Cytochrome P450 2C9, CYP2C9

**Indications for Ordering**

- Assess genetic risk of abnormal drug metabolism for drugs metabolized by CYP2C9
- Investigate genetic causes that might contribute to a personal or family history of an adverse drug event or therapeutic failure involving a drug metabolized by CYP2C9

**Test Description**

Polymerase chain reaction (PCR)/fluorescence monitoring

- Variant alleles detected – *2, *3

**Tests to Consider**

Primary test
*Cytochrome P450 2C9, CYP2C9 – 2 Variants 2012766*

- May aid in drug selection and dose planning for drugs metabolized by CYP2C9

Related tests

- Many drugs can be metabolized by alternative cytochrome P450 (CYP) enzymes
- Single gene tests available separately
  - *Cytochrome P450 2C19, CYP2C19 – 9 Variants 2012769*
  - *Cytochrome P450 2D6 (CYP2D6) 15 Variants and Gene Duplication 2014547*
  - *Cytochrome P450 3A5 Genotyping, CYP3A5, 2 Variants 2012740*

- Panel includes a comprehensive medication guide based on the genotypes detected
  - *Cytochrome P450 Genotype Panel 2013098*
  - See sample Enhanced Report for panel test

- Therapeutic drug monitoring and/or metabolic ratios may be useful for evaluating the pharmacokinetics of a particular drug for a particular patient
  - See the ARUP Laboratory Test Directory (www.aruplab.com/) for a list of available drug-specific testing (search by test name or number)

*Warfarin Sensitivity, CYP2C9 and VKORC1, 3 Variants 2012772*

- Identify individuals with inherited variants that affect metabolism and/or sensitivity to warfarin

**Disease Overview**

**Prevalence** – allele frequencies differ among ethnic groups

- CYP2C9*2 – Caucasians 13%, African Americans 3%, Asians <1%
- CYP2C9*3 – Caucasians 7%, Asians 4%, African Americans 2%

**Predicted Phenotypes**

- Poor metabolizer
  - 2 impaired alleles
  - May result in few to no drug metabolites when the parent drug is a substrate of CYP2C9
- Intermediate metabolizer
  - 1 impaired allele and 1 functional allele
  - May result in lower levels of drug metabolites when the parent drug is a substrate of CYP2C9
- Normal metabolizer
  - 2 functional alleles
  - Normal levels of drug metabolites when the parent drug is a substrate of CYP2C9

**Treatment issues**

- CYP2C9 is an isoenzyme involved in the metabolism of many clinically used drugs, including
  - Glipizide
  - Ibuprofen
  - Phenobarbital
  - Phenytoin
  - Tolbutamide
  - Warfarin
- Some drugs are inactivated by the pathway (eg, phenytoin)
- Pharmacogenetic variation may lead to inappropriate concentrations of drugs and metabolites resulting in
  - Toxicity and risk for adverse drug reactions
  - Lack of therapeutic benefit
- Actual metabolic phenotype is subject to
  - Drug/drug interactions
  - Clinical factors
  - Other nongenetic factors

**Treatment guidelines**

- The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published dosing guidelines for CYP2C9 genotypes and
  - Phenytoin (eg, Dilantin) – refer to [CPIC dosing guideline](https://www.pharmgkb.org/guideline/PA166122806)
  - Warfarin (eg, Coumadin) – refer to [CPIC dosing guideline](https://www.pharmgkb.org/guideline/PA166104949)
Genetics

Gene – CYP2C9

Inheritance – autosomal codominant

Penetrance – drug dependent

Variants detected
- *2 (rs1799853, c.430C>T) decreased function allele
- *3 (rs1057910, c.1075A>C) decreased function allele
- Variants are numbered according to NM_000771 transcript

Structure/function
Located on chromosome 10

Test Interpretation

Sensitivity/specificity
- Clinical sensitivity – drug dependent
- Analytical sensitivity/specificity – >99%

Results
- By report

Limitations
- Only the targeted CYP2C9 variants will be detected
- Diagnostic errors can occur due to rare sequence variations
- Risk of therapeutic failure or adverse reactions with CYP2C9 substrates may be affected by genetic and nongenetic factors that are not detected by this test
- This result does not replace the need for therapeutic drug or clinical monitoring

References