Test Definition: CARPO

Carbamazepine PGx Panel, Saliva

Overview

Useful For

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

Genotyping patients who prefer not to have their blood drawn

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
- Multiple Saliva Genotype Tests
- Pharmacogenomic Associations Tables
- Informed Consent for Genetic Testing (Spanish)

Method Name

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

NY State Available

Yes

Specimen

Specimen Type

Saliva

Specimen Required

Multiple saliva genotype tests can be performed on a single specimen after a single extraction. See Multiple Saliva Genotype Tests in Special Instructions for a list of tests that can be ordered together.

Supplies: DNA Saliva Collection Kit (T651)

Container/Tube: Oragene DNA Self-Collection Kit (T651: fees apply)

Specimen Volume: Full tube

Collection Instructions:

1. Fill tube to line.

2. Send specimen in original container per kit instructions.

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 in Special Instructions:

-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:

-Pharmacogenomics Test Request (T797)

-Therapeutics Test Request (T831)

Specimen Minimum Volume

1 mL

Reject Due To

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

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Saliva	Ambient		

Clinical and Interpretive

Clinical Information

Carbamazepine is an aromatic anticonvulsant. Oxcarbamazepine, eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital are also in this category. Carbamazepine is FDA-approved for the treatment of epilepsy, trigeminal neuralgia, and bipolar disorder. A minority of carbamazepine-treated persons have cutaneous adverse reactions that vary in prevalence and severity, with some forms associated with substantial morbidity and mortality. More severe reactions, such as the hypersensitivity syndrome, are associated with mortality of up to 10% and include symptoms such as rash, fever, eosinophilia, hepatitis, and nephritis. 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.

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, including 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.Â 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 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 oxcarbamazepine 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.

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 heterologous blood transfusions or allogeneic hematopoietic stem cell transplantation (AHSCT). 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 AHSCT 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 Pharacol 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 saliva. Amplification for the *HLA-B*15:02* and *HLA-A*31:01* alleles and an internal control gene is performed by real-time 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) and Time(s) Test Performed

Monday, Wednesday through Friday; 8 a.m.

Analytic Time

1 day (not reported on Saturday or Sunday)

Maximum Laboratory Time

5 days

Specimen Retention Time

Saliva: 2 weeks; Extracted DNA: 2 months

Performing Laboratory Location

Rochester

Fees and 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 Regional Manager. 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. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

81381 x 2

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
CARPO	Carbamazepine PGx Panel, Saliva	94855-4

Result ID	Test Result Name	Result LOINC Value
37300	HLA-A3101 Genotype	79712-6
37301	HLA-B1502 Genotype	57979-7
37302	Carbamazepine PGx Panel Phenotype	93308-5
37303	Carbamazepine PGx Panel Interpretation	69047-9
37408	Reviewed by	18771-6