Warfarin Sensitivity (CYP2C8, CYP2C9, CYP4F2, VKORC1) Genotyping

Warfarin (Coumadin) is an anticoagulant widely used throughout the world. Testing may be indicated for warfarin-naïve individuals prior to starting warfarin therapy, individuals with a personal or family history of difficulty with warfarin, and adherent patients taking warfarin but who are difficult to treat. Testing is also indicated for individuals currently on warfarin and required to discontinue therapy, such as prior to an invasive procedure or surgery, to estimate the time required to eliminate the drug.

DISEASE OVERVIEW

Pathophysiology
- 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)
  - VKOR 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 or underdosing can result in life-threatening events (e.g., 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 international normalized ratio (INR)
  - May be difficult to achieve therapeutic INR in some individuals (e.g., those requiring <21 mg per week or >49 mg per week to maintain INR).

GENETICS

Genes Tested
CYP2C8, CYP2C9, CYP4F2, VKORC1

Variants Tested

<table>
<thead>
<tr>
<th>Gene (Transcript)</th>
<th>Allele</th>
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<tbody>
<tr>
<td>CYP2C8 (NM_000770)</td>
<td>CYP2C8*1C: rs17110453, c.-370T&gt;G</td>
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<tr>
<td></td>
<td>CYP2C8*2: rs11572103, c.805A&gt;T</td>
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<td></td>
<td>CYP2C8*3: rs1059681, c.1196A&gt;G</td>
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<tr>
<td></td>
<td>CYP2C8*4: rs1058930, c.792C&gt;G</td>
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<tr>
<td>Gene (Transcript)</td>
<td>Allele</td>
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<tr>
<td>CYP2C9 (NM_000771)</td>
<td>CYP2C9*2: rs1799853, c.430C&gt;T</td>
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<td>CYP2C9*3: rs1057910, c.1075A&gt;C</td>
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<td>CYP2C9*4: rs56165452, c.1076T&gt;C</td>
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<td>CYP2C9*5: rs28371686, c.1080C&gt;G</td>
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<td>CYP2C9*6: rs9332131, c.818delA</td>
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<td>CYP2C9*8: rs7900194, c.449G&gt;A</td>
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<td>CYP2C9*11: rs28371685, c.1003C&gt;T</td>
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<td>CYP4F2 (NM_001082)</td>
<td>CYP4F2*3: rs2108622, c.1297G&gt;A</td>
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<tr>
<td>VKORC1 (NM_024006)</td>
<td>VKORC1*2: rs9923231, c.-1639G&gt;A</td>
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</table>

Allele frequencies and phenotype predictions are available at www.pharmvar.org or www.pharmgkb.org.

Inheritance
Autosomal codominant

**TEST INTERPRETATION**

**Sensitivity/Specificity**
- Clinical sensitivity – genetic factors and known nongenetic factors account for ~50% of the variability in warfarin dose
- Analytical sensitivity and specificity – &gt;99%

**Results**
-Variant(s) detected:
  - **VKORC1***2 allele is associated with reduced expression of the warfarin target, vitamin K epoxide reductase (VKOR), and a reduced dose requirement
  - The **CYP4F2***3 allele is associated with an increased dose requirement
  - **CYP2C8/9** variants are associated with a reduced rate of warfarin catabolism, which is associated with a decreased dose requirement and an increased time required to achieve steady state
    - Loading doses may be required
    - Vulnerability to drug-drug interactions may also be increased
- No variants detected: predictive of *1 functional alleles
- Genotype should be interpreted with clinical information
- Genetic information and nongenetic factors can be used in combination with warfarin dose calculators, such as through www.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)

**Limitations**
- Only the targeted **CYP2C8**, **CYP2C9**, **CYP4F2** and **VKORC1** variants will be detected by this panel, and assumptions about phase and content are made to assign alleles.
- Diagnostic errors can occur due to rare sequence variations
- Risk of therapeutic failure or adverse reactions with **CYP2C8** or **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**