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 | Investigational
---|---
Testing of cytochrome p450 2C9 (CYP2C9) and vitamin K epoxide reductase subunit C1 (VKORC1) | Genotyping for (CYP2C9) 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><strong>CPT</strong></td>
<td></td>
</tr>
<tr>
<td>81355</td>
<td>VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G&gt;A, c.173+1000C&gt;T)</td>
</tr>
<tr>
<td><strong>HCPCS</strong></td>
<td></td>
</tr>
<tr>
<td>G9143</td>
<td>Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)</td>
</tr>
</tbody>
</table>

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Related Information

In August 2007, FDA approved updated labeling for Coumadin®, to include information on genetic 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 according to genotyping results for CYP2C9 and VKORC1, providing a table of genotypes and suggested initial dose ranges for each. However, suggested starting doses also are provided for 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 regarding bleeding risk.

Evidence Review

Description

Variants in CYP2C9 and VKORC1 genes result in differences in how warfarin is metabolized. Using information about an individual’s CYP2C9 and VKORC1 genotypes may reduce the time needed to stabilize the dose and select the appropriate maintenance dose, thereby avoiding 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 closely monitored. Dose adjustments are made until a stable international normalized ratio (INR) value between 2

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 the 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). Using the results of CYP2C9 and VKORC1 genetic testing to predict a warfarin starting dose that approximates a patient's likely maintenance dose may benefit patients by decreasing the risk of serious bleeding events and the time to achieve a stable INR. Algorithms have been developed that incorporate not only genetic variation but also other significant patient characteristics and clinical factors to predict the best starting dose.
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 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 than 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 2 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. Therefore this type of testing is considered investigational.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. 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>Ongoing</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</td>
</tr>
<tr>
<td>NCT00964353</td>
<td>The Hospital and Economics CERT: Project 1: The Clinical and Economic Implications of Genetic Testing for Warfarin</td>
<td>268</td>
<td>Dec 2018</td>
</tr>
</tbody>
</table>
### Practice Guidelines and Position Statements

**American College of Medical Genetics**

The 2008 American College of Medical Genetics policy statement concluded:

> There is insufficient evidence, at this time, to recommend for or against routine CYP2C9 and VKORC1 testing in warfarin-naive patients.\(^{82}\)

**American College of Chest Physicians**


> For patients initiating VKA [vitamin K antagonist] therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B).\(^{83}\)

**Conference in Biomedicine on Pharmacogenetics and Pharmacogenomics**

In 2011, The 3rd European Science Foundation–University of Barcelona Conference in Biomedicine on Pharmacogenetics and Pharmacogenomics published a summary on CYP2C9 and VKORC1 genotyping for warfarin dosing. The report noted the Food and Drug Administration’s addition of genetic information to the warfarin label but stated that the
European Medicines Agency has not yet decided whether to include this information in European drug labels.\textsuperscript{84}

**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 August 2009, the Centers for Medicare and Medicaid Services (CMS) published a national coverage determination (available online at: \url{http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=333&ncdver=1&bc=AgAAQAAAAAAA%3d%3d&}) on pharmacogenomic testing for warfarin response.\textsuperscript{85} CMS states 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 under §1862(a)(1)(A) of the Act”.

However, CMS also “believes that the available evidence supports that coverage with evidence development (CED) under §1862(a)(1)(E) of the Social Security Act (the Act) 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 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 2). 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 (CLIA). 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 along with clinical evaluation and other tools, including the INR, to predict the initial dose that best approximates the maintenance dose for patients.

### Table 2. 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><strong>eSensor® Warfarin Sensitivity Test</strong>&lt;sup&gt;a&lt;/sup&gt; (GenMark Dx, Carlsbad, CA)</td>
<td>CYP*2 and *3, VKORC1 1639G&gt;A</td>
<td>3-4</td>
</tr>
<tr>
<td><strong>Rapid Genotyping Assay</strong>&lt;sup&gt;b&lt;/sup&gt; (ParagonDx, Morrisville, NC)</td>
<td>CYP*2 and *3, VKORC1 1173 C&gt;T</td>
<td>Not reported&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Verigene® Warfarin Metabolism Nucleic Acid Test</strong>&lt;sup&gt;c&lt;/sup&gt; (Nanosphere, Northbrook, IL)</td>
<td>CYP*2 and *3, VKORC1 1173C&gt;T</td>
<td>≤2</td>
</tr>
<tr>
<td><strong>Infiniti® 2C9-VKORC1 Multiplex Assay for Warfarin</strong>&lt;sup&gt;c&lt;/sup&gt; (AutoGenomics, Vista, CA)</td>
<td>CYP2C9*2 and *3, VKORC1 1639G&gt;A</td>
<td>6-8</td>
</tr>
<tr>
<td><strong>eQ-PCR™ LightCycler® Warfarin Genotyping Kit</strong>&lt;sup&gt;c&lt;/sup&gt; (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.


<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>2</sup>

<sup>c</sup> The expanded Infiniti CYP450 2C9 assay offers testing for CYP2C9*2, *3, *4, *5, *6, and *11, VKORC1 1639G>A, and 6 additional VKORC variants.

### 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 &quot;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&quot; 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 2.04.500 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 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>
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<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>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>--------</td>
<td>--------------------------------------------------------------------------</td>
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<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>
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<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>
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</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 S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

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Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) ti bilbilaa.

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Hmoob (Hmong):

Ilokro (Ilocano):
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