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.

Clinical Coverage Guideline

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.14

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

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** – No applicable codes.

**Covered HCPCS Level II ®Code**

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

**ICD-9-CM Procedure Codes** – No applicable codes.

**2015 ICD-10-PCS Codes** – No applicable codes.

**Covered ICD-9-CM Diagnosis Codes**

- **Primary Diagnosis Code which meets medical necessity as defined above.**
  - V70.7 Examination of a participant in a clinical trial
Secondary Diagnosis Codes
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
453.81-453.9 Venous embolism and thrombosis of other specified veins
V43.3 Heart Valve Replacement
V45.01 Cardiac pacemaker in situ

Covered 2015 ICD-10-CM Diagnosis Codes
Primary Diagnosis Code which meets medical necessity as defined above.
Z00.6 Encounter for examination for normal comparison and control in clinical research program

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


REFERENCES

MEDICAL POLICY COMMITTEE HISTORY AND REVISIONS

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<tr>
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