Introduction

Warfarin (Coumadin) is a blood thinner that works by reducing the blood’s ability to clot. It’s often prescribed to prevent blood clot formation in people who have conditions like atrial fibrillation. Finding the correct dose can be complicated. Too high a dose can cause bleeding. Too low a dose can result in blood clots being formed. Factors such as age, weight, use of other medications, and smoking go into the calculation of how much is prescribed. Once the drug is prescribed, the doctor then adjusts the dose based on blood tests. Two genes have been associated with how well the body processes warfarin. Genetic tests have been developed to look at these genes to try to determine warfarin dosing. These genetic tests are investigational (unproven). Medical studies do not show whether genetic testing to try to adjust warfarin doses leads to better health results. More studies are needed.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
### Test

| Testing of cytochrome p450 2C9 (CYP2C9), P450 4F2 (CYP4F2), and vitamin K epoxide reductase subunit C1 (VKORC1) | Genotyping for CYP2C9, CYP4F2, and VKORC1 variants is considered investigational to manage the administration and dosing of warfarin, including:
- Guiding the initial warfarin dose
- Decreasing the time needed to achieve a stable international normalized ratio (INR)
- Reducing the risk of serious bleeding |

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>Drug metabolism (warfarin drug response), targeted sequence analysis (ie, CYP2C9, CYP4F2, VKORC1, rs12777823) (new code effective 1/1/18)</td>
</tr>
<tr>
<td>HCPCS</td>
<td>Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

### Related Information

**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 (see Table 1). 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 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table 1. 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 2. 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 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.
Evidence Review

Description

Using information about an individual's genotypes 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.

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 2 to 5 mg and are frequently monitored with dose adjustments until a stable international normalized ratio value (a standardized indicator of clotting time) between 2 and 3 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, two in the CYP2C9 gene and one in the VKORC1 gene play key roles in determining the effect of warfarin therapy on coagulation.\textsuperscript{1-10} 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. CYP2C9 and VKORC1 genetic variants account for approximately 55% of the variability in warfarin maintenance dose.\textsuperscript{1,11} Recent genome-wide association studies have also identified that a single nucleotide variant 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).\textsuperscript{12,13} Studies have predicted that CYP4F2
variants explain 2% to 7% of the variability in warfarin dose in models, including other genetic and nongenetic factors.\textsuperscript{13,14}

Using the results of \textit{CYP2C9} and \textit{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 international normalized ratio. Algorithms have incorporated not only genetic variation but also other significant patient characteristics and clinical factors to predict the best starting dose.\textsuperscript{2,15-21} Studies have compared the ability of different algorithms to predict stable warfarin dose accurately.\textsuperscript{22-26} Currently, there does not appear to be consensus for a single algorithm.\textsuperscript{25}

Several studies have examined associations between \textit{CYP2C9} and \textit{VKORC1} variants and warfarin dosing requirements in children.\textsuperscript{27-29}

There are different frequencies of variants related to warfarin pharmacokinetics across different races and ethnicities. Many of the original studies identifying associations between genes and prediction of warfarin dosing as well as studies developing algorithms were derived from cohorts composed largely of people of European descent. Evidence has suggested these algorithms do not perform as well in other ethnic groups.\textsuperscript{16-18,30} For example, \textit{CYP2C9*2} and \textit{CYP2C9*3} are not as useful in predicting warfarin dosing in African Americans, but other important variants have been identified such as \textit{CYP2C9*5, *6, *8, and *11}.\textsuperscript{31} Studies have also identified new genetic variants and/or evaluated clinical genetic algorithms for warfarin dose in African American,\textsuperscript{32-34} Puerto Rican,\textsuperscript{35} Thai,\textsuperscript{36} Egyptian,\textsuperscript{37,38} Chinese,\textsuperscript{39-41} Japanese,\textsuperscript{42} Arabic,\textsuperscript{43} Turkish,\textsuperscript{44} and Scandinavian\textsuperscript{45} populations.

\textbf{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. Relevant outcomes are morbid events, medication use, and treatment-related mortality and morbidity. Fourteen RCTs were identified. While 5 of the 14 RCTs reported statistically significant differences in outcomes related to the international normalized ratio, none of the trials or pooled meta-analyses of the trials have shown a benefit for outcomes of major bleeding or venous thromboembolism. In the pooled analysis including 2223 participants, 87 events of the composite outcome (mortality, major bleed, and thromboembolic events) occurred (relative risk, 0.85; 95% confidence interval, 0.54 to 1.34; p=0.48). In the GIFT trial, which included 1650 participants, conducted after the pooled analysis, 2 vs 8 major bleeding events occurred (relative risk, 0.24; 95% confidence interval, 0.05 to 1.15), 33 vs 38 venous thromboembolism events.
occurred (relative risk, 0.85; 95% confidence interval, 0.54 to 1.34), and there were no deaths.

Very few trials have 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.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 3.

**Table 3. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01633957</td>
<td>A Trial of Genotype-based Warfarin Initiation in Patients With Mechanical Prosthetic Heart Valve (SYSU-WARFA)</td>
<td>200</td>
<td>Aug 2016 (ongoing)</td>
</tr>
<tr>
<td>NCT00700895</td>
<td>A Randomized Controlled Trial to Assess the Clinical Benefits of a Pharmacogenetics-Guided Dosing Regimen for Calculating Warfarin Maintenance Dose</td>
<td>320</td>
<td>Aug 2017 (ongoing)</td>
</tr>
<tr>
<td>NCT00964353</td>
<td>The Hospital and Economics CERT: Project 1: The Clinical and Economic Implications of Genetic Testing for Warfarin Management</td>
<td>268</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT03479684</td>
<td>Randomized Trial of Genotype-guided Versus Standard for Warfarin Dosing</td>
<td>560</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>NCT02592980</td>
<td>Evaluation of a Pharmacogenetic-based Warfarin Dosing Algorithm in Patients With Low Time in Therapeutic Range - Study Design</td>
<td>300</td>
<td>Dec 2019</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01305148a</td>
<td>Warfarin Adverse Event Reduction For Adults Receiving Genetic Testing at Therapy INitiation (WARFARIN)</td>
<td>3800</td>
<td>Dec 2015 (suspended)</td>
</tr>
<tr>
<td>NCT02065388</td>
<td>Pharmacogenetic Dosing of Warfarin</td>
<td>300</td>
<td>Dec 2013 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

*a* Denotes industry-sponsored or cosponsored trial.
Practice Guidelines and Position Statements

American College of Medical Genetics

The 2008 American College of Medical Genetics policy statement on pharmacogenetics testing concluded:

“There is insufficient evidence, at this time, to recommend for or against routine CYP2C9 and VKORC1 testing in warfarin-naive patients.”

American College of Chest Physicians

The 9th edition of the American College of Chest Physicians evidence-based clinical practice guidelines (2012) 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).”

Clinical Pharmacogenetics Implementation Consortium

The Clinical Pharmacogenetics Implementation Consortium updated guidelines for pharmacogenetics-guided warfarin dosing in 2017. 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.”

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force has not addressed genotype-guided warfarin therapy.
Medicare National Coverage

In 2009, the Centers for Medicare and Medicaid Services 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:

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

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 4). 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 4. 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, Carlsbad, CA)</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 reported^b</td>
</tr>
<tr>
<td>Verigene® Warfarin Metabolism Nucleic Acid Test (Nanosphere, Northbrook, IL)</td>
<td>CYPC9*2 and *3, VKORC1 1173C&gt;T</td>
<td>≤2</td>
</tr>
<tr>
<td>Infiniti® 2C9-VKORC1 Multiplex Assay for Warfarin (AutoGenomics, Vista, CA)</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>

Adapted from Cavallari et al (2011).^46

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.22

In 2007, 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 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, FDA did not include information on genetic variation in the label’s black box warning on bleeding risk.

References


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/13/07</td>
<td>Add to Pathology/Laboratory section - New Policy</td>
</tr>
<tr>
<td>01/13/09</td>
<td>Replace Policy - Policy updated with literature search. Policy statement updated to include “for the purpose of managing the administration and dosing of warfarin, including use in guiding the initial warfarin dose to decrease time to stable INR and reduce the risk of serious bleeding” in the investigational statement. References added.</td>
</tr>
<tr>
<td>02/09/10</td>
<td>Replace Policy - Policy updated with literature search; no change to the policy statement. References added.</td>
</tr>
<tr>
<td>02/08/11</td>
<td>Replace Policy - Policy updated with literature search; no change in policy statement. References 25, 26, 34-38, 40 and 41 added; reference 31 updated.</td>
</tr>
<tr>
<td>02/14/12</td>
<td>Replace Policy – Policy updated with literature review; no changes to policy statements. References 33, 38, 44-46, 53, 58, 60 added. Codes 81227 and 81355 added.</td>
</tr>
<tr>
<td>05/24/12</td>
<td>Policy renumbered to 12.04.48 (previously 2.04.48) and reassigned to new Genetic Testing category. Related Policies also updated; 2.04.38 is now 12.04.48 and 2.04.50 is now 12.04.500.</td>
</tr>
<tr>
<td>10/09/12</td>
<td>Update Related Policies – Remove 12.04.500 as it was archived; ICD-10 codes are now</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>effective 10/01/2014.</td>
</tr>
<tr>
<td>02/13/13</td>
<td>Replace policy. Policy updated with literature review; no changes to policy statement. References 18, 29, 40, 42, 43, 52, 57, 62 added. Codes 81227 and 81335 are no longer status B codes, effective 1/1/13; notation added to policy.</td>
</tr>
<tr>
<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
</tr>
<tr>
<td>02/24/14</td>
<td>Replace policy. Policy updated with literature review through November 14, 2013; no changes to policy statement. References 17, 53, 57, 59-60, 62-64, and 71-73 added; references renumbered. CPT codes 88384-86 and Modifier 9B are deleted and have been removed from the policy.</td>
</tr>
<tr>
<td>02/10/15</td>
<td>Annual Review. Policy updated with literature review through October 30, 2014; references 49-51, 69-72, and 78 added; policy statement unchanged.</td>
</tr>
<tr>
<td>04/01/16</td>
<td>Update Related Policies. Remove 12.04.38 as it was deleted and replaced with 12.04.517.</td>
</tr>
<tr>
<td>08/01/17</td>
<td>Annual Review, approved July 25, 2017. Policy moved into new format. Policy updated with literature review through April 25, 2017; no references were added. Policy revised with updated genetics nomenclature; statement otherwise unchanged.</td>
</tr>
<tr>
<td>09/01/18</td>
<td>Annual Review, approved August 10, 2018. Policy updated with literature review through April 2018; references 5, 31, 51, 52-54, 56-57, 63-66, and 69 were added. Investigational policy statement expanded to include genotyping for CYP4F2. Title changed to reflect focus on genotype-guided dosing as an intervention; title changed from “Genetic Testing for Warfarin Dose” to “Genotype-Guided Warfarin Dosing”. Added CPT code 0030U. Removed CPT codes 81227 and 81355.</td>
</tr>
</tbody>
</table>

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Email AppealsDepartmentInquiries@Premera.com

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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