2.04.48	Genotype-Guided Warfarin Dosing		
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Section:	2.0 Medicine	**Page:**	Page 1 of 22

Policy Statement

I. 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 (INR) and to reduce the risk of serious bleeding.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding

There are CPT codes determining cytochrome p450 2C9 (CYP2C9) and vitamin K epoxide reductase subunit C1 (VKORC1) for the purpose of managing the administration and dosing of warfarin:

- **81227**: CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)
- **81355**: VKORC1 (vitamin K epoxide reductase complex, subunit 1) (e.g., warfarin metabolism), gene analysis, common variant(s) (e.g., -1639G>A, c.173+1000C>T)

The following PLA code represents the Warfarin Response Genotype test from the Mayo Clinic:

- **0030U**: Drug metabolism (warfarin drug response), targeted sequence analysis (i.e., CYP2C9, CYP4F2, VKORC1, rs12777823)

The Centers for Medicare & Medicaid Services (CMS) issued the following HCPCS code to facilitate administration of their new national coverage decision on warfarin responsiveness testing.

- **G9143**: Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)

Indications for warfarin therapy include, but are not limited to, the following conditions:

- Artificial heart valves
- Atrial fibrillation
- Cardioembolic stroke
- Deep vein thrombosis
- Following major orthopedic surgery (total hip or knee arthroplasty, long bone fractures)
- Pulmonary embolism

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.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 (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]	*CYP2C9*2* and **3*, *VKORC1* 1639G>A	3-4
Rapid Genotyping Assay (ParagonDx)	*CYP2C9*2* and **3*, *VKORC1* 1173C>T	Not reported[b]
Verigene® Warfarin Metabolism Nucleic Acid Test (Nanosphere)	*CYP2C9*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).[48,]
CYP2C9: cytochrome P450 2C9 enzyme; FDA: Food and Drug Administration; VKORC1: vitamin K epoxide reductase complex, subunit 1.
[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.

Rationale

Background

Warfarin

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.

Enzyme Variant Impact on Warfarin Metabolism

Warfarin, which is primarily metabolized in the liver by the cytochrome P450 2C9 (*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.[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,] 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 INR. 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 a 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.[27,28,29,]

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.[16,17,18,30,]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,[32,33,34,] Puerto Rican,[35,] Thai,[36,] Egyptian,[37,38,] Chinese,[39,40,41,] Japanese,[42,] Arabic,[43,] Turkish,[44,] African,[45,] Russian,[46,] and Scandinavian[47,] populations.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of the condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The primary goal of pharmacogenomics testing and personalized medicine is to achieve better clinical outcomes compared with the standard of care. Drug response varies greatly between individuals, and genetic factors are known to play a role. However, in most cases, the genetic variation only explains a modest portion of the variance in the individual response because clinical outcomes are also affected by a wide variety of factors including alternate pathways of metabolism and patient- and disease-related factors that may affect absorption, distribution, and elimination of the drug. Therefore, assessment of clinical utility cannot be made by a chain of evidence from clinical validity data alone. In such cases, evidence evaluation requires studies that directly demonstrate that the pharmacogenomic test alters clinical outcomes; it is not sufficient to demonstrate that the test predicts a disorder or a phenotype.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Genotype-Guided Warfarin Dosing

Clinical Context and Therapy Purpose

The purpose of genotype-guided warfarin dosing is to guide an individual's initiation and maintenance dose of warfarin by incorporating demographic, clinical, and genotype data. In theory, this should lead to a predicted dose that will decrease the probability of over- or undercoagulation thereby avoiding the downstream consequences of thromboembolism or bleeding.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients being considered for treatment with warfarin.

Interventions
A number of commercial tests for individual genes or panel tests are available and listed in Table 1. Numerous algorithms have been developed to guide warfarin dosing based on the results of genetic tests and other demographic and clinical factors.

Comparators
The comparator of interest is standard clinical management without genetic testing.

Outcomes
Specific outcomes of interest are listed in Table 2. The interest is in whether genotype-guided warfarin dosing reduces adverse events during the dose adjustment period. Therefore, outcomes in the first 1 to 2 months are relevant.

Table 2. Outcomes of Interest for Individuals Undergoing Genotyping to Guide Warfarin Therapy

Outcomes	Details
Morbid events	Bleeding, thromboembolism
Medication use	Initial and maintenance dose selection
Treatment-related mortality	Death due to under- or overtreatment
Treatment-related morbidity	Time to achieve therapeutic INR, time in therapeutic INR, bleeding, thromboembolism

INR: international normalized ratio.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Systematic Reviews and Meta-Analyses
Several systematic reviews and meta-analyses have assessed genotype-guided warfarin dosing compared with clinical dosing. A comparison of the trials included in more recent systematic reviews and meta-analyses is shown in Table 3. The systematic reviews and meta-analyses included a total of 30 trials published between 2005 and 2020. The reviews used similar eligibility criteria leading to a similar set of overlapping studies. In the discussion below, we focus on the 6 most recent and comprehensive reviews, conducted by Belley-Cote et al (2015)[50], Tse et al (2018),[51] the Washington State Health Technology Assessment Program (Washington HTA; 2018),[52] Yang et al (2019),[53] Sridharan and Sivaramakrishnan (2020),[54] and Wang et al (2022).[55] Characteristics and results of these reviews are summarized in Tables 4 and 5.

Table 3. RCTs Included in Systematic Reviews of Genotype vs Clinical Dosing of Warfarin

Trials	Systematic Reviews					
	Belley-Cote et al (2015)[50]	Tse et al (2018)[51]	Washington HTA (2018)[52]	Yang et al (2019)[53]	Sridharan and Sivaramakrishnan (2020)[54]	Wang et al (2022)[55]
Hillman et al (2005)[56]	●	●	●	●	●	●
Anderson et al (2007)[57]	●		●	●	●	●

Trials	Systematic Reviews					
Caraco et al (2008)[58],	●	●	●		●	●
Huang et al (2009)[59],	●	●	●	●	●	●
Burmester et al (2011)[60],	●		●	●	●	●
McMillin et al (2011)[61],					●	
Korneva et al (2011)[62],						●
Borgman et al (2012)[63],	●		●	●	●	●
Wang et al (2012)[64],	●		●	●	●	●
Radhakrishnan et al (2012)[65],	●				●	●
Jonas et al (2013)[66],	●		●	●	●	●
Kimmel et al (2013)[67],	●		●	●	●	●
Pirmohamed et al (2013)[68],	●	●	●	●	●	●
Verhoef et al (2013)[69],	●				●	
Li et al (2014)[70],		●		●	●	●
Pengo et al (2015)[71],		●	●	●	●	●
Supe et al (2015)[72],		●			●	●
Duan (2016)[73],		●			●	●
Gage (2017)[5],		●	●	●	●	●
Jin (2017)[74],		●		●	●	●
Wen (2017)[75],		●	●	●	●	●
Jiang (2016)[76],				●		
Makar-Ausperger et al (2018)[77],					●	●
Xu et al (2018)[78],					●	●
Syn et al (2018)[79],					●	●
Hao et al (2019)[80],						●
Guo et al (2020)[81],					●	●
Lee et al (2020)[82],					●	●
Panchenko et al (2020)[47],					●	●
Zhu et al (2020)[83],						●

RCT: randomized controlled trial.

Table 4. Summary of Systematic Reviews of RCTs of Genotype vs Clinical Dosing of Warfarin

Study	Dates	Participants	RCTs	N (Range)	Duration
Belley-Cote et al (2015)[50],	To Feb 2014	Adults requiring initiation of anticoagulation for any indication	12	3217 (34-1015)	1-6 mo
Tse et al (2018)[51],	2000-2015	Genotype-guided vs. conventional warfarin dosing (population not specified)	18	5230 (NR)	1-3 mo
Washington HTA[52],	To January 2018	Adults and children initiating or changing dosage of oral anticoagulant medications	13	4788 (34-1650)	1-6 mo
Yang et al (2019)[53],	To October 2017	Patients with any indication for warfarin therapy	15	4852 (26-1597)	1-3 mo

Study	Dates	Participants	RCTs	N (Range)	Duration
Sridharan and Sivaramakrishnan (2020)[54],	To August 2020	Genotype-guided (using strategies based on *CYP2C9* alone; *CYP2C9* and *VKORC1*; or *CYP2C9, VKORC1*, and *CYP4F2*) vs. conventional warfarin dosing (population not specified)	26	7898 (38-1650)	1-3 mo
Wang et al (2022)[55],	To July 2021	Patients taking warfarin for any indication in studies comparing genotyped-guided warfarin dosing to conventional warfarin dosing	27	9906 (26-2264)	21-360 days

CYP2C9: cytochrome P450 2C9 enzyme; NR: not reported; RCT: randomized controlled trial; VKORC1: vitamin K epoxide reductase complex, subunit 1.

Table 5. Results of Systematic Reviews of RCTs of Genotype vs Clinical Dosing of Warfarin

Study	TEEs	Major Bleeding, %	INR >4, %	% Time INR in Therapeutic Range	Deaths	Time to First Therapeutic INR	Time to Reach Stable INR or Warfarin Dose
Belley-Cote et al (2015)[50],	TEEs, major bleeding, or death						
Total N	2223		NR	2767	NR	NR	NR
Pooled effect (95% CI); p	RR, 0.85 (0.54 to 1.34);.48			MD, 4.3 (0.4 to 8.3);.03			
I^2 (p)	10% (.35)			79% (<.001)			
Tse et al (2018)[51],							
Total N	NR	NR	NR		NR	NR	NR
Pooled effect (95% CI); p	RR, 0.84 (0.56 to 1.26);.40	RR, 0.82 (0.69 to 0.98); <.05	RR, 0.87(0.78 to 0.98); <.05	MD, 3.1% standard error 1.2%; <.01	RR, 1.16 (0.46 to 2.91);.76		
I^2 (p)	0%	31%	0%	80%	0%		
Washington HTA (2018)[52],							
Total N	4241	4241	4056	4378	3540	NR	NR
Pooled effect (95% CI); p	RR, 0.85 (0.56 to 1.28);.44	RR, 0.43 (0.22 to 0.84);.01	RR, 0.91 (0.80 to 1.04);.16	MD, 3.11 (-0.28 to 6.50);.07	RR, 1.17 (0.43 to 3.22);.76		
I^2 (p)	0%	0%	0%	78%; <.00001	0%		
Yang (2019)[53],							
Total N	NR	NR	NR	3831	NR	NR	NR
Pooled effect (95% CI); p	RR, 0.27 (0.03 to 2.38);.239 [vs. fixed-dose warfarin] RR, 0.89 (0.58 to 1.35);.572 [vs. clinically adjusted warfarin]	RR, 0.16 (0.01 to 3.96);.265 [vs. fixed-dose warfarin] RR, 0.32 (0.13 to 0.74);.008 [vs. clinically adjusted warfarin]	RR, 0.83 (0.67 to 1.03);.085 [vs. fixed-dose warfarin] RR, 0.95 (0.78 to 1.15);.586 [vs.	WMD, 3.36 (-2.12 to 8.84);.229 [vs. fixed-dose warfarin] WMD, 0.88 (-2.26 to 4.02);.582 [vs. clinically	RR, 2.56 (0.50 to 13.05);.258 [vs. fixed-dose warfarin] RR, 0.72 (0.20 to 2.62);.622 [vs. clinically adjusted warfarin]		

Study	TEEs	Major Bleeding, %	INR >4, %	% Time INR in Therapeutic Range	Deaths	Time to First Therapeutic INR	Time to Reach Stable INR or Warfarin Dose
			clinically adjusted warfarin]	adjusted warfarin]			
I² (p)	0% (NR)	0% [clinically adjusted] (NR)	0% [fixed dose] (NR); 31.2% [clinically adjusted] (NR)	59.2% [fixed dose] (NR); 63% [clinically adjusted] (NR)	0% (NR)	41.2% [fixed dose] (NR)	93.5% [fixed dose] (NR); 55.2% [clinically adjusted] (NR)
Sridharan and Sivaramakrishnan (2020)[54,]							
Total N	3636	6246		6356	2000		
Pooled effect (95% CI); p	OR, 0.35 (0.01 to 9.18); NR [*CYP2C9* vs. clinically adjusted warfarin] OR, 0.93 (0.33 to 2.59); NR [*CYP2C9* and *VKORC1* vs. clinically adjusted warfarin] OR, 0.81 (0.51 to 1.29); NR [*CYP2C9, VKORC1,* and *CYP4F2* vs. clinically adjusted warfarin]	OR, 0.30 (0.10 to 0.86); NR [*CYP2C9* vs. clinically adjusted warfarin] OR, 0.86 (0.59 to 1.30); NR [*CYP2C9* and *VKORC1* vs. clinically adjusted warfarin] OR, 0.73 (0.30 to 1.74); NR [*CYP2C9, VKORC1,* and *CYP4F2* vs. clinically adjusted warfarin]		WMD, 0.2 (-15.82 to 16.22); NR [*CYP2C9* vs. clinically adjusted warfarin] WMD, 3.91 (1.18 to 6.63); NR [*CYP2C9* and *VKORC1* vs. clinically adjusted warfarin] WMD, 2.80 (-0.23 to 5.83); NR [*CYP2C9, VKORC1,* and *CYP4F2* vs. clinically adjusted warfarin]	OR, 0.87 (0.18 to 4.14); NR [*CYP2C9* and *VKORC1* vs. clinically adjusted warfarin] OR, 0.65 (0.11 to 3.99); NR [*CYP2C9, VKORC1,* and *CYP4F2* vs. clinically adjusted warfarin]	WMD, -2.73 (-3.41 to -2.05); NR [*CYP2C9* vs. clinically adjusted warfarin] WMD, -1.92 (-3.23 to -0.61); NR [*CYP2C9* and *VKORC1* vs. clinically adjusted warfarin]	WMD, -8.10 (-12.54 to -3.66); NR [*CYP2C9* vs. clinically adjusted warfarin] WMD, -4.60 (-6.87 to -2.34); NR [*CYP2C9* and *VKORC1* vs. clinically adjusted warfarin] WMD, -1.58 (-4.28 to 1.12); NR [*CYP2C9, VKORC1,* and *CYP4F2* vs. clinically adjusted warfarin]
I² (p)	NR	NR		NR	NR	NR	NR
Wang et al (2022)[55,]							
Total N	6993	7175	5251	FU ≤30 days: 5241 FU >30 days: 2946	5943	4075	3156
Pooled effect (95% CI); p	RR, 0.69 (0.49 to 0.96);.03	RR, 0.50 (0.33 to 0.75);.0008	RR, 0.90 (0.80 to 1.01);.08	FU ≤30 days: MD, 5.95 (2.41 to 9.49);.001	RR, 0.75 (0.36 to 1.56);.44	MD, -1.80 days (-2.69 to -0.92);<.0001	MD, -5.08 days (-7.09 to -3.07);<.00001

Study	TEEs	Major Bleeding, %	INR >4, %	% Time INR in Therapeutic Range	Deaths	Time to First Therapeutic INR	Time to Reach Stable INR or Warfarin Dose
				FU >30 days: MD, 4.93 (1.40 to 8.47);.006			
I² (p)	0% (.8)	0% (.44)	0% (.8)	FU ≤30 days: 87% (<.00001) FU >30 days: 78% (<.00001)	0% (.84)	92% (<.00001)	96% (<.00001)

CI: confidence interval; CYP2C9: cytochrome P450 2C9 enzyme; FU: follow-up; INR: international normalized ratio; MD: mean difference; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; TEE: thromboembolic event; VKORC1: vitamin K epoxide reductase complex, subunit 1; WMD: weighted mean difference.

All 6 reviews found that 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. In the Belley-Cote et al (2015) review, there was no difference between groups on the composite outcome of thromboembolic events (TEEs), major bleeding, or death. Similarly, Sridharan and Sivaramakrishnan evaluated these outcomes independently in a network meta-analysis and found no significant differences between clinically adjusted warfarin and genotype-guided dosing, except that bleeding risk was lower with cytochrome P450 2C9 (*CYP2C9)*-guided dosing compared with clinically adjusted warfarin. Wang et al (2022) was the only systematic review to find a significant reduction in TEEs with genotype-guided warfarin dosing, driven mainly by the Zhu et al (2020) RCT.[55,] There was also a reduction in major bleeding events but not deaths, in the genotype-guided warfarin group compared to the control group. Meta-analyses in the most recent systematic reviews were heavily weighted by the large Genetics Informatics Trial (GIFT), published in 2017.[5,] Authors of these reviews found no difference between genotype-guided dosing and clinical dosing for mortality but genotype-guided dosing was associated with a lower risk of major bleeding. For example, the Washington HTA reviewers found a 57% reduction for risk of major bleeding in the pharmacogenetic testing group compared to controls (relative risk [RR], 0.43; 95% confidence interval [CI], 0.22 to 0.84; p=.01).[52,] The absolute number of major bleeding events was low, with an anticipated 8.6 fewer major bleeding events per 1000 people with pharmacogenetic testing (95% CI, 2.7 to 14.4 fewer major bleeding episodes per 1000 people). Subgroup analyses by comparator groups showed this difference was statistically significant only when pharmacogenetic testing was compared to using a clinical algorithm to guide initial dosing (RR, 0.39; 95% CI, 0.19 to 0.81), and not when compared to a fixed dose (RR, 0.70; 95% CI, 0.14 to 3.53). Washington HTA reviewers rated the overall quality of the evidence for major bleeding as moderate due to the imprecision of the estimate.

Belley-Cote et al (2015)[50,] used the GRADE approach to evaluate the quality of evidence. A summary of the risk of bias of individual studies is as follows: (1) the trials inconsistently reported allocation concealment; (2) only 1 study blinded participants, clinicians, research personnel, and outcome assessors; (3) patients who died during the trial period were excluded from analysis in 2 trials; (4) the 3 studies with highest loss to follow-up had losses of 12%, 16%, and 23%, respectively; and (5) 5 studies did not report the definitions used for bleeding events. Reviewers found that genotype-guided vitamin K antagonist dosing compared with standard dosing algorithms did not decrease a composite outcome of death, thromboembolism and major bleeding (n=2223, 87 events; RR=0.85; 95% CI, 0.54 to 1.34; p=.48) but did result in an improved time of INR in the therapeutic range. The improvement in time in therapeutic range was reported in a pooled analysis of RCTs with fixed dosing algorithms but not with clinical algorithms. Of the 13 trials included in the Washington HTA systematic review, 3 were judged to be at low-risk of bias, 4 at moderate-risk of bias, and 6 at high-

risk of bias. Study limitations included inadequate methods of randomization and allocation concealment and lack of blinding of outcomes.[52,] Yang et al (2019)[53,] also completed a risk of bias assessment of included RCTs. All trials claimed to be randomized in nature; however, the random sequence generation was only explicitly described in 9 studies. Additionally, only 7 studies discussed allocation concealment; blinding was not implemented in most of the included RCTs as administration of an initial fixed warfarin dose would potentially imply to the participants and study personnel that the subject was randomized to the conventional dosing versus genotype-guided arm. Sridharan and Sivaramakrishnan assessed the quality of evidence as follows for the assessed outcomes and comparisons: time to first therapeutic INR with *CYP2C9*: low; time to first therapeutic INR with *CYP2C9* and vitamin K epoxide reductase complex, subunit 1 (*VKORC1*): moderate; time to stable INR or warfarin dose with *CYP2C9*: very low; time to stable INR with *CYP2C9* and *VKORC1*: very low; and percentage of time the INR was in therapeutic range with *CYP2C9* and *VKORC1*: very low.[54,]The quality of evidence was often downgraded because of high risk of bias, potential for publication bias, and imprecision. Wang et al (2022)[55,] assessed risk of bias of their included studies. Three studies were identified as unclear on all of the bias assessments because they were conference abstracts with limited data. In the selection bias category, 3 studies were assigned high risk of bias. In the reporting bias category, 4 studies were identified as high risk of bias. For performance bias, 2 studies were assigned high risk. Overall, the majority of trials had a low risk of detection and attrition bias.

Randomized Controlled Trials

A total of 30 RCTs comparing genotype-guided with clinical dosing of warfarin are included in this policy, all of which were included in at least 1 systematic review (Table 3). Characteristics and results of key RCTs included in these systematic reviews and meta-analyses are presented in Tables 6 and 7. Most RCTs were single-center studies including fewer than 250 patients. The trials used varying algorithms in both the genotype-guided and clinical dosing arms. Most studies included mixed indications for warfarin use. The trials primarily included patients of European descent. Twenty-seven percent of the participants in the multicenter Clarification of Optimal Anticoagulation through Genetics (COAG) trial[67,] were Black.

While a few of the RCTs reported differences in the percentage of time the INR was in therapeutic range or the proportion of patients with an INR greater than 4, none reported statistically significant differences in major bleeding, and only 1 (Zhu et al [2020]) reported significant reduction in TEEs (ischemic stroke) with genotype-guided dosing.[83,] However, it is important to note that the event rates were very low in the selected trials and the studies were not powered to show differences in rates of major bleeding or TEEs.

Three multicenter RCTs with more than 400 patients have been reported: COAG,[67,] European Pharmacogenetics of Anticoagulant Therapy (EU-PACT), [68,] and GIFT.[5,] These larger RCTs, along with the large single center trial by Zhu et al (2020),[83,] are discussed in the following paragraphs and summarized in Tables 6 and 7. The systematic reviews discussed above included these large trials. The Belley-Cote systematic review was published prior to GIFT.

Table 6. Characteristics of Key RCTs of Genotype-guided Warfarin Dosing

Study; Trial	Countries	Sites	Dates	Participants	Interventions
Kimmel et al (2013) [67,] COAG	US	18	2009 -2013	• Adults initiating warfarin therapy with expected duration ≥1 mo • 27% Black race	Algorithm including clinical variables only
Pirmohamed et al (2013)[68,] EU-PACT	UK, Sweden	2	2010-2013	• Age >18 y; warfarin-naive; anticoagulation for AF or VTE	Clinical dosing algorithm including age, sex, height, weight, and amiodarone use

Study; Trial	Countries	Sites	Dates	Participants	Interventions
				• 99% White race	
Gage (2017)[84], GIFT	US	6	2011-2016	• Patients aged ≥65 y initiating warfarin for elective hip or knee arthroplasty • INR <1.35 • 91% White race	WarfarinDosing.org algorithm excluding genotype data
Zhu et al (2020)[83],	China	1	2016-2018	• Elderly Chinese patients (≥60 y) with AF	Dosing algorithm including *CYP2C9* and *VKORC1* genotype and clinical data vs Dosing algorithm using clinical data only

AF: atrial fibrillation; CYP2C9: cytochrome P450 2C9 enzyme; INR: international normalized ratio; RCT: randomized controlled trial;VKORC1: vitamin K epoxide reductase complex, subunit 1; VTE: venous thromboembolism.

Table 7. Results of Key RCTs of Genotype-guided Warfarin Dosing

Study	Major Bleeding	TEEs	INR >4	% Time in Therapeutic Range	Deaths
Kimmel et al (2013) [67], COAG					
N	1015	1015	955	955	1015
Genotype-guided dosing, n (%)	4 (1)	5 (1)	100 (19)	45%	2
Control, n (%)	10 (2)	4 (1)	92 (18)	45%	1
TE (95% CI); p	HR, 0.41 (0.13 to 1.31);.13	HR, 1.27 (0.34 to 4.73);.72	HR, 1.08 (0.81 to 1.44);.59	NR;.91	HR, 2.09 (0.19 to 23.22);.55
Pirmohamed et al (2013)[68], EU-PACT					
N	427	427	427	427	427
Genotype-guided dosing, n (%)	0	0	57 (27)	67.4%	5
Control, n (%)	0	1	79 (37)	60.3%	2
TE (95% CI); p			OR, 0.63 (0.41 to 0.97);.03	MD, 7.0 (3.3 to 10.6); <.001	
Gage (2017)[84], GIFT					
N	1597	1597	1597	1588	1597
Genotype-guided dosing, n (%)	2 (0.2)	33 (4.1)	56 (6.9)	55%	0
Control, n (%)	8 (1.0)	38 (4.8)	77 (9.8)	51%	0
TE (95% CI); p	RD, 0.8 (-0.2 to 1.8);.06	RD, 0.7 (-1.3 to 2.8);.48	RD, 2.8 (0.1 to 5.6);.04	MD, 3.4 (1.1 to 5.8);.004	
Zhu et al (2020)[83],					
N	507	507[b]	NR	507	NR
Genotype-guided dosing, n (%)	18 (8.61)	5 (2.39)		70.80% (SD, 24.39)	
Control, n (%)	14 (10.61)	9 (6.82)		53.44% (SD, 26.73)	
TE (95% CI); p-value	HR, 0.75 (0.35 to 1.58);.43	HR, 0.22 (0.065 to 0.77);.017		MD, 17.36% (11.82 to 22.89); <.001	

CI: confidence interval; HR: hazard ratio; INR: international normalized ratio; MD: mean difference; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; RD: risk difference; SD: standard deviation; TE: treatment effect; TEE: thromboembolic event.
[a] Values are in person-months.
[b]Reported as ischemic stroke.

Two larger RCTs of pharmacogenetic dosing algorithms were published by Kimmel et al (2013) and Pirmohamed et al (2013).[67,68,] The larger of these, the COAG trial, was conducted in the U.S. by the National Heart, Lung, and Blood Institute,[67,] and the smaller trial was conducted in Sweden and England by the EU-PACT consortium.[68,] In both trials, the intervention period was the first 5 days of dosing; genotyping comprised the *CYP2D6*2* and **3* and *VKORC1* 1639G>A alleles; the primary outcome was the mean percentage of time in the therapeutic INR range of 2.0 to 3.0. Neither trial reported an intention-to-treat analysis.

In the COAG trial, 1015 individuals, 6 to 70 years old, 51% male, and 27% Black were randomized to warfarin doses for the first 5 days of therapy based on their clinical and genetic characteristics or their clinical characteristics alone.[67,] Patients were followed for 4 additional weeks during which time their drug doses were adjusted based on standard protocols. Ninety-four percent (n=955) of patients completed the 5-day intervention period and were included in efficacy analyses. Results showed that INR was within the desired range 45% (p=.91) of the time in both groups during the 28-day monitoring period, based on standardized blood clotting tests. The principal secondary outcome (a composite of INR ≥4, major bleeding [fatal hemorrhage, intracranial bleeding, or symptomatic bleeding requiring overnight hospitalization, transfusion, angiographic intervention, or surgery], or thromboembolism) was also similar in the 2 groups (20% vs 21%, respectively; p=.93). A subgroup analysis of 255 Black patients showed that the clinically-guided group fared better than the genotype-guided group (INR was within the desired range 43.5% vs 35.2%, respectively; p=.01).

In the EU-PACT trial, 455 individuals, 24 to 90 years old, 99% White, were randomized to warfarin doses for the first 3 days based on their clinical and genetic characteristics or their clinical characteristics alone.[68,] Patients were followed for 12 additional weeks during which time their drug doses were adjusted based on standard protocols. Ninety-four percent of patients had 13 or more days of INR data and were included in efficacy analyses. Results showed that INR was within the desired range 67% of the time in the genotype-guided dosing group compared with 60% in the clinically-guided group (p<.001). There were no differences in secondary outcomes assessed (bleeding or TEEs). However, the percentage of patients with an INR >4 was lower in the genotype-guided group (27%) than in the clinically-guided group (37%). The time to achieving therapeutic INR was also shorter in the genotype-guided group (21 days) than in the clinically-guided group (29 days).

Gage et al (2017) reported on the results of the GIFT RCT, which evaluated genotype-guided warfarin dosing (n=831) and clinically-guided dosing (n=819) in patients aged 65 years or older initiating warfarin for elective hip or knee arthroplasty; the trial was conducted at 6 U.S. medical centers.[84,] Patients were genotyped for *VKORC1*-1639G>A, *CYP2C9*2*, *CYP2C9*3*, and *CYP4F2* V433M variants. The primary endpoint was the composite of major bleeding, INR ≥4, venous thromboembolism, or death. The mean age of randomized patients was 72, 64% of participants were women, and 91% were White. Randomized participants who received 1 or more doses of warfarin were included in the analysis (808 in the genotype-guided group vs 789 in the clinically-guided group). Eighty-seven (11%) patients in the genotype-guided group vs 116 (15%) patients in the clinically-guided group met at least 1 of the components of the composite outcome (absolute difference, 3.9%; 95% CI, 0.7% to 7.2%; p=.02). The difference in the composite outcome was primarily driven by the difference in the percent of patients with INR ≥4 (56 vs 77; RR=0.71; 95% CI, 0.51 to 0.99). There were 2 versus 8 major bleeding events in the genotype vs clinical groups (RR=0.24; 95% CI, 0.05 to 1.15) and 33 versus 38 venous TEEs (RR=0.85; 95% CI, 0.54 to 1.34). There were no deaths.

Zhu et al (2020) randomized elderly Chinese patients, aged 60 years or greater, with nonvalvular atrial fibrillation to receive their warfarin dose based on an algorithm using genetic and clinical factors (genetic group, n=313) or an algorithm using clinical factors only (n=194).[83,] Investigators found that INR time in therapeutic range was improved with genotype-guided dosing based on *CYP2C9* and *VKORC1* compared with clinically-guided dosing. Additionally, bleeding events did not differ between groups, but ischemic stroke occurred less frequently with genotype-guided dosing. Risk of bias and quality of evidence assessments for the RCTs included in the Belley-Cote (2015),[50,] Washington HTA (2018),[52,] Yang (2019),[53,] Sridharan and Sivaramakrishnan (2020),[54,]and Wang (2022)[55,]systematic reviews were summarized in the previous section.

Section Summary: Genotype-Guided Warfarin Dosing

Multiple randomized trials and meta-analyses of these trials have examined the use of pharmacogenomic algorithms to guide initial warfarin dosing. A total of 30 RCTs and 6 recent systematic reviews and meta-analyses of genotype-guided dosing of warfarin were identified. Most RCTs were single-center studies including fewer than 250 patients. The trials used varying algorithms in both the genotype-guided and the clinical dosing arms. Most studies included mixed indications for warfarin use. The trials primarily included patients of European descent; 27% of the participants in the multicenter COAG trial[67,] were Black. While a few of the RCTs reported differences in the percentage of time the INR was in therapeutic range or the proportion of patients with an INR >4, none reported statistically significant differences in major bleeding, and only 1 (Zhu et al [2020]) reported a significant reduction in TEE (ischemic stroke) with genotype-guided dosing. However, it is important to note that the event rates were very low in the selected trials and the studies were not powered to show differences in rates of major bleeding or TEEs.

Six systematic reviews found that the percentage of time the INR was in the therapeutic range was higher in patients treated with genotype-guided warfarin therapy; however, the heterogeneity between studies was high for this outcome. Recent systematic reviews including the large, multicenter GIFT trial found no difference between genotype-guided dosing and clinical dosing for mortality , but genotype-guided dosing was associated with a lower risk of major bleeding. The absolute number of major bleeding events was low, with an anticipated 8.6 fewer major bleeding events per 1000 people with pharmacogenetic testing (95% CI, 2.7 to 14.4 fewer major bleeding episodes per 1000 people). Subgroup analyses by comparator groups showed that this difference was statistically significant only when pharmacogenetic testing was compared to using a clinical algorithm to guide initial dosing (RR, 0.39; 95% CI, 0.19 to 0.81), and not when compared to a fixed dose (RR, 0.70; 95% CI, 0.14 to 3.53).

Very few trials have included a sufficient number of subgroups that were not White. In the COAG study, Black individuals (constituting 27% of trial participants) 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. There are completed, registered studies that have not been published, so the possibility of publication bias cannot be excluded.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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 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)."[85,] The updated 2021 guidelines make no mention of genotype-guided warfarin dosing.[86,]

Clinical Pharmacogenetics Implementation Consortium

In 2017, the Clinical Pharmacogenetics Implementation Consortium updated guidelines for pharmacogenetics-guided warfarin dosing.[87,] The guideline provides recommendations for genotype-guided warfarin dosing to achieve a target international normlized ratio (INR) of 2 to 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.[88,] 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 [coverage with evidence development], 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 8.

Table 8. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT01305148[a]	Warfarin Adverse Event Reduction For Adults Receiving Genetic Testing at Therapy INitiation (WARFARIN)	3800	Dec 2015 (suspended)
NCT03479684	Randomized Trial of Genotype-guided Versus Standard for Warfarin Dosing	560	Dec 2021 (completed)
NCT03797534	Individualized Administration of Warfarin by Polymorphisms of VKORC1 and CYP2C9 Genes: A Randomized Controlled Trial, Multi-Center Trial	600	Jan 2023 (unknown)

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

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0030U	Drug metabolism (warfarin drug response), targeted sequence analysis (i.e., CYP2C9, CYP4F2, VKORC1, rs12777823)
	81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)
	81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (e.g., warfarin metabolism), gene analysis, common variant(s) (e.g., -1639G>A, c.173+1000C>T)
HCPCS	G9143	Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
03/01/2016	BCBSA Medical Policy Adoption
08/01/2017	Policy revision without position change
05/01/2018	Coding update
08/01/2018	Policy title change from Genetic Testing for Warfarin Dose Policy revision without position change
08/01/2019	Policy revision without position change
08/01/2020	Annual review. No change to policy statement. Policy guidelines and literature review updated.
08/01/2021	Annual review. No change to policy statement. Policy guidelines and literature review updated.
08/01/2022	Annual review. No change to policy statement. Policy guidelines and literature review updated.
08/01/2023	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Genotype-Guided Warfarin Dosing 2.04.48 **Policy Statement:** I. 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 (INR) and to reduce the risk of serious bleeding.	**Genotype-Guided Warfarin Dosing 2.04.48** **Policy Statement:** I. 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 (INR) and to reduce the risk of serious bleeding.