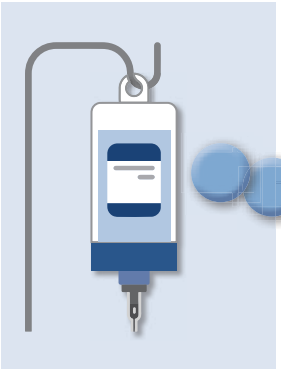
U.S. Department of Veterans Affairs
Veterans Health Administration
PBM Academic Detailing Services

Applying Pharmacogenomic (PGx) Testing to Phenytoin and Fosphenytoin Pharmacotherapy

HLA-B and CYP2C9 variations and increased risk

Individuals with certain *HLA-B* and *CYP2C9* variations are at an increased risk of experiencing **Stevens-Johnson syndrome (SJS)**, **toxic epidermal necrosis (TEN)**, and **central nervous system (CNS) toxicity** on **phenytoin/fosphenytoin** therapy compared to those without these variations.[1-6]

Phenytoin (oral) and fosphenytoin (intravenous prodrug)



- Used in the management and treatment of **epilepsy**, **generalized bilateral tonic clonic seizures**, **focal seizures**, and **status epilepticus**.
- Highly **allergenic** and associated with **multiple dose-related and idiosyncratic adverse effects** influenced by variation of genes that encode **HLA** and the **cytochrome P450 2C9 (*CYP2C9*) enzyme**.[1,3]

Adverse effects[3,7,8]

- **CNS** toxicity (sedation, ataxia, dizziness, nystagmus, nausea, cognitive impairment)
- **Severe Cutaneous Adverse Reactions (SCARs)** (rash ranging from mild eruptions to SJS/TEN)
- **Hematologic** toxicity (leukopenia or pancytopenia)
- **Hepatic** toxicity (with rash)
- **Suicidal ideation/behavior**

See the **Resources section** for more helpful links.

Refer to the National Pharmacogenomics SharePoint for PGx testing availability within Veterans Affairs (VA) and information regarding send out HLA testing to laboratory vendors. VA PGx tests take 10 to 20 days for results to become available.

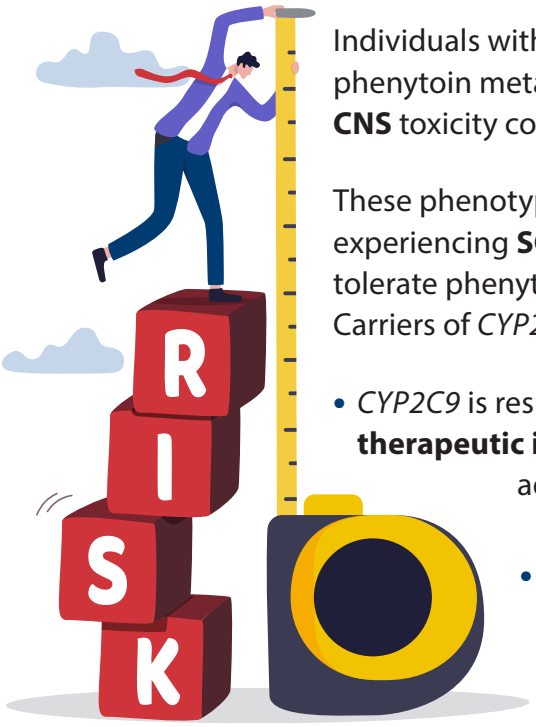
Prior to initiating *non-urgent phenytoin/fosphenytoin pharmacotherapy, order PGx testing to inform risk of HLA and CYP2C9-related adverse effects.*

HLA-B*15:02

Refer to the PGx Testing & HLA Associated Adverse Drug Reactions clinician guide for information about other HLA impacted medications.

HLA genes are highly polymorphic and function to process and present antigens to the immune system.[3,8,9] Individuals experiencing SJS/TEN on phenytoin/fosphenytoin therapy are **five times more likely** to carry the **HLA-B*15:02** variation compared to those not experiencing SCARs. These SCARs have mortality rates as high as 30%.[1,2,4,8-12]

- If *HLA-B*15:02* positive and on therapy for **≥3 months without incidence of SCARs**, cautiously consider future use. The latency period for drug induced SJS/TEN with continuous dosing and adherence is 4 to 28 days with most **cases occurring within 3 months of dosing**.[3]
- **Carbamazepine/oxcarbazepine** should be **avoided** as alternatives to phenytoin/fosphenytoin due to the strong association between SJS/TEN and *HLA-B*15:02*.
- While the strength of the association with **eslicarbazepine**, **lamotrigine**, and **phenobarbital** is not well defined, they also have evidence linking **SJS/TEN** with the *HLA-B*15:02* allele.[1,3]
- Previous tolerance of phenytoin is ***not*** indicative of tolerance to other aromatic anticonvulsants.[3] Refer to the American Academy of Neurology practice guidelines for treatment alternatives.
- An *HLA-B*15:02* negative test indicates normal risk of phenytoin-induced SCARs and provides additional information to optimize safe medication therapy. However, a negative result **does not eliminate the risk of phenytoin induced SJS/TEN**. Patients should be carefully monitored according to standard practice.[3]



CYP2C9

Individuals with *CYP2C9* phenotypes associated with clinically significant reduced phenytoin metabolism (activity score from 0 to 1) may be **twice as likely** to develop **CNS** toxicity compared to those with normal or intermediate function.[13]

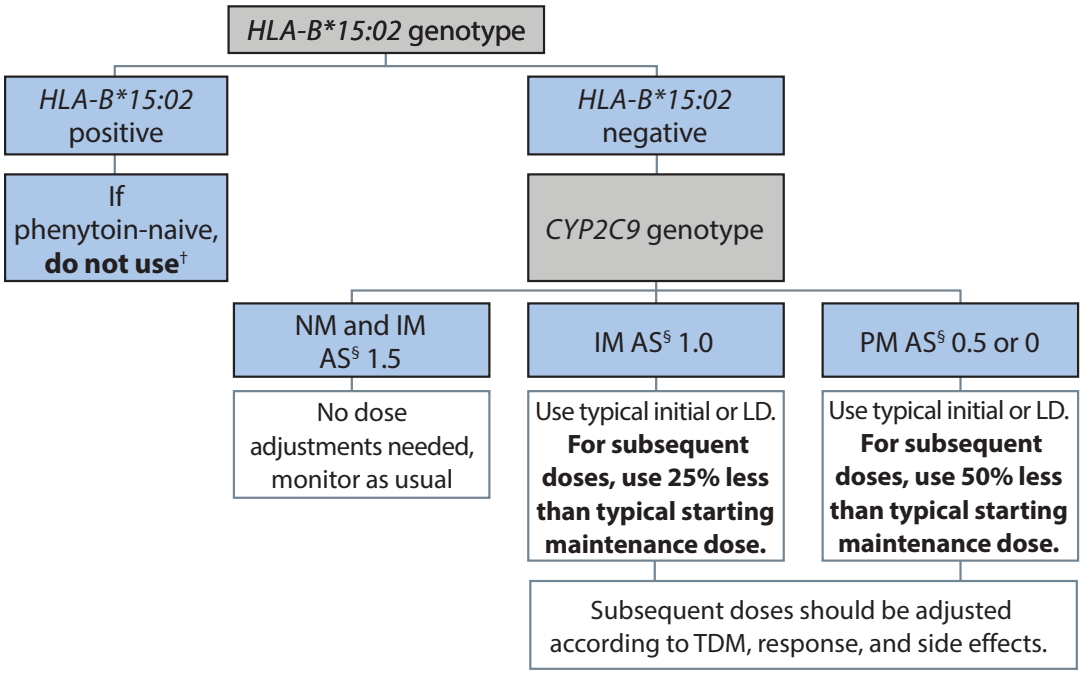
These phenotypes are **11 times more likely** to be identified in individuals experiencing **SCARs** when given standard doses compared to individuals who tolerate phenytoin therapy. This strong association is independent of *HLA-B* status. Carriers of *CYP2C9*3*, a loss of function variant, may be at particularly elevated risk.[1,3-6]

- *CYP2C9* is responsible for 90% of phenytoin's metabolism and its **narrow therapeutic index**.[3,13,14] Therapy requires weight, age, and sex-based dose adjustments in addition to therapeutic drug monitoring in some clinical scenarios.[3,14]
- *CYP2C9* polymorphisms increase phenytoin blood concentrations and the risk of toxicities.[3,8,13]

Table 1. Clinical Pharmacogenomics Implementation Consortium (CPIC) *CYP2C9* phenotype implications[3]

CYP2C9 Phenotype	Activity Score (AS)	Implication
Normal	2	Normal metabolism
Intermediate	1.5	Slightly reduced metabolism that does not appear to translate into increased side effects
Intermediate	1.0	Reduced metabolism results in higher plasma concentrations and **increased probability of toxicities**
Poor	0.5 or 0	

Figure 1. CPIC pharmacotherapy algorithm for phenytoin/fosphenytoin based on *CYP2C9* and HLA-B genotype[3]



See figure 1 for information related to continuation of †existing therapy and §activity score. The extent of dose reduction beyond the first maintenance dose needed to prevent phenytoin/fosphenytoin related toxicities is uncertain. Genotype-guided therapy should not replace TDM.
AS = activity score;
IM = intermediate metabolizer;
LD = loading dose;
NM = normal metabolizer;
PM = poor metabolizer;
TDM = therapeutic drug monitoring

Table 2. Food & Drug Administration (FDA) labeling and recommendations for phenytoin/fosphenytoin[7,15,16]

Implicated gene	*HLA-B*15:02*	*CYP2C9*
FDA prescribing information	**Warnings and Precautions** Studies have demonstrated a strong association between HLA-B and *CYP2C9* allele variants and risk of SJS/TEN. Genotyping is not a substitute for clinical vigilance and patient management.	
Therapeutic management recommendations	Patients positive for ***HLA-B*15:02*** may be at **increased risk of SJS/TEN**.	**Intermediate and poor metabolizers** may have higher systemic concentrations and risk of **CNS toxicity**. Refer to FDA labeling for specific dosing recommendations.
	Consider **avoiding** phenytoin/fosphenytoin as an alternative to CBZ in patients who are positive for *HLA-B*15:02*.	Carriers of ***CYP2C9*3*** alleles may be at **increased risk of SCARs**. Consider **avoiding phenytoin/fosphenytoin as alternatives** to CBZ in patients who are CYP2C9*3 carriers.

CBZ = carbamazepine

A note on ancestry

While more prevalent in certain populations, HLA variations have been seen at some frequency across most major ancestral groups.[3] **PGx testing is the only way to confirm the presence of a variation and risk of associated adverse events**.

Clinical Pharmacist Practitioners (CPP)

PGx CPPs are Advanced Practice Providers who are highly trained members of the healthcare team with additional education or experience in PGx. Consult services are available in the electronic medical record orders package for providers to request CPP assistance. CPPs can evaluate pharmacotherapy based on the PGx test results, provide recommendations, and contact patients for follow-up education.

For more information

RESOURCES:

- American Academy of Neurology Clinical Practice Guidelines (https://www.aan.com/practice/guidelines)
- PGx Testing & HLA Associated Adverse Drug Reactions clinician guide (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5733150/)
- National Pharmacogenomics SharePoint (http://tinyurl.com/jztks5n8)
- Send out HLA testing (https://dvagov.sharepoint.com/sites/vhapgx/SitePages/Genes-in-the-Latest-PGx-Panel-Test.aspx)

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