The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. **Preauthorization is not required but is recommended if despite this Protocol position, you feel this service is medically necessary; supporting documentation must be submitted to Use Management.** Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

### 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 CKORC1 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 two and three 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* and *VKORC1* variants have been cleared by the U.S. Food and Drug Administration (FDA) for marketing. 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.
Corporate Medical 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.

Medicare Advantage

This service may be considered medically necessary for Medicare Advantage members, but only if enrolled in a qualifying Clinical Trial. In this case, services are covered by and billed to Original Medicare, not Medicare Advantage.

services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


61. National Coverage Determination (NCD) for Pharmacogenomic Testing for Warfarin Response (90.1).