CPIC® Guideline for Rasburicase and G6PD

Most recent guideline publication:

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Rasburicase Therapy in the context of *G6PD* Deficiency Genotype (August 2014)

Updates since publication:

September 2018: The CPIC authors recommend that the *G6PD A* variant be categorized as IV/normal function (previously II-IV/Deficient-Normal function) based on new evidence supporting function (PMID 27040960 and 30206300). This change has been incorporated into *G6PD* allele definition table.

Tables and figure provided in the main manuscript of the guideline:

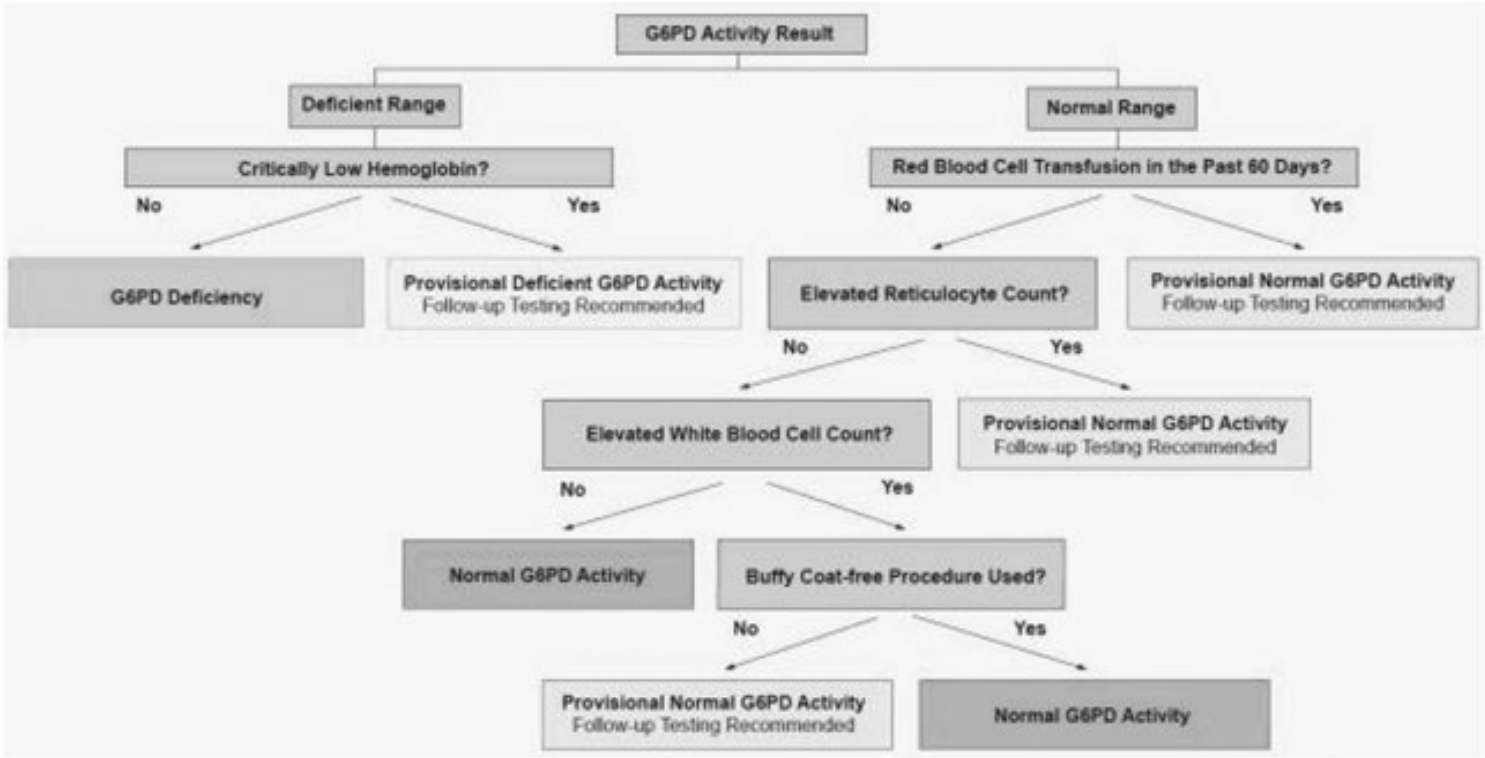
Table 1. Assignment of likely G6PD phenotypes based on genotype/diplotype
Table 2. Recommended therapeutic use of rasburicase in relation to G6PD phenotype
Figure 1. Workflow for interpreting *G6PD* genotype and for assessing the need for an enzyme activity test.

Supplement to: Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Rasburicase Therapy in the context of *G6PD* Deficiency Genotype (August

G6PD CPIC guideline update goals:

- Expand beyond rasburicase
- Update and reformat tables:
  - Allele definition
  - Allele functionality---coordinate with WHO, document evidence
  - allele frequency tables
- Acknowledge limitations of phenotype test

Fig. 1



G6PD activity interference assessment algorithm.

Activity can misclassify patients: Genotyping reassigned phenotype in 5/438 patients with discordant genotype and activity results:
3 switched from normal to deficient
2 two switched from deficient to normal

Morris et al, *Pharmacogenetics*, 2021

Original Article *Ann Clin Biochem* 1994; **31**: 50–55

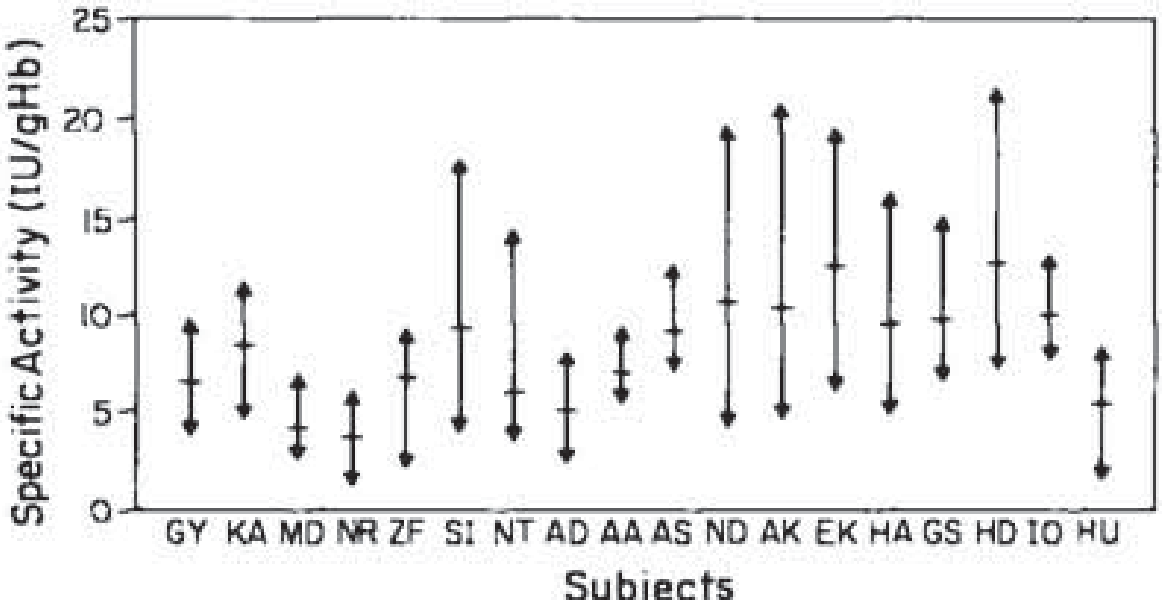
Studies on red cell glucose-6-phosphate dehydrogenase: evaluation of reference values

Günes T Yüregir, Kiymet Aksoy, Abdullah Arpaci, Isa Ünlükurt and Abdullah Tuli
From the Biochemistry Department, Çukurova University Medical School, 01330 Balcali, Adana, Turkey

Intra-individual variation > inter-individual variation; one single measurement does not suffice

TABLE 2. *Components of variation (CV) and indices derived for red blood cell glucose-6-phosphate dehydrogenase of 18 normal healthy subjects (%)*

Analytical variation (total)	CV_A	8·67
Intra-individual variation	CV_I	32·75
Inter-individual variation	CV_G	31·8



G6PD

- Evidence review: evidence showing a drug's association with hemolytic anemia in G6PD deficiency
  - high, moderate, weak evidence
- Assignment of drug to risk category
  - high-risk, medium-risk, low-to-no risk, vs no recommendation
- 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

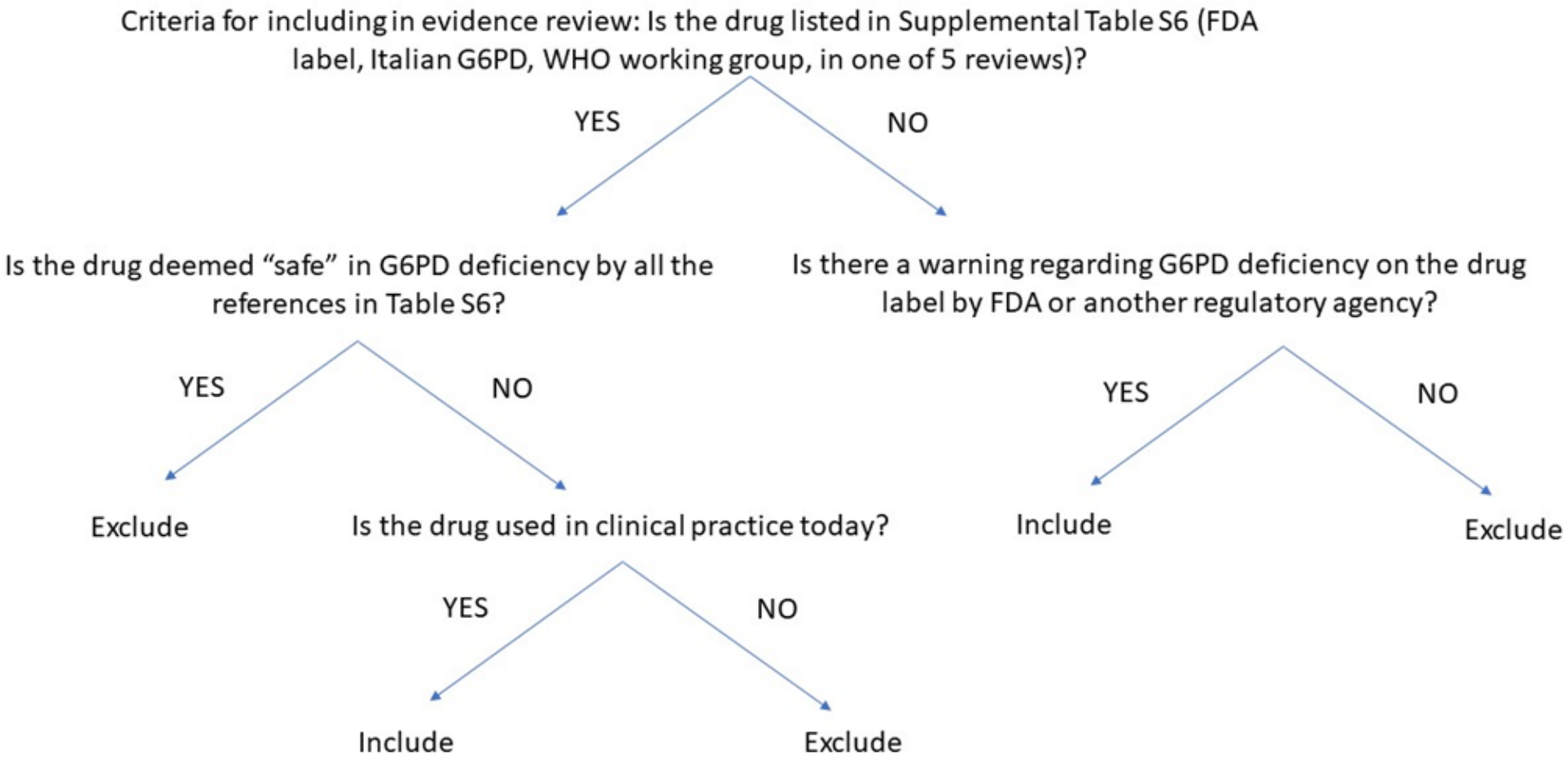
MV Relling[1], EM McDonagh[2], T Chang[3], KE Caudle[1], HL McLeod[4], CE Haidar[1], T Klein[2] and L Luzzatto[5]

> 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 48 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

Member Resources

- Manage your CPIC profile (including your password)
- Conference call minutes
- CPIC guideline drafts (for member review)
- CPIC SOP
- Draft allele function SOP
- CPIC authorship guidelines and conflict of interest standards
- CPIC Informatics Working Group
- CPIC Dissemination Working Group
- CPIC Scientific Advisory Board

Score the evidence

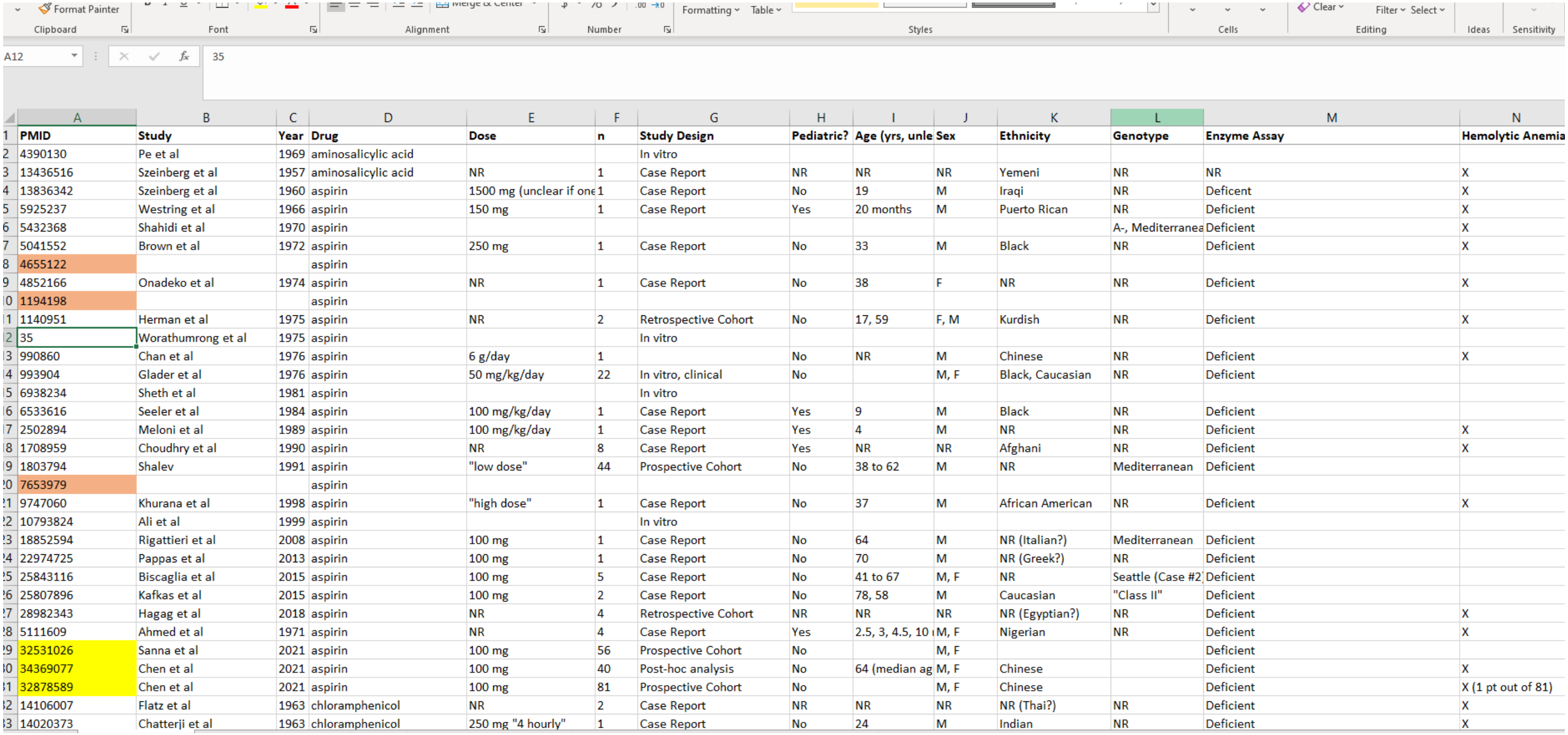
Initially, three or more authors will independently evaluate the literature. These authors will be responsible for presenting studies and recommending a level of evidence for each major finding to all guideline authors on a series of conference calls. All authors will be responsible for reviewing the 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

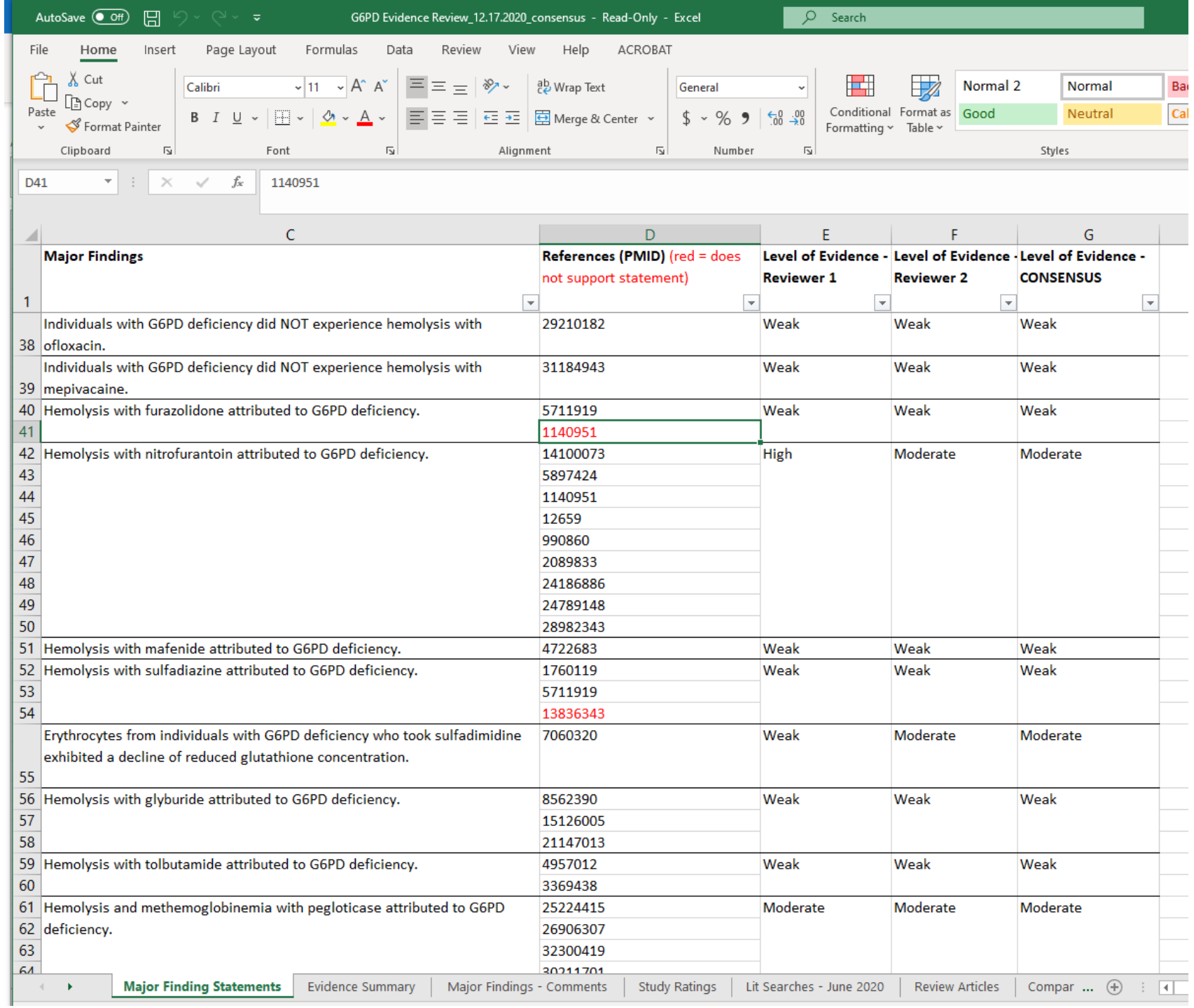
High evidence	Moderate evidence	Weak evidence
• Good quality studies supporting G6PD involvement with control groups; OR • Case reports with strong biological mechanism (e.g., production of H_20_2), especially if drug rarely used; AND • No convincing contradictory data	• Medium quality studies supporting 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

Iterative process



AutoSave Off — G6PD Evidence Review_12.17.2020_consensus - Read-Only - Excel — Search

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Cut Copy Format Painter Paste — Clipboard — Calibri 11 — Font — Wrap Text Merge & Center — Alignment — General — Number — Conditional Formatting Format as Table — Normal 2 Normal Good Neutral — Styles

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	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 tables for primaquine (dose-dependent)
- We have assigned a strength of prescribing recommendation to each drug for its use in G6PD deficiency

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

Strong regulatory warnings: "contraindicated; avoid" (more than just "caution")

Strength of recommendations

From CPIC SOP

Member Resources

- Manage your CPIC profile (including your password)
- Conference call minutes
- CPIC guideline drafts (for member review)
- CPIC SOP
- Draft allele function SOP
- CPIC authorship guidelines and conflict of interest standards
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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.

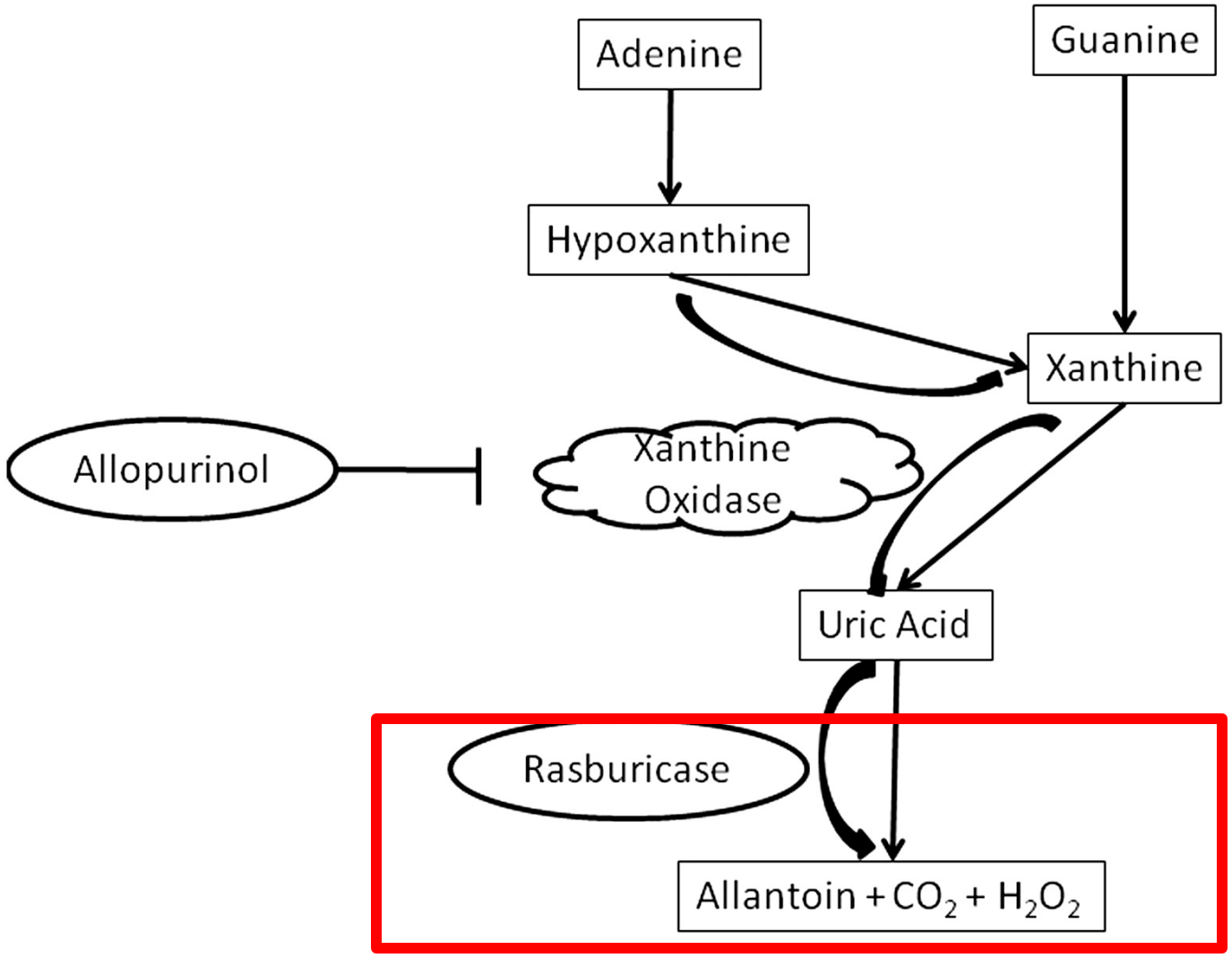
No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time

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

Raburicase (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 weak and 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												

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											

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

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 deficiency

Dapsone
Methylthioninium chloride (methylene blue)
Nitrofurantoin
Phenazopyridine
Primaquine
Rasburicase
Tolonium chloride (toluidine blue)

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

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	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	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	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	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 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 doses used for a prolonged duration of therapy	Avoid primaquine, except in the following cases where established expert consensus guidelines for the treatment of malaria should be followed: (1) Treating *P. falciparum* malaria by using primaquine as a gametocytocide: 0.25 mg/kg x1 dose (WHO); and (2) treating *Plasmodium vivax* or *P. 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). If primaquine is used, monitor 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	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	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.

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

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

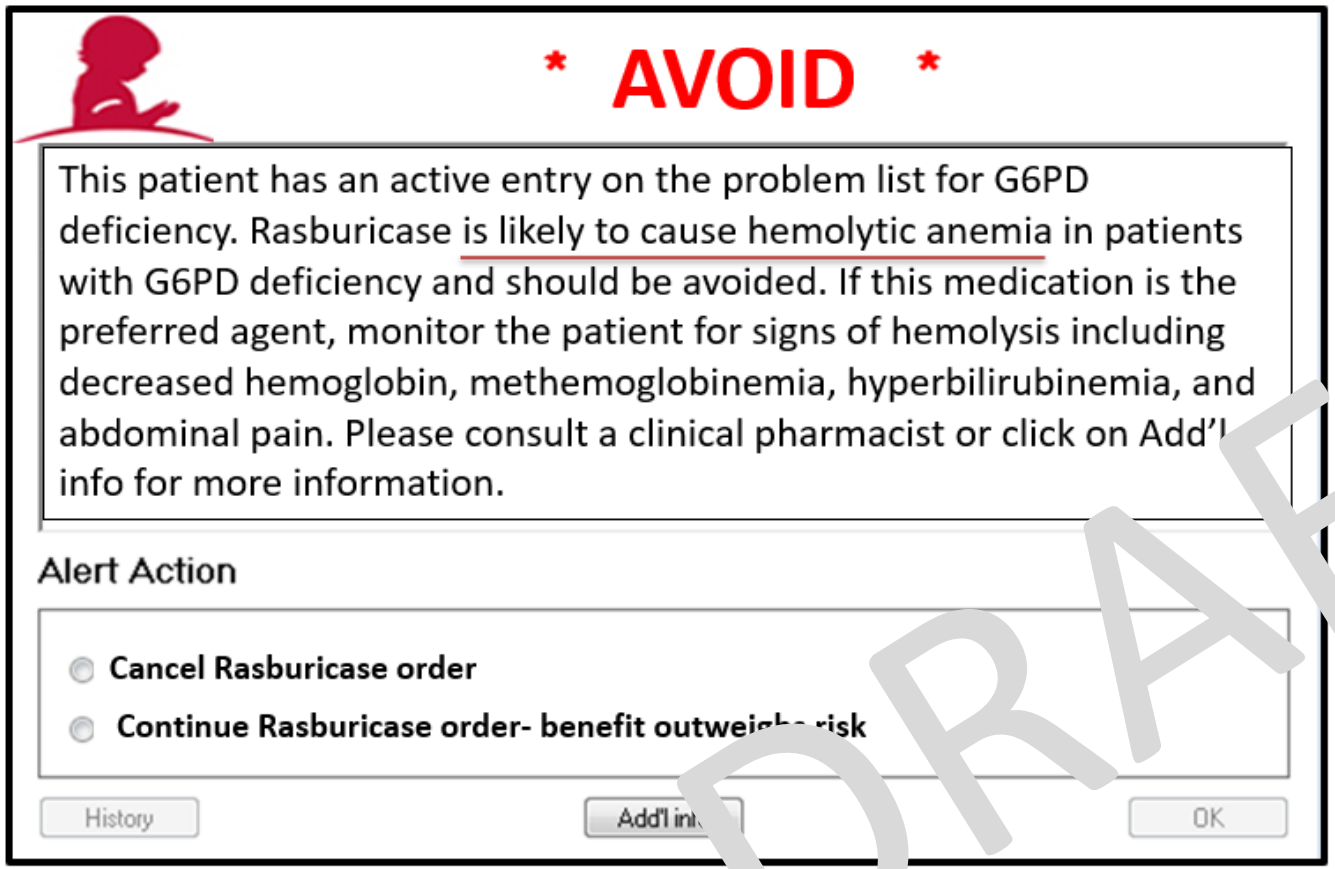
Predicted G6PD phenotype based on genotype	Implications for phenotypic measures	Therapeutic recommendations for low-to-no risk drugs	Classification of recommendations[a]	Considerations
Normal	Low-to-no risk of acute hemolytic anemia	No reason to avoid a low-to-no risk drug based on G6PD status.	Strong	
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.

CDS alert language

- To be done

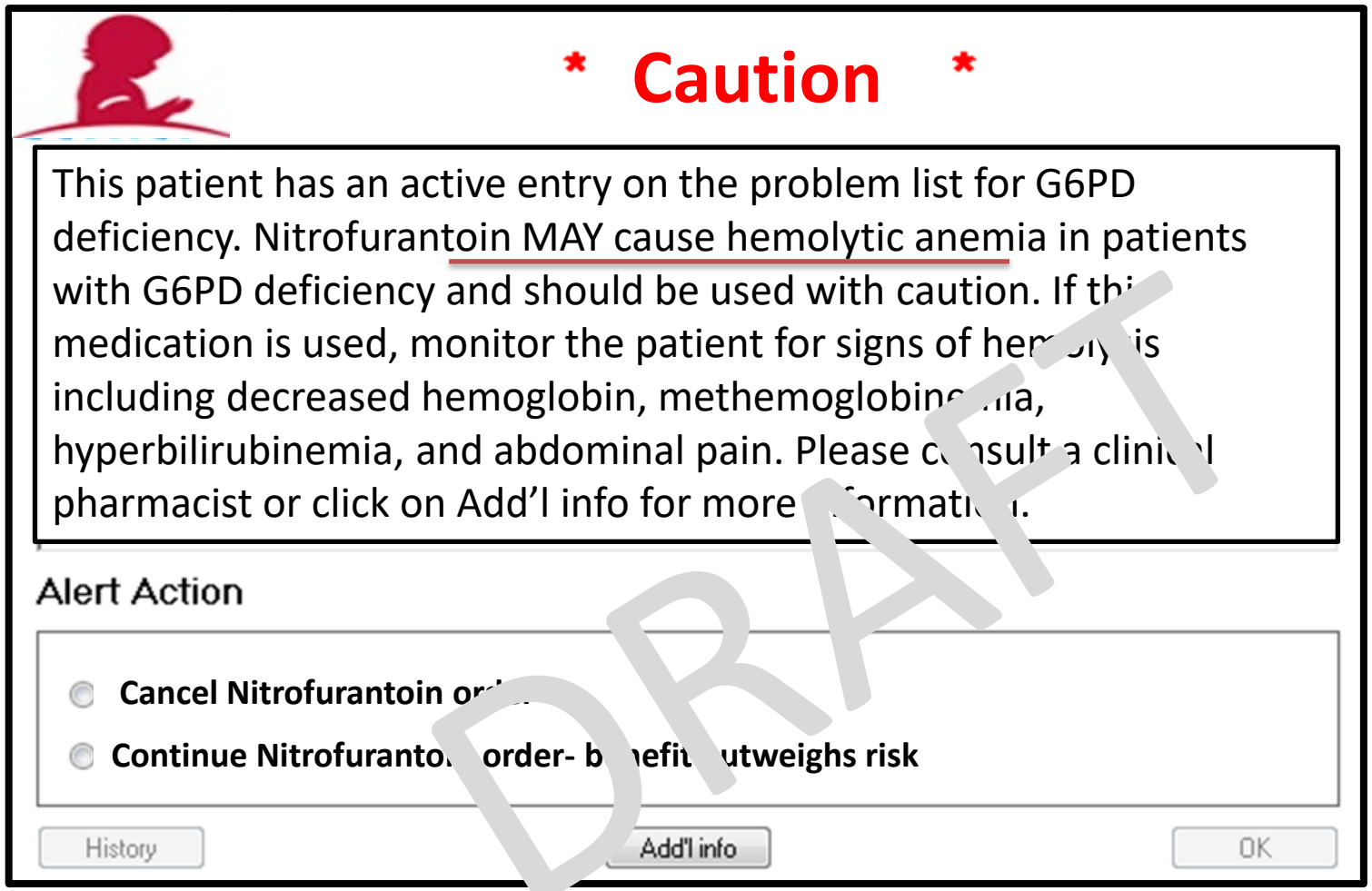
G6PD Deficiency Avoid Alert



Avoid

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

G6PD Deficiency Caution Alert

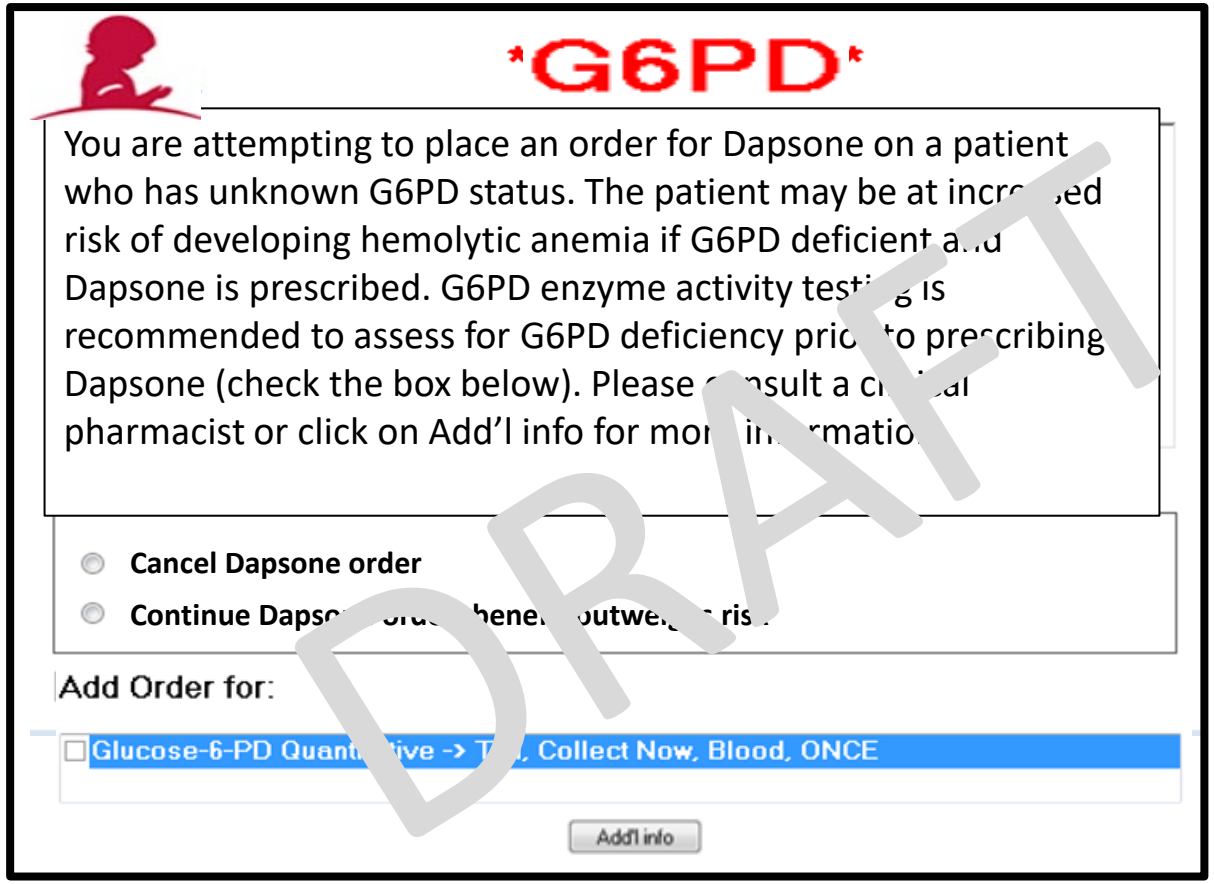


Use with caution

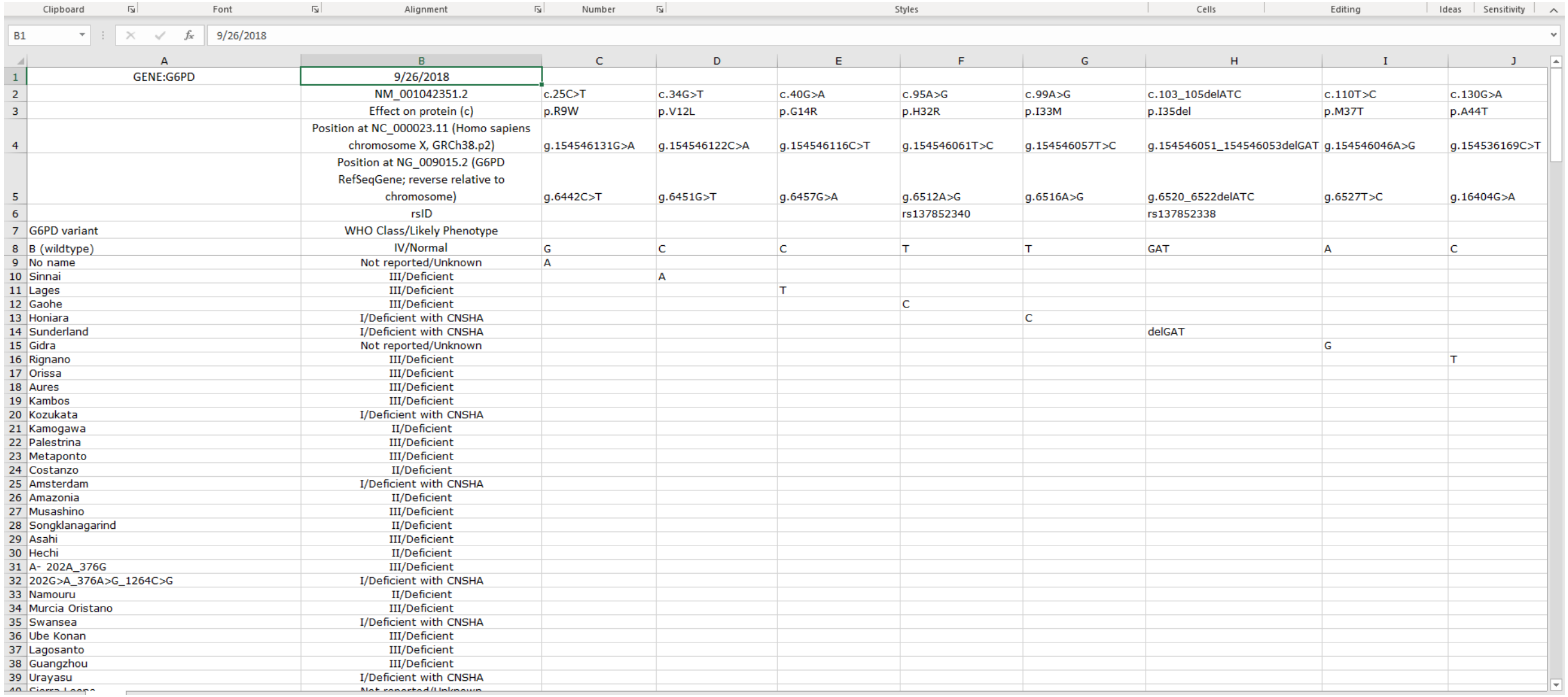
- Nitrofurantoin
- Primaquine—low dose

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



Existing G6PD allele definition table



	A	B	C	D	E	F	G	H	I	J
1	GENE:G6PD	9/26/2018								
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
3		Effect on protein (c)	p.R9W	p.V12L	p.G14R	p.H32R	p.I33M	p.I35del	p.M37T	p.A44T
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
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
6		rsID				rs137852340		rs137852338		
7	G6PD variant	WHO Class/Likely Phenotype								
8	B (wildtype)	IV/Normal	G	C	C	T	T	GAT	A	C
9	No name	Not reported/Unknown	A							
10	Sinnai	III/Deficient		A						
11	Lages	III/Deficient			T					
12	Gaohe	III/Deficient				C				
13	Honiara	I/Deficient with CNSHA					C			
14	Sunderland	I/Deficient with CNSHA						delGAT		
15	Gidra	Not reported/Unknown							G	
16	Rignano	III/Deficient								T
17	Orissa	III/Deficient								
18	Aures	III/Deficient								
19	Kambos	III/Deficient								
20	Kozukata	I/Deficient with CNSHA								
21	Kamogawa	II/Deficient								
22	Palestrina	III/Deficient								
23	Metaponto	III/Deficient								
24	Costanzo	II/Deficient								
25	Amsterdam	I/Deficient with CNSHA								
26	Amazonia	II/Deficient								
27	Musashino	III/Deficient								
28	Songklanagarind	II/Deficient								
29	Asahi	III/Deficient								
30	Hechi	II/Deficient								
31	A- 202A_376G	III/Deficient								
32	202G>A_376A>G_1264C>G	I/Deficient with CNSHA								
33	Namouru	II/Deficient								
34	Murcia Oristano	III/Deficient								
35	Swansea	I/Deficient with CNSHA								
36	Ube Konan	III/Deficient								
37	Lagosanto	III/Deficient								
38	Guangzhou	III/Deficient								
39	Urayasu	I/Deficient with CNSHA								

Malaria Policy Advisory Committee Meeting
2–4 October 2019, Geneva, Switzerland
Background document for Session 7

World Health Organization

Updating the WHO G6PD classification of variants and the International Classification of Diseases, 11th Revision (ICD-11)

October 2019

G6PD guideline authors

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Question slides

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

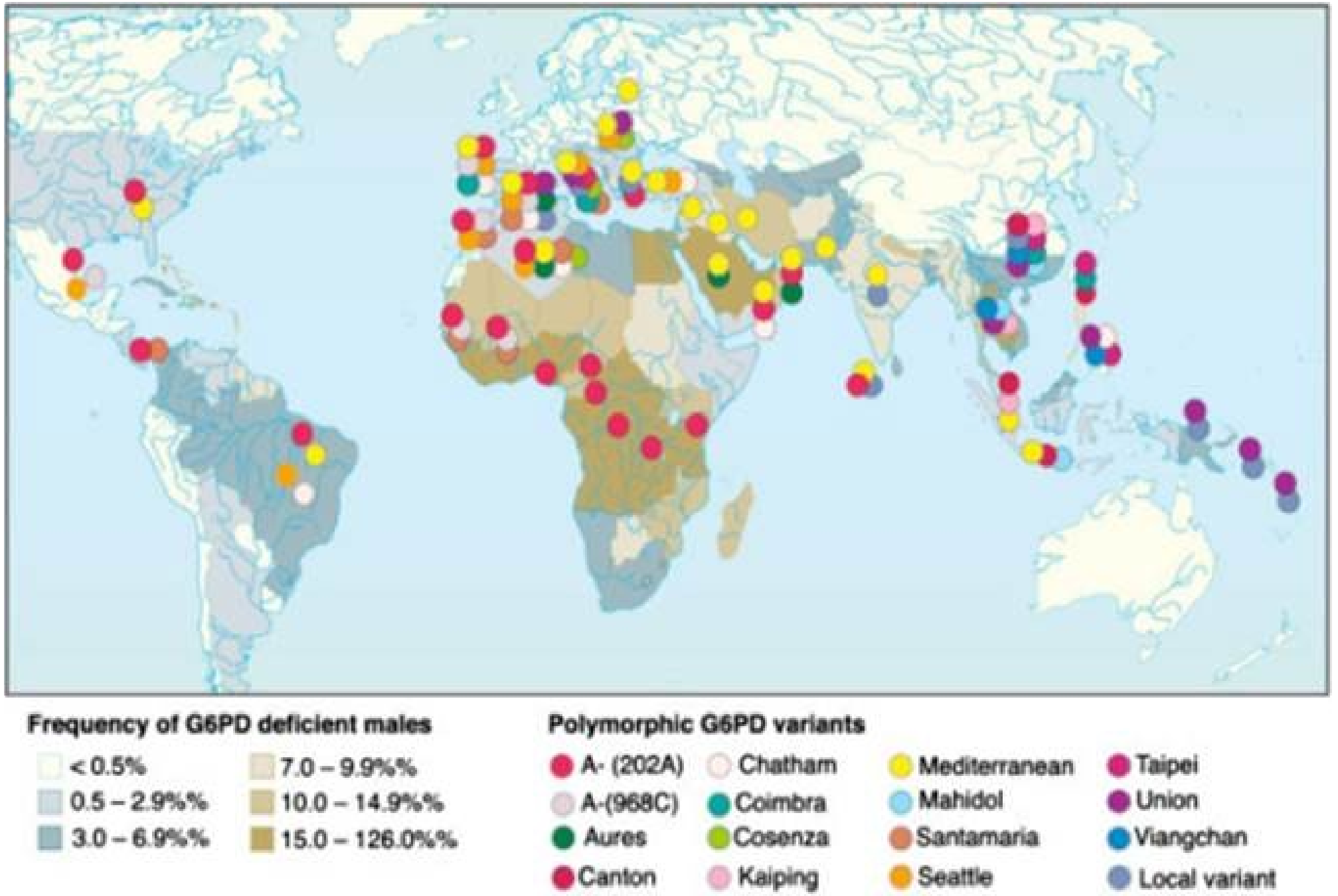
G6PD deficiency favism association. https://www.g6pd.org/en/G6PDDeficiency/SafeUnsafe.aspx.

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.



> 190 variants described, but most are very rare

Most common Class I-III variant observed was A- (we found in 8.7% of blacks)

SJ patients

A- rs1050828
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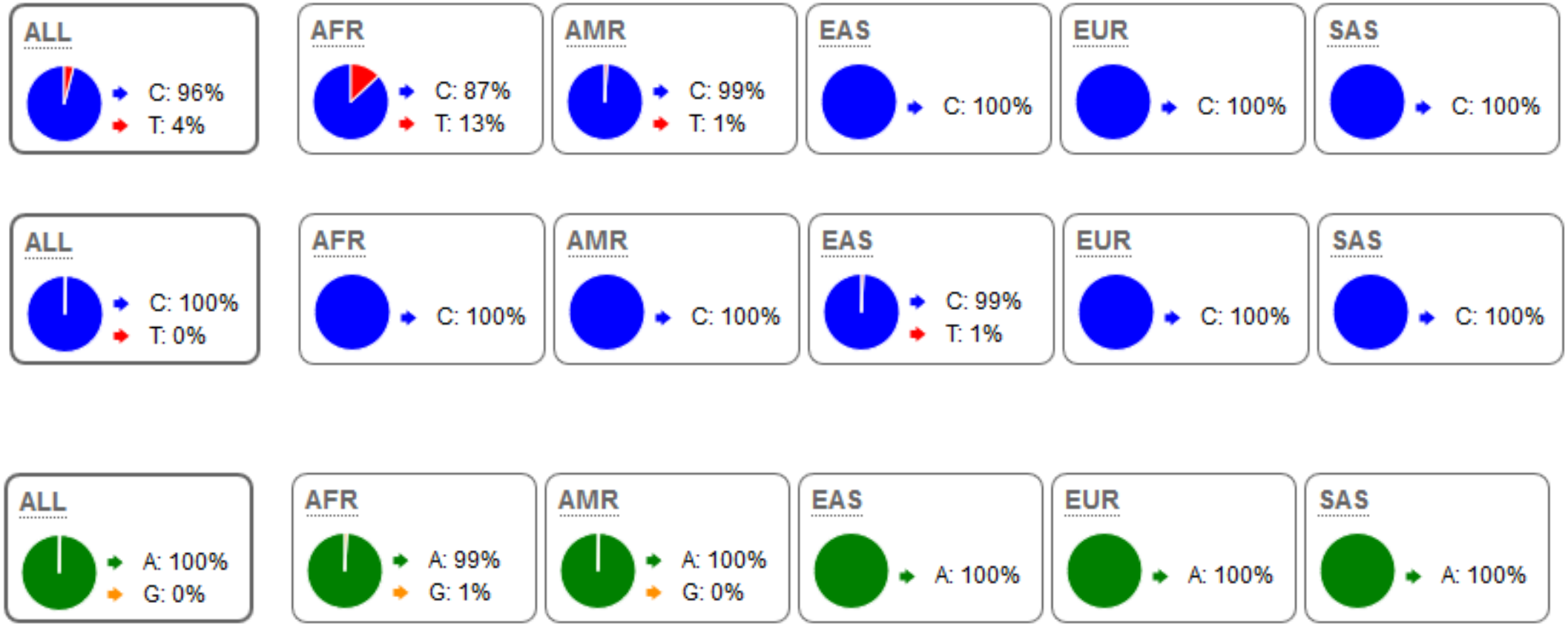
1000 Genomes Project Phase 3 allele frequencies



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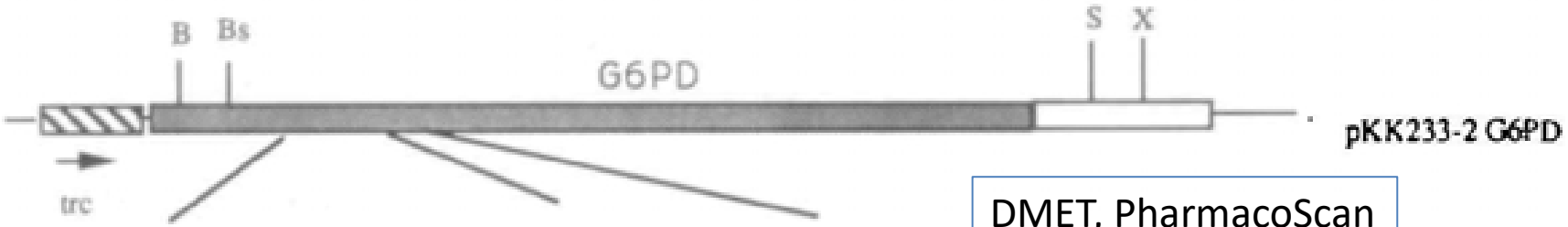
Department of Haematology, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 ONN, UK



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

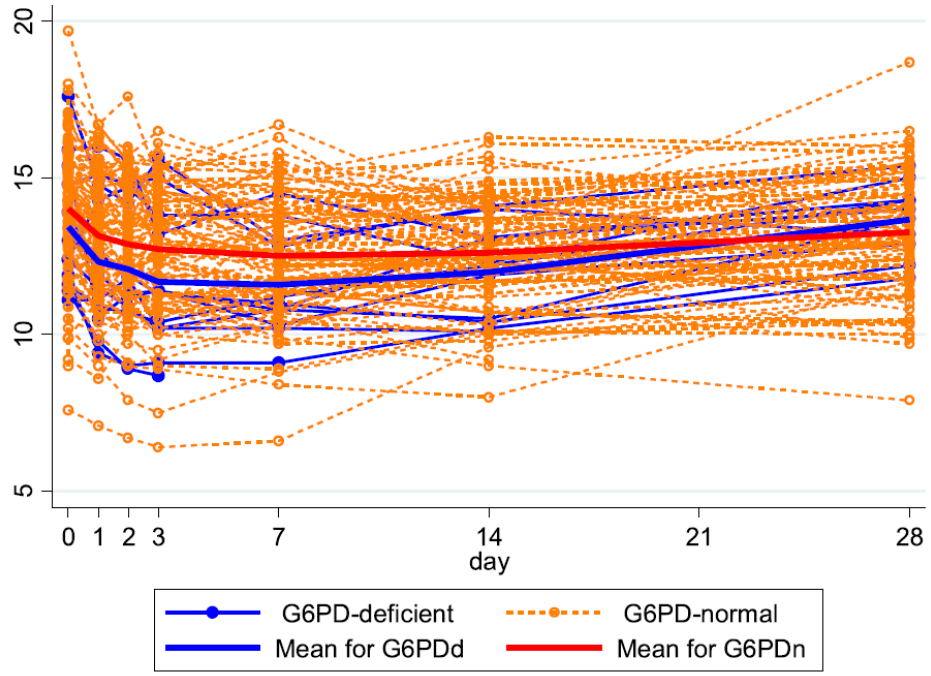
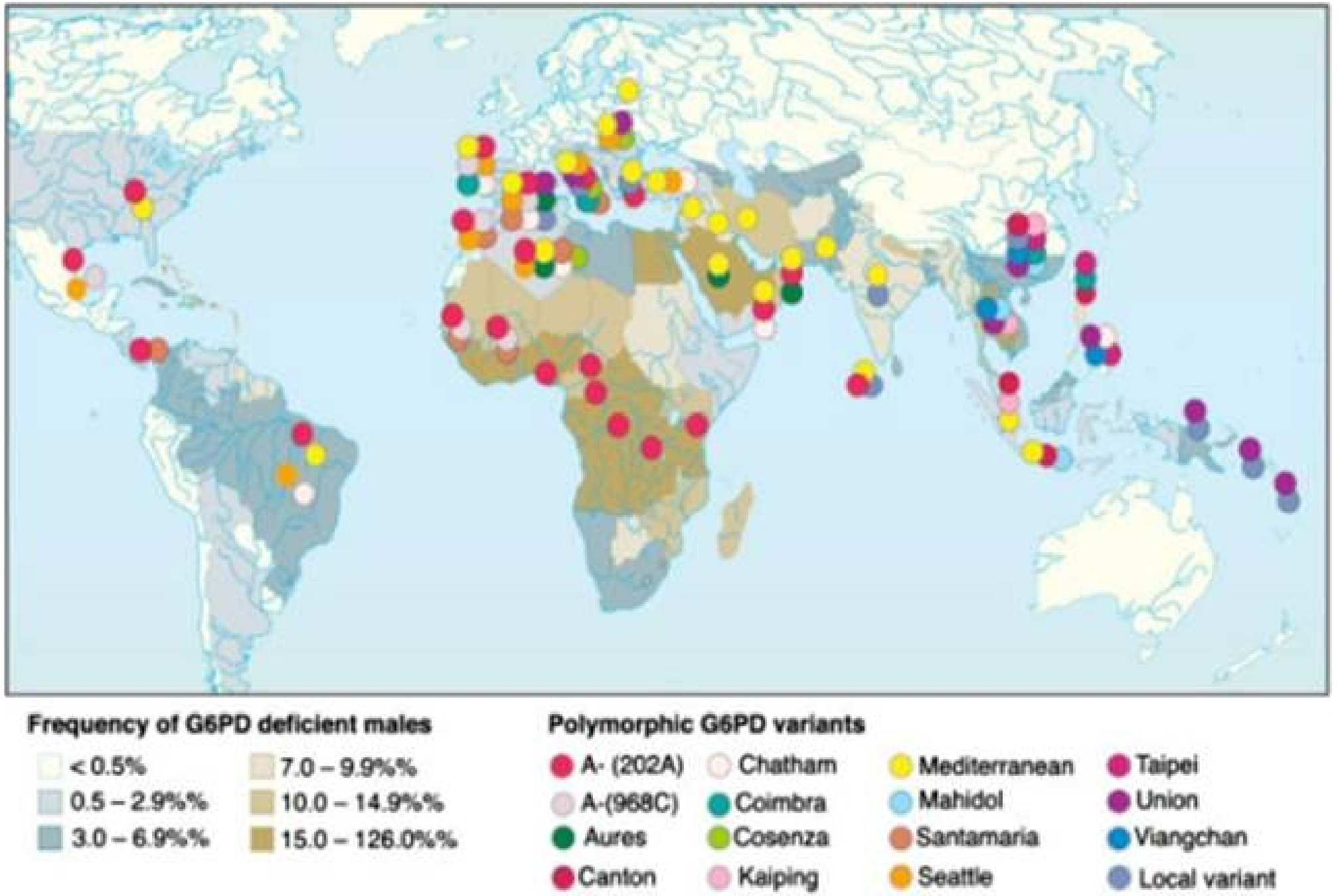


Fig. 3 Haemoglobin dynamics of the HemoCue measured hemoglobin concentrations as a function of glucose-6-phosphate dehydrogenase (G6PD) status

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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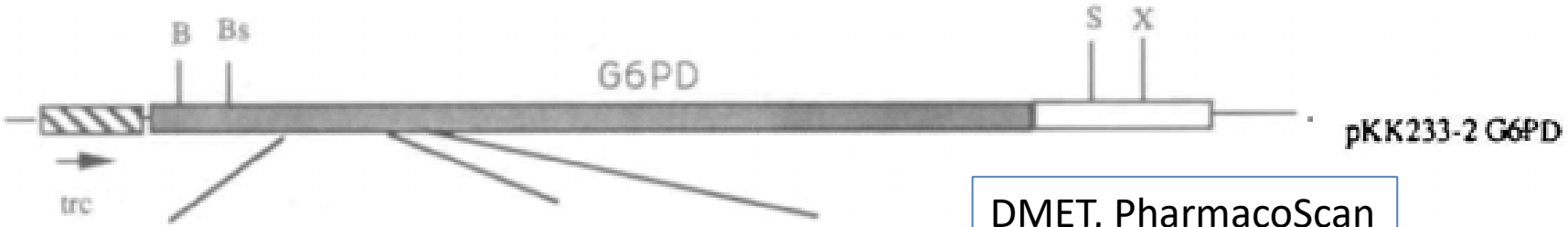

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Val	Glu	Asn	119E	
Met	Glu	Asn	119E,68M	

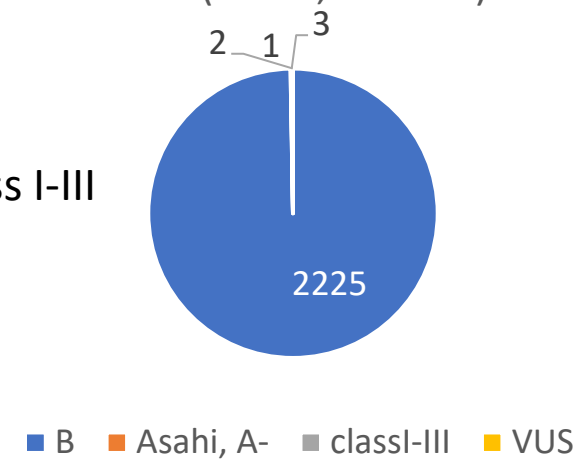
PharmacoScan

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

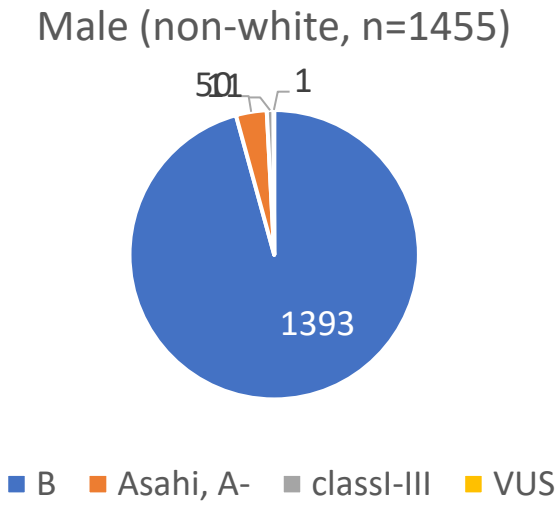
Male (white, n=2231)

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



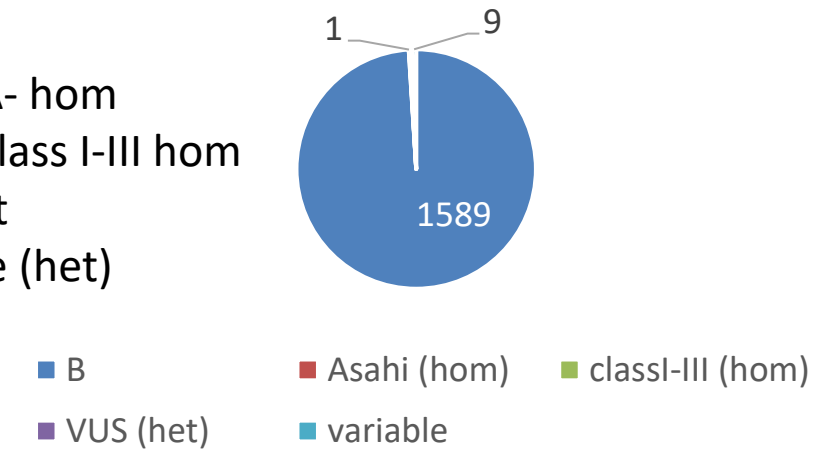
Male (non-white, n=1455)

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



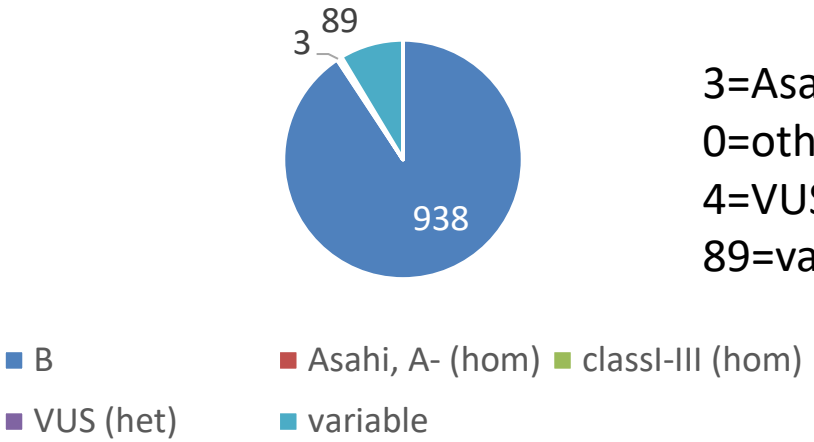
Female (white, n=1599)

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
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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
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p.D194E	NA	VUS	Not Interrogated	0	0	1	2	0	3	0.000402	0.001303
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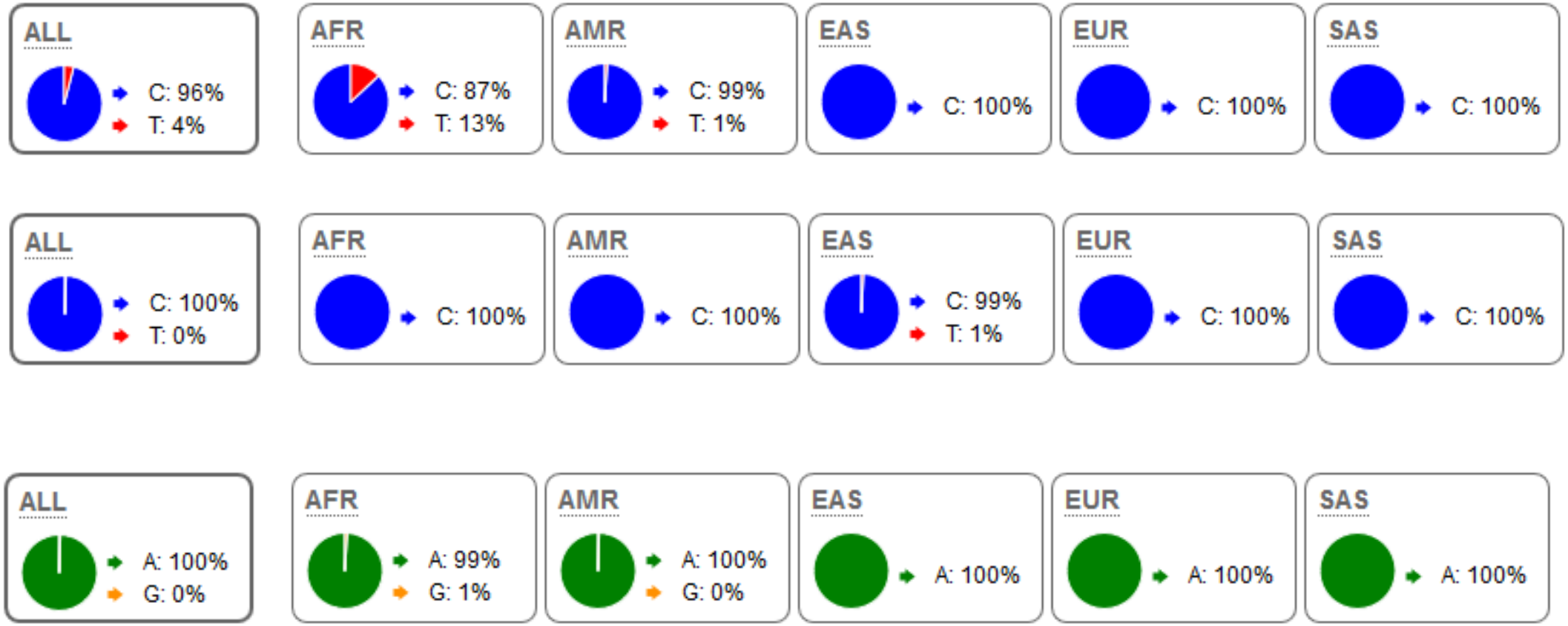

Plus we found one Pawnee variant (< 1 in 100,000 Exac)

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	

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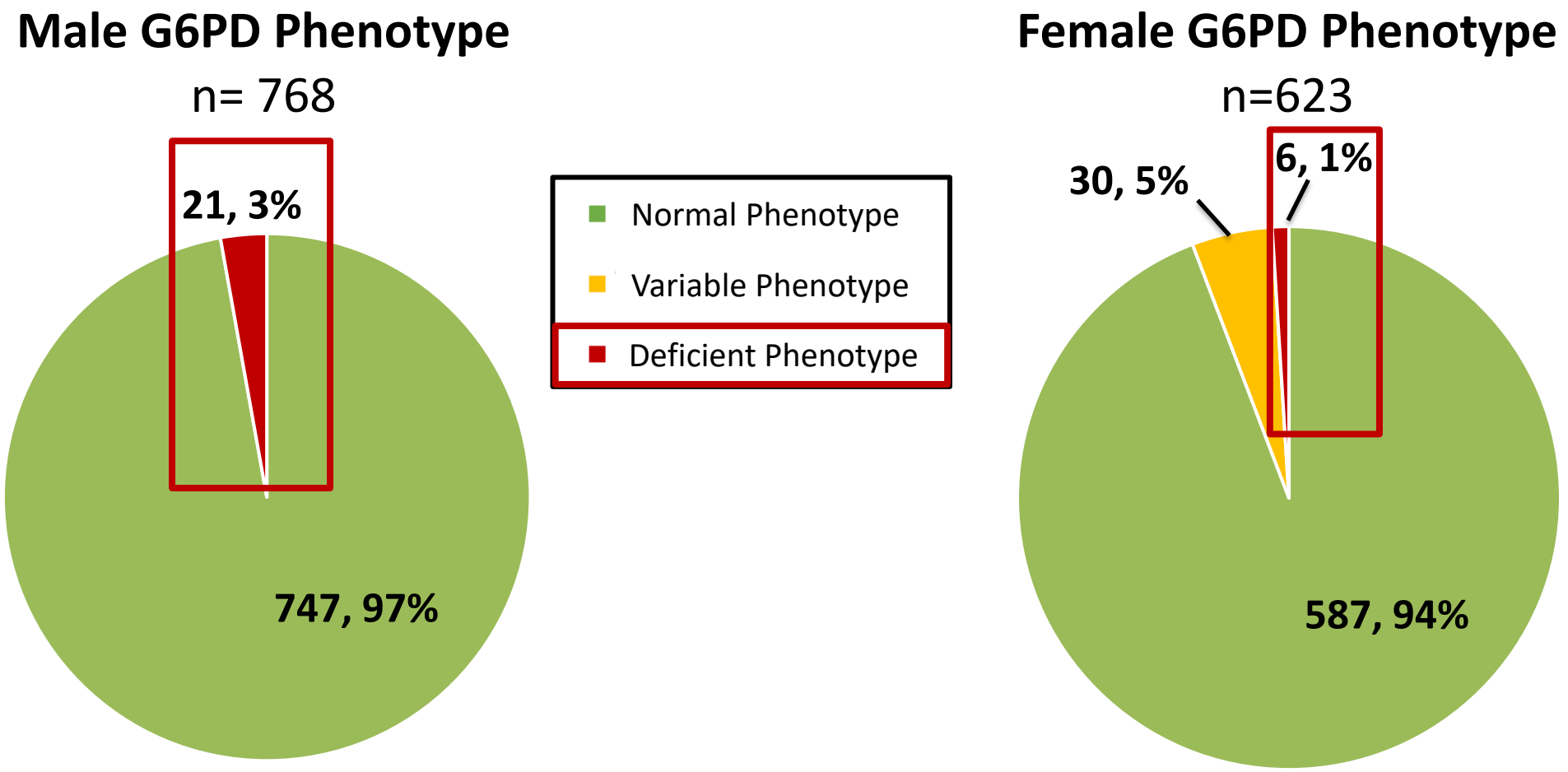
G6PD phenotype based on genotype by gender



PG4KDS data on PharmacoScan™ from 06/2020