Genotype-Guided Warfarin Dosing

**Description**

Using information about an individual's genotype may help in guiding warfarin dosing and could reduce the time to dose stabilization and selection of an appropriate maintenance dose that might avoid the consequences of too much or too little anticoagulation.

**OBJECTIVE**

The objective of this evidence review is to determine whether genotype-guided warfarin dosing improves the net health outcome (e.g., to prevent or treat thromboembolic events) in individuals who require warfarin therapy.

**POLICY STATEMENT**

Genotyping to determine cytochrome P450 2C9 (CYP2C9), P450 4F2 (CYP4F2), and vitamin K epoxide reductase subunit C1 (VKORC1) genetic variants is considered investigational for the purpose of managing the administration and dosing of warfarin, including use in guiding the initial warfarin dose to decrease time to stable international normalized ratio and to reduce the risk of serious bleeding.

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Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td></td>
<td>variant</td>
<td></td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated</td>
<td>Disease-associated variant identified in a proband for use in</td>
</tr>
<tr>
<td></td>
<td>variant</td>
<td>subsequent targeted genetic testing in first-degree relatives</td>
</tr>
</tbody>
</table>

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling

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helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

### Benefit Application

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

### FDA Regulatory Status

Several tests to help assess warfarin sensitivity, by determining the presence or absence of the relevant CYP2C9, VKORC1, and CYP4F2 variants, have been cleared by the U.S. Food and Drug Administration (FDA) for marketing (see Table 1). Similar tests also may be available as laboratory-developed services; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The tests are not identical regarding the specific variants and number of variants detected. Generally, such tests are not intended as stand-alone tools to determine optimum drug dosage but should be used with clinical evaluation and other tools, including the international normalized ratio, to predict the initial dose that best approximates the maintenance dose for patients.

Table 1. FDA-Cleared Warfarin Tests

<table>
<thead>
<tr>
<th>Test (Laboratories)</th>
<th>Alleles Tested</th>
<th>Estimated Time to Completion, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>eSensor Warfarin Sensitivity Test (GenMark Dx)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CYP2C9&lt;sup&gt;*&lt;/sup&gt;2 and *3, VKORC1 1639G&gt;A</td>
<td>3-4</td>
</tr>
<tr>
<td>Rapid Genotyping Assay (ParagonDx)</td>
<td>CYP2C9&lt;sup&gt;*&lt;/sup&gt;2 and *3, VKORC1 1173 C&gt;T</td>
<td>Not reported&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Verigene Warfarin Metabolism Nucleic Acid Test (Nanosphere)</td>
<td>CYP2C9&lt;sup&gt;*&lt;/sup&gt;2 and *3, VKORC1 1173C&gt;T</td>
<td>≤2</td>
</tr>
<tr>
<td>Infiniti 2C9-VKORC1 Multiplex Assay for Warfarin (AutoGenomics)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CYP2C9&lt;sup&gt;*&lt;/sup&gt;2 and *3, VKORC1 1639G&gt;A</td>
<td>6-8</td>
</tr>
<tr>
<td>eQ-PCR™ LightCycler Warfarin Genotyping Kit (TrimGen)</td>
<td>CYP2C9&lt;sup&gt;*&lt;/sup&gt;2 and *3, VKORC1 1639G&gt;A</td>
<td>≤2</td>
</tr>
</tbody>
</table>

Adapted from Cavallari et al (2011).<sup>31</sup>

FEP: Food and Drug Administration.


<sup>b</sup> Langley et al (2009) reported a turnaround time of 1.5 hours for the ParagonDx SmartCycler, which may be a precursor assay.<sup>22</sup>

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The FDA (2007) approved updated labeling for Coumadin to include information on testing for gene variants that may help "personalize" the starting dose for each patient and reduce the number of serious bleeding events. The label was updated again in 2010. With each update, manufacturers of warfarin (Coumadin) were directed to add similar information to their product labels. The 2010 update added information on guiding initial dose by genotyping results for CYP2C9 and VKORC1, providing a table of genotypes, and suggested initial dose ranges for each. However, suggested starting doses are also provided when genotyping information is unavailable, indicating that genetic testing is not required. Furthermore, the FDA did not include information on genetic variation in the label's black box warning on bleeding risk.

**RATIONALE**

### Summary of Evidence

For individuals with conditions requiring warfarin treatment who receive genotype-guided warfarin dosing, the evidence includes multiple RCTs and systematic reviews of the RCTs. The relevant outcomes are morbid events, medication use, and treatment-related mortality and morbidity. Twenty-four RCTs and four systematic reviews were identified. Most RCTs were single-center studies including fewer than 250 patients. Systematic reviews found the percentage of time the INR was in therapeutic range was higher in patients treated with genotype-guided warfarin therapy; however, the heterogeneity between studies was high for this outcome. No RCT reported statistically significant differences in major bleeding or TEEs, but studies were not powered to show differences in these outcomes. Meta-analyses of RCTs found no difference between genotype-guided dosing and clinical dosing for mortality or TEEs, but genotype-guided dosing was associated with a lower risk of major bleeding. Very few trials enrolled sufficient numbers of subpopulations except white participants. In the COAG study, which included 27% African American participants, African Americans fared better in the clinically guided group than in the genotype-guided group. The evidence is insufficient to determine the effects of the technology on health outcomes.

### SUPPLEMENTAL INFORMATION

#### Practice Guidelines and Position Statements

**American College of Medical Genetics**

The American College of Medical Genetics (2008) policy statement on pharmacogenetic testing concluded: "There is insufficient evidence, at this time, to recommend for or against routine CYP2C9 and VKORC1 testing in warfarin-naive patients."64.

**American College of Chest Physicians**

The ninth edition of the American College of Chest Physicians' (2012) evidence-based clinical practice guidelines on antithrombotic therapy and prevention of thrombosis stated: "For patients initiating VKA [vitamin K antagonist] therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B)."65.

**Clinical Pharmacogenetics Implementation Consortium**

The Clinical Pharmacogenetics Implementation Consortium (2017) updated guidelines for pharmacogenetics-guided warfarin dosing.66. The guideline provides recommendations for genotype-guided warfarin dosing to achieve a target international normalized ratio of 2-3 for adult and pediatric patients specific to continental ancestry. The guideline also states that "Although there is substantial evidence associating CYP2C9 and VKORC1 variants with warfarin dosing, randomized clinical trials have demonstrated inconsistent results in terms of clinical outcomes."
The Centers for Medicare & Medicaid Services (2009) published a national coverage determination on pharmacogenomic testing for warfarin response. The Centers for Medicare & Medicaid Services stated that "the available evidence does not demonstrate that pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness improves health outcomes in Medicare beneficiaries outside the context of CED, and is therefore not reasonable and necessary...." However, the Centers also "believes that the available evidence supports that coverage with evidence development (CED) ... is appropriate for pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness by any method, and is therefore covered only when provided to Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin who:

1. Have not been previously tested for CYP2C9 or VKORC1 alleles; and
2. Have received fewer than five days of warfarin in the anticoagulation regimen for which the testing is ordered; and
3. Are enrolled in a prospective, randomized, controlled clinical study when that study meets described standards."

REFERENCES


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### Policy History

This policy was approved by the FEP® Pharmacy and Medical Policy Committee according to the history below:

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2012</td>
<td>New policy</td>
<td>Policy updated with literature review; no changes to policy statement. References 18, 29, 40, 43, 52, 57, 62 added.</td>
</tr>
<tr>
<td>March 2013</td>
<td>Replace policy</td>
<td>Policy updated with literature review through November 14, 2013; no changes to policy statement. References 17, 53, 57, 59-60, 62-64, 71-73 and 75 added; references renumbered.</td>
</tr>
<tr>
<td>March 2014</td>
<td>Replace policy</td>
<td>Policy updated with literature review through October 30, 2014; references 49-51, 69-72, and 78 added; policy statement unchanged.</td>
</tr>
<tr>
<td>June 2015</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 9, 2018; references 5, 31, 51, 52-54, 56-57, 63-66, and 69 were added. Policy revised with updated genetics nomenclature. Investigational policy statement expanded to include genotyping for CYP4F2. Title changed to reflect focus on genotype-guided dosing as an intervention.</td>
</tr>
<tr>
<td>September 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 18, 2019; references added. Policy statement unchanged.</td>
</tr>
</tbody>
</table>

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