Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Genotype-Guided Warfarin Dosing

Description/Background

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 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 starting dose for warfarin that approximates the individual patient's likely maintenance dose may benefit patients by decreasing the risk of serious bleeding events and the time to stable INR. Algorithms have also been developed that incorporate 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 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.[16,17,18,30,] 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,[32-34] Puerto Rican,[35] Thai,[36] Egyptian,[37,38] Chinese,[39-41] Japanese,[42] Arabic,[43] Turkish,[44] African[45], Russian[46] and Scandinavian[47] 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 rationale). Similar tests also may be available as laboratory-developed tests in laboratories licensed under Clinical Laboratory Improvement Amendments for high-complexity testing. 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 could 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[1]

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

eQ-PCR™ LightCycler® Warfarin Genotyping Kit (TrimGen, Sparks Glencoe, MD)	CYPC9*2 and *3, VKORC1 1639G>A	≤2

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

On August 16, 2007, FDA approved updated labeling for Coumadin®, to include information on genetic testing for gene variants that may help "personalize" the starting dose for each patient and reduce the number of serious bleeding events. The label was updated again on January 22, 2010. With each update, manufacturers of warfarin (generic for Coumadin®) were directed to add similar information to their products' labels. The 2010 update added information on personalizing initial dose according to genotyping results for *CYP2C9* and *VKORC1*, providing a table of genotypes and suggested initial dose ranges for each. However, suggested starting doses also are provided for when genotyping information is unavailable, indicating that genetic testing is not required. Furthermore, FDA did not include information on genetic variation in the label's black box warning regarding bleeding risk.

Medical Policy Statement

Genetic testing for warfarin dosing is experimental/investigational. The clinical utility of genetic testing to determine cytochrome p450 2C9 (*CYP2C9*), P450 4F2 (CYP4F2), and vitamin K epoxide reductase subunit C1(*VKORC1*) genetic polymorphisms and other warfarin responsive testing for the purpose of determining warfarin dosing has not been demonstrated. The peer reviewed medical literature has not yet shown that this testing has sufficient diagnostic accuracy to provide clinically relevant information for patient management.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

G9143 81227 81355

Rationale

The primary goal of pharmacogenomics testing and personalized medicine is to achieve better clinical outcomes as 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.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 that 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 a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one 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. RCTs are rarely large enough 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.

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 under coagulation thereby avoiding the downstream consequences of thromboembolism or bleeding.

The following **PICOs** were used to select literature to inform this review.

Populations

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

Interventions

A number of commercial tests for individual genes or panel testing are available and listed in Table 1. Numerous algorithms have been developed to guide warfarin dosing based on 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 are listed in the Table 2.

Table 2. Outcomes of Interest for Individuals Undergoing *CYP2C9* and *VKORC1* Genotyping

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

INR: international normalized ratio

Review of Evidence

Systematic Reviews and Meta-Analyses

Several recent systematic reviews and meta-analyses have assessed genotype-guided warfarin dosing compared to with clinical dosing. A comparison of the trials included in the systematic reviews and meta-analyses is shown in Table 3. The systematic reviews and meta-analyses include a total of 27 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 5 most recent and comprehensive reviews, conducted by Belley-Cote et al (2015),[49] Tse et al (2018),[50] and the Washington State Health Technology Assessment Program (Washington HTA, 2018),[51] Yang et al (2019)[52], Sridharan and Sivaramakrishnan (2020)[53] . and Wang et al (2022). 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)[49],	**Tse et al (2018)[50],**	**Washington HTA (2018)[51],**	**Yang et al (2019)[52],**	**Sridharan and Sivaramakrishnan (2020)[53],**
Hillman et al (2005)	●	●	●	●	●
Anderson et al (2007)	●		●	●	●
Caraco et al (2008)	●	●	●		●
Huang et al (2009)	●	●	●	●	●
Burmester et al (2011)	●		●	●	●

McMillin et al (2011)					●
Borgman et al (2012)	●		●	●	●
Wang et al (2012)[61,]	●		●	●	●
Radhakrishnan et al (2012)	●				●
Jonas et al (2013)	●		●	●	●
Kimmel et al (2013)	●		●	●	●
Pirmohamed et al (2013)	●	●	●	●	●
Verhoef et al (2013)[,]	●				●
Li et al (2014)		●		●	●
Pengo et al (2015)		●	●	●	●
Supe et al (2015)		●			●
Duan (2016)		●			●
Gage (2017)		●	●	●	●
Jin (2017)		●		●	●
Wen (2017)		●	●	●	●
Jiang (2016)				●	
Makar-Ausperger et al (2018)					●
Xu et al (2018)					●
Syn et al (2018)					●
Guo et al (2020)					●
Lee et al (2020)					●
Panchenko et al (2020)					●
Zhu et al (2020)					●

RCT: randomized controlled trial.

Table 4. Summary of Systematic Reviews of RCT's of Genotype vs. Clinical Dosing of Warfarin

Study	Dates	Participants	RCTs	N (Range)	Duration
Belley-Cote et al (2015)	To Feb 2014	Adults requiring initiation of anticoagulation for any indication	12	3217 (34-1015)	1-6 mo
Tse et al (2018)	2000-2015	Genotype-guided vs. conventional warfarin dosing (population not specified)	18	5230 (NR)	1-3 mo
Washington HTA	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)	To October 2017	Patients with any indication for warfarin therapy	15	4852 (26-1597)	1-3 mo
Sridharan and Sivaramakrishnan (2020)	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)	To July 2021	Patients taking warfarin for any indication in studies comparing genotyped-guided warfarin dosing to conventional warfarin dosing	27	9906 (26-2264)	

NR: not reported; RCT: randomized controlled trial.

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)	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)							
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),							
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	0.91 (0.80 to	MD 3.11 (-0.28 to 6.50);.07	RR 1.17 (0.43 to 3.22);.76		

			1.04);.16				
I^2 (p)	0%	0%	0%	78%; <.00001	0%		
Yang (2019)							
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. clinically adjusted warfarin]	WMD 3.36 (-2.12 to 8.84);.229 [vs. fixed-dose warfarin] WMD 0.88 (-2.26 to 4.02);.582 [vs. clinically adjusted warfarin]	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]		
I^2 (p)	0%	0% [clinically adjusted]	0% [fixed dose]; 31.2% [clinically adjusted]	59.2% [fixed dose]; 63% [clinically adjusted]	0%		
Sridharan and Sivaramakrishnan (2020)							
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 0.30 (0.10 to 0.86); NR [*CYP2C9* vs. clinically adjusted warfarin]		WMD 0.2 (-15.82 to 16.22); NR [*CYP2C9* vs. clinically adjusted warfarin]	OR 0.87 (0.18 to 4.14); NR [*CYP2C9* and *VKORC1* vs. clinically adjusted warfarin]	WMD -2.73 (-3.41 to -2.05); NR [*CYP2C9* vs. clinically adjusted warfarin]	WMD -8.10 (--12.54 to -3.66); 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 0.86 (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 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 0.65 (0.11 to 3.99); NR [*CYP2C9, VKORC1,* and *CYP4F2* vs. clinically adjusted warfarin]	WMD -1.92 (-3.23 to -0.61); NR [*CYP2C9* and *VKORC1* 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]
I^2 (p)	NR	NR		NR	NR	NR	NR
Wang et al (2022)							
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						
I^2 (p)							

CI: confidence interval; INR: international normalized ratio; MD: mean difference; NR: not reported; RCT: randomized controlled trial; RR: relative risk; TEE: thromboembolic event; CYP2C9: cytochrome P450 2C9 enzyme; FU: follow-up;

All six 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 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 *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.[54.] 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.[4] Authors of these reviews 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. For example, the Washington HTA reviewers found a 57% reduction for risk of major bleeding in the pharmacogenetic testing group compared to controls (RR, 0.43; 95% CI, 0.22 to 0.84; p=0.01).[51] 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)[49], 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; 0.54 to 1.34; p=0.48) 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 recent 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.[51] Yang et al (2019)[52] 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 *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.[53] The quality of evidence was often downgraded because of high risk of bias, potential for publication bias, and imprecision. Wang et al (2022)[54,] 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 were identified, all of which were included in at least one Systematic Review and meta-analyses (see Table 3).

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. Twenty-seven percent of the participants in the multicenter Clarification of Optimal Anticoagulation through Genetics (COAG) trial (Kimmel et al [2013]) were African American.[66]

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 four, none reported statistically significant differences in major bleeding or thromboembolic events and only 1 (Zhu et al [2020]) reported significant reduction in TEEs (ischemic stroke) with genotype-guided dosing.[82] 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 thromboembolic events.

Three multicenter RCTs with more than 400 patients have been reported: COAG,[66]European Pharmacogenetics of Anticoagulant Therapy (EU-PACT),[67] and GIFT.[4] These larger RCTs are discussed in the following paragraphs and summarized in Tables 6 and 7. Three of the systematic reviews discussed above included all of these large trials. The Belley-Cote systematic review was published prior to GIFT.

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

Study; Trial	Countries	Sites	Dates	Participants	Interventions
Kimmel et al (2013) 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) EU-PACT	UK, Sweden	2	2010-2013	•Age >18 y; warfarin-naïve; indications for anticoagulation with AF or VTE •99% white race	Clinical dosing algorithm including age, sex, height, weight, and amiodarone use
Gage (2017) 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)	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; INR: international normalized ratio; RCT: randomized controlled trial; SOM: school of medicine; VTE: venous thromboembolism.

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

Study	Major Bleeding	TEEs	INR>4	% of Time in Therapeutic Range	Deaths
Kimmel et al (2013) 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); 0.13	HR=1.27 (0.34 to 4.73); 0.72	HR=1.08 (0.81 to 1.44); 0.59	p=0.91	HR=2.09 (0.19 to 23.22); 0.55
Pirmohamed et al (2013) 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); 0.03	MD=7.0 (3.3 to 10.6); <0.001	
Gage (2017) 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); 0.06	RD=0.7 (-1.3 to 2.8); 0.48	RD=2.8 (0.1 to 5.6); 0.04	MD=3.4 (1.1 to 5.8); 0.004	
Zhu et al (2020)					
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	

HR: hazard ratio; INR: international normalized ratio; MD: mean difference; MI: myocardial infarction; NR: not reported OR: odds ratio; RCT: randomized controlled trial; RD: risk difference; TE: treatment effect; TEE: thromboembolic event.
[a] Values are in person-months.

Two larger RCTs of pharmacogenetic dosing algorithms were published by Kimmel et al (2013) and Pirmohamed et al (2013).[66,67] The larger of these, the Clarification of Optimal Anticoagulation through Genetics (COAG) trial, was conducted in the U.S. by the National Heart, Lung, and Blood Institute,[66] and the smaller trial was conducted in Sweden and England by the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) consortium.[67] 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% African American were randomized to warfarin doses for the first 5 days of therapy based on their clinical and genetic characteristics or their clinical characteristics alone.[66] 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=0.91) 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=0.93). 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=0.01).

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.[67] 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 genotyped-guided dosing group compared with 60% in clinically guided group (p<0.001). There were no differences in secondary outcomes assessed (bleeding or thromboembolism events). However, the percentage of patients with INR greater than 4 was lower in genotype-guided group (27%) than in the clinically guided group (37%). The time to achieving therapeutic INR was also shorter in the genotyped-guided group (21 days) than in the clinically guided group (29 days).

Gage et al (2017) reported on 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.[83] Patients were genotyped for *VKORC1*-1639G>A, *CYP2C9*2*, *CYP2C9*3*, and *CYP4F2* V433M variants. The primary end point was the composite of major bleeding, INR of 4 or greater, 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 genotype-guided group vs. 789 in 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=0.02). The difference in the composite outcome was primarily driven by the difference in percent of patients with INR of 4 or greater (56 vs 77; RR=0.71; 95% CI, 0.51 to 0.99). There were 2 vs. 8 major bleeding events in the genotype vs clinical groups (RR=0.24; 95% CI, 0.05 to 1.15) and 33 vs. 38 venous thromboembolism events (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).[82,] 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.

A risk of bias and quality of evidence assessments for RCTs included in the Belley-Cote (2015)[49], Washington HTA (2018)[51], Yang (2019)[52], Sridharan and Sivaramakrishnan[53] , and Wang (2022)[54] systematic review was summarized in the previous section. An assessment of

the gaps for the remaining RCTs is shown in Tables 8 and 9. No major relevance, design or conduct gaps were identified for the Gage (2017) RCT, and it is a low risk of bias.

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 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; Twenty-seven percent of the participants in the multicenter COAG trial (Kimmel et al [2013]) were African American. 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 four, none reported statistically significant differences in major bleeding or TEEs . 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 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 or TEEs, 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, which included 27% African American participants, African Americans fared better in the clinically guided group than in the genotype-guided group. There are completed, registered studies that have not been published, so the possibility of publication bias cannot be excluded.

SUMMARY OF EVIDENCE

For individuals with conditions requiring warfarin treatment who receive genotype-guided warfarin dosing, the evidence includes multiple RCTs and systematic reviews of the RCTs. The relevant outcomes are morbid events, medication use, and treatment-related mortality and morbidity. Thirty RCTs and six systematic reviews were identified. Most RCTs were single-center studies including fewer than 250 patients. Systematic reviews found the percentage of time the 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 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 COAG 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.

Ongoing and Unpublished Clinical Trials

Some currently 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
Ongoing			
Unpublished			
NCT01305148[a]	Warfarin adverse event reduction for adults receiving genetic testing at therapy Initiation (WARFARIN)	3800	Dec 2015 (suspended)
NCT03797534	Individualized Administration of Warfarin by Polymorphisms of VKORC1 and CYP2C9 Genes: A Randomized Controlled Trial, Multi-Center Trial	600	Jan 2023
NCT03479684	Randomized trial of genotype-guided vs. standard for warfarin dosing	560	Dec 2020

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

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Medical Genetics

The 2008 American College of Medical Genetics (ACMG) policy statement concluded: "There is insufficient evidence, at this time, to recommend for or against routine *CYP2C9* and *VKORC1* testing in warfarin-naive patients."[84]

American College of Chest Physicians

The 9th edition of the *American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on Antithrombotic and Thrombolytic Therapy*, published in 2012 states, "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

The Clinical Pharmacogenetics Implementation Consortium updated guidelines for pharmacogenetics-guided warfarin dosing in 2017.[87] The guideline provides recommendations for genotype-guided warfarin dosing to achieve a target international normalized ratio 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."

Government Regulations
National/Local:

On August 3, 2009, the Centers for Medicare and Medicaid Services (CMS) published a National Coverage Analysis (available online at: http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=333&ncdver=1&bc=AgAAgAAAAAAAAA%3d%3d&) regarding pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness.[84] CMS states that the available evidence does not demonstrate that such testing improves health outcomes in Medicare beneficiaries and that "pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness is not reasonable and necessary under §1862(a) (1) (A) of the Social Security Act. However, we do believe the available evidence supports that Coverage with Evidence Development (CED) under §1862(a) (1) (E) of the Social Security Act is appropriate."

CMS now covers pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness 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 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 described standards.

The CMS believes 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.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing for Cytochrome P450 Polymorphisms

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/08	11/26/07	11/14/07	Joint policy established
5/1/09	12/9/08	12/21/08	Routine maintenance
11/1/10	8/28/10	8/17/10	Routine maintenance; procedure code G9143 added to policy
11/1/11	8/16/11	8/16/11	Updated description, rationale and references. No change in policy status.
11/1/12	8/21/12	8/21/12	Updated description and rationale to mirror BCBSA policy. Added new CPT code, 81355, deleted G9143. Description, rationale and references updated to mirror BCBSA policy. No change in policy status.
11/1/13	8/22/13	8/27/13	Routine maintenance; rationale and references updated. Policy status unchanged.
11/1/14	8/21/14	8/25/14	Routine maintenance, rationale and references updated. Policy status unchanged.
11/1/15	8/24/15	9/14/15	Routine maintenance, rationale and references updated. Policy status unchanged.
9/1/16	6/21/16	6/21/16	Routine maintenance. Policy status unchanged.
9/1/17	6/20/17	6/20/17	Routine maintenance. Policy status unchanged.
9/1/18	6/19/18	6/19/18	Routine policy maintenance, no change in policy status.

9/1/19	6/18/19		Policy updated with literature review through April 9, 2018; references 5, 31, 51, 52-54, 56-57, 63-66, and 69 were added. Investigational policy statement expanded to include genotyping for *CYP4F2.* Title changed to reflect focus on genotype-guided dosing as an intervention. Added “and other warfarin responsive testing” to MPS.
9/1/20	6/16/20		Updated rationale section, some references removed, others added. No change in policy status.
9/1/21	6/15/21		Routine policy maintenance, no change in policy status.
9/1/22	6/21/22		Updated rationale section, added references 52, 53 and 79. No change in policy status.
9/1/23	6/13/23		Routine policy update, no change in policy status. Vendor managed: N/A (ds)
9/1/24	6/11/24		Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)

Next Review Date: 2nd Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENOTYPE-GUIDED WARFARIN DOSING

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

N/A