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

Pharmacogenomic (PGx) Testing & Human Leukocyte Antigen (HLA) Associated Adverse Drug Reactions

Using PGx testing to improve safety

Variations in HLA gene expression can lead to rare but severe cutaneous adverse drug reactions (SCARs) that are associated with **mortality rates as high as 30%**.[1,2]

PGx testing confirms the presence of HLA genetic variation.

Table 1. HLA nomenclature[3,4]

Example: HLA-B*15:02	
Name	**Description**
HLA	Region on chromosome 6
B	A particular HLA gene in this region
15	The allele group
02	The specific HLA allele

Table 2. Drug-hypersensitivity SCARs associated with HLA genetic variations[1,4-6]

SCARs	Reaction description
Stevens Johnson Syndrome (SJS)	Epidermal detachment affecting up to 10% of the body surface area (BSA)
Toxic Epidermal Necrosis (TEN)	Epidermal detachment affecting >30% of the BSA
Maculopapular exanthema (MPE)	Milder reaction with presence of a rash
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Generalized MPE with systemic manifestations
Acute Generalized Exanthema Pustulosis (AGEP)	Acute widespread pustular eruption with neutrophilia and fever

There is SJS/TEN overlap with 10 to 30% of BSA affected.

- HLA genes **code for more than 200 proteins**, are among the most **highly polymorphic** in the human genome and are also on the surfaces of almost all cells to present antigens to the immune system.[3,4]
- If derived from a pathogen or transplanted tissue, the antigen may be identified as "**non-self**", triggering an immune response.[4]
- **Variations in HLA gene expression** can cause certain medications to be identified as "**non-self**" and trigger a **hypersensitivity reaction** presenting as **SCARs**.[1,4,5]
- Unlike other PGx tests, the HLA allele has no impact on pharmacodynamics or kinetics; it only informs the likelihood of a **hypersensitivity reaction**.[6,7]
- Refer to the National Pharmacogenomics SharePoint for up-to-date PGx testing capabilities within VA and information regarding HLA testing capabilities at send out laboratory vendors. VA PGx tests currently take up to 10 to 20 days for results to process.

Table 3. HLA PGx impacted medications with Food & Drug Administration (FDA) labeling[1,6-10]

		Abacavir	Allopurinol	Carbamazepine (CBZ) Oxcarbazepine	Phenytoin Fosphenytoin
Indications		Human Immunodeficiency Virus (HIV)	Gout Nephrolithiasis Tumor lysis syndrome	Epilepsy Trigeminal neuralgia Bipolar disorder	Seizure disorders Status epilepticus
FDA Labeling & Pharmacogenetic Associations	Boxed warning	**Test prior to initiation in all patients**[†]	**Not applicable**	**Test prior to initiation in patients with ancestry in genetically at-risk populations**[§]	**Not applicable**
	Management recommendations or potential impact on safety or response	Do not use in patients positive for HLA-B*57:01	Higher risk of SCARs in patients positive for HLA-B*58:01; discontinue at first sign of rash; consider testing in certain ancestral populations	Avoid use in patients positive for HLA-B*15:02; higher risk of SCARs in patients positive for HLA-B*15:02	Avoid as an alternative to CBZ in patients positive for HLA-B*15:02

[†]PGx testing prior to abacavir initiation is the current standard of care. See Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for additional information.

[§]A note on ancestry

There is wide genetic variation across ancestral groups at chromosome 6 containing the HLA region that impacts immune responses. While more prevalent in certain populations, HLA variation has been seen at some frequency across all major ancestral groups.[4] **PGx testing is the only way to confirm the presence of a variation and risk of HLA associated adverse events**.

Prevent severe cutaneous adverse drug reactions by ordering HLA testing for patients prior to initiating carbamazepine or oxcarbazepine therapy.

HLA-B*15:02

26x more likely!

- SJS and TEN are the most frequent SCARs associated with **HLA-B*15:02** variation.[3,10]
- A meta-analysis of 46 studies evaluating 8,431 patients showed that individuals with the HLA-B*15:02 allele are **more likely to experience SJS/TEN** with CBZ compared to those without any HLA variation.[5]
- Testing for the presence of HLA risk variants prior to initiation and using alternative therapies in those with the variation has been associated with a lower incidence of CBZ-induced SJS/TEN.[2]

CBZ has a **boxed warning** specific for HLA-B*15:02 due to the **strong predictive evidence** linking this variation to potentially fatal dermatologic reactions. The FDA recommends PGx testing **prior to initiating therapy** in certain ancestral populations and avoiding use in those who possess these genetic variants.[8,9,11]

Table 4. CPIC guidelines for CBZ based on HLA-B*15:02 and HLA-A*31:01 genotype[1]

	HLA-B*15:02	HLA-A*31:01	Implication	Therapeutic recommendation
Genotype	Negative	Negative	Normal risk of SCARs	Use per standard dosing guidelines.
	Positive	Negative, positive, or **Unknown**	Greater risk of CBZ-induced SJS/TEN	If CBZ-naïve, **do not use**.
	Negative	Positive	Greater risk of CBZ-induced SCARs	• If CBZ-naïve and alternatives available, **do not use**.[†] • If alternatives are unavailable, consider use with increased monitoring and discontinue at first signs of cutaneous adverse reaction.[†]

[†]See Figure 1 for guidance in patients already on CBZ/oxcarbazepine.

Table 5. CPIC guidelines for oxcarbazepine based on HLA-B*15:02 genotype[1]

HLA-B*15:02 genotype	Implication	Therapeutic recommendation
Negative	Normal risk of SJS/TEN	Use per standard dosing guidelines.
Positive	Greater risk of oxcarbazepine-induced SJS/TEN	If oxcarbazepine naïve, **do not use**.[†]

[†]See Figure 1 for guidance with patients already on CBZ/oxcarbazepine.

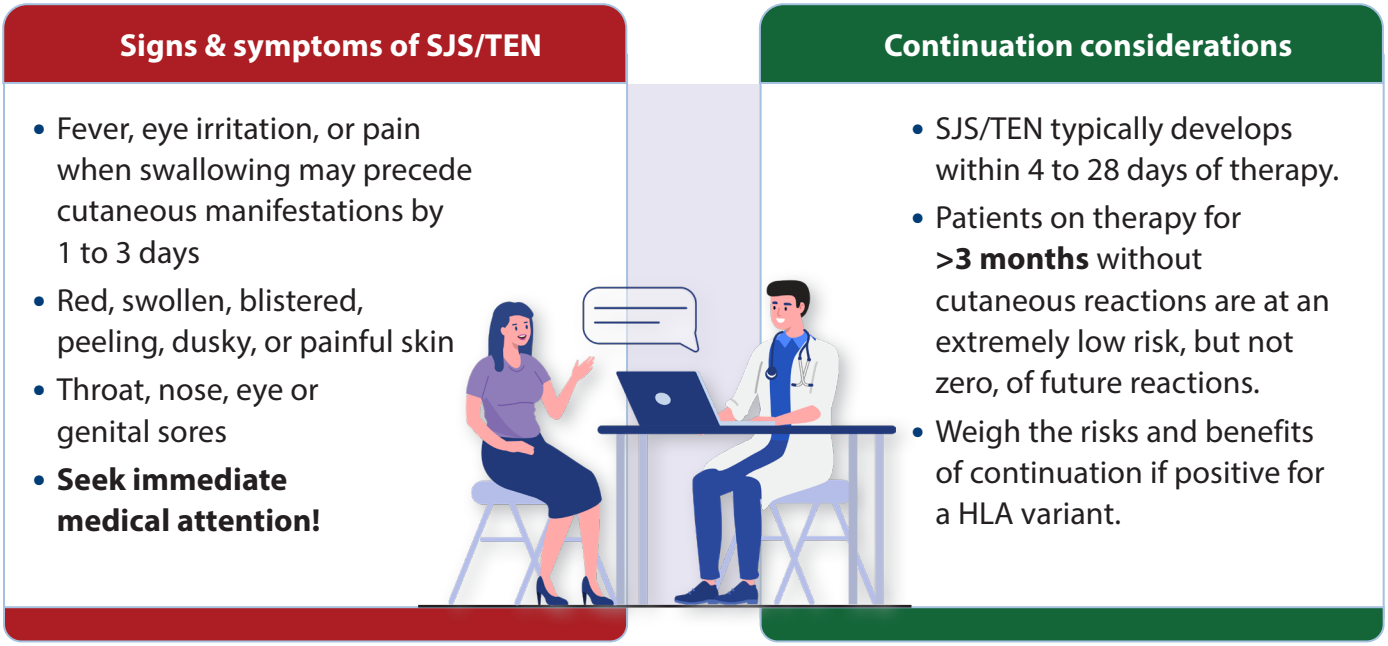
Phenytoin/Fosphenytoin

? DID YOU KNOW

- Phenytoin/fosphenytoin metabolism is also impacted by **CYP2C9 genotype**. When both HLA and CYP2C9 phenotypes are known, **CPIC recommends considering HLA genotype first to determine if use should be avoided prior to using a CYP2C9 genotype-guided dosing strategy**.[9] Refer to CPIC dosing guidelines for more information.
- Identification of an HLA variation might result as an incidental finding when performing PGx testing for another indication. Therapy changes may not be necessary depending on the duration of therapy.[9] See Figure 1 for more information.

Talk to your patient about HLA PGx results

Figure 1. Patient education and therapy continuation considerations with CBZ/oxcarbazepine or phenytoin/fosphenytoin therapy[4,10]



For general information on talking to your patient about PGx testing, refer to the Pharmacogenomics Clinician Guide or consult your PGx Clinical Pharmacist Practitioner (CPP). You will be notified when VA PGx test results come back, and the patient will receive a copy in the mail. Patients are instructed not to make any changes to their medication therapy until results are reviewed with their provider.

For more information

RESOURCES:

- National Pharmacogenomics SharePoint (http://tinyurl.com/jztks5n8)
- PGx testing (http://tinyurl.com/ytu78a9y)
- Pharmacogenomics Clinician Guide (http://tinyurl.com/2juazb6v)

REFERENCES:‡ **1.** Chang CJ, Chen CB, Hung SI, Ji C, Chung WH. Pharmacogenetic Testing for Prevention of Severe Cutaneous Adverse Drug Reactions. *Front Pharmacol*. 2020;11:969. doi:10.3389/fphar.2020.00969. **2.** Chen P, Lin JJ, Lu CS, et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. *The New England journal of medicine*. Mar 24 2011;364(12):1126-33. doi:10.1056/NEJMoa1009717. **3.** Dean L. Carbamazepine Therapy and HLA Genotype. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kattman BL, Malheiro AJ, eds. *Medical Genetics Summaries*. National Center for Biotechnology Information (US); 2012. **4.** Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. *Clin Pharmacol Ther*. Apr 2018;103(4):574-581. doi:10.1002/cpt.1004. **5.** Biswas M, Ershadian M, Shobana J, Nguyen AH, Sukasem C. Associations of HLA genetic variants with carbamazepine-induced cutaneous adverse drug reactions: An updated meta-analysis. *Clin Transl Sci*. Aug 2022;15(8):1887-1905. doi:10.1111/cts.13291. **6.** Saito Y, Stamp LK, Caudle KE, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update. *Clin Pharmacol Ther*. Jan 2016;99(1):36-7. doi:10.1002/cpt.161. **7.** Martin MA, Klein TE, Dong BJ, Pirmohamed M, Haas DW, Kroetz DL. Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and abacavir dosing. *Clin Pharmacol Ther*. Apr 2012;91(4):734-8. doi:10.1038/clpt.2011.355. **8.** Table of Pharmacogenetic Associations. 2022. **9.** Table of Pharmacogenomic Biomarkers in Drug Labeling. Federal Drug Administration2022. **10.** Karnes JH, Rettie AE, Somogyi AA, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing: 2020 Update. *Clin Pharmacol Ther*. Feb 2021;109(2):302-309. doi:10.1002/cpt.2008. **11.** Prescribing Information: Tegretol®-XR (carbamazepine extended-release tablets) (2020).

‡All "**doi**'s" use NIH's NLM Pub Med to search for the article.