Clinical Pharmacogenetics Implementation Consortium Guideline for *HLA* Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update

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The variant allele *HLA-B*15:02* is strongly associated with greater risk of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in patients treated with carbamazepine or oxcarbazepine. The variant allele *HLA-A*31:01* is associated with greater risk of maculopapular exanthema, drug reaction with eosinophilia and systemic symptoms, and SJS/TEN in patients treated with carbamazepine. We summarize evidence from the published literature supporting these associations and provide recommendations for carbamazepine and oxcarbazepine use based on *HLA* genotypes.

Human leukocyte antigen (*HLA*) genetic variation is implicated in the development of specific cutaneous adverse reactions to aromatic anticonvulsants. The purpose of this guideline is to interpret *HLA-B*15:02* and *HLA-A*31:01* genotyping results to guide the use of carbamazepine and oxcarbazepine. Detailed guidelines regarding the selection of alternative therapies, when to conduct genotype testing, and cost-effectiveness analyses are beyond the scope of this document. The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are periodically updated at https://cpicpgx.org/guidelines and http://www.pharmgkb.org.

FOCUSED LITERATURE REVIEW AND UPDATE

A systematic literature review focused on *HLA-B*15:02* and *HLA-A*31:01* genotypes and carbamazepine- and oxcarbazepine-induced cutaneous adverse reactions was conducted (details in **Supplemental Material**).

This guideline is an update to the 2013 CPIC guideline for *HLA-B*15:02* and carbamazepine use.[1] The recommendations provided in the original guideline have not changed and are included here. However, the scope of the existing recommendations has now expanded to include the use of carbamazepine and oxcarbazepine based on *HLA-A*31:01* and *HLA-B*15:02* genotypes, respectively. Furthermore, the accompanying **Supplemental Material** now includes resources to facilitate the incorporation of *HLA* genotype results into electronic health records with clinical decision support (https://cpicpgx.org/guidelines/guideline-for-carbamazepine-and-hla-b/).

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Table 1 Assignment of *HLA-B* and *HLA-A* genotypes

Genotype	Definition	Examples of diplotypes
*HLA-B*15:02* negative	Homozygous for an allele other than *HLA-B*15:02*	**X*[a]/**X*[a]
*HLA-B*15:02* positive	Heterozygous or homozygous variant	**15:02/*X*[a], **15:02/*15:02*
*HLA-A*31:01* negative	Homozygous for an allele other than *HLA-A*31:01*	**Y*[b]/**Y*[b]
*HLA-A*31:01* positive	Heterozygous or homozygous variant	**31:01/*Y*[b], **31:01/*31:01*

[a]Where *X = any *HLA-B* allele other than *HLA-B*15:02*. [b]Where *Y = any *HLA-A* allele other than *HLA-A*31:01*.

GENES: *HLA-B* AND *HLA-A*

Background

HLA-B and *HLA-A* are part of a large cluster of genes known as the human major histocompatibility complex (MHC). The cluster contains three subgroups: class I, II, and III. The *HLA-B* and *HLA-A* genes are part of the class I complex, along with *HLA-C*. These genes encode cell surface proteins that present intracellular antigens to the immune system. Intracellular antigens are usually the normal breakdown products of intracellular proteins and are recognized as "self." However, if the antigen presented derives from a pathogen or, in some cases, a transplanted tissue, it may be recognized as "nonself" and trigger an immune response. HLA is inherited in a codominant fashion with one set of class I and II alleles being inherited from each parent where both have full phenotypic expression.

Because HLA proteins present a wide variety of peptides for immune recognition, the *HLA* genes are among the most highly polymorphic genes in the human genome. *HLA* polymorphisms were previously ascertained serologically, but standard molecular approaches that now use DNA sequence-based typing methods either by standard Sanger or next-generation sequencing have revealed much greater complexity of genetic variation within this locus. For example, according to the World Health Organization (WHO) Nomenclature Committee for Factors of the *HLA* System (http://hla.alleles.org), there are more than 4,000 identified *HLA-B* alleles and more than 3,000 identified *HLA-A* alleles, many of which differ by more than one nucleotide from one another. Each allele is designated by the gene name followed by an asterisk and a four- or six-digit identifier giving information about the allele type (designated by the first two digits) and specific protein subtype (second set of digits). The details of HLA nomenclature have been described in a previous CPIC guideline.[2]

The guideline presented here specifically discusses the class I HLA alleles *HLA-B*15:02* and *HLA-A*31:01* as they relate to carbamazepine- and oxcarbazepine-induced cutaneous adverse reactions, including Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and maculopapular exanthema (MPE).

Genetic test interpretation

Clinical genotyping tests exist for identifying *HLA-B* and *HLA-A* alleles, including *HLA-B*15:02* and *HLA-A*31:01*. Genotyping results are presented as "positive" if one or two copies of the variant allele are present or "negative" if no copies of the variant allele are present. There is no intermediate genotype. Genotype definitions for *HLA-B*15:02* and *HLA-A*31:01* are summarized in **Table 1**. Nucleotide and amino acid sequence alignments for *HLA-B*15:02* and *HLA-A*31:01* and the corresponding reference sequences are available in **Supplemental Figures S1–S4**.

Available genetic test options

Commercially available genetic testing options change over time. Additional information about pharmacogenetic testing can be found at the Genetic Testing Registry website (http://www.ncbi.nlm.nih.gov/gtr/).

Incidental findings

Although *HLA* alleles have been studied in the context of specific responses to HIV and other pathogens, there are currently no specific diseases or conditions that have been strongly linked to *HLA-B*15:02* or *HLA-A*31:01* independent of drug use.[3–5] However, *HLA-B*15:02* has also been associated with SJS/TEN from phenytoin use, and other *HLA-B* alleles have been strongly associated with adverse drug reactions. For example, *HLA-B*57:01* is associated with abacavir-induced hypersensitivity reaction, and *HLA-B*58:01* is associated with allopurinol-induced severe cutaneous adverse reactions (including SJS/TEN and DRESS). CPIC guidelines are available to guide prescribing of phenytoin,[6] abacavir,[7] and allopurinol,[8] based on *HLA-B* genotype.

Other considerations

*HLA-B*15:02* and *HLA-A*31:01* have distinct ethnic and geographical distributions that are important for evaluating population risk (see ***HLA-A* and *HLA-B* Allele Frequency Table**). The frequency of *HLA-B*15:02* is highest in East Asian (6.9%), Oceanian (5.4%), and South/Central Asian (4.6%) populations. However, not all East Asian subpopulations carry this allele in such high frequencies. *HLA-B*15:02* frequency is much lower in Japanese (<1%) and Korean (<2.5%) populations. The allele is also quite rare in African populations (not observed), African Americans, Middle Easterners, Caucasians, and Hispanics/South Americans (<1%). In contrast, the frequency of the *HLA-A*31:01* allele is higher than the *HLA-B*15:02* allele in Caucasians (3%) and Hispanic/South Americans (6%). However, it is

also found in high frequencies in some East Asians, specifically Japanese (8%) and South Koreans (5%), and South/Central Asians (2%). While these frequencies are helpful in determining broad population risks, they cannot replace genotypes on an individual basis.

DRUGS: CARBAMAZEPINE AND OXCARBAZEPINE

Background

Carbamazepine. Carbamazepine, an aromatic anticonvulsant related to the tricyclic antidepressants, is US Food and Drug Administration (FDA)-approved for the treatment of epilepsy, trigeminal neuralgia, and bipolar disorder. Carbamazepine reduces the propagation of abnormal impulses in the brain by producing a frequency- and voltage-dependent block of sodium channels, thereby inhibiting the generation of repetitive action potentials in the epileptic focus.[8,9] Carbamazepine-induced adverse effects that may have known dose- or concentration-dependency include dizziness, ataxia, and nystagmus. Other adverse effects such as aplastic anemia, hyponatremia, leukopenia, osteoporosis, liver injury, and hypersensitivity reactions such as MPE, DRESS, and SJS/TEN have a complex dose–response relationship such that it is difficult to delineate a clear linear dose–response relationship. For additional information regarding the pharmacokinetics and pharmacogenomics of carbamazepine, please refer to the PharmGKB website: http://www.pharmgkb.org/pathway/PA165817070.[10]

Oxcarbazepine. Oxcarbazepine is the keto-analog of carbamazepine. With its similar structure, oxcarbazepine shares many therapeutic indications and adverse effects with carbamazepine. Furthermore, patients who have had hypersensitivity reactions to carbamazepine may also be predisposed to hypersensitivity reactions with oxcarbazepine; these patients should only be treated with oxcarbazepine if the potential benefit justifies the potential risk.

Linking genetic variability to variability in drug-related phenotypes

There is evidence linking the *HLA-B*15:02* genotype with the risk of carbamazepine- and oxcarbazepine-induced SJS/TEN (**Supplemental Table S1**) and linking *HLA-A*31:01* genotype with the risk of carbamazepine-induced SJS/TEN, DRESS, and MPE (**Supplemental Table S2**). Application of a grading system to evidence linking *HLA* genotypic variations to phenotypic variability with respect to cutaneous adverse reactions indicates a high quality of evidence in the majority of cases. This body of evidence provides the basis for the recommendations in **Table 2** and **Table 3**.

HLA-B*15:02. *HLA-B*15:02* is specific for carbamazepine- and oxcarbazepine-induced SJS and TEN, although the data are strongest for carbamazepine. SJS is characterized by epidermal detachment affecting up to 10% of the body surface area (BSA), while TEN usually involves more than 30% of the BSA. Patients with between 10–30% of the BSA blistered are defined as having an SJS/TEN overlap syndrome. Mortality rates are typically below 5% for SJS and can be above 30% for TEN, with sepsis being the most frequent cause of death.[11] Mortality from SJS/TEN is also related to age, the drug half-life, and how early the drug is discontinued.[12,13] An immune-mediated etiology has been shown for these reactions, which is consistent with the anamnestic response often seen clinically on drug rechallenge.[14] In terms of the immunopathology, cytotoxic T cells, or CD8 + T cells (lymphocytes matured in the thymus that express the CD8 protein on their surface), are involved in SJS and TEN.[15,16] Further discussion on the mechanism of carbamazepine-induced SJS/TEN is presented in the **Supplemental Material**.

Consistent with the regional and ethnic distribution of the *HLA-B*15:02* allele, studies have shown the genetic risk of carbamazepine-associated SJS/TEN to be higher in several Asian countries with increased frequency of the *HLA-B*15:02* allele, including Vietnam,[17] Cambodia,[17] Reunion Islands,[17] Thailand,[18,19] some parts of India,[20] Malaysia,[21] and Hong Kong.[22] The *HLA-B*15:02* allele has not been observed in cases of SJS/TEN in some ancestral groups, such as Japanese and Korean populations or non-Asian descendants in Europe or North America,[17,23–26] where the frequency of the allele is very low. In the Han Chinese population, the sensitivity of *HLA-B*15:02* as a predictive test for SJS/TEN has been estimated at 98% and specificity at 97%[23]; the positive predictive value is estimated at 7.7% and negative predictive value at 100%.[27] However, it is important to note that in one study, in a group of individuals thought to be of European origin, four of 12 individuals with SJS/TEN carried the *HLA-B*15:02* allele.[24] Subsequently, they were found to have some Southeast Asian ancestry. This example underscores the importance of considering the *HLA-B*15:02* allele carrier status in therapeutic decision-making regardless of self-reported ethnicity.

Based on the strong evidence linking *HLA-B*15:02* to carbamazepine-induced SJS/TEN, the FDA issued a Health Alert in 2007 about changes to package labeling and recommendations for genetic testing in patients treated with carbamazepine.[28] The FDA label for carbamazepine carries a boxed warning about the risk of SJS/TEN with the presence of the *HLA-B*15:02* allele and states that patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk. The FDA label for oxcarbazepine does not carry this boxed warning, but there is mention of the association between *HLA-B*15:02* and the risk of SJS/TEN in the warnings and precautions section that advises avoiding oxcarbazepine in *HLA-B*15:02* positive patients unless the benefit clearly outweighs the risk. The positive predictive value of *HLA-B*15:02* for oxcarbazepine-induced SJS/TEN is estimated to be 0.73%, which is much lower than that of carbamazepine-induced SJS/TEN (7.7%); however, the negative predictive value for both nears 100% in Southeast Asian populations.[29]

HLA-A*31:01. Unlike *HLA-B*15:02*, the *HLA-A*31:01* allele is associated with a wider range of carbamazepine hypersensitivity reactions, including MPE, DRESS, and SJS/TEN, in many different populations.[30] DRESS is a severe hypersensitivity reaction characterized by generalized cutaneous eruptions with systemic

Table 2 Recommendations for carbamazepine therapy based on *HLA-B* and *HLA-A* genotypes

Genotype[a]	Implication	Therapeutic recommendation	Classification of recommendation	Considerations for other aromatic anticonvulsants
*HLA-B*15:02* negative and *HLA-A*31:01* negative	Normal risk of carbamazepine-induced SJS/TEN, DRESS, and MPE	Use carbamazepine per standard dosing guidelines.[b]	Strong	N/A
*HLA-B*15:02* negative and *HLA-A*31:01* positive	Greater risk of carbamazepine-induced SJS/TEN, DRESS, and MPE	If patient is carbamazepine-naïve and alternative agents are available, do not use carbamazepine.	Strong	Other aromatic anticonvulsants[d] have very limited evidence, if any, linking SJS/TEN, DRESS, and/or MPE with the *HLA-A*31:01* allele, and thus no recommendation can be made with respect to choosing another aromatic anticonvulsant as an alternative agent.
		If patient is carbamazepine-naïve and alternative agents are not available, consider the use of carbamazepine with increased frequency of clinical monitoring. Discontinue therapy at first evidence of a cutaneous adverse reaction.	Optional	N/A
		The latency period for cutaneous adverse drug reactions is variable depending on phenotype; however, all usually occur within three months of regular dosing. Therefore, if the patient has previously used carbamazepine consistently for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine.	Optional	Previous tolerance of carbamazepine is not indicative of tolerance to other aromatic anticonvulsants.[d]
*HLA-B*15:02* positive[c] and any *HLA-A*31:01* genotype (or *HLA-A*31:01* genotype unknown)	Greater risk of carbamazepine-induced SJS/TEN	If patient is carbamazepine-naïve, do not use carbamazepine.	Strong	Other aromatic anticonvulsants[d] have weaker evidence linking SJS/TEN with the *HLA-B*15:02* allele; however, caution should still be used in choosing an alternative agent.
		The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (~4-28 days), and cases usually occur within three months of dosing; therefore, if the patient has previously used carbamazepine consistently for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine in the future.	Optional	Previous tolerance of carbamazepine is not indicative of tolerance to other aromatic anticonvulsants.[d]

DRESS, drug reaction with eosinophilia and systemic symptoms; MPE, maculopapular exanthema; N/A, not applicable; SJS = Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

[a]If only *HLA-B*15:02* was tested, assume *HLA-A*31:01* is negative and vice versa. [b]*HLA-B*15:02* has a 100% negative predictive value for carbamazepine-induced SJS/TEN, and its use is currently recommended to guide use of carbamazepine and oxcarbazepine only. Because there is a much weaker association and less than 100% negative predictive value of *HLA-B*15:02* for SJS/TEN associated with other aromatic anticonvulsants, using these drugs instead of carbamazepine or oxcarbazepine in the setting of a negative *HLA-B*15:02* test in Southeast Asians will not result in prevention of anticonvulsant-associated SJS/TEN.[40] [c]In addition to *HLA-B*15:02*, risk for carbamazepine-induced SJS/TEN has been reported in association with the most common B75 serotype alleles in Southeast Asia, *HLA-B*15:08, HLA-B*15:11*, and *HLA-B*15:21*. Although not described, the possibility of carbamazepine-induced SJS/TEN in association with less frequently carried B75 serotype alleles, such as *HLA-B*15:30* and *HLA-B*15:31*, should also be considered. [d]Aromatic anticonvulsants include carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital.

Table 3 Recommendations for oxcarbazepine therapy based on *HLA-B* genotype

Genotype	Implication	Therapeutic recommendation	Classification of recommendation	Considerations for other aromatic anticonvulsants
*HLA-B*15:02* negative	Normal risk of oxcarbazepine-induced SJS/TEN	Use oxcarbazepine per standard dosing guidelines.	Strong	N/A
*HLA-B*15:02* positive	Greater risk of oxcarbazepine-induced SJS/TEN	If patient is oxcarbazepine-naïve, do not use oxcarbazepine.	Strong	Other aromatic anticonvulsants[a] have weaker evidence linking SJS/TEN with the *HLA-B*15:02* allele; however, caution should still be used in choosing an alternative agent.
		The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (~4-28 days), and cases usually occur within three months of dosing; therefore, if the patient has previously used oxcarbazepine consistently for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of oxcarbazepine in the future.	Optional	Previous tolerance of oxcarbazepine is not indicative of tolerance to other aromatic anticonvulsants.[a]

N/A, not applicable; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
[a]Aromatic anticonvulsants include carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital.

manifestations that can be life-threatening, whereas MPE is a milder reaction with only the presence of rash without mucosal or organ involvement, or systemic features. Available evidence suggests an association between the presence of *HLA-A*31:01* and carbamazepine-induced MPE, DRESS, and SJS/TEN, with the data strongest for DRESS and SJS/TEN in European and Japanese populations, where the allele frequency is higher; however, no such evidence exists for oxcarbazepine.

In Southeast Asian populations, the strong association between *HLA-B*15:02* and carbamazepine-induced SJS/TEN would overwhelm any potential association between *HLA-A*31:01* and carbamazepine-induced SJS/TEN. In European, African, and Japanese populations where the carriage rate of *HLA-B*15:02* is less than 1%, *HLA-A*31:01* appears to be the primary driver of carbamazepine-induced SJS/TEN and other hypersensitivity reactions. *HLA-A*31:01* is also a risk factor for MPE and DRESS in Han Chinese populations. The positive predictive value and number needed to test to prevent one case of all carbamazepine-induced hypersensitivity reactions (most influenced by MPE >>> DRESS) combined are most favorable for European populations, and they are estimated at 43% and 47, respectively.[31] Limited, if any, evidence exists to support an association between *HLA-A*31:01* and hypersensitivity associated with other aromatic anticonvulsants, including lamotrigine,[32] oxcarbazepine, eslicarbazepine, phenytoin, fosphenytoin, and phenobarbital, and thus no recommendations can be given regarding the safety of these agents in *HLA-A*31:01* positive patients. In light of evidence supporting clinical crossreactivity among aromatic anticonvulsants, however, in the instance where a severe hypersensitivity reaction has occurred with one agent, avoidance of the others is recommended.[33]

Therapeutic recommendations

The therapeutic recommendations for *HLA-B*15:02* and carbamazepine remain unchanged from the original guideline,[1] but in this update they are now also applicable to oxcarbazepine (**Tables 2**, **3**). These recommendations hold irrespective of the patient's region of origin or ethnic group. For patients who are *HLA-B*15:02* negative, carbamazepine or oxcarbazepine may be prescribed per standard guidelines. If a patient is carbamazepine-naïve or oxcarbazepine-naïve and *HLA-B*15:02* positive, carbamazepine and oxcarbazepine should be avoided, respectively, due to the greater risk of SJS/TEN. Other aromatic anticonvulsants, including eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital, have very limited evidence, if any, linking SJS/TEN with the *HLA-B*15:02* allele; however, caution should still be used when choosing an alternative agent. With regular dosing, carbamazepine- or oxcarbazepine-induced SJS/TEN usually develops within the first 4–28 days of therapy; therefore, patients who have been continuously taking carbamazepine or oxcarbazepine for longer than 3 months without developing cutaneous reactions are at extremely low risk (but not zero) of carbamazepine- or oxcarbazepine-induced adverse events in the future, regardless of *HLA-B*15:02* status.[34,35]

For patients who are *HLA-A*31:01* negative, carbamazepine may be prescribed per standard guidelines (**Table 2**). If a carbamazepine-naïve patient also received testing for *HLA-B*15:02* and is positive for this allele, carbamazepine should be avoided regardless of the *HLA-A*31:01* genotype result. If a patient is carbamazepine-naïve and *HLA-A*31:01* positive, and if alternative agents are available, carbamazepine should be avoided

due to the greater risk of SJS/TEN, DRESS, and MPE. Other aromatic anticonvulsants, including oxcarbazepine, have very limited evidence, if any, linking SJS/TEN, DRESS, and/or MPE with the *HLA-A*31:01* allele, and thus no recommendation can be made with respect to choosing another aromatic anticonvulsant as an alternative agent. If alternative agents are not available, consider the use of carbamazepine with increased frequency of clinical monitoring. Discontinue therapy at the first evidence of a cutaneous adverse reaction. As previously mentioned, since the latency period for cutaneous adverse drug reactions is known, if the patient is *HLA-A*31:01* positive and has previously used carbamazepine for longer than 3 months without incidence of a cutaneous adverse reaction, cautiously consider use of carbamazepine.

Pediatrics. Data describing the relationship between *HLA-B*15:02* and *HLA-A*31:01* genotype and carbamazepine- or oxcarbazepine-induced cutaneous adverse reactions in pediatric patients are scarce (**Supplemental Tables S1, S2**). In the absence of data suggesting a different relationship between these *HLA* alleles and drug-induced hypersensitivity in pediatric patients, the recommendations may be used to guide use of carbamazepine and oxcarbazepine in both adult and pediatric patients.

Recommendations for incidental findings

Aromatic anticonvulsants that are structurally similar to carbamazepine have also been associated with SJS/TEN and *HLA-B*15:02*. The drug-specific evidence linking *HLA-B*15:02* and SJS/TEN is discussed in the **Supplemental Material** and may have implications for choosing alternatives to carbamazepine in those who carry the *HLA-B*15:02* allele.

Other considerations

***HLA-B75* serotypes.** *HLA-B*15:02* is the most common *HLA-B75* serotype allele in Southeast Asia. Other less frequently carried members of the *HLA-B75* serotype include *HLA-B*15:08, HLA-B*15:11*, and *HLA-B*15:21*. The HLA proteins coded by these alleles share structural similarity and peptide binding grooves, and hence peptide binding specificities, with *HLA-B*15:02* and have also been reported in association with carbamazepine-induced SJS/TEN.[26,36–38] Currently, the majority of available data focuses on the risk of carbamazepine-induced SJS/TEN conferred by the presence of *HLA-B*15:02* and is the basis for the design of efficient single allele molecular typing assays. However, some labs may provide high-resolution *HLA-B* typing and the possibility of carbamazepine-induced SJS/TEN with *HLA-B*15:08, HLA-B*15:11, HLA-B*15:21*, and even less common *HLA-B75* serotype alleles such as *HLA-B*15:30* and *HLA-B*15:31* where carbamazepine-induced SJS/TEN has yet to be described, needs to be considered a potential risk if this information is available.

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

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

A potential benefit of *HLA-B*15:02* and *HLA-A*31:01* testing is a reduction in the incidence of serious, and sometimes fatal, cutaneous adverse reactions to carbamazepine and oxcarbazepine by identifying those who are at significant risk and using alternative therapy. The success of *HLA-B*15:02* prospective screening in reducing the rate of SJS/TEN has been demonstrated clinically in a Chinese population.[39]

A potential risk of *HLA-B*15:02* or *HLA-A*31:01* testing is ruling out the use of carbamazepine or oxcarbazepine in patients who may not ever develop a hypersensitivity reaction to the drug. This risk is mitigated by the fact that there are often alternatives to carbamazepine or oxcarbazepine with comparable effectiveness; however, consideration must be given to the risk of cutaneous adverse reactions with other anticonvulsants. For example, it has been demonstrated in an Asian population that an *HLA-B*15:02* screening policy for carbamazepine will not decrease the overall rate of SJS/TEN if other anticonvulsants associated with SJS/TEN (e.g., phenytoin) are used instead of carbamazepine.[40] The risk of phenytoin-associated SJS/TEN is described in more detail in the CPIC guideline for *CYP2C9* and *HLA-B* genotypes and phenytoin dosing.[6] Furthermore, other anticonvulsants may be associated with more unfavorable adverse effect profiles compared to carbamazepine or oxcarbazepine.

Although genotyping is considered reliable when performed in qualified clinical laboratories, laboratory error and sample mix-up is always a distinct possibility. If an *HLA-B*15:02*-negative, Southeast Asian individual who does not carry another B75 serotype of *HLA* develops carbamazepine-induced SJS/TEN, for instance, the *HLA* typing should be repeated to rule out sample or typing error. Genotype results are associated with a patient for a lifetime; as such, a genotyping error could have a broader impact on healthcare should other *HLA-B*15:02* or *HLA-A*31:01* associations be identified in the future.

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

If a patient has taken carbamazepine or oxcarbazepine consistently for more than 3 months, it is highly unlikely that a severe cutaneous adverse reaction will occur after that time. As a result, known *HLA-B*15:02* or *HLA-A*31:01* genotypes will be less helpful for treatment-experienced patients compared to treatment-naïve patients. Furthermore, because extensive ethnic admixture has occurred globally and not all carbamazepine- and oxcarbazepine-induced cutaneous adverse reactions can be attributed to *HLA-B*15:02* or *HLA-A*31:01*, clinicians should carefully monitor all patients as standard practice.

SUPPLEMENTARY MATERIAL is linked to the online version of the article at http://www.cpt-journal.com

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CONFLICT OF INTEREST

The authors declare no competing interests for this work.

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1. Leckband, S.G. *et al*. Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and carbamazepine dosing. *Clin. Pharmacol. Ther*. **94**, 324–328 (2013).
2. Martin, M.A. *et al*. Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and abacavir dosing. *Clin. Pharmacol. Ther*. **91**, 734–738 (2012).
3. Das Ghosh, D. *et al*. Impact of genetic variations and transcriptional alterations of HLA class I genes on cervical cancer pathogenesis. *Int. J. Cancer* **140**, 2498–2508 (2017).
4. da Silva, F.P. *et al*. HLA-A*31 as a marker of genetic susceptibility to sepsis. *Rev. Bras. Ter. Intensiva* **25**, 284–289 (2013).
5. Kuang, X.T. *et al*. Impaired Nef function is associated with early control of HIV-1 viremia. *J. Virol*. **88**, 10200–10213 (2014).
6. Caudle, K.E. *et al*. Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. *Clin. Pharmacol. Ther*. **96**, 542–548 (2014).
7. Martin, M.A. *et al*. Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B genotype and abacavir dosing: 2014 update. *Clin. Pharmacol. Ther*. **95**, 499–500 (2014).
8. Saito, Y. *et al*. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update. *Clin. Pharmacol. Ther*. **99**, 36–37 (2016).
9. McLean, M.J. & Macdonald, R.L. Carbamazepine and 10,11-epoxycarbamazepine produce use- and voltage-dependent limitation of rapidly firing action potentials of mouse central neurons in cell culture. *J. Pharmacol. Exp. Ther*. **238**, 727–738 (1986).
10. Thorn, C.F. *et al*. PharmGKB summary: carbamazepine pathway. *Pharmacogenet. Tenomics* **21**, 906–910 (2011).
11. Roujeau, J.C. & Stern, R.S. Severe adverse cutaneous reactions to drugs. *N. Engl. J. Med*. **331**, 1272–1285 (1994).
12. Garcia-Doval, I., LeCleach, L., Bocquet, H., Otero, X.L. & Roujeau, J.C. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death?, *Arch. Dermatol*. **136**, 323–327 (2000).
13. Paulmann, M. & Mockenhaupt, M. Severe drug hypersensitivity reactions: clinical pattern, diagnosis, etiology and therapeutic options. *Curr. Pharm. Des*. **22**, 6852–6861 (2016).
14. Nassif, A. *et al*. Drug specific cytotoxic T-cells in the skin lesions of a patient with toxic epidermal necrolysis. *J. Invest. Dermatol*. **118**, 728–733 (2002).
15. Nassif, A. *et al*. Toxic epidermal necrolysis: effector cells are drug-specific cytotoxic T cells. *J. Allergy Clin. Immunol*. **114**, 1209–1215 (2004).
16. Naisbitt, D.J. *et al*. Hypersensitivity reactions to carbamazepine: characterization of the specificity, phenotype, and cytokine profile of drug-specific T cell clones. *Mol. Pharmacol*. **63**, 732–741 (2003).
17. Lonjou, C. *et al*. A marker for Stevens-Johnson syndrome. . .: ethnicity matters. *Pharmacogenomics J*. **6**, 265–268 (2006).
18. Locharernkul, C. *et al*. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. *Epilepsia* **49**, 2087–2091 (2008).
19. Tassaneeyakul, W. *et al*. Association between HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population. *Epilepsia* **51**, 926–930 (2010).
20. Mehta, T.Y. *et al*. Association of HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome among Indians. *Indian J. Dermatol. Venereol. Leprol*. **75**, 579–582 (2009).
21. Chang, C.C., Too, C.L., Murad, S. & Hussein, S.H. Association of HLA-B*1502 allele with carbamazepine-induced toxic epidermal necrolysis and Stevens-Johnson syndrome in the multi-ethnic Malaysian population. *Int. J. Dermatol*. **50**, 221–224 (2011).
22. Man, C.B. *et al*. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. *Epilepsia* **48**, 1015–1058 (2007).
23. Alfirevic, A., Jorgensen, A.L., Williamson, P.R., Chadwick, D.W., Park, B.K. & Pirmohamed, M. HLA-B locus in Caucasian patients with carbamazepine hypersensitivity. *Pharmacogenomics* **7**, 813–818 (2006).
24. Lonjou, C. *et al*. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet. Genomics* **18**, 99–107 (2008).
25. Kaniwa, N. *et al*. HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics* **9**, 1617–1622 (2008).
26. Kim, S.H. *et al*. Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. *Epilepsy Res*. **97**, 190–197 (2011).
27. Hung, S.I. *et al*. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet. Genomics* **16**, 297–306 (2006).
28. Ferrell, P.B., Jr. & McLeod, H.L. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. *Pharmacogenomics* **9**, 1543–1546 (2008).
29. Chen, C.B. *et al*. Risk and association of HLA with oxcarbazepine-induced cutaneous adverse reactions in Asians. *Neurology* **88**, 78–86 (2017).
30. Yip, V.L., Marson, A.G., Jorgensen, A.L., Pirmohamed, M. & Alfirevic, A. HLA genotype and carbamazepine-induced cutaneous adverse drug reactions: a systematic review. *Clin. Pharmacol. Ther*. **92**, 757–765 (2012).
31. Yip, V.L. & Pirmohamed, M. The HLA-A*31:01 allele: influence on carbamazepine treatment. *Pharmgenom. Pers. Med*. **10**, 29–38 (2017).
32. Kim, B.K. *et al*. HLA-A*31:01 and lamotrigine-induced severe cutaneous adverse drug reactions in a Korean population. *Ann. Allergy Asthma Immunol*. **118**, 629–630 (2017).

33. Phillips, E.J., Chung, W.H., Mockenhaupt, M., Roujeau, J.C. & Mallal, S.A. Drug hypersensitivity: pharmacogenetics and clinical syndromes. *J. Allergy Clin. Immunol*. **127**, S60–66 (2011).
34. Tennis, P. & Stern, R.S. Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. *Neurology* **49**, 542–546 (1997).
35. Roujeau, J.C. *et al*. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N. Engl. J. Med*. **333**, 1600–1607 (1995).
36. Kaniwa, N. *et al*. HLA-B*1511 is a risk factor for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients. *Epilepsia* **51**, 2461–2465 (2010).
37. Shi, Y.W. *et al*. Association between HLA and Stevens-Johnson syndrome induced by carbamazepine in Southern Han Chinese: genetic markers besides B*1502?, *Basic Clin. Pharmacol. Toxicol*. **111**, 58–64 (2012).
38. Jaruthamsophon, K., Tipmanee, V., Sangiemchoey, A., Sukasem, C. & Limprasert, P. HLA-B*15:21 and carbamazepine-induced Stevens-Johnson syndrome: pooled-data and in silico analysis. *Sci. Rep*. **7**, 45553 (2017).
39. Chen, P. *et al*. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. *N. Engl. J. Med*. **364**, 1126–1133 (2011).
40. Chen, Z., Liew, D. & Kwan, P. Effects of a HLA-B*15:02 screening policy on antiepileptic drug use and severe skin reactions. *Neurology* **83**, 2077–2084 (2014).