Test Definition: 2C9QT

Cytochrome P450 2C9 Genotype, Varies

Overview

Useful For

Identifying individuals who may be at risk for altered metabolism of drugs that are modified by cytochrome P450 2C9

Special Instructions

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

Method Name

Real-Time Polymerase Chain Reaction (PCR) with Allelic Discrimination Analysis

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

If patient is or will be using warfarin, the preferred test is WARSQ / Warfarin Response Genotype, Varies, which includes testing of *CYP2C9*, *VKORC1, CYP4A2,* and rs12777823.

Testing is available as the single gene assay (this test) or as a part of a focused pharmacogenomics panel, which includes testing for the following genes: *CYP*s *1A2, 2C9, 2C19, 2D6, 3A4, 3A5, 4F2, SLCO1B1,* and *VKORC1*.

If multiple pharmacogenomic genotype testing is needed, order PGXQP / Focused Pharmacogenomics Panel, 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
Patient Preparation: Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.
Supplies:
DNA Saliva Kit High Yield (T1007)
Saliva Swab Collection Kit (T786)
Container/Tube:
Preferred: High-yield DNA saliva kit
Acceptable: Saliva swab
Specimen Volume: 1 Tube if using T1007 or 2 swabs if using T786
Collection Instructions: Collect and send specimen per kit instructions.
Specimen Stability Information: Ambient (preferred) 30 days/Refrigerated 30 days
Additional Information: Saliva specimens are acceptable but not recommended. Due to lower quantity/quality of DNA yielded from saliva, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.

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)/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:
-Neurology Specialty Testing Client Test Request (T732)
-Therapeutics Test Request (T831)

Specimen Minimum Volume

Blood: 0.4 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

Primary metabolism of many drugs is performed by the cytochrome P450 (CYP) enzymes, a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues, but primarily in the intestines and liver. One of these CYP enzymes, CYP2C9, participates in the metabolism of a wide variety of drugs including warfarin and phenytoin.

CYP2C9-mediated drug metabolism is variable among individuals. Some individuals have *CYP2C9* genetic variants that lead to severely diminished or absent CYP2C9 catalytic activity (ie, poor metabolizers). These individuals may metabolize various drugs at a slower rate than normal and may require dosing adjustments to prevent adverse drug reactions.

A number of specific *CYP2C9* variants have been identified that result in enzymatic deficiencies. The following information outlines the relationship between the variants detected in the assay and their effect on enzyme activity:

Table. Enzyme Activity of Individual Star Alleles

***CYP2C9* allele**	**cDNA nucleotide change** (NM_000771.3)	**Effect on enzyme metabolism**
**1*	None (wild type)	Normal activity
**2*	c.430C>T	Reduced activity
**3*	c.1075A>C	No activity
**4*	c.1076T>C	Reduced activity
**5*	c.1080C>G	Reduced activity
**6*	c.818delA	No activity
**8*	c.449G>A	Reduced activity
**9*	c.752A>G	Normal activity
**11*	c.1003C>T	Reduced activity
**12*	c.1465C>T	Reduced activity
**13*	c.269C>T	No activity
**14*	c.374G>A	Reduced activity
**15*	c.485C>A	No activity
**16*	c.895A>G	Reduced activity
**17*	c.1144C>T	Reduced activity
**18*	c.1190A>C	No activity
**25*	c.353_362del	No activity
**26*	c.389C>G	Reduced activity
**28*	c.641A>T	Reduced activity
**30*	c.1429G>A	Reduced activity
**33*	c.395G>A	No activity

*35	c.374G>T;430C>T	No activity

CYP2C9 drug metabolism is dependent on the specific genotype detected and also on the number and type of drugs administered to the patient. Phenotyping is derived from the Pharmacogene Variation Consortium website(1), the Clinical Pharmacogenetics Implementation Consortium website (2), published guidelines (3-5), and an exhaustive review of the *CYP2C9* literature (6-7). Individuals without a detectable *CYP2C9* variant will have the predicted phenotype of an extensive drug metabolizer and are designated as *CYP2C9* *1/*1. If an individual is homozygous or compound heterozygous for an allele with no activity, the individual is predicted to be a poor metabolizer. If an individual is heterozygous for an allele with no activity, the individual is predicted to be an intermediate metabolizer. In some cases, a range of potential phenotypes may be given, depending on the combination of alleles identified.

Patients who are poor metabolizers may benefit from dose alteration or selection of a comparable drug that is not primarily metabolized by CYP2C9. It is important to interpret the results of testing in the context of other coadministered drugs.

Reference Values

An interpretive report will be provided.

Interpretation

An interpretive report will be provided.

The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium.(1)

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

Drug-drug interactions and drug/metabolite inhibition must be considered in the case of all metabolizer categories except poor metabolizer.

It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and patient age.

Cautions

Rare variants may be present that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings (phenotype), additional testing should be considered.

Samples may contain donor DNA if obtained from patients who received non-leukoreduced 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. For individuals who have received allogeneic hematopoietic stem cell transplantation, a pretransplant DNA specimen is recommended for testing.

CYP2C9 genetic test results in patients who have undergone liver transplantation may not accurately reflect the patient's *CYP2C9* status.

This method may not detect all variants that result in altered CYP2C9 activity. Therefore, absence of a detectable variant does not rule out the possibility that a patient has altered CYP2C9 metabolism due to other *CYP2C9* variants that cannot be detected with this method. Furthermore, when 2 or more variants are identified, the cis-/trans- status (whether the variants are on the same or opposite chromosomes) is not always known.

Clinical Reference

1. PharmVar: Pharmacogene Variation Consortium. Updated March 3, 2021. Accessed March 22, 2021. Available at www.pharmvar.org/
2. Clinical Pharmacogenetics Implementation Consortium (CPIC). Accessed October 14, 2020. Available at https://cpicpgx.org/
3. 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. 2021 Feb;109(2):302-309. doi: 10.1002/cpt.2008
4. Johnson JA, Caudle KE, Gong L, et al: Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. Clin Pharmacol Ther. 2017 Sep;102(3):397-404. doi: 10.1002/cpt.668
5. Theken KN, Lee CR, Gong L, et al: Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther. 2020 Aug;108(2):191-200. doi: 10.1002/cpt.1830
6. Niemi M, Cascorbi I, Timm R, Kroemer HK, Neuvonen PJ, Kivisto KT: Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. Clin Pharmacol Ther. 2002;72(3):326-332. doi: 10.1067/mcp.2002.127495
7. Blaisdell J, Jorge-Nebert LF, Coulter S, et al: Discovery of new potentially defective alleles of human CYP2C9. Pharmacogenetics. 2004;14(8):527-537. doi: 10.1097/01.fpc.0000114759.08559.51

Performance

Method Description

Genomic DNA is extracted from whole blood or saliva. Genotyping for the *CYP2C9* alleles is performed using a polymerase chain reaction (PCR)-based 5'-nuclease assay. Fluorescently labeled detection probes anneal to the target DNA. PCR is used to amplify the section of DNA that contains the variant. If the detection probe is an exact match to the target DNA, the 5'-nuclease polymerase degrades the probe, the reporter dye is released from the effects of the quencher dye, and a fluorescent signal is detected. Genotypes are assigned based on the allele-specific fluorescent signals that are detected.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Monday through Friday

Report Available

3 to 8 days

Specimen Retention Time

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

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

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

81227

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
2C9QT	CYP2C9 Genotype, V	46724-1

Result ID	Test Result Name	Result LOINC® Value
610096	CYP2C9 Genotype	46724-1
610568	CYP2C9 Activity Score	104668-9
610098	Interpretation	69047-9
610099	Additional Information	48767-8
610100	Method	85069-3
610101	Disclaimer	62364-5
610102	Reviewed by	18771-6
610097	CYP2C9 Phenotype	79716-7