MEDICAL POLICY

Excellus

MEDICAL POLICY DETAILS	
Medical Policy Title	**GENOTYPING CYTOCHROME P450 2C9 (CYP2C9) AND VITAMIN K EPOXIDE REDUCTASE SUBUNIT CI (VKORC) THAT AFFECT RESPONSE TO WARFARIN**
Policy Number	**2.02.33**
Category	**Laboratory Tests**
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Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.* • *If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.*

POLICY STATEMENT

Based upon our criteria and review of peer-reviewed literature, genotyping to determine cytochrome p450 2C9 (CYP2C9) and vitamin K epoxide reductase subunit C1 (VKORC1) genetic polymorphisms is considered **investigational** to detect variants that affect response to warfarin.

Refer to Corporate Medical Policy # 2.02.30 regarding Genotyping - Cytochrome P450 for Drug Metabolism.

Refer to Corporate Medical Policy #11.01.03 regarding Experimental and Investigational Services.

POLICY GUIDELINES

The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION

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 initiated on 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. Finally, stable warfarin dose varies among individuals. 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.

Genetic variants of CYP2C9 result in enzymes with decreased activity, increased serum warfarin concentration at standard doses, and a higher risk of serious bleeding. VKORC1 genetic variants alter the degree of warfarin affect 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.

It has been proposed that 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 been developed that incorporate not only genetic variation but also other significant factors to predict the best starting dose.

On August 16, 2007, the FDA announced the approval of 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. Manufacturers of warfarin (generic for Coumadin®) are to add similar information to their products' labels. The FDA stated, "warfarin is the second most common drug - after insulin - implicated in emergency room visits for adverse drug events". According to the FDA, 2 million patients are initiated on warfarin per year in the U.S.

Because of the current lack of outcomes (clinical utility) data, some experts do not believe that genetic testing for warfarin dosing is ready for routine clinical use. To accommodate uncertainty, the FDA did not include information on genetic variation in the label's black box warning.

In a "Questions and Answers" document and during a call hosted by the FDA, several important points regarding the new labeling were made:

I. Healthcare professionals are not required to conduct CYP2C9 and VKORC1 testing before initiating warfarin therapy, nor should genetic testing delay the start of warfarin therapy.
II. Genetic testing is not appropriate for patients already on warfarin.
III. Genetic testing does not replace INR monitoring.

Based on available evidence, not all patients with one or more genetic variants in CYP2C9 or VKORC1 will have a serious bleeding event, nor will all patients without gene variants avoid a bleeding episode.

RATIONALE

On September 17, 2007, the FDA approved the Nanosphere Verigene Warfarin Metabolism Nucleic Acid Test to detect some variants in the two genes, CYP2C9 and VKORC1that affect response to warfarin. Since then, the FDA has also cleared the following test kits that detect the same variants: eSensor Warfarin SEnsitivity Test (Osmetech); Rapid Genotyping Assay (ParagonDx); Verigene Warfarin Metabolism Nucleic Acid Test (Nanosphere); ¼INFINITI 2C9-VKORC1 Multiplex Assay for Warfarin (AutoGenomics); and the eQ-PCR LightCycler Warfarin Genotyping Kit (TrimGen). Kit inserts for FDA-cleared test kits summarize the extensive analytic validity data required for FDA clearance. Genetic testing for CYP2C9 and VKORC1 is also available at a number of laboratories that have developed in-house tests; these do not require FDA clearance and information on analytic validity may not be generally available. Some in-house assays use commercially available reagents that are individually cleared by the FDA as analyte-specific reagents. One study (King, et al. 2008) compared one FDA-cleared kit and 3 in-house assays using commercially available reagents and assay platforms; the authors concluded that the assays provided accurate and rapid genotype information.

Turnaround times for these assays range from about 1.5 to 8 hours. Patients not near a testing lab may be subject to longer turnaround times to accommodate sample transport to distant laboratories; it is not known how soon test results are needed during the warfarin initiation phase for full benefit (if projected benefits are realized in outcomes studies). In general, the test is not intended to be a stand-alone tool to determine optimum drug dosage, but should be used along with clinical valuation and other tools, including the INR, to determine the best maintenance dose for patients.

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

I. Analytic validity: measures technical performance, i.e., does the test accurately and reproducibly detect the gene markers of interest.

II. Clinical validity: measures the strength of the associations between the selected genetic markers and dose, therapeutic efficacy, and/or adverse events.
III. 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.

A systematic review (McClain, et al. 2007) commissioned by the American College of Medical Genetics, evaluated CYP2C9 and VKORC1 genetic testing prior to warfarin dosing and concluded the following:

I. Analytic validity: Nearly all available data for analytic validity refer to two variants in the CYP2C9 gene; less data is available for the variants in the VKORC1 gene. Based on these data, analytic sensitivity and specificity are likely near 100%. Depending on methodology, 1% to 10% of samples may experience repeated assay failures resulting in inconclusive test results.
II. 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 would require less. Time to steady state warfarin levels varies by CYP2C9 genotype (3 to 5 days vs. 5 to 8 vs. 12 to 15 for the three most common genotypes). CYP2C9 positive predictive value (PPV) for serious bleeding events is estimated to be 7%; the negative predictive value (NPV) is 96%. Similar information for VKORC1 was not available.
III. 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 INR values (over-anticoagulation) that are associated with an increased risk of serious bleeding events. No large study has yet shown this to be acceptable or effective. Several randomized trials are underway to determine the clinical utility. The number needed to treat to avoid one serious bleeding event is estimated to range from 48 to 385.

An October 2007 review by The Canadian Agency for Drugs and Technologies in health (CADTH) concluded:

I. Dosing algorithms tailored to individual genetic, demographic, and clinical factors may minimize the risk for bleeding during the initiation of warfarin therapy.
II. Pharmacogenomic testing should be used in addition to (rather than replacing) routine International Normalized Ratio (INR) monitoring.
III. Prospective studies are needed to determine whether pharmacogenomic testing improves patient outcomes, identify which subgroups of patients may benefit, and clarify the risks and costs associated with the use of these tests. Several randomized controlled trials are currently evaluating the impact of pharmacogenomics on dosing accuracy, time to achieve and maintain target INR, incidence of bleeding or thromboembolic events, and monitoring requirements.

Two cohort studies evaluated algorithm-guided dosing, which included genetic factors, in patients beginning warfarin treatment. Wen, et al. (2008) reported that 83% of the cohort reached and maintained therapeutic INR in the first 2 weeks, and that 69% of the maintenance dose matched the predicted dose; no control arm treated by standard, empirical dosing was included for comparison. Millican, et al. (2007) reported using partial genetic information in 2 cohorts to guide initial dosing and retrospectively developed an algorithm that explained 79% of the variance in maintenance dose.

Few studies have included ethnically diverse populations. 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.

The International Warfarin Pharmacogenetics Consortium reported the results from development of two algorithms for warfarin dosing; a dose algorithm that was based on clinical variables only and an algorithm in which genetic information was added to the clinical variables. The largest effect was seen for 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 international normalized ratio. The pharmacogenetic algorithm predicted doses in the ideal range for significantly more patients than did the clinical algorithm for these two groups. These two groups accounted for 46% of the entire cohort. Limitations of the study include that potentially important factors such as smoking status, vitamin K intake, or alcohol consumption, and other genetic factors or environmental factors that could help predict the stable therapeutic dose of warfarin were not incorporated into the study.

Thus, no single dosing algorithm has yet been agreed upon that is readily generalizable to a diverse population and that has been tested in a large, representative validation cohort. Nor have any large, well-designed randomized clinical trials been completed and published that address clinical utility (e.g., evaluate the net benefit of using genetic factors or algorithms that include genetic factors to guide initial dosing compared to empirical dosing). Such trials should also address the degree to which INR must continue to be monitored, in order to ensure that physicians do not overly rely on dosing algorithms and monitor too infrequently, potentially resulting in adverse events. Several large clinical trials, including some randomized, comparative clinical trials, which address clinical utility, are currently in progress.

The 9th edition of the "American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on Antithrombotic and Thrombolytic Therapy," published in 2012, states, "For patients initiating VKA therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of vitamin K antagonist (VKA)" (Grade 1B).

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

CPT Codes

Code	Description
81227 **(E/I)**	CYP2C9 (cytochrome P450, family 2, subfamily #, polypeptide 6) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)
81355 **(E/I)**	VKORC1 (Vitamin K epoxside reductase complex, subunit 1) (e.g., warfarin metabolism), gene analysis, common variants (e.g, 1639/3673)
81479	Unlisted molecular pathology procedure
0030U **(E/I)**	Drug metabolism (warfarin drug response), targeted sequence analysis (ie, CYP2C9, CYP4F2, VKORC1, rs12777823) (effective 1/1/2018)

HCPCS Codes

Code	Description
No code(s)	

ICD10 Codes

Code	Description
	Investigational for all codes

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*Key Article

KEY WORDS

Coumadin®, CYP450, Cytochrome p450, VKORC1, Vitamin K epoxide reductase subunit C1, Warfarin

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a National Coverage Determination (NCD) for Pharmacogenomic Testing for **Warfarin** Response. Please refer to the following NCD website for Medicare Members:
https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=333&ncdver=1&bc=AgAAgAAAAAAAAA%3d%3d&

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare Members:
https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ver=59&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=All&bc=AggAAAIAIAAAAA%3d%3d&