

## Overview

### Useful For

Identifying individuals with increased risk of risk of carbamazepine- or oxcarbazepine-associated cutaneous adverse reactions

### Genetics Test Information

Detection of the *HLA-B\*15:02* allele (HLA00165) in the *HLA-B* gene (NM\_005514).

Detection of the *HLA-A\*31:01* allele (HLA00097) in the *HLA-A* gene (NM\_001242758).

### Special Instructions

- [Informed Consent for Genetic Testing](#)
- [Pharmacogenomic Association Tables](#)
- [Multiple Genotype Test List](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)

### Method Name

Qualitative Allele-Specific Real-Time Polymerase Chain Reaction (PCR)

### NY State Available

Yes

## Specimen

### Specimen Type

Varies

### Specimen Required

Multiple genotype tests can be performed on a single specimen after a single extraction. See [Multiple Genotype Test List](#) for a list of tests that can be ordered together.

### Submit only 1 of the following specimens:

**Specimen Type:** Whole blood

**Container/Tube:** Lavender top (EDTA)

**Specimen Volume:** 3 mL

#### Collection Instructions:

1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**

**Specimen Stability Information:** Ambient (preferred) 9 days/Refrigerated 30 days

**Specimen Type:** Saliva

**Supplies:** Saliva Swab Collection Kit (T786)

**Patient Preparation:** Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.

**Specimen Volume:** 1 Swab

**Collection Instructions:** Collect and send specimen per kit instructions.

**Specimen Stability Information:** Ambient 30 days

**Specimen Type:** Extracted DNA

**Container/Tube:** 2-mL screw top tube

**Specimen Volume:** 100 mcL (microliters)

**Collection Instructions:**

1. The preferred volume is 100 mcL at a concentration of 50 ng/mcL.
2. Provide concentration of DNA and volume on tube.

**Specimen Stability Information:** Frozen (preferred) 1 year/Ambient/Refrigerated

## Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available:

-[Informed Consent for Genetic Testing \(T576\)](#)

-[Informed Consent for Genetic Testing-Spanish \(T826\)](#)

2. If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:

-[Therapeutics Test Request \(T831\)](#)

-[Neurology Specialty Testing Client Test Request \(T732\)](#)

## Specimen Minimum Volume

Blood: 0.35 mL

[Saliva, extracted DNA: see Specimen Required](#)

## Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

## Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

## Clinical & Interpretive

### Clinical Information

Carbamazepine and oxcarbazepine are aromatic anticonvulsants, as are eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital. Carbamazepine is FDA-approved for the treatment of epilepsy, trigeminal neuralgia, and bipolar disorder. Oxcarbazepine is FDA-approved for the treatment of partial seizures. A minority of carbamazepine-

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or oxcarbazepine-treated persons have cutaneous adverse reactions that vary in prevalence and severity, with some forms associated with substantial morbidity and mortality. The most severe reactions, such as the Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), are characterized by a blistering rash affecting a variable percentage of the body-surface area. TEN is the rarest of these phenotypes and is associated with mortality of up to 30%. Drug reaction with eosinophilia and systemic symptoms (DRESS) and maculopapular exanthema (MPE) may also be related to carbamazepine exposure. According to the FDA-approved label for carbamazepine, the estimated incidence of SJS-TEN is 1 to 6 cases in 10,000 persons of European ancestry who are exposed to the drug. The rate of SJS-TEN as a result of carbamazepine exposure is about 10 times higher in some Asian countries. According to the FDA label for oxcarbazepine, the rate of TEN and SJS among individuals exposed to oxcarbazepine exceeds the background incidence by a factor of 3- to 10-fold, but this is expected to be an underestimate due to underreporting.

Clinical studies have demonstrated associations between some human leukocyte antigen (HLA) genotypes and drug-associated cutaneous adverse reactions. The presence of the *HLA-B\*15:02* allele varies throughout Asia: 10% to 15% frequency in Chinese; 2% to 4% frequency in Southeast Asians and Indians; and less than 1% frequency in Japanese and Koreans. This allele is strongly associated with greater risk of SJS and TEN in patients treated with carbamazepine or oxcarbazepine and has also been associated with SJS/TEN with phenytoin use. There is very limited evidence associating SJS/TEN/DRESS or MPE and other aromatic anticonvulsants in patients who are positive for *HLA-B\*15:02*.

The *HLA-A\*31:01* allele, which has a prevalence of 2% to 5% in Northern European populations, 6% among Hispanic/South American populations, and 8% among Japanese populations, has been significantly associated with greater risk of MPE, DRESS, and SJS/TEN among patients treated with carbamazepine. In the absence of *HLA-A\*31:01*, the risk for drug-associated cutaneous adverse reactions is 3.8%, but in the presence of this allele, the risk increases to 26%. The evidence linking other aromatic anticonvulsants with SJS/TEN in the presence of the *HLA-A\*31:01* allele is weaker; however, an alternative medication should be chosen with caution.

The FDA-approved label for carbamazepine states that the screening of patients in genetically at-risk populations (ie, patients of Asian descent) for the presence of the *HLA-B\*15:02* allele should be carried out prior to initiating treatment with carbamazepine. The FDA-approved label also notes the association of *HLA-A\*31:01* allele with drug-associated cutaneous adverse reactions regardless of ethnicity, but it does not specifically mandate screening of patients. The FDA-approved label for oxcarbazepine indicates that testing for the presence of the *HLA-B\*15:02* allele should be considered in patients with ancestry including genetically at-risk populations prior to initiation of therapy.

According to the most recent Clinical Pharmacogenetic Implementation Consortium (CPIC) guideline, patients who are *HLA-B\*15:02* positive should not be prescribed carbamazepine or oxcarbazepine if alternative agents are available; however, caution should be used in selecting an alternative medication as there is weaker evidence that also links other aromatic anticonvulsants with SJS/TEN in patients positive for *HLA-B\*15:02*. Furthermore, phenytoin is the subject of a separate CPIC guideline with recommendations to avoid phenytoin in *HLA-B\*15:02* positive individuals, along with additional recommendations based on *CYP2C9* genotype. Patients who are *HLA-A\*31:01* positive should not be prescribed carbamazepine if alternative agents are available. However, although very limited evidence links SJS/TEN/DRESS/MPE with other aromatic anticonvulsants, among *HLA-A\*31:01*-positive patients, caution should be used in selecting an alternative medication.

### Reference Values

An interpretive report will be provided.

### Interpretation

The presence of the *HLA-B\*15:02* and/or *HLA-A\*31:01* allele confers increased risk for hypersensitivity to carbamazepine. The presence of the *HLA-B\*15:02* allele also confers increased risk for hypersensitivity to oxcarbazepine and phenytoin.

For additional information regarding pharmacogenomic genes and their associated drugs, see the [Pharmacogenomic Associations Tables](#). This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

### Cautions

Rare reported or unreported *HLA-A* and *HLA-B* alleles may occur and may interfere with this assay, resulting in a false-positive or false-negative call. Examples of alleles that may interfere include other *HLA-A\*31* alleles (including *HLA-A \*31:01:23*), *HLA-B\*15:13*, *HLA-B\*15:31*, *HLA-B\*15:55*, *HLA-B\*15:88*, *HLA-B\*15:89*, *HLA-B\*18:20*, *HLA-B\*15:112*, *HLA-B\*15:121*, *HLA-B\*15:144*, and *HLA-B\*15:170*. However, most of these alleles are rare and exist only in specific ethnicities, and it is not known if any of these subtypes are associated with hypersensitivity. For example, *HLA-B\*15:13*, while rare, has been observed more in Asian populations than other populations.

Samples may contain donor DNA if obtained from patients who received non-leukoreduced blood transfusions or allogeneic hematopoietic stem cell transplantation (AH SCT). Results from samples obtained under these circumstances may not accurately reflect the recipient's genotype. For individuals who have received blood transfusions, the genotype usually reverts to that of the recipient within 6 weeks. The impact of AH SCT on risk of adverse cutaneous reactions is not defined in the literature.

### Clinical Reference

1. 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.* 2018;103(4):574-581
2. Caudle KE, Rettie AE, Whirl-Carrillo M, et al: Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. *Clin Pharmacol Ther.* 2014;96(5):542-548
3. McCormack M, Alfirevic A, Bourgeois S, et al: HLA-A\*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *N Engl J Med.* 2011;364:1134-1143
4. Amstutz U, Shear NH, Rieder MJ, et al: Recommendations for HLA-B\*15:02 and HLA-A\*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. *Epilepsia.* 2014;55:496-506
5. Caudle KE, Rettie AE, Whirl-Carrillo M, et al: Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. *Clin Pharmacol Ther.* 2014;96(5):542-548

### Performance

#### Method Description

Genomic DNA is extracted from whole blood. Amplification for the *HLA-B\*15:02* and *HLA-A\*31:01* alleles and an internal control gene is performed by real-time polymerase chain reaction (PCR) in the presence of SYBR Green, which fluoresces when bound to double-stranded DNA. A genotype is assigned based on the allele-specific SYBR Green fluorescent signals that are detected. (Unpublished Mayo method)

**PDF Report**

No

**Day(s) Performed**

Monday, Wednesday through Friday

**Report Available**

1 to 5 days

**Specimen Retention Time**

Whole Blood/Saliva: 2 weeks; Extracted DNA: 2 months

**Performing Laboratory Location**

Rochester

**Fees & Codes****Fees**

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact [Customer Service](#).

**Test Classification**

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

**CPT Code Information**

81381 x 2

**LOINC® Information**

Test ID	Test Order Name	Order LOINC® Value
CARBR	Carbamazepine PGx Panel, V	94855-4

Result ID	Test Result Name	Result LOINC® Value
610657	HLA-A*31:01 Genotype	79712-6
610658	HLA-B*15:02 Genotype	57979-7
610659	Carbamazepine PGx Panel Phenotype	93308-5
610660	Interpretation	69047-9
610661	Additional Information	48767-8
610662	Method	85069-3
610663	Disclaimer	62364-5

## Test Definition: CARBR

Carbamazepine Hypersensitivity  
Pharmacogenomics, Varies

610664	Reviewed by	18771-6
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