BlueCross BlueShield of Alabama

Name of Policy:
~~Genetic Testing for~~ Genotype-Guided Warfarin Dosing

Policy #: 525
Category: Laboratory/Medicine
Latest Review Date: July 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *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 that patient's illness, injury or disease.*

Description of Procedure or Service:

Using information about an individual's genotypes may help in guiding warfarin dosing and could reduce the time to dose stabilization and selection of appropriate maintenance dose that might avoid consequences of too much or too little anticoagulation.

Warfarin is administered to prevent and treat thromboembolic events in high-risk patients; warfarin dosing is a challenging process, due to the narrow therapeutic window, variable response to dosing, and serious bleeding events in 5% or more of patients (depending on definition). Patients are typically given a starting dose of 2–5 mg and monitored frequently with dose adjustments until a stable International Normalized Ratio (INR) value (a standardized indicator of clotting time) between two and three is achieved. During this adjustment period, a patient is at high risk for bleeding.

Stable or maintenance warfarin dose varies among individuals by more than an order of magnitude. Factors influencing stable dose include body mass index (BMI), age, interacting drugs, and indication for therapy.

Warfarin, which is primarily metabolized in the liver by the CYP2C9 enzyme, exerts an anticoagulant effect by inhibiting the protein vitamin K epoxide reductase complex, subunit 1 (VKORC1). Three single-nucleotide variants (SNVs), two in the *CYP2C9* gene and one in the *VKORC1* gene play key roles in determining the effect of warfarin therapy on coagulation. *CYP2C9*1* metabolizes warfarin normally, *CYP2C9*2* reduces warfarin metabolism by 30%, and *CYP2C9*3* reduces warfarin metabolism by 90%. Because warfarin given to patients with **2* or **3* variants will be metabolized less efficiently, the drug will remain in circulation longer, so lower warfarin doses will be needed to achieve anticoagulation. CYP2C9 and VKORC1 genetic variants account for approximately 55% of the variability in warfarin maintenance dose. Recent genome-wide association studies have also identified that a single nucleotide variant in the *CYP4F2* gene has been reported to account for a small proportion of the variability in stable dose (the *CYP4F2* gene encodes a protein involved in vitamin K oxidation). Studies have predicted that CYP4F2 variants explain 2% to 7% of the variability in warfarin dose in models, including other genetic and nongenetic factors.

Using the results of *CYP2C9* and *VKORC1* genetic testing to predict a warfarin starting dose that approximates 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. Studies have compared the ability of different algorithms to predict stable warfarin dose accurately. Currently, there does not appear to be consensus for a single algorithm.

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

There are different frequencies of variants related to warfarin pharmacokinetics across different races and ethnicities. Many of the original studies identifying associations between genes and prediction of warfarin dosing as well as studies developing algorithms were derived from cohorts

composed largely of people of European descent. Evidence has suggested these algorithms do not perform as well in other ethnic groups. For example, *CYP2C9*2* and *CYP2C9*3* are not as useful in predicting warfarin dosing in African Americans, but other important variants have been identified such as *CYP2C9*5,*6,*8,* and **11*. Studies have also identified new genetic variants and/or evaluated clinical genetic algorithms for warfarin dose in African American, Puerto Rican, Thai, Egyptian, Chinese, Japanese, Arabic, Turkish, and Scandinavian populations.

Policy:

Genotyping to determine cytochrome p450 2C9 (CYP2C9), P450 4F2 (CYP4F2), and/or vitamin K epoxide reductase subunit C1 (VKORC1) genetic ~~polymorphisms~~ variants for the purpose of managing the **administration and dosing of warfarin**, including use in guiding the initial warfarin dose to decrease time to stable INR and reduce the risk of serious bleeding **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administer benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature review was performed through April 9, 2018.

The primary goal of pharmacogenomics testing and personalized medicine is to achieve better clinical outcomes in 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 Test 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 question addressed in this evidence review is: Does genotype-guided warfarin dosing improve health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients 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 1.

Table 1. 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 overtreatment
Treatment-related morbidity	Time to achieve therapeutic INR, time in therapeutic INR, bleeding, thromboembolism

INR: international normalized ratio.

Timing
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.

Setting
Patients requiring treatment with warfarin are managed by multiple specialists, including but not limited to cardiologists, cardiovascular surgeons, pulmonologists, internists, critical care physicians, and neurologists based on the clinical indication. Warfarin is used in both inpatient and outpatient settings.

Systematic Reviews
Several published systematic reviews have assessed comparing genotype-guided warfarin dosing with clinical dosing. A comparison of the trials included in the systematic reviews is shown in Table 2. The systematic reviews include a total of 12 trials published before 2015, and most trials overlap in the reviews.

Table 2. RCTs Included in Systematic Reviews of Genotype vs Clinical Dosing of Warfarin

Trials	Systematic Reviews				
	Stergiopoulos et al (2014)	**Franchini et al (2014)**	**Goulding et al (2015)**	**Liao et al (2015)**	**Belley-Cote et al (2015)**
Hillman et al (2005)	●	●	●	●	●
Anderson et al (2007)	●	●	●	●	●
Caraco et al (2008)	●	●	●	●	●
Huang et al (2009)			●		●
Burmester et al (2011)	●	●	●		●
Borgman et al (2012)	●	●	●		●
Wang et al (2012)			●	●	●
Radhakrishnan et al (2012)					●
Jonas et al (2013)	●	●		●	●
Kimmel et al (2013)	●	●	●	●	●
Pirmohamed et al (2013)	●	●	●	●	●
Verhoef et al (2013)[a]	●	●	●[1]		●

RCT: randomized controlled trial.
a Verhoef et al (2013) was included but not categorized as a warfarin study; warfarin analogues were used.

Characteristics of the systematic reviews are shown in Table 3. The reviews all included similar eligibility criteria leading to a similar set of overlapping studies. Results are shown in Table 4. In general, reviewers found that the percentage of time the international normalized ratio (INR) was in therapeutic range have been higher in patients treated with genotype-guided warfarin therapy; however, the heterogeneity between studies was high for this outcome. Reviewers also varied in their definitions for clinical outcomes, but none of the reviews found differences in rates of major bleeding, thromboembolic events, or death.

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

Study	Dates	Participants	RCTs	N (Range)	Duration
Stergiopoulos et al (2014)	To Dec 2013	Patients with indications for oral anticoagulation with warfarin, acenocoumarol, or phenprocoumon.	9	2812 (NR)	1-3 mo
Franchini et al (2014)	1980-Mar 2014	Adults using anticoagulation with a VKA	9	2812 (26-1015)	1-3 mo
Goulding et al (2015)	1980-Dec 2013	Patients in RCTs comparing genotype-guided prescribing with nongenetically informed prescribing (only warfarin trials reviewed)	9	2344 (26-1015)	14 d to 3 mo
Liao et al (2015)	1995-Jan 2014	Patients with any conditions requiring warfarin treatment	7	1910 (38-1015)	NR
Belley-Cote et al (2015)	To Feb 2014	Adults requiring initiation of anticoagulation for any indication	12	3217 (34-1015)	1-6 mo

NR: not reported; RCT: randomized controlled trial; VKA: vitamin K antagonist.

Table 4. 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
Stergiopoulos et al (2014)					
Total N	2586	2586	2621	2812	NR
Pooled effect (95% CI); p	RR=0.97 (0.46 to 2.05); 0.93	RR=0.60 (0.29 to 1.22); 0.16	RR=0.92 (0.82 to 1.05); 0.21	MD=0.14 (-0.10 to 0.39); 0.25	
I^2 (p)[a]		0%	0%	88% (NR)	
Franchini et al (2014)					
Total N	NR	NR	NR	NR	NR
Pooled effect (95% CI); p	RR=0.98 (0.45 to 2.11); 0.96	RR=0.48 (0.23 to 0.97); 0.04	RR=0.92 (0.81 to 1.04); 0.22		RR=0.71 (0.19 to 2.60); 0.62
I^2 (p)[a]	0%	0%	0%		0%
	Thromboembolic or Bleeding Events				
Goulding et al (2015)					
Total N	2211		NR	1952	NR
Pooled effect (95% CI); p	RR=0.57 (0.33 to 0.99); 0.04			MD=6.7 (1.3 to 12.0); 0.01	
I^2 (p)[a]	60% (0.02)			NR (NR)	
	Adverse Events[b]				
Liao et al (2015)					
Total N	1763		1571	1729	NR
Pooled effect (95% CI); p	RR=0.94 (0.84 to 1.04)		RR=1.36 (0.46 to 4.05)	MD=0.08 (-0.02 to 0.17); 0.02	
I^2 (p)[a]	0%		10% (0.33)	65% (NR)	
	TEE, Major Bleeding Event, or Death				

Study	TEEs, %	Major Bleeding, %	INR >4, %	% Time INR in Therapeutic Range	Deaths
Belley-Cote et al (2015)					
Total N	2223		NR	2767	NR
Pooled effect (95% CI); p	RR=0.85 (0.54 to 1.34); 0.48			MD=4.3 (0.4 to 8.3); 0.03	
I^2 (p)[a]	10% (0.35)			79% (<0.001)	

CI: confidence interval; INR: international normalized ratio; MD: mean difference; NR: not reported; RCT: randomized controlled trial; RR: relative risk; TEE: thromboembolic event.
a Heterogeneity value.
b Included major bleeding, thromboembolism, myocardial infarction, death, relevant nonmajor bleeding or other emergency treatment.

Given that the Belley-Cote et al (2015) review included all 12 trials published up to the search date and used the GRADE approach to evaluate the quality of evidence, the following discussion focused on that systematic review. Reviewers identified 12 published RCTs (total N=3217 patients) and evidence that at least 3 trials were completed but not yet published. Only 1 study was rated as low risk of bias (Kimmel et al [2013]) for all domains. A summary of the risk of bias 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.

Randomized Controlled Trials

RCTs comparing genotype-guided warfarin dosing with clinical dosing were included with no limitations on the indication for warfarin use. Fourteen RCTs comparing genotype-guided with clinical dosing of warfarin were identified. Most RCTs were single-center studies including less than 250 patients. Four multicenter RCTs with more than 400 patients have been reported. RCT characteristics are shown in Table 5. 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; 2 trials were conducted in China. Twenty-seven percent of the participants in the COAG (Kimmel et al [2013]) trial were African American.

Table 5. Characteristics of RCTs of Genotype vs Clinical Dosing of Warfarin

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Hillman et al (2005)	U.S.	1	NR	• White adults, age > 40 y, eligible for warfarin therapy based on diagnosis • 100% White race	*CYP2C9* gene-based multivariate initiation dosage calculator	Initial daily warfarin dose of 5 mg; adjustments by validated algorithm
Anderson et al (2007); COUMA-GEN Study; NCT00334464	U.S.	1	2006-2007	• Age >18 y; indication for anticoagulation • 94% white race	Regression equation developed by authors	Previously published 10-mg warfarin nomogram
Caraco et al (2008)	Israel	1	2001-2006	• Warfarin-naive adults, age ≥18 y, with indication for anticoagulation • INR ≤1.4	Guided by 6 *CYP2C9* genotype-adjusted algorithms	Previously published algorithm
Huang et al (2009)	China	1	2007-2008	• Patients undergoing heart valve replacement • INR between 0.8 and 1.2	Guided by study-specific algorithm but not >3.5 mg/d	Initiated at 2.5 mg/d and adjusted based on INR
Burmester et al (2011); NCT00484640	U.S.	1	2007-2009	• White adults; age ≥40 y; warfarin-naive and restart therapy without a stable warfarin dose • 100% white race	Marshfield Pharmacogenetic model	Marshfield Anticoagulation Service guidelines
Borgman et al (2012); PerMIT; NCT00993200	U.S.	1	2009-2010	• Warfarin-naive; age ≥18 y; indications for warfarin for ≥12 wk • 93% white race	PerMIT software–based method	Standard of care based on clinician discretion and previously published warfarin nomogram
Wang et al (2012)	China	1	2010	• Adults ≥18 y, scheduled for mechanical prosthetic valve replacement • INR between 0.8 to 1.2 • 100% Chinese Han nationality	Algorithm previously published (same as Huang et al [2009])	Initiated at 2.5 mg/d and adjusted according to standard practice based on INR
Jonas et al (2013); WARFPGX; NCT00904293	U.S.	1	2008-2012	• Age ≥18 y with indications for warfarin for ≥90 d • 73% white race	Algorithm developed at Washington University SOM	Same algorithm including only clinical factors
Kimmel et al (2013); COAG; NCT00839657	U.S.	18	2009-2013	• Adults initiating warfarin therapy with expected duration ≥1 mo	Algorithm including clinical variables and genotype data	Algorithm including clinical variables only

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
				• 27% black race		
Pirmohamed et al (2013); EU-PACT Warfarin; NCT01119300	U.K., Sweden	2	2011-2013	• Age >18 y; warfarin-naive; indications for anticoagulation with AF or VTE • 99% white race	Modification of the International Warfarin Pharmacogenetics Consortium algorithm	Local practice
Verhoef et al (2013); EU-PACT - Acenocoumarol; NCT01119261	Netherlands, Greece	2	2010-2013	• Warfarin-naive patients with AF or VTE with ≥12 wk of acenocoumarol or phenprocoumon therapy • 97% white race	Genotype-guided algorithm plus age, sex, height, weight, and amiodarone use	Clinical dosing algorithm including age, sex, height, weight, and amiodarone use
Pengo et al (2015)	Italy	1	2009-2012	• Patients with nonvalvular, AF, age >18 y • Baseline INR ≤1.2	Pharmacogenetic algorithm	Initiated at 5 mg and adjusted based on previously published algorithm
Gage et al (2017); GIFT; NCT01006733	U.S.	6	2011-2016	• Patients aged ≥65 y initiating warfarin for elective hip or knee arthroplasty • INR <1.35 • 91% white race	WarfarinDosing.org algorithm including genotype data	WarfarinDosing.org algorithm excluding genotype data
Makar-Aušperger et al (2017)	Croatia	1	2012-2016	• Adults (≥18 y) with AF, deep vein thrombosis, or pulmonary embolism	WarfarinDosing.org algorithm including genotype data	Initiated at 6.0 mg/d and adjusted by INR

AF: atrial fibrillation; INR: international normalized ratio; RCT: randomized controlled trial; SOM: school of medicine; VTE: venous thromboembolism.

Results of the RCTs are shown in Table 6. 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 or thromboembolic events. 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. Details on the larger studies are also provided in the following paragraphs.

Table 6. Results of RCTs of Genotype vs Clinical Dosing of Warfarin

Study	Major Bleeding	TEEs	INR >4	% Time INR in Therapeutic Range	Deaths
	Major Bleeding or TEEs				
Hillman et al (2005)					
N	38		38	38	NR
Genotype-guided dosing, n (%)	2 (11%)		6 (33%)	41.7%	
Control, n (%)	5 (25%)		6 (30%)	41.5%	
TE (95% CI); p	NR		NR	NR	

	Major Bleeding Events, TEEs, Stroke, MI, or Death				
Anderson et al (2007)					
N	200		NR	200	NR
Genotype-guided dosing, n (%)	4 (4)			69.7%	
Control, n (%)	5 (5)			68.3%	
TE (95% CI); p	OR=0.78 (0.20 to 2.98); 0.71			OR=1.29 (0.71 to 2.36); 0.41	
Caraco et al (2008)					
N	185	185	NR	185	NR
Genotype-guided dosing	0	0		80%	
Control	1	0		63%	
TE (95% CI); p				NR (NR); <0.001	
	Adverse Events, Not Defined		**INR >3.5**	**Days**	
Huang et al (2009)					
N	121		121	121	142
Genotype-guided dosing	12%		5	28	1
Control, %	13%		5	22	2
TE (95% CI); p	NR (NR); 0.76			NR (NR); 0.001	
	Major Bleeding or TEEs				
Burmester et al (2011)					
N	NR		225	225	NR
Genotype-guided dosing, n (%)	54		43 (38)	29.1%	2
Control, n (%)	61		39 (35)	30.8%	3
TE (95% CI); p	NR		NR (NR); 0.94	NR (NR); 0.56	NR
Borgman et al (2012)					
N	26	26	26	26	26
Genotype-guided dosing	0	0	40%	63.4%	0
Control	0	0	40%	55.3%	0
TE (95% CI); p				NR (NR); 0.18	
Wang et al (2012)					
N	101	NR	NR	NR	NR
Genotype-guided dosing, n (%)	5 (10)				
Control, n (%)	8 (16)				
TE (95% CI); p	NR (NR); 0.55				
Jonas et al (2013)					
N	106	106	106	106	106
Genotype-guided dosing, n (%)	1 (2)	0	25 (45)	45%	0
Control, n (%)	4 (7)	3 (6)	26 (49)	49%	2
TE (95% CI); p	NR (NR); 0.17	NR (NR); 0.08	NR (NR); 0.65	NR (NR); 0.50	NR (NR); 0.15
Kimmel et al (2013)					
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)					
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	
Verhoef et al (2013)					
N	484	484	484	484	NR
Genotype-guided dosing	0.38[a]	0.18[a]	31%	62%	
Control	0.38[a]	0.02[a]	33%	60%	
TE (95% CI); p	NR (NR); 0.94	NR (NR); 0.62	NR (NR); 0.02	MD=1.4 (-2.8 to 5.5); 0.52	
Pengo et al (2015)					
N	180	180	180	180	
Genotype-guided dosing	0	0	8% (1% to 25%)	52% (48% to 56%)	NR
Control	0	0	25% 11% to 45%)	53% (49%to 57%)	
TE (95% CI); p			NR (NR); 0.16	NR (NR); 0.71	
Gage et al (2017)					
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	
Makar-Aušperger et al (2018)					
N	NR	NR	NR	205	NR
Genotype-guided dosing				14%	
Control				16%	
TE (95% CI); p				MD = -2 (-7 to 4); 0.51	

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). 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, and the smaller trial was conducted in Sweden and England by the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) consortium. 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. 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. 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. 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.

A risk of bias assessment for RCTs included in the Belley-Cote (2015) systematic review was summarized in the previous section. An assessment of the gaps for the remaining RCTs is shown in Tables 7 and 8. No major relevance, design or conduct gaps were identified for the Gage (2017) RCT, and it is a low risk of bias.

Table 7. Relevance Gaps of RCTs of Genotype vs Clinical Dosing of Warfarin

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
Pengo et al (2015)				6. Clinically significant difference not justified	
Gage et al (2017)					
Makar-Aušperger et al (2017)				1. Major bleeding and thromboembolic events not reported by treatment group 5. No discussion of clinically important differences	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
FU: follow-up.
a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 8. Study Design and Conduct Gaps of RCTs of Genotype vs Clinical Dosing of Warfarin

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Pengo et al (2015)	3. Allocation concealment not described			5,6. Patients not compliant or discontinued intervention were excluded		
Gage et al (2017)						
Makar-Aušperger et al (2017)	1. Stated to be randomized but also stated that "those admitted to the Department of Cardiology, no pharmacogenetic assessment was performed prior to anticoagulation therapy start, while patients admitted to the Department of Internal Medicine were pharmacogenetically evaluated before being started on warfarin" 3. Allocation		1. Registration not mentioned	1. Flow of participants not described, missing data unclear	1. No power calculations	

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
	concealment not described					

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
b Blinding key: 1. Not blinded to results of reference or other comparator tests.
c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

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.

- Five of the 14 RCTs reported statistically significant differences favoring genotype-guided warfarin dosing for outcomes related to time in the therapeutic range for INR and/or the outcome related to events of INR greater than 4.
- None of the trials or pooled analyses of the trials showed a benefit for patient-important outcomes like major bleeding or venous thromboembolism.
- A 2015 systematic review including 12 trials (total N=3217 patients) did not report a decrease a composite outcome of death, thromboembolism and major bleeding (87 events, RR=0.85; 95% CI, 0.54 to 1.34) with genotype-guided dosing.
- A 2017 RCT (n=1650) demonstrated an improvement in the composite outcome of major bleeding, INR of 4 or greater, venous thromboembolism, or death (absolute difference, 3.9%; 95% CI, 0.7% to 7.2%) favoring genotype-guided dosing that was driven primarily by the difference in the INR component. There were no statistically significant differences in clinical events in genotype vs clinical groups: 2 vs 8 major bleeding events, 33 vs 38 venous thromboembolism events, and no deaths.

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

For individuals with conditions requiring warfarin treatment who receive genotype-guided warfarin dosing, the evidence includes multiple randomized controlled trial (RCTs) and systematic reviews of RCTs. Relevant outcomes are morbid events, medication use, and treatment-related morbidity. Fourteen RCTs were identified. While 5 of the 14 RCTs reported statistically significant differences in outcomes related to the international normalized ratio, none of the trials or pooled meta-analyses of the trials have shown a benefit for outcomes of major bleeding or venous thromboembolism. In the pooled analysis including 2223 participants, 87 events of the composite outcome (mortality, major bleed, and thromboembolic events) occurred (relative risk, 0.85; 95% confidence interval, 0.54 to 1.34; p=0.48). In the GIFT trial, which included 1650 participants, conducted after the pooled analysis, 2 vs 8 major bleeding events

occurred (relative risk, 0.24; 95% confidence interval, 0.05 to 1.15), 33 vs 38 venous thromboembolism events occurred (relative risk, 0.85; 95% confidence interval, 0.54 to 1.34), and there were no deaths. Very few trials have 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.

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."

American College of Chest Physicians

The 9th edition of the "American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on Antithrombotic Therapy and Prevention of Thrombosis," 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)."

Clinical Pharmacogenetics Implementation Consortium

The Clinical Pharmacogenetics Implementation Consortium updated guidelines for pharmacogenetics-guided warfarin dosing in 2017.69 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."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Key Words:

Warfarin, Coumadin, CYP450, CYP2C9, cytochrome p450, VKORC1, vitamin K epoxide reductase subunit C1, genotyping, P450 4F2, CYP4F2

Approved by Governing Bodies:

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. 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. Generally, such tests are not intended as stand-alone tools to determine optimum drug dosage but should be used along with clinical evaluation and other

tools, including the INR, to predict the initial dose that best approximates the maintenance dose for patients.

Table 9. 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]	*CYP2C9*2* and **3*, *VKORC1* 1639G>A	6-8
eQ-PCR™ LightCycler® Warfarin Genotyping Kit (TrimGen, Sparks Glencoe, MD)	*CYP2C9*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*, **4*, **5*, **6*, and **11*, *VKORC1* 1639G>A, and 6 additional *VKORC* variants.

On August 16, 2007, the 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 are also provided for when genotyping information is not available, indicating that genetic testing is not required. Furthermore, the FDA did not include information on genetic variation in the label's black box warning regarding bleeding risk.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

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 variants (e.g., -1639G>A, c173+1000>T)
0030U	Drug metabolism (warfarin drug response), targeted sequence analysis (i.e., CYP2C9, CYP4F2, VKORC1, rs12777823) **(Effective 01/01/2018)**

HCPCS codes:

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

References:

1. Alzahrani AM, Ragia G, Hanieh H et al. Genotyping of CYP2C9 and VKORC1 in the Arabic population of Al-Ahsa, Saudi Arabia. Biomed Res Int 2013; 2013:315980.
2. Anderson JL, Horne BD, Stevens SM et al. A randomized and clinical effectiveness trial comparing two pharmacogenetic algorithms and standard care for individualizing warfarin dosing (CoumaGen-II). Circulation 2012; 125(16):1997-2005.
3. Anderson JL, Horne BD, Stevens SM et al. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. Circulation 2007; 116(22):2563-70.
4. Aomori T, Obayashi K, Fujita Y et al. Influence of CYP2C9 and vitamin k oxide reductase complex (VKORC)1 polymorphisms on time to determine the warfarin maintenance dose. Pharmazie 2011; 66(3):222-5.
5. Avery PJ, Jorgensen A, Hamberg AK et al. A proposal for an individualized pharmacogenetics-based warfarin initiation dose regimen for patients commencing anticoagulation therapy. Clin Pharmacol Ther 2011; 90(5):701-6.
6. Bazan NS, Sabry NA, Rizk A et al. Validation of pharmacogenetic algorithms and warfarin dosing table in Egyptian patients. Int J Clin Pharm 2012; 34(6):837-44.
7. Becquemont L, Alfirevic A, Amstutz U et al. Practical recommendations for pharmacogenomics-based prescription: 2010 ESF-UB Conference on Pharmacogenetics and Pharmacogenomics. Pharmacogenomics 2011; 12(1):113-24.
8. Belley-Cote EP, Hanif H, D'Aragon F, et al. Genotype-guided versus standard vitamin K antagonist dosing algorithms in patients initiating anticoagulation. A systematic review and meta-analysis. Thromb Haemost. Oct 2015;114(4):768-777.
9. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Special Report: Genotyping for Cytochrome P450 Polymorphisms to Determine Drug-metabolizer Status: TEC Assessments 2004; Volume 19, Tab 9.
10. Borgiani P, Ciccacci C, Forte V et al. CYP4F2 genetic variant (rs2108622) significantly contributes to warfarin dosing variability in the Italian population. Pharmacogenomics 2009; 10(2):261-6.
11. Borgman MP, Pendleton RC, McMillin GA, et al. Prospective pilot trial of PerMIT versus standard anticoagulation service management of patients initiating oral anticoagulation. Thromb Haemost. Sep 2012;108(3):561-569.
12. Burmester JK, Berg RL, Yale SH et al. A randomized controlled trial of genotype-based Coumadin initiation. Genet Med 2011; 13(6):509-18.

13. Caldwell MD, Awad T, Johnson JA et al. CYP4F2 genetic variant alters required warfarin dose. Blood 2008; 111(8):4106-12.
14. Caraco Y, Blotnick S, Muszkat M. CYP2C9 genotype-guided warfarin prescribing enhances the efficacy and safety of anticoagulation: a prospective randomized controlled study. Clin Pharmacol Ther. Mar 2008; 83(3):460-470.
15. Cavallari LH, Momary KM, Patel SR et al. Pharmacogenomics of warfarin dose requirements in Hispanics. Blood Cells Mol Dis 2011; 46(2):147-50.
16. Cavallari LH, Shin J, Perera MA. Role of pharmacogenomics in the management of traditional and novel oral anticoagulants. Pharmacotherapy 2011; 31(12):1192-207.
17. Daly A. Optimal dosing of warfarin and other coumarin anticoagulants: the role of genetic polymorphisms. Arch Toxicol 2013; 87(3):407-20.
18. D'Andrea G, D'Ambrosio RL, Di Perna P et al. A polymorphism in the VKORC1 gene is associated with an interindividual variability in the dose-anticoagulant effect of warfarin. Blood 2005; 105(2):645-9.
19. Epstein RS, Moyer TP, Aubert RE et al. Warfarin genotyping reduces hospitalization rates results from the MM-WES (Medco-Mayo Warfarin Effectiveness study). J Am Coll Cardiol 2010; 55(25):2804-12.
20. Ferder NS, Eby CS, Deych E et al. Ability of VKORC1 and CYP2C9 to predict therapeutic warfarin dose during the initial weeks of therapy. J Thromb Haemost 2010; 8(1):95-100.
21. Flockhart DA, O'Kane D, Williams MS et al. Pharmacogenetic testing of CYP2C9 and VKORC1 alleles for warfarin. Genet Med 2008; 10(2):139-50.
22. Franchini M, Mengoli C, Cruciani M, et al. Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a systematic review and meta-analysis. J Thromb Haemost. 2014; 12(9):1480-1487.
23. Gage BF, Bass AR, Lin H, et al. Effect of genotype-guided warfarin dosing on clinical events and anticoagulation control among patients undergoing hip or knee arthroplasty: the GIFT Randomized Clinical Trial. JAMA. Sep 26 2017; 318(12):1115-1124.
24. Gage BF, Eby C, Johnson JA et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. Clin Pharmacol Ther 2008; 84(3):326-31.
25. Gage BF, Eby C, Milligan PE et al. Use of pharmacogenetics and clinical factors to predict the maintenance dose of warfarin. Thromb Haemost 2004; 91(1):87-94.
26. Gan GG, Phipps ME, Lee MM et al. Contribution of VKORC1 and CYP2C9 polymorphisms in the interethnic variability of warfarin dose in Malaysian populations. Ann Hematol 2011; 90(6):635-41.
27. Geisen C, Watzka M, Sittinger K et al. VKORC1 haplotypes and their impact on the inter-individual and inter-ethnical variability of oral anticoagulation. Thromb Haemost 2005; 94(4):773-9.
28. Gong IY, Tirona RG, Schwarz UI et al. Prospective evaluation of a pharmacogenetics-guided warfarin loading and maintenance dose regimen for initiation of therapy. Blood 2011; 118(11):3163-71.
29. Goulding R, Dawes D, Price M, et al. Genotype-guided Drug Prescribing: A Systematic Review and Meta-analysis of Randomized Control Trials. Br J Clin Pharmacol. Jul 24 2014.

30. Guyatt GH, Akl EA, Crowther M et al. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl):7S-47S.
31. Hamberg AK, Wadelius M. Pharmacogenetics-based warfarin dosing in children. Pharmacogenomics. 2014;15(3):361-374.
32. Hatch E, Wynne H, Avery P et al. Application of a pharmacogenetic-based warfarin dosing algorithm derived from British patients to predict dose in Swedish patients. J Thromb Haemost 2008; 6(6):1038-40.
33. Hawcutt DB, Ghani AA, Sutton L, et al. Pharmacogenetics of warfarin in a paediatric population: time in therapeutic range, initial and stable dosing and adverse effects. Pharmacogenomics J. Jul 8 2014.
34. Hillman MA, Wilke RA, Caldwell MD et al. Relative impact of covariates in prescribing warfarin according to CYP2C9 genotype. Pharmacogenetics 2004; 14(8):539-47.
35. Hillman MA, Wilke RA, Yale SH, et al. A prospective, randomized pilot trial of model-based warfarin dose initiation using CYP2C9 genotype and clinical data. Clin Med Res. Aug 2005; 3(3):137-145.
36. Hirsh J, Guyatt G, Albers GW et al. Antithrombotic and thrombolytic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6 Suppl):110S-12S.
37. Horne BD, Lenzini PA, Wadelius M et al. Pharmacogenetic warfarin dose refinements remain significantly influenced by genetic factors after one week of therapy. Thromb Haemost 2012; 107(2):232-40.
38. Huang SW, Chen HS, Wang XQ, et al. Validation of VKORC1 and CYP2C9 genotypes on interindividual warfarin maintenance dose: a prospective study in Chinese patients. Pharmacogenet Genomics. 2009; 19(3):226-234.
39. Johnson JA, Caudle KE, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. Clin Pharmacol Ther. Sep 2017; 102(3):397-404.
40. Jonas DE, Evans JP, McLeod HL et al. Impact of genotype-guided dosing on anticoagulation visits for adults starting warfarin: a randomized controlled trial. Pharmacogenomics 2013; 14(13):1593-603.
41. Jonas DE, McLeod HL. Genetic and clinical factors relating to warfarin dosing. Trends Pharmacol Sci 2009; 30(7):375-86.
42. Kangelaris KN, Bent S, Nussbaum RL, et al. Genetic testing before anticoagulation? A systematic review of pharmacogenetic dosing of warfarin. J Gen Intern Med. 2009; 24(5):656-664.
43. Kaye JB, Schultz LE, Steiner HE, et al. Warfarin pharmacogenomics in diverse populations. Pharmacotherapy. Sep 2017; 37(9):1150-1163.
44. Kimmel SE, French B, Kasner SE et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. N Engl J Med 2013; 369(24):2283-2293.
45. King CR, Porche-Sorbet RM, Gage BF et al. Performance of commercial platforms for rapid genotyping of polymorphisms affecting warfarin dose. Am J Clin Pathol 2008; 129(6):876-83.
46. Klein TE, Altman RB, Eriksson N et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med 2009; 360(8):753-64.

47. Langley MR, Booker JK, Evans JP et al. Validation of clinical testing for warfarin sensitivity: comparison of CYP2C9-VKORC1 genotyping assays and warfarin-dosing algorithms. J Mol Diagn 2009; 11(3):216-25.
48. Lenzini P, Wadelius M, Kimmel S et al. Integration of genetic, clinical, and INR data to refine warfarin dosing. Clin Pharmacol Ther 2010; 87(5):572-8.
49. Liang R, Wang C, Zhao H et al. Influence of CYP4F2 genotype on warfarin dose requirement-a systematic review and meta-analysis. Thromb Res 2012; 130(1):38-44.
50. Liao Z, Feng S, Ling P, et al. Meta-analysis of randomized controlled trials reveals an improved clinical outcome of using genotype plus clinical algorithm for warfarin dosing. J Thromb Thrombolysis. Jun 25 2014.
51. Limdi NA, Wadelius M, Cavallari L et al. Warfarin pharmacogenetics: a single VKORC1 polymorphism is predictive of dose across 3 racial groups. Blood 2010; 115(18):3827-34.
52. Limdi NA, Wiener H, Goldstein JA et al. Influence of CYP2C9 and VKORC1 on warfarin response during initiation of therapy. Blood Cells Mol Dis 2009; 43(1):119-28.
53. Lubitz SA, Scott SA, Rothlauf EB et al. Comparative performance of gene-based warfarin dosing algorithms in a multiethnic population. J Thromb Haemost 2010; 8(5):1018-26.
54. Ma C, Zhang Y, Xu Q et al. Influence of warfarin dose-associated genotypes on the risk of hemorrhagic complications in Chinese patients on warfarin. Int J Hematol 2012; 96(6):719-28.
55. Makar-Aušperger K, Krzelj K, Lovric Bencic M, et al. Warfarin dosing according to the genotype-guided algorithm is most beneficial in patients with atrial fibrillation: a randomized parallel group trial. Ther Drug Monit. Feb 27 2018.
56. McClain MR, Palomaki GE, Piper M et al. A rapid-ACCE review of CYP2C9 and VKORC1 alleles testing to inform warfarin dosing in adults at elevated risk for thrombotic events to avoid serious bleeding. Genet Med 2008; 10(2):89-98.
57. McMillin GA, Melis R, Wilson A et al. Gene-based warfarin dosing compared with standard of care practices in an orthopedic surgery population: a prospective, parallel cohort study. Ther Drug Monit 2010; 32(3):338-45.
58. Meckley LM, Wittkowsky AK, Rieder MJ et al. An analysis of the relative effects of VKORC1 and CYP2C9 variants on anticoagulation related outcomes in warfarin-treated patients. Thromb Haemost 2008; 100(2):229-39.
59. Mega JL, Walker JR, Ruff CT, et al. Genetics and the clinical response to warfarin and edoxaban: findings from the randomised, double-blind ENGAGE AF-TIMI 48 trial. Lancet. Jun 6 2015; 385(9984):2280-2287.
60. Millican EA, Lenzini PA, Milligan PE et al. Genetic-based dosing in orthopedic patients beginning warfarin therapy. Blood 2007; 110(5):1511-5.
61. Moreau C, Pautas E, Gouin-Thibault I et al. Predicting the warfarin maintenance dose in elderly inpatients at treatment initiation: accuracy of dosing algorithms incorporating or not VKORC1/CYP2C9 genotypes. J Thromb Haemost 2011; 9(4):711-8.
62. Ozer M, Demirci Y, Hizel C et al. Impact of genetic factors (CYP2C9, VKORC1 and CYP4F2) on warfarin dose requirement in the Turkish population. Basic Clin Pharmacol Toxicol 2013; 112(3):209-14.
63. Pautas E, Moreau C, Gouin-Thibault I et al. Genetic factors (VKORC1, CYP2C9, EPHX1, and CYP4F2) are predictor variables for warfarin response in very elderly, frail inpatients. Clin Pharmacol Ther 2010; 87(1):57-64.

64. Pengo V, Zambon CF, Fogar P, et al. A randomized trial of pharmacogenetic warfarin dosing in naive patients with non-valvular atrial fibrillation. PLoS One. Dec 2015; 10(12):e0145318.
65. Perera MA, Cavallari LH, Limdi NA et al. Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study. Lancet 2013; 382(9894):790-6.
66. Perera MA, Gamazon E, Cavallari LH et al. The missing association: sequencing-based discovery of novel SNPs in VKORC1 and CYP2C9 that affect warfarin dose in African Americans. Clin Pharmacol Ther 2011; 89(3):408-15.
67. Perlstein TS, Goldhaber SZ, Nelson K et al. The Creating an Optimal Warfarin Nomogram (CROWN) Study. Thromb Haemost 2012; 107(1):59-68.
68. Pirmohamed M, Burnside G, Eriksson N et al. A randomized trial of genotype-guided dosing of warfarin. N Engl J Med 2013; 369(24): 2294-2303.
69. Radhakrishnan AV, D.; Tayur, S.; et al. Genotype Guided Therapeutic Dosing of Warfarin in Geriatric Patients. J Am Coll Cardiol. 2012; 59:E1696.
70. Ramirez AH, Shi Y, Schildcrout JS et al. Predicting warfarin dosage in European-Americans and African-Americans using DNA samples linked to an electronic health record. Pharmacogenomics 2012; 13(4):407-18.
71. Rieder MJ, Reiner AP, Gage BF et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med 2005; 352(22):2285-93.
72. Roper N, Storer B, Bona R et al. Validation and comparison of pharmacogenetics-based warfarin dosing algorithms for application of pharmacogenetic testing. J Mol Diagn 2010; 12(3):283-91.
73. Rosove MH, Grody WW. Should we be applying warfarin pharmacogenetics to clinical practice? No, not now. Ann Intern Med 2009; 151(4):270-3, W95.
74. Sagreiya H, Berube C, Wen A et al. Extending and evaluating a warfarin dosing algorithm that includes CYP4F2 and pooled rare variants of CYP2C9. Pharmacogenet Genomics 2010; 20(7):407-13.
75. Sangviroon A, Panomvana D, Tassaneeyakul W et al. Pharmacokinetic and pharmacodynamic variation associated with VKORC1 and CYP2C9 polymorphisms in Thai patients taking warfarin. Drug Metab Pharmacokinet 2010; 25(6):531-8.
76. Schelleman H, Chen J, Chen Z et al. Dosing algorithms to predict warfarin maintenance dose in Caucasians and African Americans. Clin Pharmacol Ther 2008; 84(3):332-9.
77. Schwarz UI, Ritchie MD, Bradford Y et al. Genetic determinants of response to warfarin during initial anticoagulation. N Engl J Med 2008; 358(10):999-1008.
78. Sconce EA, Khan TI, Wynne HA et al. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. Blood 2005; 106(7):2329-33.
79. Shahin MH, Khalifa SI, Gong Y et al. Genetic and nongenetic factors associated with warfarin dose requirements in Egyptian patients. Pharmacogenet Genomics 2011; 21(3):130-5.
80. Shaw PB, Donovan JL, Tran MT et al. Accuracy assessment of pharmacogenetically predictive warfarin dosing algorithms in patients of an academic medical center anticoagulation clinic. J Thromb Thrombolysis 2010; 30(2):220-5.

81. Skov J, Bladbjerg EM, Leppin A et al. The influence of VKORC1 and CYP2C9 gene sequence variants on the stability of maintenance phase warfarin treatment. Thromb Res 2013; 131(2):125-9.
82. Stergiopoulos K, Brown DL. Genotype-guided vs clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. JAMA Intern Med. Aug 2014; 174(8):1330-1338.
83. Takeuchi F, McGinnis R, Bourgeois S et al. A genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose. PLoS Genet 2009; 5(3):e1000433.
84. Valentin, II, Vazquez J, Rivera-Miranda G et al. Prediction of warfarin dose reductions in Puerto Rican patients, based on combinatorial CYP2C9 and VKORC1 genotypes. Ann Pharmacother 2012; 46(2):208-18.
85. Vear SI, Ayers GD, Van Driest SL, et al. The impact of age and CYP2C9 and VKORC1 variants on stable warfarin dose in the paediatric population. Br J Haematol 2014; 165(6):832-835.
86. Verhoef TI, Ragia G, de Boer A, et al. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. N Engl J Med. Dec 12 2013; 369(24):2304-2312.
87. Wadelius M, Chen LY, Downes K et al. Common VKORC1 and GGCX polymorphisms associated with warfarin dose. Pharmacogenomics J 2005; 5(4):262-70.
88. Wadelius M, Chen LY, Eriksson N et al. Association of warfarin dose with genes involved in its action and metabolism. Hum Genet 2007; 121(1):23-34.
89. Wadelius M, Chen LY, Lindh JD et al. The largest prospective warfarin-treated cohort supports genetic forecasting. Blood 2009; 113(4):784-92.
90. Wadelius M, Sorlin K, Wallerman O et al. Warfarin sensitivity related to CYP2C9, CYP3A5, ABCB1 (MDR1) and other factors. Pharmacogenomics J 2004; 4(1):40-8.
91. Wang M, Lang X, Cui S, et al. Clinical application of pharmacogenetic-based warfarin-dosing algorithm in patients of Han nationality after rheumatic valve replacement: a randomized and controlled trial. Int J Med Sci. Aug 2012; 9(6):472-479.
92. Wells PS, Majeed H, Kassem S et al. A regression model to predict warfarin dose from clinical variables and polymorphisms in CYP2C9, CYP4F2, and VKORC1: Derivation in a sample with predominantly a history of venous thromboembolism. Thromb Res 2010; 125(6):e259-64.
93. Wen MS, Lee M, Chen JJ et al. Prospective study of warfarin dosage requirements based on CYP2C9 and VKORC1 genotypes. Clin Pharmacol Ther 2008; 84(1):83-9.
94. Wu AH, Wang P, Smith A et al. Dosing algorithm for warfarin using CYP2C9 and VKORC1 genotyping from a multi-ethnic population: comparison with other equations. Pharmacogenomics 2008; 9(2):169-78.
95. Xu Q, Xu B, Zhang Y et al. Estimation of the warfarin dose with a pharmacogenetic refinement algorithm in Chinese patients mainly under low-intensity warfarin anticoagulation. Thromb Haemost 2012; 108(6):1132-40.
96. You JH, Wong RS, Waye MM et al. Warfarin dosing algorithm using clinical, demographic and pharmacogenetic data from Chinese patients. J Thromb Thrombolysis 2011; 31(1):113-8.
97. Yuan HY, Chen JJ, Lee MT et al. A novel functional VKORC1 promoter polymorphism is associated with inter-individual and inter-ethnic differences in warfarin sensitivity. Hum Mol Genet 2005; 14(13):1745-51.

98. Zambon CF, Pengo V, Padrini R et al. VKORC1, CYP2C9 and CYP4F2 genetic-based algorithm for warfarin dosing: an Italian retrospective study. Pharmacogenomics 2011; 12(1):15-25.
99. Zhu Y, Shennan M, Reynolds KK et al. Estimation of warfarin maintenance dose based on VKORC1 (-1639 G>A) and CYP2C9 genotypes. Clin Chem 2007; 53(7):1199-205.

Policy History:

Medical Policy Group, April 2010 **(1)**
Medical Policy Administration Committee, May 2010
Available for comment May 7-June 21, 2010
Medical Policy Group, April 2011 **(1):** Consolidated all coverage criteria related to cytochrome p450 to this policy and Updated Policy, Key Points, Key Words and References
Medical Policy Administration Committee, May 2011
Available for comment May 11 – June 27, 2011
Medical Policy Group, December 2011 **(1):** Update to Codes with 2012 information
Medical Policy Group, February 2012 **(1):** Update to Codes with addition of G9143
Medical Policy Group, March 2012 **(1):** Update to Key Points and References related to MPP update on warfarin dosing
Medical Policy Group, January 2013 **(1):** Codes 88384-88386, 83890-83914 and modifier -9B moved to previous codes due to deletion 01/01/13
Medical Policy Panel, December 2012
Medical Policy Group, January 2013 **(1):** 2013 Update to Key Points and References related to warfarin dosing; no change in policy statement
Medical Policy Group, May 2013 **(1):** Separated genetic testing for warfarin dosing from policy 425 to create this policy
Medical Policy Panel, December 2013
Medical Policy Group, January 2014 **(1):** 2014 Update to Key Points and References; no change in policy statement
Medical Policy Panel, December 2014
Medical Policy Group, January 2015 (**1**): 2015 Update to Key Points and References; no change in policy statement.
Medical Policy Group, November 2015: 2016 Annual Coding Update. Revised CPT code 81355.
Medical Policy Panel, December 2015
Medical Policy Group, January 2016 **(3):** 2016 Updates to Key Points and References. No change to policy statement.
Medical Policy Panel, June 2017
Medical Policy Group, June 2017 **(3)**: 2017 Updates to Description & Key Points; no new References to add; no changes to Policy Statement; removed Previous coding for codes deleted on or before 01/01/13
Medical Policy Group, December 2017: Annual Coding Update 2018. Added new CPT code 0030U to the Current Coding section.
Medical Policy Panel, June 2018
Medical Policy Group, July 2018 **(4):** Updates to Title, Description, Policy, Key Points, Key Words, and References. Update to policy title. Added another variant to IV policy statement of P450 4F2 (CYP4F2). Added key words P450 4F2 and CYP4F2.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.