



**PHARMCOGENOMIC TESTING
FOR WARFARIN RESPONSE
HS-130**



Harmony Behavioral Health, Inc.

Harmony Behavioral Health of Florida, Inc.

Harmony Health Plan of Illinois, Inc.

HealthEase of Florida, Inc.

*'Ohana Health Plan, a plan offered by
WellCare Health Insurance of Arizona, Inc.*

WellCare Health Insurance of Illinois, Inc.

WellCare Health Insurance of New York, Inc.

WellCare Health Plans of New Jersey, Inc.

WellCare of Florida, Inc.

WellCare of Connecticut, Inc.

WellCare of Georgia, Inc.

WellCare of Kentucky, Inc.

WellCare of Louisiana, Inc.

WellCare of New York, Inc.

WellCare of Ohio, Inc.

WellCare of Texas, Inc.

WellCare Prescription Insurance, Inc.

**Pharmacogenomic Testing
For Warfarin Response**

Policy Number: HS-130

Original Effective Date: 9/17/2009

Revised Date(s): 9/24/2010; 9/1/2011

DISCLAIMER

The Clinical Coverage Guideline is intended to supplement certain standard WellCare benefit plans. 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 Clinical Coverage Guideline. When a conflict exists between the two documents, the Member's Benefit Plan always supersedes the information contained in the Clinical Coverage Guideline. Additionally, Clinical Coverage Guidelines relate exclusively to the administration of health benefit plans and are NOT recommendations for treatment, nor should they be used as treatment guidelines. 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.

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.

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.

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.

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.

A rating of C was given by Hayes (2008) for patients starting warfarin treatment. "The patients who may benefit from pharmacogenetics-based warfarin dosing are those with venous thrombosis, pulmonary embolism, chronic atrial fibrillation, prosthetic heart valves, and those undergoing joint replacement surgery" (Hayes, 2008).

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) (Cigna, 2011).

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

POSITION STATEMENT

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 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 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 (**V70.7**) **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-9 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-9 diagnosis code V70.7;
- 8-digit clinical trial number (when present on the claim);
- HCPCS modifier Q0; and,
- HCPCS code G9143 (to be carrier-priced for claims with dates of service on and after Aug. 3, 2009, processed prior to Jan. 2011 CLFS update)

CPT® Codes - This list may not be all inclusive

- 83891** Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type; DNA or RNA
- 83894** Molecular diagnostics; separation by gel electrophoresis (e.g., agarose, polyacrylamide)
- 83896** Molecular diagnostics; nucleic acid probe, each
- 83898** Molecular diagnostics; amplification, target, each nucleic acid sequence
- 83900** Molecular diagnostics; amplification, target, each nucleic acid sequence
- 83901+** Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2
+Add on code (List separately in addition to code for primary procedure)
- 83904** Molecular diagnostics; mutation identification by sequencing, single segment, each segment
- 83908** Molecular diagnostics; amplification signal, each nucleic acid sequence
- 83909** Molecular diagnostics; separation and identification by high resolution technique, (capillary)

electrophoresis), each nucleic acid preparation

83912 Molecular diagnostics; interpretation and report

88384 Array based evaluation of multiple molecular probes; 11 through 50 probes.

88385 Array based evaluation of multiple molecular probes; 51 through 250 probes.

88386 Array based evaluation of multiple molecular probes; 251 through 500 probes.

ICD-9-CM Procedure Codes - No applicable Codes

HCPCS Level II ©Code

G9143 Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)

ICD-9-CM Diagnosis Codes - This list is not all inclusive.

V70.7 Examination of a participant in a clinical trial

415.19 Pulmonary Embolism

427.31 Atrial Fibrillation

444.21 Arterial Embolism of upper extremity

444.22 Arterial Embolism of lower extremity

453.40 Venous embolism and thrombosis of unspecified deep vessels of lower extremity

453.41 Venous embolism and thrombosis of deep vessels of proximal lower extremity

453.42 Venous embolism and thrombosis of deep vessels of distal lower extremity

453.8 Venous embolism and thrombosis of other specified veins

V43.3 Heart Valve Replacement

V45.01 Cardiac pacemaker in situ

*Current Procedural Terminology (CPT®) ©2011 American Medical Association: Chicago, IL.

REFERENCES

Peer Reviewed

1. Ansell, J., Hirsh, J., Hylek, E., Jacobson, A., Crowther, M., & Palareti, G. (2008). Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*, 133(6), 160S-198S. doi 10.1378/chest.08-0670.
2. Flockhart, D.A., O'Kane, D., Williams, M.S., Watson, M.S., Gage, B., Gandolfi, R., et al. (2008). ACMG working group on pharmacogenetic testing of CYP2C9, VKORC1 alleles for Warfarin use. *Genet Med*, 10(2):139-50.
3. Hayes Directory. (2008). CYP2C9 and VKORC1 variant testing. Retrieved from <http://www.hayesinc.com>.

Government Agencies, Professional and Medical Organizations

1. Centers for Medicare and Medicaid Services. (2010, April 5). National coverage determination for pharmacogenomic testing for Warfarin response (90.1). Retrieved from <http://www.cms.hhs.gov/mcd/search.asp>
4. Centers for Medicare and Medicaid Services. (2009, August 3). Decision memo for pharmacogenomic testing for Warfarin response (CAG-00400N). Retrieved from <http://www.cms.hhs.gov/mcd/search.asp>
5. Centers for Medicare and Medicaid Services. (2009, December 18). Medicare National Coverage Determinations; Transmittal 111, Change Request 6715 (Pub 100-03). Retrieved from <http://www.cms.hhs.gov/mcd/search.asp>
6. Centers for Medicare and Medicaid Services. (2010, January 8). Pharmacogenomic testing for Warfarin response (MM6715 rev). Retrieved from <http://www.cms.hhs.gov/mcd/search.asp>

Other

1. Cigna. (2011). Cigna Medical Coverage Policy: pharmacogenetic testing for Warfarin metabolism (Policy Number 0484). Retrieved from http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/.

HISTORY AND REVISIONS

Date	Action
12/1/2011	<ul style="list-style-type: none">• New template design approved by MPC.
9/1/2011	<ul style="list-style-type: none">• Approved by MPC.