Supplemental Material

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP2C9* and *HLA-B* Genotype and Phenytoin Dosing

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Literature Review

We searched the PubMed database (1966 to April 2014 and Ovid MEDLINE (1950 to April 2014) for the keywords ([HLA OR HLA-B OR *HLA-B*15:02*] AND [phenytoin OR fosphenytoin]) and ([CYP2C9 OR cytochrome P450-2C9] AND [phenytoin OR fosphenytoin]) or [pharmacogenetics OR polymorphism] AND [phenytoin OR fosphenytoin]. A more general search was also conducted using the search terms ([phenytoin hypersensitivity] OR [phenytoin Stevens-Johnson]).

Frequency of CYP2C9*2 (rs1799853) and *3 (rs1057910) alleles

*CYP2C9*2* and **3* allele frequencies for different populations were obtained from two different sources (**Supplemental Table S5**), the first one is Phase 1 results of 1000 Genome Project [1] that contain frequency information for 14 different populations and the other source is subjects in the International Warfarin Pharmacogenetic Consortium that contain three major continental populations [2]. Haplotype and diplotype frequencies for *CYP2C9*2* and **3* alleles were calculated using genotypes from the 1000 Genome Project and calculated diplotype frequencies are presented in **Supplemental Tables S6 and S7**.

Literature Review for HLA-B*15:02 Allele Frequency

A table of frequencies of the *HLA-B*15:02* allele in different ethnic populations around the world was assembled from several sources. Frequencies were included from the Allele Frequencies in Worldwide Populations website (http://www.allelefrequencies.net/) which lists frequency data for *HLA-B*15:02* from 100 different samples and populations. Where possible, the original paper from which the allele frequencies were obtained was reviewed for the inclusion criteria listed below. Allele frequencies were also obtained by conducting a search of the PubMed database (1966 to June 2012) and Ovid MEDLINE (1950 to June 2012) using the following criteria: ([HLA or HLA-B or *HLA-B*15:02*] AND [genotype or allele or frequency]) with filter limits set to retrieve "full-text" and "English" literature. Studies from both sources were considered for inclusion if, 1) the ethnicity of the population was clearly indicated; 2) either allele frequencies or alleles for *HLA-B* genotypes were reported; 3) the method by which *HLA-B* was genotyped was reliable and proven; 4) the sample population consisted of at least 50 individuals; 5) the study represented publication of novel data, not literature reviews or meta-analyses of previously published data; and 6) the population studied did not have a concomitant disease (such as an autoimmune condition) that would be expected to result in a distribution of *HLA-B* alleles that were different from the general population. In instances where genotype data from large cohorts of

ethnically-diverse individuals were reported without respect to ethnicity, studies were only considered if one ethnicity was ≥95% of the majority. In some cases, sample sizes or allele frequencies were updated to reflect only subjects successfully genotyped for *HLA-B* (rather than the total sample size of the study) or to correct errata in the original publication. The combined analysis included 271 Africans, 371 non-Caucasian Americans, 14,397 East Asians, 30,640 Europeans including Caucasians worldwide, 491 Middle Easterners, 201 Oceanians, and 235 South or Central Asians (**Supplemental Tables S3 and S5**).

Gene: *HLA-B*15:02*

Background

The exact interactions between *HLA-B*15:02* and phenytoin have not been established. Three hypotheses currently explain that the interactions between specific HLA, T cell receptor (TCR) and drug-peptide can lead to an immune response and causes Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The hapten hypothesis proposes that T lymphocytes recognize chemically reactive drug/drug metabolite bound covalently to a protein or MHC-bound peptides and forms a hapten-carrier complex, this modified protein can induce an immune response. The "p-i concept" (direct pharmacological interaction of drugs with immune receptors) suggests that some drugs that lack hapten characteristics can bind directly and reversibly (noncovalently) to TCRs and thereby stimulate the cells [3]. Studies using endogenous peptides of *HLA-B*15:02* in carbamazepine-induced SJS/TEN have shown a non-covalent interaction between drug/peptide/HLA and TCR, thus supporting the p-i concept model [4]. However, whether phenytoin undergoes the same pathway needs to be further studied. Lastly, a recent hypothesis postulates that a drug can bind directly to specific HLA molecules and alters its specificity for peptide binding. This has been shown for *HLA-B*57:01* and abacavir induced hypersensitivity [5].

Other Antiepileptics With An Aromatic Ring

Several drugs structurally and therapeutically similar to phenytoin have also been associated with drug-induced adverse cutaneous reactions and *HLA-B*15:02*.

Oxcarbazepine is the keto-analog of carbamazepine. As with carbamazepine, oxcarbazepine has been used in the treatment of partial seizures with and without generalization and in the treatment of neuropathic pain. There are three cases reported of oxcarbazepine-induced SJS in carriers of *HLA-*

*B*15:02* [6-8]. There is also one case report in a patient of Han Chinese decent of mild maculopapular eruptions (MPE) (without progression to SJS/TEN) after the use of oxcarbazepine [9].

Eslicarbazepine acetate is a prodrug which is activated to eslicarbazepine, an active metabolite of oxcarbazepine. To date, no cases of eslicarbazepine-induced SJS/TEN have been reported; however, based on its structural similarity to oxcarbazepine, caution should be used in susceptible individuals positive for *HLA-B*15:02*.

Lamotrigine has been associated with SJS/TEN, particularly with rapid dose escalation or when used in combination with valproic acid. A possible trend of association between *HLA-B*15:02* and lamotrigine-induced SJS/TEN in Han Chinese has been reported in two studies [10, 11] but not in another [12]. A recent meta-analysis (including these studies and original data) showed a marginal association between *HLA-B*15:02* and lamotrigine-induced SJS/TEN (p=0.03) [13]. One studied identified two significantly increased alleles of *HLA-A*30:01* and *HLA-B*13:02* (P=0.013 and P=0.013, respectively) in patients (Han Chinese) with lamotrigine-induced maculopapular exanthema when compared with those in the lamotrigine-tolerant group suggesting additional immunological mechanisms that may contribute to the risk cutaneous adverse reactions [14].

Available Genetic Test Options

Commercially available genetic testing options change over time. Information for *HLA-B*15:02*, *CYP2C9*2* or **3* is available on the Pharmacogenetic Tests section (http://pharmgkb.org/resources/forScientificUsers/pharmacogenomic_tests.jsp) of PharmGKB. Furthermore, the Genetic Testing Registry (GTR) provides a central location for voluntary submission of genetic test information by providers and is available at http://www.ncbi.nlm.nih.gov/gtr/. At the time of this publication, no genetic test information has been submitted to the GTR regarding *HLA-B*15:02*, *CYP2C9*2* or **3*.

Several academic clinical and some reference laboratories offer *CYP2C9* testing done by genotyping or sequencing. Interpretation of results is straight forward for the commonly occurring alleles; individuals have one or two copies of the decreased activity allele(s).

Genetic Test Interpretation

CYP2C9 function associated with selected *CYP2C9* allelic variants is summarized in **Supplemental Table S2**. The dosing recommendations in this guideline are specific for variant alleles in which there are clear data linking *CYP2C9* genotype to phenytoin toxicity (**2* and **3*) (**Supplemental Table S8**). However, several other CPY2C9 variants have been reported to be associated with reduced enzyme activity, albeit with somewhat weaker evidence for phenytoin. Furthermore, CYP2C9 functional metabolic effects may be substrate specific and extrapolations may not be reliable. These variants have been categorized as "probable reduced-function" based on the lack of clinical studies linking these genotypes to phenytoin toxicity and in vitro activity studies using phenytoin as the substrate. However, these alleles could be informative in predicting a patient's CYP2C9 metabolizer status.

The *HLA-B*15:02* allele is a complex variant consisting of numerous nucleotide and resultant amino acid substitutions. Comparison of nucleotide sequences for a reference *HLA-B* allele with that of *HLA-B*15:02* reveals 42 differences within the open reading frame of the gene. These nucleotide sequence differences translate to a peptide exhibiting 27 amino acid substitutions in the variant allele (see CPIC Carbamazepine guideline online supplement [15]).

A variety of companies provide clinical testing services for the detecting of *HLA-B*15:02*. They primarily employ two different detection methods. One is direct sequencing of the gene. Alleles are assigned by comparison of the sequence to the known variants that define *HLA-B*15:02* and reported as the diplotype of both *HLA-B* alleles. Genotyping is another common approach in which the sequence variants that define *HLA-B*15:02* are directly detected through a panel of DNA tests. Allele specific polymerase chain reaction (PCR) is commonly employed where PCR primers specific for each nucleotide variant are used. The PCR products can then be detected using gel electrophoresis or other methods. A variety of other genotyping methods may also be used to directly detect each of the nucleotide variants for *HLA-B*15:02*. As the test is specific for *HLA-B*15:02*, the test will only report its presence and absence as opposed to the full diplotype available through sequencing.

Another option is the genotyping of one or more single nucleotide polymorphisms (SNPs) that are near the HLA-B locus and in linkage disequilibrium with the *HLA-B*15:02* allele. However, as this test is indirect and depends upon linkage disequilibrium which may vary between different populations, it may

have lower accuracy. It also requires genotyping and may not be any faster or less expensive than genotyping of the specific defining variants.

Drugs: Phenytoin and fosphenytoin

Background

In humans, phenytoin is metabolized to both 5-(4'-hydroxyphenyl)-5-phenylhydantoin (*p*-HPPH) and 5-(3'-hydroxyphenyl)-5-phenylhydantoin (*m*-HPPH) (**Supplementary Figure S1**). *In vivo,* 67-88% of an administered phenytoin dose is excreted as *p*-HPPH, which is conjugated mainly to glucuronic acid [16], with only a trace amount of *m*-HPPH formed [17]. Phenytoin is a pro-chiral molecule and, besides this regio-selectivity of hydroxylation, metabolite formation is also highly stereo-selective, as evidenced by the urinary (*S*)/(*R*) ratio for *p*-HPPH which is typically >20:1 [18].

Strong *in vitro* evidence from recombinant CYP2C9 studies recapitulates the high *in vivo* stereo-selectivity (>20:1) in the formation of (S)-*p*-HPPH, supporting CYP2C9 as the dominant phase I clearance pathway for phenytoin [19]. In contrast, a second P450 enzyme - CYP2C19 – is much less stereo-selective, forming only ~60% (S)-*p*-HPPH [19]. CYP2C19 forms most of the (*R*)-*p*-HPPH encountered *in vivo* [20], but this enzyme assumes a minor role in phenytoin hydroxylation, unless the CYP2C9 pathway becomes saturated at higher doses of the drug [19]. Because phenytoin therapeutic plasma levels can be sufficiently high to saturate CYP2C9 and CYP2C19, the dosing of phenytoin is complicated by nonlinear pharmacokinetics; *i.e.* increases in phenytoin plasma concentrations are not proportional to increases in dose [21].

Fosphenytoin is a water-soluble, phosphate ester pro-drug of phenytoin that was developed to overcome complications associated with parenteral phenytoin administration, including cardiac arrhythmias and hypotension [22]. Fosphenytoin is rapidly and completely metabolized to phenytoin by alkaline

phosphatase (ALP) enzymes that, importantly for pro-drug activations, are found at high levels in plasma and the brush-border of the gastrointestinal tract [23]. Metabolism by ALP forms a transient carbinolamine intermediate that spontaneously decomposes to phenytoin **(Supplementary Figure S2**). Effects of genetic variation of ALP enzymes in fosphenytoin bioactivation have not been described.

Levels of Evidence

The evidence summarized in **Supplemental Tables S8 and S9** is graded using a scaled modified slightly from Valdes et al. [24]

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information

Strength of Recommendations

CPIC's dosing recommendations are based weighting the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines (2). Some of the factors that are taken into account include in vivo clinical outcome for reference drug, in vivo PK/PD for reference drug, in vitro enzyme activity for reference drug, and in vitro enzyme functional activity (protein stability or enzyme activity with another drug) only.

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

clearly outweigh the undesirable effects; and optional, in which the desirable effects are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action.

Strong recommendation for the statement

Moderate recommendation for the statement

Optional recommendation for the statement

Resources to Incorporate Pharmacogenetics into an EHR with CDS

Use of clinical decision support (CDS) tools within electronic health records (EHRs) can assist clinicians to use genetic information to optimize drug therapy [25-29]. Supplementary material provides resources from CPIC to support the adoption of CPIC guidelines within an EHR [30]. Based on the capabilities of various EHRs and local preferences, we recognize approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating the use of *HLA-B* 15:02* and *CYP2C9* genotype results to guide phenytoin dosing in any EHR.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. First, pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR [31]. Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient summary section; these phenotypes are best stored in the EHR at the "person level" rather than at the date-centric "encounter level." Second, results should be entered as standardized and discrete terms to facilitate using them to provide point of care CDS [32, 33]. Because pharmacogenetic results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. Point-of-care CDS should be designed to effectively remind clinicians of prescribing implications at any time after the test result is entered into the EHR. Guidance to achieve these objectives is provided in diagrams that illustrate how *HLA-B*15:02* and/or *CYP2C9* pharmacogenetic test results could be entered into an EHR (**Supplemental Figure S3a and b**) and be used for point-of-care CDS (**Supplemental Figure S4a, b, and c**). **Supplemental Tables S10** and **S11** provide a cross-reference to widely used nomenclature systems for the drug and the gene, respectively.

To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Supplemental Tables S12a and b**). **Supplemental Tables S13a and b** further translate results into a coded diplotype/phenotype summary, priority result notification, and sample interpretative result text. The result tables provide summary genotype/phenotype terms, example text for documentation in the EHR and point-of-care alerts. Finally, sample point-of-care alert text that corresponds to the workflow described in **Supplemental Figure S4a, b, and c** is provided in **Supplemental Table S14a, b, and c**.

Supplemental Table S1. Genotypes that constitute the * alleles for *CYP2C9*

Allele	Constituted by genotypes at:[a]	Amino acid
**1*	Reference allele at all positions	
**2*	C>T at rs1799853	R144C
**3*	A>C at rs1057910	I359L
**4*	T>C at rs56165452	I359T
**5*	C>G at rs28371686	D360E
**6*	del A at rs9332131	273frameshift
**7*	C>A at rs67807361	L19I
**8*	G>A at rs7900194	R150H
**9*	A>G at rs2256871	H251R
**10*	A> G atrs9332130	E272G
**11*	C>T at rs28371685	R335W
**12*	C>T at rs9332239	P489S
**13*	T>C at rs72558187	L90P
**14*	G>A at rs72558189	R125H
**15*	C>A at rs72558190	S162X
**16*	A>G at rs72558192	T299A
**17*	1144C>T	P382S
**18*	A>C at rs1057910, A>C at rs72558193, A>T at rs1057911	I359L, D397A
**19*	1362G>C	Q454H
**20*	208G>C	G70R
**21*	C>T at rs142240658	P30L
**22*	121A>G	N41D
**23*	226G>A	V76M
**24*	1060G>A (may also have **2* 430C>T)	E354K
**25*	delAGAAATGGAA at rs72558188	118frameshift
**26*	389C>G	T130R
**27*	449G>T	R150L
**28*	641A>T	Q214L
**29*	C>A at rs182132442	P279T
**30*	1429G>A	A477T
**31*	T>C at rs57505750	I327T
**32*	1468G>T	V490F
**33*	G>A at rs72558184	R132Q
**34*	1004G>A	R335Q
**35*	374G>T, C>T at rs1799853	R125L, R144C
**36*	A>G at rs114071557	M26V
**37*	146A>G	D49G
**38*	287G>C	G96A
**39*	293G>T	G98V
**40*	329T>C	F110S
**41*	356A>G	K119R
**42*	G>A at rs12414460	R124Q
**43*	370C>T	R124W

**44*	C>T at rs200965026	T130M
**45*	C>T at rs199523631	R132W
**46*	445G>A	A149T
**47*	488C>T	P163L
**48*	620T>C	I207T
**49*	664A>G	I222V
**50*	679C>T	P227S
**51*	850A>G	I284V
**52*	896C>G	T299R
**53*	949C>T	P317S
**54*	1029C>A	S343R
**55*	1081C>A	L361I
**56*	1159A>G	I387V
**57*	610A>C	N204H

Alleles are derived from the Human Cytochrome P450 (CYP) Allele Nomenclature Database (http://www.cypalleles.ki.se/cyp2c9.htm). See http://www. pharmgkb.org/gene/PA126 for updates on *CYP2C9* alleles and nomenclature.

[a]rsID is provided as it is catalogued in dbSNP, otherwise cDNA location is provided (M61857.1)

Supplemental Table S2. Association between allelic variants and CYP2C9 function

Functional Status[a, b]	Alleles	In Vitro Activity	
		Substrate	Percent reduction of in vitro metabolism vs CYP2C9*1
Normal Activity	**1*		
	**9*	S-warfarin Tolbutamide Tolbutamide	82% of Cl_{int} [34] 96% of wild-type activity [34] 93% of Cl_{int} [35]
Decreased Activity	**2*	S-warfarin Tolbutamide Phenytoin	32% of Cl_{int} [34] 42% of wild-type activity [34] 71% of Cl_{int} [36]
	**3*	S-warfarin Tolbutamide Tolbutamide Phenytoin Phenytoin	21% of wild-type activity [34] 28% of wild-type activity [34] 26% of Cl_{int} [37] 5% of Cl_{int} [36] 7% of Cl_{int} [38]
No Activity	**6*	N/A	Frameshift mutation [34]
	**15*	N/A Tolbutamide	Nonsense mutation No expression [39]
	**25*	N/A	Frameshift mutation [34]
Possible Decreased Activity (no available phenytoin in vitro activity studies)	**4*	S-warfarin Tolbutamide	16% of wild-type activity [34] 22% of wild-type activity [34]
	**5*	S-warfarin Tolbutamide S-warfarin	19% of wild-type activity [34] 24% of wild-type activity [34] 8% of Cl_{int} [40]
	**8*	S-warfarin Tolbutamide	41% of Cl_{int} [34] 74% of wild-type activity [34]
	**11*	S-warfarin Tolbutamide Tolbutamide	41% of wild-type activity [34] 71% of wild-type activity [34] 43% of Cl_{int} [35]
	**12*	S-warfarin Tolbutamide Tolbutamide	32% of Cl_{int} [34] 48% of wild-type activity [34] 40% of wild-type activity [35]
	**13*	S-warfarin Tolbutamide Tolbutamide	16% of wild-type activity [34] 0% of wild-type activity [34] 9% of Cl_{int} [37]
	**31*	S-warfarin Tolbutamide	33% of wild-type activity [34] 52% of wild-type activity [34]

unclear/contradictory unknown/ evidence	**7, *10, *16, *17, *18, *19, *20, *21, *22, *23, *24, *26, *27, *28, *29, *30, *32, *33, *34, *35, *36, *37, *38, *39, *40, *41, *42, *43, *44, *45, *46, *47, *48, *49, *50, *51, *52, *53, *54, *55, *56, *57*

[a]An important caveat for all genotyping tests is that the decision to assign an allele a "wild-type" status is based upon a genotyping test that interrogates only the most common and already-proven sites of functional variation. In human DNA, it is always possible that a new, previously undiscovered (and therefore un-interrogated) site of variation may confer loss-of-function in an individual, and thus lead to the rare possibility of a non-functional allele being erroneously called as "wild-type."
[b]Functional status describes the resulting phenotype of the single variant allele (e.g., **1*, etc.) and not the diplotype (e.g., **1/*2*, etc.). See **Table 1** in main manuscript guideline for assignment of phenotype based on diplotype.

Supplemental Table S3. Worldwide Allele Frequencies* of *HLA-B*15:02* - Summary by Region

Race/Ethnic Designation	Allele Frequency	Sample Size
African	0.0	271
Non-Caucasian American	0.0039	371
East Asian	0.043	14,397
European	0.000057	30,640
Middle Eastern	0.0045	491
Oceanian	0.107	201
South/Central Asian	0.0134	235

*Updated HLA-B allele frequencies can also be found at [41]

Supplemental Table S4. Worldwide Allele Frequencies of *HLA-B*15:02* - Detailed by Sample

HGDP-CEPH Grouping	Population/Ethnicity	Allele Frequency	Sample Size
Africa	Morocco Nador Metalsa pop 2 [42]	0	73
Africa	Morocco Settat Chaouya [43]	0	98
Africa	South Africa Natal Zulu [44]	0	100
Americas	Mexico City Mestizo [45]	0.008	121
Americas	Mexico Puebla Mestizo [45]	0.005	99
Americas	Mexico Sinaloa Mestizo [45]	0	56
Americas	Brazil Belo Horizonte Caucasian [44]	0	95
East Asia	China Beijing pop 2 [46]	0.1287	826
East Asia	China Beijing Shijiazhuang Tianjian Han [47]	0.024	618
East Asia	China Canton Han [48]	0.073	264
East Asia	China Guangdong Province [49]	0.035	100
East Asia	China Guangxi Region Maonan [50]	0.148	108
East Asia	China Guizhou Province Bouyei [51]	0.155	109
East Asia	China Guizhou Province Miao pop 2 [51]	0.042	85
East Asia	China Guizhou Province Shui [51]	0.156	153
East Asia	China Inner Mongolia Region [52]	0.015	102
East Asia	China North Han [53]	0.019	105
East Asia	China Qinghai Province Hui [52]	0.027	110
East Asia	China Southwest Dai [46]	0.069	124
East Asia	China Yunnan Province Bulang [54]	0.358	116
East Asia	China Yunnan Province Han [55]	0.124	101
East Asia	China Yunnan Province Hani pop 2 [54]	0.1	150
East Asia	China Yunnan Province Jinuo [56]	0.238	109
East Asia	China Yunnan Province Lisu [49]	0.123	111
East Asia	China Yunnan Province Nu [49]	0.09	107
East Asia	China Yunnan Province Wa [56]	0.21	119
East Asia	Japan Central [57]	0.001	371
East Asia	Japan pop 3 [58]	0.001	1,018

East Asia	Malaysia [59]	0.081	75
East Asia	Singapore Chinese [44, 60]	0.057	149
East Asia	South Korea pop 3 [61]	0.002	485
East Asia	South Korea pop 8 [62]	0.022	7,096
East Asia	Taiwan pop 2 [63]	0.052	364
East Asia	Taiwan pop 3 [64]	0.06	212
East Asia	Taiwan Tzu Chi Cord Blood Bank [65]	0.042	710
East Asia	Thailand Northeast pop 2 [66]	0.084	400
Europe	Cuba Caucasians [44, 60]	0	70
Europe	Bulgaria [67]	0	55
Europe	Germany pop 6 [68]	0.0002	8,862
Europe	Ireland Northern [69, 70]	0	1,000
Europe	Poland DKMS [71]	0	20,653
Middle East	United Arab Emirates pop 2 [72]	0.006	373
Middle East	Oman [44, 60]	0	118
Oceania	Indonesia Sundanese and Javanese [73]	0.107	201
South/Central Asia	India Mumbai Marathas [74]	0.01	72
South/Central Asia	India Mumbai Maratha [74]	0.019	91
South/Central Asia	India North pop 2 [75]	0.01	72

Supplemental Table S5. *CYP2C9*2* (rs1799853) and **3* (rs1057910) allele frequencies (%) in A) 1000 Genomes populations and B) Populations from International Warfarin Pharmacogenetic Consortium

A)	Group	Population	*CYP2C9*2*	*CYP2C9*3*
	European	CEU (Utah Residents (CEPH) with Northern and Western European ancestry)	6.8	4.3
		TSI (Toscani in Italia)	16.3	6.6
		GBR (British in England and Scotland)	9.0	5.6
		FIN (Finnish in Finland)	9.1	5.9
		IBS (Iberian population in Spain)*	14.3	10.7
	East Asian	CHS (Southern Han Chinese)	1.0	5.5
		JPT (Japanese in Tokyo, Japan)	0.0	2.2
		CHB (Han Chinese in Bejing, China)	0.0	4.1
	Hispanic	MXL (Mexican Ancestry from Los Angeles USA)	9.8	5.3
		CLM (Colombians from Medellin, Colombia)	10.8	8.3
		PUR (Puerto Ricans from Puerto Rico)	17.3	3.6
	African-American /African	ASW (Americans of African Ancestry in SW USA)	7.4	2.5
		LWK (Luhya in Webuye, Kenya)	0.0	0.0
		YRI (Yoruba in Ibadan, Nigeria)	16.3	6.6
B)	Group**			
	White (3062)		13.0	7.0
	Asian (1063)		0.0	4.0
	Black (645)		3.0	2.0

*IBS (Iberian population in Spain) low n number (n=14). Number of subjects in other 1000 Genomes populations vary (n=55 to 100).

**Number of subjects are given in parenthesis

Supplemental Table S6. Diplotype frequencies (%) for *CYP2C9* alleles in 1000 Genomes populations

Group	Population	Diplotypes (%)						Diplotype Combinations (%)		
		*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3	*1/*1 + *1/*2	*1/*3 + *2/*2	*3/*3 + *2/*3
European	CEU	68.2	16.5	8.2	4.7	2.4	0.0	84.7	12.9	2.4
	TSI	57.1	26.5	13.3	3.1	0.0	0.0	83.7	16.3	0.0
	GBR	73.0	14.6	10.1	1.1	1.1	0.0	87.6	11.2	1.1
	FIN	72.0	16.1	9.7	0.0	2.2	0.0	88.2	9.7	2.2
	IBS[a]	57.1	21.4	14.3	0.0	7.1	0.0	78.6	14.3	7.1
East Asian	CHS	88.0	2.0	9.0	0.0	0.0	1.0	90.0	9.0	1.0
	JPT	95.5	0.0	4.5	0.0	0.0	0.0	95.5	4.5	0.0
	CHB	91.8	0.0	8.2	0.0	0.0	0.0	91.8	8.2	0.0
Hispanic	MXL	69.7	19.7	10.6	0.0	0.0	0.0	89.4	10.6	0.0
	CLM	63.3	20.0	15.0	0.0	1.7	0.0	83.3	15.0	1.7
	PUR	61.8	29.1	5.5	1.8	1.8	0.0	90.9	7.3	1.8
Afr/Afr-Am	ASW	82.0	13.1	3.3	0.0	1.6	0.0	95.1	3.3	1.6
	LWK	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0
	YRI	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0

[a]IBS (Iberian population in Spain) low n number (n=14). Number of subjects in other 1000 Genomes populations vary (n=55 to 100).

Supplemental Table S7. Regional Diplotype frequencies (%) for *CYP2C9* alleles in 1000 Genomes populations

Group	Diplotypes (%)						Diplotype Combinations (%)		
	**1/*1*	**1/*2*	**1/*3*	**2/*2*	**2/*3*	**3/*3*	**1/*1 + *1/*2*	**1/*3 + *2/*2*	**3/*3 + *2/*3*
European	67.0	18.7	10.6	2.1	1.6	0.0	85.8	12.7	1.6
East Asian	91.6	0.7	7.3	0.0	0.0	0.3	92.3	7.3	0.3
Hispanic	65.2	22.7	10.5	0.6	1.1	0.0	87.8	11.0	1.1
Afr/Afr-Am*	95.5	3.3	0.8	0.0	0.4	0.0	98.8	0.8	0.4

* Other alleles such as *CYP2C9*8* may be more frequent in African ancestry [76] .

Supplemental Table S8. Evidence linking *HLA-B*1502* genotype to phenytoin cutaneous adverse drug reaction phenotype.

Type of Experimental model (in vitro, in vivo, preclinical, or clinical)	Major Findings	References	Level of evidence*
Clinical	Significant association between *HLA-B*15:02* genotype and Han Chinese patients with phenytoin induced SJS/TEN compared to phenytoin tolerant patients and/or healthy controls.	Hung *et al*. (2010)[11] Man *et al*. (2007)[77] Neuman *et al*. (2012)[78] Cheung *et al*. (2013) [13]	High
Clinical	Significant association between *HLA-B*15:02* genotype and Thai patients with phenytoin induced SJS/TEN compared to phenytoin tolerant patients and/or healthy controls.	Locharernkul *et al*. (2008)[79]	Moderate
Clinical	Case report of Han Chinese patient with phenytoin induced SJS/TEN and *HLA B*15:02* genotype.	Min *et al*. (2011)[80]	Weak

***** High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information

Supplemental Table S9. Evidence linking *CYP2C9* genotype to phenytoin metabolism and/or toxicities.

Type of Experimental model (in vitro, in vivo, preclinical, or clinical)	Major Findings	References	Level of evidence*
In vitro	*CYP2C9*2* results in a 29% reduction in phenytoin clearance as compared with *1.	Rettie *et al*. (1999)[36]	Moderate
In vitro	*CYP2C9*3* results in a 93-95% reduction in phenytoin clearance as compared with *1.	Rettie *et al*. (1999)[36] Takanashi *et al*. (2000)[38]	Moderate
Clinical	*CYP2C9*3* is associated with reduced (S)/(R) ratio of p-HPPH in urine samples.	Argikar *et al*. (2006)[81]	Moderate
Clinical	*CYP2C9*3* carriers have significantly increased serum concentrations of phenytoin after a single dose in healthy volunteers.	Aynacioglu *et al*. (1999)[82] Kerb *et al*. (2001)[83] Caraco *et al*. (2001)[84]	High
Clinical	*CYP2C9*3* carriers have significantly increased phenytoin serum concentrations under steady state conditions.	Odani *et al*. (1997)[85] Ramasamy *et al*. (2010)[86] Soga *et al*. (2004)[87] Phabphal *et al*. (2013)[88] Phabphal *et al*. (2013)[89]	High
Clinical	*CYP2C9*2* carriers have significantly increased serum concentrations of phenytoin after a single dose in healthy volunteers.	Aynacioglu *et al*. (1999)[82] Kerb *et al*. (2001)[83]	Moderate
Clinical	*CYP2C9*2* carriers have significantly increased phenytoin serum concentrations under steady state conditions.	Ramasamy *et al*. (2010)[86]	Moderate
Clinical	*CYP2C9*3* carriers have significantly reduced serum p-HPPH/P ratio compared to wild-type carriers.	Aynacioglu *et al*. (1999)[82] Kerb *et al*. (2001)[83]	Moderate
Clinical	*CYP2C9*2* have significantly reduced serum p-HPPH/P ratio compared to wild-type carriers.	Aynacioglu *et al*. (1999)[82] Kerb *et al*. (2001)[83]	Moderate
Clinical	*CYP2C9*3* carriers have significantly lower maximal elimination rates than do compared to wild-type carriers.	Hung *et al*. (2004)[90] Mamiya *et al*. (1998)[91] Odani *et al*. (1997)[85] Yamamoto *et al.* (2011)[92]	High

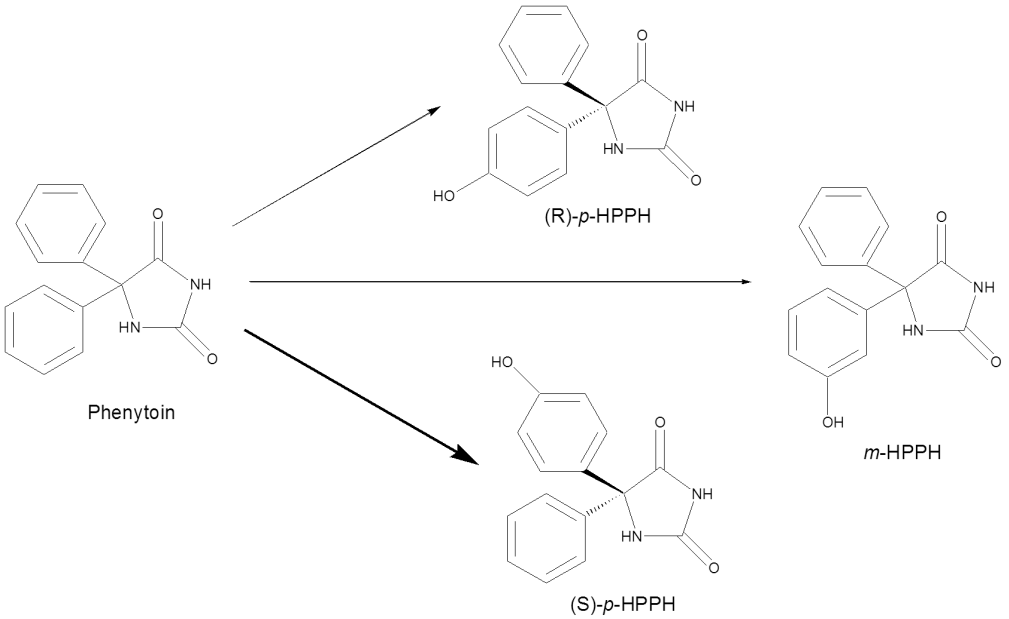
Clinical	*CYP2C9*1/*3* associated with increased likelihood of ADR when treated with phenytoin in patients with epilepsy.	Hennessy *et al*. (2009)[93] Kesavan *et al*. (2010)[94] Lee *et al*. (2004)[95]	High
Clinical	*CYP2C9*2* and **3* associated with increased likelihood of phenytoin toxicity.	Ramasamy *et al*. (2010)[94]	Moderate
Clinical	*CYP2C9*2* and **3* associated with a significant reduction in cerebellar white matter volume but not in total cerebellar volume in patients receiving chronic phenytoin (>1 year).	Twardowschy et al. (2013)[96]	Moderate
Clinical	*CYP2C9*2/*2* associated with increased likelihood of ADR when treated with phenytoin in patients with epilepsy.	Hennessy *et al*. (2009)[93]	Moderate
Clinical	*CYP2C9*2* and **3* associated with phenytoin toxicity.	Depondt *et al*. (2011)[97] Thakkar *et al*. (2012) [98]	Moderate
Clinical	*CYP2C9*3/*3* observed in patient with phenytoin toxicity.	Ramasamy *et al*. (2007)[99] Babu *et al*. (2013) [100]	Moderate
Clinical	*CYP2C9*1/*3* observed in patient with phenytoin intoxication.	Citerio *et al*. (2003)[101] McCluggage *et al*. (2009)[102] Ninomiya *et al*. (2000)[103]	Moderate
Clinical	*CYP2C9*2/*2* observed in patient with neurological phenytoin toxicity.	Dorado *et al*. (2012)[104]	Weak
Clinical	In epileptic patients receiving phenytoin, *CYP2C9*3* is associated with decreased maximum tolerable dose of phenytoin.	Tate *et al*. (2005)[105] van der Weide *et al*. (2001)[106]	High
Clinical	Epileptic patients who are *CYP2C9*3* carriers require significantly lower maintenance doses of phenytoin as compared to wild-type carriers.	Hung et al. (2012) [107]	Moderate
Clinical	In epileptic patients receiving phenytoin, *CYP2C9*2* is associated with decreased maximum tolerable dose of phenytoin.	van der Weide *et al*. (2001)[106]	Moderate
Clinical	*CYP2C9*5*, **6*, **8*, and **11* are associated with reduced urinary excretion of (S)-p-HPPH (8-hour urine collection after single dose).	Allabi *et al*. (2005) [108]	Moderate
Clinical	*CYP2C9*9* does NOT affect phenytoin metabolism.	Allabi *et al*. (2005) [108]	Moderate

Clinical	*CYP2C9*1/*3* is NOT associated increased likelihood of ADR when treated with phenytoin in patients with epilepsy.	Twardowschy *et al*. (2011)[109]	Weak
Clinical	*CYP2C9*2* is NOT associated with increased maximum dose of phenytoin.	Tate *et al*. (2005)[53]	Weak

***** High: Evidence includes consistent results from well-designed, well-conducted studies.

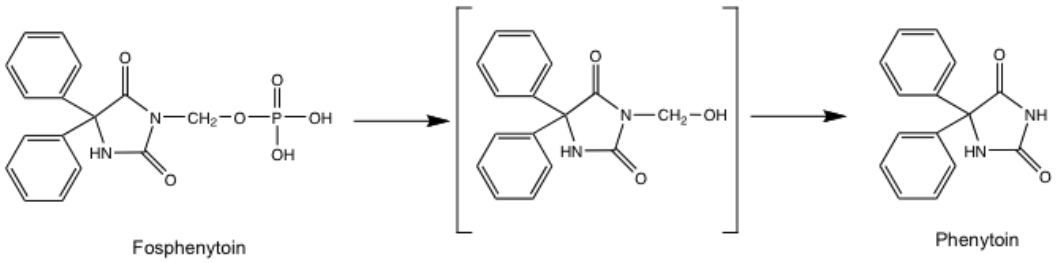
Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence,or lack of information

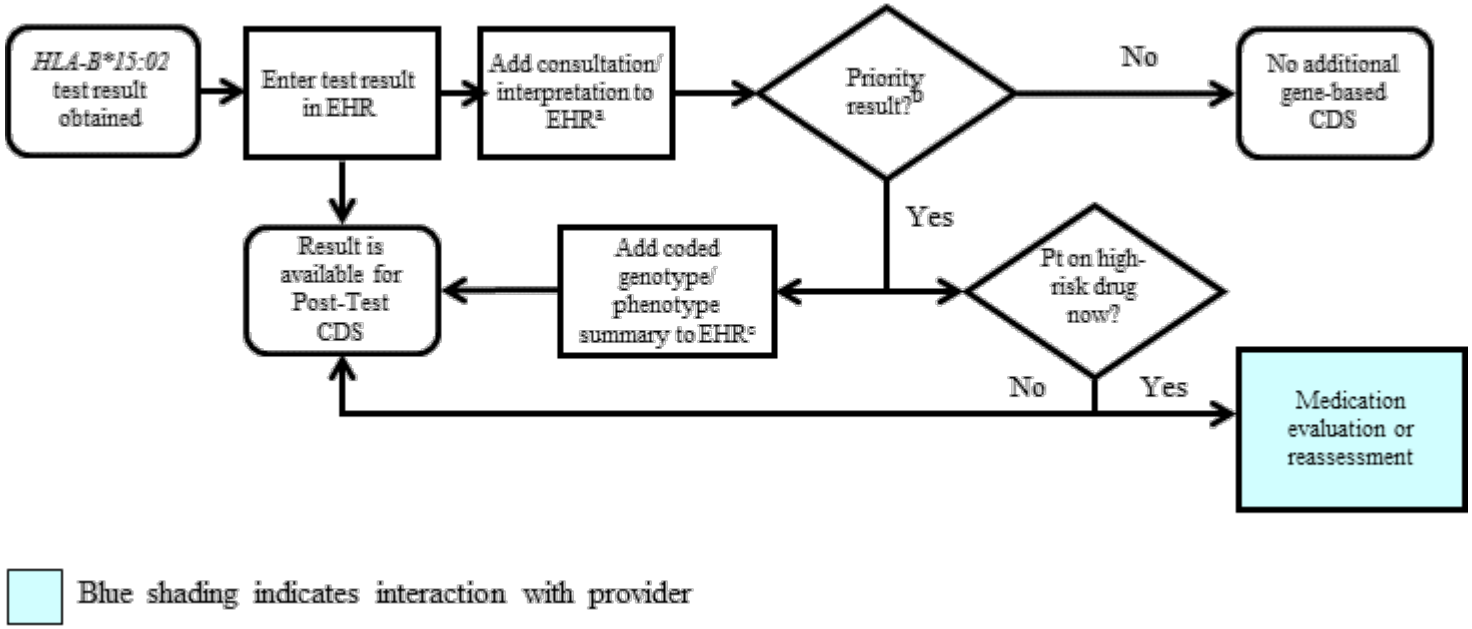


Supplementary Figure S1. Metabolism of phenytoin

(R)-p-HPPH, R-isomer of 5-(4'-hydroxyphenyl)-5-phenylhydantoin (p-HPPH); (S)-p-HPPH, S-isomer of 5-(4'-hydroxyphenyl)-5-phenylhydantoin; m-HPPH 5-(3'-hydroxyphenyl)-5-phenylhydantoin



Supplementary Figure S2. Metabolism of fosphenytion to phenytoin.

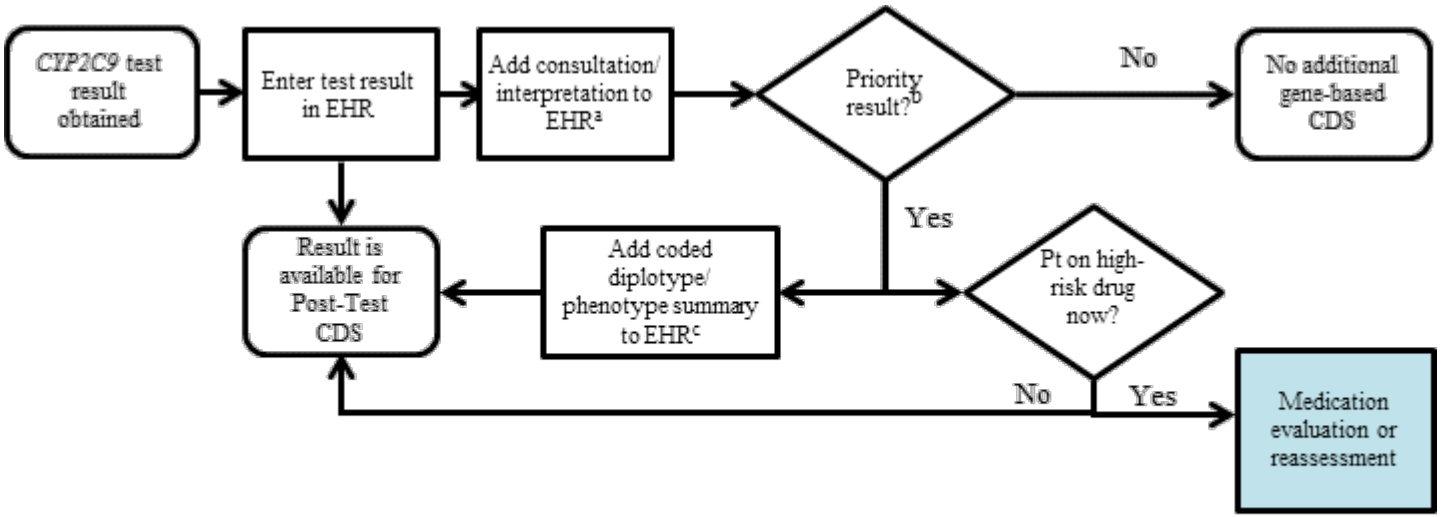


Supplemental Figure S3a. *HLA-B*15:02* Pharmacogenetic Test Result: Clinical Implementation Workflow for EHR

[a]See **Supplementary Table S13a** for diplotype/phenotype specific example

[b]"Priority result" is defined as a genetic test result that necessitates a change in drug, drug dose, or drug monitoring now or potentially in the future.

[c]Documentation in the EHR is institution specific. Optimally, the phenotype and/or genotype are available in the EHR to permanently inform prescribing decisions. See **Supplementary Table S13a** for genotype/phenotype-specific summaries.

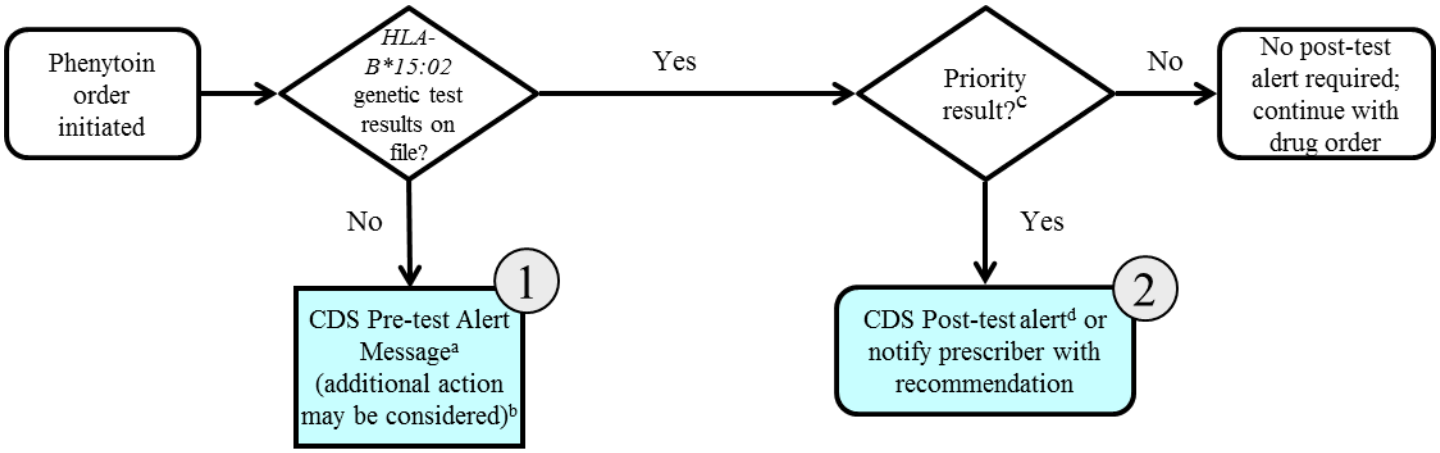


Supplemental Figure S3b. *CYP2C9* Pharmacogenetic Test Result: Clinical Implementation Workflow for EHR

[a]See **Supplementary Table S13b** for diplotype/phenotype specific example

[b]"Priority result" is defined as a genetic test result that necessitates a change in drug, drug dose, or drug monitoring now or potentially in the future.

[c]Documentation in the EHR is institution specific. Optimally, the phenotype and/or genotype are available in the EHR to permanently inform prescribing decisions. See **Supplementary Table S13b** for genotype/phenotype-specific summaries.



..... Dashed lines indicate optional steps

Supplemental Figure S4a. *HLA-B*15:02* Genotype[e] and Phenytoin[f]: Point of Care Clinical Decision Support

[a]See **Supplementary Table S14a** for diplotype/phenotype specific pre-test alert example.

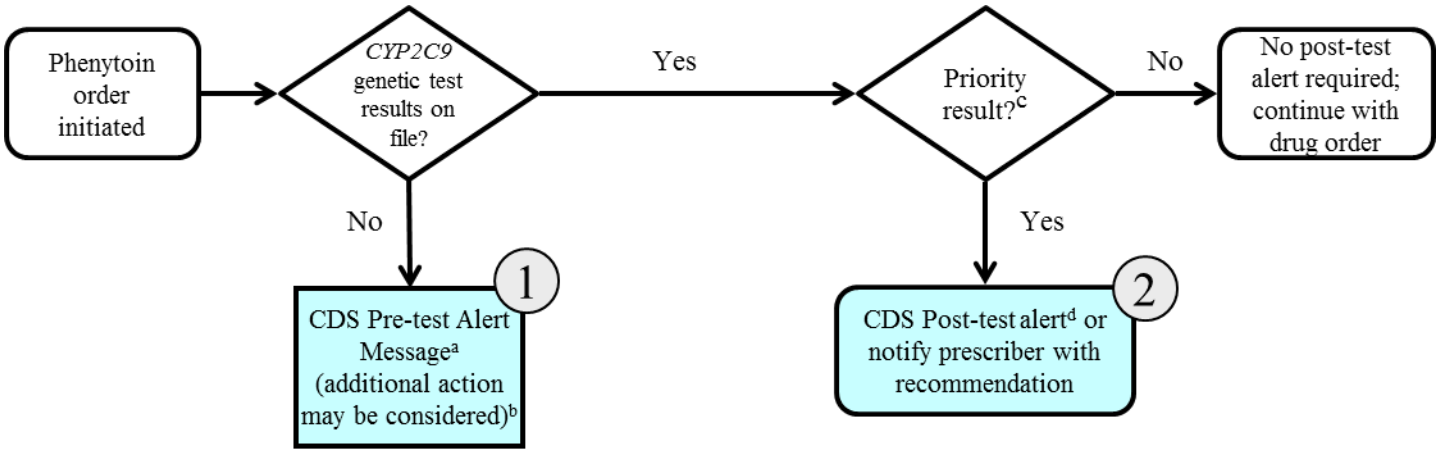
[b]Additional actions may include ordering a pharmacogenetic test, preventing the clinician from ordering the medication or allowing the clinician to cancel out of the alert.

[c]Priority result defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.

[d]See **Supplementary Table S14a** for diplotype/phenotype specific post-test alert example.

[e]Only *HLA-B*15:02* genotype available

[f]Phenytoin or fosphenytoin



..... Dashed lines indicate optional steps

Supplemental Figure S4b. *CYP2C9* Genotype[e] and Phenytoin[f]: Point of Care Clinical Decision Support

[a]See **Supplementary Table S14b** for diplotype/phenotype specific pre-test alert example.

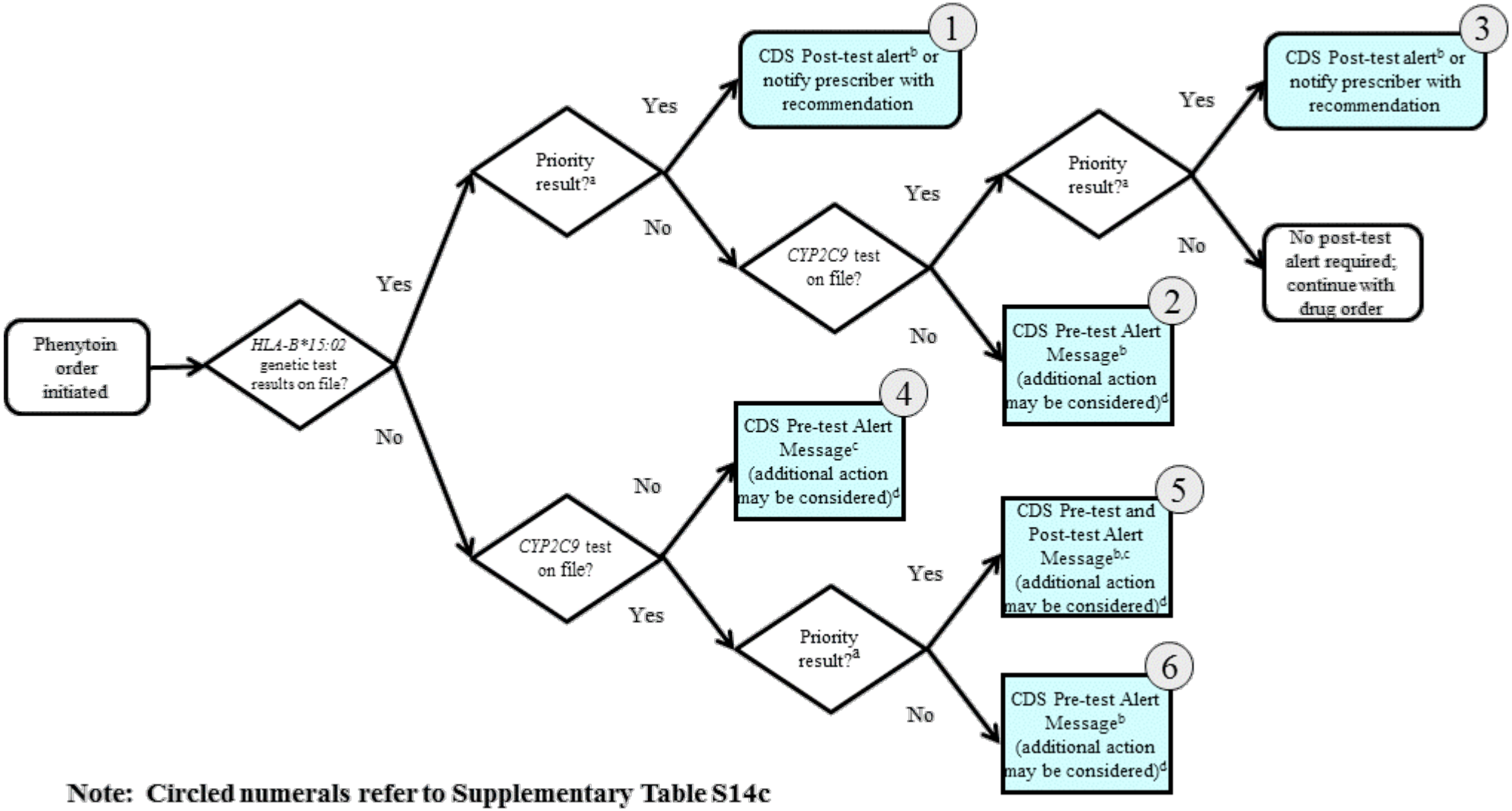
[b]Additional actions may include ordering a pharmacogenetic test, preventing the clinician from ordering the medication or allowing the clinician to cancel out of the alert.

[c]Priority result defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.

[d]See **Supplementary Table S14b** for diplotype/phenotype specific post-test alert example.

[e]Only *CYP2C9* genotype available

[f]Phenytoin or fosphenytoin



Note: Circled numerals refer to Supplementary Table S14c

Supplemental Figure S4c. *HLA-B*15:02* and *CYP2C9* Genotype[e] and Phenytoin[f]: Point of Care Clinical Decision Support[f]

[a]Priority result defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.

[b]See **Supplementary Table S14c** for diplotype/phenotype specific post-test alert example.

[c]See **Supplementary Table S14c** for diplotype/phenotype specific pre-test alert example.

[d]Additional actions may include ordering a pharmacogenetic test, preventing the clinician from ordering the medication or allowing the clinician to cancel out of the alert.

[e]Both *HLA-B*15:02* and *CYP2C9* genotypes are available

[f]Phenytoin or fosphenytoin

Supplemental Table S10. Drug(s) that pertain to this guideline.

Drug or Ingredient	Source	Code Type	Code
Phenytoin	RxNorm	RxCUI	C0031507
Phenytoin	DrugBank	Accession Number	DB00252
Phenytoin	ATC	ATC Code	N03AB02
Phenytoin	PharmGKB	PharmGKB ID	PA450947
Fosphenytoin	RxNorm	RxCUI	C0244656
Fosphenytoin	DrugBank	Accession Number	DB01320
Fosphenytoin	ATC	ATC Code	N03AB
Fosphenytoin	PharmGKB	PharmGKB ID	PA164746820

Supplemental Table S11. Genes that pertain to this guideline.

Gene Symbol	Source	Code Type	Code
HLA-B	HGNC	Symbol	HLA-B
HLA-B	HGNC	HGNC ID	4932
HLA-B	NCBI	Gene ID	3106
HLA-B	Ensembl	Ensembl ID	ENSG00000234745
HLA-B	PharmGKB	PharmGKB ID	PA35056
CYP2C9	HGNC	Symbol	CYP2C9
CYP2C9	HGNC	HGNC ID	2623
CYP2C9	NCBI	Gene ID	1559
CYP2C9	Ensembl	Ensembl ID	ENSG00000138109
CYP2C9	PharmGKB	PharmGKB ID	PA126

Supplemental Table S12a. Translation of HLA-B Genotype Test Results into Interpreted Phenotype[a]

Test Result for *HLA-B*15:02*[b]	Examples of Diplotypes[c]	Interpreted Phentoype[d]
Negative	*X/X*	Normal or reduced risk of phenytoin-related cutaneous ADR
Positive	*X/15:02 or 15:02/15:02*	Increased risk of phenytoin-related cutaneous ADR

[a]This table corresponds to the recommendations in the CPIC guideline manuscript.
[b]Genetic tests for *HLA-B*15:02* are usually reported as positive (patient is a carrier of the *HLA-B*15:02* allele) or negative (patient is not a carrier of the allele).
[c]Reference laboratories may or may not report diplotypes. In these examples, "15:02" refers to the *HLA-B*15:02* allele and "X" refers to any other allele.
[d]The interpreted phenotype is shown for each test result. Refer to the full CPIC guideline for more information.

Supplemental Table S12b. Translation of CYP2C9 Genotype Test Results into Interpreted Phenotype[a]

Assignment of likely CYP2C9 phenotypes based on genotypes		
Interpreted Phenotype[a]	**Genotype Definition**	**Examples of diplotypes**
Extensive metabolizer (normal activity)	An individual carrying 2 normal activity[b] alleles	**1/*1*
Intermediate metabolizer (heterozygote or intermediate activity)	An individual carrying 1 normal activity allele plus one decreased function allele[b]	**1/*3, *1/*2*
Poor metabolizer (homozygous variant, mutant, low, or deficient activity)	An individual carrying 2 decreased function alleles[b]	**2/*2, *3/*3, *2/*3*

[a]This table corresponds to **Table 1** in the CPIC guideline manuscript

[b]Alleles defined in **Supplemental Table S2**.

Supplemental Table S13a. Example Implementation of this Guideline for HLA-B: Pharmacogenetic Genotype/Phenotype Summary Entries[a]

Test Result for *HLA-B*15:02*[b]	**Coded Genotype/Phenotype Summary[c]**	**EHR Priority Result Notation[d]**	**Consultation (Interpretation) Text Provided with Test Result[e]**
Negative	None	Normal/Low Risk	The *HLA-B*15:02* allele, associated with drug-related (e.g., phenytoin/fosphenytoin and carbamazepine) cutaneous adverse drug reaction (ADR), was not detected in this patient. This means that there is no reason not to prescribe these drugs based on the *HLA-B*15:02* genotype. Please refer to the hospital formulary guidelines for specific dosing information. It should be noted that a negative *HLA-B*15:02* result does not absolutely rule out the possibility of some form of ADR.
Positive	*HLA-B*15:02* Carrier	Abnormal/Priority/High Risk	The *HLA-B*15:02* allele, associated with drug-related (e.g. phenytoin and carbamazepine) cutaneous ADR , was detected in this patient. *HLA-B*15:02* positive patients should **NOT** be prescribed certain medications (e.g., phenytoin/fosphenytoin and carbamazepine). Please consult a clinical pharmacist[f] for more specific information about how *HLA-B*15:02* influences drug response.

[a]This table is provided to show examples of how a test result could be translated into discrete fields within an EHR, including a brief interpretation that summarized the result. The information presented here is consistent with the guideline but may need to be adapted to a given EHR's design and capabilities. Various EHRs or organizations may require different terms, and so different options are provided.

[b]Genetic tests for *HLA-B*15:02* are usually reported as positive (patient has the *HLA-B*15:02* allele) or negative (patient does not have the allele).

[c]The coded genotype/phenotype summary is used to store an interpretation of the test result. This is a design decision that may differ among sites.

[d]For this example, a priority result is defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.
[e]The specific wording of the interpretive text may differ among sites.
[f] Pharmacist, pharmacologist, or a clinician with pharmacogenetic expertise/training.

Supplemental Table S13b. Example Implementation of this Guideline for CYP2C9: Pharmacogenetic Genotype/Phenotype Summary Entries[a]

Test Result for *CYP2C9*	Coded Diplotype/ Phenotype Summary[b]	EHR Priority Result Notation[c]	Consultation (Interpretation) Text Provided with Test Result[d]
**1/*1*	None	Normal/Routine/ Low Risk	This result signifies that the patient has two copies of a normal function allele. Based on the genotype result, this patient is predicted to have normal CYP2C9 function (extensive metabolizer). Based only on the CYP2C9 genotype, there is no reason to adjust the dose of most medications that are affected by CYP2C9 (including phenytoin or fosphenytoin). Please consult a clinical pharmacist[e] for more specific information about how CYP2C9 function influences drug dosing.
**1/*2*	CYP2C9 Intermediate Metabolizer	Abnormal/Priority/ High Risk	This result signifies that the patient has one copy of a normal function allele and one copy of a decreased function allele. Based on the genotype result, this patient is predicted to be a CYP2C9 intermediate metabolizer. This patient may be at risk for an adverse response to medications that are affected by CYP2C9 (such as phenytoin or fosphenytoin). Please consult a clinical pharmacist[e] for more specific information about how CYP2C9 intermediate metabolizer status influences drug dosing.
**1/*3*	CYP2C9 Intermediate Metabolizer	Abnormal/Priority/ High Risk	This result signifies that the patient has one copy of a normal function allele and one copy of a decreased function allele. Based on the genotype result, this patient is predicted to be a CYP2C9 intermediate metabolizer. This patient may be at risk for an adverse response to medications that are affected by CYP2C9 (such as phenytoin or fosphenytoin). Please consult a clinical pharmacist[e] for more specific information about how CYP2C9 intermediate metabolizer status influences drug dosing.

**2/*2*	CYP2C9 Poor Metabolizer	Abnormal/Priority/ High Risk	This result signifies that the patient has two copies of a decreased function allele. Based on the genotype result, this patient is predicted to be a CYP2C9 poor metabolizer. Based on the genotype result, this patient is predicted to be a CYP2C9 poor metabolizer. This patient may be at high risk for an adverse response to medications that are affected by CYP2C9 (such as phenytoin or fosphenytoin). Please consult a clinical pharmacist[e] for more specific information about how CYP2C9 intermediate metabolizer status influences drug dosing.
**2/*3*	CYP2C9 Poor Metabolizer	Abnormal/Priority/ High Risk	This result signifies that the patient has two copies of a decreased function allele. Based on the genotype result, this patient is predicted to be a CYP2C9 poor metabolizer. This patient may be at high risk for an adverse response to medications that are affected by CYP2C9 (such as phenytoin or fosphenytoin). Please consult a clinical pharmacist[e] for more specific information about how CYP2C9 intermediate metabolizer status influences drug dosing.
**3/*3*	CYP2C9 Poor Metabolizer	Abnormal/Priority/ High Risk	This result signifies that the patient has two copies of a decreased function allele. Based on the genotype result, this patient is predicted to be a CYP2C9 poor metabolizer. This patient may be at high risk for an adverse response to medications that are affected by CYP2C9 (such as phenytoin or fosphenytoin). Please consult a clinical pharmacist[e] for more specific information about how CYP2C9 intermediate metabolizer status influences drug dosing.

[a]This table is provided to show examples of how a test result could be translated into discrete fields within an EHR, including a brief interpretation that summarized the result. The information presented here is consistent with the guideline but may need to be adapted to a given EHR's design and capabilities. Various EHRs or organizations may require different terms, and so different options are provided. A more comprehensive table of genotype/phenotype EHR entries for possible diplotype combinations of all variants listed in **Supplemental Table S2** is available at PharmGKB http://www.pharmgkb.org/drug/PA450947.

[b]The coded diplotype/phenotype summery is used to store an interpretation of the test result. This is a design decision that may differ among sites.

[c]For this example, a priority result is defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.

[d]The specific wording of the interpretive text may differ among sites.

[e]Pharmacist, pharmacologist, or a clinician with pharmacogenetic expertise/training.

Supplemental Table S14a. Example Implementation of this Guideline: Point of Care Clinical Decision Support

Flow Chart Reference Point (See Supplemental Figure S4a)	CDS Context, Relative to Genetic Testing	Trigger Condition	CDS Alert Text[a]
1	Pre-Test	No *HLA-B*15:02* result on file	*HLA-B*15:02* genotype may be important for phenytoin adverse events. An *HLA-B*15:02* genotype does not appear to have been ordered for this patient. Use of an alternative antiepileptic may be recommended. Please consult a clinical pharmacist[b] for more information.
2	Post-Test	*HLA-B*15:02* Carrier	The *HLA-B*15:02* allele has been detected in this patient. This allele is associated with high risk of cutaneous adverse drug reaction to phenytoin[c]. DO NOT prescribe phenytoin. If patient has previously used phenytoin for longer than 3 months without incidence of cutaneous adverse reactions, reinitiate phenytoin with caution. Please choose an alternate antiepileptic drug. For more information, please consult a clinical pharmacist[b].

[a]The specific wording of the alert text may differ among sites.
[b]Pharmacist, pharmacologist, or a clinician with pharmacogenetic expertise/training.
[c]Phenytoin or fosphenytoin

Supplemental Table S14b. Example Implementation of this Guideline: Point of Care Clinical Decision Support

Flow Chart Reference Point (See Supplemental Figure S4b)	CDS Context, Relative to Genetic Testing	Trigger Condition	CDS Alert Text[a]
1	Pre-Test	No *CYP2C9* result on file	*CYP2C9* diplotype may be important for phenytoin dosing. A *CYP2C9* genotype does not appear to have been ordered for this patient. Use of an alternative dose may be recommended. Please consult a clinical pharmacist[b] for more information.
2	Post-Test	CYP2C9 Intermediate Metabolizer	Based on the genotype result, this patient is predicted to be a CYP2C9 Intermediate Metabolizer and is at increased risk for developing phenytoin[c]-induced toxicities. Consider a 25% reduction of recommended starting maintenance dose. Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response. Please consult a clinical pharmacist[b] for more information.
2	Post-Test	CYP2C9 Poor Metabolizer	Based on the genotype result, this patient is predicted to be a CYP2C9 Poor Metabolizer and is at increased risk for developing phenytoin-induced toxicities. Consider a 50% reduction of recommended starting maintenance dose. Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response. Please consult a clinical pharmacist[b] for more information.

[a]The specific wording of the alert text may differ among sites.
[b]Pharmacist, pharmacologist, or a clinician with pharmacogenetic expertise/training.
[c]Phenytoin or fosphenytoin

Supplemental Table S14c. Example Implementation of this Guideline: Point of Care Clinical Decision Support

Flow Chart Reference Point (See Supplemental Figure S4c)	CDS Context, Relative to Genetic Testing	Trigger Condition (*HLA-B*15:02*)	Trigger Conditions (*CYP2C9*)	CDS Alert Text[a]
1	Post-Test	*HLA-B*15:02* Carrier	Not relevant	The *HLA-B*15:02* allele has been detected in this patient. This allele is associated with high risk of cutaneous adverse drug reaction to phenytoin[c]. DO NOT prescribe phenytoin. Please choose an alternate antiepileptic drug. If patient has previously used phenytoin for longer than 3 months without incidence of cutaneous adverse reactions, reinitiate phenytoin with caution. For more information, please consult a clinical pharmacist[b].
2	Pre-Test	*HLA-B*15:02* non-carrier	No *CYP2C9* result on file	*CYP2C9* diplotype may be important for phenytoin dosing. A *CYP2C9* genotype does not appear to have been ordered for this patient. Use of an alternative dose may be recommended. Please consult a clinical pharmacist[b] for more information.
3	Post-Test	*HLA-B*15:02* non-carrier	CYP2C9 Intermediate Metabolizer	Based on the genotype result, this patient is predicted to be a CYP2C9 Intermediate Metabolizer and is at increased risk for developing phenytoin[c]-induced toxicities. Consider a 25% reduction of recommended starting maintenance dose. Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response. Please consult a clinical pharmacist[b] for more information.

3	Post-Test	*HLA-B*15:02* non-carrier	CYP2C9 Poor Metabolizer	Based on the genotype result, this patient is predicted to be a CYP2C9 Poor Metabolizer and is at increased risk for developing phenytoin-induced toxicities. Consider a 50% reduction of recommended starting maintenance dose. Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response. Please consult a clinical pharmacist[b] for more information.
4	Pre-Test	No *HLA-B*15:02* result on file	No *CYP2C9* result on file	*HLA-B*15:02* and *CYP2C9* genotype may be important for phenytoin adverse events. Neither an *HLA-B*15:02* nor a *CYP2C9* genotype appears to have been ordered for this patient. Use of an alternative antiepileptic or dose reduction may be recommended. Please consult a clinical pharmacist[b] for more information.
5	Pre/Post-Test	No *HLA-B*15:02* result on file	CYP2C9 Intermediate Metabolizer	*HLA-B*15:02* and *CYP2C9* genotype may be important for phenytoin adverse events. An *HLA-B*15:02* genotype does not appear to have been ordered for this patient. If the patient is an *HLA-B*15:02* carrier, use of an alternative antiepileptic may be recommended. A *CYP2C9* genotype is on file for this patient. This patient is predicted to be a CYP2C9 Intermediate Metabolizer and is at increased risk for developing phenytoin[c]-induced toxicities. If this patient is an *HLA-B*15:02* non-carrier, consider a 25% reduction of recommended starting maintenance dose. Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response. Please consult a clinical pharmacist[b] for more information.

5	Pre/Post-Test	No *HLA-B*15:02* result on file	CYP2C9 Poor Metabolizer	*HLA-B*15:02* and *CYP2C9* genotype may be important for phenytoin adverse events. An *HLA-B*15:02* genotype does not appear to have been ordered for this patient. If the patient is an *HLA-B*15:02* carrier, use of an alternative antiepileptic may be recommended. A *CYP2C9* genotype is on file for this patient. Based on the genotype result, this patient is predicted to be a CYP2C9 Poor Metabolizer and is at increased risk for developing phenytoin-induced toxicities. If this patient is an *HLA-B*15:02* non-carrier, consider a 50% reduction of recommended starting maintenance dose. Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response. Please consult a clinical pharmacist[b] for more information.
6	Pre-Test	No *HLA-B*15:02* result on file	CYP2C9 Extensive Metabolizer	*HLA-B*15:02* genotype may be important for phenytoin adverse events. An *HLA-B*15:02* genotype does not appear to have been ordered for this patient. Use of an alternative antiepileptic may be recommended. Please consult a clinical pharmacist[b] for more information.

[a]The specific wording of the alert text may differ among sites.
[b]Pharmacist, pharmacologist, or a clinician with pharmacogenetic expertise/training.
[c]Phenytoin or fosphenytoin

References

1. Genomes Project, C., et al., *An integrated map of genetic variation from 1,092 human genomes.* Nature, 2012. **491**(7422): p. 56-65.
2. International Warfarin Pharmacogenetics, C., et al., *Estimation of the warfarin dose with clinical and pharmacogenetic data.* N Engl J Med, 2009. **360**(8): p. 753-64.
3. Pichler, W.J., et al., *Pharmacological interaction of drugs with immune receptors: the p-i concept.* Allergol Int, 2006. **55**(1): p. 17-25.
4. Wei, C.Y., et al., *Direct interaction between HLA-B and carbamazepine activates T cells in patients with Stevens-Johnson syndrome.* J Allergy Clin Immunol, 2012.
5. Illing, P.T., et al., *Immune self-reactivity triggered by drug-modified HLA-peptide repertoire.* Nature, 2012. **486**(7404): p. 554-8.
6. Lin, L.C., et al., *Oxcarbazepine-induced Stevens-Johnson syndrome: a case report.* Kaohsiung J Med Sci, 2009. **25**(2): p. 82-6.
7. Shankarkumar, U., K.N. Shah, and K. Ghosh, *Letter: HLA B*1502 allele association with oxcarbamazepine-induced skin reactions in epilepsy patient from India.* Epilepsia, 2009. **50**(7): p. 1837-8.
8. Chen, Y.C., C.Y. Chu, and C.H. Hsiao, *Oxcarbazepine-induced Stevens-Johnson syndrome in a patient with HLA-B*1502 genotype.* J Eur Acad Dermatol Venereol, 2009. **23**(6): p. 702-3.
9. Hu, F.Y., et al., *Pilot association study of oxcarbazepine-induced mild cutaneous adverse reactions with HLA-B*1502 allele in Chinese Han population.* Seizure, 2011. **20**(2): p. 160-2.
10. An, D.M., et al., *Association study of lamotrigine-induced cutaneous adverse reactions and HLA-B*1502 in a Han Chinese population.* Epilepsy Research, 2010. **92**(2-3): p. 226-30.
11. Hung, S.I., et al., *Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese.* Pharmacogenomics, 2010. **11**(3): p. 349-56.
12. Shi, Y.W., et al., *Hla-B alleles and lamotrigine-induced cutaneous adverse drug reactions in the Han Chinese population.* Basic Clin Pharmacol Toxicol, 2011. **109**(1): p. 42-6.
13. Cheung, Y.K., et al., *HLA-B alleles associated with severe cutaneous reactions to antiepileptic drugs in Han Chinese.* Epilepsia, 2013.
14. Li, L.J., et al., *Predictive markers for carbamazepine and lamotrigine-induced maculopapular exanthema in Han Chinese.* Epilepsy Res, 2013. **106**(1-2): p. 296-300.
15. Leckband, S.G., et al., *Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for HLA-B Genotype and Carbamazepine Dosing.* Clin Pharmacol Ther, 2013.
16. Dickinson, R.G., et al., *Extent of urinary excretion of p-hydroxyphenytoin in healthy subjects given phenytoin.* Ther. Drug Monit., 1985. **7**(3): p. 283-9.
17. Butler, T.C., et al., *Studies of the metabolism of 5,5-diphenylhydantoin relating principally to the stereoselectivity of the hydroxylation reactions in man and the dog.* J. Pharmacol. Exp. Ther., 1976. **199**(1): p. 82-92.
18. Argikar, U.A., et al., *Paradoxical urinary phenytoin metabolite (S)/(R) ratios in CYP2C19*1/*2 patients.* Epilepsy Res., 2006. **71**(1): p. 54-63.
19. Bajpai, M., et al., *Roles of cytochrome P4502C9 and cytochrome P4502C19 in the stereoselective metabolism of phenytoin to its major metabolite.* Drug Metab. Dispos., 1996. **24**(12): p. 1401-3.
20. Giancarlo, G.M., et al., *Relative contributions of CYP2C9 and 2C19 to phenytoin 4-hydroxylation in vitro: inhibition by sulfaphenazole, omeprazole, and ticlopidine.* Eur. J. Clin. Pharmacol., 2001. **57**(1): p. 31-6.

21. Glazko, A.J., et al., *Metabolic disposition of diphenylhydantoin in normal human subjects following intravenous administration.* Clin. Pharmacol. Ther., 1969. **10**(4): p. 498-504.
22. Eriksson, K., T. Keranen, and R. Kalviainen, *Fosphenytoin.* Expert Opin Drug Metab Toxicol, 2009. **5**(6): p. 695-701.
23. Halling Linder, C., et al., *Isozyme profile and tissue-origin of alkaline phosphatases in mouse serum.* Bone, 2013. **53**(2): p. 399-408.
24. Valdes, R., D.A. Payne, and M.W. Linder, *Laboratory analysis and application of pharmacogenetics to clinical practice.*, 2010: Washington, DC, NACB.
25. Shuldiner, A.R., et al., *The Pharmacogenomics Research Network Translational Pharmacogenetics Program: overcoming challenges of real-world implementation.* Clin Pharmacol Ther, 2013. **94**(2): p. 207-10.
26. Wilke, R.A., et al., *The emerging role of electronic medical records in pharmacogenomics.* Clin Pharmacol Ther, 2011. **89**(3): p. 379-86.
27. Peterson, J.F., et al., *Electronic health record design and implementation for pharmacogenomics: a local perspective.* Genet Med, 2013. **15**(10): p. 833-41.
28. Gottesman, O., et al., *The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future.* Genet Med, 2013. **15**(10): p. 761-71.
29. Kullo, I.J., et al., *Leveraging the electronic health record to implement genomic medicine.* Genet Med, 2013. **15**(4): p. 270-1.
30. Martin, M.A., et al., *Clinical pharmacogenetics implementation consortium guidelines for hla-B genotype and abacavir dosing: 2014 update.* Clin Pharmacol Ther, 2014. **95**(5): p. 499-500.
31. Hicks, J.K., et al., *A clinician-driven automated system for integration of pharmacogenetic interpretations into an electronic medical record.* Clin Pharmacol Ther, 2012. **92**(5): p. 563-6.
32. Bell, G.C., et al., *Development and use of active clinical decision support for preemptive pharmacogenomics.* J Am Med Inform Assoc, 2013.
33. Pulley, J.M., et al., *Operational implementation of prospective genotyping for personalized medicine: the design of the Vanderbilt PREDICT project.* Clin Pharmacol Ther, 2012. **92**(1): p. 87-95.
34. Niinuma, Y., et al., *Functional characterization of 32 CYP2C9 allelic variants.* Pharmacogenomics J, 2013.
35. Blaisdell, J., et al., *Discovery of new potentially defective alleles of human CYP2C9.* Pharmacogenetics, 2004. **14**(8): p. 527-37.
36. Rettie, A.E., et al., *A common genetic basis for idiosyncratic toxicity of warfarin and phenytoin.* Epilepsy Res, 1999. **35**(3): p. 253-5.
37. Guo, Y., et al., *Catalytic activities of human cytochrome P450 2C9*1, 2C9*3 and 2C9*13.* Xenobiotica, 2005. **35**(9): p. 853-61.
38. Takanashi, K., et al., *CYP2C9 Ile359 and Leu359 variants: enzyme kinetic study with seven substrates.* Pharmacogenetics, 2000. **10**(2): p. 95-104.
39. DeLozier, T.C., et al., *Functional characterization of novel allelic variants of CYP2C9 recently discovered in southeast Asians.* J Pharmacol Exp Ther, 2005. **315**(3): p. 1085-90.
40. Dickmann, L.J., et al., *Identification and functional characterization of a new CYP2C9 variant (CYP2C9*5) expressed among African Americans.* Mol Pharmacol, 2001. **60**(2): p. 382-7.
41. Gonzalez-Galarza, F.F., et al., *Allele frequency net: a database and online repository for immune gene frequencies in worldwide populations.* Nucleic Acids Res, 2011. **39**(Database issue): p. D913-9.
42. Piancatelli, D., et al., *Human leukocyte antigen-A, -B, and -Cw polymorphism in a Berber population from North Morocco using sequence-based typing.* Tissue Antigens, 2004. **63**(2): p. 158-72.

43. Canossi, A., et al., *Correlation between genetic HLA class I and II polymorphisms and anthropological aspects in the Chaouya population from Morocco (Arabic speaking).* Tissue Antigens, 2010. **76**(3): p. 177-93.
44. Williams, F., et al., *Analysis of the distribution of HLA-B alleles in populations from five continents.* Hum Immunol, 2001. **62**(6): p. 645-50.
45. Barquera, R., et al., *HLA class I and class II haplotypes in admixed families from several regions of Mexico.* Mol Immunol, 2008. **45**(4): p. 1171-8.
46. Liang, Y., et al., *Targeted agents for chronic myelogenous leukemia: will that be the end of allogeneic bone marrow transplantation for that disease?* Biol Blood Marrow Transplant, 2010. **16**(6): p. 848-53.
47. Yang, G., et al., *HLA-A, -B, and -DRB1 polymorphism defined by sequence-based typing of the Han population in Northern China.* Tissue Antigens, 2006. **67**(2): p. 146-52.
48. Trachtenberg, E., et al., *HLA class I (A, B, C) and class II (DRB1, DQA1, DQB1, DPB1) alleles and haplotypes in the Han from southern China.* Tissue Antigens, 2007. **70**(6): p. 455-63.
49. Chen, S., et al., *Origin of Tibeto-Burman speakers: evidence from HLA allele distribution in Lisu and Nu inhabiting Yunnan of China.* Hum Immunol, 2007. **68**(6): p. 550-9.
50. Ogata, S., et al., *Polymorphisms of human leucocyte antigen genes in Maonan people in China.* Tissue Antigens, 2007. **69**(2): p. 154-60.
51. Chen, S., et al., *Human leukocyte antigen class I polymorphism in Miao, Bouyei, and Shui ethnic minorities of Guizhou, China.* Hum Immunol, 2007. **68**(11): p. 928-33.
52. Hong, W., et al., *HLA class I polymorphism in Mongolian and Hui ethnic groups from Northern China.* Hum Immunol, 2007. **68**(5): p. 439-48.
53. Hong, W., et al., *Distributions of HLA class I alleles and haplotypes in Northern Han Chinese.* Tissue Antigens, 2005. **66**(4): p. 297-304.
54. Shi, L., et al., *Genetic link among Hani, Bulang and other Southeast Asian populations: evidence from HLA -A, -B, -C, -DRB1 genes and haplotypes distribution.* Int J Immunogenet, 2010. **37**(6): p. 467-75.
55. Yao, Y., et al., *Distribution of HLA-A, -B, -Cw, and -DRB1 alleles and haplotypes in an isolated Han population in Southwest China.* Tissue Antigens, 2009. **73**(6): p. 561-8.
56. Shi, L., et al., *Distribution of HLA alleles and haplotypes in Jinuo and Wa populations in Southwest China.* Hum Immunol, 2008. **69**(1): p. 58-65.
57. Saito, S., et al., *Allele frequencies and haplotypic associations defined by allelic DNA typing at HLA class I and class II loci in the Japanese population.* Tissue Antigens, 2000. **56**(6): p. 522-9.
58. Itoh, Y., et al., *High-throughput DNA typing of HLA-A, -B, -C, and -DRB1 loci by a PCR-SSOP-Luminex method in the Japanese population.* Immunogenetics, 2005. **57**(10): p. 717-29.
59. Jinam, T.A., et al., *Molecular analysis of HLA Class I and Class II genes in four indigenous Malaysian populations.* Tissue Antigens, 2010. **75**(2): p. 151-8.
60. Middleton, D., et al., *Analysis of the distribution of HLA-A alleles in populations from five continents.* Hum Immunol, 2000. **61**(10): p. 1048-52.
61. Lee, K.W., et al., *Allelic and haplotypic diversity of HLA-A, -B, -C, -DRB1, and -DQB1 genes in the Korean population.* Tissue Antigens, 2005. **65**(5): p. 437-47.
62. Yoon, J.H., et al., *HLA-A, -B, -DRB1 allele frequencies and haplotypic association from DNA typing data of 7096 Korean cord blood units.* Tissue Antigens, 2010. **75**(2): p. 170-3.
63. Yang, K.L., et al., *High-resolution human leukocyte antigen (HLA) haplotypes and linkage disequilibrium of HLA-B and -C and HLA-DRB1 and -DQB1 alleles in a Taiwanese population.* Hum Immunol, 2009. **70**(4): p. 269-76.
64. Yu, K.J., et al., *Association of human leukocyte antigens with nasopharyngeal carcinoma in high-risk multiplex families in Taiwan.* Hum Immunol, 2009. **70**(11): p. 910-4.

65. Wen, S.H., M.J. Lai, and K.L. Yang, *Human leukocyte antigen-A, -B, and -DRB1 haplotypes of cord blood units in the Tzu Chi Taiwan Cord Blood Bank.* Hum Immunol, 2008. **69**(7): p. 430-6.
66. Romphruk, A.V., et al., *HLA class I and II alleles and haplotypes in ethnic Northeast Thais.* Tissue Antigens, 2010. **75**(6): p. 701-11.
67. Ivanova, M., et al., *HLA polymorphism in Bulgarians defined by high-resolution typing methods in comparison with other populations.* Tissue Antigens, 2002. **60**(6): p. 496-504.
68. Schmidt, A.H., et al., *Estimation of high-resolution HLA-A, -B, -C, -DRB1 allele and haplotype frequencies based on 8862 German stem cell donors and implications for strategic donor registry planning.* Hum Immunol, 2009. **70**(11): p. 895-902.
69. Williams, F., et al., *Allele resolution of HLA-A using oligonucleotide probes in a two-stage typing strategy.* Tissue Antigens, 1999. **54**(1): p. 59-68.
70. Middleton, D., et al., *Frequency of HLA-B alleles in a Caucasoid population determined by a two-stage PCR-SSOP typing strategy.* Hum Immunol, 2000. **61**(12): p. 1285-97.
71. Schmidt, A.H., et al., *High-resolution human leukocyte antigen allele and haplotype frequencies of the Polish population based on 20,653 stem cell donors.* Hum Immunol, 2011. **72**(7): p. 558-65.
72. Valluri, V., et al., *Frequencies of HLA-A, HLA-B, HLA-DR, and HLA-DQ phenotypes in the United Arab Emirates population.* Tissue Antigens, 2005. **66**(2): p. 107-13.
73. Yuliwulandari, R., et al., *Polymorphisms of HLA genes in Western Javanese (Indonesia): close affinities to Southeast Asian populations.* Tissue Antigens, 2009. **73**(1): p. 46-53.
74. Shankarkumar, U., et al., *Human leucocyte antigen class II DRB1 and DQB1 associations in human immunodeficiency virus-infected patients of Mumbai, India.* Int J Immunogenet, 2010. **37**(3): p. 199-204.
75. Rajalingam, R., et al., *Distinctive KIR and HLA diversity in a panel of north Indian Hindus.* Immunogenetics, 2002. **53**(12): p. 1009-19.
76. Liu, Y., et al., *Decreased warfarin clearance associated with the CYP2C9 R150H (*8) polymorphism.* Clin Pharmacol Ther, 2012. **91**(4): p. 660-5.
77. Man, C.B., et al., *Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese.* Epilepsia, 2007. **48**(5): p. 1015-8.
78. Neuman, M.G., et al., *Genetic and immune predictors for hypersensitivity syndrome to antiepileptic drugs.* Transl Res, 2012. **159**(5): p. 397-406.
79. Locharernkul, C., et al., *Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population.* Epilepsia, 2008. **49**(12): p. 2087-91.
80. Min, F.L., et al., *HLA-B*1502 genotyping in two Chinese patients with phenytoin-induced Stevens-Johnson syndrome.* Epilepsy Behav, 2011. **20**(2): p. 390-1.
81. Argikar, U.A., et al., *Paradoxical urinary phenytoin metabolite (S)/(R) ratios in CYP2C19*1/*2 patients.* Epilepsy Res, 2006. **71**(1): p. 54-63.
82. Aynacioglu, A.S., et al., *Frequency of cytochrome P450 CYP2C9 variants in a Turkish population and functional relevance for phenytoin.* Br J Clin Pharmacol, 1999. **48**(3): p. 409-15.
83. Kerb, R., et al., *The predictive value of MDR1, CYP2C9, and CYP2C19 polymorphisms for phenytoin plasma levels.* Pharmacogenomics J, 2001. **1**(3): p. 204-10.
84. Caraco, Y., M. Muszkat, and A.J. Wood, *Phenytoin metabolic ratio: a putative marker of CYP2C9 activity in vivo.* Pharmacogenetics, 2001. **11**(7): p. 587-96.
85. Odani, A., et al., *Genetic polymorphism of the CYP2C subfamily and its effect on the pharmacokinetics of phenytoin in Japanese patients with epilepsy.* Clin Pharmacol Ther, 1997. **62**(3): p. 287-92.
86. Ramasamy, K., et al., *Influence of CYP2C9 genetic polymorphism and undernourishment on plasma-free phenytoin concentrations in epileptic patients.* Ther Drug Monit, 2010. **32**(6): p. 762-6.

87. Soga, Y., et al., *CYP2C polymorphisms, phenytoin metabolism and gingival overgrowth in epileptic subjects.* Life Sci, 2004. **74**(7): p. 827-34.
88. Phabphal, K., et al., *The association between CYP 2C9 polymorphism and bone health.* Seizure, 2013. **22**(9): p. 766-71.
89. Phabphal, K., et al., *Role of CYP2C9 polymorphism in phenytoin-related metabolic abnormalities and subclinical atherosclerosis in young adult epileptic patients.* Seizure, 2013. **22**(2): p. 103-8.
90. Hung, C.C., et al., *Dosage recommendation of phenytoin for patients with epilepsy with different CYP2C9/CYP2C19 polymorphisms.* Ther Drug Monit, 2004. **26**(5): p. 534-40.
91. Mamiya, K., et al., *The effects of genetic polymorphisms of CYP2C9 and CYP2C19 on phenytoin metabolism in Japanese adult patients with epilepsy: studies in stereoselective hydroxylation and population pharmacokinetics.* Epilepsia, 1998. **39**(12): p. 1317-23.
92. Yamamoto, Y., et al., *[Development of rapid genotyping methods for single nucleotide polymorphisms of cytochrome P450 2C9 (CYP2C9) and cytochrome P450 2C19 (CYP2C19) and their clinical application in pediatric patients with epilepsy].* Yakugaku Zasshi, 2011. **131**(5): p. 809-15.
93. Hennessy, S., et al., *CYP2C9, CYP2C19, and ABCB1 genotype and hospitalization for phenytoin toxicity.* J Clin Pharmacol, 2009. **49**(12): p. 1483-7.
94. Kesavan, R., S.K. Narayan, and C. Adithan, *Influence of CYP2C9 and CYP2C19 genetic polymorphisms on phenytoin-induced neurological toxicity in Indian epileptic patients.* Eur J Clin Pharmacol, 2010. **66**(7): p. 689-96.
95. Lee, A.Y., et al., *Genetic polymorphism of cytochrome P450 2C9 in diphenylhydantoin-induced cutaneous adverse drug reactions.* Eur J Clin Pharmacol, 2004. **60**(3): p. 155-9.
96. Twardowschy, C.A., et al., *The role of CYP2C9 polymorphisms in phenytoin-related cerebellar atrophy.* Seizure, 2013. **22**(3): p. 194-7.
97. Depondt, C., et al., *A candidate gene study of antiepileptic drug tolerability and efficacy identifies an association of CYP2C9 variants with phenytoin toxicity.* Eur J Neurol, 2011. **18**(9): p. 1159-64.
98. Thakkar, A.N., et al., *Association of CYP2C9 polymorphisms with phenytoin toxicity in Indian patients.* Neurol India, 2012. **60**(6): p. 577-80.
99. Ramasamy, K., et al., *Severe phenytoin toxicity in a CYP2C9*3*3 homozygous mutant from India.* Neurol India, 2007. **55**(4): p. 408-9.
100. Babu, S.P., et al., *Cytochrome P450 2C9 gene polymorphism in phenytoin induced gingival enlargement: A case report.* J Pharm Bioallied Sci, 2013. **5**(3): p. 237-9.
101. Citerio, G., et al., *Severe intoxication after phenytoin infusion: a preventable pharmacogenetic adverse reaction.* Neurology, 2003. **60**(8): p. 1395-6.
102. McCluggage, L.K., S.A. Voils, and M.R. Bullock, *Phenytoin toxicity due to genetic polymorphism.* Neurocrit Care, 2009. **10**(2): p. 222-4.
103. Ninomiya, H., et al., *Genetic polymorphism of the CYP2C subfamily and excessive serum phenytoin concentration with central nervous system intoxication.* Ther Drug Monit, 2000. **22**(2): p. 230-2.
104. Dorado, P., et al., *Neurological toxicity after phenytoin infusion in a pediatric patient with epilepsy: influence of CYP2C9, CYP2C19 and ABCB1 genetic polymorphisms.* Pharmacogenomics J, 2012.
105. Tate, S.K., et al., *Genetic predictors of the maximum doses patients receive during clinical use of the anti-epileptic drugs carbamazepine and phenytoin.* Proc Natl Acad Sci U S A, 2005. **102**(15): p. 5507-12.
106. van der Weide, J., et al., *The effect of genetic polymorphism of cytochrome P450 CYP2C9 on phenytoin dose requirement.* Pharmacogenetics, 2001. **11**(4): p. 287-91.

107. Hung, C.C., et al., *Effects of polymorphisms in six candidate genes on phenytoin maintenance therapy in Han Chinese patients.* Pharmacogenomics, 2012. **13**(12): p. 1339-49.
108. Allabi, A.C., J.L. Gala, and Y. Horsmans, *CYP2C9, CYP2C19, ABCB1 (MDR1) genetic polymorphisms and phenytoin metabolism in a Black Beninese population.* Pharmacogenet Genomics, 2005. **15**(11): p. 779-86.
109. Twardowschy, C.A., et al., *CYP2C9 polymorphism in patients with epilepsy: genotypic frequency analyzes and phenytoin adverse reactions correlation.* Arq Neuropsiquiatr, 2011. **69**(2A): p. 153-8.