Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2C9* and *HLA-B* Genotypes and Phenytoin Dosing: 2020 Update

Jason H. Karnes[1,2], Allan E. Rettie[3], Andrew A. Somogyi[4], Rachel Huddart[5], Alison E. Fohner[6,7], Christine M. Formea[8], Ming Ta Michael Lee[9], Adrian Llerena[10], Michelle Whirl-Carrillo[5], Teri E. Klein[5,11], Elizabeth J. Phillips[12], Scott Mintzer[13], Andrea Gaedigk[14,15], Kelly E. Caudle[16] and John T. Callaghan[17,*]

Phenytoin is an antiepileptic drug with a narrow therapeutic index and large interpatient pharmacokinetic variability, partly due to genetic variation in *CYP2C9*. Furthermore, the variant allele *HLA-B*15:02* is associated with an increased risk of Stevens–Johnson syndrome and toxic epidermal necrolysis in response to phenytoin treatment. We summarize evidence from the published literature supporting these associations and provide therapeutic recommendations for the use of phenytoin based on *CYP2C9* and/or *HLA-B* genotypes (updates on cpicpgx.org).

The purpose of this guideline is to provide information for the interpretation of human leukocyte antigen B (*HLA-B*) and/or cytochrome P450 2C9 (*CYP2C9*) genotype test results to guide use and/or dosing of phenytoin. Guidelines for phenytoin use and cost-effectiveness of genetic testing are outside the scope of this report. This guideline updates the 2014 Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2C9* and *HLA-B* Genotypes and Phenytoin Dosing.[1] CPIC guidelines are periodically updated at www.cpicpgx.org.

FOCUSED LITERATURE REVIEW

We reviewed literature focused on *CYP2C9* and *HLA* variation and phenytoin use (details in **Supplementary Material**). Evidence is summarized in **Table S1** and **Table S2**.

Genes: *HLA-B* and *CYP2C9*

Background. This guideline discusses *HLA-B* and the risk of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) with phenytoin and *CYP2C9* as it relates to phenytoin metabolism and dosing. Updated *CYP2C9* allele function assignments are provided using the activity score system.

HLA-B. *HLA-B* is part of a gene cluster designated as the human major histocompatibility complex located on the short arm of chromosome 6. The cluster contains three classes (I, II, and III). Major histocompatibility complex class I contains three genes: *HLA-A*, *HLA-B*, and *HLA-C*. These genes encode a cell surface protein that binds peptides generated by proteolysis and extruded from proteasomes. The presentation of these cell surface peptides enables the immune system to distinguish self-proteins from foreign proteins (see **Supplementary Material** for further discussion).

HLA genes, specifically *HLA-B*, are among the most highly polymorphic genes in the human genome. *HLA* polymorphisms were previously ascertained serologically, but DNA sequencing methods have identified genetic variability in the *HLA* region with greater precision. More than 7,000 *HLA-B* alleles, many of which differ by more than one nucleotide from each other, were deposited to the World Health Organization Nomenclature Committee for Factors of the HLA System (http://hla.alleles.org). Each allele is designated by the gene name followed by an asterisk and up to an eight-digit (4 pairs) identifier, which gives information about the allele type (designated by the first 2 digits) followed by the specific protein subtypes (second set of up to 6 digits). The first four digits typically differ in at least one amino acid substitution and give the

[1]Department of Pharmacy Practice & Science, University of Arizona College of Pharmacy, Tucson, Arizona, USA; [2]Sarver Heart Center, University of Arizona College of Medicine, Tucson, Arizona, USA; [3]Department of Medicinal Chemistry, University of Washington School of Pharmacy, Seattle, Washington, USA; [4]Discipline of Pharmacology, Adelaide Medical School, University of Adelaide, Adelaide, South Australia, Australia; [5]Department of Biomedical Data Science, Stanford University, Stanford, California, USA; [6]Department of Epidemiology, University of Washington, Seattle, Washington, USA; [7]Institute of Public Health Genetics, University of Washington, Seattle, Washington, USA; [8]Department of Pharmacy and Intermountain Precision Genomics, Intermountain Healthcare, Salt Lake City, Utah, USA; [9]Genomic Medicine Institute, Geisinger Health System, Danville, Pennsylvania, USA; [10]INUBE Extremadura University Biosanitary Research Institute and Medical School, Badajoz, Spain; [11]Department of Medicine, Stanford University, Stanford, California, USA; [12]Division of Infectious Diseases, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; [13]Department of Neurology, Thomas Jefferson University Hospital Methodist Hospital Division of Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, USA; [14]Division of Clinical Pharmacology, Toxicology & Therapeutic Innovation, Children's Mercy Kansas City, Kansas City, Missouri, USA; [15]School of Medicine, University of Missouri-Kansas City, Kansas City, Missouri, USA; [16]Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; [17]Department of Veteran Affairs and Departments of Medicine and Pharmacology/Toxicology, Indiana University School of Medicine, Indianapolis, Indiana, USA. *Correspondence: John T. Callaghan (jcallagh@iu.edu).

Received April 24, 2020; accepted June 25, 2020. doi:10.1002/cpt.2008

most important functional information. For more information on the description of the current *HLA* allele nomenclature see http://hla.alleles.org/nomenclature/naming.html and a previous CPIC guideline.[2] This guideline discusses only the *HLA-B*15:02* allele as it relates to the phenytoin-induced cutaneous adverse drug reactions (ADRs), including SJS and TEN.

CYP2C9. The hepatic CYP2C9 enzyme system metabolizes many clinically relevant drugs, including phenytoin (http://www.pharmgkb.org/pathway/PA145011115). The *CYP2C9* gene is highly polymorphic, with at least 61 variant alleles and multiple suballeles (see *CYP2C9* Allele Definition Table in references[3,4] https://www.pharmvar.org/gene/CYP2C9)[5]. Each *CYP2C9* star (*) allele is defined by one or more single nucleotide polymorphisms or nucleotide deletions that may alter enzyme activity. The two most common variants with decreased enzyme activity are *CYP2C9*2* (rs1799853) and *CYP2C9*3* (rs1057910).[6] *CYP2C9* allele and diplotype frequencies differ between racial/ethnic groups[7] (*CYP2C9* Frequency Table[3,4]). *In vitro* and clinical studies suggest that *CYP2C9* decreased function and no function alleles generate variant enzymes with activities that are substrate-dependent (*CYP2C9* Allele Functionality Table[3,4]). Therefore, assigning function to *CYP2C9* alleles requires careful evaluation of individual drugs.

Genetic test interpretation

HLA-B. Clinical genotyping test results for *HLA-B*15:02* are interpreted as "positive" if one or two copies of *HLA-B*15:02* are present or "negative" if no copies of *HLA-B*15:02* are found. *HLA-B* alleles do not affect the pharmacokinetics or pharmacodynamics of phenytoin. Phenotype assignments for *HLA-B*15:02* genotypes are summarized in **Table 1**. *HLA-B*15:02* is most prevalent in East Asian and Central/South Asian populations with allele frequency ranging from 1% to over 20%. *HLA-B*15:02* is less frequent in European populations (0–1%) and was not detected in several sub-Saharan African populations (*HLA-B* Frequency Table[3,4,8]).

CYP2C9. Most clinical laboratories reporting *CYP2C9* genotype use the star (*) allele nomenclature and may interpret the patient's predicted metabolizer phenotype based on the combination of *CYP2C9* alleles (diplotype; **Table 2**; CYP2C9 Diplotype to Phenotype Table[3,4]). Not all *CYP2C9* allelic variants may be tested, and this influences the accuracy of the genotype-based dose prediction. Misclassification occurs primarily in individuals of Asian or African ancestry who carry decreased function *CYP2C9* alleles other than **2* or **3* (*CYP2C9* Frequency Table[3,4]). An activity value is assigned to each *CYP2C9* allele ranging from 0 to 1 (i.e., 0 for no function, 0.5 for decreased function, and 1.0 for normal function). Activity values are summed to calculate the activity score (AS) of a diplotype.[3,4] The CYP2C9 AS is translated into phenotypes as follows: individuals with an AS of 0 or 0.5 are poor metabolizers (PMs), those with a score of 1 or 1.5 are intermediate metabolizers (IMs), and those with a score of 2 are normal metabolizers (**Table 2**; *CYP2C9* Diplotype to Phenotype Table[3,4]). Of note, as there are no known increased function alleles for *CYP2C9*, no ultrarapid or rapid CYP2C9 metabolizer phenotypes currently exist. Reference laboratories providing clinical *CYP2C9* genotyping may use various methods to assign phenotypes. Thus, before making phenytoin therapeutic decisions, we strongly advise referring to the online *CYP2C9* Diplotype to Phenotype Table[3,4] that lists all the possible *CYP2C9* diplotypes and phenotype assignments.

Of note, **Table 2** denotes a change to the previous (2014) genotype to phenotype translation tables for diplotypes containing *CYP2C9*2* and other decreased function alleles (see **Supplementary Material** for details). The *CYP2C9*2/*2* diplotype (AS = 1) is now translated into the IM phenotype group (originally translated to PM). This change is based on data for multiple substrates (flurbiprofen, celecoxib, phenytoin, and warfarin) showing a similar effect of *CYP2C9*1/*3* (AS = 1) and *CYP2C9*2/*2* on metabolic ratio and dose requirements (warfarin).[9–11] Furthermore, *CYP2C9*3* and alleles with a similar clinical effect and function are classified as "no function" alleles with a value of 0 for AS calculation. This is based on *CYP2C9*3/*3*, which represents the diplotype with the lowest metabolic activity and slowest pharmacokinetic clearance. Other alleles with similarly low function have also been classified as "no function" (see *CYP2C9* Allele Functionality Table[3,4]).

Available genetic test options

See **Supplementary Material** and the Genetic Testing Registry (https://www.ncbi.nlm.nih.gov/gtr/) for more information on commercially available clinical testing options.

Incidental findings

Although multiple autoimmune diseases are associated with *HLA-B* alleles, *HLA-B*15:02* has not been reproducibly associated with these or other non-drug-induced diseases.[12] No diseases have been linked to genetic variations in *CYP2C9*, except for a small study that associated *CYP2C9*2* and **3* variants and phenytoin with a higher frequency of cerebellar atrophy.[13]

Other considerations

Not applicable.

Table 1 Assignment of likely HLA-B phenotypes based on genotypes

HLA phenotype	Genotype	Examples of diplotypes
*HLA-B*15:02* negative	Homozygous for an allele other than *HLA-B*15:02*	**X/*X* Where *X = any *HLA-B* allele other than *HLA-B*15:02*.
*HLA-B*15:02* positive	Heterozygous or homozygous variant	**15:02/*X, *15:02/*15:02* Where *X = any *HLA-B* allele other than *HLA-B*15:02*.

Table 2 Assignment of likely CYP2C9 phenotypes based on genotypes

CYP2C9 phenotype[a,b]	Activity score	Genotypes	Examples of diplotypes
Normal metabolizer	2	An individual carrying two normal function alleles	**1/*1*
Intermediate metabolizer	1.5	An individual carrying one normal function allele plus one decreased function allele;	**1/*2*
		OR	
	1	One normal function allele plus one no function allele OR two decreased function alleles	**1/*3*, **2/*2*
Poor metabolizer	0.5	An individual carrying one no function allele plus one decreased function allele;	**2/*3*
		OR	
	0	two no function alleles	**3/*3*

[a]Assignment of allele function and associated citations can be found at https://www.pharmgkb.org/page/cyp2c9RefMaterials (see *CYP2C9* Allele Definition Table and *CYP2C9* Allele Functionality Table in references 3, 4). For a complete list of *CYP2C9* diplotypes and resulting phenotypes, see the *CYP2C9* Diplotype to Phenotype Table in references 3, 4. [b]See the *CYP2C9* Frequency Table in references 3, 4 for population-specific allele and phenotype frequencies.

DRUGS: PHENYTOIN AND FOSPHENYTOIN

Phenytoin and its prodrug fosphenytoin are commonly used treatments for both focal and generalized convulsive status epilepticus. Phenytoin is indicated for control of generalized tonic-clonic (grand mal) and complex partial (psychomotor and temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.[14] Once a mainstay of treatment, phenytoin's complex dosing and propensity for side effects and drug-drug interactions have led to a decline in its use.

Phenytoin dosing is complex owing to its nonlinear dose accumulation pharmacokinetics and requirements for adjustments based on patient weight, sex, and age (see **Supplementary Material** and **Figure S1** and **Figure S2**). Outpatient therapy is generally initiated at 5–7 mg/kg/day in adults (slightly higher in children) and may be given once daily (or twice daily in children). The starting dose must be lower in the setting of hepatic impairment. Careful dose adjustments must then be made to stabilize drug concentrations within the targeted therapeutic range (typically 10–20 mcg/mL). In urgent situations, such as status epilepticus, intravenous loading doses of 15–20 mg/kg are given over 1-3 mg/kg/min or 50 mg/min, whichever is slower, with cardiac monitoring,[14] followed by intravenous or oral maintenance doses, as above. Acute dose-related side effects include sedation, ataxia, dizziness, nystagmus, nausea, and cognitive impairment. The drug is highly allergenic, and rashes ranging from mild eruptions to life-threatening hypersensitivity reactions may be seen. *HLA-B*15:02* is associated with phenytoin-induced SJS and TEN. Subacutely, hematologic and hepatic toxicity can occur. Hepatic toxicity is likely a hypersensitivity reaction and is usually accompanied by rash,[15] whereas the hematologic toxicity may reflect leukopenia or pancytopenia. Suicide ideation/behavior has also been linked to phenytoin (twofold greater risk than placebo), as described in the US Food and Drug Administration (FDA) label.[14]

Because of the narrow therapeutic index of the drug, initial maintenance dose selection is important. Higher plasma concentrations increase the probability of toxicity.[16] However, nonlinear saturable pharmacokinetics, CYP2C9 autoinduction, and *CYP2C9* pharmacogenetics complicate dose-selection. The CYP2C9 PM phenotype and CYP2C9 drug interactions, such as concomitant use with voriconazole, can significantly increase phenytoin exposure.[17] Variability in protein binding, primarily related to changes in albumin concentrations, can confound the relationship of therapeutic drug monitoring, unless unbound drug concentrations are assayed.[18] Use of phenytoin for outpatient therapy has declined in the last decade owing to its potential for drug interactions, chronic metabolic effects, including bone loss, and the aforementioned pharmacokinetic difficulties that make phenytoin dose adjustments challenging (see **Supplementary Material** for further discussion).

Linking genetic variability to variability in drug-related phenotypes

Substantial evidence links *CYP2C9* and *HLA-B*15:02* genotypes with phenotypic variability (see **Table S1** and **Table S2**). Application of a grading system that evaluates the relationship between genetic variation and phenotypic variability produces consistent, high quality evidence. The evidence presented in the **Supplementary Text** and in **Table S1** and **Table S2** provides the basis for the dosing recommendations in **Table 3**. In this guideline, all clinical recommendations were based on evidence graded at either high (evidence includes consistent results from well-designed, well-conducted studies) or 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).

Therapeutic recommendations

***HLA-B*15:02* and *CYP2C9* dosing recommendations.** **Table 3** summarizes the dosing recommendations for phenytoin based on genotype-derived *HLA-B*15:02* and CYP2C9 phenotypes. If both *HLA-B*15:02* and *CYP2C9* genotypes are known, consider the *HLA-B*15:02* genotype first, then *CYP2C9* genotype (**Figure 1**; **Table 3**).

***HLA-B*15:02* recommendations.** If a patient is phenytoin-naïve and *HLA-B*15:02* positive, the patient has an increased risk

Table 3 Recommended dosing of phenytoin/fosphenytoin based on *HLA-B*15:02* and *CYP2C9* phenotype/genotype

*HLA-B*15:02* phenotype	CYP2C9 phenotype	Implication	Therapeutic recommendation	Classification of recommendation	Considerations
*HLA-B*15:02* positive	Any CYP2C9 phenotype	Increased risk of phenytoin-induced SJS/TEN	If patient is phenytoin-naïve, do not use phenytoin/fosphenytoin. Avoid carbamazepine and oxcarbazepine.	Strong	Other aromatic anticonvulsants, including eslicarbazepine, lamotrigine, and phenobarbital, have weaker evidence linking SJS/TEN with the *HLA-B*15:02* allele; however, caution should still be used in choosing an alternative agent.
			If the patient has previously used phenytoin continuously for longer than 3 months without incidence of cutaneous adverse reactions, cautiously consider use of phenytoin in the future. The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (4–28 days), and cases usually occur within 3 months of dosing.	Optional	Previous tolerance of phenytoin is not indicative of tolerance to other aromatic anticonvulsants.
*HLA-B*15:02* negative	CYP2C9 NM	Normal phenytoin metabolism	No adjustments needed from typical dosing strategies. Subsequent doses should be adjusted according to therapeutic drug monitoring, response, and side effects. An *HLA-B*15:02* negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.	Strong	
*HLA-B*15:02* negative	CYP2C9 IM AS 1.5	Slightly reduced phenytoin metabolism; however, this does not appear to translate into increased side effects.	No adjustments needed from typical dosing strategies. Subsequent doses should be adjusted according to therapeutic drug monitoring, response and side effects. An *HLA-B*15:02* negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.	Moderate	
*HLA-B*15:02* negative	CYP2C9 IM AS 1.0	Reduced phenytoin metabolism; higher plasma concentrations will increase probability of toxicities.	For first dose, use typical initial or loading dose. For subsequent doses, use ~ 25% less than typical maintenance dose. Subsequent doses should be adjusted according to therapeutic drug monitoring, response and side effects. An *HLA-B*15:02* negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.	Moderate	
*HLA-B*15:02* negative	CYP2C9 PM	Reduced phenytoin metabolism; higher plasma concentrations will increase probability of toxicities.	For first dose, use typical initial or loading dose. For subsequent doses use ~ 50% less than typical maintenance dose. Subsequent doses should be adjusted according to therapeutic drug monitoring, response, and side effects. An *HLA-B*15:02* negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.	Strong	
*HLA-B*15:02* negative	Indeterminate	n/a	n/a	No recommendation	

AS, activity score; IM, intermediate metabolizer; n/a, not applicable; NM, normal metabolizer; PM, poor metabolizer; SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

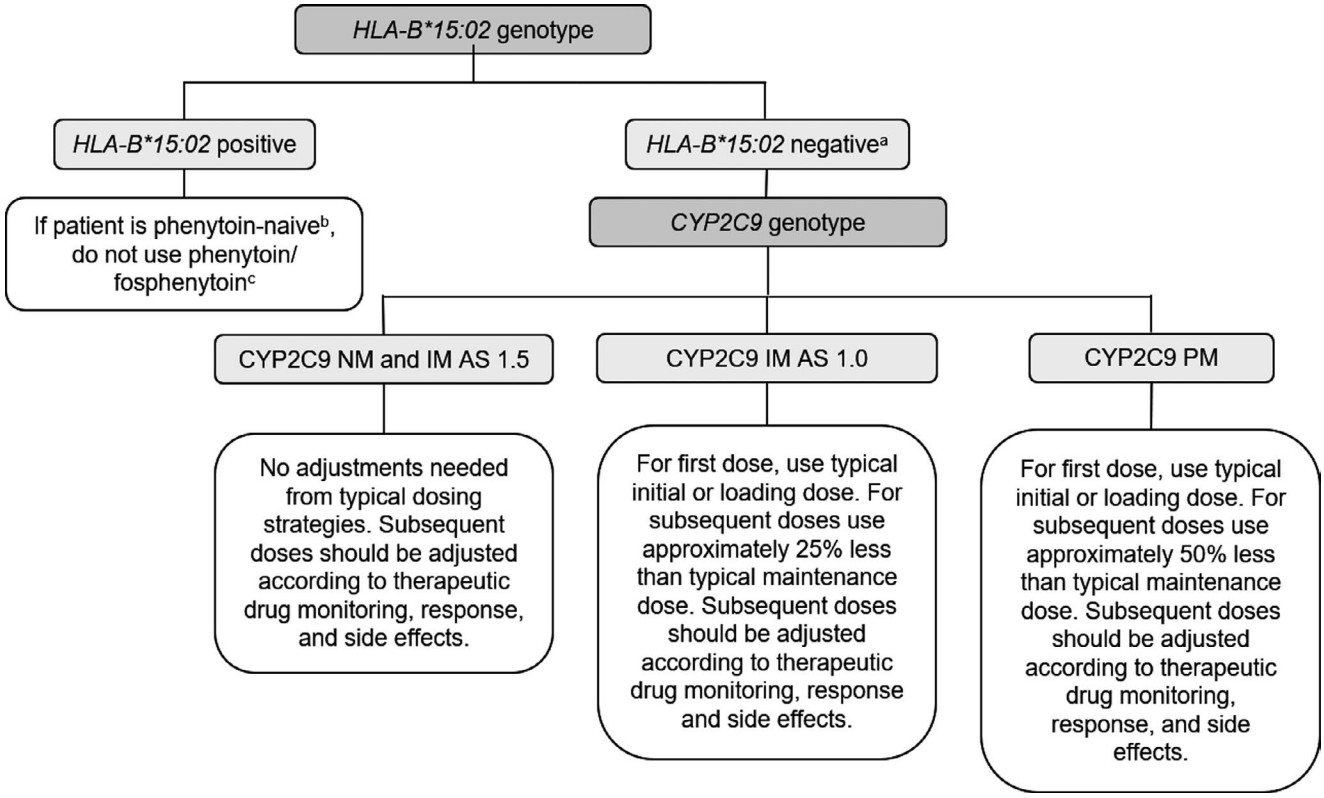

Figure 1 Algorithm for suggested clinical actions based on *HLA-B*15:02* and *CYP2C9* genotype. AS, activity score; IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer. [a]An *HLA-B*15:02* negative test does not completely eliminate the risk of phenytoin-induced Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), and patients should be carefully monitored according to standard practice. [b]If the patient has previously used phenytoin continuously for longer than 3 months without incidence of cutaneous adverse reactions, cautiously consider use of phenytoin in the future. The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (4–28 days), and cases usually occur within three months of dosing. [c]Other aromatic anticonvulsants, including eslicarbazepine, lamotrigine, and phenobarbital, have weaker evidence linking SJS/TEN with the *HLA-B*15:02* allele; however, caution should still be used in choosing an alternative agent.

of SJS/TEN and the recommendation is to consider using an anticonvulsant other than phenytoin unless the benefits of treating the underlying disease clearly outweigh the risks (see **Table 3**). Carbamazepine and oxcarbazepine should also be avoided if a patient is *HLA-B*15:02*-positive.[19] Alternative medications, such as eslicarbazepine acetate and lamotrigine, have limited evidence linking SJS/TEN with the *HLA-B*15:02* allele. These alternatives to phenytoin should be chosen with caution (see **Supplementary Material** for details). With standard dosing, phenytoin-induced SJS/TEN usually develops within the first 4–28 days of therapy.[20–22] Therefore, patients who have evidence of adherence and continuous dosing of phenytoin or fosphenytoin for longer than 3 months without the development of cutaneous reactions are at low risk of hypersensitivity events related to phenytoin in the future, regardless of *HLA-B*15:02* status (**Figure 1**; **Table 3**). The FDA warning for phenytoin states "Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for *HLA-B*15:02* due to the increased risk of SJS/TEN in patients of Asian ancestry."[14] The evidence linking *HLA-B*15:02* to phenytoin-induced SJS/TEN was generated primarily in individuals of Asian ancestry as the frequency of *HLA-B*15:02* is very low in other populations (see *HLA-B* Frequency Table[3,4]). However, this allele may also occur in other populations throughout the world that have yet to be studied, and patients may be unaware of, or fail to disclose, Asian ancestry in their families.[23,24]

If a patient is phenytoin-naïve and *HLA-B*15:02* negative, the patient has a normal risk of phenytoin-induced SJS/TEN and the recommendation is to use phenytoin with dosage adjustments based on *CYP2C9* genotype (if known) or standard dosing guidelines (if *CYP2C9* genotype is unknown). However, an *HLA-B*15:02*-negative test does not eliminate the risk of phenytoin-induced SJS/TEN (see **Supplementary Material** for additional guidance).

***CYP2C9* recommendations.** Phenytoin and fosphenytoin dose should first be adjusted according to a patient's clinical characteristics. The recommended phenytoin initial or loading and maintenance doses do not need adjustments based on genotype for CYP2C9 normal metabolizers and IMs with an AS of ≥ 1.5. Available evidence does not clearly indicate the extent of dose reduction needed to prevent phenytoin-related toxicities in CYP2C9 IMs with an AS of 1.0 and PMs with an

AS of 0 or 0.5. Furthermore, multiple case studies have observed that CYP2C9 PMs are at increased risk for exposure-related phenytoin toxicities, and multiple studies have observed an association between the *CYP2C9*3* allele and SJS/TEN.[25–27] Although carriage of the *CYP2C9*3* allele is insufficient to predict phenytoin-induced SJS/TEN, these and other data suggest that the risk of SJS/TEN is dose-related and provide an additional rationale for reducing phenytoin dose in CYP2C9 PMs.[28] Thus, our recommendations are conservative given the variability surrounding phenytoin dosing. Based on the doses reported in the pharmacokinetic and pharmacogenetic studies mentioned above[29–31] and in **Table S2**, a typical initial or loading dose followed by at least a 25% reduction in the recommended starting maintenance dose may be considered for CYP2C9 IMs with AS of 1.0. Subsequent maintenance doses should be adjusted based on therapeutic drug monitoring and response. For CYP2C9 PMs, use a typical initial or loading dose then consider at least a 50% reduction of starting maintenance dose with subsequent maintenance doses adjusted based on therapeutic drug monitoring and response.

Pediatrics. Much of the evidence (summarized in **Table S1**) linking *HLA-B*15:02* to phenytoin-induced SJS/TEN was generated in both children and adults. Therefore, the above recommendation is made regardless of *CYP2C9* genotype, individual age, race, or ancestry. For pediatric patients who are CYP2C9 IMs or PMs, dose adjustment as described in **Table 3** with therapeutic drug monitoring is recommended. Although limited data are available for effects of *CYP2C9* alleles on phenytoin metabolism in pediatric patient populations, there is no compelling data to indicate that *CYP2C9* polymorphisms will affect phenytoin metabolism differently in children compared with adults. As such, the pediatric recommendation is extrapolated using adult data. Special considerations in neonates and older pediatric patients, including a high degree of dose variability and dosage forms, and evidence from pediatric populations is included in the supplement (see Pediatrics section of the **Supplementary Material** for details).

Other considerations

HLA. *HLA-B*15:02* is linked to SJS and TEN but not to a predisposition for other phenytoin-induced cutaneous ADRs, such as mild maculopapular eruptions or drug hypersensitivity syndrome.[32] Other *HLA-B* alleles have also been associated with phenytoin-induced drug reactions with eosinophilia and systemic symptoms and are associated with hypersensitivity reactions to other drugs.[26,33] CPIC guidelines are available for *HLA-B*15:02* and *HLA-A*31:01* and carbamazepine-induced and oxcarbazepine-induced SJS and TEN.[2,19] Although the structural similarity between phenytoin and carbamazepine and the shared association of the *HLA-B*15:02* allele with SJS and TEN might suggest cross-reactivity with *HLA-A*31:01*, no association between *HLA-A*31:01* and phenytoin-induced SJS and TEN has been presently found. CPIC guidelines are also available for *HLA-B*57:01* and abacavir-induced hypersensitivity reactions and *HLA-B*58:01* and allopurinol-induced severe cutaneous adverse reactions.[2,19,34]

CYP2C9. Because of its potent CYP-inducing properties, phenytoin can contribute to a large number of drug interactions, especially involving increased metabolism of other agents with subsequent decrease in their plasma concentrations.[35] A full discussion of these is beyond the scope of this guideline, but agents prominently and significantly affected include antineoplastic and immunosuppressive agents, lipid-lowering agents, psychotropics, oral contraceptives, antifungals, and warfarin. Furthermore, inhibitors of CYP2C9 can cause phenytoin overexposure and toxicity. Although there are several potent CYP2C9 enzyme inhibitors, such as fluconazole and amiodarone, other less potent drugs can produce significant elevations in phenytoin plasma concentrations. Therefore, it is important to interpret the results of pharmacogenetic testing in the context of other co-administered drugs.

CYP2C9 genetic variation does not account for all observed pharmacokinetic variability in phenytoin metabolism. Some studies suggest that variants in other genes also contribute to altered phenytoin metabolism (e.g., *CYP2C19*, *CYP1A1*, and *EPHX1*; see ref. 36 for a review) and combined genetic analysis might improve the prediction of phenytoin metabolism.[29,30] However, these studies evaluating the effect of multiple gene variation and phenytoin dose requirements are limited and have not been replicated. Consequently, this guideline on genotype-directed phenytoin dosing is limited to *CYP2C9*.

Implementation of this guideline

The guideline **Supplementary Material** and CPIC website (https://cpicpgx.org/guidelines/guideline-for-phenytoin-and-cyp2c9-and-hla-b/) contains resources that can be used within electronic health records to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see Resources to incorporate pharmacogenetics into an electronic health record with clinical decision support in the **Supplementary Material**).

Recommendations for incidental findings

Case reports have identified cross-reactions to lamotrigine and other anti-epileptic drugs in the presence of *HLA-B*15:02* (see **Supplementary Material** for further discussion). However, larger replication studies are warranted.

CYP2C9 metabolizes substrates from several drug classes, including nonsteroidal anti-inflammatory drugs and oral hypoglycemics. Patients with enhanced sensitivity to warfarin may have a decreased capacity to metabolize phenytoin owing to the presence of one or more *CYP2C9* variant alleles.[37]

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

The potential benefit for patients with existing *CYP2C9* and/or *HLA-B*15:02* genotype information is avoidance of adverse effects in patients who are CYP2C9 IMs (AS of 1.0) and CYP2C9 PMs by making significant reductions in their initial maintenance dose or by selecting alternative agents for patients who carry *HLA-B*15:02*. A potential risk is that phenytoin

therapy may have been needlessly avoided in patients who may not have developed SJS/TEN; however, this risk is mitigated because alternatives to phenytoin with comparable effectiveness exist. Another potential risk would be an error in genotyping. In addition, many commercially available genotyping tests do not detect all known alleles or *de novo* variants (for example, *HLA-B* alleles in the same B75 serotype family as *HLA-B*15:02*). Other *HLA* alleles are not well-characterized, resulting in uncertainty when predicting the phenotype for some genetic test results. Because an *HLA-B*15:02*-negative test does not eliminate the risk of phenytoin-induced SJS/TEN and because genetic tests may not detect rare *CYP2C9* variants, a patient with a high ADR risk could be prescribed phenytoin or a patient with reduced CYP2C9 activity could be prescribed a higher than needed phenytoin dose. Moreover, because not all phenytoin-induced adverse events are attributed to *HLA-B*15:02* or CYP2C9 metabolizer status, particularly in non-East and Central/South Asian populations, clinicians should carefully monitor all patients according to standard practices.

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

The application of genotype-based dosing is most appropriate when initiating phenytoin maintenance therapy. Obtaining genetic information after months of drug therapy is less informative, given that the drug dose may have already been adjusted based on therapeutic drug monitoring. As with all diagnostic tests, genetic tests are only one of several pieces of clinical information that should be considered before initiating and maintaining drug therapy.

DISCLAIMER

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 variations 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.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

ACKNOWLEDGMENTS

The authors acknowledge the critical input of members of CPIC of the Pharmacogenomics Research Network (PGRN), particularly Dr. Mary V. Relling (St. Jude Children's Research Hospital).

FUNDING

This work is funded by National Institutes of Health (NIH) grants CPIC (R24GM115264 and U24HG010135) and PharmGKB (R24 GM61374), R24GM123930 (AG), GM092666 (CEH), GM32165 (AER), UO1 GM092676, and U01 HL0105918. JHK is supported by grants from the NIH's National Heart Lung and Blood Institute (NHLBI) under award number K01HL143137, the American College of Clinical Pharmacy, and the Flinn Foundation. AAS is supported by grant APP108798 by the National Health and Medical Research Council of Australia. EJP receives funding from the NIH (R01 HG010863-01, 1P50GM115305-01, R21AI139021 and R34AI136815) and NHMRC (APP1123499).

CONFLICTS OF INTEREST

E.J.P. is a consultant for Biocryst. She is section editor for drug allergy (uptodate) and is co-director of IIID, Pty Ltd that holds a patent for *HLA-B*57:01* testing for abacavir hypersensitivity. She holds a provisional patent for *HLA-A*32:01* testing for vancomycin-induced drug reactions with eosinophilia and systemic symptoms. All other authors declared no competing interests for this work.

1. Caudle, K.E. *et al*. Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. *Clin. Pharmacol. Ther.* **96**, 542–548 (2014).
2. Martin, M.A., Klein, T.E., Dong, B.J., Pirmohamed, M., Haas, D.W. & Kroetz, D.L. Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and abacavir dosing. *Clin. Pharmacol. Ther.* **91**, 734–738 (2012).
3. Clinical Pharmacogenetics Implementation Consortium (CPIC). CPIC® Guideline for Phenytoin and CYP2C9 and HLA-B <https://cpicpgx.org/guidelines/guideline-for-phenytoin-and-cyp2c9-and-hla-b/>.
4. PharmGKB. Gene-specific Information Tables for CYP2C9 <https://www.pharmgkb.org/page/cyp2c9RefMaterials>.
5. Gaedigk, A. *et al*. The pharmacogene variation (PharmVar) consortium: incorporation of the human cytochrome P450 (CYP) allele nomenclature database. *Clin. Pharmacol. Ther.* **103**, 399–401 (2018).
6. Lee, C.R., Goldstein, J.A. & Pieper, J.A. Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data. *Pharmacogenetics* **12**, 251–263 (2002).
7. Cespedes-Garro, C. *et al*. Worldwide interethnic variability and geographical distribution of CYP2C9 genotypes and phenotypes. *Expert Opin. Drug Metab. Toxicol.* **11**, 1893–1905 (2015).
8. Gonzalez-Galarza, F.F. *et al*. Allele frequency net database (AFND) 2020 update: gold-standard data classification, open access genotype data and new query tools. *Nucleic Acids Res.* **48**, D783–D788 (2020).
9. Vogl, S., Lutz, R.W., Schonfelder, G. & Lutz, W.K. CYP2C9 genotype vs. metabolic phenotype for individual drug dosing–a correlation analysis using flurbiprofen as probe drug. *PLoS One* **10**, e0120403 (2015).
10. Kusama, M., Maeda, K., Chiba, K., Aoyama, A. & Sugiyama, Y. Prediction of the effects of genetic polymorphism on the pharmacokinetics of CYP2C9 substrates from in vitro data. *Pharm. Res.* **26**, 822–835 (2009).
11. Lindh, J.D., Holm, L., Andersson, M.L. & Rane, A. Influence of CYP2C9 genotype on warfarin dose requirements–a systematic review and meta-analysis. *Eur. J. Clin. Pharmacol.* **65**, 365–375 (2009).
12. Karnes, J.H. *et al*. Phenome-wide scanning identifies multiple diseases and disease severity phenotypes associated with HLA variants. *Sci. Transl. Med.* **9**, eaai8708 (2017).
13. Twardowschy, C.A., Werneck, L.C., Scola, R.H., Borgio, J.G., De Paola, L. & Silvado, C. The role of CYP2C9 polymorphisms in phenytoin-related cerebellar atrophy. *Seizure* **22**, 194–197 (2013).

14. US Food and Drug Administration (FDA). Phenytoin drug label <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=010151>. Accessed January 10, 2020.
15. Parker, W.A. & Shearer, C.A. Phenytoin hepatotoxicity: a case report and review. *Neurology* **29**, 175–178 (1979).
16. Greenberg, R.G. *et al*. Therapeutic index estimation of antiepileptic drugs: a systematic literature review approach. *Clin. Neuropharmacol.* **39**, 232–240 (2016).
17. Purkins, L., Wood, N., Ghahramani, P., Love, E.R., Eve, M.D. & Fielding, A. Coadministration of voriconazole and phenytoin: pharmacokinetic interaction, safety, and toleration. *Br. J. Clin. Pharmacol.* **56** (suppl. 1), 37–44 (2003).
18. Ter Heine, R., Kane, S.P., Huitema, A.D.R., Krasowski, M.D. & van Maarseveen, E.M. Nonlinear protein binding of phenytoin in clinical practice: development and validation of a mechanistic prediction model. *Br. J. Clin. Pharmacol.* **85**, 2360–2368 (2019).
19. Phillips, E.J. *et al*. Clinical pharmacogenetics implementation consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine: 2017 update. *Clin. Pharmacol. Ther.* **103**, 574–581 (2018).
20. Tennis, P. & Stern, R.S. Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. *Neurology* **49**, 542–546 (1997).
21. Roujeau, J.C. *et al*. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N. Engl. J. Med.* **333**, 1600–1608 (1995).
22. Sassolas, B. *et al*. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis: comparison with case-control analysis. *Clin. Pharmacol. Ther.* **88**, 60–68 (2010).
23. Fang, H. *et al*. A screening test for HLA-B(*)15:02 in a large United States patient cohort identifies broader risk of carbamazepine-induced adverse events. *Front. Pharmacol.* **10**, 149 (2019).
24. Lonjou, C. *et al*. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharm. Genom.* **18**, 99–107 (2008).
25. Yampayon, K. *et al*. Influence of genetic and non-genetic factors on phenytoin-induced severe cutaneous adverse drug reactions. *Eur. J. Clin. Pharmacol.* **73**, 855–865 (2017).
26. Tassaneeyakul, W. *et al*. Associations between HLA class I and cytochrome P450 2C9 genetic polymorphisms and phenytoin-related severe cutaneous adverse reactions in a Thai population. *Pharm. Genom.* **26**, 225–234 (2016).
27. Chung, W.H. *et al*. Genetic variants associated with phenytoin-related severe cutaneous adverse reactions. *JAMA* **312**, 525–534 (2014).
28. Karnes, J.H. *et al*. Applications of immunopharmacogenomics: predicting, preventing, and understanding immune-mediated adverse drug reactions. *Annu. Rev. Pharmacol. Toxicol.* **59**, 463–486 (2019).
29. Hung, C.C. *et al*. Effects of polymorphisms in six candidate genes on phenytoin maintenance therapy in Han Chinese patients. *Pharmacogenomics* **13**, 1339–1349 (2012).
30. Hung, C.C., Lin, C.J., Chen, C.C., Chang, C.J. & Liou, H.H. Dosage recommendation of phenytoin for patients with epilepsy with different CYP2C9/CYP2C19 polymorphisms. *Ther. Drug Monit.* **26**, 534–540 (2004).
31. van der Weide, J., Steijns, L.S., van Weelden, M.J. & de Haan, K. The effect of genetic polymorphism of cytochrome P450 CYP2C9 on phenytoin dose requirement. *Pharmacogenetics* **11**, 287–291 (2001).
32. Yip, V.L., Marson, A.G., Jorgensen, A.L., Pirmohamed, M. & Alfirevic, A. HLA genotype and carbamazepine-induced cutaneous adverse drug reactions: a systematic review. *Clin. Pharmacol. Ther.* **92**, 757–765 (2012).
33. Ihtisham, K. *et al*. Association of cutaneous adverse drug reactions due to antiepileptic drugs with HLA alleles in a North Indian population. *Seizure* **66**, 99–103 (2019).
34. Hershfield, M.S. *et al*. Clinical pharmacogenetics implementation consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing. *Clin. Pharmacol. Ther.* **93**, 153–158 (2013).
35. Mintzer, S. *et al*. Effects of antiepileptic drugs on lipids, homocysteine, and C-reactive protein. *Ann. Neurol.* **65**, 448–456 (2009).
36. Thorn, C.F., Whirl-Carrillo, M., Leeder, J.S., Klein, T.E. & Altman, R.B. PharmGKB summary: phenytoin pathway. *Pharmacogenet. Genom.* **22**, 466–470 (2012).
37. Bochner, F., Hooper, W.D., Eadie, M.J. & Tyrer, J.H. Decreased capacity to metabolize diphenylhydantoin in a patient with hypersensitivity to warfarin. *Aust. N. Z. J. Med.* **5**, 462–466 (1975).