

Corporate Medical Policy

Pharmacogenetic Testing for Warfarin Dose

File Name: pharmacogenetic_testing_for_warfarin_dose
Origination: 3/2008
Last CAP Review: 10/2011
Next CAP Review: 10/2012
Last Review: 10/2011

Description of Procedure or Service

Warfarin (Coumadin ®) is an oral anticoagulant indicated for patients with a history of atrial fibrillation, myocardial infarction, deep vein thrombosis, or pulmonary embolism, and for patients with certain types of artificial heart valves. Despite its proven efficacy, warfarin is underutilized among individuals who could benefit from this therapy due to the high rate of adverse events, the lack of precise warfarin dosing parameters and the need to monitor patients on a regular basis. Warfarin dosing is a challenging process. It has a narrow therapeutic window, variable response to dosing, and serious bleeding events in 5% or more of patients. Warfarin is the second most common drug, after insulin, implicated in emergency room visits for adverse drug events.

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 between 2 and 3 is achieved. During this adjustment period, a patient is at high risk for bleeding. Stable warfarin dose varies among individuals by more than an order of magnitude.

A person's environment, diet, age, gender, and general state of health can all influence the response to medication. Another key factor is genes. The study of how people respond differently to medications due to their genetic makeup is called pharmacogenetics. Research has shown that the two most important genes affecting the pharmacokinetic and pharmacodynamic parameters of warfarin are cytochrome p450 2C9 (CYP2C9) and vitamin K epoxide reductase subunit C1 (VKORC1). These two genes, together with environmental factors, partly explain the inter-individual variation in warfarin dose requirements. Knowing how an individual will respond to warfarin would help in tailoring the dose needed to maintain appropriate anticoagulation.

Pharmacogenetics-based warfarin dosing has the potential to reduce the risk for bleeding, increase dosing accuracy, shorten the time to dose stabilization, and help identify individuals who may require more frequent monitoring with long-term therapy.

In August of 2007, the U.S. Food and Drug Administration (FDA) approved the updated labeling for warfarin to include information in the "precautions" section that individuals with variations in CYP2C9 and VKORC1 may require a lower initial dose of the drug. However, the FDA emphasized that there are not enough clinical data to make this test mandatory at this time.

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

Pharmacogenetic testing is considered 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. BCBSNC does not provide coverage for

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investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Pharmacogenetic Testing for Warfarin Dose is covered

Not Applicable

When Pharmacogenetic testing for Warfarin Dose is not covered

Genotyping to determine cytochrome p450 2C9 (CYP2C9) and vitamin K epoxide reductase subunit C1 (VKORC1) genetic polymorphisms is considered 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.

Policy Guidelines

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 VKORC genetic variants improve 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: G9143, 81227, 81355

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For Evidence Based Guideline titled Pharmacogenetic Testing for Warfarin Dose

BCBSA Medical Policy Reference Manual [Electronic Version] 2.04.48, 9/18/07

Rieder MJ, Reiner AP, Gage BF, Nickerson DA, Eby CS, McLeod HL, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *N Engl J Med* 2005; 352: 2285-93

Ndegwa, S. Pharmacogenomics and warfarin therapy [Issues in emerging health technologies issue 104]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007.

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Caldwell MD, Berg RL, Zhang KQ, Glurich I, Schmelzer JR, Yale SH, et al. Evaluation of genetic factors for warfarin dose prediction. *Clin Med Res*. 2007 Mar; 5(1):8-16

Anderson JL, Horne BD, Stevens SM, Grove AS, Barton S, Nicholas ZP, et al. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. *Circulation* 2007; 116: 2563-2570

McClain MR, Palomaki GE, Piper M, Haddow JE. Commissioned by American College of Medical Genetics (ACMG). A rapid ACCE review of CYP2C9 and VKORC1 allele testing to inform warfarin dosing in adults at elevated risk for thrombotic events to avoid serious bleeding. Updated August 20, 2007. Retrieved 2/15/08 from <http://www.acmg.net/AM/Template.cfm?Section=Home3&Template=/CM/ContentDisplay.cfm&ContentID=2263>

U.S. Food and Drug Administration (FDA). FDA News. FDA approves updated warfarin (Coumadin) prescribing information. August 16, 2007. Retrieved 2/14/08 from <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01684.html>

California Technology Assessment Forum. Use of genetic testing to guide the initiation of warfarin therapy; A Technology Assessment. Retrieved 8/7/09 from <http://www.ctaf.org/content/assessment/detail/814>

BCBSA Medical Policy Reference Manual [Electronic Version] 2.04.48, 11/13/08

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.48, 12/10/09

Langley MR, Booker JK, Evans JP et al. Validation of clinical testing for warfarin sensitivity: Comparison of CYP2C9-VKORC1 genotyping assays and warfarin-dosing algorithms. *J Mol Diagn* 2009; 11(3):216-225.

The International Warfarin Pharmacogenetics Consortium. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med* 2009; 360(8):753-64. Retrieved on September 20, 2010 from <http://www.nejm.org/doi/pdf/10.1056/NEJMoa0809329>

Kangelaris KN, Bent S, Nussbaum RL et al. Genetic testing before anticoagulation? A systematic review of pharmacogenetic dosing of warfarin. *J Gen Intern Med* 2009 Sep 16. Retrieved on September 20, 2010 from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2669873/pdf/11606_2009_Article_949.pdf

Specialty Matched Consultant Advisory Panel review 10/2010

For Corporate Medical Policy titled Pharmacogenetic Testing for Warfarin Dose

BCBSA Medical Policy Reference Manual 2.04.48, 12/09/10

American College of Chest Physicians. Antithrombotic and thrombolytic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Retrieved on September 16, 2011 from <http://www.chestnet.org/accp/guidelines/antithrombotic-and-thrombolytic-therapy-8th-edition>

Specialty Matched Consultant Advisory Panel review 10/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.48, 12/8/11

Policy Implementation/Update Information

Pharmacogenetic Testing for Warfarin Dose

For Evidence Based Guideline titled Pharmacogenetic Testing for Warfarin Dose

4/7/2008 New Evidence Based Guideline. Genotyping to determine cytochrome p450 2C9 (CYP2C9) and vitamin K epoxide reductase subunit C1 (VKORC1) genetic polymorphisms is considered 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. (adn)

5/19/08 Statement in Evidence Based Guideline deleted and replaced with the following: "Pharmacogenetic testing is not recommended for the purpose of managing the administration and dosing of warfarin." The deleted statement in the Evidence Based Guideline section was moved to the Not Recommended section. (adn)

12/7/09 Specialty Matched Consultant Advisory Panel review meeting 10/30/09. No change to policy statement. (adn)

6/22/10 Policy Guideline Number(s) removed (amw)

11/23/10 Specialty Matched Consultant Advisory Panel review 10/2010. References updated. Added code G9143 to Billing/Coding section. (mco)

For Corporate Medical Policy titled Pharmacogenetic Testing for Warfarin Dose

11/8/11 Specialty Matched Consultant Advisory Panel review. Evidence Based Guideline revised to Corporate Medical Policy. Genotyping to determine cytochrome p450 2C9 (CYP2C9) and vitamin K epoxide reductase subunit C1 (VKORC1) genetic polymorphisms is considered 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. References updated. Policy Guidelines updated. (mco)

12/30/11 CPT codes 81355 and 81227 added to "Billing/Coding" section and will be effective 1/1/2012. Policy Guidelines updated. References updated. (mco)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.