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/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
- Additional genotyping tests are available for *CYP2C19* (2012769), *CYP2D6* (0051232), and *CYP3A5* (2012740) as single gene tests or in a panel (2013098)
  - Panel includes a comprehensive medication guide based on the genotypes detected
- 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

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%

Treatment issues
- CYP2C9 is an isoenzyme involved in the metabolism of many clinically used drugs, including
  - Glipizide
  - Ibuprofen
  - Phenobarbital
  - Phenytoin
  - Tolbutamide
  - Warfarin
- 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, available along with the 2011 supplement and other relevant resources at www.pharmgkb.org
- Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2C9 and HLA-B genotype and phenytoin dosing, available along with the 2014 supplement and other relevant resources at www.pharmgkb.org
- The human cytochrome P450 (CYP) allele nomenclature database, available at http://www.cypalleles.ki.se/