Genotype-Guided Warfarin Dosing

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genotyping to determine cytochrome P450 2C9 (CYP2C9), P450 4F2 (CYP4F2), and vitamin K epoxide reductase subunit C1 (VKORC1) genetic variants for the purpose of managing the administration and dosing of warfarin, including use in guiding the initial warfarin dose to decrease time to a stable International Normalized Ratio (INR) and to reduce the risk of serious bleeding to be **investigational.***

Background/Overview

Warfarin is administered to prevent and treat thromboembolic events (TEEs) 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 (INR) 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, 2 in the *CYP2C9* gene and 1 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. *CYP2C9* and *VKORC1* genetic variants account for approximately 55% of the variability in warfarin maintenance dose. 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). Studies have predicted that *CYP4F2* variants explain 2% to 7% of the variability in warfarin dose in models, including other genetic and nongenetic factors.

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. Studies have compared the ability of different algorithms to predict a stable warfarin dose accurately. Currently, there does not appear to be a consensus for a single algorithm.

Several studies have examined associations between *CYP2C9* and *VKORC1* variants and warfarin dosing requirements in children.

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. 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*. Studies have also identified new genetic variants and/or evaluated clinical genetic algorithms for warfarin dose in African American, Puerto Rican, Thai, Egyptian, Chinese, Japanese, Arabic, Turkish, African, Russian, and Scandinavian populations.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 (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 INR, 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* 1173C>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).
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.
[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.

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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/Source

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 RCTs. Relevant outcomes are morbid events, medication use, and treatment-related mortality and morbidity. Twenty-seven RCTs and 5 recent 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 (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, and only 1 reported a significant reduction in thromboembolic events (TEEs) with genotype-guided dosing, 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 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. One trial of elderly Chinese patients with atrial fibrillation experienced improved time with INR in the therapeutic range and a reduced risk of ischemic stroke, but no difference in bleeding events.

The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Medical Genetics

In 2008, the American College of Medical Genetics 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."

American College of Chest Physicians

In 2012, the ninth edition of the American College of Chest Physicians' 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)."

Clinical Pharmacogenetics Implementation Consortium

In 2017, the Clinical Pharmacogenetics Implementation Consortium updated guidelines for pharmacogenetics-guided warfarin dosing. The guideline provides recommendations for genotype-guided warfarin dosing to achieve a target INR 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

Not applicable.

Medicare National Coverage
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 5 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."

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03479684	Genotype-guided Versus Standard for Warfarin Dosing	560	Dec 2020
NCT04482842	Gene-guided Warfarin for Anticoagulation Therapy in Patients With Acute Ischemic Stroke	340	Aug 2022
Unpublished			

NCT01305148[a]	Warfarin Adverse Event Reduction For Adults Receiving Genetic Testing at Therapy INitiation (WARFARIN)	3800	Dec 2015 (suspended)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Policy History

Original Effective Date: 12/16/2009
Current Effective Date: 09/13/2021

12/04/2009	Medical Policy Committee approval
12/16/2009	Medical Policy Implementation Committee approval. New Policy
12/01/2010	Medical Policy Committee review
12/15/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/08/2011	Medical Policy Committee review
12/21/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/06/2012	Medical Policy Committee review
12/19/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/23/2013	Coding updated
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. No change to coverage.
04/02/2015	Medical Policy Committee review
04/20/2015	Medical Policy Implementation Committee approval. No change to coverage.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
04/07/2016	Medical Policy Committee review

Genotype-Guided Warfarin Dosing

Policy # 00245
Original Effective Date: 12/16/2009
Current Effective Date: 09/13/2021

04/20/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
04/06/2017	Medical Policy Committee review
04/19/2017	Medical Policy Implementation Committee approval. No change to coverage.
08/01/2017	Coding update
02/06/2018	Coding update
04/01/2018	Coding update
05/03/2018	Medical Policy Committee review
05/16/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. Investigational policy statement expanded to include genotyping for CYP4F2. Changed "polymorphisms" to "variants" in the investigational policy statement and throughout the policy. Title change to Genotype-Guided Warfarin Dosing.
08/01/2014	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/06/2020	Medical Policy Committee review
08/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/05/2021	Medical Policy Committee review
08/11/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 08/2022

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0030U, 81227, 81355
HCPCS	G9143
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.