**APPLICATION STATEMENT**

The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

**DISCLAIMER**

The Clinical Coverage Guideline (CCG) is intended to supplement certain standard WellCare benefit plans and aid in administering benefits. Federal and state law, contract language, etc. take precedence over the CCG (e.g., Centers for Medicare and Medicaid Services [CMS] National Coverage Determinations [NCDs], Local Coverage Determinations [LCDs] or other published documents). The terms of a member's particular Benefit Plan, Evidence of Coverage, Certificate of Coverage, etc., may differ significantly from this Coverage Position. For example, a member's benefit plan may contain specific exclusions related to the topic addressed in this CCG. Additionally, CCGs relate exclusively to the administration of health benefit plans and are NOT recommendations for treatment, nor should they be used as treatment guidelines. Providers are responsible for the treatment and recommendations provided to the member. The application of the CCG is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations, and any state-specific Medicaid mandates. Links are current at time of approval by the Medical Policy Committee (MPC) and are subject to change. Lines of business are also subject to change without notice and are noted on www.wellcare.com. Guidelines are also available on the site by selecting the Provider tab, then “Tools” and “Clinical Guidelines”.

**BACKGROUND**

Warfarin sodium is an orally administered anticoagulant drug that is marketed most commonly as Coumadin®. Anticoagulant drugs are sometimes referred to as blood thinners by the lay public. According to a National Center for Health Statistics (NCHS) 2007 report about the most frequently prescribed classes of drugs prescribed during ambulatory care encounters for both men and women 65 years of age or greater, use of drugs which prevent blood clot formation (anticoagulants) or increase the rate of dissolution of blood clots (thrombolytics) increased as a class during the last decade. Other studies suggest that millions of persons in the United States are on warfarin therapy at any given time.¹⁴

Warfarin affects the vitamin K-dependent clotting factors II, VII, IX and X. Warfarin is thought to interfere with clotting factor synthesis by inhibition of the C1 subunit of the vitamin K epoxide reductase (VKORC1) enzyme complex,
thereby reducing the regeneration of vitamin K1 epoxide. The elimination of warfarin is almost entirely by metabolic conversion to inactive metabolites by cytochrome P450 (CYP) enzymes in liver cells. CYP2C9 is the principal cytochrome P450 enzyme that modulates the anticoagulant activity of warfarin. From results of clinical studies, genetic variation in the CYP2C9 and/or VKORC1 genes can, in concert with clinical factors, predict how each individual responds to warfarin.5

Based on the evidence reviewed, CMS believes that the evidence is insufficient to determine that pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness improves patient oriented health outcomes related to the underlying indication for warfarin anticoagulation or adverse events related to warfarin therapy itself. In addition, CMS believes that the evidence is insufficient to determine that pharmacogenomic testing to predict warfarin responsiveness leads to changes in physician management of beneficiaries’ anticoagulation therapy that would result in positive outcomes. Thus CMS has concluded that pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness is not reasonable and necessary under section 1862(a)(1)(A) of the Act. However, CMS does believe the available evidence supports that Coverage with Evidence Development (CED) under §1862(a)(1)(E) of the Social Security Act is appropriate.1-4

The American College of Chest Physicians (ACCP) states “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)” (2008). Grades are used to determine the benefit of such therapy - Grade 1 (“we recommend”) states that benefits do or do outweigh the risks, burdens, and costs while Grade 2 (“we suggest”) takes into consideration a patient’s values may lead to different choices (p. 160S). A letter rating is given with respect to quality – high, moderate, or low (A, B or C, respectively).6

Flockhart et al. (2008) notes the position of the American College of Medical Genetics (ACMG): 7

“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.” In addition, the ACMG cites three recommendations:

- 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 be 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.

**POSITION STATEMENT**

**Applicable To:**
- ☑ Medicaid – All Markets
- ☑ Medicare – All Markets

**Exclusions**
Pharmacogenomic testing of CYP2C9 and VKORC1 alleles to predict warfarin responsiveness is considered NOT medically necessary except if the member is a Medicare member participating in a scientific study as described below:

**Coverage**
Coverage of pharmacogenomic testing of CYP2C9 and VKORC1 alleles to predict Warfarin responsiveness is considered appropriate through the Coverage with Evidence Development (CED) mechanism. Through the CED
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mechanism, testing is covered only when provided to Medicare members who are candidates for anticoagulation therapy with warfarin AND:

- Have not been previously tested for CYP2C9 or VKORC1 alleles: AND,
- Have received fewer than 5 days of Warfarin in the anticoagulation regimen for which the testing is ordered: AND,
- Are enrolled in a prospective, randomized, controlled clinical study when that study meets all standards of scientific integrity.

CODING

Institutional clinical trial claims for pharmacogenomic testing for warfarin response are identified through the presence of all of the following elements:

- Value Code D4 and 8-digit clinical trial number (when present on the claim);
- ICD-10 diagnosis code V70.7;
- Condition Code 30

Practitioner clinical trial claims for pharmacogenomic testing for warfarin response are identified through the presence of all of the following elements:

- ICD-10 diagnosis code Z00.6;
- 8-digit clinical trial number (when present on the claim);
- HCPCS modifier Q0; and,
- HCPCS code G9143

CPT® Codes – No applicable codes.

Covered HCPCS Level II ©Code
G9143 Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)

ICD-10-PCS Codes – No applicable codes.

Covered ICD-10-CM Diagnosis Codes
Primary Diagnosis Code which meets medical necessity as defined above.
Z79.01 Long term (current) use of anticoagulants

Secondary Diagnosis Codes
I26.09, I26.99 Other pulmonary embolism without acute cor pulmonale
I48.0, I48.2, I48.91 Atrial fibrillation
I74.2 -174.4 Embolism and thrombosis of arteries
I82 Other venous embolism and thrombosis
Z95.0 Presence of cardiac pacemaker
Z95.2 Presence of prosthetic heart valve
Z00.6 Encounter for examination for normal comparison and control in clinical research program

Coding information is provided for informational purposes only. The inclusion or omission of a CPT, HCPCS, or ICD-10 code does not imply member coverage or provider reimbursement. Consult the member’s benefits that are in place at time of service to determine coverage (or non-coverage) as well as applicable federal / state laws.

REFERENCES


Clinical Coverage Guideline

PHARMOCOGENOMIC TESTING FOR WARFARIN RESPONSE

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MEDICAL POLICY COMMITTEE HISTORY AND REVISIONS

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