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

Indications for Ordering

May be indicated in

- Warfarin (Coumadin)-naïve individuals who are being considered for warfarin therapy
- Individuals with personal or family history of difficulty with warfarin
- Individuals who are adherent to warfarin therapy, but are difficult to treat (eg, those requiring <21 mg per week or >49 mg per week to maintain therapeutic international normalized ratio [INR])
- Individuals who expect to be taken off of warfarin, such as prior to an invasive procedure or surgery, to estimate time required to eliminate the drug

Test Description

Polymerase chain reaction/fluorescence monitoring

- Variants tested
  - *CYP2C9* *2 (rs1799853, c.430C>T)
  - *CYP2C9* *3 (rs1057910, c.1075A>C)
  - *VKORC1**2 (rs9923231, c.-1639G>A)

Tests to Consider

Primary test

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

Related test

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

- Assess genetic risk of abnormal drug metabolism for drugs metabolized by CYP2C9
- May aid in drug selection and dose planning for drugs metabolized by CYP2C9

Disease Overview

Incidence – allele frequencies differ among ethnic groups

- *CYP2C9**2 – Caucasian 13%, African American 3%, Asian <1%
- *CYP2C9**3 – Caucasian 7%, Asian 4%, African American 2%
- *VKORC1**2 – Asian 91%, Caucasian 39%, African American 11%

Pathophysiology

Warfarin – an anticoagulant widely used throughout the world

- Warfarin is administered as a racemic mixture; s-warfarin is more potent than r-warfarin and is thought to mediate most of the anticoagulant activity of warfarin
- Primary mechanism of action is to inhibit vitamin K epoxide reductase (VKOR)
- VROR recycles vitamin K and activates clotting factors II, VII, IX, and X
- Exerts anticoagulant effects by reducing the concentration of these activated clotting factors

Diagnostic issues

- Individual response to warfarin varies
  - Factors affecting response include age, gender, body mass, diet, concomitant medications, and genetic variants
  - An estimated 40-63% of the variability in therapeutic warfarin dose is accounted for by the *CYP2C9**2 and *3 and the *VKORC1**2 variant alleles
- Overdosing and underdosing can result in life-threatening events (eg, bleeding or thrombosis)
  - ~1% of individuals die due to bleeding complications associated with warfarin
  - ~15% of individuals experience minor bleeding complications
- Dose adjustments are often necessary
  - Usually based on INR
  - May be difficult to achieve therapeutic INR in some individuals
- Identifying inherited variants involved with warfarin metabolism and sensitivity can be used to
  - Optimize selection of warfarin doses
  - Reduce time to achieve a therapeutic INR, such as calculating an appropriate loading dose
  - Guide washout time required when warfarin is temporarily discontinued
- Warfarin dosing algorithms based on common genetic variants and clinical factors are publically available, such as WarfarinDosing.org
- Additional dosing guidance is available through drug labeling and professional guidance documents, such as those published by the American College of Chest Physicians (CHEST) and the Clinical Pharmacogenetics Implementation Consortium (CPIC)

Genetics

Genes – *CYP2C9, VKORC1*
Inheritance – autosomal codominant
Penetrance – drug dependent

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity – ~90% in Caucasians when both *CYP2C9* and *VKORC1* are performed
  - Less characterized in other populations
- Analytical sensitivity and specificity – >99% for *CYP2C9* and *VKORC1*

Results

- Positive – *CYP2C9* or *VKORC1* variant(s) detected
  - Lower maintenance doses are predicted
  - Genotype should be interpreted with clinical information
    - Consultation with a clinical pharmacy professional is recommended
- Negative – no variants detected is predictive of *1 functional alleles and normal enzyme activity and VKOR expression
  - No predicted increased risk for warfarin sensitivity

Limitations

- Only the targeted *CYP2C9* and *VKORC1* variants will be detected by this panel
- Diagnostic errors can occur due to rare sequence variations
- Risk of therapeutic failure or adverse reactions with warfarin may be affected by genetic and non-genetic factors that are not detected by this test
- This result does not replace the need for therapeutic drug or clinical monitoring
- This test does not identify patients at risk for warfarin resistance

References

- Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline information for warfarin and CYP2C9, VKORC1, 2014 (www.pharmgkb.org/guideline/PA166104949)
- Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline information for phenytoin and CYP2C9, HLA-B, 2015 (www.pharmgkb.org/guideline/PA166122806)
- American College of Chest Physicians (CHEST) Antithrombotic Guidelines, 9th Ed, 2012 (www.chestnet.org/Guidelines-and-Resources/Guidelines-and-Consensus-Statements/Antithrombotic-Guidelines-9th-Ed)