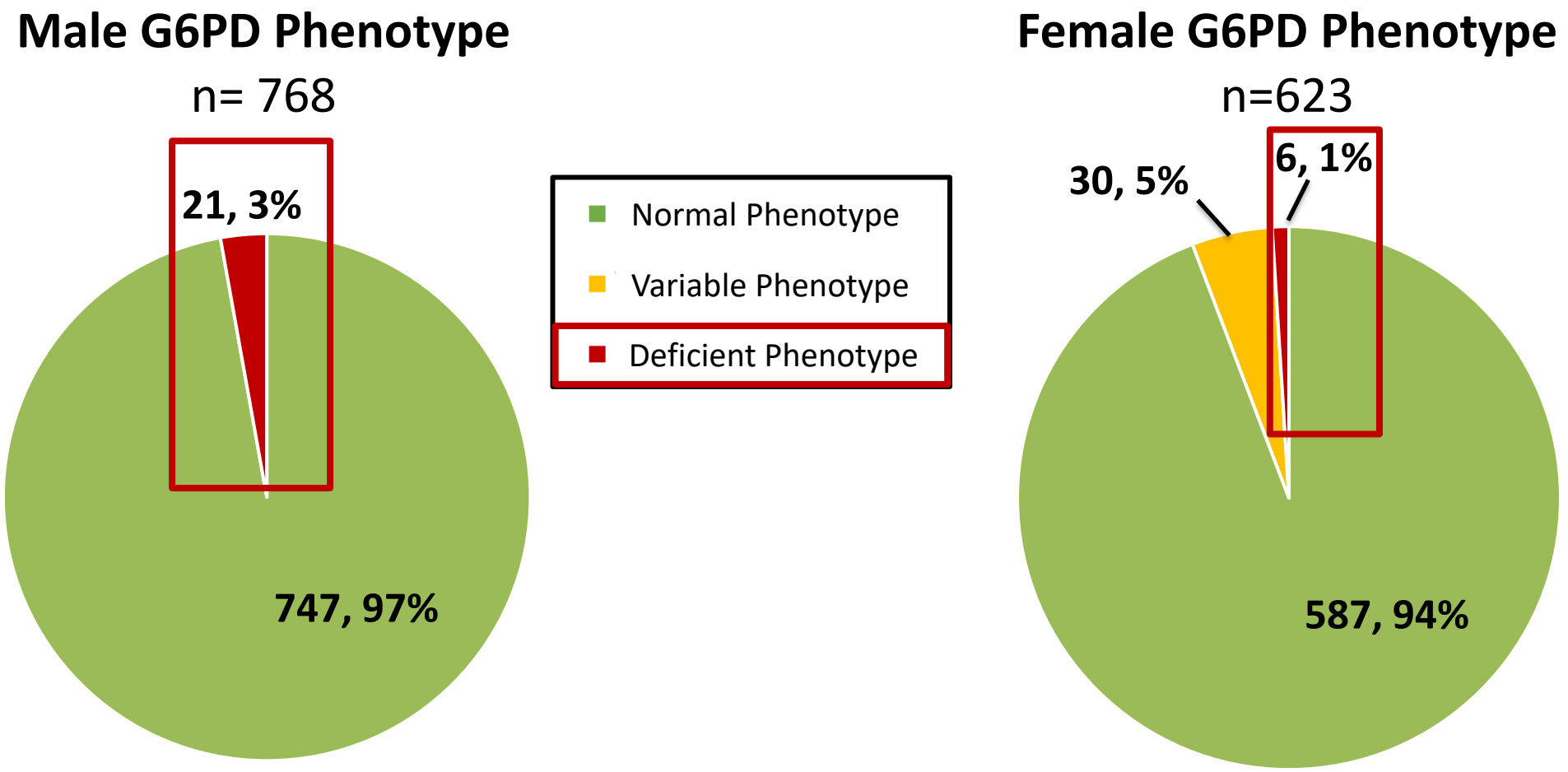
Plus we found one Pawnee variant (< 1 in 100,000 Exac)

Even with WES, no additional genotypes significantly correlated with G6PD activity besides the A- variant

pos	platform	multi. coef	multi.p	n.typed	maf	white. maf	black. maf	gene. func	snp.func	allele
153764217	exomechip,wes,snp6	2.635	3.19E-05	406	0.034	0	0.117	exonic	nonsynonymous	A-
153763492	wes,dmet	1.459	5.06E-03	563	0.075	0	0.328	exonic	nonsynonymous	A
153759858	wes	0.698	2.40E-01	374	0.306	0.118	0.837	UTR3		
153776107	wes	-0.911	2.82E-01	350	0.009	0	0.034	upstream		
153760654	wes	0.442	6.04E-01	375	0.141	0.108	0.223	exonic	synonymous	

Robinson KM, et al. Pharmacogenomics J. 2019;19(3):305-14.

G6PD phenotype based on genotype by gender



PG4KDS data on PharmacoScan™ from 06/2020

Journal of Infection (2010) 61, 399–402

ELSEVIER

www.elsevierhealth.com/journals/jinf

Prevalence of G6PD deficiency in a large cohort of HIV-infected patients

Jose A. Serpa [a,*], Erick Villarreal-Williams [a], Thomas P. Giordano [a,b]

- 75 of 1110 (6.8%) HIV pts had G6PD deficiency
- 37 deficient pts prescribed TMP/SMZ (160/800 qd or BID), 5 developed AHA (one due to surgery)
- AHA was not assessed in the non-deficient pts