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| **Lab Dept:** | **Anatomic Pathology** |
| **Test Name:** | **CYTOCHROME P450 2C9 GENOTYPE SEQUENCING** |

### *General Information*

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| **Lab Order Codes:** | 2C9S |
| **Synonyms:** | P450 Genotyping |
| **CPT Codes:** | 81227 – CYP2C9 gene analysis, common variants |
| **Test Includes:** | An interpretive report detailing the patient's 2C9 phenotype and ability to metabolize drugs affected by CYP2C9. |

### *Logistics*

**Test Indications:**

Predicting metabolism status for drugs that are modified by CYP2C9.

Evaluating patients for adverse drug reactions involving fluoxetine. As an aid in altering dosing of antiepileptic drugs such as phenytoin.

Primary metabolism of many drugs is performed by cytochrome P450, a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP450 enzymes, CYP2C9, metabolizes a wide variety of drugs including warfarin and many nonsteroidal anti-inflammatory drugs. It is also partially responsible for metabolizing other drugs such as fluoxetine, fluvastatin, oral hypoglycemic drugs, and phenytoin.

CYP2C9-mediated drug metabolism is variable. Some individuals have altered CYP2C9 gene sequence that result in synthesis of enzyme devoid of catalytic activity or in enzyme with diminished catalytic activity. These individuals may metabolize various drugs at a slower rate than normal and may require dosing adjustments to prevent adverse drug reactions. However, CYP2C9 alleles with "reduced function" may metabolize different drugs at different rates, ranging from near normal to poor, but the literature is incomplete at this time.

Individuals without inactivating polymorphisms have the phenotype of an extensive drug metabolizer and are designated as CYP2C9*1/*1. All of the indentified polymorphisms are autosomal recessive. Consequently, only individuals who are homozygous or who are compound heterozygous for these polymorphisms are poor metabolizers. Individuals who are heterozygous, with 1 normal gene and 1 polymorphic gene, will have metabolism intermediate between the extensive (normal) and poor metabolizers. The CYP2C9*2 allele has greater residual activity than other alleles. Consequently, an individual homozygous for the *2 allele is predicted to be an

intermediate metabolizer.

Dosing of drugs that are metabolized through CYP2C9 may require adjustment for the individual patient. Patients who are poor metabolizers may benefit by dose alteration or by being switched to other comparable drugs that are not metabolized primarily by CYP2C9. The following is a partial listing of drugs known to affect CYP2C9 activity as of the date of this report.

Drugs that undergo metabolism primarily or in part by CYP2C9:
•Antgiotensin II blockers: irgesartan, losartan
•Anticoagulants: warfarin
•Antidepressantas: amitriptyline (minor), fluoxetine (minor)
•Nonsteroidal anti-inflammatory drugs (NSAIDS): celecoxib, diclofenac, ibuprofen, naproxen, piroxicam, suprofen
•Oral hypoglycemic agents: glipizide, glimepiridine, glyburide/glibenclamide, nateglinide, tolbutamide
•Miscellaneous drugs: fluvastatin, phenytoin, rosuvastatin (minor), sulfamethoxazole, tamoxifen, torsemide
•Coadministration may decrease the rate of elimination of other drugs metabolized by CYP2C9.

Drugs known to increase CYP2C9 activity:
•Rifampin, secobarbital, Phenobarbital
•Coadministration of these drugs increases the concentration of CYP2C9 and increases the elimination of drugs metabolized by CYP2C9.

Drugs known to decrease CYP2C9 activity:
•Amiodarone, fluconazole, fluvastatin, fluvoxamine, isoniazid, lovastatin, phenylbutazone, sertraline, sulfamethoxazole, sulfaphenazole, teniposide, ticlopidine, voriconazole, zafirlukast
•Coadministration will decrease the rate of metabolism of CYP2C9-metabolized drugs, increasing the possibility of toxicity, particularly in heterozygous individuals.

**Lab Testing Section:** Anatomic Pathology - Sendouts

**Referred to:** Mayo Medical Laboratories (MML Test: 2C9/60528)

**Phone Numbers:** MIN Lab: 612-813-6280

STP Lab: 651-220-6550

**Test Availability:** Daily, 24 hours

**Turnaround Time:** 2 - 5 days

**Special Instructions:** N/A

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***Specimen***

**Specimen Type:** Whole blood

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| **Container:** | Lavender top tube |
| **Draw Volume:** | 3 mL (minimum: 0.3 mL) blood |
| **Processed Volume:** | Same as Draw Volume |
| **Collection:** | Routine venipuncture |
| **Special Processing:** | Lab Staff: **Do Not** centrifuge. **Do Not** freeze. Submit specimen in original collection container. Store and ship at room temperature. |
| **Patient Preparation:** | Transfusions will interfere with testing. Wait 4-6 weeks post-transfusion to draw. Bone marrow and liver transplants will also interfere with testing. |
| **Sample Rejection:** | Mislabeled or unlabeled specimens |

## *Interpretive*

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| **Reference Range:** | An interpretive report will be provided.<br><br>Drug-drug interactions and drug/metabolite inhibition must be considered when dealing with heterozyqous individuals and individual homozygous for the *2 allele.<br><br>Drug/metabolite inhibition can occur, resulting in inhibition of residual functional CYP2C9 catalytic activity.<br><br>Patients may also develop toxicity problems if liver and kidney function are impaired. |
| **Limitations:** | Patients sho have received a heterologous blood transfusion within the preceding 6 weeks, or who have received an allogeneic blood or marrow transplant, can have inaccurate genetic test results due to presence of donor DNA.<br><br>CYP2C9 genetic test results in patients who have undergone liver transplantation may not accurately reflect the patient's CYP2C9 status.<br><br>Direct DNA testing will not detect all known mutations that result in decreased or inactive CYP2D6. Absence of a detectable gene mutation or polymorphism does not rule out the possibility that a patient has an intermediate or poor metabolizer phenotype.<br><br>This test does not detect polymorphisms. Additional findings, such as small insertions and deletions or novel mutations, will be reported if found. Other polymorphisms in the primer binding regions can affect the testing, and ultimately, the genotyping assessments made. |
| **Methodology:** | Polymerase Chain Reaction (PCR) with Allele-Specific Primer Extension (ASPE)/Bead Hybridization with Fluorescence Detection |

**References:** Mayo Medical Laboratories September 2014