

# Pharmacogenomic Testing for Warfarin Response (NCD 90.1)

<b>Policy Number</b>	90.1	<b>Approved By</b>	UnitedHealthcare Medicare Reimbursement Policy Committee	<b>Current Approval Date</b>	01/08/2014
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### IMPORTANT NOTE ABOUT THIS REIMBURSEMENT POLICY

This policy is applicable to UnitedHealthcare Medicare Advantage Plans offered by UnitedHealthcare and its affiliates.

You are responsible for submission of accurate claims. This reimbursement policy is intended to ensure that you are reimbursed based on the code or codes that correctly describe the health care services provided. UnitedHealthcare reimbursement policies use Current Procedural Terminology (CPT®\*), Centers for Medicare and Medicaid Services (CMS), or other coding guidelines. References to CPT or other sources are for definitional purposes only and do not imply any right to reimbursement.

This reimbursement policy applies to all health care services billed on CMS 1500 forms and, when specified, to those billed on UB04 forms (CMS 1450). Coding methodology, industry-standard reimbursement logic, regulatory requirements, benefits design and other factors are considered in developing reimbursement policy. This information is intended to serve only as a general resource regarding UnitedHealthcare’s reimbursement policy for the services described and is not intended to address every aspect of a reimbursement situation. Accordingly, UnitedHealthcare may use reasonable discretion in interpreting and applying this policy to health care services provided in a particular case. Further, the policy does not address all issues related to reimbursement for health care services provided to UnitedHealthcare enrollees. Other factors affecting reimbursement may supplement, modify or, in some cases, supersede this policy. These factors may include, but are not limited to: legislative mandates, the physician or other provider contracts, and/or the enrollee’s benefit coverage documents. Finally, this policy may not be implemented exactly the same way on the different electronic claims processing systems used by UnitedHealthcare due to programming or other constraints; however, UnitedHealthcare strives to minimize these variations.

UnitedHealthcare may modify this reimbursement policy at any time by publishing a new version of the policy on this Website. However, the information presented in this policy is accurate and current as of the date of publication.

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**Application**  
This reimbursement policy applies to services reported using the Health Insurance Claim Form CMS-1500 or its

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electronic equivalent or its successor form, and services reported using facility claim form CMS-1450 or its electronic equivalent or its successor form. This policy applies to all products, all network and non-network physicians, and other health care professionals.

The HCPCS/CPT code(s) may be subject to Correct Coding Initiative (CCI) edits. This policy does not take precedence over CCI edits. Please refer to the CCI for correct coding guidelines and specific applicable code combinations prior to billing UnitedHealthcare. It is not enough to link the procedure code to a correct, payable ICD-9-CM diagnosis code. The diagnosis must be present for the procedure to be paid. Compliance with the provisions in this policy is subject to monitoring by pre-payment review and/or post-payment data analysis and subsequent medical review. The effective date of changes/additions/deletions to this policy is the committee meeting date unless otherwise indicated. CPT codes and descriptions are copyright 2010 American Medical Association (or such other date of publication of CPT). All rights reserved. CPT is a registered trademark of the American Medical Association. Applicable FARS/DFARS restrictions apply to Government use. Fee schedules, relative value units, conversion factors, and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Current Dental Terminology (CDT), including procedure codes, nomenclature, descriptors, and other data contained therein, is copyright by the American Dental Association, 2002, 2004. All rights reserved. CDT is a registered trademark of the American Dental Association. Applicable FARS/DFARS apply.

### Summary

#### Overview

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.

#### Reimbursement Guidelines

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

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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](http://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

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clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

### 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.

### 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.

### CPT/HCPCS Codes

Code	Description
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6) (Not appropriate to use these codes per NCD)
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (eg, -1639/3673) (Not appropriate to use these codes per NCD)
G9143	Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)

### Modifiers

Code	Description
Q0	Investigational clinical service provided in a clinical research study that is in an approved clinical research study
Q1	Routine clinical service provided in a clinical research study that is in an approved clinical research study

### Condition Codes

Code	Description
30	Qualifying Clinical Trial

### Questions and Answers

1	<b>Q:</b>	What is the correct code to bill for pharmacogenomic testing for warfarin response?
	<b>A:</b>	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.

### References Included (but not limited to):

#### CMS NCD

NCD 90.1 Pharmacogenomic Testing for Warfarin Response

#### CMS LCD(s)

Numerous LCDs

#### CMS Claims Processing Manual

Chapter 32; § 250-250.3 Pharmacogenomic Testing for Warfarin Response

#### CMS Transmittals

Transmittal 111, Change Request 6715, Dated 12/18/2009 (Pharmacogenomic Testing for Warfarin Response)

Transmittal 310, Change Request 5790, Dated 01/18/2008 (Requirements for Including an 8-Digit Clinical Trial Number on Claims)

Transmittal 1418, Change Request 5805, Dated 2008 (New HCPCS Modifiers when Billing for Patient Care in Clinical Research Studies)

Transmittal 1880, Change Request 6715, Dated 12/18/2009 (Pharmacogenomic Testing for Warfarin Response)

Transmittal 1889, Change Request 6715, Dated 01/08/2010 (Pharmacogenomic Testing for Warfarin Response)

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### UnitedHealthcare Medicare Advantage Coverage Summaries

Laboratory Tests and Services

### UnitedHealthcare Reimbursement Policies

Molecular Pathology/Molecular Diagnostics/Genetic Testing

### MLN Matters

Article MM5790, Use of an 8-Digit Registry Number on Clinical Trial Claims

Article MM8401, Mandatory Reporting of an 8-Digit Clinical Trial Number on Claims

Article SE1344, Further Information on Mandatory Reporting of an 8-Digit Clinical Trial Number on Claims

### Others

Provider Inquiry Assistance, Pharmacogenomic Testing for Warfarin Response – JA6715, CMS Website

### History

Date	Revisions
01/08/2014	Annual review, added CPT codes 81227 and 81355
11/06/2013	Administrative Updates
08/14/2013	No change