Genetic Testing for Warfarin Dose

Policy # 00245
Original Effective Date: 12/16/2009
Current Effective Date: 04/19/2017

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

Background/Overview
Variants in CYP2C9 and VKORC1 genes result in differences in warfarin metabolization. Using information about an individual's CYP2C9 and VKORC1 genotypes, as well as other known characteristics, to personalize starting dose may reduce the time to warfarin dose stabilization and avoid serious bleeding events.

Warfarin is administered for preventing and treating thromboembolic events in high-risk patients; warfarin dosing is a challenging process, due to the narrow therapeutic window, variable response to dosing, and serious bleeding events in 5% or more of patients (depending on definition). Patients are typically given a starting dose of 2 to 5 mg and monitored frequently with dose adjustments until a stable 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. In addition, genetic variants of cytochrome p450 2C9 (CYP2C9) and vitamin K epoxide reductase subunit C1 (VKORC1) genes together account for a substantial proportion of inter-individual variability. More recently, a single nucleotide polymorphism (SNP; change in a single base-pair in a DNA sequence) in the CYP4F2 gene has been reported to account for a small proportion of the variability in stable dose; CYP4F2 encodes a protein involved in vitamin K oxidation.

Using the results of CYP2C9 and VKORC1 genetic testing to predict a warfarin starting dose that approximates a patient’s likely maintenance dose may benefit patients by decreasing the risk of serious bleeding events and the time to stable INR. Algorithms have been developed that incorporate not only genetic variation but also other significant patient characteristics and clinical factors to predict the best starting dose.
FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Several tests to help assess warfarin sensitivity by determining presence or absence of the relevant CYP2C9, VKORC1, and CYP4F2 variants have been cleared by FDA for marketing (see Rationale section). 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.

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

Centers for Medicare and Medicaid Services (CMS)

On August 3, 2009, the CMS published a National Coverage Analysis regarding pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin response. CMS states that “the available evidence does not demonstrate that [such testing] improves health outcomes” in Medicare beneficiaries and that “pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act. However, we do believe the available evidence supports that Coverage with Evidence Development under §1862(a)(1)(E) of the Social Security Act is appropriate.”

CMS now covers pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin response only when provided to Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin and 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

Validation of genotyping to improve pharmacologic treatment outcomes is a multistep process. In general, important steps in the validation process address the following:

- Analytic validity: Measures technical performance, ie, whether the test accurately and reproducibly detects the gene markers of interest.
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- **Clinical validity:** Measures the strength of the associations between the selected genetic markers and dose, therapeutic efficacy, and/or adverse events.
- **Clinical utility:** Determines whether the use of genotyping for specific genetic markers to guide prescribing and/or dosing improves patient outcomes such as therapeutic effect, time to effective dose, and/or adverse event rate compared with standard treatment without genotyping.

Warfarin is metabolized by the cytochrome p450 enzyme *CYP2C9*; genetic variants of *CYP2C9* result in enzymes with decreased activity, increased serum warfarin concentration at standard doses, and a higher risk of serious bleeding. Information on cytochrome p450 pharmacogenetics was summarized in a 2004 TEC Assessment; application to warfarin dosing and important nongenetic influences are discussed in several publications. *VKORC1* genetic variants alter the degree of warfarin effect on its molecular target and are associated with differences in maintenance doses. *CYP2C9* and *VKORC1* genetic variation accounts for approximately 55% of the variability in warfarin maintenance dose. In 2009, a genome-wide association study identified a single SNP, found in the gene *CYP4F2*, that also is associated with warfarin dose; this association was confirmed in a separate, candidate gene study. Subsequent studies predicted that the *CYP4F2* polymorphism explains 2% to 7% of the variability in warfarin dose in models including other genetic and nongenetic factors. Other factors influencing dose include body mass index, age, interacting drugs, and indication for therapy.

**Analytic Validity**

Genetic testing for *CYP2C9* and *VKORC1* is available at a number of laboratories that have developed in-house tests; these do not require U.S. FDA clearance, and information on analytic validity may not be generally available. Some laboratory-developed assays use commercially available reagents that are individually cleared by FDA as analyte-specific reagents. Test kits cleared for marketing by FDA include eSensor Warfarin Sensitivity Test (GenMark); Rapid Genotyping Assay (ParagonDx); Verigene Warfarin Metabolism Nucleic Acid Test (Nanosphere); Infiniti 2C9-VKORC1 Multiplex Assay for Warfarin (AutoGenomics); and eQ-PCR LightCycler Warfarin Genotyping Kit (TrimGen) (Table 1). Kit inserts for FDA-cleared test kits summarize the extensive analytic validity data required for FDA clearance. Two studies compared kits with FDA clearance and laboratory-developed assays using commercially available reagents and assay platforms; in each, the authors concluded that the assays provided accurate and rapid genotype information for the most common polymorphisms evaluated. However, a 2009 review noted that due to a lack of standardization, tests may detect as few as 2 *CYP2C9* variants or as many as 6. A 2013 review indicated that 7 *CYP2C9* alleles are important for warfarin response (*CYP2C9*2, *3, *5, *6, *8, *11, and *13), and the frequencies of these vary across ethnic groups. For *VKORC1*, several known polymorphisms are in strong linkage disequilibrium with one another; thus haplotypes (a combination of polymorphisms at nearby locations) formed from various combinations can be used to assess status. Whether specific haplotypes can improve predictive value is unknown.

Turnaround times for these assays range from approximately 1.5 to 8 hours, not including sample transportation, processing, and delays due to assay scheduling. It is unknown how soon test results might be needed during the warfarin initiation phase should outcome studies indicate net benefit of testing.

<table>
<thead>
<tr>
<th>Table 1. FDA-Approved Warfarin Tests</th>
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<tbody>
<tr>
<td><strong>Name of Test</strong></td>
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Completion, h

<table>
<thead>
<tr>
<th>Test Description</th>
<th>CYPC9*2 and *3, VKORC1-1639G/A</th>
<th>Completion, h</th>
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<tbody>
<tr>
<td>eSensor Warfarin Sensitivity Test (GenMark Dx, Carlsbad, CA)</td>
<td></td>
<td>3-4</td>
</tr>
<tr>
<td>Rapid Genotyping Assay (ParagonDx, Morrisville, NC)</td>
<td>CYP39*2 and *3, VKORC1-1173 C/T</td>
<td>Not reported</td>
</tr>
<tr>
<td>Verigene Warfarin Metabolism Nucleic Acid Test (Nanosphere Inc., Northbrook, IL)</td>
<td>CYP39*2 and *3, VKORC1-1173 C/T</td>
<td>≤2</td>
</tr>
<tr>
<td>Infiniti 2C9-VKORC1 Multiplex Assay for Warfarin (AutoGenomics Inc., Vista, CA)</td>
<td>CYP2C9*2 and *3, VKORC1-1173 C/T</td>
<td>6-8</td>
</tr>
<tr>
<td>eQ-PRC LightCycler Warfarin Genotyping Kit (Trimgen Corp., Sparks Glencoe, MD)</td>
<td>CYP2C9*2 and *3, VKORC1-1173 C/T</td>
<td>≤2</td>
</tr>
</tbody>
</table>

FDA: Food and Drug Administration.

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

Section Summary
Currently, 5 genotype assays for reduced function CYPC9 and VKORC1 variants are FDA-approved. Evidence for the analytic validity of these tests is provided in the product labels. Although information on analytic validity of laboratory-developed tests is generally unavailable, 2 studies reported comparable analytic validity of FDA-approved and laboratory-developed tests.

Clinical Validity
A 2008 systematic review, commissioned by the American College of Medical Genetics (ACMG), evaluated CYP2C9 and VKORC1 genetic testing before warfarin dosing and concluded the following:
- “Clinical validity: CYP2C9 and VKORC1 genotypes contribute significant and independent information to the stable warfarin dose and, compared to the most common combination, some individuals with other genotype combinations will need more than the usual dose, while others will require less.”

Authors of several studies of clinical validity, mainly in Caucasian patients already at maintenance doses evaluated retrospectively, have developed algorithms that incorporate VKORC1 and CYP2C9 genetic variant information, as well as patient characteristics and other clinical information, and have evaluated the extent to which these algorithms predict various outcomes such as maintenance dose, time to stable INR, time spent in target INR range, and serious bleeding events. These algorithms vary in the nongenetic variables included, and in general, account for up to approximately 60% of warfarin maintenance dose variance. CYP4F2 genotyping also was added to a retrospective evaluation of several algorithms that already included CYP2C9 and VKORC1; CYP4F2 polymorphisms, however, added only 4% to the fraction of the variability in stable dose explained by the best performing algorithms. A 2012 systematic review and meta-analysis by Liang et al suggested a more substantial contribution of CYP4F2 genetic variants. Compared with wild-type patients, carriers of CYP4F2 variants required warfarin doses 11% and 21% higher for heterozygous and homozygous patients, respectively.
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Cohort studies that evaluated algorithm-guided dosing in patients starting warfarin reported that algorithms explained 69% to 79% of the variance in maintenance dose. In 2009, the International Warfarin Pharmacogenetics Consortium (IWPC) compared an algorithm based only on clinical variables with one that also included genetic factors in a validation cohort of 1009 patients treated with warfarin. The pharmacogenetic algorithm was significantly more accurate at predicting an initial dose that was close to the maintenance dose in the 46% of patients who required low (≤21 mg/wk) or high (≥49 mg/wk) warfarin doses. The analysis did not address whether a more precise initial dose of warfarin resulted in improved clinical end points. Avery et al (2011) found that 42% of the variability in maintenance dose on days 4 to 7 was explained by the algorithm and that 40% of maintenance dose variability was explained on days 8 to 15.

Other cohort studies also have evaluated the initiation phase of warfarin treatment, reporting the impact of genetic factors on time to therapeutic INR, time to first supratherapeutic (overcoagulation) INR, time above therapeutic range, etc. In 2009, Limdi et al estimated that CYP2C9 and VKORC1 explained 6.3% of the variance in dose change over the first 30 days of therapy. Pautas et al (2010) reported that in elderly patients with multiple comorbidities and polypharmacy who were starting warfarin, individuals with multiple variant alleles were at highest risk for overanticoagulation, with an odds ratio of 12.8 (95% confidence interval [CI], 2.8 to 60.0). Ferder et al (2010) reported that the predictive ability of CYP2C9 and VKORC1 genetic variants in patients from the PREVENT (Prevention of Recurrent Venous Thromboembolism) trial gradually diminished over time, from 43% at day 0 (warfarin initiation) to 12% at day 7, 4% at day 14, and 1% at day 21. Moreau et al (2011) studied 187 elderly patients starting warfarin using a “geriatric dosing-algorithm.” Adding CYP2C9 and VKORC1 genotype variants to the initial dosing model increased the explained variance in maintenance dose from less than 10% to 31%. By day 3, VKORC1 was no longer a significant predictor of maintenance dose; however, CYP2C9 genotype remained a significant predictor. By day 6, neither CYP2C9 nor VKORC1 genotype variants were predictive of maintenance dose. These studies indicate that if genotyping results are clinically useful, it is likely only within the first week or less of beginning warfarin therapy.

Gong et al (2011) conducted a prospective cohort study of patients requiring warfarin therapy for atrial fibrillation or venous thromboembolism using a novel pharmacogenetic warfarin initiation protocol. Practical daily loading doses were prescribed for 2 days and were dependent on VKORC1 and CYP2C9 genotypes and, as necessary, on weight. Maintenance dose was determined in a regression model by combining key patient clinical parameters known to influence warfarin dose requirement with genotype. When VKORC1 and CYP2C9 genotypes were incorporated into warfarin initial dose determinations, they had no additional significant effect on time required to reach the first INR within therapeutic range, on risk of overcoagulation (INR ≥4), or on time to stable anticoagulation.

A 2012 study by Horne et al assessed whether pharmacogenetic algorithms can contribute to dose refinements after INR response to warfarin is known. Based on a population (N=1684) drawn from 3 continents and 16 study sites, an algorithm for determining warfarin dose was derived and included a novel treatment response index, comprising previous warfarin dose and INR measurements. The pharmacogenetic warfarin dose-refinement algorithm explained more variability in dosing (R²=71.8%) compared with the clinical algorithm (R²=64.8%). In addition to these patients, a prospective external
A validation cohort (n=43) was recruited to determine the safety and accuracy of the clinical algorithm. The pooled pharmacogenetic algorithm explained 58% to 79% of the variation in therapeutic dose, and the time in therapeutic range during days 11 to 30 was 62%. The new pooled clinical algorithm was significantly more accurate than previously validated algorithms.

A 2012 prospective study by Perlstein et al assessed the validity of 3 warfarin-dosing algorithms to predict time in therapeutic range and time to first therapeutic INR in a predominantly Caucasian population (N=344). Dosing algorithms were developed sequentially to select both an initial warfarin dose and a titration scheme intended to maximize the likelihood of achieving and maintaining the target INR. Algorithm A determined initial dosing with a decision tree including both clinical and genetic factors based on best practices in the hospital’s anticoagulation management service and the published literature. Algorithm B was generated from an analysis of warfarin dose, INR, genetic factors, demographic factors, and concomitant drug therapy from a group of 74 patients treated with algorithm A. Algorithm C was an update to algorithm B, with a revision of the half maximal inhibitory concentration for VKORC1 haplotypes. The authors found a significant (p=0.04) progressive improvement in mean percentage time in therapeutic range over the entire study period for algorithm A (58.9%), algorithm B (59.7%), and algorithm C (65.8%). The secondary end point of per-patient percentage of INRs outside of the therapeutic range had a similar statistically significant trend across algorithms (p=0.004) with algorithm A reporting 21.6%, algorithm B, 22.8%, and algorithm C, 16.8%. Time to stable therapeutic anticoagulation decreased significantly across algorithms (p<0.001), but time to first therapeutic INR did not vary significantly among the 3 algorithm subgroups. No differences in rates of adverse events were observed during this study.

Several studies have compared the ability of different algorithms to accurately predict stable warfarin dose. In general, there does not appear to be consensus for a single algorithm at this time. Rather, it may be necessary to select the algorithm best suited to the treatment population due to differences. For example, not all algorithms include the use of drugs that interact with warfarin; in fact, some studies have excluded patients taking interacting drugs. Hatch et al (2008) applied an algorithm developed in patients not taking interacting drugs and showed that when applied to a small number of patients taking interacting drugs, the proportion of dose variance explained by the algorithm decreased by approximately 10 percentage points.

Several authors have examined associations between CYP2C9 and VKORC1 variants and warfarin dosing requirements in children. Findings are preliminary. Proposed dosing algorithms require evaluation in large, prospective, randomized trials in comparison with current standard-of-care approaches to determine net health benefit.

Ethnicity

Several studies have included ethnically diverse populations, but it is unclear whether one or several algorithms are needed to address ethnicity. The algorithm developed by Gage et al (2008) explained 55% of the variance in a Caucasian validation cohort but only 40% of the variation in a small African-American cohort. Schelleman et al (2008) developed separate predictive algorithms for Caucasian and African-American populations, which explained 42% of the variance in Caucasians but only 28% in African-Americans. Wu et al (2008) included several different ethnicities in developing their predictive algorithm, which included an ethnicity variable and overall explained 59% of warfarin dose variation. Limdi et al (2010)
reported that the contribution of VKORC1 to dose requirement is higher in whites than in nonwhites but that genotype predicts similar dose requirements across Caucasian, African-American, and Asian populations; genotyping for additional VKORC1 variants (ie, other than 1639 G/A and 1173 C/T, the most commonly tested variants) did not improve dose prediction in any group.

Cavallari et al (2011) tested the performance of published warfarin dosing algorithms derived from non-Hispanic cohorts in the Hispanic population. The combination of the VKORC1 and CYP2C9 genotypes and clinical factors explained 56% of patient variability in warfarin dose. The predicted dose was within 1.0 mg/day of the therapeutic dose for 40% to 50% of patients. Gan et al (2011) studied Asian populations and found that patients from India, compared with Chinese and Malay patients, required a dose of 4.9 mg/d versus 3.5 mg/d and 3.3 mg/d, respectively. The higher warfarin doses correlated with particular VKORC1 genotypes found more commonly in the Indian population.

Perera et al (2011) identified novel genetic markers in VKORC1 and CYP2C9 associated with higher warfarin dosing in African-Americans. A regression model, encompassing both genetic and clinical variables, explained 40% of the variability in warfarin maintenance dose. In 2013, Perera et al reported another novel marker in the CYP2C cluster (on chromosome 10) that was associated with reduced warfarin dosing in African-Americans. The proportion of variability in warfarin maintenance dosing explained by adding this novel marker to the IWPC algorithm increased from 21% to 26%. Ramirez et al (2012) developed a predictive algorithm for calculating dose variation in African-Americans including variants in CYP2C9*6 and CALU (which encodes calumenin, a cofactor in the vitamin K epoxide reductase complex). The authors validated an expanded pharmacogenomic dosing algorithm and compared it with the IWPC algorithm with the algorithms explaining 41% and 29% of variation, respectively. Other studies have identified new genetic variants and/or evaluated clinical-genetic algorithms for warfarin dose in Thai, Egyptian, Chinese, Japanese, Arabic, Turkish, and Scandinavian populations. In general, genetic factors helped models explain 30% to 54% of the overall variance but were not always statistically significant.

Valentin et al (2012) examined a retrospective cohort of Puerto Rican patients (N=97) to determine the influence of CYP2C9 and VKORC1 polymorphisms on warfarin dose in this population. Blood samples were collected during routine INR testing and underwent HILOmet PhyzioType assay to detect 5 single nucleotide polymorphisms (SNPs) in CYP2C9 and 7 SNPs in VKORC1. Median actual effective warfarin doses were compared across CYP2C9 and VKORC1 carrier status (wild type/noncarriers, single, double, triple and quadruple carriers). Significant differences (p<0.001) in warfarin dose were observed between wild type (5.71 mg/d), single carrier (4.64 mg/d), double carrier (3.43 mg/d), triple carriers (2.36 mg/d) and quadruple carriers (1.86 mg/d). No significant difference in time to target INR was identified between groups (p=0.34). Predicted daily warfarin dose was assessed by comparing IWPC pharmacogenomic-guided algorithm, clinical algorithm, and fixed-dose approach. In the low-dose subgroup, the pharmacogenetic algorithm provided dose estimates that were more accurate, and closer to the actual doses required, than the estimates derived from fixed-dose or clinical algorithm (p<0.001 for both comparisons). No differences were detected among the intermediate-dose patients between algorithms, and in the high-dose subgroup, a marginal difference between pharmacogenetic algorithm and clinical algorithm was found (p=0.042). This study is the first to describe the association between SNPs in CYP2C9 and VKORC1 genes and effective warfarin dose in Puerto Rican patients.
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Section Summary
In primarily Caucasian populations, several retrospective and prospective cohort studies have documented that pharmacogenomic algorithms can explain 6% to 79% of the variance in warfarin maintenance dosing. In ethnically diverse populations, such algorithms can explain 40% to 59% of the variance. Accuracy of the algorithms appears to depend on the alleles tested; number of reduced function alleles present; use of interacting drugs; ethnicity; time of warfarin dosing after initiation; and maintenance dose eventually required (high or low). Evidence for the ability of pharmacogenomic algorithms to predict maintenance warfarin dose and to increase time in the therapeutic INR range comes from retrospective and cohort studies and is inconsistent. A single dosing algorithm readily generalizable to a diverse population and prospectively tested in a large, representative validation cohort has not been developed.

Clinical Utility
Systematic Reviews
In 2014, 4 systematic reviews with meta-analyses compared genotype-guided warfarin dosing with other dose selection strategies. Meta-analyses used random effects models or fixed effects models when statistical heterogeneity (I²) was 0%. Two systematic reviews included the same 9 randomized controlled trials (RCTs) comparing genotype-guided versus clinically guided warfarin dosing (total N=2812); several RCTs reviewed below were included, all of which were rated high quality. Range of follow-up duration was 4 to 24 weeks (median, 12 weeks). Publication bias was not detected. With 1 exception, pooled results from both systematic reviews were consistent: There was no statistical difference between dosing strategies in the percentage of time that the INR was in therapeutic range (I²=89%), the proportion of INRs that exceeded 4 (I²=0%), or thromboembolic events (I²=0%). However, Stergiopoulos et al found no difference in major bleeding events (pooled relative risk [RR], 0.60; 95% CI, 0.29 to 1.22; I²=0%), and Franchini et al found reduced major bleeding events with genotype-guided warfarin dosing (pooled RR=0.48; 95% CI, 0.23 to 0.97; I²=0%). This inconsistency may be attributed to the exclusion of the EU-PACT trial (reviewed below; N=455) from the Franchini et al systematic review. EU-PACT reported no major bleeding events in either warfarin dosing group.

A 2014 systematic review by Goulding et al reported improved clinical outcomes with genotype-guided versus other (ie, fixed or clinically guided) warfarin dosing. Literature was reviewed through December 2013; 9 RCTs were included, 7 of which overlapped with the systematic reviews previously described, and 6 of which were rated high or very high quality. Range of follow-up duration was 2 to 12 weeks. Pooled mean difference in the percentage of time within the therapeutic range was 6.67 percentage points (95% CI, 1.34 to 12.00; I²=80%). However, this meta-analysis included 1 trial that showed benefit of genotype-guided dosing compared with fixed initial warfarin dosing (2.5 mg/d), and excluded 2 trials (described below) that showed no benefit of genotype-guided dosing compared with clinically guided dosing. Meta-analysis also showed decreased risk of bleeding or thromboembolic events with genotype-guided dosing (pooled risk ratio, 0.57; 95% CI, 0.33 to 0.99; I²=60%).

A 2014 systematic review by Liao et al reported increased time in the therapeutic range with genotype-guided dosing compared with fixed initial warfarin dosing (3 RCTs; I²=48%) but not compared with clinically guided dosing (2 RCTs; I²=0%). These authors also found no overall difference between pooled groups in adverse events (major bleeding [defined as a decrease in hemoglobin ≥2 g/dL], clinically relevant non-major
bleeding, thromboembolism, myocardial infarction, death from any cause, or other condition requiring emergency medical management; 4 RCTs; \( f = 0\% \) or mortality (3 RCTs; \( f = 10\% \)).

The ACMG’s 2008 systematic review of \textit{CYP2C9} and \textit{VKORC1} genetic testing before warfarin dosing (cited earlier) concluded the following:

- “Clinical utility: The purpose of genetic testing in this clinical scenario is to predict an individual’s likely stable warfarin dose by incorporating demographic, clinical, and genotype data (\textit{CYP2C9} and \textit{VKORC1}), and initiate warfarin at that predicted dose as a way to limit high INR values (overanticoagulation) that are associated with an increased risk of serious bleeding events. No large study had at the time shown this to be acceptable or effective. Based on limited clinical data, the number needed to treat to avoid 1 serious bleeding event was estimated to range from 48 to 385.”

Randomized Controlled Trials

Few large, well-designed RCTs to address clinical utility have been published. Such studies would evaluate the net benefit of using genetic factors, or algorithms that include genetic factors, to guide initial dosing compared with empirical initial dosing or dosing guided by clinical factors, such as age and body surface area. Additionally, such trials should address the degree to which INR must continue to be monitored to ensure that physicians do not overly rely on dosing algorithms and monitor patients less frequently, potentially increasing adverse events.

Mega et al published a supplemental analysis to the ENGAGE AF-TIMI 48 trial that examined the clinical response to warfarin among patients with genetic variants. This study included 14,348 patients, 4833 of whom were taking warfarin and 9515 of whom were taking 1 of 2 doses of edoxaban. All patients taking warfarin were classified by genetic status as normal (62%), sensitive (35%), or highly sensitive (2.9%). Patients who were sensitive or highly sensitive responders had higher risks of bleeding than normal responders. For sensitive responders, the hazard ratio was 1.31 (95% CI, 1.05 to 1.61) compared with normal responders, and for highly sensitive responders, the hazard ratio was 2.66 (95% CI, 1.7 to 4.2).

In 2007, Anderson et al reported an RCT comparing algorithm (including genetic variables)-guided initial warfarin dosing (\( n = 101 \)) to empirical dosing (\( n = 99 \)). The primary outcome measure was “per-patient percentage of out-of-range INRs.” Algorithm-predicted doses more accurately approximated maintenance doses, resulting in significantly fewer dose changes, but the primary end point was not achieved (\( p = 0.47 \)); the secondary outcome of serious adverse events also did not differ between study groups (\( p = 0.71 \)). Study patients were carefully managed by a dedicated anticoagulation service, and patients treated with empirical dosing had better than expected outcomes. The authors speculated that empirical therapy “might be less successful in less closely managed and outpatient-based initiation programs” and that a larger trial would be needed to demonstrate utility. McMillin et al (2010) conducted a nonrandomized study (\( N = 229 \)) in which a gene-based dosing algorithm was compared with standard dosing in patients receiving warfarin after joint replacement surgery. The primary end point was reduction in the incidence of adverse events, and secondary end points were related to INR; no end point reached statistical significance. Patients in this study also were managed by a dedicated and experienced anticoagulation service team. Results of these studies suggest that larger, community-based studies are needed to determine clinical utility.
Jonas et al (2013) conducted a double-blind RCT in 109 adults who were initiating long-term warfarin therapy. Patients were randomized to warfarin dosing by an algorithm that contained both genetic (specifically, CYP2D6*2 and *3 and VKORC1-1639G>A [also known as VKORC1-3673G>A]) and clinical factors or clinical factors only. Most patients (70%) were Caucasian, and 30% were African-American. Primary efficacy outcomes were the mean number of anticoagulation visits (to clinic or physician) in 90 days and time in the therapeutic range (TTR). The trial was powered to detect a difference of 2 visits and a 10% difference in TTR. There were no statistically significant differences between intervention groups for any primary or secondary outcome. (Secondary outcomes included emergency visits, hospitalizations, minor [not requiring hospitalization or transfusion] and major hemorrhagic events, thrombotic events and deaths, but the trial was not powered to detect differences in these outcomes.) The authors concluded, “Overall, the current evidence from our trial and from previously published trials does not establish clinical utility of genotype-guided warfarin dosing.”

Two larger RCTs of pharmacogenetic dosing algorithms also were published in 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; and 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. The COAG trial compared 2 dosing algorithms in 1015 patients who were initiating a minimum 1-month course of warfarin therapy (58% for deep vein thrombosis or pulmonary embolism, 22% for atrial fibrillation, 11% for other indications). Median patient age was 58 years (interquartile range [IQR], 46-70). Patients were stratified by self-reported race (black [27%] or nonblack [73%]), randomized in double-blind fashion to an algorithm of both clinical and genetic factors or clinical factors only, and followed for 4 weeks. Ninety-four percent of patients (n=955) completed the 5-day intervention period and were included in efficacy analyses. The between-group difference in the primary outcome was not statistically significant (45.2% vs 45.4% of INRs were in the therapeutic range in the genotype-guided and clinically guided groups, respectively; p=0.91). Among 255 black patients, a statistically significant difference favored the clinically guided group (35.2% vs 43.5% of INRs were in the therapeutic range in the genotype-guided and clinically guided groups, respectively; p=0.01). 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) occurred in 20% and 21% of the genotype- and clinically guided groups, respectively (p=0.93). Incidences of each component of the composite outcome also were similar between groups, although the trial was not powered for these outcomes.

The EU-PACT trial compared algorithm-based dosing, using clinical and genetic information, with standard fixed-dose warfarin initiation (with a 10-mg loading dose on day 1) in 455 patients with atrial fibrillation (72%) or venous thromboembolism (28%). Almost all patients (99%) were white. Mean patient age was 67.5 years (range, 24-90). Patients were randomized to one of the 2 treatment groups and followed for 12 weeks. Ninety-four percent of patients had 13 or more days of INR data and were included in efficacy analyses. The between-group difference in the primary outcome favored genotype-guided dosing (67.4% vs 60.3% of INRs were in the therapeutic range in the genotype-guided and fixed-dose groups, respectively;
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p<0.001). The median time to reach a therapeutic INR (a secondary outcome, calculated as the median time to the first of 2 target INR values, measured at least 1 week apart) was 21 days (IQR, 8-36) in the genotype-guided group and 29 days (IQR, 14-58) in the fixed-dose group (p<0.001); the percentage of TTR was no longer statistically different between groups after week 8. Excessive anticoagulation (INR ≥4.0) occurred in fewer patients in the genotype-guided group (27%) than in the control group (37%; p=0.03). Bleeding events occurred in approximately 38% of patients in each group, and most consisted of bruising and nosebleeds. One thromboembolic event occurred in the control group.

In association with the Agency for Healthcare Research and Quality and Third Wave Technologies, Burmester et al (2011) conducted a prospective, blinded, randomized trial to compare 2 warfarin dosing algorithms. One algorithm used relevant genetic polymorphisms and clinical parameters (genetic and clinical arm), and the other used only usual clinical parameters (clinical-only arm). A total of 230 primarily hospitalized patients were enrolled. The model including genotype predicted therapeutic warfarin dose better than the clinical-only model (p<0.001); both models predicted dose better than the standard starting dose of 5 mg/d. However, median percent time in therapeutic INR range was the same (28.6% in each group). Median time to stable therapeutic dose also was similar in both arms (approximately 30 days). INR greater than 4.0 occurred in 35% of patients in the clinical-only arm and in 38% of patients in the genetic clinical arm (p=0.94). Thus, clinical outcomes were similar despite improved prediction with genetic information. Patients in this trial may have had frequent INR measurements and dose adjustments in a hospital setting; results may not reflect those likely to be obtained in an outpatient community setting.

A blinded RCT (CoumaGen-II) by Anderson et al (2012) investigated whether 2 pharmacogenetic-guided (PG) testing algorithms were better than standard empiric warfarin dosing. A parallel control group (n=1866) included patients initiating warfarin treatment during the study period, and for these patients, warfarin dose was determined by physician/health care provider. Same day genotyping of CYP2C9 and VKORC1 was provided to 504 patients (257 randomized to a 1-step arm [IWPC algorithm], 247 randomized to a 3-step arm [modified IWPC algorithm]). Most patients (approximately 92%) were white. Primary end points were the percentage of out-of-therapeutic range INRs and time in therapeutic INR range during the first month and through the third month of warfarin therapy. Both PG approaches were equivalent at 1 and 3 months for all outcomes with a stable maintenance dose determined in 444 patients (88%). There was an inverse relation between the number of reduced function alleles and stable maintenance dose (p<0.001). Pharmacogenomic guidance was more accurate in wild-type patients and in those with multiple variants (p<0.001). Both PG arms were pooled and were observed to be superior to the standard dosing approach with significant (p<0.001) reductions in percent of time out of INR range and percent of time in therapeutic range at 1 and 3 months after controlling for relevant variables. Adverse events (hemorrhagic events, thromboembolic events, or other serious adverse events) were greater in the control group (9.4%) compared with the PG group (4.5%), with an adjusted RR of 0.44 (95% CI, 0.28 to 0.70; p<0.001).

Cohort Studies
In association with Medco, a pharmacy benefits management organization, Epstein et al (2010) conducted a cohort study with historical control in patients initiating warfarin therapy who were invited to participate and receive free genotyping. Hospitalization rates (the primary outcome) during the next 6 months were compared with those of a historical control group of similar patients who had initiated warfarin therapy the
previous year. The authors reported that the genotyped cohort had 31% fewer hospitalizations overall compared with controls (adjusted hazard ratio [HR], 0.69; 95% CI, 0.58 to 0.82; p=0.001) and 28% fewer hospitalizations for bleeding or thromboembolism (HR=0.72; 95% CI, 0.53 to 0.97; p=0.029). However, the number of patients who were offered enrollment but declined was omitted from publication, making it impossible to exclude selection bias. A high patient refusal rate could produce a highly selected population, not comparable to unselected historical controls. Additionally, hospitalizations related to bleeding or thromboembolism were reduced by 2.2% in absolute terms, and all-cause hospitalizations had a much larger reduction of 7.1%. The latter is more than triple that expected if only due to reductions in hospitalizations from bleeding or thromboembolism by improved warfarin dosing. In the absence of selection bias, changes in warfarin dosing would not be expected to impact hospitalizations for nonhematologic reasons. The question of selection bias could have been avoided in this study if genotyping results had been sent randomly to only half of the physicians caring for patients tested.

Section Summary: Clinical Utility
Randomized trials and meta-analyses of these trials have examined the use of pharmacogenomic algorithms to guide initial warfarin dosing and yielded inconsistent results. Several trials showed improved ability to predict maintenance dose when genetic information was added to clinical algorithms. However, effects on INR or clinical outcomes were not always statistically significant. The ability of pharmacogenomic algorithms to improve these outcomes and net health benefit compared with current clinical data monitoring approaches has not been demonstrated.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

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<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
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<td>A Randomized Controlled Trial to Assess the Clinical Benefits of a Pharmacogenetics-Guided Dosing Regimen for Calculating Warfarin Maintenance Dose</td>
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<td>NCT01633957</td>
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<td>NCT01006733</td>
<td>Genetics Informatics Trial (GIFT) of Warfarin to Prevent Deep Venous Thrombosis (DVT)</td>
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<td>NCT01318057</td>
<td>Pharmacogenetics of Warfarin in Puerto Rican Patients Using a Physiogenomics Approach</td>
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<td>NCT01305148*a</td>
<td>Warfarin Adverse Event Reduction For Adults Receiving Genetic Testing at Therapy INitiation (WARFARIN)</td>
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NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored trial.

Summary of Evidence

The evidence for genetic testing to determine warfarin dose in patients who have a warfarin treatment regimen includes RCTs, systematic reviews of RCTs, and cohort studies. Relevant outcomes are test accuracy and validity, other test performance measures, morbidity events, medication use, and treatment-related morbidity. Although the evidence supports a strong association between genetic variants and stable warfarin dose, and, to a lesser extent, between genetic variants and international normalized ratio and bleeding outcomes, the evidence is not sufficient to conclude that testing for CYP2C9 and VKORC1 (and possibly CYP4F2) genetic variants improves health outcomes. Genetic testing may help predict the initial warfarin dose within the first week of warfarin treatment, but the evidence, including several meta-analyses of RCTs, does not provide consistent evidence that clinically relevant outcomes (eg, bleeding rates, thromboembolism) are improved. The evidence is insufficient to determine the effects of the technology on health outcomes.

References


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12/04/2009 Medical Policy Committee approval
12/16/2009 Medical Policy Committee approval. New Policy
12/01/2010 Medical Policy Committee review
12/08/2011 Medical Policy Committee review
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
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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
04/06/2016 Medical Policy Committee review
04/19/2017 Medical Policy Implementation Committee approval. No change to coverage.
08/01/2017 Coding update

Next Scheduled Review Date: 04/2018

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*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:

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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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