Expanded Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Medication Use in the Context of *G6PD* Genotype

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ABSTRACT

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is associated with development of acute hemolytic anemia in the setting of oxidative stress, which can be caused by medication exposure. Regulatory agencies worldwide warn against the use of certain medications in G6PD deficient persons, but in many cases, this information is conflicting, and the clinical evidence is sparse. This guideline provides information on using *G6PD* genotype as part of the diagnosis of G6PD deficiency and classifies medications that have been previously implicated as unsafe in G6PD deficient individuals by one or more sources. We classify these medications as high, medium, or low-to-no risk based on a systematic review of the published evidence of the gene-drug associations and regulatory warnings. In patients with G6PD deficiency, high risk medications should be avoided, medium risk medications should be used with caution, and low-to-no risk medications can be used with standard precautions, without regard to G6PD phenotype. This new document replaces the prior Clinical Pharmacogenetics Implementation Consortium guideline for rasburicase therapy in the context of *G6PD* genotype (updates at www.cpicpgx.org).

INTRODUCTION

Many drugs have been putatively associated with a higher risk of acute hemolytic anemia (AHA) in the presence of glucose-6-phosphate dehydrogenase (G6PD) deficiency. Depending on the sources referenced, the classification of a medication as "safe" or "unsafe" for use in patients with G6PD deficiency may be conflicting. G6PD deficiency increases an individual's susceptibility to oxidative stress caused not only by drugs but also by concurrent illnesses (such as infection) and by dietary stressors (such as fava beans, *Vicia faba*, which contain potent oxidative agents); often, these confounding stressors are inadequately documented in literature reports and their contribution to AHA development cannot be fully determined. The purpose of this guideline is to provide guidance on how to interpret the results of clinical *G6PD* genotype tests and on which medications should have prescribing informed by G6PD status and which can be used without regard to G6PD phenotype. Detailed guidelines on other aspects of the use of drugs discussed in this guideline, including analyses of cost-effectiveness of testing, are beyond the scope of this document. The CPIC website https://cpicpgx.org/gene/g6pd/ should be consulted for updates to this guideline.

FOCUSED LITERATURE REVIEW

A systematic literature review focusing on G6PD, associated medications, and the risk of AHA in the setting of G6PD deficiency was conducted (see **Supplement, Literature Review**). The strategy for selecting drugs to include in the literature review, as well as specialized search approaches for primaquine, sulfamethoxazole, aspirin, vitamin C, and vitamin K, are outlined in the **Supplement**. Reviews (1-3) were used to summarize background information and to identify citations missed by the literature review. The evidence is summarized in **Table S1**.

GENE: *G6PD*

Background

The *G6PD* gene encodes the G6PD enzyme, which converts glucose-6-phosphate into 6-phosphogluconolactone, the first step of the pentose phosphate pathway (PPP) (https://www.pharmgkb.org/pathway/PA165971634) (4). G6PD produces NADPH from NADP. G6PD is ubiquitously expressed, but it is particularly important in erythrocytes where, along with 6-phosphogluconate dehydrogenase (6PGD), it is the only available source of NADPH. NADPH is required to protect erythrocytes from oxidative stress, which can be imposed by various substances, including oxygen free radicals and hydrogen peroxide, that may be generated physiologically or may result from exposure to exogenous agents such as drugs, fava beans, and disease states such as infection (1-3). Thus, drugs are not themselves substrates for the G6PD enzyme, but the enzyme deficiency predisposes individuals to hemolysis when some drugs are administered. G6PD deficient erythrocytes are thus more susceptible to drug-induced lysis, which can manifest clinically as AHA. Furthermore, oxidation of hemoglobin iron results in the formation of methemoglobin, and methemoglobinemia may accompany anemia in G6PD deficiency.

The *G6PD* gene, which is located on the X chromosome, has over 150 reported alleles (***G6PD* Allele Definition Table**) (5-9). Most of the variants are missense variants resulting in single amino acid substitutions and some are in-frame deletions (***G6PD* Allele Functionality Table**) (5, 6, 8). Variants can be found alone or in combination on the same chromosome (haplotypes). We will use the term "allele" throughout this manuscript to refer to both single variants and haplotypes. The lack of large deletions and frameshift variants appears consistent with the finding that a complete absence of G6PD enzyme activity is fatal *in utero*, as has been

shown in *G6PD* knock-out mice (10). Most of the alleles that result in low G6PD enzyme activity affect enzyme stability, with the most severe alleles causing alterations predominantly at or near the dimer interface of the G6PD protein in exon 10, which affects dimer formation and substrate binding (8, 11).

G6PD alleles have historically been divided into classes by the World Health Organization (WHO) (12), from class I (severe enzyme deficiency) to class IV (normal enzyme activity). In 2022, the WHO assembled a working group to revise this classification system. The proposed new classification system will include four classes: A (<20% of G6PD activity/chronic hemolysis), B (<45% of G6PD activity/acute, triggered hemolysis), C (60-150% of G6PD activity/no hemolysis), and U (any G6PD activity/uncertain clinical significance) (13). For the purposes of this guideline, the historical classification (class I-class IV) will be used as *G6PD* alleles have not yet been mapped to the new classes; however, updates will be made available on the CPIC website when applicable. These classification systems are based on two criteria: (i) the level of G6PD activity in erythrocytes and (ii) clinical presentation of individuals bearing those alleles (**Table S2**). Given that *G6PD* is on the X chromosome, the classifications were primarily based on assessments in males; with only one copy of the gene, their erythrocyte enzyme activity reflects the only allele they carry (**Table S2**) (9, 12, 14). *G6PD* alleles are defined as class I when they are associated with chronic non-spherocytic hemolytic anemia (CNSHA): they are found in patients who have hemolysis even in the absence of any challenge and usually have a G6PD activity less than 10% of normal in erythrocytes (2, 9, 12). Class I alleles are very rare, and the estimated frequency of CNSHA is less than 10 per million (2). Therefore, data on further drug-induced worsening of anemia in such patients is essentially nonexistent. It was proposed that class II alleles have G6PD activity less than 10% but without CNSHA, and that class III

alleles are those with G6PD activity between 10 and 60% of normal; however, both class II and III alleles are considered to confer deficiency and they increase the risk of drug-induced AHA. Because, by definition, class II alleles have a mean G6PD enzyme activity lower than that of class III alleles, it is reasonable to conclude that AHA may be more severe with the former than with the latter. However, this does not mean that Class III alleles can be regarded as 'mild'; for example, in trials of dapsone in children with *G6PD* A- (class III), 98% of G6PD deficient males developed AHA, 11% of whom required a blood transfusion (15). Thus, a division between class II and III alleles may not be clinically useful (2), and such alleles will likely be pooled as class B in the future under the new WHO classification system. As per gnomAD, some of the most common low-function alleles (excluding haplotypes), often named after the place the variant was first discovered, include Seattle, Lodi, Modena, Ferrara II, Athens-like at 0.11% in individuals of European ancestry; Kaiping, Anant, Dhon, Sapporo-like at 0.7% in individuals of East Asian ancestry; Ilesha at 0.12% and 0.05% in those of Native American and Sub-Saharan African ancestry; and Kaylan-Kerala, Jamnaga, Rohini at 1.1% in individuals of Central/South Asian ancestry (***G6PD* Frequency Table** (5, 6)). In a group of 2139 unselected racially diverse North American children with leukemia whose *G6PD* gene was sequenced, 85% of 48 Class II-III deficient alleles were accounted for by the A- or Asahi (Class III) alleles (16). Class IV are alleles with normal enzyme activity (2). Class V was designated to be assigned to alleles associated with increased enzyme activity. However, only one such case has been reported (named G6PD Hektoen), but the causative allele was never determined, and thus the Class V designation is no longer used (17).

In this guideline, the categories of G6PD phenotypes include G6PD deficient with CNSHA, G6PD deficient, G6PD normal, and G6PD variable (**Table 1**) (2). Thus, nearly all

individuals classified as "G6PD deficient" are those with WHO Class II or Class III alleles (2). Individuals classified in the "variable" category are those (generally females) who carry one non-deficient (Class IV) and one deficient (Class I-III) allele. Due to X-linked mosaicism, it is impossible to predict their activity based on genotype alone; in such patients, enzyme activity testing is needed to diagnose G6PD deficiency. In addition, it is not possible to distinguish between G6PD deficiency with and without CNSHA based on measures of G6PD activity alone.

Almost 5% of the world's population is estimated to have G6PD deficiency, with nearly all of them carrying Class II and/or III alleles (18). Given that heterozygosity for G6PD deficiency is associated with protection against malaria mortality (2), the average frequency of G6PD deficiency in malaria endemic countries such as in Asia and Africa is higher, with a prevalence in certain population groups as high as 30% or more (***G6PD* Frequency Table** (5, 6)).

Genetic Test Interpretation

The *G6PD* gene is on the X chromosome (Xq28) (3). Genotype results associated with G6PD deficiency may be reported as: 1) hemizygous (persons with one X chromosome carrying a Class I-III allele), 2) homozygous (persons with two identical deficient Class I-III alleles), 3) compound heterozygous (persons with two different deficient Class I-III alleles), and 4) heterozygous (persons with one normal Class IV allele and one deficient Class I-III allele) (**Table 1**). Known decreased function alleles (Class I, II, and III) are provided in the ***G6PD* Allele Definition and *G6PD* Functionality Tables** (5, 6). If these alleles are present, they may be interpreted as defined in **Table 1**: a diagnosis of G6PD deficiency can be made on the basis of genotypic results for hemizygous, homozygous, and compound heterozygous persons. *G6PD* genotype depends on the number of X chromosomes the person has rather than their sex assigned

at birth. For example, persons who may self-identify as male but have XXY chromosomes (i.e., Klinefelter syndrome) have *G6PD* genotypes based on the presence of two *G6PD* alleles (19, 20). Additional inherited sex chromosome copy number conditions can further complicate interpretations of genotype in rare patients.

Determining G6PD phenotype in heterozygous persons (generally females with one normal Class IV and one deficient Class I-III allele) is not possible based on genetic testing alone due to X-linked chromosome inactivation. Random X-chromosome inactivation, an epigenetic event which occurs in a variable percentage of somatic cells, inactivates either the normal or the decreased function allele, and translates into heterozygous persons having a mosaic of G6PD normal and G6PD deficient erythrocytes. The overall enzyme activity will be variable because the ratio of the two types of erythrocytes is highly variable and can change over time (3, 21). G6PD activity in heterozygous persons can potentially span the full range from normal to deficient, and thus heterozygotes may display a drug-induced AHA profile similar to homozygotes (3, 15) (see **Supplement, G6PD Heterozygotes**). Thus, an enzyme activity test is needed to assign G6PD phenotype in heterozygous persons.

Most diagnoses of G6PD deficiency are currently made via tests of enzyme activity rather than genotype because of the unpredictable phenotype for heterozygous persons as well as issues related to genetic testing, including the slow uptake, slow turn-around time, and the limited allele coverage of some genetic tests (18). However, there is a risk of misclassification of patients based on G6PD activity tests alone, which are generally performed on whole blood samples. Among normal healthy volunteers sampled at multiple time points, intra- and inter-individual variability in G6PD activity were nearly identical (21). Newborns tend to have higher activity than older children and adults (22-24). Recent hemolysis (because G6PD content in

reticulocytes and in young erythrocytes is higher) or recent blood transfusion (because the transfused blood is likely to be G6PD normal) may shift a G6PD deficient enzyme level to within the normal range. In persons with more than one X chromosome, there may be more intra-individual variability in G6PD activity than in those with one X chromosome (see **Supplement**, **G6PD Heterozygotes**). G6PD activity is positively correlated with leukocyte count and platelet count, and corrections for hematologic abnormalities are not standardized nor known to be useful in accurately classifying G6PD status. Thus, G6PD activity measures may be particularly unreliable in patients with anemia or acute leukemia (25), and unfortunately, these are patients for whom reliable G6PD status assignment may be particularly important. Universal neonatal screening programs for G6PD deficiency via the use of semi-quantitative fluorescent spot tests or quantitative enzyme activity assays have been instituted or proposed in areas with a high incidence of G6PD deficiency, such as Asia, Africa, and the Middle East (see the ***G6PD* Allele Frequency Table** (5, 6)).

Available Genetic Test Options

Commercially available genetic testing options change over time (**Supplement**, **Available Genetic Test Options** and https://www.ncbi.nlm.nih.gov/gtr/) and vary in their specificity and sensitivity (16, 18).

Incidental Findings

Hemolytic anemia. In addition to drugs (**Table 2**), AHA may be triggered by exposure to certain chemicals, fava beans (*Vicia faba*), or infection. Although some resources suggest that foods other than fava beans may cause AHA in G6PD deficiency, we were unable to confirm peer-reviewed evidence supporting the risk from other foods (1, 26). When a drug is given because of infection, it may be difficult to know whether the cause of AHA is from the former or the latter

(3, 27). AHA after the ingestion of fava beans (broad beans) in G6PD-deficient individuals is termed 'favism' and can be fatal, mostly in children (3, 12). Individuals with a Class I *G6PD* allele are extremely rare and already exhibit anemia in the absence of exogenous triggering agents. For this reason, and due to lack of data on drugs of any risk category, caution and careful surveillance should be used when administering any medications to patients with CNSHA.

Neonatal Jaundice. Along with other factors, G6PD deficiency is associated with an increased risk of neonatal hyperbilirubinemia, which if left untreated can result in kernicterus, cerebral palsy, and death (2, 12, 28). Risk may be further increased in those with the *UGT1A1*28* allele (rs8175347) associated with Gilbert syndrome (29).

Sex chromosome abnormalities. Given that the *G6PD* gene is located on the X chromosome, the number of *G6PD* alleles returned from a pharmacogenomic test will indicate the number of X chromosomes that a patient has. This result could therefore reveal a sex chromosome abnormality (e.g., Klinefelter syndrome [XXY] and Turner syndrome [XO]) that was previously undiagnosed. In addition, for gender non-conforming patients, a *G6PD* test could reveal their sex assigned at birth.

Other clinical manifestations of G6PD deficiency. Numerous studies have investigated associations between G6PD activity and a variety of diseases; a critical analysis of evidence for these associations is beyond the scope of this guideline.

Other Considerations

The extent of G6PD deficiency and clinical symptoms varies between and within individuals and is dependent on the type of *G6PD* allele, the number of X chromosomes a person has, the triggering agent and its dosage, the presence of concurrent infection, and other inherited factors which may affect erythrocyte physiology (3, 11, 12, 21) (see **Supplement, Other Considerations**).

DRUGS

Linking Genetic Variability to Variability in Drug-Related Phenotypes

In the prior version of the *G6PD* CPIC guideline, only the drug rasburicase was specifically reviewed, although the supplement mentioned over 80 drugs and chemical compounds cited by one or more sources as either being safe or unsafe in the setting of G6PD deficiency. In this *G6PD* guideline, a primary literature review for evidence linking drugs with AHA in the setting of G6PD deficiency was performed for rasburicase and an additional 47 drugs (**Table 2**). Most of the literature associating G6PD deficiency with drug-induced hemolysis is based on assessing G6PD status from whole blood activity measures; we assume that such associations are also true for G6PD deficiency diagnosed by genotype.

The primary goal of the literature review was to assess the strength of published evidence linking the identified 48 drugs to AHA in the setting of G6PD deficiency, as opposed to drug-induced anemia unrelated to G6PD status. The evidence ratings (high, moderate, weak) were as per other CPIC guidelines, though specific criteria were developed to classify major findings into each category (**Supplement, Levels of Evidence**). This G6PD CPIC guideline differs from

others in that there is a large number of drugs carrying regulatory or literature warnings for use in G6PD deficient patients, with the vast majority being based on limited and old case reports, without controls of patients or subjects who are not G6PD deficient, and sometimes with inadequate tests to rule out other causes of anemia. Presumably on the basis of such case reports, several regulatory agencies included warnings in the drug labeling for some medications, and additional medications have inherited such labeling warnings simply by virtue of being in the same chemical or pharmacologic class. Authors considered current warnings from the U.S. Food and Drug Administration (FDA); European Medicines Agency (EMA); Pharmaceuticals and Medical Devices Agency, Japan (PMDA), and Health Canada (Santé Canada) (HCSC) (**Table S3**). Strong regulatory warnings were those that indicated that the drug was "contraindicated" or should be "avoided" in patients with G6PD deficiency; language that indicated drugs should be used with "caution" was not considered strong. Inconsistent regulatory warnings were considered to be those that were present for some but not all of these four agencies. Many more medications carry warnings for their use in G6PD deficiency than can be supported by evidence in the literature. For example, a comprehensive review of 30 medications mentioned in various textbooks and other sources to avoid in G6PD deficiency concluded that only seven of those drugs had literature supporting the warnings (30).

Therefore, an additional step was added to this CPIC guideline to assign drugs into three groups: those that can be considered high risk for AHA in the presence of G6PD deficiency (and thus should generally be avoided), those that are considered medium risk in G6PD deficiency (and thus should be used with caution), and those that can be considered low-to-no risk (with no added risk of AHA in those that are deficient for G6PD versus those with normal G6PD status) (**Table 2**).

In order to assign drugs into risk groups, the authors considered not only the strength of the evidence in the primary peer-reviewed literature, but also the frequency of drug use, the presence of regulatory agency warnings, and the presence or absence of a mechanism by which reactive oxygen species might be generated and contribute to hemolysis in G6PD deficiency (**Supplement, Assigning Risk Level**). Authors were mindful that regulatory warnings may have hindered the use of some medications in G6PD deficiency, thus resulting in a lack of available studies of the drug in G6PD deficiency. In addition, the paucity of reports of AHA for extremely widely used drugs, such as sulfonamides or low-dose aspirin, coupled with the lack of any positive studies, strongly suggests that such drugs are not associated with AHA in G6PD deficiency. For drugs with no relevant published articles linking that drug to an increased risk of AHA in the setting of G6PD deficiency, there is no recommendation (CPIC Level C) (**Table 2**). See the **Supplement** for more information.

It is worthwhile to note that the purpose of a CPIC guideline is to guide the prescribing of medications when *G6PD* genotype is known; it is not the purpose of this guideline to define whether *G6PD* testing should be performed prior to prescribing a given drug.

A brief review of evidence and rationale for risk assignment for select drugs follows. Due to space constraints, the complete classification of reviewed drugs into their risk categories, summary of evidence, strength of evidence, strength of prescribing recommendations, and suggested language for clinical decision support alerts are found in the **Supplement**.

Rasburicase and pegloticase (high risk drugs)

Background. Rasburicase (Elitek®, Fasturtec®, Rasuritek®) is a recombinant urate oxidase enzyme that breaks down uric acid to allantoin and hydrogen peroxide (31-33) and is used for prophylaxis and treatment of hyperuricemia, especially during chemotherapy for malignancies. It

is on the WHO list of essential medicines (34). A pegylated form of urate oxidase, pegloticase (Krystexxa®), is used for the treatment of refractory gout. Rasburicase can cause severe, potentially fatal hemolysis in G6PD deficient individuals (35, 36). Rasburicase is contraindicated for use in patients with known G6PD deficiency by the FDA, EMA, PMDA, and HCSC (https://www.pharmgkb.org/chemical/PA10176/labelAnnotation). Pegloticase is contraindicated for use in patients with known G6PD deficiency by the FDA; the EMA also contraindicated its use in G6PD deficiency until it was withdrawn from the market for commercial reasons in the European Union in 2016.

Risk category for rasburicase and pegloticase in G6PD deficiency. Based on literature strength (high level of evidence) linking AHA and methemoglobinemia to use of the drugs in the setting of G6PD deficiency (**Table S1**), the mechanism of action of urate oxidase (generation of hydrogen peroxide) (31), and strong, consistent regulatory warnings (**Table S3**), rasburicase and pegloticase are considered to be in the high risk category.

Therapeutic recommendations. As high risk drugs, rasburicase and pegloticase should be avoided in patients with G6PD deficiency (**Table 3**). However, as for any drug, the risk of the adverse effects (AHA and/or methemoglobinemia) must be weighed against the risk of hyperuricemia, particularly in patients with newly diagnosed malignancies in whom tumor lysis is anticipated. Tumor lysis syndrome itself can be life-threatening, and alternative uric acid-lowering therapy, such as allopurinol, may not be as efficacious as rasburicase at lowering uric acid levels, and has other potential adverse effects.

Primaquine (risk category is dosage-dependent)

Background. It is well-established that primaquine, an 8-aminoquinoline antimalarial, confers an increased risk of AHA in G6PD deficient patients (37). The ability of primaquine to induce AHA in individuals with G6PD deficiency was first discovered in the 1950s and termed "primaquine sensitivity" (38, 39). Although the risk of AHA is likely dose-related for all drugs, primaquine is a special case because multiple studies have been conducted to identify alternative dosing schedules that are safe and effective in the treatment of malaria in G6PD deficient patients (**Table S1**); this is reflected in the evidence-based treatment guidelines from the WHO and U.S. Centers for Disease Control and Prevention (CDC) (40, 41).

Risk category for primaquine in G6PD deficiency. Primaquine at standard anti-relapse dosages of 0.25-0.5 mg/kg daily for 14 days for the treatment of *Plasmodium vivax* or *Plasmodium ovale* is considered in the high risk category because there is a high level of evidence linking it to AHA (37), but primaquine at lower doses is considered in either the medium or low-to-no risk category because it has been specifically studied in G6PD deficient patients (**Table S1**). The benefit of using primaquine may outweigh any possible risk of hemolysis, which is lower or negligible with these lower dose regimens.

Therapeutic recommendations. It is recommended to avoid primaquine at standard (or higher) anti-relapse dosages of 0.25-0.5 mg/kg daily for 14 days for the treatment of *Plasmodium vivax* or *Plasmodium ovale* in G6PD deficiency. For the anti-gametocyte treatment of *Plasmodium falciparum* malaria, the single dose regimen of 0.25 mg/kg is considered safe and effective (low-to-no risk in G6PD deficiency) (40). For the treatment of *Plasmodium vivax* or *Plasmodium*

ovale malaria for radical cure of liver-stage infections, 0.75 mg/kg once weekly for eight weeks (WHO) or 45 mg for adults once weekly for eight weeks (CDC) is considered in the medium risk category, and patients should be monitored closely for hemolysis (40, 41) (**Table 6**). No dose of primaquine is considered safe in patients who are G6PD deficient with CNSHA and thus should be avoided.

Nitrofurantoin (medium risk drug)

Background. Nitrofurantoin has been widely used worldwide for more than 70 years as an antimicrobial, often to treat or suppress urinary tract infections, and is on the list of WHO essential medicines (34). Several regulatory agencies have warnings related to use of nitrofurantoin in G6PD deficiency. There was some disagreement among authors as to whether the evidence linking nitrofurantoin to AHA in G6PD deficiency should be deemed moderate or weak; despite the extremely widespread use of nitrofurantoin, there are only a few published cases of AHA following nitrofurantoin administration. One group reviewed a database for adverse drug reactions and found AHA after nitrofurantoin was reported in approximately 1 in 100,000 prescriptions, which was deemed a frequency too low to be consistent with G6PD deficiency predisposing to AHA (42). However, the study did not include G6PD testing for the majority of cases, and prescriptions were not explicitly recorded. Herman et al. (43) studied possible causes of AHA in 129 G6PD deficient patients and found that AHA occurred in 3 of 6 such patients who received nitrofurantoin, and in another study, Chan et al. demonstrated that nitrofurantoin caused a shortened half-life of red cells from G6PD deficient patients comparable to that caused by primaquine (44).

Risk category for nitrofurantoin in G6PD deficiency. Nitrofurantoin is considered in the medium risk category because although the evidence from primary literature linking it to AHA is moderate at best, there have been relatively strong long-standing regulatory warnings that may have hindered its use in G6PD deficient patients (**Table S3**).

Therapeutic recommendations. The recommendation to use nitrofurantoin with caution in known G6PD deficiency is given an optional strength, given that evidence is moderate at best, and the paucity of case reports is surprising given how commonly the drug has been used worldwide (**Table 4**).

Sulfamethoxazole (low-to-no risk drug)

Background. Sulfamethoxazole is used as an antimicrobial to treat and prevent infections, and it is commonly available in combination with trimethoprim. It is included in the WHO list of essential medicines (34) and is among the top 300 prescribed drugs in the U.S. (45).

Risk category for sulfamethoxazole in G6PD deficiency. Sulfamethoxazole is considered in the low-to-no risk category because the evidence linking it to AHA is weak (mostly case reports, frequently confounded by the presence of infection, fava beans, or other drugs), and several studies show safe use in G6PD deficiency (46, 47). One study showing a lack of AHA from this drug in G6PD deficiency was reported in 10 deficient infants (46). Although there are some regulatory agency warnings, most are weak. Moreover, sulfamethoxazole is widely used, providing further weight to the lack of studies supporting significant risk.

Therapeutic recommendations. As a low-to-no risk medication, it is recommended to use sulfamethoxazole normally without regard to G6PD status (**Table 5**), although the strength of the recommendation is "optional," given that the authors recognize it is the subject of "caution" from some regulatory agencies.

Pediatrics

There are data supporting or refuting certain drugs associated with increased risk of AHA in the setting of G6PD deficiency reported in pediatric patients (**Table S1**). There is no reason to think that genetically-based recommendations in this guideline should differ for children versus adults.

Recommendations for incidental findings

Patients with G6PD deficiency should be advised that they are at an increased risk of hemolysis after exposure to fava beans or to high risk drugs or chemicals (**Table 2**), and that it is recommended to avoid such substances. Other conditions, such as infection, hyperuricemia, and sepsis that lead to generation of activated oxygen species, also place the patient at risk of AHA.

Furthermore, because the *G6PD* gene is located on the X chromosome, self-identified males who have a *G6PD* diplotype indicating the presence of two *G6PD* alleles may have an inherited sex chromosome disorder such as Klinefelter syndrome. This syndrome occurs in ~1 in 600 persons assigned male at birth, and there are possible medical interventions that may be indicated once that diagnosis is confirmed. Consideration for involvement of genetic counselors and procedures to confirm the diagnosis of Klinefelter syndrome should be in place for those who routinely test *G6PD* genotype (48).

Other considerations

Recommendations for the testing of other genetic markers are beyond the scope of this guideline. Agents known to induce or inhibit *G6PD* expression may also influence the risk of AHA (49). The higher the systemic exposure to reactive oxygen species, due to multiple drug challenges, higher dosages or decreased clearance of offending drugs, as well as the presence of infection or other oxidative stress conditions, could also increase the risk (3); as such, some drugs in the medium or low risk category could pose a higher risk if exposure is higher than what had been studied previously in the context of G6PD status.

Because there is a paucity of data on drug use in patients with G6PD deficiency and CNSHA, and because these individuals experience hemolytic anemia at baseline (2, 50), our recommendations are conservative and recommend against the use of any high risk and medium risk drugs in such patients, and caution for use of any drugs, including low-to-no risk drugs.

A *G6PD* genotype may not be sufficient to determine G6PD status, and thus G6PD enzyme activity testing may be necessary for an accurate assessment of risk for drug-induced AHA. Due to the limitations of genotyping and enzyme activity testing, integrating both testing approaches may be more informative than using either method alone (25).

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

Using *G6PD* genotype to inform medication use has the potential to prevent AHA and subsequent complications for patients. However, as for any medication, a decision must be made as to whether benefit of the intended drug outweighs the risk of AHA in potentially G6PD deficient patients, particularly in emergent situations in which G6PD status may not be available to inform prescribing or in settings where G6PD testing is not widely available (e.g.,

underdeveloped countries). For example, rasburicase is the most effective agent for preventing hyperuricemia and possible renal failure for patients at high risk of tumor lysis syndrome, but in some cases, G6PD status may not be available in time to inform prescribing (or concurrent hyperleukocytosis/anemia may confound interpretation of G6PD activity measures), and clinicians must weigh the risk of AHA and methemoglobinemia from rasburicase against the risk of complications of tumor lysis syndrome**.** Similarly, for primaquine, clinicians need to balance the risk of hemolytic anemia with adequate treatment of malaria in rural communities where G6PD testing may not be accessible.

CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

Several commercially available genetic tests screen only for some of the more common *G6PD* alleles. Therefore, any patient could have a rare, different, or novel allele; thus, a genetic test may be reported as "negative," but the patient could nonetheless have G6PD deficiency. Consideration of a patient's ancestry may be informative for assessing whether a particular *G6PD* genotyping assay captures the most relevant alleles, as allele frequency varies across diverse populations (***G6PD* Allele Frequency Table** (5, 6)). Patients with a variable G6PD phenotype based on genotype require enzyme activity testing to determine the presence of G6PD deficiency.

CONCLUSION

The use of high risk drugs, such as rasburicase, is contraindicated in those with G6PD deficiency. Recent data indicate that genetic test results are reliable, particularly in persons with

one X chromosome (25). G6PD activity measures will continue to have a role in establishing G6PD status, especially in persons with more than one X chromosome (e.g., females). Based on a systematic review of published literature, many drugs previously labeled as potentially hazardous in G6PD deficiency do not have published evidence supporting those labeled hazards. In the future, as an increasing number of patients will have informative *G6PD* genotypes in their medical records, the use of genetic test results will likely increase and supplement the decision-making process regarding whether it is safe to use certain medications in patients with G6PD deficiency.

DISCLAIMER

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written, and are intended only to assist clinicians in decision-making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health care provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC's guidelines, or for any errors or omissions.

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Table 1. Assignment of predicted G6PD phenotype based on genotype

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

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

[a]WHO classifications from (8), other details from (14). Class I alleles are extremely rare; the distinction between Class II and III alleles is not clear. Almost all patients will carry class II, III, or IV alleles.

[b]Due to the large number of *G6PD* alleles, other genotypes may be possible besides those given as examples here; see the ***G6PD* Allele Definition Table** (5, 6) for a more comprehensive list of alleles and ***G6PD* Allele Functionality Table** (5, 6) for their assigned function (WHO class). Note that some labs use the designation "B allele" to indicate an allele carrying no known class I-III variants. The ***G6PD* Frequency Table** (5, 6) can be referenced for the frequency of *G6PD* alleles across major biogeographical groups.

[c]Due to X-linked mosaicism, persons heterozygous (generally females) for one non-deficient (class IV) and one deficient (class I-III alleles) allele may display a normal or a deficient phenotype. It is therefore difficult to predict the phenotype of these individuals (see **Supplement**, **G6PD Heterozygotes**).

[d]Such genotypes have never been seen and are presumably exceedingly rare.

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

Drug	**Risk**	**Classification of Recommendation**
Dapsone	High	Strong
Methylene blue	High	Moderate
Pegloticase	High	Strong
Primaquine – ≥ standard dose (0.25-0.5 mg/kg daily for 14 days)	High	Strong
Rasburicase	High	Strong
Tafenoquine	High	Strong
Toluidine blue	High	Moderate[a]
Nitrofurantoin	Medium	Optional
Primaquine – medium dose (0.75 mg/kg or 45 mg once weekly for 8 weeks) for *Plasmodium vivax* malaria	Medium	Strong
4-aminosalicylic acid	Low-to-no	Optional
Aspirin ≤ 1 g/day	Low-to-no	Moderate
Chloramphenicol	Low-to-no	Moderate
Chloroquine	Low-to-no	Moderate
Ciprofloxacin	Low-to-no	Optional
Dimercaprol	Low-to-no	Optional
Doxorubicin	Low-to-no	Optional
Furazolidone	Low-to-no	Optional
Glyburide	Low-to-no	Optional
Hydroxychloroquine	Low-to-no	Moderate
Mafenide	Low-to-no	Optional
Nalidixic acid	Low-to-no	Optional
Norfloxacin	Low-to-no	Optional
Ofloxacin	Low-to-no	Optional
Phenazopyridine	Low-to-no	Optional
Primaquine – single low dose (0.25 mg/kg) for *Plasmodium falciparum* malaria	Low-to-no	Strong
Quinine	Low-to-no	Optional
Sulfadiazine	Low-to-no	Optional
Sulfadimidine	Low-to-no	Optional
Sulfamethoxazole	Low-to-no	Optional
Sulfanilamide	Low-to-no	Optional
Sulfasalazine	Low-to-no	Optional
Sulfisoxazole	Low-to-no	Optional

Tolbutamide	Low-to-no	Optional
Vitamin C	Low-to-no	Moderate
Vitamin K	Low-to-no	Moderate
Aspirin > 1 g/day	n/a	No recommendation
Chlorpropamide	n/a	No recommendation
Dabrafenib	n/a	No recommendation
Gliclazide	n/a	No recommendation
Glimepiride	n/a	No recommendation
Glipizide	n/a	No recommendation
Mepacrine	n/a	No recommendation
Mesalazine	n/a	No recommendation
Moxifloxacin	n/a	No recommendation
Nicorandil	n/a	No recommendation
Nitrofural	n/a	No recommendation
Probenecid	n/a	No recommendation
Sodium nitrite	n/a	No recommendation
Sulfacetamide	n/a	No recommendation
Tolazamide	n/a	No recommendation
Trametinib	n/a	No recommendation

n/a = not applicable (not assigned a risk level)

[a]Based on extrapolation from methylene blue data.

Table 3. Recommended therapeutic use of high risk drugs[a] in relation to G6PD phenotype

Predicted G6PD phenotype based on genotype	**Implications for phenotypic measures**	**Therapeutic recommendations for high risk drugs**	**Classification of recommendations[b]**	**Considerations**
Normal	Low risk of acute hemolytic anemia	No reason to avoid high risk drugs based on G6PD status	Strong	Tafenoquine's safety has been established for a G6PD enzyme activity ≥70% of normal.[c]
Deficient	High risk of acute hemolytic anemia	Avoid use of high risk drugs	See **Table 2** for drug-specific strength of recommendations	
Deficient with CNSHA	High risk of acute exacerbation of chronic hemolysis	Avoid use of high risk drugs	Strong	Although there are no published data in individuals with the G6PD Deficient with CNSHA phenotype, there is a strong rationale to avoid these drugs based on evidence in G6PD Deficient individuals.
Variable	Variable risk of acute hemolytic anemia	To ascertain G6PD status, enzyme activity must be measured. Drug use should be guided per the recommendations based on the activity-based phenotype.	Moderate	Due to X-linked mosaicism, individuals with more than one X chromosome (e.g., females, individuals with Klinefelter syndrome) and heterozygous for one

				non-deficient (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. Tafenoquine's safety has been established for a G6PD enzyme activity ≥70% of normal.[c]
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	

CNSHA, chronic non-spherocytic hemolytic anemia; G6PD, glucose-6-phosphate dehydrogenase

[a]Drugs are classified as high, medium, or low-to-no risk for acute hemolytic anemia based on evidence review and 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 is to occur). Because primaquine has been well studied at high, medium and low dosages, see **Table 6** for primaquine-specific recommendations.

[b]Rating scheme described in **Supplement** *(see Strength of Recommendations* material*)*

[c]Inclusion criteria for clinical trials involving tafenoquine included G6PD activity ≥70% (51).

Table 4. Recommended therapeutic use of medium risk drugs[a] in relation to G6PD phenotype

Predicted G6PD phenotype based on genotype	**Implications for phenotypic measures**	**Therapeutic recommendations for medium risk drugs**	**Classification of recommendations[b]**	**Considerations**
Normal	Low risk of acute hemolytic anemia	No reason to avoid medium risk drugs based on G6PD status	Strong	
Deficient	Medium risk of acute hemolytic anemia	Use medium risk drugs at standard doses with caution and with close monitoring for anemia	See **Table 2** for drug-specific strength of recommendations	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 multiple medium and low-to-no risk drugs.
Deficient with CNSHA	High risk of acute exacerbation of 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 exacerbation of chronic hemolysis.
Variable	Variable risk of acute hemolytic anemia	If deemed necessary to ascertain G6PD status, enzyme activity must be measured. Drug use should be guided per the recommendations based on the activity-based phenotype.	Moderate	Due to X-linked mosaicism, individuals with more than one X chromosome (e.g., females, individuals with Klinefelter syndrome) and heterozygous for one non-deficient (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	

CNSHA, chronic non-spherocytic hemolytic anemia; G6PD, glucose-6-phosphate dehydrogenase

[a]Drugs are classified as high, medium, or low-to-no risk for acute hemolytic anemia based on evidence review and 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 is to occur). Because primaquine has been well studied at high, medium and low dosages, see **Table 6** for primaquine-specific recommendations.

[b]Rating scheme described in **Supplement** *(see Strength of Recommendations* material*)*

Table 5. Recommended therapeutic use of low-to-no risk drugs[a] 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[b]**	**Considerations**
Normal	Low-to-no risk of acute hemolytic anemia	No reason to avoid low-to-no risk drugs 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** for drug-specific strength of recommendations	Closer monitoring may be indicated for higher-than-normal dosages, and in the setting of infection or other oxidative stress, including concomitant use of multiple medium and low-to-no risk drugs.
Deficient with CNSHA	High risk of acute exacerbation of chronic hemolysis	Use all drugs cautiously in this group; if a drug is used, close monitoring for acute exacerbation of chronic hemolysis is recommended.	Optional	There are insufficient data in patients with the G6PD Deficient with CNSHA phenotype, but the risk of using any drug should be weighed carefully against the benefits in these rare patients due to the underlying pathophysiology that confers high risk for acute exacerbation of chronic hemolysis.

Variable	Low-to-no risk of acute hemolytic anemia	No reason to avoid low-to-no risk drugs 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 non-deficient (class IV) and one deficient (class I–III) allele may display a normal or a deficient phenotype.
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	

CNSHA, chronic non-spherocytic hemolytic anemia; G6PD, glucose-6-phosphate dehydrogenase

[a]Drugs are classified as high, medium, or low-to-no risk for acute hemolytic anemia based on evidence review and 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 is to occur). Because primaquine has been well studied at high, medium and low dosages, see **Table 6** for primaquine-specific recommendations.

[b]Rating scheme described in **Supplement** *(see Strength of Recommendations* material*)*

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 (or higher than standard) anti-relapse dosages for *Plasmodium vivax* or *Plasmodium ovale* of 0.25-0.5 mg/kg daily for 14 days	Avoid primaquine, except in the following cases where established expert consensus guidelines for the treatment of malaria should be followed: (1) Treating *Plasmodium vivax* or *Plasmodium ovale* malaria for radical cure of liver-stage infections: 0.75 mg/kg once weekly x8 weeks (WHO) or 45 mg once weekly x8 weeks (CDC) - with close monitoring for hemolysis; (2) Treating *Plasmodium falciparum* malaria by using primaquine single dose as a gametocytocide at 0.25 mg/kg (WHO) - without need for monitoring 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 (39) and the U.S. Centers for Disease Control and Prevention (40).

Deficient with CNSHA	High risk of acute exacerbation of chronic hemolysis	Avoid primaquine	Strong	The strength of evidence among patients with the G6PD Deficient phenotype provides strong rationale to also avoid primaquine in the setting of the more severe G6PD Deficient with CNSHA phenotype.
Variable	Variable risk of acute hemolytic anemia	To ascertain G6PD status, enzyme activity must be measured. Drug use should be guided per the recommendations based on the activity-based phenotype.	Moderate	Due to X-linked mosaicism, individuals with more than one X chromosome (e.g., females, individuals with Klinefelter syndrome) and heterozygous for one nondeficient (class IV) and one deficient (class I–III) allele may display a normal or a deficient phenotype; an enzyme activity test is needed to guide treatment 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	

CNSHA, chronic non-spherocytic hemolytic anemia; G6PD, glucose-6-phosphate dehydrogenase
[a]Rating scheme described in **Supplement** *(see Strength of Recommendations* material*)*

REFERENCES

(1) Luzzatto, L. & Arese, P. Favism and Glucose-6-Phosphate Dehydrogenase Deficiency. *N Engl J Med* **378**, 60-71 (2018).

(2) Luzzatto, L., Ally, M. & Notaro, R. Glucose-6-phosphate dehydrogenase deficiency. *Blood* **136**, 1225-40 (2020).

(3) Cappellini, M.D. & Fiorelli, G. Glucose-6-phosphate dehydrogenase deficiency. *Lancet* **371**, 64-74 (2008).

(4) Relling, M.V. *et al.* Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for rasburicase therapy in the context of G6PD deficiency genotype. *Clin Pharmacol Ther* **96**, 169-74 (2014).

(5) CPIC. *CPIC Guideline for G6PD*. <https://cpicpgx.org/cpic-guideline-for-g6pd/> (2021). Accessed October 18 2021.

(6) PharmGKB. *Gene-specific Information Tables for G6PD*. <https://www.pharmgkb.org/page/g6pdRefMaterials>. Accessed October 18 2021.

(7) Nomenclature of glucose-6-phosphate dehydrogenase in man. *American journal of human genetics* **19**, 757-61 (1967).

(8) Minucci, A., Moradkhani, K., Hwang, M.J., Zuppi, C., Giardina, B. & Capoluongo, E. Glucose-6-phosphate dehydrogenase (G6PD) mutations database: review of the "old" and update of the new mutations. *Blood Cells Mol Dis* **48**, 154-65 (2012).

(9) Yoshida, A., Beutler, E. & Motulsky, A.G. Human glucose-6-phosphate dehydrogenase variants. *Bulletin of the World Health Organization* **45**, 243-53 (1971).

(10) Longo, L. *et al.* Maternally transmitted severe glucose 6-phosphate dehydrogenase deficiency is an embryonic lethal. *EMBO J* **21**, 4229-39 (2002).

(11) Mason, P.J., Bautista, J.M. & Gilsanz, F. G6PD deficiency: the genotype-phenotype association. *Blood reviews* **21**, 267-83 (2007).

(12) Glucose-6-phosphate dehydrogenase deficiency. WHO Working Group. *Bulletin of the World Health Organization* **67**, 601-11 (1989).

(13) *Meeting report of the technical consultation to review the classification of glucose-6-phosphate dehydrogenase (G6PD)*. <https://www.who.int/publications/m/item/WHO-UCN-GMP-MPAG-2022.01> (2022). Accessed April 21 2022.

(14) Standardization of procedures for the study of glucose-6-phosphate dehydrogenase. Report of a WHO Scientific Group. *World Health Organ Tech Rep Ser* **366**, 1-53 (1967).

(15) Pamba, A. *et al.* Clinical spectrum and severity of hemolytic anemia in glucose 6-phosphate dehydrogenase-deficient children receiving dapsone. *Blood* **120**, 4123-33 (2012).

(16) Robinson, K.M. *et al.* Concordance between glucose-6-phosphate dehydrogenase (G6PD) genotype and phenotype and rasburicase use in patients with hematologic malignancies. *Pharmacogenomics J* **19**, 305-14 (2019).

(17) Dern, R.J., McCurdy, P.R. & Yoshida, A. A new structural variant of glucose-6-phosphate dehydrogenase with a high production rate (G6PD Hektoen). *J Lab Clin Med* **73**, 283-90 (1969).

(18) Nkhoma, E.T., Poole, C., Vannappagari, V., Hall, S.A. & Beutler, E. The global prevalence of glucose-6-phosphate dehydrogenase deficiency: a systematic review and meta-analysis. *Blood Cells Mol Dis* **42**, 267-78 (2009).

(19) Au, W.Y., Tse, J., So, J.C., Wan, T.S. & Young, K. Unexpected glucose-6-phosphate dehydrogenase deficiency. *Br J Haematol* **145**, 680 (2009).
(20) Tada, K. & Hayashi, T. Erythrocyte Glucose-6-Phosphate Dehydrogenase Activity in Klinefelter's Syndrome. *Tohoku J Exp Med* **85**, 248-51 (1965).
(21) Yuregir, G.T., Aksoy, K., Arpaci, A., Unlukurt, I. & Tuli, A. Studies on red cell glucose-6-phosphate dehydrogenase: evaluation of reference values. *Ann Clin Biochem* **31 (Pt 1)**, 50-5 (1994).
(22) Algur, N., Avraham, I., Hammerman, C. & Kaplan, M. Quantitative neonatal glucose-6-phosphate dehydrogenase screening: distribution, reference values, and classification by phenotype. *J Pediatr* **161**, 197-200 (2012).
(23) Riskin, A., Gery, N., Kugelman, A., Hemo, M., Spevak, I. & Bader, D. Glucose-6-phosphate dehydrogenase deficiency and borderline deficiency: association with neonatal hyperbilirubinemia. *J Pediatr* **161**, 191-6 e1 (2012).
(24) Kaplan, M., Algur, N. & Hammerman, C. Intermediate values of glucose-6-phosphate dehydrogenase. *J Pediatr* **161**, 571; author reply -2 (2012).
(25) Morris, S.A. *et al.* Incorporating G6PD genotyping to identify patients with G6PD deficiency. *Pharmacogenet Genomics*, (2021).
(26) Lee, S.W., Chaiyakunapruk, N. & Lai, N.M. What G6PD-deficient individuals should really avoid. *Br J Clin Pharmacol* **83**, 211-2 (2017).
(27) Beutler, E. G6PD deficiency. *Blood* **84**, 3613-36 (1994).
(28) Weng, Y.H., Chiu, Y.W., Cheng, S.W. & Hsieh, M.Y. Risk assessment for adverse outcome in term and late preterm neonates with bilirubin values of 20 mg/dL or more. *Am J Perinatol* **28**, 405-12 (2011).
(29) Kaplan, M., Hammerman, C. & Beutler, E. Hyperbilirubinaemia, glucose-6-phosphate dehydrogenase deficiency and Gilbert syndrome. *Eur J Pediatr* **160**, 195 (2001).
(30) Youngster, I. *et al.* Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Saf* **33**, 713-26 (2010).
(31) Navolanic, P.M. *et al.* Elitek-rasburicase: an effective means to prevent and treat hyperuricemia associated with tumor lysis syndrome, a Meeting Report, Dallas, Texas, January 2002. *Leukemia* **17**, 499-514 (2003).
(32) Pui, C.H. Rasburicase: a potent uricolytic agent. *Expert Opin Pharmacother* **3**, 433-42 (2002).
(33) Elitek (R) drug label(Sanofi-aventis U.S. LLC, B., NJ,). <from the DailyMed website https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0ae10bc4-6b65-402f-9db5-2d7753054922 (c) 2008>.
(34) Persaud, N. *et al.* Comparison of essential medicines lists in 137 countries. *Bulletin of the World Health Organization* **97**, 394-404C (2019).
(35) Bucklin, M.H. & Groth, C.M. Mortality following rasburicase-induced methemoglobinemia. *Ann Pharmacother* **47**, 1353-8 (2013).
(36) Zaramella, P. *et al.* Lethal effect of a single dose of rasburicase in a preterm newborn infant. *Pediatrics* **131**, e309-12 (2013).
(37) Bancone, G. & Chu, C.S. G6PD Variants and Haemolytic Sensitivity to Primaquine and Other Drugs. *Front Pharmacol* **12**, 638885 (2021).
(38) Hockwald, R.S., Arnold, J., Clayman, C.B. & Alving, A.S. Toxicity of primaquine in Negroes. *J Am Med Assoc* **149**, 1568-70 (1952).

(39) Alving, A.S., Carson, P.E., Flanagan, C.L. & Ickes, C.E. Enzymatic deficiency in primaquine-sensitive erythrocytes. *Science* **124**, 484-5 (1956).
(40) *WHO Guidelines for Malaria* <https://www.who.int/publications/i/item/guidelines-for-malaria>. Accessed November 4 2021.
(41) *Treatment of Malaria: Guidelines for Clinicians (United States)*. <https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Guidelines.pdf>. Accessed November 4 2021
(42) Gait, J.E. Hemolytic reactions to nitrofurantoin in patients with glucose-6-phosphate dehydrogenase deficiency: theory and practice. *DICP* **24**, 1210-3 (1990).
(43) Herman, J. & Ben-Meir, S. Overt hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency: a survey in general practice. *Isr J Med Sci* **11**, 340-6 (1975).
(44) Chan, T.K., Todd, D. & Tso, S.C. Drug-induced haemolysis in glucose-6-phosphate dehydrogenase deficiency. *Br Med J* **2**, 1227-9 (1976).
(45) *The top 300 of 2019*. <https://clincalc.com/DrugStats/Top300Drugs.aspx>. Accessed November 4 2021.
(46) Chan, M.C. & Wong, H.B. Letter: Glucose-6-phosphate dehydrogenase deficiency and co-trimoxazole. *Lancet* **1**, 410 (1975).
(47) Markowitz, N. & Saravolatz, L.D. Use of trimethoprim-sulfamethoxazole in a glucose-6-phosphate dehydrogenase-deficient population. *Rev Infect Dis* **9 Suppl 2**, S218-29 (1987).
(48) Fullerton, S.M. *et al.* Return of individual research results from genome-wide association studies: experience of the Electronic Medical Records and Genomics (eMERGE) Network. *Genet Med* **14**, 424-31 (2012).
(49) Kletzien, R.F., Harris, P.K. & Foellmi, L.A. Glucose-6-phosphate dehydrogenase: a "housekeeping" enzyme subject to tissue-specific regulation by hormones, nutrients, and oxidant stress. *FASEB J* **8**, 174-81 (1994).
(50) Vulliamy, T.J. *et al.* Clinical and haematological consequences of recurrent G6PD mutations and a single new mutation causing chronic nonspherocytic haemolytic anaemia. *Br J Haematol* **101**, 670-5 (1998).
(51) Lacerda, M.V.G. *et al.* Single-Dose Tafenoquine to Prevent Relapse of Plasmodium vivax Malaria. *N Engl J Med* **380**, 215-28 (2019).