

Pharmacogenomic Testing for Warfarin Response (NCD 90.1)

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[↪ Terms and Conditions](#)

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Related Medicare Advantage Policy Guidelines
<ul style="list-style-type: none"> Clinical Diagnostic Laboratory Services Molecular Pathology/Molecular Diagnostics/Genetic Testing
Related Medicare Advantage Coverage Summaries
<ul style="list-style-type: none"> Laboratory Tests and Services Genetic Testing

Policy Summary

[↪ See Purpose](#)

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.) 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. Anticoagulant drugs are sometimes referred to as blood thinners.

Pharmacogenomics is 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.

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.

Guidelines

Nationally Covered Indications

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:

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

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
- Other thromboembolic event
- Mortality
- Thromboembolism related to the primary indication for anticoagulation

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

- The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
- 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.
- All aspects of the research study are conducted according to the appropriate standards of scientific integrity. d. The research study design is appropriate to answer the research question being asked in the study.
- The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
- 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.
- The research study does not unjustifiably duplicate existing studies.
- The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.
- 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.
- 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.
- 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.
- 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.
- 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.

Nationally Non - Covered Indications

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.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this guideline does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

Coding Clarification: CMS, as part of the national coverage determination (NCD) may determine coverage of an item or service only in the context of a clinical study. The clinical trial identifier number is required for all items/services provided in relation to participation in a clinical trial, clinical study, or registry that may result from coverage with evidence development (CED).

Specifically, include the clinical trial identifier number if:

- The beneficiary is enrolled in an approved clinical trial; and
- The claim is for the investigational item or service, and/or,
- The costs are related to the investigational item or service, and/or
- The costs are related to routine care for the condition in the clinical trial.

See the related MLN Matters.

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

Modifier	Description
CED Only	
Q0	Investigational clinical service provided in a clinical research

Condition Code	Description
CED Only	
30	Qualifying clinical trial

Diagnosis Code	Description
CED Only	
Z00.6	Encounter for examination for normal comparison and control in clinical research program (In any position)
Z79.01	Long term (current) use of anticoagulants

Questions and Answers

1	Q:	Have you verified the CPT/HCPCS code(s) on your claim may have limited coverage under CED (Coverage with Evidence Development)?
	A:	<ul style="list-style-type: none"> If no, clinical trial number, modifier Q0 and diagnosis code Z00.6 and Z79.01 should not be submitted. If yes, the three requirements listed above are required. Claims without the required information will be denied.

References

CMS National Coverage Determinations (NCDs)

[NCD 90.1 Pharmacogenomic Testing for Warfarin Response](#)

CMS Local Coverage Determinations (LCDs) and Articles

LCD	Article	Contractor	Medicare Part A	Medicare Part B
N/A	A53848 NCD - Pharmacogenomic Testing for Warfarin Response	First Coast	FL, PR, VI	FL, PR, VI
L35000 Molecular Pathology Procedures	A56199 Billing and Coding: Molecular Pathology Procedures	NGS	CT, IL, MA, ME, MN, NH, NY, RI, VT	CT, IL, MA, ME, MN, NH, NY, RI, VT
L36310 MoIDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing Retired 08/16/2020	<p>A55179 Billing and Coding MoIDX: CYP2C9 and/or VKORC1 Gene Testing for Warfarin Response Retired 11/04/2020</p> <p>A57378 Billing and Coding: MoIDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing Retired 08/16/2020</p>	Noridian	AS, CA, GU, HI, MP, NV	AS, CA, GU, HI, MP, NV
L36312 MoIDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing Retired 08/16/2020	<p>A55180 Billing and Coding: MoIDX: CYP2C9 and/or VKORC1 Gene Testing for Warfarin Response Guidelines Retired 11/04/2020</p> <p>A57522 Billing and Coding: MoIDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing Retired 08/16/2020</p>	Noridian	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY
N/A	A53524 Billing and Coding: MoIDX: CYP2C9 and/or VKORC1 Gene Testing for Warfarin Response Retired 08/10/2020	Palmetto	AL, GA, NC, SC, TN, VA, WV	AL, GA, NC, SC, TN, VA, WV
N/A	A54687 Billing and Coding: MoIDX: CYP2C9 and/or VKORC1 Gene Testing for Warfarin Response Retired 08/10/2020	CGS	KY, OH	KY, OH

LCD	Article	Contractor	Medicare Part A	Medicare Part B
L36398 MoIDX: Genetic Testing for CYP2C19, CYP2D6, CYP2C9, and VKORC1 Retired 08/10/2020	A55532 Billing and Coding: MoIDX: CYP2C9 and/or VKORC1 Gene Testing for Warfarin Response Retired 08/10/2020	WPS	AK, AL, AR, AZ, CT, FL, GA, IA, ID, IL, IN, KS, KY, LA, MA, ME, MI, MN, MO, MS, MT, NC, NE, NH, NJ, OH, OR, RI, SC, SD, TN, UT, VA, VI, VT, WA, WI, WV, WY	IA, IN, MI, MO, NE
L35332 MoIDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing Retired 07/25/2020	A56864 Billing and Coding: MoIDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing Retired 07/25/2020	CGS	KY, OH	KY, OH
L35072 MoIDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing Retired 07/25/2020	A56842 Billing and Coding: MoIDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing Retired 07/25/2020	Palmetto	NC, SC, VA, WV	NC, SC, VA, WV
L36398 MoIDX: Genetic Testing for CYP2C19, CYP2D6, CYP2C9, and VKORC1 Retired 07/25/2020	A57717 Billing and Coding: MoIDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing Retired 07/25/2020	WPS	AK, AL, AR, AZ, CT, FL, GA, IA, ID, IL, IN, KS, KY, LA, MA, ME, MI, MN, MO, MS, MT, NC, NE, NH, NJ, OH, OR, RI, SC, SD, TN, UT, VA, VI, VT, WA, WI, WV, WY	IA, IN, MI, MO, NE

CMS Claims Processing Manual

[Chapter 32: § 250 - 250.3 Pharmacogenomic Testing for Warfarin Response](#)

CMS Transmittal(s)

[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 1165, Change Request 8109, Dated 01/18/2013 \(International Classification of Diseases \(ICD\) - 10 Conversion from ICD - 9 and Related Code Infrastructure of the Medicare Shared Systems as They Relate to CMS National Coverage Determinations \(NCDs\) \(CR\)\)](#)

[Transmittal 1418, Change Request 5805, Dated 01/18/2008 \(New HCPCS Modifiers when Billing for Patient Care in Clinical Research Studies\)](#)

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

[Transmittal 1658, Change Request 9540, Dated 04/29/2016 \(Coding Revisions to National Coverage Determinations\)](#)

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](#)

[Article MM9540, Coding Revisions to National Coverage Determinations](#)

Other(s)

[Coverage with Evidence Development, Pharmacogenomic Testing For Warfaring Response, CMS Website](#)
[Provider Inquiry Assistance, Pharmacogenomic Testing for Warfarin Response - JA6715, CMS Website](#)

Guideline History/Revision Information

Revisions to this summary document do not in any way modify the requirement that services be provided and documented in accordance with the Medicare guidelines in effect on the date of service in question.

Date	Summary of Changes
04/01/2021	Template Update <ul style="list-style-type: none">Reformatted policy; transferred content to new template
01/13/2021	Supporting Information <ul style="list-style-type: none">Updated <i>References</i> section to reflect the most current information; no change to guidelinesArchived previous policy version MPG244.05

Purpose

The Medicare Advantage Policy Guideline documents are generally used to support UnitedHealthcare Medicare Advantage claims processing activities and facilitate providers' submission of accurate claims for the specified services. The document can be used as a guide to help determine applicable:

- Medicare coding or billing requirements, and/or
- Medical necessity coverage guidelines; including documentation requirements.

UnitedHealthcare follows Medicare guidelines such as NCDs, LCDs, LCAs, and other Medicare manuals for the purposes of determining coverage. It is expected providers retain or have access to appropriate documentation when requested to support coverage. Please utilize the links in the [References](#) section below to view the Medicare source materials used to develop this resource document. This document is not a replacement for the Medicare source materials that outline Medicare coverage requirements. Where there is a conflict between this document and Medicare source materials, the Medicare source materials will apply.

Terms and Conditions

The Medicare Advantage Policy Guidelines are applicable to UnitedHealthcare Medicare Advantage Plans offered by UnitedHealthcare and its affiliates.

These Policy Guidelines are provided for informational purposes, and do not constitute medical advice. Treating physicians and healthcare providers are solely responsible for determining what care to provide to their patients. Members should always consult their physician before making any decisions about medical care.

Benefit coverage for health services is determined by the member specific benefit plan document* and applicable laws that may require coverage for a specific service. The member specific benefit plan document identifies which services are covered, which are excluded, and which are subject to limitations. In the event of a conflict, the member specific benefit plan document supersedes the Medicare Advantage Policy Guidelines.

Medicare Advantage Policy Guidelines are developed as needed, are regularly reviewed and updated, and are subject to change. They represent a portion of the resources used to support UnitedHealthcare coverage decision making. UnitedHealthcare may modify these Policy Guidelines at any time by publishing a new version of the policy on this website. Medicare source materials used to develop these guidelines include, but are not limited to, CMS National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), Medicare Benefit Policy Manual, Medicare Claims Processing Manual, Medicare Program Integrity Manual, Medicare Managed Care Manual, etc. The information presented in the Medicare Advantage Policy Guidelines is believed to be accurate and current as of the date of publication and is provided on an "AS IS"

basis. Where there is a conflict between this document and Medicare source materials, the Medicare source materials will apply.

You are responsible for submission of accurate claims. Medicare Advantage Policy Guidelines are intended to ensure that coverage decisions are made accurately based on the code or codes that correctly describe the health care services provided. UnitedHealthcare Medicare Advantage Policy Guidelines 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 or guarantee claims payment.

Medicare Advantage Policy Guidelines are the property of UnitedHealthcare. Unauthorized copying, use, and distribution of this information are strictly prohibited.

*For more information on a specific member's benefit coverage, please call the customer service number on the back of the member ID card or refer to the [Administrative Guide](#).