This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

### Populations

<table>
<thead>
<tr>
<th>Individuals:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• With conditions requiring warfarin treatment</td>
</tr>
</tbody>
</table>

### Interventions

<table>
<thead>
<tr>
<th>Interventions of interest are:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Genetic testing for CYP2C9 and VKORC1 variants to determine warfarin dose</td>
</tr>
</tbody>
</table>

### Comparators

<table>
<thead>
<tr>
<th>Comparators of interest are:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical management without genetic testing</td>
</tr>
</tbody>
</table>

### Outcomes

<table>
<thead>
<tr>
<th>Relevant outcomes include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Test accuracy</td>
</tr>
<tr>
<td>• Test validity</td>
</tr>
<tr>
<td>• Other test performance measures</td>
</tr>
<tr>
<td>• Morbid events</td>
</tr>
<tr>
<td>• Medication use</td>
</tr>
<tr>
<td>• Treatment-related morbidity</td>
</tr>
</tbody>
</table>

### Description

Variants in the CYP2C9 and VKORC1 genes result in differences in warfarin metabolism. Using information about an individual’s CYP2C9 and VKORC1 genotypes may help in personalizing warfarin dosing and could reduce the time to dose stabilization and selection of appropriate maintenance dose that might avoid consequences of too much or too little anticoagulation.

### Summary of Evidence

For individuals with conditions requiring warfarin treatment who are being managed with genetic testing for CYP2C9 and VKORC1 variants to determine warfarin dose, the evidence includes multiple randomized controlled trial (RCTs), systematic reviews of the RCTs, and cohort studies. Relevant outcomes are test accuracy and validity, other test performance measures, morbid events, medication use, and treatment-related morbidity. The evidence on clinical validity from several retrospective and prospective cohort studies has shown that algorithms incorporating genetic variants and clinical factors explain greater variance in warfarin dosing over that predicted by clinical factors alone. However, the incremental gain using genetic testing depends on multiple factors, including ethnicity. Further, there is no consensus on a single algorithm that could be generalized to a diverse population. Multiple smaller randomized trials and meta-analyses of these trials have examined the clinical utility of genetic tests to guide warfarin dose and reported inconsistent results. Two large adequately powered RCTs attempted to address this inconsistency but reported contrasting results. Of these two trials, the larger U.S.-based RCT found no utility in adding genetic testing to a clinical dosing algorithm. The percentage of time in
the therapeutic international normalized ratio range was similar when genetic testing was and was not added. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

Genotyping to determine cytochrome p450 2C9 (CYP2C9) 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 reduce the risk of serious bleeding.

Policy Guidelines

Genetics Nomenclature Update

Human Genome Variation Society (HGVS) 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). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and 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 variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></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

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
Medicare Advantage

For Medicare Advantage there may be potential for benefit under coverage with evidence development (CED) when the members 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 CMS standards.

For Medicare Advantage the available evidence does not demonstrate that pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness improves health outcomes outside the context of CED, and is therefore **not medically necessary**.

Background

Warfarin is administered to prevent and treat thromboembolic events in high-risk patients; warfarin dosing is a challenging process, due to the narrow therapeutic window, variable response to dosing and serious bleeding events in 5% or more of patients (depending on definition). Patients are typically given a starting dose of two to five mg and monitored frequently with dose adjustments until a stable international normalized ratio (INR) value (a standardized indicator of clotting time) between two and three is achieved. During this adjustment period, a patient is at high risk of bleeding.

Stable or maintenance warfarin dose varies among patients by more than an order of magnitude. Factors influencing stable dose include body mass index, age, interacting drugs, and indication for therapy.

Warfarin, which is primarily metabolized in the liver by the CYP2C9 enzyme, exerts an anticoagulant effect by inhibiting the protein vitamin K epoxide reductase complex, subunit 1 (VKORC1). Three single-nucleotide variants (SNVs), two in the CYP2C9 gene and one in the VKORC1 gene play key roles in determining the effect of warfarin therapy on coagulation. CYP2C9*1 metabolizes warfarin normally, CYP2C9*2 reduces warfarin metabolism by 30%, and CYP2C9*3 reduces warfarin metabolism by 90%. Because warfarin given to patients with *2 or *3 variants will be metabolized less efficiently, the drug will remain in circulation longer, so lower warfarin doses will be needed to achieve anticoagulation. Recent genome-wide association studies have also identified that a SNV in the CYP4F2 gene has been reported to account for a small proportion of the variability in stable dose (the CYP4F2 gene encodes a protein involved in vitamin K oxidation).

Using the results of CYP2C9 and VKORC1 genetic testing to predict a warfarin starting dose that approximates a likely maintenance dose may benefit patients by decreasing the risk of serious bleeding events and the time to stable INR. Algorithms have incorporated not only genetic variation but also other significant patient characteristics and clinical factors to predict the best starting dose.

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 in terms of 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 Test

<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, Carlsbad, CA)a</td>
<td>CYPC9*2 and *3, VKORC1 1639G&gt;A</td>
<td>3-4</td>
</tr>
<tr>
<td>Rapid Genotyping Assay (ParagonDx, Morrisville, NC)</td>
<td>CYPC9*2 and *3, VKORC1 1173 C&gt;T</td>
<td>Not reportedb</td>
</tr>
<tr>
<td>Verigene® Warfarin Metabolism Nucleic Acid Test (Nanosphere, Northbrook, IL)</td>
<td>CYPC9*2 and *3, VKORC1 1173 C&gt;T</td>
<td>≤ 2</td>
</tr>
<tr>
<td>Infiniti® 2C9-VKORC1 Multiplex Assay for Warfarin (AutoGenomics, Vista, CA)c</td>
<td>CYP2C9*2 and *3, VKORC1 1639G&gt;A</td>
<td>6-8</td>
</tr>
<tr>
<td>eQ-PCR™ LightCycler® Warfarin Genotyping Kit (TrimGen, Sparks Glencoe, MD)</td>
<td>CYP2C9*2 and *3, VKORC1 1639G&gt;A</td>
<td>≤ 2</td>
</tr>
</tbody>
</table>

FDA: Food and Drug Administration.


b Langley et al (2009) reported a turnaround time of 1.5 hours for the ParagonDx SmartCycler, which may be a precursor assay.2


In August 2007, the FDA 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 January 2010. With each update, manufacturers of warfarin (generic for Coumadin®) were directed to add similar information to their products’ labels. The 2010 update added information on personalizing 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.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


