

Evidence Based Guideline

Pharmacogenetic Testing for Warfarin Dose

File Name: pharmacogenetic_testing_for_warfarin_dose
Origination: 3/2008
Last CAP Review: 10/2009
Next CAP Review: 10/2011
Last Review: 10/2009

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 simply are not enough clinical data to make this test mandatory at this time.

Evidence Based Guideline for Pharmacogenetic Testing for Warfarin Dose

Pharmacogenetic testing is not recommended for the purpose of managing the administration and dosing of warfarin.

Medical Evidence regarding Pharmacogenetic Testing for Warfarin Dose indicates

Policy: Pharmacogenetic Testing for Warfarin Dose

it is not recommended in the following situations:

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.

Prospective studies are needed to determine whether pharmacogenetic 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 pharmacogenetics on dosing accuracy, time to achieve and maintain target INR, incidence of bleeding or thromboembolic events, and monitoring requirements. At this time the precise role of pharmacogenetics is not completely clear, and further evidence on its clinical and economic utility will help define its place in individualized warfarin therapy. Since the impact of this testing on clinical outcomes (clinical utility) is not currently known, this testing is considered investigational.

Benefits Application

Please refer to certificate for availability of benefit. This guideline relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore certificate language should be reviewed before applying the terms of the policy.

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 codes: no specific code

Medical Term Definitions

International Normalized Ratio (INR)

a laboratory test that measures the time it takes for blood to clot.

pharmacodynamics

the study of the mechanisms of action of drugs and other biochemical and physiologic effects.

pharmacokinetics

the study of the movement of drugs in the body, including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion.

Scientific Background and Reference Sources

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

Policy: Pharmacogenetic Testing for Warfarin Dose

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

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

Policy Implementation/Update Information

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)

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.