SUPPLEMENTAL MATERIAL

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

Authors

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CPIC Updates

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are published in full on the PharmGKB website (http://www.pharmgkb.org/page/cpic). Information relevant to this guideline will be periodically reviewed and updated guidelines will be published online.

Focused Literature Review

We searched the PubMed database (1966 to August 2013) and OVID MEDLINE (1950 to August 2013) for keywords (rasburicase OR urate oxidase OR uricase OR elitek OR Fasturtec) AND (G6PD OR glucose-6-phosphate dehydrogenase OR G-6-PD). General searches for (rasburicase OR urate oxidase OR uricase OR elitek OR Fasturtec and (G6PD OR glucose-6-phosphate dehydrogenase OR G-6-PD were also carried out. Definitive reviews (1-10) were relied upon to summarize much of the earlier literature.

G6PD Genetic Variant Nomenclature and WHO Class

Criteria for the identification and characterization of *G6PD* variants were established by the WHO Scientific Group starting in 1967 (11), based primarily on samples from hemizygous males. Characteristics used to classify alleles have included G6PD activity in red blood cells, electrophoretic migration as compared to the normal B enzyme, thermal stability, and Michaelis constant for G6P and rate of utilization. Nomenclature guidelines were outlined before the cDNA position for each was reported, and suggested the use of geographical or trivial names for new variants (11).

Along with being grouped by how much evidence existed for a particular variant, in 1971 the *G6PD* variants were also divided into 5 classes depending on phenotype, as determined by extent of enzyme deficiency and associated clinical manifestations (see Supplementary Table 2) (12). Standardized criteria for determining the class were defined and included erythrocyte activity level and electrophoretic mobility performed on samples from hemizygous males. It should be noted that the variants were “somewhat

arbitrarily divided into five classes" and that the "distinction between these classes is not always clear" (12). For example, although the Mediterranean variant (rs5030868 563C>T) is assigned a class II definition, it has also been associated with chronic nonspherocytic hemolytic anemia (CNSHA), consistent with the definition of class I variants (12). Some class I variants have higher enzyme activity *in vitro* than those of class III variants (12) and *in vivo* enzyme activity can be altered by numerous factors (1, 3). This class system was again reported in a WHO update article with slight differences in enzyme activity for class IV (normal activity described as 60-150%) and class V (described simply as increased activity)(10). This five class system describing phenotypes for *G6PD* variants has been used since; (13) however, recent school of thought and evidence suggests that the clinical phenotype is blurred between class II and III variants. Thus, class II and III variants should not be considered separate risk phenotypes and instead three phenotype classes should be used (11, 14), as we have used in this guideline (Tables 1 and 2 main manuscript). See Supplementary Table S1 for a list of *G6PD* variants, nucleotide and amino acid substitutions, and associated WHO class and phenotype, based on a published update of *G6PD* variants (13) and previous publications (15).

Despite establishing nomenclature rules, the same genetic variant may have several different names; for example Mediterranean, Dallas, Panama, Sassari, Birmingham and Cagliari are all conferred by allele T at position 563 (rs5030868) but the enzyme variation was discovered in different populations (15). In addition, restriction endonuclease analysis of DNA revealed that several G6PD variants thought to be the same had different underlying genetic variants; for example, the A- enzyme is a combination of the A variant (376A>G, rs1050829) and another variant, either 202A (rs1050828), or 680T (rs137852328), or 968C (rs76723693) (16). Worldwide estimates of G6PD deficiency prevalence (17) are listed in Supplementary Table S3. World distribution of G6PD low-function alleles correlates with malaria endemic regions, and this originally prompted the notion that G6PD deficiency confers protection from malaria. Populations from Asia, Africa and the Middle East are associated with the highest prevalence of G6PD deficiency (Supplemental Table S3, S4 and S5).

Frequencies of alleles in major race/ethnic groups are listed in Supplementary Table S4. See Supplementary Table S5 for a detailed listing of racial/ethnic group assignments.

G6PD Heterozygotes

Determining G6PD phenotype in heterozygous females (one normal class IV allele and one deficient class I-III allele) is not possible based on genetic testing alone due to X-linked chromosome inactivation. For example, in a study of Afghan refugees, the majority of women heterozygous for the Mediterranean variant (class II) had normal G6PD enzyme activity (by colorimetric assay), but one quarter were G6PD deficient (18). Variation in the percentage of G6PD deficient cells can change in the same individual over the space of a year, from 0% to 31% (19). Age is also a factor due to skewing of X chromosome inactivation. Newborn heterozygotes have a red cell population distribution skewed towards G6PD normal red blood cells, whereas heterozygous adults tend to show a more symmetrical distribution (20). Inactivation of the G6PD normal X chromosome increases in elderly heterozygotes, correlating with decreased G6PD activity levels (20, 21). This may mean as heterozygous females age they become more susceptible to clinical manifestations (21). For example, in a case report in which a novel class I variant was identified (Tondela), the mother was heterozygous and displayed chronic hemolytic anemia due to almost exclusive mRNA expression of the variant allele in reticulocytes resulting in G6PD deficiency, however two of her daughters were also heterozygous but asymptomatic with normal G6PD activity in red blood cells (22).

Determining whether a heterozygous female is at increased risk of drug-induced hemolytic anemia is therefore not possible without measuring G6PD activity. Previous studies of dapsone treatment in A- heterozygote children with uncomplicated malaria infection seemed to show they were not at an increased risk of drug-induced AHA, until data from several studies was combined (23). The report showed that average risk is somewhere in between that of children with G6PD deficiency (hemizygous or homozygous A-) and those with normal G6PD, but individually this risk is highly variable due to X-linked mosaicism; with some individuals showing severe hemolysis upon dapsone treatment with a similar profile to that of deficient children, whilst others

had very similar responses in hemoglobin levels as 'normal' children (23). The studies support the idea that the A- variant cannot be considered 'mild', as depending on the strength of the drug challenge, can cause severe life-threatening AHA (23). It is not known if these children may have had other genetic variants that could have contributed to the severity, and malaria infection should also be taken into account. For example, in a separate study a 21-month girl heterozygous for A- suffered severe anemia with an anti-malarial regime containing methylene blue, she also however had high parasitaemia, and overall heterozygotes were not reported to have a higher risk of hemoglobin decrease than wild-type children (24). Whether the response to rasburicase would be similar to that of dapsone is not known, as there are (to our knowledge) no known reported cases in heterozygous females (Supplemental Table S6).

Compound heterozygotes (carrying two deficient class I-III alleles with different variants) seem to be rarely reported in the literature; this may be due to most studies screening for a limited number of genetic variants rather than gene sequencing. Examples include: an 86 year-old Chinese female who displayed G6PD deficiency with the Canton/ Viangchan genotype (class II/II) (21), Mediterranean/ Clatham (class II/II) and Asahi/ Clatham (class III/II) in Saudi women with G6PD deficiency (25). This assignment of compound heterozygous status is based on the assumption that each *G6PD* allele carries a deficient variant, rather than the two different variants residing on the same chromosome.

Available Genetic Test Options

Several testing services for *G6PD* are available; however, commercially available genetic testing options change over time. An updated and fully linked table is available at http://www.pharmgkb.org/gene/PA28469. Furthermore, the Genetic Testing Registry (GTR) provides a central location for voluntary submission of genetic test information by providers and is available at http://www.ncbi.nlm.nih.gov/gtr/tests/?term=g6pd.

Recommendations for Incidental Findings

There are a number of medications that have been suggested to be avoided in G6PD deficient individuals (Supplemental Table S7) (1, 4, 10, 26, 27). The development of a list of unsafe drugs in the setting of G6PD deficiency was historically developed through observations of hemolysis after ingestion of a drug or clinical investigations with ^{51}Cr-labeled erythrocytes to determine erythrocyte survival (1). More recently, several groups have attempted to consolidate the varying recommendations for safe and unsafe drugs in G6PD deficient individuals and have found that the evidence supporting a clear association with drug-induced hemolysis exists only for a small number of agents (3, 4). Future CPIC guidelines will provide additional information on the non-rasburicase G6PD drug substrates. Many drugs previously thought to be unsafe (i.e. aspirin) can be safely administered at therapeutic doses without evidence of hemolysis (4). Patients and clinicians should be aware of signs and symptoms that may indicate an acute hemolytic crisis or methemoglobinemia.

Other Considerations

Physiological factors other than genetic variants in the *G6PD* gene may result in differences in G6PD enzyme expression (28). As G6PD activity is usually measured in erythrocytes, conditions affecting reticulocytosis and blood transfusions could affect G6PD activity. Exogenous agents may also cause hemolysis in an individual at one time when previously it had no effect (10). Susceptibility to drug-induced hemolytic anemia can be influenced by factors that are not constant; dosage and drug pharmacokinetics, the pharmacodynamic effects of the drug on G6PD activity, the presence of additional oxidative stresses such as concomitant drug administration, drug-drug interactions and infection, or baseline characteristics such as hemoglobin concentration and erythrocyte population age (3).

Other inherited enzyme deficiencies may increase a patient's risk for hemolytic anemia, such as catalase deficiency (acatalasaemia) or the risk of methemoglobinemia, for example cytochrome b5 reductase deficiency or Hemoglobin M (29-31). Due to lower levels of enzymes that protect from oxidative stress, such as catalase, cytochrome b5

reductase and glutathione peroxidase, newborns are more susceptible to methemoglobinemia (31-33).

Unsafe Drugs for G6PD deficient patients. Supplementary Table S7 summarizes the available drug and compound safety reviews for G6PD deficient patients available from the FDA, the Associazione Italiana Favismo from their website (www.g6pd.org) and published articles.

Levels of Evidence Linking Genotype to Phenotype

The evidence linking *G6PD* genotype to phenotype (adverse reaction to rasburicase) is summarized in Supplemental Table S6 and is graded using a scale modified slightly from Valdes, *et al (34)*:

> **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.

Strength of Recommendations

CPIC's dosing recommendations are based weighting the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account include: *in vivo* clinical outcome for rasburicase, *in vivo* pharmacodynamics for rasburicase, *in vitro* enzyme activity for reference drug, *in vivo* clinical outcome with another drug plus variant type, *in vivo* pharmacokinetics/pharmacodynamics for another drug plus variant type, *in vitro* enzyme activity with another drug plus variant type, *in vitro* enzyme

activity with probe substrate only, *in vivo* clinical outcome with another drug only, *in vivo* pharmacokinetics/pharmacodynamics for another drug only, and *in vitro* enzyme functional (protein stability or enzyme activity with another drug).

Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians. We chose to use a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of retroviral agents (http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf): strong, where "the evidence is high quality and the desirable effects clearly outweigh the undesirable effects"; moderate, in which "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects; and optional, in which the desirable effects are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action.

Strong recommendation for the statement
Moderate recommendation for the statement
Optional recommendation for the statement

Supplemental Table S1. G6PD genetic variants and likely conferred enzyme phenotype[a]

Variant Name[a]	cDNA nucleotide substitution (Negative chromosomal strand) Constituted by genotypes at: [a, b]	dbSNP rsID[c]	Amino acid substitution[a]	Codon[a]	WHO Class[a, d]	Likely Phenotype[e]	References[a]
Villeurbanne	1000_1002delACC		Thr	334	I	Deficient with CNSHA	(35)
Torun	1006A->G		Thr->Ala	336	I	Deficient with CNSHA	(36)
Sunderland	105_107delCAT		Ile	33 or 34	I	Deficient with CNSHA	(37)
Iwatsuki	1081G->A		Ala->Thr	361	I	Deficient with CNSHA	(38)
Serres	1082C->T		Ala->Val	361	I	Deficient with CNSHA	(39)
Tondela	1084_1101delCTGAACGAGCGCAAGGCC		Leu-Asn-Glu-Arg-Lys-Ala	362-367	I	Deficient with CNSHA	(22)
Loma Linda	1089C->A		Asn->Lys	363	I	Deficient with CNSHA	(40)
Aachen	1089C->G		Asn->Lys	363	I	Deficient with CNSHA	(41)
Tenri	1096A->G		Lys->Glu	366	I	Deficient with CNSHA	(42)
Montpellier	1132G>A		Gly>Ser	378	I	Deficient with CNSHA	(35)
Calvo Mackenna	1138A->G		Ile->Val	380	I	Deficient with CNSHA	(43)
Riley	1139T->C		Ile->Thr	380	I	Deficient with CNSHA	(43)
Olomouc	1141T->C		Phe->Leu	381	I	Deficient with CNSHA	(43)
Tomah	1153T->C		Cys->Arg	385	I	Deficient with CNSHA	(43)
Lynwood	1154G->T		Cys->Phe	385	I	Deficient with CNSHA	(38)
Madrid	1155C->G		Cys->Trp	385	I	Deficient with CNSHA	(44)
Iowa, Walter Reed, Springfield	1156A->G		Lys->Glu	386	I	Deficient with CNSHA	(45)
Guadalajara	1159C->T		Arg->Cys	387	I	Deficient with CNSHA	(46)

Variant Name[a]	cDNA nucleotide substitution (Negative chromosomal strand) Constituted by genotypes at: [a, b]	dbSNP rsID[c]	Amino acid substitution[a]	Codon[a]	WHO Class[a, d]	Likely Phenotype[e]	References[a]
Beverly Hills, Genova, Iwate, Niigata, Yamaguchi	1160G->A		Arg->His	387	I	Deficient with CNSHA	(47, 48)
Hartford	1162A->G		Asn->Asp	388	I	Deficient with CNSHA	(38)
Praha	1166A->G		Glu->Gly	389	I	Deficient with CNSHA	(49)
Krakow	1175T>C		Ile>Thr	392	I	Deficient with CNSHA	(50)
Wisconsin	1177C->G		Arg->Gly	393	I	Deficient with CNSHA	(43)
Nashville, Anaheim, Portici	1178G->A		Arg->His	393	I	Deficient with CNSHA	(40, 51)
Alhambra	1180G->C		Val->Leu	394	I	Deficient with CNSHA	(49)
Bari	1187C->T		Pro->Leu	396	I	Deficient with CNSHA	(52)
Puerto Limon	1192G->A		Glu->Lys	398	I	Deficient with CNSHA	(53)
Covao do Lobo	1205C>A		Thr>Asn	402	I	Deficient with CNSHA	(54)
Clinic	1215G->A		Met->Ile	405	I	Deficient with CNSHA	(55)
Utrecht	1225C->T		Pro->Ser	409	I	Deficient with CNSHA	(56)
Suwalki	1226C->G		Pro->Arg	409	I	Deficient with CNSHA	(57)
Riverside	1228G->T		Gly->Cys	410	I	Deficient with CNSHA	(45)
Japan, Shinagawa	1229G->A		Gly->Asp	410	I	Deficient with CNSHA	(58, 59)
Kawasaki	1229G->C		Gly->Ala	410	I	Deficient with CNSHA	(38)
Munich	1231A->G		Met->Val	411	I	Deficient with CNSHA	(60)
Georgia	1284C->A		Tyr->End	428	I	Deficient with CNSHA	(49)
Sumare	1292T->G		Val->Gly	431	I	Deficient with CNSHA	(61)

Variant Name[a]	cDNA nucleotide substitution (Negative chromosomal strand) Constituted by genotypes at: [a, b]	dbSNP rsID[c]	Amino acid substitution[a]	Codon[a]	WHO Class[a, d]	Likely Phenotype[e]	References[a]
Telti/Kobe	1318C->T		Leu->Phe	440	I	Deficient with CNSHA	(62)
Santiago de Cuba, Morioka	1339G->A		Gly->Arg	447	I	Deficient with CNSHA	(48, 63)
Harima	1358T->A		Val->Glu	453	I	Deficient with CNSHA	(38)
Figuera da Foz	1366G->C		Asp->His	456	I	Deficient with CNSHA	(64)
Amiens	1367A>T		Asp>Val	456	I	Deficient with CNSHA	(35)
Bangkok Noi	1376G->T, 1502T->G	rs72554665, unknown	Arg->Leu, Phe-Cys	459, 501	I	Deficient with CNSHA	(65)
Fukaya	1462G->A		Gly->Ser	488	I	Deficient with CNSHA	(38)
Campinas	1463G->T		Gly->Val	488	I	Deficient with CNSHA	(66)
Buenos Aires	1465C>T		Pro->Ser	489	I	Deficient with CNSHA	(67)
Arakawa	1466C->T		Pro->Leu	489	I	Deficient with CNSHA	(38)
Brighton	1488_1490delGAA		Lys	497	I	Deficient with CNSHA	(68)
Kozukata	159G->C		Trp->Cys	53	I	Deficient with CNSHA	(69)
Amsterdam	180_182delTCT		Leu	61	I	Deficient with CNSHA	(70)
No name	202G->A, 376A->G, 1264C>G	rs1050828, rs1050829, unknown	Val->Met, Asn->Asp, Leu>Val	68, 126, 422	I	Deficient with CNSHA	(71)
Swansea	224T->C		Leu->Pro	75	I	Deficient with CNSHA	(72)
Urayasu	281_283delAGA		Lys	95	I	Deficient with CNSHA	(73)
Vancouver	317C->G544C->T592C->T		Ser>Cys, Arg->Trp, Arg>Cys	106, 182, 198	I	Deficient with CNSHA	(74)
Mt Sinai	376A->G, 1159C->T	rs1050829, unknown	Asn->Asp, Arg->His	126, 387	I	Deficient with CNSHA	(75)
Plymouth	488G->A		Gly->Asp	163	I	Deficient with CNSHA	(76)

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Volendam	514C->T		Pro->Ser	172	I	Deficient with CNSHA	(77)
Shinshu	527A->G		Asp->Gly	176	I	Deficient with CNSHA	(58)
Chikugo	535A->T		Ser->Cys	179	I	Deficient with CNSHA	(38)
Tsukui	561_563delCTC		Ser	188 or 189	I	Deficient with CNSHA	(78)
Pedoplis-Ckaro	573C>G		Phe>Leu	191	I	Deficient with CNSHA	(50)
Santiago	593G->C		Arg->Pro	198	I	Deficient with CNSHA	(59)
Minnesota, Marion, Gastonia, LeJeune	637G->T		Val->Leu	213	I	Deficient with CNSHA	(40, 79)
Cincinnati	637G->T, 1037A->T		Val->Leu\ Asn>Ile	213, 346	I	Deficient with CNSHA	(80)
Harilaou	648T->G		Phe->Leu	216	I	Deficient with CNSHA	(81)
North Dallas	683_685delACA		Asn	229	I	Deficient with CNSHA	(38)
Asahikawa	695G->A		Cys->Tyr	232	I	Deficient with CNSHA	(82)
Durham	713A->G		Lys->Arg	238	I	Deficient with CNSHA	(83)
Stonybrook	724_729delGGCACT		Gly-Thr	242-243	I	Deficient with CNSHA	(59)
Wayne	769C->G		Arg->Gly	257	I	Deficient with CNSHA	(84)
Aveiro	806G->A		Cys->Tyr	269	I	Deficient with CNSHA	(85)
Cleveland Corum	820G->A		Glu->Lys	274	I	Deficient with CNSHA	(49, 76)
Lille	821A>T		Glu>Val	274	I	Deficient with CNSHA	(35)
Bangkok	825G>C		Lys>Asn	275	I	Deficient with CNSHA	(65)
Sugao	826C->T		Pro->Ser	276	I	Deficient with CNSHA	(86)
La Jolla	832T->C		Ser->Pro	278	I	Deficient with CNSHA	(87)

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Wexham	833C->T		Ser->Phe	278	I	Deficient with CNSHA	(76)
Piotrkow	851T>C		Val>Ala	284	I	Deficient with CNSHA	(50)
West Virginia	910G->T		Val->Phe	303	I	Deficient with CNSHA	(49)
Omiya	921G->C		Gln->His	307	I	Deficient with CNSHA	(38)
Nara	953_976delCCACCAAAGGGTACCTGGACGACC		Thr-Lys-Gly-Tyr-Leu-Asp-Asp-Pro	319-326	I	Deficient with CNSHA	(88)
Manhattan	962G->A		Gly->Glu	321	I	Deficient with CNSHA	(38)
Rehevot	964T->C		Tyr->His	322	I	Deficient with CNSHA	(89)
Honiara	99A->G, 1360C->T		Ile->Met, Arg->Cys	33, 454	I	Deficient with CNSHA	(90)
Tokyo, Fukushima	1246G->A		Glu->Lys	416	I-II	Deficient with CNSHA-Deficient	(48, 91)
Chatham	1003G->A	rs5030869	Ala->Thr	335	II	Deficient	(63)
Fushan	1004C->A		Ala->Asp	335	II	Deficient	(49)
Partenope	1052G->T		Gly->Val	351	II	Deficient	(92)
Ierapetra	1057C->T		Pro->Ser	353	II	Deficient	(59)
Anadia	1193A->G		Glu->Gly	398	II	Deficient	(38, 64)
Abeno	1220A->C		Lys->Thr	407	II	Deficient	(38, 93)
Surabaya	1291G->A		Val->Met	431	II	Deficient	(94)
Pawnee	1316G->C		Arg->Pro	439	II	Deficient	(59)
S. Antioco	1342A->G		Ser->Gly	448	II	Deficient	(92)
Cassano	1347G->C		Gln->His	449	II	Deficient	(95, 96)
Hermoupolis	1347G->C, 1360C->T		Gln->His, Arg->Cys	449, 454	II	Deficient	(96)
Union,Maewo, Chinese-2, Kalo	1360C->T		Arg->Cys	454	II	Deficient	(95, 97, 98)
Andalus	1361G->A		Arg->His	454	II	Deficient	(99)
Cosenza	1376G->C	rs72554665	Arg->Pro	459	II	Deficient	(95)
Canton, Taiwan-Hakka, Gifu-like, Agrigento-like	1376G->T	rs72554665	Arg->Leu	459	II	Deficient	(100, 101)
Flores	1387C->A		Arg->Ser	463	II	Deficient	(102)

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Kaiping, Anant, Dhon, Sapporo-like, Wosera	1388G->A		Arg->His	463	II	Deficient	(98, 101)
Kamogawa	169C->T		Arg->Trp	57	II	Deficient	(69)
Costanzo	179T>C		Leu>Pro	60	II	Deficient	(13)
Amazonia	185C->A		Pro->His	62	II	Deficient	(103)
Songklanagarind	196T->A		Phe->Ile	66	II	Deficient	(104)
Hechi	202G->A, 871G->A	rs1050828, unknown	Val->Met, Val->Met	68, 291	II	Deficient	(105)
Namouru	208T->C		Tyr->His	70	II	Deficient	(55)
Bao Loc	352T>C		Tyr>His	118	II	Deficient	(106)
Crispim	375G->T, 379G->T383T->C384C>T		Met->Ile, Ala->Ser, Leu->Pro	125, 127, 128	II	Deficient	(103)
Acrokorinthos	376A->G, 463C->G	rs1050829, unknown	Asn->Asp, His->Asp	126, 155	II	Deficient	(99)
Santa Maria	376A->G, 542A->T	rs1050829, unknown	Asn->Asp, Asp->Val	126, 181	II	Deficient	(107, 108)
Ananindeua	376A->G, 871G->A	rs1050829, unknown	Asn->Asp, Val->Met	126, 291	II	Deficient	(103)
Vanua Lava	383T->C		Leu->Pro	128	II	Deficient	(109)
Valladolid	406C->T		Arg->Cys	136	II	Deficient	(44)
Belem	409C->T		Leu->Phe	137	II	Deficient	(13)
Liuzhou	442G->A		Glu->Lys	148	II	Deficient	(105)
Shenzen	473G>A		Cys>Tyr	158	II	Deficient	(110)
Taipei ,ÄúChinese-3,Äù	493A->G		Asn->Asp	165	II	Deficient	(111)
Toledo	496C>T		Arg>Cys	166	II	Deficient	(35)
Naone	497G->A		Arg->His	166	II	Deficient	(112)
Nankang	517T->C		Phe->Leu	173	II	Deficient	(113, 114)
Miaoli	519C->G		Phe->Leu	173	II	Deficient	(115)
Mediterranean, Dallas, Panama, Sassari, Cagliari, Birmingham	563C->T	rs5030868	Ser->Phe	188	II	Deficient	(63)
Coimbra Shunde	592C->T		Arg->Cys	198	II	Deficient	(116, 117)
Nilgiri	593G>A		Arg>His	198	II	Deficient	(118)
Radlowo	679C->T		Arg->Trp	227	II	Deficient	(36)
Roubaix	811G>C		Val>Leu	271	II	Deficient	(35)

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Haikou	835A->G		Thr->Ala	279	II	Deficient	(119)
Chinese-1	835A->T		Thr->Ser	279	II	Deficient	(120)
Mizushima	848A>G		Asp>Gly	283	II	Deficient	(121)
Osaka	853C->T		Arg->Cys	285	II	Deficient	(38, 93)
Viangchan, Jammu	871G->A		Val->Met	291	II	Deficient	(79, 122)
Seoul	916G->A		Gly->Ser	306	II	Deficient	(38)
Ludhiana	929G->A		Gly->Glu	310	II	Deficient	(38)
Farroupilha	977C->A		Pro->His	326	II/III	Deficient	(123)
Chinese-5	1024C->T		Leu->Phe	342	III	Deficient	(117)
Rignano	130G>A		Ala>Thr	44	III	Deficient	(124)
Orissa	131C->G	rs78478128	Ala->Gly	44	III	Deficient	(125, 126)
G6PDNice	1380G>C		Glu>Asp	460	III	Deficient	(35)
Kamiube, Keelung	1387C->T		Arg->Cys	463	III	Deficient	(48, 115)
Neapolis	1400C->G		Pro->Arg	467	III	Deficient	(127)
Aures	143T->C		Ile->Thr	48	III	Deficient	(128, 129)
Split	1442C->G		Pro->Arg	481	III	Deficient	(130)
Kambos	148C->T		Pro->Ser	50	III	Deficient	(131)
Palestrina	170G>A		Arg>Glu	57	III	Deficient	(13)
Metaponto	172G->A		Asp->Asn	58	III	Deficient	(132)
Musashino	185C->T		Pro->Leu	62	III	Deficient	(109)
Asahi	202G->A	rs1050828	Val->Met	68	III	Deficient	(112)
A- (202), Ferrara I	202G->A, 376A->G	rs1050828, rs1050829	Val->Met, Asn->Asp	68, 126	III	Deficient	(63)
Murcia Oristano	209A->G		Tyr->Cys	70	III	Deficient	(76, 126)
Ube Konan	241C->T		Arg->Cys	81	III	Deficient	(126, 133)
Lagosanto	242G->A		Arg->His	81	III	Deficient	(134)
Guangzhou	274C->T		Pro->Ser	92	III	Deficient	(135)
Hammersmith	323T->A		Val->Glu	108	III	Deficient	(15, 136)
Sinnai	34G->T		Val->Leu	12	III	Deficient	[3](123)
A- (680)	376A->G, 680G->T	rs137852328, rs1050829	Asn->Asp, Arg->Leu	126, 227	III	Deficient	(16)
A- (968), Betica,Selma, Guantanamo	376A->G, 968T->C	rs76723693, rs1050829	Asn->Asp, Leu->Pro	126, 323	III	Deficient	(16)
Salerno Pyrgos	383T>G		Leu>Arg	128	III	Deficient	(35, 126)
Quing Yan	392G->T		Gly->Val	131	III	Deficient	(117)

Variant Name[a]	cDNA nucleotide substitution (Negative chromosomal strand) Constituted by genotypes at: [a, b]	dbSNP rsID[c]	Amino acid substitution[a]	Codon[a]	WHO Class[a, d]	Likely Phenotype[e]	References[a]
Lages	40G->A		Gly->Arg	14	III	Deficient	(137)
Ilesha	466G->A		Glu->Lys	156	III	Deficient	(138)
Mahidol	487G->A		Gly->Ser	163	III	Deficient	(139)
Malaga	542A->T		Asp->Val	181	III	Deficient	(140)
Sibari	634A->G		Met->Val	212	III	Deficient	(95)
Mexico City	680G->A		Arg->Gln	227	III	Deficient	(59)
Nanning	703C->T		Leu->Phe	235	III	Deficient	(105)
Seattle, Lodi, Modena, Ferrara II, Athens-like	844G->C		Asp->His	282	III	Deficient	(121, 141, 142)
Bajo Maumere	844G->T		Asp->Tyr	282	III	Deficient	(143)
Montalbano	854G->A		Arg->His	285	III	Deficient	(144)
Kalyan-Kerala, Jamnaga, Rohini	949G->A	rs137852339	Glu->Lys	317	III	Deficient	(145, 146)
Gaohe	95A->G		His->Arg	32	III	Deficient	(38)
A	376A->G	rs1050829	Asn->Asp	126	III-IV	Deficient-Normal	(147)
Mira d'Aire	1048G->C		Asp->His	350	IV	Normal	(38)
Sao Borja	337G->A		Asp->Asn	113	IV	Normal	(148)
Insuli	989G->A		Arg->His	330	IV	Normal	(149)
B	'Wildtype'/ Reference	NA	NA	NA	IV	Normal	(16)
Hektoen					V	Normal	(150, 151)
Gidra	110T>C		Met->Thr	37	Not reported	unknown	(69)
Yunan	1381G->A		Ala->Thr	461	Not reported	unknown	(152)
Laibin	1414A->C		Ile->Leu	472	Not reported	unknown	(105)
No name	25C>T		Arg>Trp	9	Not reported	unknown	(153)
Cairo	404A->C		Asn->Thr	135	Not reported	unknown	(38)
Gond	477G>C		Met>Ile	159	Not reported	unknown	(154)
Dagua	595A->G		Ile>Val	199	Not reported	unknown	(155)
Papua	849C->A		Asp->Glu	283	Not reported	unknown	(156)

Variant Name[a]	cDNA nucleotide substitution (Negative chromosomal strand) Constituted by genotypes at: [a, b]	dbSNP rsID[c]	Amino acid substitution[a]	Codon[a]	WHO Class[a, d]	Likely Phenotype[e]	References[a]
Sierra Leone	311G>A, 376A>G	unknown, rs1050829	Arg>His, Asn->Asp	104, 126	Not reported	unknown	(157)
Mediterranean Haplotype	1311C>T, 563T				Not reported	Unknown	(158)

[a] This modified table of G6PD variants is from (13), https://grenada.lumc.nl/LOVD2/MR/home.php?select_db=G6PD, with several additional variants.

[b] cDNA sequence GenBank accession number X03674.1 (http://www.ncbi.nlm.nih.gov/nuccore/X03674.1). Allele A of the ATG start codon is numbered here as +1, and is position 471 in the X03674.1 cDNA sequence, therefore subtract 470 nucleotides from the GenBank cDNA sequence. For genomic DNA nucleotide position information, see (13, 159). Please note that the G6PD gene is on the minus chromosomal strand, and therefore alleles represented on www.pharmgkb.org may be represented on the plus chromosomal strand in a complementary manner.

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

[d] Please note; WHO class as reported in (13, 14) or individual references. This class may have been assigned based on just clinical manifestations and not enzyme activity level or characterization of the enzyme variant.

[e] Likely phenotype as referenced in this guideline, based on converting assigned WHO class to 3 phenotypes. “Normal” defined as very mild or no enzyme deficiency (>60% normal enzyme levels); “Deficient” defined as mild to severely deficient (<10-60% normal) enzyme levels; “Deficient with CNSHA” defined as severe G6PD enzyme deficiency (<10% activity) with chronic non-spherocytic hemolytic anemia (14). See main text for further explanation, and Table 1 for examples of diplotypes.

NA = not applicable

Supplemental Table S2. Association between allelic variants and G6PD function as defined by the WHO (10, 12).

Functional Status	Alleles
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
Increased activity, >150% normal enzyme activity	WHO Class V

*See Supplemental Table S1 for classification of alleles by WHO class

Supplemental Table S3. World-wide estimates of G6PD deficiency prevalence overall and for males from (17).

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

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.

Supplemental Table S5. Frequencies of *G6PD* variants in specific populations.

HGDP-CEPH Grouping	Population/ Ethnicity	Sample Size	Genotyping details	Reference	G6PD Allele	Allele Frequency
Africa	São Tomé e Príncipe (West Africa)	52, males and females (males were all B)	376G/202A, 376G/968C, 376G/542T PCR-RFLP analysis of haplotype diversity.	Manco *et al.* 2007 (160)	B	0.698
					A	0.194
					A-	0.108
					Betica	ND
					Santa Maria	ND
Africa	Fulani, ethnic group, Burkino Faso.	59 (42 females, 17 males)	202A-G by PCR-RFLP analysis.	(161) (Modiano et al, 2001)	position 202 allele G (rs1050828), referred to as A- in the publication.	0.069 (SE 0.025)
Africa	Mossi ethnic group, Burkino Faso.	148 (114 females, 34 males)	202A-G by PCR-RFLP analysis.	(161) (Modiano et al, 2001)	position 202 allele G (rs1050828), referred to as A- in the publication.	0.195 (SE 0.024)
Africa	Rimaibé ethnic group, Burkino Faso.	79 (56 females, 23 males)	202A-G by PCR-RFLP analysis.	(161) (Modiano et al, 2001)	position 202 allele G (rs1050828), referred to as A- in the publication.	0.185 (SE 0.033)
Africa	Newborns of Comorian origin living in Marseilles	467 (246 females, 221 males)	A-: 202 A>G and 376 G>A, Mediterranean: defined by positions 563C>T and 1311C>T. PCR-RFLP analysis. Only those found to be G6PD deficient by enzyme activity assay were then genotyped.	(162) (Badens et al, 2000)	A-	n= 14/17 alleles in G6PD deficient individuals = 0.82
					Mediterranean	n=3/17 alleles in G6PD deficient individuals = 0.18

Africa	Dienga, Gabon	77 male children.	A- 376A>G and 202G>A, by PCR-RFLP analysis.	(163) (Migot-Nabias et al, 2000)	A-	Males: 0.16
Africa	Dienga, Gabon	271 children (note that amplification of each allele could not be achieved in some samples)	376A>G and 202G>A, by PCR-RFLP analysis.	(164)(Mombo et al, 2003)	A-	0.155
					A	0.330
					B	0.515
Africa	Ibadan, and Abanla (95% Yoruba tribe), South-West Nigeria	n=314 males.	PCRs and sequence-specific probes for positions 202, 376, 542, 680, 968.	(May et al, 2000) (165)	A- (202A, 376G)	0.242
					A (376G)	0.175
					B	0.583
Africa	Ibadan, and Abanla (95% Yoruba tribe), South-West Nigeria	n=292 females.	PCRs and sequence-specific probes for positions 202, 376, 542, 680, 968.	(165) (May et al, 2000)	A- (202A, 376G)	0.184
					A (376G)	0.214
					B	0.603
Africa	Abidjan, Ivory Coast	39 newborn males	376 A>G, 202 G>A, by PCR-RFLP analysis.	(166) (Coulibaly et al, 2000)	A-	0.21
					A	0.28
					B	0.51
Africa	Abidjan, Ivory Coast	72 newborn females	376 A>G, 202 G>A, by PCR-RFLP analysis.	(166) (Coulibaly et al, 2000)	A-	0.22
					A	0.26
					B	0.51
Africa	Sereer ethnic group, Niakhar area, Senegal	n=430 children (220 girls, 210 boys)	376G, 202A, 542T, 680T, 968C by PCR with 5'biotinylated primers and reverse dot blot hybridization.	(167) (De Araujo et al, 2006)	A-(376G/202A)	0.01

					A-(376G/680T)	0
					A-(376G/968C)	0.09
					Santamaria (376G/542T)	0.01
					A	0.20
					B	0.68
India	Andaman & Nicobar Islands, India	n=29	Position 1311, PCR amplification followed by restriction digest	(168) (Murhekar et al, 2001)	Orissa	Only one individual was G6PD deficient – a female who had the Orissa variant.
Southeast Asia	Shan State, Myanmar	n=563 females (Males: reported hemi and homozygous males therefore did not include these figures)	PCR-RFLP analysis.	(169) (Than et al, 2005)	Mahidol	Females: 0.12
					Viangchan	ND
Middle East	Kuwait	n=206	563C>T, 376A>G, 202G>A, 680G>T, 968T>C PCR/RFLP analysis	(170) (Samilchuk et al, 1999)	A-	0.0111
					A	0.0215
					Mediterranean	0.0503
Middle East	Kuwait	n=1209	PCR-RFLP analysis for positions 563C>T, 202G>A, 376A>G, and 143T>C, negative samples were then sequences in exon 9 to detect 1003G>A.	(171) (Afadhli et al, 2005)	A-	0.0074
					Mediterranean	0.035
					Chatham	0.0046
					Aures	0.0023
Middle East	Jordan (Amman	n=981 males	PCRof and sequencing	(172) (Karadsheh et	A- (376G, 202A)	0.006

					Asahi (202A)	0.001
					Chatham	0.003
					Valladolid	0.002
					Aures	0.001
					Mediterranean	0.017
Mixed	Mixed	n=178 (88 males, 90 females)	Position 1311 by PCR and sequencing or oligonucleotide hybridization.	(158) Beutler et al, 1990	1311C>T - Oriental	0.051
					1311C>T - South American	0.100
					1311C>T - White non-Jewish	0.132
					1311C>T - Sicilians	0.167
					1311C>T - White Jewish	0.220
					1311C>T - African	0.25
					1311C>T - Indian	0.45

ND: not detected

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.					

Aldesulfone sodium (sulfoxone)		Risk level: high, for all.	(sulphoxone) Should be avoided by all G6PD deficient patients.		Doubtful association with hemolysis in G6PD deficient patients.			
Aminophenazone (aminopyrine)		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.		Safe for Class 2, 3.	Safe at therapeutic doses in those with G6PD deficiency.	
Aminosalicyclic acid (4-aminosalicyclic acid, p-aminosalicyclic acid)			Should be avoided by G6PD deficient patients of Asian, Middle Eastern or Mediterranean origin.		Doubtful association with hemolysis in G6PD deficient patients.		No evidence to suggest unsafe in G6PD deficient patients.	
Antazoline (antistine)		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.			No evidence to suggest unsafe in G6PD deficient patients.	
Ascorbic acid (vitamin c)	Caution should be	Risk level: low, for all.		Safe at therapeutic	Possible association	Safe for Class 2, 3.	Safe at therapeutic	Possible risk of hemolysis
Ascorbic acid (vitamin c)	Caution should be taken in patients with G6PD deficiency	Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA	Possible association with hemolysis in G6PD deficient patients.	Safe for Class 2, 3.	Safe at therapeutic doses in those with G6PD deficiency.	Possible risk of hemolysis

Arsine		Risk level: high, for all.	Should be avoided by all G6PD deficient patients.					
Aspirin (acetylsalicylic acid)		Risk level: high, for Medit., Asian.	Should be avoided by G6PD deficient patients of Asian, Middle Eastern or Mediterranean origin.	Safe at therapeutic doses in those with G6PD deficiency without NSHA.	Possible association with hemolysis in G6PD deficient patients.	Safe for Class 2, 3.	Safe at therapeutic doses in those with G6PD deficiency.	Possible risk of hemolysis* *up to 20mg/kg probably safe
Beta-Naphthol (2-Naphthol)		Risk level: high, for all.	Should be avoided by all G6PD deficient patients.					
Chloramphenicol		Risk level: high, for Medit., Asian.	Should be avoided by G6PD deficient patients of Asian, Middle Eastern or Mediterranean origin.	Safe at therapeutic doses in those with G6PD deficiency without NSHA.	Possible association with hemolysis in G6PD deficient patients.	Safe for Class 2, 3.	Safe at therapeutic doses in those with G6PD deficiency.	Possible risk of hemolysis
Chloroquine	Should be administered	Risk level: high, for Medit.,	Should be avoided by	Safe at therapeutic	Possible association	Safe for Class 2, 3.	Safe at therapeutic	Possible risk of hemolysis
Chloroquine	Should be administered with caution to G6PD patients.	Risk level: high, for Medit., Asian. If required, this substance may be taken under	Should be avoided by G6PD deficient patients of Asian,	Safe at therapeutic doses in those with G6PD deficiency without	Possible association with hemolysis in G6PD deficient patients.	Safe for Class 2, 3.	Safe at therapeutic doses in those with G6PD deficiency.	Possible risk of hemolysis

Ciprofloxacin		Risk level: high, for Medit., Asian. Hemolytic reactions to this substance have been reported only in few, isolated cases and no written reference exists as of this time.			Possible association with hemolysis in G6PD deficient patients.		Safe at therapeutic doses in those with G6PD deficiency.	Definite risk of hemolysis
Colchicine		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.		Safe for Class 2, 3.	No evidence to suggest unsafe in G6PD deficient patients.	
Dapsone (diaphenylsulfone)	Should be administered with caution to G6PD patients.	Risk level: high, for all. These substances taken in high quantities might cause hemolysis also with normal subjects.	Should be avoided by all G6PD deficient patients.		Definite association with hemolysis in G6PD deficient patients.	Unsafe for Class 1, 2, 3.	Should be avoided by G6PD deficient patients.	Definite risk of hemolysis
Dimercaprol		Risk level: high, for all.	Should be avoided by all G6PD deficient patients.		Doubtful association with hemolysis in G6PD deficient			
Dimercaprol		Risk level: high, for all.	Should be avoided by all G6PD deficient patients.		Doubtful association with hemolysis in G6PD deficient patients.			

Diphenhydramine (difenilhydramine)		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.		Safe for Class 2, 3.	No evidence to suggest unsafe in G6PD deficient patients.	
Dipyrone (metamizole)							Safe at therapeutic doses in those with G6PD deficiency.	
Doxorubicin		Risk level: high, for Medit., Asian.			Doubtful association with hemolysis in G6PD deficient patients.		No evidence to suggest unsafe in G6PD deficient patients.	
Furazolidone		Risk level: high, for all.	Should be avoided by all G6PD deficient patients.	Should be avoided by G6PD deficient patients.		Unsafe for Class 1, 2, 3.	Safe at therapeutic doses in those with G6PD deficiency.	
Glibenclamide (glyburide)	Caution should be taken in patients with G6PD deficiency and a non-	Risk level: high, for all. Hemolytic reactions to this substance have been reported only in few,			Possible association with hemolysis in G6PD deficient patients.		Safe at therapeutic doses in those with G6PD deficiency.	Possible risk of hemolysis
Glibenclamide (glyburide)	Caution should be taken in patients with G6PD deficiency	Risk level: high, for all. Hemolytic reactions to this substance have been reported			Possible association with hemolysis in G6PD deficient patients.		Safe at therapeutic doses in those with G6PD deficiency.	Possible risk of hemolysis

Glucosulfone (glucosulphone sodium, promin)		Risk level: high, for all.	Should be avoided by all G6PD deficient patients.					
Isobutyl Nitrite		Risk level: high, for Medit., Asian.		Should be avoided by G6PD deficient patients.				
Isoniazid		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.		Safe for Class 2, 3.	Safe at therapeutic doses in those with G6PD deficiency.	
Isosorbide dinitrate							Safe at therapeutic doses in those with G6PD deficiency.	
Levodopa (L-DOPA)		Dopamine: Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.		Safe for Class 2, 3.	No evidence to suggest unsafe in G6PD deficient patients.	
Menadione (menaphthone,		Risk level: high, for all.		Safe at therapeutic		Safe for Class 2, 3.		Possible risk of hemolysis
Menadione (menaphthone, vitamin K3)		Risk level: high, for all.		Safe at therapeutic doses in those with G6PD deficiency without		Safe for Class 2, 3.		Possible risk of hemolysis

Menadione sodium bisulfite (vitamin K3 sodium bisulfite)		Risk level: high, for all.				Safe at therapeutic doses in those with G6PD deficiency without NSHA.		Possible risk of hemolysis
Mepacrine (quinacrine)		Risk level: high, for Medit., Asian.	Should be avoided by all G6PD deficient patients.		Doubtful association with hemolysis in G6PD deficient patients.		Safe at therapeutic doses in those with G6PD deficiency.	
Mesalazine (5-aminosalicylic acid, mesalamine)		Risk level: high, for Medit., Asian.			Possible association with hemolysis in G6PD deficient patients.			
Methylthioninium chloride (methylene blue)	Should be avoided by G6PD deficient patients.	Risk level: high, for all.	Should be avoided by all G6PD deficient patients.	Should be avoided by G6PD deficient patients.	Definite association with hemolysis in G6PD deficient patients.	Unsafe for Class 1, 2, 3.	Should be avoided by G6PD deficient patients.	Definite risk of hemolysis
Moxifloxacin								Definite risk of hemolysis
Nalidixic acid	Caution should be taken in patients with G6PD deficiency.	Risk level: high, for Medit., Asian. Hemolytic reactions to this substance have	Should be avoided by G6PD deficient patients with the A-	Should be avoided by G6PD deficient patients.	Definite association with hemolysis in G6PD deficient patients.	Unsafe for Class 1, 2, 3.	Safe at therapeutic doses in those with G6PD deficiency.	Definite risk of hemolysis
Nalidixic acid	Caution should be taken in patients with G6PD deficiency.	Risk level: high, for Medit., Asian. Hemolytic reactions to this substance have	Should be avoided by G6PD deficient patients with the A-	Should be avoided by G6PD deficient patients.	Definite association with hemolysis in G6PD deficient patients.	Unsafe for Class 1, 2, 3.	Safe at therapeutic doses in those with G6PD deficiency.	Definite risk of hemolysis

Napthalene, pure (naphtalin)		Risk level: high, for all.	(naphthalene) Should be avoided by all G6PD deficient patients.	Should be avoided by G6PD deficient patients.	Definite association with hemolysis in G6PD deficient patients.	Unsafe for Class 1, 2, 3.		
Niridazole		Risk level: high, for all.	Should be avoided by all G6PD deficient patients.	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
Nitrofural (nitrofurazone)		Risk level: high, for all.	Should be avoided by all G6PD deficient patients.					
Nitrofurantoin	Warning section – hemolytic anemia linked to G6PD deficiency.	Risk level: high, for all.	Should be avoided by all G6PD deficient patients.	Should be avoided by G6PD deficient patients.	Definite association with hemolysis in G6PD deficient patients.	Unsafe for Class 1, 2, 3.	Should be avoided by G6PD deficient patients.	Definite risk of hemolysis
Norfloxacin	Precautions section – hemolytic reactions have been reported in G6PD deficient	Risk level: low, for all.					Safe at therapeutic doses in those with G6PD deficiency.	Definite risk of hemolysis
Norfloxacin	Precautions section – hemolytic reactions have been reported in	Risk level: low, for all.					Safe at therapeutic doses in those with G6PD deficiency.	Definite risk of hemolysis

Ofloxacin								Definite risk of hemolysis
Pamaquine		Risk level: high, for all.	Should be avoided by all G6PD deficient patients.		Definite association with hemolysis in G6PD deficient patients.			Definite risk of hemolysis
Para-aminobenzoic acid (4-aminobenzoic acid)		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.		Safe for Class 2, 3.	No evidence to suggest unsafe in G6PD deficient patients.	
Paracetamol (acetaminophen)		Risk level: low, for all.	Safe alternative to aspirin or phenacetin in G6PD deficient patients of Asian, Middle Eastern or Mediterranean origin..	Safe at therapeutic doses in those with G6PD deficiency without NSHA.	Doubtful association with hemolysis in G6PD deficient patients.	Safe for Class 2, 3.	Safe at therapeutic doses in those with G6PD deficiency.	
Pentaquine		Risk level: high, for all.						
Phenacetin (acetophenetidin)		Risk level: high, for Medit., Asian. Probably	Should be avoided by G6PD	Safe at therapeutic doses in those	Doubtful association with hemolysis	Safe for Class 2, 3.	No evidence to suggest unsafe in	
Phenacetin (acetophenetidin)		Risk level: high, for Medit., Asian. Probably safe in moderate doses.	Should be avoided by G6PD deficient patients of Asian,	Safe at therapeutic doses in those with G6PD deficiency without	Doubtful association with hemolysis in G6PD deficient patients.	Safe for Class 2, 3.	No evidence to suggest unsafe in G6PD deficient patients.	

Phenazone (antipyrine)		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.			Safe at therapeutic doses in those with G6PD deficiency.	
Phenazopyridine		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.	Should be avoided by G6PD deficient patients.	
Phenylbutazone		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.			No evidence to suggest unsafe in G6PD deficient patients.	
Phenytoin		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.		Safe for Class 2, 3.	No evidence to suggest unsafe in G6PD deficient patients.	
Phynylhydrazine		Risk level: high, for all.	(Phenylhydrazine) Should be avoided by all G6PD	Should be avoided by G6PD deficient patients.		Unsafe for Class 1, 2, 3.		
Phynylhydrazine		Risk level: high, for all.	(Phenylhydrazine) Should be avoided by all G6PD deficient	Should be avoided by G6PD deficient patients.		Unsafe for Class 1, 2, 3.		

Phytomenadione (vitamin k1)		Risk level: low, for all.						Possible risk of hemolysis
Primaquine	Precaution – G6PD deficient patients should be closely observed.	Risk level: high, for all. May be given in reduces doses under medical supervision.	Should be avoided by all G6PD deficient patients. May be safe in those with A- under surveillance and reduced dosage.	Should be avoided by G6PD deficient patients.	Definite association with hemolysis in G6PD deficient patients.	Unsafe for Class 1, 2, 3.	Should be avoided by G6PD deficient patients.	Definite risk of hemolysis
Probenecid	Adverse reactions section – hemolytic anemia may be related to G6PD deficiency.	Risk level: high, for all.	Should be avoided by all G6PD deficient patients.	Safe at therapeutic doses in those with G6PD deficiency without NSHA.	Doubtful association with hemolysis in G6PD deficient patients.	Safe for Class 2, 3.	No evidence to suggest unsafe in G6PD deficient patients.	
Procainamide		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.		Safe for Class 2, 3.	No evidence to suggest unsafe in G6PD deficient patients.	
Proguanil (chlorguanidine)		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD			No evidence to suggest unsafe in G6PD	
Proguanil (chlorguanidine)		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without			No evidence to suggest unsafe in G6PD deficient patients.	

Pyrimethamine		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.		Safe for Class 2, 3.	No evidence to suggest unsafe in G6PD deficient patients.	
Quinidine		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.		Safe for Class 2, 3.		
Quinine		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.	Doubtful association with hemolysis in G6PD deficient patients.	Safe for Class 2, 3.	Safe at therapeutic doses in those with G6PD deficiency.	Possible risk of hemolysis
Rasburicase (urate oxidase)	Contraindicated in patients with G6PD deficiency.	Risk level: high, for Medit., Asian.		Should be avoided by G6PD deficient patients.			Should be avoided by G6PD deficient patients.	Possible risk of hemolysis
Stibophen (2-(2-oxido-3,5-disulphonatophenoxy)-1,3,2,benzodioxastibole-4-6-		Risk level: high, for all.	(Stibophan) Should be avoided by all G6PD deficient patients.					
Stibophen (2-(2-oxido-3,5-disulphonatophenoxy)-1,3,2,benzodioxastibole-4-6-		Risk level: high, for all.	(Stibophan) Should be avoided by all G6PD deficient patients.					

Streptomycin		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.		Safe for Class 2, 3.	No evidence to suggest unsafe in G6PD deficient patients.	
Succimer (dimercaptosuccinic acid)							Safe at therapeutic doses in those with G6PD deficiency.	
Sulfacetamide		Risk level: high, for all.	Should be avoided by all G6PD deficient patients.	Should be avoided by G6PD deficient patients.	Definite association with hemolysis in G6PD deficient patients.	Unsafe for Class 1, 2, 3.	Safe at therapeutic doses in those with G6PD deficiency.	
Sulfacytine		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.			No evidence to suggest unsafe in G6PD deficient patients.	
Sulfadiazine	Warning section – hemolysis may occur in some G6PD individuals.	Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without	Doubtful association with hemolysis in G6PD deficient patients.		No evidence to suggest unsafe in G6PD deficient patients.	Possible risk of hemolysis
Sulfadiazine	Warning section – hemolysis may occur in some G6PD individuals.	Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without	Doubtful association with hemolysis in G6PD deficient patients.		No evidence to suggest unsafe in G6PD deficient patients.	Possible risk of hemolysis

Sulfadimidine		Risk level: high, for all.	Should be avoided by all G6PD deficient patients.		Possible association with hemolysis in G6PD deficient patients.			
Sulfafurazole (sulfafurazone, sulfisoxazole)	Precaution section – hemolysis may occur in G6PD deficient individuals.	Risk level: high, for Medit., Asian.	(sulphafurazone) Should be avoided by G6PD deficient patients of Asian, Middle Eastern or Mediterranean origin.	Safe at therapeutic doses in those with G6PD deficiency without NSHA.	Doubtful association with hemolysis in G6PD deficient patients.	Safe for Class 2, 3.	Safe at therapeutic doses in those with G6PD deficiency.	
Sulfaguanidine		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.			No evidence to suggest unsafe in G6PD deficient patients.	
Sulfamerazine		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.			No evidence to suggest unsafe in G6PD deficient patients.	
Sulfamethoxazole	(Trimethopri	Risk level: high,	(Septra -	Should be	Definite	Unsafe for	(Cotrimoxaz	Definite risk of
Sulfamethoxazole	(Trimethoprim and sulfamethoxazole drug label) precaution	Risk level: high, for all.	(Septra - Trimethoprim and sulfamethoxazole) Should be	Should be avoided by G6PD deficient patients.	Definite association with hemolysis in G6PD deficient patients.	Unsafe for Class 1, 2, 3.	(Cotrimoxazole - trimethoprim and sulfamethoxazole) Safe	Definite risk of hemolysis

Sulfamethoxypyridazine		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.		Safe for Class 2, 3.	No evidence to suggest unsafe in G6PD deficient patients.	
Sulfanilamide (Sulphanilamide)		Risk level: high, for all.	Should be avoided by all G6PD deficient patients.	Should be avoided by G6PD deficient patients.	Definite association with hemolysis in G6PD deficient patients.	Unsafe for Class 1, 2, 3.	Safe at therapeutic doses in those with G6PD deficiency.	
Sulfapyridine		Risk level: high, for all.	Should be avoided by all G6PD deficient patients.	Should be avoided by G6PD deficient patients.	Definite association with hemolysis in G6PD deficient patients.	Unsafe for Class 1, 2, 3.		
Sulfasalazine, Salazosulfapyridine (salazopyrin)	Precaution section – G6PD patients should be closely observed for signs of hemolytic anemia.	Risk level: high, for all.	Should be avoided by all G6PD deficient patients.		Possible association with hemolysis in G6PD deficient patients.		Safe at therapeutic doses in those with G6PD deficiency.	Possible risk of hemolysis
Thiazosulfone (thiazolesulfone)		Risk level: high, for Medit., Asian.		Should be avoided by G6PD		Unsafe for Class 1, 2, 3.	Safe at therapeutic doses in	
Thiazosulfone (thiazolesulfone)		Risk level: high, for Medit., Asian.		Should be avoided by G6PD deficient patients.		Unsafe for Class 1, 2, 3.	Safe at therapeutic doses in those with G6PD deficiency.	

Tiaprofenic acid		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.			No evidence to suggest unsafe in G6PD deficient patients.	
Tolonium chloride, (toluidine blue)		Risk level: high, for all.	Should be avoided by all G6PD deficient patients.	Should be avoided by G6PD deficient patients.		Unsafe for Class 1, 2, 3.	Should be avoided by G6PD deficient patients.	
Trihexyphynidyl (benzhexol)		Risk level: low, for all.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.			No evidence to suggest unsafe in G6PD deficient patients.	
Trimethoprim	(Trimethoprim and sulfamethoxazole drug label) precaution section – hemolysis may occur in G6PD deficient individuals.	Risk level: low, for all.	Septrin - Trimethoprim and sulfamethoxazole) Should be avoided by all G6PD deficient patients.	Safe at therapeutic doses in those with G6PD deficiency without NSHA.	Definite association with hemolysis in G6PD deficient patients.	Safe for Class 2, 3.	Cotrimoxazole - trimethoprim and sulfamethoxazole - Safe at therapeutic doses in those with G6PD deficiency.	
Trinitrotoluene		Risk level: high,		Should be	Definite	Unsafe for		

Trinitrotoluene (2,4,6-trinitrotoluene)		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.		
Tripelennamine		Risk level: low, for Medit., Asian.		Safe at therapeutic doses in those with G6PD deficiency without NSHA.		Safe for Class 2, 3.	No evidence to suggest unsafe in G6PD deficient patients.	
Vitamin K		(Menadiol Sodium Sulfate (vitamin K4 sodium sulfate)). Risk level: high, for all. Synthetic substitutes of natural vitamin K. It is probable that natural vitamin K1 (phyto-	Should be avoided by all G6PD deficient patients.	Safe at therapeutic doses in those with G6PD deficiency without NSHA.	Possible association with hemolysis in G6PD deficient patients.	Safe for Class 2, 3.	No evidence to suggest unsafe in G6PD deficient patients.	

Table Key

Shaded rows are those in which all references with an available review for the drug are in agreement that there is a risk of hemolysis in G6PD deficient individuals (dark grey) or they are in agreement that there is a low level of risk in G6PD deficient individuals who do not have NSHA (light grey). Blank cells are those for which no information for the particular drug was available.

[a]Drugs labels were searched for and downloaded at DailyMed, and manually read for information regarding G6PD deficiency. http://dailymed.nlm.nih.gov/dailymed/about.cfm?CFID=19319725&CFTOKEN=58cf841e285ab349-4BB80DDF-DED0-E0BA-8A9AD8C4DF2D7FCF&jsessionid=843066c9aeb61c0b912ef102d65774752f44 (accessed November 29th 2012).
Drug labels with highlighted pharmacogenetic information can be found at https://www.pharmgkb.org/gene/PA28469#tabview=tab0&subtab=32

[b]Italian G6PD Deficiency Association www.g6pd.org

Abbreviations:
NSHA = nonspherocytic hemolytic anemia

Supplemental Table S7. Evidence linking G6PD deficiency to Rasburicase-induced hemolysis or methemoglobinemia

Type of experimental model *(in vitro, in vivo preclinical, or clinical)*	**Major findings**	**References**	**Level of evidence[a]**
Clinical	G6PD deficient individuals (as determined by enzyme assay) developed acute hemolysis or methemoglobinemia after exposure to rasburicase or urate oxidase.	Ducros et al. (1991) (173) Pui et al (1997) (174) Bosly et al. (2003) (175) Browning and Kruse (2005) (176) Borinstein et al. (2007) (177) Bhat et al. (2008) (178) Vadhan-Raj et al. (2011) (179) Sonbol et al. (2012) (180) Zaramella et al. (2012) (181) Cheah et al. (2013) (182)	Strong
Clinical	G6PD deficient individuals (as determined by genotype) developed acute hemolysis after exposure to rasburicase or urate-oxidase.	Bain et al. (2010) (183) Zaramella et al. (2012) (181) Joly et al. (2009) (184)	Moderate
Clinical	Probable G6PD deficient individuals (no G6PD enzyme activity or genetic test to determine G6PD status) developed acute hemolysis after exposure to rasburicase or urate oxidase.	Ng et al. (2011) (185) Patte et al. (2002) (186) Kizer et al (2006) (187)	Moderate
Clinical	G6PD normal individuals (as determined by enzyme assay) developed acute hemolysis after exposure to rasburicase or urate-oxidase.	Goldman et al. (2001) (188) Kizer et al. (2006) (187) Bauters et al. (2010) (189) Bauters et al. (2011) (190)	Moderate

[a]See above for description of '**Levels of Evidence Linking Genotype to Phenotype**'. Some of the case studies, although not strong individually, collectively do support a strong level of evidence.

Abbreviations:
G6PD – glucose-6-phosphate dehydrogenase

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