CMS Manual System	Department of Health & Human Services (CMS)
Pub 100-03 Medicare National Coverage Determinations	Centers for Medicare & Medicaid Services (DHHS)
Transmittal 111	Date: December 18, 2009
	Change Request 6715

SUBJECT: PharmacogenomicTesting for Warfarin Response

I. SUMMARY OF CHANGES: There has been considerable public interest in the use of pharmacogenomic testing to predict a patient's response to warfarin, 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. Pharmacogenomics is the study of how an individual's genetic makeup, or genotype, affects the body's response to drugs. It is an examination of the inherited components and variations in genes that dictate drug/medication response. Pharmacogenomics explores the ways these variations can be used to try to predict whether a patient will have a good response to a drug, a bad response, or no response at all. It is claimed that genetic variability in the CYP2C9 and/or VKORC1genes, in combination with many other factors, may partially predict a patient's response to warfarin.
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NEW / REVISED MATERIAL
EFFECTIVE DATE: AUGUST 3, 2009
IMPLEMENTATION DATE: APRIL 5, 2010

Disclaimer for manual changes only: The revision date and transmittal number apply only to red italicized material. Any other material was previously published and remains unchanged. However, if this revision contains a table of contents, you will receive the new/revised information only, and not the entire table of contents.

II. CHANGES IN MANUAL INSTRUCTIONS: (N/A if manual is not updated)
R=REVISED, N=NEW, D=DELETED

R/N/D	CHAPTER / SECTION / SUBSECTION / TITLE
R	1/Table of Contents
N	1/90.1/Pharmacogenomic Testing to Predict Warfarin Responsiveness (Effective August 3, 2009)

III. FUNDING:

SECTION A: For Fiscal Intermediaries and Carriers:
No additional funding will be provided by CMS; contractor activities are to be carried out within their operating budgets.

SECTION B: For Medicare Administrative Contractors (MACs):
The Medicare Administrative Contractor is hereby advised that this constitutes technical direction as defined in your contract. CMS does not construe this as a change to the MAC Statement of Work. The contractor is not obligated to incur costs in excess of the amounts allotted in your contract unless and until specifically authorized by the contracting officer. If the contractor considers anything provided, as described above, to be outside the current scope of work, the contractor shall withhold performance on the part(s) in question

and immediately notify the contracting officer, in writing or by e-mail, and request formal directions regarding continued performance requirements.

IV. ATTACHMENTS:

Business Requirements
Manual Instruction

Unless otherwise specified, the effective date is the date of service.

Attachment - Business Requirements

Pub. 100-03	Transmittal: 111	Date: December 18, 2009	Change Request: 6715

SUBJECT: PharmacogenomicTesting for Warfarin Response

EFFECTIVE DATE: AUGUST 3, 2009

IMPLEMENTATION DATE: APRIL 5, 2010

I. GENERAL INFORMATION

A. Background: There has been considerable public interest in the use of pharmacogenomic testing to predict a patient's response to warfarin, 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. Pharmacogenomics is the study of how an individual's genetic makeup, or genotype, affects the body's response to drugs. It is an examination of the inherited components and variations in genes that dictate drug/medication response. Pharmacogenomics explores the ways these variations can be used to try to predict whether a patient will have a good response to a drug, a bad response, or no response at all. It is claimed that genetic variability in the CYP2C9 and/or VKORC1genes, in combination with many other factors, may partially predict a patient's response to warfarin.

On August 4, 2008, The Centers for Medicare & Medicaid Services (CMS) opened a National Coverage Analysis to determine if the use of pharmacogenomic testing for warfarin responsiveness is reasonable and necessary under the Medicare program. On August 3, 2009, CMS issued a final decision stating that the available evidence does not demonstrate that pharmacogenomic testing to predict warfarin responsiveness improves health outcomes in Medicare beneficiaries. However, the decision further states that the available evidence does support pharmacogenomic testing for warfarin responsiveness under coverage with evidence development (CED).

B. Policy: Effective August 3, 2009, pharmacogenomic testing to predict warfarin responsiveness is covered only when provided to Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin; 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 only then in the context of a prospective, randomized, controlled clinical study when that study meets certain criteria as outlined in Pub 100-03, section 90.1, of the NCD Manual.

NOTE: A new temporary HCPCS Level II code effective August 3, 2009, G9143, warfarin responsiveness testing by genetic technique using any method, any number of specimen(s), was developed to enable implementation of CED for this purpose. This is a once-in-a-lifetime test absent any reason to believe that the patient’s personal genetic characteristics would change over time.

NOTE: 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) - Refer to Transmittal 310, Change Request 5790, dated January 18, 2008;
- ICD-9 diagnosis code V70.7 - Refer to Transmittal 310, Change Request 5790, dated January 18, 2008;
- Condition Code 30 - Refer to Transmittal 310, Change Request 5790, dated January 18, 2008;
- HCPCS modifier Q0: outpatient claims only - Refer to Transmittal 1418, Change Request 5805, dated January 18, 2008; and,

- HCPCS code G9143 (mandatory with the April 2010 Integrated Outpatient Code Editor and the January 2011 clinical laboratory fee schedule (CLFS) updates. Prior to these times, any trials should bill FIs for this test as they currently do absent these instructions, and the FIs should process and pay those claims accordingly.)

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 or after August 3, 2009, that are processed prior to the January 2011 CLFS update).

II. BUSINESS REQUIREMENTS TABLE

Use"Shall" to denote a mandatory requirement

Number	Requirement	Responsibility (place an "X" in each applicable column)									
		A/B MAC	DME MAC	FI	CARRIER	RHHI	Shared-System Maintainers				OTHER
							FISS	MCS	VMS	CWF	
6715.1	Effective for claims with dates of service on and after August 3, 2009, contractors shall cover pharmacogenomic testing to predict warfarin responsiveness only in the context of an approved, clinical study, in addition to the coverage criteria outlined in Pub 100-03, section 90.1, of the NCD Manual and chapter 32, section 240, Medicare Claims Processing Manual.	X		X	X						

III. PROVIDER EDUCATION TABLE

Number	Requirement	Responsibility (place an "X" in each applicable column)									
		A/B MAC	DME MAC	FI	CARRIER	RHHI	Shared-System Maintainers				OTHER
							FISS	MCS	VMS	CWF	
6715.2	A provider education article related to this instruction will be available at http://www.cms.hhs.gov/MLNMattersArticles/ shortly after the CR is released. You will receive notification of the article release via the established "MLN Matters" listserv. Contractors shall post this article, or a direct link to this article, on their Web site and include information about it in a listserv message within one week of the availability of the provider education article. In addition, the provider education article shall be included in your next regularly	X		X	X						

Number	Requirement	Responsibility (place an "X" in each applicable column)									
		A/B MAC	DME MAC	FI	CARRIER	RHHI	Shared-System Maintainers				OTHER
							FISS	MCS	VMS	CWF	
	scheduled bulletin. Contractors are free to supplement MLN Matters articles with localized information that would benefit their provider community in billing and administering the Medicare program correctly.										

IV. SUPPORTING INFORMATION

Section A: For any recommendations and supporting information associated with listed requirements: ***Use "Should" to denote a recommendation.***

X-Ref Requirement Number	Recommendations or other supporting information:

Section B: For all other recommendations and supporting information: N/A

V. CONTACTS

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Post-Implementation Contact(s): Regional offices

VI. FUNDING

Section A: For *Fiscal Intermediaries (FIs), Regional Home Health Intermediaries (RHHIs),* and/or *Carriers*:

No additional funding will be provided by CMS; contractor activities are to be carried out within their operating budgets.

Section B: *For Medicare Administrative Contractors (MACs)*:

The Medicare Administrative Contractor is hereby advised that this constitutes technical direction as defined in your contract. CMS does not construe this as a change to the MAC Statement of Work. The contractor is not obligated to incur costs in excess of the amounts allotted in your contract unless and until specifically authorized by the contracting officer. If the contractor considers anything provided, as described above, to be outside the current scope of work, the contractor shall withhold performance on the part(s) in question and immediately notify the contracting officer, in writing or by e-mail, and request formal directions regarding continued performance requirements.

Medicare National Coverage Determinations Manual

Chapter 1, Part 2 (Sections 90 – 160.26)
Coverage Determinations

Table of Contents
(Rev.111, 12-18-09)

90.1 – Pharmacogenomic Testing to Predict Warfarin Responsiveness (Effective August 3, 2009)

90.1 - Pharmacogenomic Testing to Predict Warfarin Responsiveness (Effective August 3, 2009)

(Rev.111, Issued: 12-18-09, Effective: 08-03-09, Implementation: 04-05-10)

A. General

Warfarin sodium is an orally administered anticoagulant drug that is marketed most commonly as Coumadin®. (The Food and Drug Administration (FDA) approved labeling for Coumadin® includes a Black Box Warning dating back to 2007.) Anticoagulant drugs are sometimes referred to as blood thinners by the lay public. 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*

Pharmacogenomics denotes the study of how an individual's genetic makeup, or genotype, affects the body's response to drugs. Pharmacogenomics as a science examines associations among variations in genes with individual responses to a drug or medication. In application, pharmacogenomic results (i.e., information on the patient's genetic variations) can contribute to predicting a patient's response to a given drug: good, bad, or none at all. Pharmacogenomic testing of CYP2C9 *or* VKORC1 *alleles to predict a patient's response to warfarin occurs ideally prior to initiation of the drug. This would be an once-in-a-lifetime test, absent any reason to believe that the patient's personal genetic characteristics would change over time. Although such pharmacogenomic testing would be used to attempt to better approximate the best starting dose of warfarin, it would not eliminate the need for periodic PT/INR testing, a standard diagnostic test for coagulation activity and for assessing how a patient is reacting to a warfarin dose.*

Nationally Covered Indications

Effective August 3, 2009, the Centers for Medicare & Medicaid Services (CMS) believes that the available evidence supports that coverage with evidence development (CED) under §1862(a)(1)(E) of the Social Security Act (the Act) is appropriate for pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness by any method, and is therefore covered only when provided to Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin who:

1. *Have not been previously tested for CYP2C9 or VKORC1 alleles; and*
2. *Have received fewer than five days of warfarin in the anticoagulation regimen for which the testing is ordered; and*
3. *Are enrolled in a prospective, randomized, controlled clinical study when that study meets the following standards.*

A clinical study seeking Medicare payment for pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness provided to the Medicare beneficiary who is a candidate for anticoagulation therapy with warfarin pursuant to CED must address one or more aspects of the following question:

Prospectively, in Medicare-aged subjects whose warfarin therapy management includes pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin response, what is the frequency and severity of the following outcomes, compared to subjects whose warfarin therapy management does not include pharmacogenomic testing?

- *Major hemorrhage*
- *Minor hemorrhage*
- *Thromboembolism related to the primary indication for anticoagulation*
- *Other thromboembolic event*
- *Mortality*

The study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.

b. The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.

c. The research study does not unjustifiably duplicate existing studies.

d. The research study design is appropriate to answer the research question being asked in the study.

e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.

f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the FDA, it also must be in compliance with 21 CFR Parts 50 and 56.

g. All aspects of the research study are conducted according to the appropriate standards of scientific integrity.

h. The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.

i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life-threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.

j. The clinical research study is registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.

k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. However, a full report of the outcomes must be made public no later than 3 years after the end of data collection.

l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

B. Nationally Non-Covered Indications

The CMS believes that the available evidence does not demonstrate that pharmacogenomic testing of CYP2C9 *or* VKORC1 *alleles to predict warfarin responsiveness improves health outcomes in Medicare beneficiaries outside the context of CED, and is therefore not reasonable and necessary under §1862(a)(1)(A) of the Act.*

C. Other

This NCD does not determine coverage to identify CYP2C9 or VKORC1 alleles for other purposes, nor does it determine national coverage to identify other alleles to predict warfarin responsiveness.

(This NCD last reviewed August 2009.)