Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C9* and *HLA-B* Genotypes and Phenytoin Dosing

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Phenytoin is a widely used antiepileptic drug with a narrow therapeutic index and large interpatient variability, partly due to genetic variations in the gene encoding cytochrome P450 (CYP)2C9 (*CYP2C9*). Furthermore, the variant allele *HLA-B*15:02*, encoding human leukocyte antigen, 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 recommendations for the use of phenytoin based on *CYP2C9* and/or *HLA-B* genotype (also available on PharmGKB: http://www.pharmgkb.org). The purpose of this guideline is to provide information for the interpretation of *HLA-B* and/or *CYP2C9* genotype tests so that the results can guide dosing and/or use of phenytoin. Detailed guidelines for the use of phenytoin as well as analyses of cost-effectiveness are out of scope. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are periodically updated at http://www.pharmgkb.org.

FOCUSED LITERATURE REVIEW

A literature review focused on *CYP2C9* and *HLA-B*15:02* genotypes and phenytoin use (see **Supplementary Material** online) was conducted. Reviews were included to summarize the available literature.

GENES: *HLA-B* AND *CYP2C9*

Background

In this guideline, (i) the gene encoding human leukocyte antigen B (*HLA-B*) will be discussed as it relates to phenytoin-induced cutaneous adverse drug reactions (ADRs) of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), and (ii) the gene encoding hepatic cytochrome P450 (CYP)2C9 (*CYP2C9*) and its alleles are discussed as they relate to phenytoin metabolism and dosing.

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-B*, *HLA-A*, and *HLA-C*. *HLA-B* encodes a cell surface protein that binds peptides generated by proteolysis and extruded from proteasomes. The presentation of these peptides on the cell surface enables the immune system to distinguish self-proteins from foreign proteins typically introduced by infectious organisms (e.g., viruses and bacteria) (see **Supplementary Material** online 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 genotyping and DNA sequencing methods reveal much greater genetic complexity. More than 2,000 *HLA-B* alleles, many of which differ by more than one nucleotide from each other, were deposited into the World Health Organization Nomenclature Committee for Factors of the HLA System (http://hla.alleles.org). Each allele is designated by the gene name, which is followed by an asterisk and up to an eight-digit (four pairs) identifier giving information about the allele type (designated by the first two digits) and specific protein subtypes (second set of digits). For more information and a diagram outlining the description of the current HLA allele nomenclature, see http://hla.alleles.org/

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nomenclature/naming.html. The details of HLA nomenclature are also described in a previous CPIC guideline.[1] The current guideline specifically discusses only the *HLA-B*15:02* allele as it relates to the phenytoin-induced cutaneous ADRs of SJS and TEN.

CYP2C9. The hepatic CYP2C9 enzyme contributes to the metabolism of many clinically relevant drugs, including phenytoin (http://www.pharmgkb.org/pathway/PA145011115). The *CYP2C9* gene is highly polymorphic, having more than 50 known variant alleles (http://www.cypalleles.ki.se/cyp2c9.htm, **Supplementary Tables S1** and **S2** online). Individuals homozygous for the reference *CYP2C9* allele (*CYP2C9*1*) have the "normal metabolizer" phenotype. Each named *CYP2C9* star (*) allele is defined by a genotype at one or more specific single-nucleotide polymorphisms (SNPs) with variable enzyme activity. The two most common variants with decreased enzyme function in Europeans are *CYP2C9*2* (rs1799853) and *CYP2C9*3* (rs1057910).[2]

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 as "negative" if no copies of *HLA-B*15:02* are present. Phenotype assignments for *HLA-B*15:02* genotypes are summarized in **Table 1**. The allele frequencies of *HLA-B* vary greatly among populations. Specifically, *HLA-B*15:02* is most prevalent in Oceania and in East Asian and South/Central Asian populations, ranging from 1% to more than 10%. It is less frequent in European populations (0–1%) and apparently absent in several African populations (**Supplementary Tables S3** and **S4** online). The global average derived from more than 46,000 individuals is 1.37%.

CYP2C9. Most clinical laboratories reporting *CYP2C9* genotype use the star allele nomenclature and may interpret the patient's predicted metabolizer phenotype (**Table 1**, **Supplementary Table S1** online). The combination of alleles is used to determine a patient's diplotype. Not all *CYP2C9* allelic variants may be tested, influencing the accuracy of the genotype-based dose prediction, primarily in individuals of Asian or African ancestry who carry other common functionally decreased function *CYP2C9* variant alleles (**Supplementary Table S5** online). The frequencies of the *CYP2C9*2* and **3* alleles and diplotypes derived from these and other alleles differ among racial/ethnic groups (**Supplementary Tables S5–S7** online).[2] *CYP2C9* alleles are typically characterized as wild-type (normal function) or decreased-function alleles depending on the reported activity of the enzyme that they encode.

Available genetic test options

Several methods of *CYP2C9* and *HLA-B* genotyping are commercially available. The **Supplementary Material** online and the website http://www.pharmgkb.org contain more information on available clinical testing options.

Incidental findings

HLA-B alleles are associated with hypersensitivity reactions to other drugs. CPIC guidelines are available for *HLA-B*57:01* and abacavir-induced hypersensitivity reactions, *HLA-B*58:01* and allopurinol-induced severe cutaneous adverse reactions, and *HLA-B*15:02* and carbamazepine-induced SJS and TEN.[1,3,4]

No studies have linked genetic variations in *CYP2C9* with any disease, except for a small study that linked *CYP2C9*2* and **3* variants and phenytoin use with a higher frequency of cerebellar atrophy.[5] CYP2C9 poor metabolizers may be predisposed to serious bleeding during warfarin therapy.[6]

Table 1 Assignment of likely phenotype based on genotypes

Assignment of likely CYP2C9 phenotype based on genotype		
Likely phenotype[a]	**Genotype**	**Examples of diplotypes**
Extensive metabolizer (normal activity) (constitutes ~91% of patients)	An individual carrying two normal-function alleles	**1/*1*
Intermediate metabolizer (heterozygote or intermediate activity) (constitutes ~8% of patients)[c]	An individual carrying one normal-function allele plus one decreased-function allele	**1/*3*, **1/*2*
Poor metabolizer (homozygous variant, low or deficient activity) (constitutes ~1% of patients)	An individual carrying two decreased-function alleles	**2/*2*, **3/*3*, **2/*3*
Assignment of likely HLA-B phenotype based on genotype		
Likely phenotype[b]	**Genotype**	**Examples of diplotypes**
Homozygous for an allele other than **15:02*; at "normal" or reduced risk of phenytoin-associated cutaneous adverse reactions (constitutes ~98.6% of patients)	*HLA-B*15:02* noncarrier. No **15:02* alleles reported, often reported as "negative" on a genotyping test	**X/*X*[d]
Heterozygote or homozygous variant; at significantly increased risk of phenytoin-associated cutaneous adverse reactions (constitutes ~1.4% of patients)	*HLA-B*15:02* carrier. One or two **15:02* alleles, often reported as "positive" on a genotyping test	**15:02/*X*[d], **15:02/*15:02*

CYP, cytochrome P450.

[a,b]Global frequencies presented in parentheses. Haplotype frequencies vary among populations; please see details for individual population frequencies in [a]**Supplementary Tables S5**–**S7** online for *CYP2C9*2* and **3*, and [b]**Supplementary Tables S3** and **S4** online for *HLA-B*15:02*. [c]The enzyme activity in this grouping varies widely. See **Supplementary Table S2** online for activity ranges. [d]Where **X* = any genotype other than **15:02*.

Other considerations

Not applicable.

DRUGS: PHENYTOIN AND FOSPHENYTOIN

Phenytoin and its prodrug fosphenytoin constitute one of the mainstays of treatment for both focal and generalized convulsive status epilepticus. Dosing is complex owing to the highly unusual pharmacokinetics of phenytoin, requiring adjustments to be made in line with patient weight, sex, and age (description of phenytoin and fosphenytoin metabolism available in **Supplementary Material** online and **Supplementary Figures S1** and **S2** online). 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—generally 30–40 mg at a time in 2-week intervals in adults—to stabilize the level within the typical therapeutic range (10–20 μg/dl). In urgent situations such as status epilepticus, i.v. loading doses of 15–20 mg/kg are given, followed by maintenance doses, i.v. or oral, 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. SJS is characterized by epidermal detachment involving up to 10% of body surface area, whereas TEN usually affects more than 30% of the body surface area. Subacutely, hematologic and hepatic toxicity can occur; the latter is probably a hypersensitivity reaction itself, as it is usually accompanied by rash,[7] whereas the former may consist of leukopenia or pancytopenia.

Because of the acute dose-related side effects, initial maintenance dose selection is important. Higher plasma concentrations increase the probability of these toxicities. However, nonlinear saturable pharmacokinetics, autoinductive effects with maintenance dosing, and *CYP2C9* pharmacogenetic polymorphisms complicate dose selection. CYP2C9 poor-metabolizer phenotype and CYP2C9 drug interactions, such as those produced by voriconazole, can significantly augment phenytoin exposure.[8] Variability in protein binding, primarily related to changes in albumin concentrations, can confound the relationship between therapeutic drug monitoring and pharmacodynamic expectations. Further discussion of the metabolism of phenytoin and fosphenytoin can be found in the **Supplementary Material** online.

Linking genetic variability to variability in drug-related phenotypes

Substantial evidence links *CYP2C9* and *HLA-B*15:02* genotypes with phenotypic variability (see **Supplementary Tables S8** and **S9** online). Application of a grading system to evidence linking genotypic with phenotypic variability indicates a high quality of evidence in the majority of cases (**Supplementary Tables S8** and **S9** online). The evidence presented here and in **Supplementary Tables S8** and **S9** provides the basis for the dosing recommendations in **Table 2**.

HLA-B. An increased risk of SJS/TEN has been associated with the *HLA-B*15:02* allele in Han Chinese and other Asian groups (see **Supplementary Material** online and **Supplementary Table S8** online). Cheung et al. conducted a meta-analysis of two studies in Taiwan[9] and Hong Kong,[10] comprising a total of 41 cases and 188 controls, and showed a positive association of

Table 2 Recommended dosing of phenytoin/fosphenytoin based on *HLA-B*15:02* and *CYP2C9* phenotype/genotype

	*HLA-B*15:02* carrier			*HLA-B*15:02* noncarrier		
Phenotype/ genotype	Implication	Therapeutic recommendation	Classification of recommendation[a]	Implication	Therapeutic recommendation	Classification of recommendation[a]
CYP2C9 extensive metabolizer	Increased risk of phenytoin-induced SJS/ TEN	If patient is phenytoin naive,[b] do not use phenytoin/ fosphenytoin[c]	Strong	Normal phenytoin metabolism	Initiate therapy with recommended maintenance dosed	Strong
CYP2C9 intermediate metabolizer	Increased risk of phenytoin-induced SJS/ TEN	If patient is phenytoin naive,[b] do not use phenytoin/ fosphenytoin[c]	Strong	Reduced phenytoin metabolism. Higher plasma concentrations will increase probability of toxicities	Consider 25% reduction of recommended starting maintenance dose.[d] Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response	Moderate
CYP2C9 poor metabolizer	Increased risk of phenytoin-induced SJS/ TEN	If patient is phenytoin naive,[b] do not use phenytoin/ fosphenytoin[c]	Strong	Reduced phenytoin metabolism. Higher plasma concentrations will increase probability of toxicities	Consider 50% reduction of recommended starting maintenance dose.[d] Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response	Strong

CYP, cytochrome P450; SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

[a]Rating scheme described in the **Supplementary Material** online. [b]If the patient has previously used phenytoin for longer than 3 months without incidence of cutaneous adverse reactions, reinitiate phenytoin with caution. Adjust dose based on *CYP2C9* genotype if known. [c]Carbamazepine should not be used as an alternative.[4] Alternative medications such as oxcarbazepine, eslicarbazepine acetate, and lamotrigine have some evidence linking SJS/TEN with the *HLA-B*15:02* allele, and thus caution should be used in choosing alternatives to phenytoin (see **Supplementary Material** online for details). [d]Recommended maintenance dose based on patient's clinical characteristics.

*HLA-B*15:02* with phenytoin-induced SJS/TEN ($P < 3 \times 10^{-4}$; odds ratio = 4.26; 95% confidence interval (CI) = 1.93–9.39) under a fixed-effect model with statistically insignificant heterogeneity. By pooling data directly, the association had a sensitivity of 36.6% (95% CI = 23.6–51.9) and specificity of 87.2% (95% CI = 81.7–91.3). Therefore, the absence of these variants does not rule out the possibility of a patient developing phenytoin-induced SJS/TEN. The strength of the association between phenytoin use and SJS/TEN is weaker than that of the association between carbamazepine use and SJS/TEN due to the limited number of studies and observations with phenytoin or fosphenytoin in the literature. However, taken together with the known association of carbamazepine and SJS/TEN in carriers of *HLA-B*15:02*, the association supports the US Food and Drug Administration recommendations to avoid these agents as substitutes for carbamazepine in individuals who test positive for *HLA-B*15:02*.[4]

CYP2C9. Available model estimates predict that variant *CYP2C9* alleles lower phenytoin intrinsic clearance based on the allele and number of variants. Several studies indicate that individuals with *CYP2C9*1/*3* and *CYP2C9*1/*2* genotypes have mild to moderately reduced clearance values (**Supplementary Table S9** online); these individuals are classified as intermediate metabolizers. Individuals with two decreased-activity alleles (*CYP2C9*2/*2*, *CYP2C9*3/*3*) have reduced clearance of several drugs and are classified as CYP2C9 poor metabolizers. Phenytoin maintenance doses were reported to be reduced by 23–38% in heterozygous individuals with one decreased function allele[11–13] and by 31–52% in carriers with two decreased function *CYP2C9* alleles vs. the doses for individuals homozygous for *CYP2C9*1*.[12,13] Furthermore, case reports indicate that poor metabolizers appear to be at higher risk for exposure-related toxicities than patients homozygous for the wild-type alleles.[14–17]

Therapeutic recommendations

HLA-B*15:02 recommendations. The Food and Drug Administration 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. The evidence linking *HLA-B*15:02* to phenytoin-induced SJS/TEN was generated in individuals of Asian ancestry because the frequency of *HLA-B*15:02* is very low in other populations (see **Supplementary Tables S3** and **S4** online for frequency information) that have been studied. However, *HLA-B*15:02* may also occur in other populations throughout the world yet to be studied, and patients may be unaware of or fail to disclose more distant Asian ancestry in their families. Furthermore, much of the evidence (summarized in **Supplementary Table S8** online) linking *HLA-B*15:02* to phenytoin-induced SJS/TEN was generated in both children and adults. Therefore, regardless of the *CYP2C9* genotype and the individual's ancestry or age, if the *HLA-B*15:02* test result is positive, the recommendation is to consider using an anticonvulsant other than carbamazepine and phenytoin, unless the benefits of treating the underlying disease clearly outweigh the risks (see **Table 2**). Some evidence exists linking SJS/TEN with the *HLA-B*15:02* allele in association with the use of alternative medications such as oxcarbazepine, eslicarbazepine acetate, and lamotrigine, and thus caution should be used in choosing alternatives to phenytoin (see **Supplementary Material** online for details).

CYP2C9 recommendations. Phenytoin and fosphenytoin dose should first be adjusted according to a patient's clinical characteristics. **Table 2** summarizes the gene-based dosing recommendations for phenytoin based on CYP2C9 phenotype. The recommended phenytoin maintenance dose does not need adjustment based on genotype for CYP2C9 extensive metabolizers. Available evidence does not clearly indicate the amount of dose reduction needed to prevent phenytoin-related toxicities in CYP2C9 intermediate and poor metabolizers; thus, our recommendations should be considered conservative estimates, given the variability surrounding phenytoin dosing in an individual. On the basis of the doses reported in the pharmacokinetic and pharmacogenetic studies mentioned above[11–13] and in **Supplementary Table S9** online, at least a 25% reduction of the recommended starting maintenance dose may be considered for CYP2C9 intermediate metabolizers, with subsequent maintenance doses adjusted based on therapeutic drug monitoring and response. For CYP2C9 poor metabolizers, consider at least a 50% reduction of starting maintenance dose, with subsequent maintenance doses adjusted based on therapeutic drug monitoring or response.

Furthermore, although *in vitro* data suggest that the degree of reduction of catalytic activity is greater for the *CYP2C9*3* variant than for the *CYP2C9*2* variant,[18] clinical pharmacokinetic studies indicate similar dose reductions and pharmacokinetic parameters (e.g., trough levels, and serum 5-(4′-hydroxyphenyl)-5-phenylhydantoin/phenytoin ratio) for these variants as compared with the wild-type alleles.[12,19,20] Therefore, our recommendation is to start with at least the above-recommended reduction of the maintenance dose, followed by an adjustment of dose based on therapeutic drug monitoring.

Pediatrics. Special consideration should be given to the pediatric population. Phenytoin is used in the treatment of neonatal seizures and, subsequently, after discharge from the neonatal intensive care unit. Maintaining therapeutic levels can be particularly problematic in this population. This may be due to the developmental expression of hepatic CYP2C. CYP expression and functional activities have been shown to develop at different rates within subfamilies.[21] It has been found that activity levels of CYP2C9 are at 1–2% of adult values in the fetus during the first trimester. These levels gradually increase to 30% of adult values at term. There is a high variability in these levels during the first 5 months of life, with levels eventually approaching adult values somewhere between 5 months and 2 years of age.[22] Other considerations include the fact that clearance of phenytoin is twice that of adult values in children

younger than 6 years of age. This is attributed to the finding that the maximal rate of phenytoin metabolism is inversely related to age. However, this varies significantly within age subgroups.[23] For these reasons, phenytoin therapeutic recommendations based on *CYP2C9* genotype in this population are difficult. There is only one published report describing a 2-year-old patient (*CYP2C9*2/*2* and *CYP2C19*1/*4*) presenting with phenytoin toxicity 2 h after a 15-mg/kg phenytoin loading dose with symptoms lasting 122 h.[24] The half-life was much higher than expected (112 h vs 46.7 h), which could be explained by the influence of *CYP2C9* and *CYP2C19* genetic polymorphisms (other predisposing factors such as malnourishment, renal failure, hepatic dysfunction, and inhibition of phenytoin metabolism by other drugs were ruled out). Therefore, for pediatric patients who are CYP2C9 intermediate or poor metabolizers, dose adjustment is recommended with close therapeutic drug monitoring.

HLA-B*15:02 and CYP2C9 dosing recommendation. If both *HLA-B*15:02* and *CYP2C9* genotypes are known, consider the *HLA-B*15:02* genotype first, then the *CYP2C9* genotype (**Figure 1**; **Table 2**).

The **Supplementary Material** online contains example clinical decision support (CDS) tools that can be used within electronic health records (EHRs) which assist clinicians to use genetic information to optimize drug therapy. Clinical implementation resources include cross-references for drug and gene names to widely used terminologies and standardized nomenclature systems (**Supplementary Tables S10** and **S11** online), workflow diagrams (**Supplementary Figures S3** and **S4** online), tables that translate genotype test results into an interpreted phenotype (**Supplementary Table S12** online), and example text for documentation in the EHR and point-of-care alerts (**Supplementary Tables S13** and **S14** online).

Other considerations

*HLA-B. HLA-B*15:02* is linked to SJS and TEN but not to a predisposition for other phenytoin-induced cutaneous adverse reactions such as mild maculopapular eruptions or drug hypersensitivity syndrome.[25]

CYP2C9. Because of its potent CYP-inducing properties, phenytoin is involved in a very large number of drug interactions, especially those involving increased metabolism of other agents, with subsequent decreases in their levels.[26] 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, and warfarin, to name just a few. Furthermore, inhibitors of CYP2C9 can generate phenytoin overexposure and toxicity. Although fluconazole and amiodarone are recognized

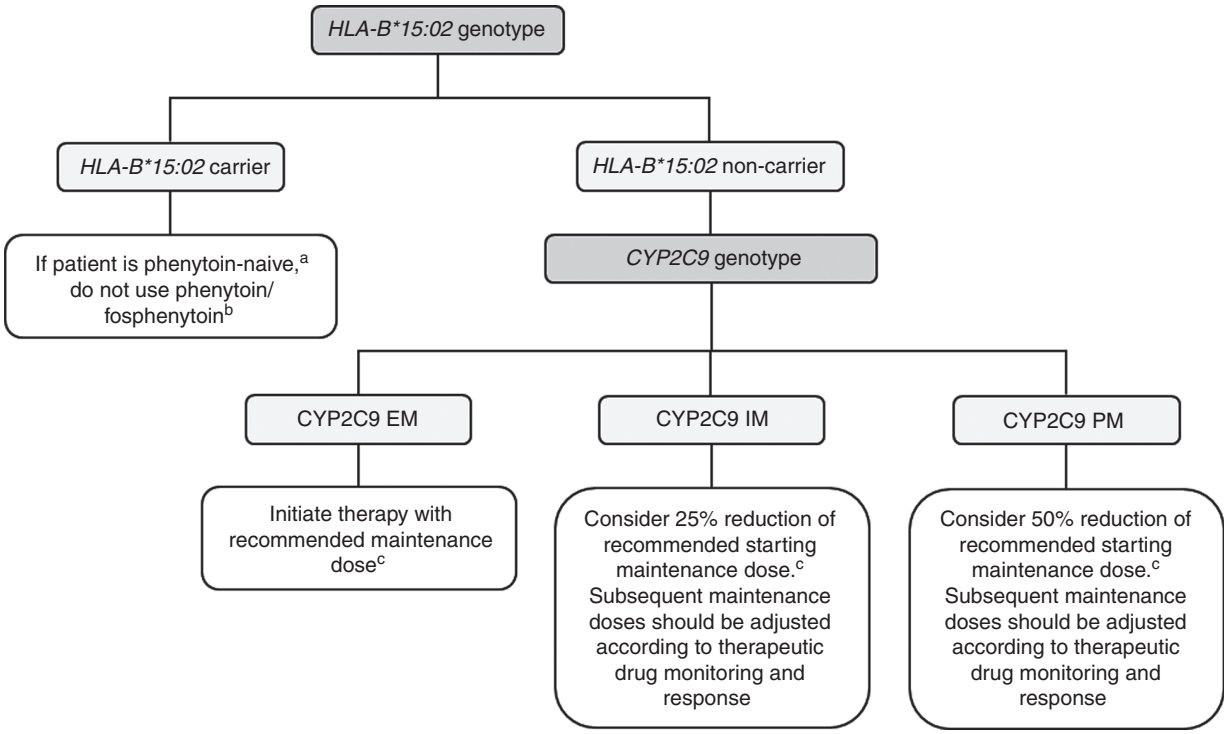

Figure 1 Algorithm for suggested clinical actions based on *HLA-B*15:02* and *CYP2C9* genotypes. [a]If patient has previously used phenytoin for longer than 3 months without incidence of cutaneous adverse reactions, reinitiate phenytoin with caution. Adjust dose based on *CYP2C9* genotype if known. [b]Carbamazepine should not be used as an alternative.[4] Alternative medications such as oxcarbazepine, eslicarbazepine acetate, and lamotrigine have some evidence linking SJS/TEN with the *HLA-B*15:02* allele, and thus caution should be used in choosing alternatives to phenytoin (see **Supplementary Material** online for details). [c]Recommended maintenance dose based on patient's clinical characteristics. EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

as potent CYP2C9 enzyme inhibitors, other less-potent drugs can produce significant elevations in phenytoin plasma concentrations. Therefore, it is important to interpret the results of genetic testing in the context of other coadministered drugs.

CYP2C9 genetic variation does not account for all of the pharmacogenetic variability in phenytoin metabolism. Some studies have implicated variants in other genes associated with phenytoin metabolism (e.g., *CPY2C19, CYP1A1,* and *EPHX1*; see ref. [27] for a review), and combined genetic analysis might improve the predictability of *CYP2C9* alone.[11,13] However, this has not been consistently replicated, and there are limited studies evaluating the effect of multiple-gene variation and phenytoin dose adjustment requirement. Consequently, this guideline on genotype-directed phenytoin dosing is limited to *CYP2C9* variant alleles.

Recommendations for incidental findings

Several drugs structurally and therapeutically similar to phenytoin, such as oxcarbazepine and carbamazepine, have also been associated with SJS/TEN and *HLA-B*15:02* in Asian populations[28–34] (see **Supplementary Material** online). The drug-specific evidence linking *HLA-B*15:02* and SJS/TEN is discussed in the CPIC guideline for *HLA-B* genotype and carbamazepine dosing[4] and may have implications for choosing alternatives to phenytoin in those who carry the *HLA-B*15:02* allele. Case reports have identified cross-reactions to lamotrigine and other antiepileptic drugs in the presence of *HLA-B*15:02* (see **Supplementary Material** online for further discussion). However, larger studies appear to be needed for confirmation.

CYP2C9 metabolism includes substrates from several drug classes, including nonsteroidal anti-inflammatory drugs, oral hypoglycemics/sulfonylureas, and a miscellaneous group of drugs. Reports support that patients with enhanced sensitivity to warfarin are likely to have a decreased capacity to metabolize phenytoin.[35]

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

The potential benefit for patients with existing *CYP2C9* and/or *HLA-B*15:02* genotyping information is in avoiding adverse effects in those patients who are CYP2C9 poor metabolizers by making significant reductions in their starting maintenance dose or by selecting alternative agents for those who are *HLA-B*15:02* carriers. For *HLA-B*15:02* carriers, 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. Furthermore, many commercially available genotyping tests do not detect alleles that are rare or *de novo* variants. Other alleles are not well characterized, resulting in uncertainty when predicting the phenotype for some genetic test results. Due to the fact that the absence of *HLA-B*15:02* does not rule out the possibility of a patient developing phenytoin-induced SJS/TEN[36] or in the event of a rare variant that is not detected by the genetic test, a high-risk patient could be prescribed phenytoin or prescribed a higher dose than needed. Moreover, because not all phenytoin-induced adverse events are attributable to *HLA-B*15:02* or CYP2C9 metabolizer status, 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 therapy. Obtaining genetic information after months of drug therapy is less helpful, given that the drug dose may have already been adjusted based on plasma concentrations, response, or side effects. As with all diagnostic tests, genetic tests constitute only one of several pieces of clinical information that should be considered before initiating drug therapy.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

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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, in addition to identifying 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 healthcare 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. The CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC guidelines, or for any errors or omissions.

CONFLICT OF INTEREST

T.E.K. is a consultant for Personalis. The other authors declared no conflict of interest.

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