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

- Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. www.pharmgkb.org. Accessed Aug 2017
- Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2C9 and HLA-B genotype and phenytoin dosing. www.pharmgkb.org. Accessed Aug 2017
- The Human Cytochrome P450 (CYP) Allele Nomenclature Database. www.pharmvar.org/htdocs/archive/index_original.htm. Accessed Nov 2017