Medical Policy

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Title: Genetic Testing for Warfarin Dose

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DESCRIPTION

Genetic variants in *CYP2C9* and *VKORC1* genes result in individual differences in the ability to metabolize warfarin. Using information regarding an individual's *CYP2C9* and VKORC1 genotypes, as well as other known characteristics to determine a personalized starting dose may reduce the time to a stable warfarin dose and avoid serious bleeding events.

Background

Warfarin is administered for preventing and treating thromboembolic events in high-risk individuals; 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 2 and 3 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. 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.

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.

Regulatory Status

Several tests to help assess warfarin sensitivity by determining presence or absence of the relevant *CYP2C9, VKORC1,* and *CYP4F2* variants have been cleared by the U.S. Food and Drug Administration (FDA) for marketing (see Rationale). Similar tests may also be available as laboratory-developed tests in laboratories licensed under Clinical Laboratory Improvement Amendments (CLIA) for high-complexity testing. The tests are not all the same in terms of the specific variants and number of variants detected. In general, such tests are not intended to be stand-alone tools to determine optimum drug dosage, but 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.

POLICY

Genotyping to determine cytochrome p450 2C9 (*CYP2C9*) and vitamin K epoxide reductase subunit C1 (*VKORC1*) genetic polymorphisms is considered **experimental / investigational** for the purpose of managing the administration and dosing of warfarin, including use in guiding the initial warfarin dose to decrease time to stable INR and reduce the risk of serious bleeding.

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RATIONALE

Test Validation

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, i.e., whether the test accurately and reproducibly detects the gene markers of interest.
- **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 to standard treatment without genotyping.

Literature Review

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 is summarized in a TEC Assessment (1); application to warfarin dosing and important nongenetic influences are discussed in several publications. (2-5) *VKORC1* genetic variants alter the degree of warfarin effect on its molecular target and are associated with differences in maintenance doses.(6-10) *CYP2C9* and *VKORC1* genetic variation accounts for approximately 55% of the variability in warfarin maintenance dose. (10, 11) A genome-wide association study identified a single SNP, found in the gene *CYP4F2*, that is also associated with warfarin dose (12); this association was confirmed in a separate, candidate gene study. (13) Recent studies predict that the *CYP4F2* polymorphism explains 2–7% of the variability in warfarin dose in models including other genetic and nongenetic factors. (13, 14) Other factors influencing dose include body mass index (BMI), age, interacting drugs, and indication for therapy.

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. Food and Drug Administration (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 the FDA as analyte-specific reagents. Test kits cleared for marketing by the 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 U.S. Food and Drug Administration (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. (15, 16) However, a recent review noted that due to lack of standardization, tests may detect as few as 2 *CYP2C9* variants or as many as 6.(16) 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 not known.(17)

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 not known how soon test results might be needed during the warfarin initiation phase should outcomes studies indicate net benefit of testing.

Table 1. Warfarin Tests Cleared by the U.S. FDA (18)

Name of Test	Alleles Tested	Estimated Time to Completion (hours)
Verigene Warfarin Metabolism Nucleic Acid Test (Nanosphere, Inc., Northbrook, Il)	*CYPC9**2 and *3, *VKORC1* 1173C/T	≤ 2
Infiniti 2C9-*VKORC1* Multiplex Assay for Warfarin (AutoGenomics, Inc., Vista, CA)[A]	*CYP2C9**2 and *3, *VKORC1* -1639G/A	6-8
eSensor Warfarin Sensitivity (GenMark Dx, Carlsbad, CA)[B]	*CYPC9**2 and *3, *VKORC1*-1639G/A	3-4
eQ-PRC LC Warfarin Genotyping Kit (Trimgen Corp., Sparks, MD)	*CYP2C9**2 and *3, *VKORC1*-1639G/A	≤ 2

[A] The expanded Infiniti *CYP450* 2C9 Assay offers testing for *CYP2C9**2, *3, *4, *5, *6 and *11, *VKORC1* – 1639G.A and six additional VKORC variants.
[B] eSensor Warfarin Plus Test offers testing for *CYP2C9**2, *3, *5, *6, *11, *14, *15, and *16, *VKORC1* -1639G>A, and *CYP4F2*

A systematic review, (19) commissioned by the American College of Medical Genetics, evaluated *CYP2C9* and *VKORC1* genetic testing prior to 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.
- **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 (*CYP2C9* and *VKORC1*), and initiate warfarin at that predicted dose as a way to limit high International Normalized Ratio (INR) values (over-anticoagulation) 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 one serious bleeding event was estimated to range from 48 to 385.

Authors of several additional studies of clinical validity, mainly of Caucasian patient cohorts already at maintenance dose and 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 non-genetic variables included, and in general, account for up to approximately 60% of warfarin maintenance dose variance. (20-27) *CYP4F2* genotyping was also 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. (28) A 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. (29) Some cohort studies have evaluated the more relevant initiation phase of warfarin treatment, reporting the significance of genetic factors on time to therapeutic INR, time to first supratherapeutic (over-coagulation) INR, time above therapeutic range, etc. (30-32) Limdi et al. estimated that *CYP2C9* and *VKORC1* explained 6.3% of the variance in dose change over the first 30 days of therapy.(33) Pautas et al. reported that in elderly patients with multiple comorbidities and polypharmacy who were starting warfarin, individuals with multiple variant alleles were at highest risk for over-anticoagulation, at an odds ratio of 12.8. (34) Ferder et al. (35) reported the predictive ability of *CYP2C9* and *VKORC1* genetic variants from PREVENT (Prevention of Recurrent Venous Thromboembolism) Trial subjects to gradually diminish over time from warfarin initiation starting with 43% at day 0, 12% at day 7, 4% at day 14, and 1% at day 21. Moreau et al. (36) 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 the 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.

Cohort studies that evaluated algorithm-guided dosing in patients beginning warfarin treatment report that algorithms explained up to 69–79% of the variance in maintenance dose. (37, 38) The International Warfarin Pharmacogenetics Consortium compared an algorithm based only on clinical variables with one that also included genetic factors in a validation cohort of 1,009 subjects 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/week) or high (>49 mg/week) warfarin doses. (39) The analysis did not address whether a more precise initial dose of warfarin results in improved clinical endpoints. Avery et al. found 41.8% of the variability in maintenance dose days 4-7 was explained by the algorithm and that 40.3% of maintenance dose variability was explained on days 8-15. (40)

Gong et al. (41) 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 it was found necessary, on weight. The maintenance dose was determined by combining key patient clinical parameters known to influence warfarin dose requirement along with genotypes in a regression model. Once *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 study by Horne and colleagues assessed if pharmacogenetic algorithms can contribute to dose refinements after INR response to warfarin is known. (42) A population (n=1,684) drawn from 3 continents and 16 study sites was utilized to derive an algorithm explaining warfarin dose including a novel treatment response index comprised of prior warfarin dose and INR measurements. The pharmacogenetic warfarin dose-refinement algorithm explained more variability in dosing (R^2=71.8%) compared to the clinical algorithm (R^2=64.8%). In addition to these patients, a prospective external 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 11-30 was 62%. The new pooled clinical algorithm was significantly more accurate than previously validated algorithms.

A prospective, single-arm study (n=344) 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. (43) The 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 the 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 the chief difference being 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 endpoint 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 sub-groups. 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. (16, 44-47) 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. (46)

Several studies have included ethnically diverse populations but it is not clear whether one or several algorithms are needed to address ethnicity. The algorithm developed by Gage et al. (22) 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. (21) 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. (23) 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. reported that the contribution of *VKORC1* toward dose requirements 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 does not improve dose prediction in any population. (48)

Cavallari et al. 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 dosage was within 1.0 mg/day of the therapeutic dose for 40-50% of the patients. (49) Gan et al. studied Asian populations and found that Indians, compared to Chinese and Malay patients, required a dose of 4.9 versus 3.5 and 3.3mg/day, respectively. The higher warfarin doses correlated with particular *VKORC1* genotypes more often found in the Indian population. (50)

Perera et al. 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. (51) Ramirez et al. developed a predictive algorithm for calculating dose variation in African-Americans including variants in *CYP2C9**6 and CALU. (52) The authors validated an expanded pharmacogenomic dosing algorithm and compared it to the previously established International Warfarin Pharmacogenomics Consortium (IWPC) algorithm with the algorithms explaining 41% and 29% of variation, respectively. Additional studies have identified new genetic variants and/or evaluated clinical-genetic algorithms for warfarin dose in Thai, (53) Egyptian, (54) Chinese, (55) and Japanese populations. (56) In general, genetic factors helped models explain 30-54% of the overall variance but were not always significant.

A retrospective cohort of Puerto Rican patients (n=97) were recruited to determine the influence of *CYP2C9* and *VKORC1* polymorphisms on warfarin dose for this population. (57) 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*.(57) Median actual effective warfarin doses were compared between *CYP2C9* and *VKORC1* carrier status as (wild type/non-carriers, single, double, triple and quadruple carriers). Significant differences ($p<0.001$) in warfarin dose were observed between wild type (5.71 mg/day), single carrier (4.64 mg/day), double carrier (3.43 mg/day), triple carriers (2.36 mg/day) and quadruple carriers (1.86 mg/day). 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 time that the association between SNPs in *CYP2C9* and *VKORC1* genes and effective warfarin dose has been described in Puerto Rican patients.

Not all algorithms include the use of drugs that interact with warfarin; in fact, some studies have excluded these populations. Hatch et al. (24) applied an algorithm developed in patients not taking interacting drugs and showed that when applied to a small number of patients taking interacting drugs, 10% less of dose variance was explained by the algorithm.

Thus, no single dosing algorithm has yet been agreed on that is readily generalizable to a diverse population and that has been prospectively tested in a large, representative validation cohort.

Few large, well-designed randomized clinical trials have been completed and published that address clinical utility i.e., evaluate the net benefit of using genetic factors or algorithms that include genetic factors to guide initial dosing compared to empirical initial dosing. Such trials should also address the degree to which INR must continue to be monitored to ensure that physicians do not overly rely on dosing algorithms and monitor too infrequently, potentially resulting in adverse events.

Anderson et al. (58) conducted a small, randomized controlled trial 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 endpoint was not achieved (p=0.47); nor was the secondary outcome of serious adverse events different between study arms (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 speculate 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. conducted a small study (n=229) in which a gene-based dosing algorithm was compared with standard dosing in patients receiving warfarin after joint replacement surgery. (59) The primary endpoint of reduction in the incidence of adverse events was not reached; nor were secondary endpoints related to INR. Patients in this study were also managed by a dedicated and experienced anticoagulation services team. The results of these studies suggest that larger, community-based studies are needed to determine clinical utility.

Burmester et al. (60) in association with the Agency for Healthcare Research and Quality and Third Wave Technologies conducted a prospective, randomized, blinded, 2-arm trial to determine whether initial warfarin dosing based on an algorithm using relevant genetic polymorphisms and clinical parameters (genetic and clinical arm) was superior to an algorithm using only usual clinical parameters (clinical-only arm) in predicting stable therapeutic dose of warfarin and in anticoagulation outcomes. A total of 230 primarily hospitalized patients were enrolled. The model including genotype predicted therapeutic dose better than the clinical-only model (p=0.0001); both models predicted dose better than the standard starting dose of 5 mg/day. However, the median percent time in INR range was the same at 28.6% in each arm. Observed times to stable therapeutic dose were also very similar in the 2 arms. During the trial, INR exceeded 4.0 in 35% of subjects in the clinical-only arm and in 38% of subjects in the genetic clinical arm. 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 out-patient community setting.

Epstein et al., in association with Medco, a pharmacy benefits management organization, conducted a comparative cohort study in which patients initiating warfarin therapy were invited to participate with free genotyping. (61) Their 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 to controls (adjusted hazard ratio [HR]: 0.69, 95% confidence interval [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 the publication, making it impossible to exclude the possibility that the results of the study are heavily influenced by 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 2.16% in absolute terms, while all-cause hospitalizations had a much larger reduction of 7.07%. 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 non-hematologic reasons. The question of selection bias could have been

avoided in this study if test results had been sent randomly to only half of the physicians caring for patients tested.

A blinded, randomized clinical trial (CoumaGen-II) by Anderson et al. investigated if 2 pharmacogenetic-guided (PG) testing algorithms were better than standard empiric warfarin dosing.(62) A parallel control group (n=1,866) 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 randomized t257 in the 1-step arm (IWPC algorithm) and 247 in the 3-step arm (modified IWPC algorithm). The vast majority of patients (91.4% in the control group and 95.4% in the PG group) were of Caucasian ancestry. Primary endpoints were the percentage out-of-range of INRs and time in therapeutic range during the first month and through the third month of warfarin therapy. Both PG approaches were observed to be equivalent at 1 and 3 months for all outcomes with a stable maintenance dose determined in 444 patients. There was an inverse relation between the number of reduced function alleles and the ability to predict a stable maintenance dose ($p<0.001$). Pharmacogenomic guidance was more accurate in wild-type patients and 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 percentage 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 (4.5%) compared to the PG group (9.4%), with an adjusted relative risk of .44 (95% CI: 0.28-0.70, $p<0.001$).

Several large clinical trials, including some randomized, comparative clinical trials, designed to address clinical utility, are currently in progress (63) and are summarized below:

- Warfarin Adverse Event Reduction For Adults Receiving Genetic Testing at Therapy INITIATION (WARFARIN) Trial conducted by Iverson Genetic Diagnostics, Inc. (NCT01305148). The trial will determine if the use of genetic information can predict warfarin dosing that will result in fewer hospitalizations and deaths related to warfarin. Setting: 16 hospitals/research centers in 7 states. Targeted enrollment: 4,300 participants. Currently recruiting. Additional information online at: www.warfarinstudy.org.
- Clarification of Optimal Anticoagulation Through Genetics (COAG) Trial conducted by the National Heart, Lung, and Blood Institute in collaboration with Bristol-Myers Squibb (NCT00839657). The trial will compare genotype-guided and clinical-guided dosing algorithms for warfarin dose. Setting: 12 hospital/university medical centers in 12 states. Targeted enrollment: 1,238 participants. Currently recruiting. The trial design was published by French, et al. (64)
- European Pharmacogenetics of AntiCoagulant Therapy – Warfarin (EU-PACT) Trial conducted by the Utrecht Institute for Pharmaceutical Sciences (NCT01119300). The trial will determine whether a dosing algorithm containing genetic information increases the time within therapeutic INR range during anticoagulant therapy with warfarin (and other anticoagulant drugs) compared to a dosing regimen not using genetic information. Setting: university medical centers and hospitals. Target enrollment: 970 participants. Not yet recruiting. The trial design was published by van Schie, et al. (65)
- Clinical and Economic Implications of Genetic Testing for Warfarin Management trial conducted by the University of Chicago, in collaboration with AHRQ (NCT00964353). The trial will determine clinical outcomes and costs associated with the use of genotype-guided

warfarin dose algorithms compared to current standards of care. Setting: University medical center. Targeted enrollment: 268 participants. Currently recruiting.

- Genotype-Guided Warfarin Therapy Trial (WARFPGX) conducted by the University of North Carolina in collaboration with UNC Institute for Pharmacogenomics and Individualized Therapy (NCT00904293). The trial will determine the clinical utility of a warfarin-dosing algorithm that incorporates genetic information for adult patients initiating warfarin therapy. Setting: 2 anticoagulation clinics at UNC Hospitals. Targeted enrollment: 198 participants. Currently active, not recruiting.
- Genetics Informatics Trial (GIFT) of Warfarin to Prevent DVT Trial conducted by the Washington University School of Medicine, in collaboration with Intermountain Health Care, University of Utah, Hospital for Special Surgery, New York, and National Heart, Lung, and Blood Institute (NCT01006733). The trial will develop strategies to improve the safety and effectiveness of clot prevention by customizing anticoagulants to individual genetic and clinical profiles. Setting: 4 hospital/university medical centers. Targeted enrollment: 1,600 participants. Currently recruiting. The trial design was published by Lenzini, et al. (26)
- Pharmacogenetics of Warfarin in Puerto Rican Patients Using a Physiogenomics Approach Trial conducted by the University of Puerto Rico, in collaboration with National Heart, Lung, and Blood Institute, Hartford Hospital, and VA Caribbean Healthcare System (NCT01318057). The trial will determine the variants of *CYP2C9* and *VKORC1* alleles associated with warfarin treatment clinical responses in order to develop a better method of dose estimation in Puerto Ricans. Setting: hospital. Targeted enrollment: 350 participants. Currently recruiting.

Summary

While the evidence supports a strong association between genetic variants and stable warfarin dose, and to a lesser extent, between genetic variants and INR 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 does not support the conclusion that clinically relevant outcomes, such as rates of bleeding or thromboembolism, are improved. Therefore, genotyping for variants to predict initial warfarin dose is considered investigational.

U.S. Food and Drug Administration Label Updates

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.

Practice Guidelines and Position Statements

The2008 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." (66)

The 8th edition of the "American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on Antithrombotic and Thrombolytic Therapy," published in 2008 and reviewed in 2009, states, "At the present time, for patients beginning [vitamin K antagonist] therapy, without evidence from randomized trials, we suggest against the use of pharmacogenetic-based initial dosing to individualize warfarin dosing (Grade 2C)."(67)

The 3rd European Science Foundation–University of Barcelona (ESF–UB) Conference in Biomedicine on Pharmacogenetics and Pharmacogenomics published a summary on *CYP2C9* and *VKORC1* genotyping for warfarin dosing. The report noted the FDA's addition of genetic information to the warfarin label but stated that the European Medicines Agency (EMA) has not yet decided whether to include this information in European drug labels." (68)

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

81227 *CYP2C9* (cytochrome P450, family 2, subfamily C, polypeptide 69 (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)

81355 VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (eg, -1639/3673)

- Effective for 2012, there are CPT codes that are specific to this testing: 81227, 81355:
- Prior to 2013, there were also specific CPT codes for array-based evaluation of multiple molecular markers: 88384 (Array-based evaluation of multiple molecular probes: 11 through 50 probes); 88385 (51 through 250 probes); 88386 (251 through 500 probes).

DIAGNOSIS

Experimental / investigational for all diagnoses codes related to this medical policy.

REVISIONS

10-26-2010	Policy added to the bcbsks.com web site.
05-20-2011	Rationale updated
	References updated
02-14-2012	In Coding section: ▪ Added CPT code: 81227 (effective 01-01-2012) ▪ Deleted HCPCS code: G9143 ▪ Added the following notations: ▪ "81227 should be used for the *CYP2C9* enzyme for genetic testing for warfarin dose, effective 01-01-2012. ▪ 88384, 88385, 88386 should be used for the *VKORC1* enzyme for genetic testing for warfarin dose effective 01-01-2012."

02-24-2012	Description section updated
	Rationale section updated
	References updated
01-15-2013	In Coding section: ▪ Removed CPT codes: 88384, 88385, 88386 (effective 12-31-2012).
03-19-2013	Description section updated
	In Coding section: ▪ Added CPT code: 81355 (effective 01-01-2012) ▪ Updated CPT code notations
	Rationale section updated
	References updated

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