



Louisiana

Genotype-Guided Warfarin Dosing

Policy # 00245

Original Effective Date: 12/16/2009

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Services Are Considered Investigational

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

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

Background/Overview

Warfarin is administered to prevent and treat thromboembolic events in high-risk patients; warfarin dosing is a challenging process, due to the narrow therapeutic window, variable response to dosing, and serious bleeding events in 5% or more of patients (depending on definition). Patients are typically given a starting dose of 2 to 5 mg and frequently monitored with dose adjustments until a stable INR value (a standardized indicator of clotting time) between 2 and 3 is achieved. During this adjustment period, a patient is at high risk of bleeding.

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

Warfarin, which is primarily metabolized in the liver by the *CYP2C9* enzyme, exerts an anticoagulant effect by inhibiting the protein vitamin K epoxide reductase complex, subunit 1 (*VKORC1*). Three single nucleotide variants, 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 a likely maintenance dose may benefit patients by decreasing the risk of serious bleeding events and the time to stable INR. Algorithms have incorporated not only genetic variation but also other significant patient characteristics and clinical factors to predict the best starting dose. Studies have

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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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Several tests to help assess warfarin sensitivity, by determining the presence or absence of the relevant *CYP2C9*, *VKORC1*, and *CYP4F2* variants, have been cleared by the U.S. FDA for marketing (see Table 1). Similar tests also may be available as laboratory-developed services; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The tests are not identical regarding the specific variants and number of variants detected. Generally, such tests are not intended as stand-alone tools to determine optimum drug dosage but should be used with clinical evaluation and other tools, including the INR, to predict the initial dose that best approximates the maintenance dose for patients.

Table 1. FDA-Cleared Warfarin Tests

Test (Laboratories)	Alleles Tested	Estimated Time to Completion, h
eSensor [®] Warfarin Sensitivity Test (GenMark Dx) ^a	<i>CYP2C9</i> *2 and *3, <i>VKORC1</i> 1639G>A	3-4
Rapid Genotyping Assay (ParagonDx)	<i>CYP2C9</i> *2 and *3, <i>VKORC1</i> 1173 C>T	Not reported ^b
Verigene [®] Warfarin Metabolism Nucleic Acid Test (Nanosphere)	<i>CYP2C9</i> *2 and *3, <i>VKORC1</i> 1173C>T	≤2
Infiniti [®] 2C9-VKORC1 Multiplex Assay for Warfarin (AutoGenomics) ^c	<i>CYP2C9</i> *2 and *3, <i>VKORC1</i> 1639G>A	6-8
eQ-PCR [™] LightCycler [®] Warfarin Genotyping Kit (TrimGen)	<i>CYP2C9</i> *2 and *3, <i>VKORC1</i> 1639G>A	≤2

Adapted from Cavallari et al (2011).

FDA: Food and Drug Administration.

^a eSensor Warfarin Plus Test offers testing for *CYP2C9**2, *3, *5, *6, *11, *14, *15, and *16, *VKORC1* 1639G>A, and *CYP4F2*.

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^b Langley et al (2009) reported a turnaround time of 1.5 hours for the ParagonDx SmartCycler, which may be a precursor assay.

^c The expanded Infiniti *CYP450* 2C9 assay offers testing for *CYP2C9**2, *3, *4, *5, *6, and *11, *VKORC1* 1639G>A, and 6 other *VKORC* variants.

In 2007, FDA approved updated labeling for Coumadin^{®†} to include information on testing for gene variants that may help “personalize” the starting dose for each patient and reduce the number of serious bleeding events. The label was updated again in 2010. With each update, manufacturers of warfarin (Coumadin) were directed to add similar information to their product labels. The 2010 update added information on guiding initial dose by genotyping results for *CYP2C9* and *VKORC1*, providing a table of genotypes, and suggested initial dose ranges for each. However, suggested starting doses are also provided when genotyping information is unavailable, indicating that genetic testing is not required. Furthermore, FDA did not include information on genetic variation in the label’s black box warning on.

Centers for Medicare and Medicaid Services (CMS)

In 2009, the Centers for Medicare & Medicaid Services published a national coverage determination on pharmacogenomic testing for warfarin response. The Centers for Medicare & Medicaid Services stated that “the available evidence does not demonstrate that pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness improves health outcomes in Medicare beneficiaries outside the context of CED, and is therefore not reasonable and necessary....”

However, the Centers also “believes that the available evidence supports that coverage with evidence development (CED) ... is appropriate for pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness by any method, and is therefore covered only when provided to Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin who:

1. Have not been previously tested for *CYP2C9* or *VKORC1* alleles; and
2. Have received fewer than 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.”

Rationale/Source

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 really want to make 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.

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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 undercoagulation 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 tests 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.

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Outcomes

Specific outcomes of interest are listed in Table 2.

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

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

INR: international normalized ratio.

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 3. The systematic reviews include a total of 12 trials published before 2015, and most trials overlap in the reviews.

Table 3. 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)	•	•	• ¹		•

RCT: randomized controlled trial.

^a Verhoef et al (2013) was included but not categorized as a warfarin study; warfarin analogues were used.

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Characteristics of the systematic reviews are shown in Table 4. The reviews all included similar eligibility criteria leading to a similar set of overlapping studies. Results are shown in Table 5. In general, reviewers found that the percentage of time the 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 4. 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 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
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%

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Study	TEEs, %	Major Bleeding, %	INR >4, %	% Time INR in Therapeutic Range	Deaths
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					
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.

^aHeterogeneity value.

^bIncluded 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.

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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 6. 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 6. Characteristics of RCTs of Genotype vs Clinical Dosing of Warfarin

Study; Trial	Countries	Site s	Dates	Participants	Interventions	
					Active	Comparator
Hillman et al (2005)	U.S.	1	NR	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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

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Study; Trial	Countries	Sites	Dates	Participants	Interventions
					previously published warfarin nomogram
Wang et al (2012)	China	1	2010	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Adults initiating warfarin therapy with expected duration ≥1 mo 27% black race 	Algorithm including clinical variables and genotype data Algorithm including clinical variables only
Pirmohamed et al (2013); EU-PACT Warfarin; NCT01119300	U.K., Sweden	2	2011-2013	<ul style="list-style-type: none"> Age >18 y; warfarin-naïve; 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	<ul style="list-style-type: none"> Warfarin-naïve 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Patients aged ≥65 y initiating warfarin for elective hip or knee arthroplasty 	WarfarinDosing.org algorithm including genotype data WarfarinDosing.org algorithm excluding genotype data

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Study; Trial	Countries	Sites	Dates	Participants	Interventions	
Makar-Aušperger et al (2017)	Croatia	1	2012-2016	<ul style="list-style-type: none"> • INR <1.35 • 91% white race • Adults (≥18 y) with AF, deep vein thrombosis, or pulmonary embolism 	Warfarin Dosing. 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 7. 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 7. 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	

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Genotype-Guided Warfarin Dosing

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Study	Major Bleeding	TEEs	INR >4	% Time INR in Therapeutic Range	Deaths
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

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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%	53%	
TE (95% CI); p			11% to 45%) NR (NR); 0.16	(49% to 57%) 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-Aușperger 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.

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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 8 and 9. No

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major relevance, design or conduct gaps were identified for the Gage (2017) RCT, and it is a low risk of bias.

Table 8. 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 9. 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		1. Registration not mentioned	1. Flow of participants not described, missing data unclear	1. No power calculations	

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Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
	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 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

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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 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. Relevant outcomes are morbid events, medication use, and treatment-related mortality and morbidity. Fourteen RCTs were identified. While 5 of the 14 RCTs reported statistically significant differences in outcomes related to the INR, 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.

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Louisiana

Genotype-Guided Warfarin Dosing

Policy # 00245

Original Effective Date: 12/16/2009

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Policy History

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12/04/2009	Medical Policy Committee approval
12/16/2009	Medical Policy Implementation Committee approval. New Policy
12/01/2010	Medical Policy Committee review
12/15/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/08/2011	Medical Policy Committee review
12/21/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/06/2012	Medical Policy Committee review
12/19/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/23/2013	Coding updated
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. No change to coverage.
04/02/2015	Medical Policy Committee review
04/20/2015	Medical Policy Implementation Committee approval. No change to coverage.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
04/07/2016	Medical Policy Committee review
04/20/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
04/06/2017	Medical Policy Committee review
04/19/2017	Medical Policy Implementation Committee approval. No change to coverage.
08/01/2017	Coding update
02/06/2018	Coding update
04/01/2018	Coding update

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05/03/2018 Medical Policy Committee review
 05/16/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
 08/09/2018 Medical Policy Committee review
 08/15/2018 Medical Policy Implementation Committee approval. Investigational policy statement expanded to include genotyping for *CYP4F2*. Changed “polymorphisms” to “variants” in the investigational policy statement and throughout the policy. Title change to Genotype-Guided Warfarin Dosing.
 Next Scheduled Review Date: 08/2019

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

Code Type	Code
CPT	81227, 81355 Code deleted 1/1/18: 0015U Code added eff 1/1/18: 0030U
HCPCS	G9143
ICD-10 Diagnosis	All related diagnoses

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

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

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

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