MAYO CLINIC LABORATORIES

Test Definition: HL57R

HLA-B*57:01 Genotype, Pharmacogenomics, Varies

Overview

Useful For

Identifying individuals with an increased risk of hypersensitivity reactions to abacavir, based on the presence of the human leukocyte antigen *HLA-B*57:01* allele

Identifying individuals taking pazopanib who have an increased risk of elevated alanine aminotransferase levels based of the presence of the human leukocyte antigen *HLA-B*57:01* allele

Testing Algorithm

See Abacavir Hypersensitivity Testing and Initial Patient Management Algorithm

For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables

Special Instructions

- Informed Consent for Genetic Testing
- Abacavir Hypersensitivity Testing and Initial Patient Management Algorithm
- 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. Include concentration 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 a Therapeutics Test Request (T831) with the specimen.

Specimen Minimum Volume

Blood: 0.4 mL
Saliva: 1 swab

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

The human leukocyte antigen (HLA) genes help the immune system recognize and respond to foreign substances (such as viruses and bacteria). The *HLA-B* gene encodes a class I HLA molecule in the major histocompatibility complex (MHC), which acts by presenting peptides to immune cells. There are more than 1500 different HLA-B alleles identified, one of which is the *HLA-B*57:01* allele. Frequency of the *HLA-B*57:01* allele varies with ethnicity, with a frequency of 6% to 7% in European populations and up to 20% in Southwest Asian populations.

The *HLA-B*57:01* allele has been associated with hypersensitivity to abacavir, a highly effective nucleoside analog reverse-transcriptase inhibitor used to treat HIV infection and AIDS. Per the Clinical Pharmacogenomics Implementation Consortium (CPIC) dosing guidelines for abacavir and HLA-B, individuals who are positive for the *HLA-B*57:01* allele are at an increased risk for abacavir hypersensitivity, and it is not recommended for use in treating these individuals.

Hypersensitivity reactions, which generally occur during the first 6 weeks of treatment, are often nonspecific and include skin rashes, gastrointestinal symptoms (eg, nausea, vomiting, diarrhea, and abdominal pain), and respiratory symptoms. Fatalities have been reported with abacavir hypersensitivity. Prospective testing for the *HLA-B*57:01* genotype and excluding *HLA-B*57:01*-positive individuals from treatment with abacavir decreases the incidence of abacavir hypersensitivity.
Pazopanib is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma and advanced soft tissue sarcoma who have received prior chemotherapy. In clinical trials with pazopanib, hepatotoxicity was observed, manifested as increases in serum transaminases such as alanine aminotransferase (ALT), aspartate aminotransferase , and bilirubin. This hepatotoxicity can be severe and fatal. Patients older than 65 years are at greater risk for hepatotoxicity. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks).

Patients who are *HLA-B*57:01* carriers and are taking pazopanib are at increased risk of elevated ALT levels.(1,2) According to the FDA label for pazopanib, in an analysis of data from 31 clinical studies of pazopanib administered as either monotherapy or in combination with other agents, elevation in ALT to levels greater than 3 times the upper limit of normal occurred in 32% (42/133) of *HLA-B*57:01* allele carriers as compared to 19% (397/2101) of noncarriers. Furthermore, elevation in ALT to levels greater than 5 times the upper limit of normal occurred in 19% (25/133) of *HLA-B*57:01* allele carriers and in 10% (213/2101) of noncarriers. All patients taking pazopanib should have hepatic function monitored, regardless of *HLA-B*57:01* carrier status, and administration of pazopanib should be interrupted, reduced, or discontinued according to recommendations in the FDA label if hepatic function is impaired.

UGT1A1 genotype is also relevant to pazopanib-induced hyperbilirubinemia and testing may also be warranted. For more information see U1A1Q / UDP-Glucuronosyltransferase 1A1 TA Repeat Genotype, *UGT1A1*, Varies.

Reference Values

Negative
An interpretive report will be provided.

Interpretation

Positivity for human leukocyte antigen allele *HLA-B*57:01* confers high risk for hypersensitivity to abacavir and higher risk of elevated alanine aminotransferase (ALT) levels in patient taking pazopanib.

For more information see Abacavir Hypersensitivity Testing and Initial Patient Management Algorithm.

For additional information regarding pharmacogenomic genes and their associated drugs, see the. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Cautions

Samples may contain donor DNA if obtained from patients who received nonleukoreduced blood transfusions or allogeneic hematopoietic stem cell transplantation. 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 hematopoietic stem cell transplantation on risk of abacavir hypersensitivity reactions is not defined in the literature.

The FDA recommends screening for the *HLA-B*57:01* allele before initiating therapy with abacavir. Genotyping is also critical when there is a clinical history of, or when the physician suspects, an abacavir hypersensitivity reaction. However, FDA guidance states that, regardless of *HLA-B*57:01* status, abacavir should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Although the negative predictive value of the test is high, a negative *HLA-B*57:01* result does not preclude the development of a hypersensitivity response to abacavir and cannot substitute for clinical vigilance whenever abacavir therapy is administered. Since symptoms of abacavir hypersensitivity are often nonspecific and can imitate other conditions commonly seen in HIV patients on antiretroviral therapy, the phenotypic diagnosis of abacavir hypersensitivity can be challenging. There is significant variability among patients identified as hypersensitive to abacavir. Not all individuals who are positive for *HLA-B*57:01* will have a hypersensitivity reaction.

All patients taking pazopanib should have hepatic function monitored, regardless of *HLA-B*57:01* carrier status, and administration of pazopanib should be interrupted, reduced, or discontinued according to recommendations in the FDA label if hepatic function is impaired.

Rare or novel variants may be present that could lead to false-negative or false-positive results. There may be rare or novel HLA-B alleles that could interfere with this assay. There are, as yet, no data indicating whether any other allele or subtypes are associated with abacavir hypersensitivity or pazopanib hepatotoxicity.

Supportive Data

Sensitivity of this assay for detecting the human leukocyte antigen *HLA-B*57:01* allele approaches 100% with specificity near 96%.(3)

Clinical Reference

1. Xu CF, Johnson T, Wang X, et al: HLA-B*57:01 confers susceptibility to pazopanib-associated liver injury in patients with cancer. Clin Cancer Res. 2016 Mar 15;22(6):1371-1377
2. Pazopanib. Package insert. Novartis Pharmaceuticals; Updated February 2022. Accessed June 29, 2022. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=eeaaaf38-fb86-4d9f-a19d-0f61daac2fd7
3. Saag M, Balu R, Brachman P, et al: High sensitivity of HLA-B*5701 in whites and blacks in immunologically-confirmed cases of abacavir hypersensitivity. Fourth IAS Conference on HIV Pathogenesis, Treatment, and Prevention. July 22-25, 2007. Sydney. Abstract WEAB305
4. Martin M, Klein T, Dong B, Pirmohamed M, Haas DW, Kroetz DL: Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B genotype and abacavir dosing. Clin Pharmacol Ther. 2012 Apr;91(4):734-738
5. Martin M, Hoffman J, Freimuth R, et al: Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B

genotype and abacavir dosing: 2014 update. Clin Pharmacol Ther. 2014 May;95(5):499-500
6. Faruki H, Heine U, Brown T, Koester R, Lai-Goldman M: HLA-B*5701 clinical testing: early experience in the United States. Pharmacogenet Genomics. 2007 Oct;17(10):857-860
7. Sun HY, Hung CC, Lin PH, et al: Incidence of abacavir hypersensitivity and its relationship with HLA-B*5701 in HIV-infected patients in Taiwan. J Antimicrob Chemother. 2007 Sep60(3):599-604. doi: 10.1093/jac/dkm243

Performance

Method Description
Genomic DNA is extracted from the sample. Amplification for the *HLA-B*57:01* allele and an internal control gene is performed by real-time polymerase chain reaction 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.(Hammond E, Mamotte C, Nolan D, Mallal S: HLA-B*5701 typing: evaluation of an allele-specific polymerase chain reaction melting assay. Tissue Antigens. 2007 Jul;70[1]:58-61)

PDF Report
No

Day(s) Performed
Monday, Wednesday through Friday

Report Available
3 to 7 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.

Test Definition: HL57R

HLA-B*57:01 Genotype, Pharmacogenomics, Varies

CPT Code Information

81381

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
HL57R	HLA-B 5701 Genotype, V	50956-2

Result ID	Test Result Name	Result LOINC® Value
610672	HLA-B *57:01 Genotype	50956-2
610673	HLA-B *57:01 Phenotype	93308-5
610674	Interpretation	69047-9
610675	Additional Information	48767-8
610676	Method	85069-3
610677	Disclaimer	62364-5
610678	Reviewed by	18771-6