MEDICAL POLICY

POLICY TITLE	GENOTYPE-GUIDED WARFARIN DOSING
POLICY NUMBER	MP 2.306

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**3/1/2024**

I. POLICY

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 stable international normalized ratio (INR) and reduce the risk of serious bleeding, is considered **investigational.** There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO:

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies .

III. DESCRIPTION/BACKGROUND

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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 monitored frequently 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.

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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. *CYP2C9* and *VKORC1* genetic variants account for approximately 55% of the variability in warfarin maintenance dose. 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). 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 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. Studies have compared the ability of different algorithms to predict stable warfarin dose accurately. Currently, there does not appear to be 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, and Scandinavian populations.

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 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 Act. The tests are not all the same in terms of

the specific variants and number of variants detected. In general, such tests are not intended to be 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 1. FDA-Cleared Warfarin Tests

Test (Laboratories)	Alleles Tested	Estimated Time to Completion, h
eSensor® Warfarin Sensitivity Test (GenMark Dx)	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)	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.

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.

IV. RATIONALE

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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. Thirty RCTs and 6 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 or thromboembolic events (TEEs) 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

V. DEFINITIONS

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GENOTYPE refers to the pair of genes present for a particular characteristic or protein.

POLYMORPHISM refers to the state or quality of existing or occurring in several different forms.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical

policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Genotyping to determine cytochrome p450 2C9 (*CYP2C9*) and vitamin K epoxide reductase subunit C1 (*VKORC1*) genetic polymorphisms for the purpose of managing the administration and dosing of warfarin is investigational; therefore, not covered:

Procedure Codes								
G9143	81227	81355	0030U					

IX. REFERENCES

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X. POLICY HISTORY

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MP-2.234	**5/12/2021 Consensus Review.** Rationale and references updated. Coding reviewed. Removal of Policy Guidelines.
	8/30/2022 Consensus Review. No changes to policy statement. Updated FEP, references, rationale. Coding reviewed.
	8/2/2023 Consensus Review. No changes to policy statement. Updated references. Coding reviewed, no changes.
	1/19/2024 Administrative update. Clinical benefit added.

MEDICAL POLICY

POLICY TITLE	GENOTYPE-GUIDED WARFARIN DOSING
POLICY NUMBER	MP 2.306

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