Protocol

Genotype-Guided Warfarin Dose

(20448)

Medical Benefit		**Effective Date**: 04/01/19	**Next Review Date**: 01/21
Preauthorization	No	**Review Dates**: 01/11, 01/12, 01/13, 01/14, 01/15, 01/16, 01/17, 01/18, 01/19, 01/20	

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	Interventions	Comparators	Outcomes
Individuals: • With conditions requiring warfarin treatment	Interventions of interest are: • Genotype-guided warfarin dosing	Comparators of interest are: • Clinically guided warfarin dosing	Relevant outcomes include: • Morbid events • Medication use • Treatment-related mortality • Treatment-related morbidity

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.

SUMMARY OF EVIDENCE

For individuals with conditions requiring warfarin treatment who receive genotype-guided warfarin dosing, the evidence includes multiple randomized controlled trials (RCTs) and systematic reviews of the RCTs. 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 international normalized ratio 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 thromboembolic events 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 thromboembolic events, 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 Clarification of Optimal Anticoagulation through Genetics 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.

POLICY

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 reduce the risk of serious bleeding.

POLICY GUIDELINES

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 protocol 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

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

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

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely Pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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.

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 2 mg to 5 mg and frequently monitored with dose adjustments until a stable international normalized ratio 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, two in the CYP2C9 gene and one in the VKORC1 gene play key roles in determining the effect of warfarin therapy on coagulation.[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.[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).[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.[13,14]

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 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.[2,15-21] Studies have compared the ability of different algorithms to predict stable warfarin dose accurately.[22-26] Currently, there does not appear to be a consensus for a single algorithm.[25]

Several studies have examined associations between CYP2C9 and VKORC1 variants and warfarin dosing requirements in children.[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.[16-18,30] For example, CYP2C9*2, and CYP2C9*3 are not as useful in predicting warfarin dosing in African Americans, but other important variants have been identified such as CYP2C9*5,*6,*8, and *11.31 Studies have also identified new genetic variants and/or evaluated clinical genetic algorithms for warfarin dose in African American,[32-34] Puerto Rican,[35] Thai,[36] Egyptian,[37,38] Chinese,[39-41] Japanese,[42] Arabic,[43] Turkish,[44] and Scandinavian[45] populations.

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

Test (Laboratories)	Alleles Tested	Estimated Time to Completion, h
eSensor® Warfarin Sensitivity Test (GenMark Dx)[a]	CYPC9*2 and *3, VKORC1 1639G>A	3-4
Rapid Genotyping Assay (ParagonDx)	CYPC9*2 and *3, VKORC1 1173 C>T	Not reported[b]
Verigene® Warfarin Metabolism Nucleic Acid Test (Nanosphere)	CYPC9*2 and *3, VKORC1 1173C>T	≤2
Infiniti® 2C9-VKORC1 Multiplex Assay for Warfarin (AutoGenomics)[c]	CYP2C9*2 and *3, VKORC1 1639G>A	6-8
eQ-PCR™ LightCycler® Warfarin Genotyping Kit (TrimGen)	CYP2C9*2 and *3, VKORC1 1639G>A	≤2

Adapted from Cavallari et al (2011).[31]
FDA: Food and Drug Administration.
[a] eSensor Warfarin Plus Test offers testing for CYP2C9*2, *3, *5, *6, *11, *14, *15, and *16, VKORC1 1639G>A, and CYP4F2.
[b] Langley et al (2009) reported a turnaround time of 1.5 hours for the ParagonDx SmartCycler, which may be a precursor assay.[22]
[c] The expanded Infiniti CYP450 2C9 assay offers testing for CYP2C9*2, *3, *4, *5, *6, and *11, VKORC1 1639G>A, and 6 other VKORC variants.

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.

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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

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