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Subject Pharmacogenetic Testing for Warfarin Metabolism

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Coverage Policy

CIGNA does not cover pharmacogenetic testing for warfarin metabolism for any indication because it is considered experimental, investigational or unproven.

General Background

Warfarin, a derivative of coumarin, is a commonly prescribed anticoagulant. Warfarin is an antagonist of vitamin K, which is a necessary element in the synthesis of clotting factors. Indications for warfarin therapy include the following (Bristol-Myers Squibb, 2010; McClain, et al., 2007):

- prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism
- prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement
- to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction

Warfarin anticoagulation needs to be sufficient to avoid thromboembolic events; however, excessive anticoagulation can result in severe, possibly fatal, bleeding events. The intensity of anticoagulation is measured

with a prothrombin (PT) test. This measurement is expressed as the prothrombin time ratio (PTR) which is a ratio of the patient's PT to the control PT of the laboratory. To account for the different sensitivities of various thromboplastin reagents across laboratories, the measurement has been standardized and replaced by the International Normalized Ratio (INR). The target INR range is 2.0–3.0 for most patients. Exceptions to this range include a slightly higher target range (e.g., 2.5–3.5) for patients with certain types of prosthetic heart valves and a lower target (e.g., 1.5) for patients with coronary artery disease at particularly high risk of coronary events (McClain, et al., 2007).

It is difficult to manage the administration of this medication because of the wide inter-individual variation in dose requirements, the narrow therapeutic range and the risk of serious bleeding. Inter-individual variation in anticoagulation response to warfarin is multifactorial. Factors that may affect warfarin dose variability include: age, gender, genetic variations, body mass index (BMI), and use of concomitant medications.

Pharmacogenetics in Warfarin Metabolism

The terms pharmacogenomics and pharmacogenetics describe a field of research focused on how genes affect individual responses to medicines. Research has led to the identification of genes that affect the metabolism of warfarin. Specifically, two genes have been identified as having an effect on the metabolism of warfarin (Gage, 2006; Rettie and Tai, 2006):

- CYP2C9: This gene encodes a member of the cytochrome P450 superfamily of enzymes that are involved in drug metabolism. Several variant alleles or single nucleotide polymorphisms (SNPs), of this gene have been identified as affecting the metabolism of warfarin in the liver. Individuals with CYP2C9*2 and CYP2C9*3 metabolize coumarins slowly and may require a lower initial dose of the drug. Other CYP2C9 alleles also associated with reduced enzymatic activity but occurring at lower frequencies include the *5,*6, *9 and *11 alleles.
- VKORC1: This gene is also known as vitamin K epoxide reductase gene, and it correlates with coumarin sensitivity. The VKORC1-1639A and VKORC1 1173T variants of this gene have been associated with variable warfarin dose requirements.

Clinical Utility: Pharmacogenetic-based treatment has the potential to identify sources of inter-individual variability in drug response, including both effectiveness and toxicity. This knowledge may assist in individualizing therapy with the intent of maximizing effectiveness and minimizing risks (U.S. Food and Drug Administration [FDA], 2005).

At this time the standard mechanism by which warfarin dosage is determined remains close monitoring of the INR. The objective of using pharmacogenetics-based warfarin therapy is to improve the safety and effectiveness of anticoagulant therapy by decreasing number of adverse events caused by bleeding and reducing the time to stable INR. It is theorized that the use of pharmacogenetic testing in initiating warfarin therapy will affect the initial warfarin dose but will have less effect once the therapeutic dose is known (Gage, 2006). A number of dosing algorithms which incorporate age, body mass index, and genetic variation as well as other factors have been developed. At present no single algorithm has been accepted as the standard of care to predict the best dose for stable anticoagulation.

Several large randomized controlled clinical trials comparing the safety and effectiveness of genotype-based dosing and standard-care dosing are ongoing. Although results of published trials are promising, at this time the clinical utility of pharmacogenetic testing to inform warfarin metabolism to predict accurate dosing is unknown.

U.S. Food and Drug Administration (FDA)

On August 16, 2007 (updated January 22, 2010), the FDA revised the drug labeling for Coumadin[®] (Bristol-Meyers Squibb Company, Princeton, NJ), a brand of warfarin, to include genomic information. In the Clinical Pharmacology section of the labeling, evidence of reduced warfarin clearance in patients carrying mutations in the genes CYP2C9 and VKORC1 is discussed. In the Precautions section, it is stated that genetic variation in the CYP2C9 and VKORC1 enzymes may influence the response of the patient to warfarin. In the Dosage and Administration section, it states that lower initial doses should be considered for patients with genetic variations in CYP2C9 and VKORC1. It is expected that generic forms of the drug will also revise the labeling. A specific recommendation to perform testing before prescribing warfarin is not included in the labeling, and the dosage recommendations have not changed.

In addition to a number of warfarin genetic assay kits and independent laboratory-developed tests for warfarin response, there are several devices that have been cleared for marketing by the FDA. They include but are not limited to:

- Verigene Warfarin Metabolism Nucleic Acid Test[®] and the Verigene system[®] (Nanosphere Inc., Northbrook IL): this test received clearance from the FDA as a class II device on September 17, 2007.
- eSensor[®] Warfarin Sensitivity Test, eSensor[®] XT-8 System (Osmetech Molecular Diagnostics, London, UK): this test was cleared by the FDA July 2008.
- INFINITI 2C9 & VKORC1 Multiplex Assay for Warfarin (AutoGenomics, Inc., Carlsbad, CA): this test was cleared by the FDA January 2008.
- Rapid Genotyping Assay-CYP2C9 & VKORC1 (Paragon DX[™], Morrisville, NC): this test was cleared for marketing April 2008.

Literature Review

Freder et al. (2010) reported on the ability of CYP2C9*2, CYP2C9*3 and VKORC1-1639 to predict therapeutic warfarin dose after seven to 21 days of therapy. The primary analysis of the importance of genetic factors in dose prediction was performed using therapeutic doses from participants randomized to long-term warfarin (n = 223) on the PREVENT clinical trial. PREVENT was a randomized, doubleblind, placebo-controlled trial of low-intensity warfarin for the prevention of recurrent venous thromboembolism. A pharmacogenetic model using data from days 0 (before therapy initiation), seven, 14, and 21 explained 54%, 68%, 75%, and 77%, respectively, of the variability in therapeutic dose (R²) because of the increasing contributions from prior doses and International Normalized Ratio (INR) response. Although CYP2C9 and VKORC1 genotypes were significant independent predictors of therapeutic dose at each weekly interval, the magnitude of their predictive ability diminished over time: partial R² of genotype was 43%, 12%, 4%, and 1% at days 0, 7, 14 and 21, respectively.

Epstein et al. (2010) reported on a prospective, observational study (Medco-Mayo Warfarin Effectiveness Study [MM-WES]) that compared the incidence of hospitalization in patients receiving warfarin genotyping (n=896) to a matched historical control group (n=2,688). The primary endpoint was the incident hospitalization rate (measured as event-free time) during the six months following the start of warfarin treatment. The event-free time was defined as the number of days between the start of warfarin and the first hospitalization due to any cause or first hospitalization due to bleeding or thromboembolism. On an unadjusted basis, the patients in the intervention group showed a 28% lower rate of hospitalization for any cause, compared with patients in the historical control group (18.5% vs. 25%, p<0.001). The intervention group demonstrated a 27% reduction in hospitalization risk for bleeding or thromboembolism, compared with the controls (6.0% vs 8.1%, p=0.039). On a per-protocol analysis, the unadjusted differences between the two groups were found to be: patients in the intervention group showed a 31% lower rate of all-cause hospitalizations (14.0% vs. 20.5%, p<0.001) and a 40% lower rate of hospitalizations for bleeding or thromboembolism (3.7% vs. 6.2%, p=0.005). The study found that for the patients who were genotyped, 29.2% had normal warfarin sensitivity, 25.4% had lower-than normal sensitivity, 12.2% had mild sensitivity, and 33.2% had moderate to very high sensitivity. The study design did not include direct monitoring of treatment changes by physicians following delivery of the genotype data. Several weeks may have elapsed between the start of therapy and delivery of the genotype results to the physician; the interval ranged from 11 to 60 days, with a median of 32 days. The authors note that since the physicians in the intervention group were aware of being enrolled in a study, it is possible that they were thus more vigilant in their care. The authors note that further research is warranted to replicate and extend the findings.

McMillin et al. (2010) reported on a prospective, parallel cohort study that compared gene-based warfarin dosing with standard of care dosing in patients receiving warfarin to prevent venous thromboembolism after joint replacement surgery. The study included 229 participants who were receiving warfarin under the direction of a dedicated anticoagulation services team and were assigned to genotype-based or standard of care dosing arms in an alternating fashion. Initial dose for patients was determined by validated algorithms. Management was based on INR, but the dose was adjusted less aggressively for patients with CYP2C9 variants. Primary endpoint in the study was reduction in the incidence of adverse events; additional endpoints included time to first therapeutic INR (1.8–2.9), time to first supratherapeutic INR, and percent of INR determinations that fell below, within, and above the therapeutic range. Genetic variants were detected in 13% (n = 29) of participants for only CYP2C9, and 44% (n = 101) for only VKORC1; variants in both genes were detected in 19% (n = 44) of participants. The study found that there were no statistically significant differences observed between the

genotype-based and standard dosing groups in the average time required to achieve a therapeutic International Normalized Ratio (INR) (approximately 4 days), or the time to first suprathreshold INR (approximately 5 days). The incidence of adverse events between the standard of care and genotype-based dosing arms was found to not be statistically different ($p=0.683$). The authors theorized that the endpoints did not achieve statistical significance, possibly due to the management of this study by a dedicated and experienced anticoagulation services team.

A large cohort study was conducted by the International Warfarin Pharmacogenetics Consortium, which is comprised of 21 research groups from nine countries. Clinical and genetic data were collected from 4043 patients to create a pharmacogenetic dose algorithm. In a validation cohort of 1009 patients the potential clinical value of each algorithm was retrospectively evaluated by calculating the percentage of patients whose predicted dose of warfarin was within 20% of the actual stable therapeutic dose. In the validation cohort, it was found that the pharmacogenetic algorithm accurately identified larger proportions of patients who required 21 mg of warfarin or less per week and of those who required 49 mg or more per week to achieve the target INR than did the clinical algorithm (49.4% vs 33.3%, $p<0.001$, among patients requiring 21 mg or less per week; and 24.8% vs 7.2%, $p<0.001$, among those requiring greater than 49 mg per week). The analysis did not address the issue of whether a precise initial dose of warfarin will lead to improved clinical outcomes, such as a reduction in the time needed to achieve a stable therapeutic INR, fewer INRs that are out of range, and a reduced incidence of bleeding or thromboembolic events (2009).

Caraco et al. (2008) conducted a study to prospectively examine whether a priori knowledge of CYP2C9 genotype may improve warfarin therapy. Patients were randomly assigned to either the control group where they received warfarin by a validated algorithm ($n=96$) or to the study group where CYP2C9 genotype-adjusted algorithms ($n=95$) was used. The first therapeutic INR and stable anticoagulation were reached 2.73 and 18.1 days earlier in the study group, respectively ($p<0.001$). The faster rate of initial anticoagulation was driven by a 28% higher daily dose in the study group ($p<0.001$). The study group patients spent more time within the therapeutic range (80.4 versus 63.4%, respectively; $p<0.001$) and experienced less minor bleeding (3.2% versus 12.5%, respectively; $p<0.02$).

Anderson et al. (2007) conducted a randomized trial that examined genotype-guided warfarin dosing compared to standard warfarin dosing in patients initiating oral anticoagulation. The study involved 206 patients that were randomized to pharmacogenetic-guided or standard dosing. A buccal swab DNA was genotyped for CYP2C9*2 and CYP2C9*3 and VKORC1 with a rapid assay. The standard dosing followed an empirical protocol. The pharmacogenetic-guided dosing followed a regression equation including the three genetic variants and age, sex and weight. INR was measured on days 0, 3, 5, 8, 21, 60, and 90. The pharmacogenetic-guided predicted doses were noted to more accurately approximate stable doses ($p<0.001$), resulting in smaller ($p=0.002$) and fewer ($p=0.03$) dosing changes and INRs ($p=0.06$). The primary end point, the percent out-of-range INRs, (pharmacogenetic=30.7%, standard=33.1%), did not differ significantly between the two arms. When restricted to wild-type patients who required larger doses ($p=0.001$) and multiple variant carriers (who required smaller doses ($p<0.001$) in exploratory analyses, the results (pharmacogenetic=29%, standard=39%) achieved nominal significance ($p=0.03$). Multiple variant allele carriers were at increased risk of an INR of ≥ 4 ($p=0.03$).

Hillman et al. (2005) reported on a prospective, randomized, single-blinded clinical pilot trial to evaluate the feasibility of applying a CYP2C9 gene-based warfarin dosing model in clinical practice. The trial included 117 patients who were recruited from a list of clinic patients who were eligible for warfarin initiation. They included patients with newly diagnosed thromboembolic disease or atrial arrhythmia, and patients anticipating elective valvuloplasty or arthroplasty. The patients were randomized to receive either a standard initiation dose of 5 mg warfarin/day or rapid CYP2C9 genotyping and an initiation dose determined using parameters estimated from a previously published multivariate model. The parameters in this model included: age, body size, comorbidity (e.g., diabetes), clinical indication (e.g., valvuloplasty) and CYP2C9 genotype. The primary outcome measurements included patient willingness to participate, physician willingness to refer, sample processing time, ability to administer calculated dosage and adequacy of follow-up. The limitations of the trial were noted that it was designed to assess the feasibility of model-based warfarin dosing, and the power was insufficient for statistical comparison of adverse event rates. Forty-three of 117 patients had no prior warfarin treatment and were eligible to participate, with five declining to participate. Twenty patients were randomized to receive a standard initiation dose of 5 mg daily. Eighteen patients were randomized to the model-based dosing. All but one participant received the assigned initiation dose. The CYP2C9 genotype distribution was similar within the two groups. Patients with a wild type homozygous CYP2C9 genotype (*1/*1) were observed at a frequency of

65% in the standard dosing group and 61% in the model-based dosing group. Six warfarin-related adverse events (in five patients) were noted in the standard dosing group with two events (in two patients) occurring in the model-based dosing group. The authors concluded that based on the results of this trial, prospective application of CYP2C9 gene-based multivariate warfarin dosing calculators are both technically feasible and acceptable to patients and providers. The authors noted that while feasible, additional outcome-based pilot trials are needed prior to implementing a larger study.

Millican et al. (2007) reported on a retrospective analysis of two cohorts of orthopedic surgery patients (n=92) conducted with the goal of developing an algorithm for initial warfarin dose. For each patient, a blood sample was collected, along with clinical variables, current medications and preoperative and postoperative laboratory values recorded. Genotype for polymorphism in CYP2C9 and VKORC1 genes was performed. Utilizing a stepwise regression, a model was developed that refined the warfarin dose. The algorithm explained four fifths of the variability in therapeutic dose. It was noted that significant predictors ($p > .05$) were INR value after three doses (47% reduction per 0.25 unit rise), first warfarin dose (+7% per 1 mg), CYP2C9*2 and CYP2C9*3 genotype (-38% and -17% per allele), estimated blood loss, smoking status (+20% in current smokers), and VKORC1 (-11% per copy of haplotype A). The authors concluded that when validated, this method may provide a safer, more effective process for initiating warfarin therapy and improving the safety and efficiency of this process.

Zhu et al. (2007) investigated the contribution of VKORC1 polymorphism to the variance in warfarin dose. Sixty-five patients with stable anticoagulation were genotyped for CYP2C9 and VKORC1. Plasma S warfarin concentrations and warfarin maintenance dose were compared among patients on the basis of the VKORC1 _1639G>A genotype. The study found that 80% of the CYP2C9*1/*1 patients stabilized on < 4.0 mg/day of warfarin and had at least one VKORC1_1639A allele. The mean warfarin doses were 6.7 (3.3), 4.3 (2.2), and 2.7 (1.2) mg/day for patients with the VKORC1_1639GG, GA, and AA genotypes, respectively. A model developed by the authors that included VKORC1 and CYP2C9 genotypes, age, sex, and body weight accounted for 61% of the variance in warfarin daily maintenance dose. The authors concluded that "The VKORC1_1639A allele accounts for low dosage requirements of most patients without a CYP2C9 variant. Higher plasma S-warfarin concentrations corresponding to increased warfarin maintenance dosages support a hypothesis for increased expression of the VKORC1_1639G allele. VKORC1 and CYP2C9 genotypes, age, sex, and body weight account for the majority of variance in warfarin dose among our study population." Regarding the model developed by the authors, they noted that it will require validation by comparison of estimated versus actual dosages of an independent population sample.

Tham et al. (2006) conducted a study with the aim of deriving a pharmacogenetic-based dosing algorithm by use of retrospective information and to validate it through a data-splitting method in a separate cohort of equal size. The study included 215 records of patients who had been recruited in a previous genotyping study for CYP2C9/VKORC1. The authors hypothesized that single-nucleotide polymorphisms in CYP2C9 and VKORC1, used to infer VKORC1 haplotype in combination with demographic factors, can accurately predict warfarin doses. Within the final model, only predictors reaching a statistical significance of $P < .05$ were retained. Data from 107 subjects undergoing maintenance warfarin therapy with an INR between two and three were used to derive the final model, as an exponential function of age, weight, CYP2C9*3 allele, and VKORC1 381 CC and TC genotypes. This model accounted for 60.2% of the variability in daily warfarin dose requirement. A separate cohort of 108 subjects validated the model and demonstrated a mean underestimation of 0.23 ± 1.21 mg/d. The authors concluded that "Warfarin dose requirements in Asians can be accurately predicted by use of a combination of patient demographics and a simplified genotyping approach for single variants in CYP2C9 and VKORC1." Additionally, it was noted by the authors that a large randomized controlled clinical trial comparing the clinical benefits of such pharmacogenetics-guided dosing approaches for warfarin is required to determine the reproducibility and clinical benefits of this approach.

Lindh et al. (2005) conducted an investigation to prospectively study the impact of CYP2C9 polymorphism (*2 and *3) on the risk of overanticoagulation during the induction phase of warfarin therapy. The subjects were a subpopulation of patients (219) included in the Warfarin Genetics (WARG) study, which is an ongoing prospective, nested, case-control study of genetic risk factors for bleeding complications in warfarin-treated patients. Patients were divided into three groups according to CYP2C9 genotype: *1 homozygous, *2 (*1/*2 and *2/*2) and *3 (any genotype containing the *3 allele). The results noted that during the first week of treatment, the relative risk of achieving at least one INR value above the therapeutic interval (2–3) was 2.8 (95% confidence interval, 1.2–6.7) and 6.1 (2.7–13.6) in the *2 and *3 groups, respectively, with *1 group being used

as control. In the second week, the corresponding values were 2.1 (1.2–3.7) and 3.5 (2.1–5.8), respectively. By the third week, a genetic impact did not appear to be evident, likely as a result of successful dose individualization. Increased INR levels (compared with the *1 group) were already demonstrated in the *2 group on the fourth treatment day. The authors concluded that the CYP2C9*2 and CYP2C9*3 polymorphisms significantly increase the risk of overanticoagulation during the first two weeks of warfarin treatment, with increased INR levels evident after only four days' treatment in the *2 carriers.

Several retrospective studies have been published that demonstrate a correlation between CYP2C9 and VKORC1 variants and warfarin dose requirements (Aquilante, et al., 2006; Reider, et al., 2005; Veenstra, et al., 2005; Wadelius, et al., 2005; Joffe, et al., 2004; Peyvandi, et al., 2004; Higashi, et al., 2002; Aithal, et al., 1999).

Systematic Reviews/Technology Assessments: An emerging technology evidence report evaluated the results of three randomized controlled trials and two nonrandomized trials comparing genotype-based dosing in 1273 individuals to standard-care dosing in a total of 3060 individuals. An additional cohort study used clinical and genetic data from 5052 individuals. The Report noted there was insufficient data to determine how genotype-based dosing compared with standard-based dosing relative to the number of serious warfarin-related adverse events and/or hospitalizations due to warfarin adverse events. In addition, the impact of genotype-based dosing compared with standard-based dosing on the time to therapeutic dose and time in therapeutic range could not be determined because the studies reported inconsistent results (ECRI, 2011).

Kangelaris et al. (2009) conducted a systematic review of randomized trials that compared a dose-selection strategy that used pharmacogenetic information to one that did not. The review included three studies. All three were small, single-center randomized clinical trials ranging from 38–238 patients. Follow-up ranged from 22 days to an average of 46 days. Each of these studies used different dosing models for the pharmacogenetic and control dosing arms. One study used dosing models that accounted only for CYP2C9 variants, while the other two utilized both CYP2C9 and VKORC1 variants. The pharmacogenetic dosing groups showed improvement in time to stable warfarin dose compared to the control groups in two of the three studies and was not reported in the third. Meta-analysis was not performed due to the heterogeneity of the trials. The authors concluded that the study did not find sufficient evidence to support the use of pharmacogenetics to guide warfarin therapy outside of clinical trials.

The Agency for Healthcare Research and Quality (AHRQ) published a technology assessment conducted by Tufts Evidence-based Practice Center (Tufts-NEMC) that reviewed pharmacogenetic tests for selected conditions (Raman, et al., 2008). The report was commissioned by the Center for Medicare and Medicaid Services (CMS). For CYP2C9 genetic variants *2 and *3, 29 studies, including two recent randomized controlled trials, were included in the systematic review. Studies chosen for this systematic review focused on the induction or maintenance phases of warfarin therapy. For VKORC1 variants twenty-eight articles were retrieved and reviewed in full text, and 19 studies reported data on the correlation of common VKORC1 with outcomes of interest. Findings of the systematic review included:

- Carriers of the variant CYP2C9 alleles *2 or *3 receiving warfarin therapy were associated with lower mean maintenance warfarin dose requirements compared with the non-carriers. There was a lack of studies investigating the role of pharmacogenetic testing (CYP2C9 or VKORC1) and warfarin dose requirements in the induction phase. Carriers of the three relatively common VKORC1 variants were more likely to need lower maintenance warfarin dose requirements, on average, compared with the non-carriers.
- Carriers of CYP2C9 variants *2 and *3 were associated with an increased rate of bleeding complications during warfarin induction phase, but the studies did not report if those patients had normal or supratherapeutic range of PT/INR.
- Risk of over-anticoagulation (INR results exceeded desired upper limits) was also noted among carriers of CYP2C9 variants *2 and *3 compared with non-carriers. Significant risk increases were noted in 5 of these 6 studies reviewed.

The review noted the following regarding the published literature:

- The majority of studies evaluated the associations of pharmacogenetic test results with intermediate, not clinical, outcomes, such as the effectiveness of drug dose, and adverse clinical outcomes, such as bleeding events.
- Only a few studies evaluated the effects of patient- and disease-related characteristics on the association between test results and intermediate or clinical outcomes.
- No studies investigated the influence of gene testing on the impact of therapeutic choices and on the benefits and harms or adverse effects for patients from their subsequent therapeutic management after pharmacogenetic testing.
- No studies evaluated whether pharmacogenetic testing among patients who are on warfarin and who have supratherapeutic INRs will result in better maintenance of therapeutic INR, fewer episodes of serious bleeding, or fewer serious thrombotic events
- It is unclear whether dose-prediction algorithms using genetic information improve clinical outcomes (fewer bleeding complications and fewer thromboembolic events) over those of standard practice. Only a few clinical trials have addressed this question, essentially three randomized clinical trials, each of which has their flaws in the design, inclusion criteria and power to reach statistical conclusions.

The California Technology Assessment Forum (CTAF) published a technology assessment regarding the use of genetic testing to guide the initiation of warfarin therapy (2008). The findings noted that due to absent or insufficient evidence for improvement of outcomes, for benefit compared to established alternatives and for improvement attainable outside the investigational setting, the use of CYP2C9 and VKORC1 did not meet its criteria for recommendation.

Sanderson et al. (2005) conducted a systematic review and meta-analysis to examine the strength and quality of existing evidence about CYP2C9 gene variants and clinical outcomes in warfarin-treated patients. Eleven studies were included in the review (3029 patients), with nine studies included in the meta-analyses (2775 patients). In order to be included, a study needed to report at least one of the following outcome measures: drug dose, indicators of anticoagulation control, and bleeding events. Results indicated that 20% of patients studied carry a variant allele: CYP2C9*2, 12.2% (9.7%–15.0%) and CYP2C9*3, 7.9% (6.5%–9.7%). The mean difference in daily warfarin dose was noted to be: CYP2C9*2—reduction of 1.92 mg (1.37–2.47 mg), a 37% reduction; CYP2C9*3—reduction of 1.47 mg (1.24–1.71 mg), a 27% reduction. The study found the relative bleeding risk for CYP2C9*2 to be 1.91 (1.16–3.17) and for CYP2C9*3 to be 1.77 (1.07–2.91). The authors note that among the implications for these findings, there are two possible roles for genotyping CYP2C9:

- Testing could identify high-risk patients who may benefit from conservative induction regimens, lower maintenance doses and more frequent clinical and laboratory monitoring.
- Testing may assist in determining the choice of drug for patients considering elective anticoagulation (e.g., nonrheumatic atrial fibrillation).

The authors note that the evidence presented in this review is insufficient to make a case for genotyping in routine clinical practice yet and that evidence of clinical utility is required. The authors concluded that “Patients with CYP2C9*2 and CYP2C9*3 alleles have lower mean daily warfarin doses and a greater risk of bleeding. Testing for gene variants could potentially alter clinical management in patients commencing warfarin. Evidence for the clinical utility and cost-effectiveness of genotyping is needed before routine testing can be recommended.”

Professional Societies/Organizations

American College of Chest Physicians (ACCP): The ACCP published evidenced based clinical practice guidelines regarding the pharmacology and management of the vitamin K antagonists (Ansell, et al., 2008). The guidelines include the following recommendations: “at the present time, for patients beginning VKA therapy without evidence from randomized trials, we suggest against the use of pharmacogenetic-based initial dosing to individualize warfarin dosing (Grade 2C)”

The ACCP notes the following regarding the grading system used in the guidelines: the strength of any recommendation depends on two factors: the trade-off between benefits, risks, burden, and cost, and the level of confidence in estimates of those benefits and risks. If benefits do or do not outweigh risks, burden, and costs, a strong recommendation is designated as Grade 1. If there is less certainty about the magnitude of the benefits and risks, burden, and costs, a weaker Grade 2 recommendation is made. Support for these recommendations

may come from high-quality, moderate-quality, or low-quality evidence, labeled, respectively, A, B, and C. The phrase “we recommend” is used for strong recommendations (Grade 1A, 1B, 1C) and “we suggest” for weaker recommendations (2A, 2B, 2C).

American College of Medical Genetics (ACMG): The ACMG published a policy statement regarding pharmacogenetic testing of CYP2C9 and VKORC1 (Flockhart, et al., 2008). The policy statement is based on an evidenced-based report: Rapid-ACCE (Analytic validity, Clinical validity, Clinical utility and Ethical, legal and social implications) Review of CYP2C9 and VKORC1 Allele Testing to Inform Warfarin Dosing in Adults at Elevated Risk for Thrombotic Events to Avoid Serious Bleeding (McClain, et al., 2008). The ACCE review makes the following notations regarding genetic testing for warfarin dosing (McClain, et al., 2007):

- Regarding analytic validity of the testing:
 - Based on seven studies reporting performance in the analytic phase of testing, assays for the common CYP2C9 genotypes (*1/*2 and *1/*3) have an analytic sensitivity of 100% (95% confidence interval [CI] 96.7% to 100%). The analytic specificity is also 100% (95% CI 98.2% to 100%).
 - Based on sparse data for the less common CYP2C9 genotypes (*2/*2, *2/*3, and *3/*3), the analytic sensitivity of selected assay systems is still 100%, but the CI interval is wider (95%, CI 75% to 100%).
 - Too few data exist to estimate these rates for VKORC1 genotyping.
- At least 12 laboratories in the U.S. now offer CYP2C9 and/or VKORC1 genotyping for clinical use. Several manufacturers offer reagents to test for variants in both genes.
- Most available data are based on DNA extracted from whole blood samples. Other sample types (e.g., mouthwash) have been mentioned, but the data is sparse for these types. .
- Regarding clinical validity of the testing:
 - INR values above 3 are more likely among CYP2C9 heterozygotes (risk ratio of 2.0 or higher), and are more likely in the first and second week (induction phase) after initiation than the third week or later.
 - With all variant CYP2C9 genotypes grouped together, the clinical sensitivity of CYP2C9 to identify serious bleeding events is 46% (95% CI 32% to 60%), indicating that half of the serious bleeding occurs among wild-type individuals.
 - Clinical specificity of CYP2C9 is 69% (95% CI 62% to 75%), indicating that non-wild CYP2C9 genotypes are relatively common.
 - Relative risk for serious bleeding is 1.7 (95% CI 0.8 to 3.6).
 - The prevalence of serious bleeding among populations varies widely (<1% to 17%) depending on many factors (e.g., indication for warfarin, age, comorbidities, definition of serious bleeding and other drug use).
- Models that predict warfarin dose should consider the following characteristics:
 - Use the logarithm of the warfarin dose (not warfarin dose) as the dependent variable
 - Allow different dosages for CYP2C9 genotypes *1/*2 and *1/*3
 - Include other important factors (e.g., age, weight, height, body mass index [BMI])
- Regarding clinical utility of the testing:
 - The intended action is to compute an individual’s initial warfarin dose by incorporating demographic, clinical, and gene variant data (both CYP2C9 and VKORC1) as a way to limit high INR values (over-anticoagulation) that are associated with serious bleeding events.
 - Many of these events will occur within the first few weeks of treatment. No study has yet shown this intervention to be effective in reducing the incidence of high INR values, the time to stable INR, or the occurrence of serious bleeding events.
 - There are several large randomized trials underway to determine the clinical effectiveness of CYP2C9 genotyping and VKORC1 haplotyping to inform warfarin dosing.

The ACMG position statement notes that “in the context of variable warfarin sensitivity, there is limited evidence at this time to support routine testing of the CYP2C9 and VKORC1 genes for functional polymorphisms that affect warfarin dosing. Although the analytic testing is currently being performed in a number of laboratories, there is less linkage of the genotype data produced with phenotypic warfarin dosing than is optimal for the development of recommendations for clinical practice.” The policy statement includes the following recommendations (Flockhart, et al., 2008):

- There is no prospective data to recommend for or against routine CYP2C9 and VKORC1 testing in warfarin-naïve patients since there are no substantive prospective study that has yet shown this intervention to be effective in reducing the incidence of high INR values, the time to stable INR, or the occurrence of serious bleeding events, while maintaining the ability of the drug to prevent thromboembolic events.
- CYP2C9 and VKORC1 genotypes can reasonably used as part of diagnostic efforts to determine the cause of an unusually low maintenance dose of warfarin or an unusually high INR during standard dosing.
- CYP2C9 testing beyond *2 and *3 alleles involves rare alleles for which there is much more limited data available to support their inclusions.

Summary

Warfarin, a derivative of coumarin, is a commonly-prescribed anticoagulant. There are difficulties in the management of this medication due to wide inter-individual variation in dose requirements, the narrow therapeutic range and the risk of serious bleeding. There are a number of studies that demonstrate the relationship between genes CYP2C9 and VKORC1 and the metabolism of warfarin; however, the impact of this information on meaningful health outcomes has not yet been demonstrated. There is insufficient evidence in the published, peer-reviewed, scientific literature to support the clinical utility of this testing. There is a lack of evidence to demonstrate that the use of this testing is effective in reducing the incidence of high INR values, the time to a stable INR, or the occurrence of serious bleeding events.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Experimental/Investigational/Unproven/Not Covered when used to report pharmacogenetic testing for warfarin metabolism:

CPT [®] * Codes	Description
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid
83894	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide), each nucleic acid preparation
83896	Molecular diagnostics; nucleic acid probe, each
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
83900	Molecular diagnostics; amplification of patient nucleic acid, multiplex, first two nucleic acid sequences
83901	Molecular diagnostics; amplification of patient nucleic acid, multiplex, each additional nucleic acid sequence (List separately in addition to code for primary procedure)
83904	Molecular diagnostics; mutation identification by sequencing, single segment, each segment
83908	Molecular diagnostics; amplification, signal, each nucleic acid sequence
83909	Molecular diagnostics; separation and identification by high resolution technique (e.g., capillary electrophoresis), each nucleic acid preparation
83912	Molecular diagnostics; interpretation and report
88384	Array-based evaluation of multiple molecular probes; 11 through 50 probes
88385	Array-based evaluation of multiple molecular probes; 51 through 250 probes
88386	Array-based evaluation of multiple molecular probes; 251 through 500 probes

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

ICD-9-CM Diagnosis Codes	Description
415.11-415.9	Pulmonary embolism and infarction
427.31	Atrial fibrillation
453.40-453.43	Acute venous embolism and thrombosis of deep vessels of lower extremities
453.50-52	Chronic venous embolism and thrombosis of deep vessels of lower extremity
453.6	Venous embolism and thrombosis of superficial vessels of lower extremity
453.71-453.79	Chronic venous embolism and thrombosis of other specified vessels
453.81-453.89	Chronic venous embolism and thrombosis of other specified veins
453.9	Venous embolism and thrombosis of unspecified site

*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	11/15/2007	0484	Pharmacogenetic Testing for Warfarin Metabolism

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