CYP2C9, VKORC1, and CYP4F2 Testing for Warfarin Response

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9 Genotyping</td>
<td>81227</td>
</tr>
<tr>
<td>VKORC1 Genotyping</td>
<td>81355</td>
</tr>
<tr>
<td>CYP4F2 Genotyping</td>
<td>81479</td>
</tr>
<tr>
<td>Warfarin responsiveness testing by genetic technique using any method</td>
<td>G9143</td>
</tr>
</tbody>
</table>

What is Warfarin sensitivity testing?

Definition

Warfarin (Coumadin®) is a commonly prescribed anticoagulant with a narrow therapeutic range and a 20-fold inter-individual variation in dose requirements. Incorrect dosage, especially during the initial dosing phase, is associated with either severe bleeding or failure to prevent thromboembolism.

- Approximately 21% of patients who receive anticoagulant therapy will experience a major or minor bleeding event. Environmental and genetic factors combined influence 55% of warfarin dose variability and include: age, height, body mass index (BMI), gender, diet, genetic variations in CYP2C9 and VKORC1, use of concomitant medications and indication for warfarin.

- The activity of two genes [cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase complex subunit-1 (VKORC1)] impact the rate of warfarin metabolism and account for up to 40% of the inter-individual dose requirements for warfarin. The addition of a third gene, cytochrome P450 4F2 (CYP4F2) accounts for an additional 2% of warfarin dosing variability.

- CYP2C9 is a p450 enzyme that influences warfarin pharmacokinetics by impacting the rate of metabolism. Poor or intermediate metabolizing 2C9 variants are seen in between 2% to 20% of the population depending on ethnicity. Carriers of alleles *2
and *3 have decreased warfarin metabolism and may require lower warfarin doses.\textsuperscript{4,6}

- Vitamin K activity is important to the blood’s ability to clot. VKORC1 influences the pharmacodynamics and sensitivity of warfarin on the vitamin K cycle. Approximately 14% to 89% of the population display VKORC1 enzyme inhibition making them more sensitive to warfarin.\textsuperscript{2} Carriers of VKORC1 AA genotype (high warfarin sensitivity) require a significantly lower warfarin dose compared to individuals with genotype GA or GG.\textsuperscript{4,6}

- CYP4F2 is a p450 enzyme that counteracts the effects of VKORC1 by limiting the excessive accumulation of Vitamin K. Depending on ethnicity, carriers of the *3 allele (AA or GA genotypes) have a moderate 8-11% increase in warfarin dosing requirements compared to individuals with genotype GG.\textsuperscript{5,6}

- Testing these three genes predicts variability in warfarin dosage requirements. The presence of gene variants in CYP2C9, VKORC1, and CYP4F2 indicate that more careful dosing and monitoring is required to achieve therapeutic anticoagulation and to decrease risk of bleeding or clotting during warfarin dose titration.\textsuperscript{6}

**Test information**

- The CYP2C9 and VKORC1 alleles are thought to be the predominant cause of the variation of warfarin dosing.\textsuperscript{5,7}

- There are approximately 37 alleles reported in the CYP complex, however many do not have a functional impact.
  - Two alleles, *2 and *3 (CYP2C9*2 and CYP2C9*3) are linked to a slower metabolism of warfarin, thereby needing an increase in warfarin dose. These alleles are found in approximately 12.2% and 7.9%, respectively, of the European Caucasian population.\textsuperscript{6,9}
  - Other variants, *4, *5, and *6 are seen in the Asian and African American populations, but typically around a <1% incidence.\textsuperscript{9}

- Diagnosis of these alleles can occur through sequence analysis of the CYP2C9, VKORC1, and CYP4F2 genes. Analytical sensitivity of alleles is expected to be greater than 98%.\textsuperscript{5,8}

**Guidelines and evidence**

- There has been a mixed response to genotyping from professional associations, payors, and other organizations, largely because data supporting the utility of genetic testing to improve clinical endpoints is conflicting. For example, two recent meta-analyses came to opposite conclusions:
  - A genotype-guided dosing strategy did not result in a greater percentage of time that the INR was within the therapeutic range, fewer patients with an INR
greater than 4, or a reduction in major bleeding or thromboembolic events compared with clinical dosing algorithms.\textsuperscript{7}

- Genotype-guided initial dosing is able to reduce serious bleeding events by approximately 50\% (RR = 0.47; 95\% CI, 0.23-0.96; P = 0.040) compared with clinically-guided dosing approaches.\textsuperscript{10}

- The Clinical Pharmacogenetics Implementation Consortium (CPIC, 2017) guidelines state “This guideline recommends that pharmacogenetic warfarin dosing be accomplished through the use of one of the pharmacogenetic dosing algorithms…The two algorithms provide very similar dose recommendations…The warfarindosing.org website contains both algorithms, the Gage algorithm as the primary algorithm and the IWPC [International Warfarin Pharmacogenetics Consortium] algorithm as the secondary algorithm…” It also notes “In patients of African ancestry, CYP2C9*5, *6, *8, *11 are important for warfarin dosing. If these genotypes are not available, warfarin should be dosed clinically without consideration for genotype.” \textsuperscript{6}

- In January 2015, the American Heart Association published a Scientific Statement on Basic Concepts and Potential Applications of Genetics and Genomics for Cardiovascular and Stroke Clinicians.\textsuperscript{11} They noted:

  - “No cardiovascular pharmacogenetic application has yet been fully validated or widely adopted.”
  - “Building on these early findings, additional clinical studies of warfarin pharmacogenetics are underway.”

- The American College of Medical Genetics (ACMG, 2008) and the American College of Chest Physicians (ACCP, 2008) both suggest against routine genotyping to guide warfarin dosing until better evidence is available to support a policy decision, but the ACMG does say that testing might be useful to explain unexpected warfarin responses.\textsuperscript{8,12}

- Product labeling for Coumadin (warfarin) has been updated based on FDA recommendation to include a table recommending initial dosing ranges for patients with different combinations of CYP2C9 and VKORC1 genotypes. Labeling also includes the range of expected therapeutic warfarin doses based on CYP2C9 and VKORC1 genotypes.\textsuperscript{4}

- Publications based on the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial data have indicated that pharmacogenomics-driven dosing algorithms may need to be age- and ethnicity-specific. This revised approach to dosing algorithms will need additional research and validation.\textsuperscript{13,14}

- A systematic meta-analysis review if 9 studies suggest that while “CYP2C9 testing could identify high-risk patients who might benefit from conservation induction regimens, lower maintenance doses, and more frequent clinical and laboratory monitoring,” there is insufficient evidence to support routine genotyping of patients due to a lack of established clinical utility and cost-effectiveness of testing.\textsuperscript{9}
Criteria
This test is considered investigational and/or experimental.

- Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.

- In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

Other considerations
CYP2C9 and VKORC1 testing for all other indications is addressed by the Pharmacogenomic Testing for Drug Toxicity and Response guideline.

References


