Decision Memo for Pharmacogenomic Testing for Warfarin Response (CAG-00400N)

Decision Summary

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. Therefore, we have determined that pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act. However, we do believe the available evidence supports that Coverage with Evidence Development (CED) under §1862(a)(1)(E) of the Social Security Act is appropriate. Thus, we are making the following decision:

Pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness is 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 Coverage with Evidence Development (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 Food and Drug Administration (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 three (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 Social Security Act (the Act), the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that the Centers for Medicare and Medicaid Services (CMS) determines meet the above-listed standards and address the above-listed research questions.

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Decision Memo

TO: Administrative File: 00400N

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SUBJECT: Decision Memorandum for Pharmacogenomic Testing to Predict Warfarin Responsiveness

DATE: August 3, 2009

I. Decision

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II. 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.

Notes on Terminology

Although some authors use the term warfarin sensitivity to describe the patient's degree of response to warfarin administration, we have chosen to use the terms response or responsiveness in this decision memorandum unless citing the work of others. We believe that this will minimize the likelihood that a reader may interpret the term warfarin sensitivity to connote an allergic reaction or some other immune-mediated response to warfarin.

Italicized abbreviations for gene names (e.g., the gene *VKORC1*) represent genes rather than their products (e.g., the enzyme VKORC1). The meanings of other non-italicized abbreviations (e.g., NCHS for the National Center for Health Statistics) will usually be clear in context. However, in quoted text from referenced sources, the use of italicization reflects usage in the original source document unless noted otherwise. Clotting factors are customarily named with Roman numerals and trailing small case letters, e.g. 'Factor Xa' refers to the activated form of plasma coagulation factor X. As suggested by NIH educational materials, we consider the term 'allele' to indicate one of the variant forms of a gene (http://ghr.nlm.nih.gov/glossary=allele).

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.

Warfarin Action and Metabolism

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 (see below under "Evidence"). A few studies have investigated possible influences on warfarin metabolism due to other genetic variants (for example, those in *CYP4F2*).

Scope of this Decision

The new science of pharmacogenomic testing continues to evolve, and we are mindful that researchers may discover more associations between warfarin responsiveness and heritable factors and develop test strategies other than those for *CYP2C9* and *VKORC1*. We also consider that *CYP2C9* and *VKORC1* may in the future be found to be relevant to the human response to other intrinsic or extrinsic agents. Thus we are explicitly describing the scope of this decision without intending to establish a precedent for the scope of future decisions.

This decision determines national coverage (as explained below) for pharmacogenomic testing by any method to identify *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness. It does not determine national coverage to identify *CYP2C9* or *VKORC1* alleles for other purposes, not does it determine national coverage to identify other alleles to predict warfarin responsiveness.

Therapeutic Use of Warfarin Anticoagulation

Retrospective studies of patients on warfarin indicate that the common indications for anticoagulation with warfarin include atrial fibrillation, venous thromboembolism, valvular heart disease, cerebrovascular disease and vascular prostheses including cardiac valve replacements (Oake 2008). The risk of thromboembolism due to atrial fibrillation increases with concomitant risk factors such as age over 65 years, diabetes, hypertension and congestive heart failure. The desired intensity or degree of anticoagulation will differ based on the specific indication and other factors. Patients at higher risk for forming thrombi, e.g. individuals with mechanical heart valves, may require a higher degree of anticoagulation.

The duration of anticoagulation therapy varies with the underlying indication and with the patient's response to therapy. Some acute conditions such as deep venous thrombosis generally require anticoagulation for only a period of a few months, while chronic conditions require long-term and possibly life-long anticoagulation. These chronic conditions, e.g. atrial fibrillation and stroke, are more common in the Medicare aged population than in younger populations. Older patients compared to younger patients generally have multiple comorbid conditions for which they take drugs of various classes known to interact with warfarin.

Alternatives to warfarin anticoagulation use in specific clinical situations are described in published review articles. Brotman discusses anticoagulation for hospitalized patients with risk factors for venous thromboembolism, including the therapeutic choices of vitamin K antagonists such as warfarin, heparin and related agents, and newer anticoagulants such as fondaparinux, a pentasaccharide inhibitor of coagulation factor Xa (Brotman 2008). It is not unreasonable to anticipate that warfarin-based anticoagulation will eventually disappear from common use as newer agents with better safety profiles become available.

Pharmacogenomic Testing

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. The recognized clinical goals of such testing fall generally into one of the following categories:

- To guide warfarin dosing in patients who are committed to anticoagulation therapy as treatment for an acute event; and
- To encourage physicians to initiate elective warfarin therapy in patients with certain chronic conditions, who are thought to be at higher risk of adverse events related to anticoagulation.

Patients in the first category are anticoagulated urgently, often in response to a thromboembolic event such as a pulmonary embolus. Patients in the latter category are more likely to have a chronic cardiac dysrhythmia such as atrial fibrillation where anticoagulation is initiated with the hope of avoiding a stroke.

Turnaround time for pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles, i.e. the elapsed time from ordering the test to the receipt of the results by the physician, may vary due to a number of factors such as the patient's location, the laboratory's location, delivery of the specimen to the laboratory, the laboratory's internal processes to prepare the specimen and perform the test, and the communication of the results to the treating physician. Advertised times to return results to the physician after receipt of the specimen range from 2 – 10 days.

Titration of Warfarin During Initiation of Therapy/determinationprocess/downloads/ Warfarin has a narrow therapeutic window, meaning that there is a small difference in dosage (at times, less than one milligram of warfarin per day) between dosing that is too little, just right, or too much. Standard clinical practice for warfarin titration requires periodic testing of its anticoagulant effect. This is assessed with the prothrombin time (PT) and the International Normalized Ratio (INR). In the PT/INR test, the ratio of the patient's PT to the mean PT for a group of normal individuals is calculated, and that ratio is then raised to a power which adjusts for differences among different types of reagents used in the test procedure. Commonly, the PT/INR is assessed frequently during the first few weeks or months while warfarin therapy is begun, and after that, less frequently when the patient demonstrates a stable response. More frequent testing may be required if the patient exhibits signs of over- or under-treatment or if the patient begins (or stops) taking another drug that is recognized to affect warfarin action or metabolism.

The Food and Drug Administration approved labeling for Coumadin® (warfarin sodium tablets) includes the following Black Box warning (FDA 2007).

WARNING: BLEEDING RISK Warfarin sodium can cause major or fatal bleeding. Bleeding is more likely to occur during the starting period and with a higher dose (resulting in a higher INR). Risk factors for bleeding include high intensity of anticoagulation (INR > 4.0), age ≥ 65, highly variable PT/INR results, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs (see **PRECAUTIONS**) and long duration of warfarin therapy. Regular monitoring of PT/INR should be performed on all treated patients. Those at high risk of bleeding may benefit from more frequent PT/INR monitoring, careful dose adjustment to desired PT/INR, and a shorter duration of therapy. Patients should be instructed about prevention measures to minimize risk of bleeding and to report immediately to physicians signs and symptoms of bleeding (see **PRECAUTIONS**: **Information for Patients**).

As the FDA notes in the body of the prescribing information, PT/INR is a standard diagnostic test for coagulation activity and for assessing how the patient is reacting to the warfarin dose.

Benefits and Adverse Effects of Warfarin Therapy

The evidence of the benefit of warfarin therapy for certain indications is well-established. According to a published meta-analysis of anti-thrombotic therapy for stroke prevention, patients with non-valvular atrial fibrillation on adjusted-dose warfarin therapy were observed to have a reduced stroke risk of 64% in comparison to placebo (Hart 2007). This meta-analysis also showed that overall deaths in trial participants on warfarin compared to the control group were decreased by 26% (110 deaths in the warfarin-treated group compared to 143 deaths in the control group).

A review of evidence about bleeding complications during various types of anticoagulant therapy summarized major determinants of bleeding in patients receiving warfarin (Levine 2004). Some of the relevant findings included:

- Multiple randomized trials in patients with atrial fibrillation showed that the annual risk of major bleeding averaged 1.3% in patients randomly assigned to warfarin therapy with a therapeutic target range for INR of 2 – 3, compared to 1% annual risk among placebo-treated controls;
- Patient age was found to be an independent risk factor for major bleeding. Major bleeding events occur at an annual rate of 5.1% among those greater than 75 years of age, as compared to a 1% annual rate among younger patients; and
- Bleeding was a more frequent complication in the first month following initiation of warfarin therapy.
- In clinical trials involving patients with deep vein thrombosis, atrial fibrillation, replacement of heart valves, or ischemic stroke, the frequency of major bleeding in patients randomly assigned to warfarin therapy targeted to reach an INR range of 2 – 3 was less than half of the frequency of bleeding in patients randomly assigned to a therapeutic range of INR > 3. Risk of intracranial hemorrhage was especially increased in patients with an INR > 4, with bleeding risk roughly doubling with each addition unit increase in INR above 3;

An observational study followed a cohort of 472 patients with atrial fibrillation after warfarin initiation with at least one year of follow-up and compared outcomes and changes in therapy for two groups: an older group of 153 patients 80 years of age or older (mean age of 84 years, range from 80-97 years, 55% female) and a younger group of 319 patients less than 80 years of age (mean age 73 years, range from 65-79 years, 43% female) (Hylek 2007). The study found:

- The older group experienced a significantly higher rate of major hemorrhage (predominantly intracranial or gastrointestinal) at 13 per 100 person-years vs. 4.75 per 100 person-years in the younger group ($p = 0.01$). The study authors noted that about half (46%) of those with major hemorrhages were on low-dose (81 mg/day) aspirin therapy at the time of the major hemorrhage; but that the proportion of those with major hemorrhages was similar to the proportion (40%) of the overall cohort on aspirin during the study period;
- The risk of stroke was increased in three circumstances: during the first 90 days of warfarin therapy; in those at least 80 years of age; and in those with INR $\geq$ 4; and
- Warfarin therapy was stopped in 134 patients by the end of the first year. Among the older group, 81% of decisions to stop warfarin were due to safety concerns. Among the younger group, 37% of decisions to stop warfarin were due to safety concerns ($p < 0.001$).

The study authors commented that the estimates of bleeding risk might be affected by the study's focus on outpatient management of warfarin therapy; that is, outpatients might be more or less subject to bleeding risk than those of similar age who resided in a long-term care institution and were ineligible for this study. The study did not include any testing for genetic factors for response to warfarin therapy.

Genetic and Other Factors Determining a Patient's Response to Warfarin Administration

The FDA approved label for Coumadin® notes many factors that can influence the anticoagulant effect of warfarin, including: dietary intake of green leafy vegetables and cranberry juice; alcohol consumption; age; Asian ethnicity; and liver function. Many other drugs affect warfarin metabolism, including analgesics, antibiotics, anticonvulsants, antineoplastics, beta adrenergic blockers, antifungals, hormone preparations and vitamins. The current label lists approximately 130 specific drugs reported to interact with coumadin.

The label also notes several clinical trials that associate genomic factors with responsiveness to warfarin dose. The label includes the suggestion that pharmacogenomic testing may contribute to the identification of patients who may be more likely to over- or under-respond to warfarin. However, the label does not require or explicitly recommend pharmacogenomic testing prior to the initiation of warfarin therapy.

Some studies have estimated that genetic factors, in combination, may account for 40-50% of inter-individual INR variability in response to oral warfarin (see comments from the American Association of Clinical Chemistry (AACC) below under Evidence Section VII(B)6). The label notes that initial response to warfarin therapy may be influenced by a multitude of factors (including diet and concomitant drug therapy) beyond genetic variation. The label also notes adjustments of warfarin dosage should be considered during initiation of therapy of elderly and/or debilitated patients, as noted in the final sentence (italics added) of the following excerpt:

"Initial Dosage

"The dosing of COUMADIN must be individualized according to patient's sensitivity to the drug as indicated by the PT/INR. Use of a large loading dose may increase the incidence of hemorrhagic and other complications, does not offer more rapid protection against thrombi formation, and is not recommended. It is recommended that COUMADIN therapy be initiated with a dose of 2 to 5 mg per day with dosage adjustments based on the results of PT/INR determinations. *The lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 and VKORC1 enzymes as well as for elderly and/or debilitated patients and patients with potential to exhibit greater than expected PT/INR responses to COUMADIN* (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**)."

III. History of Medicare Coverage

There is currently no National Coverage Determination on pharmacogenomic testing to predict warfarin responsiveness. In addition, there are no local coverage determinations (LCDs) on pharmacogenomic testing to predict warfarin responsiveness.

A. Current Request

CMS internally generated the request for this National Coverage Analysis.

B. Benefit Category

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage §1812 (Scope of Part A); §1832 (Scope of Part B) and §1861(s) (Definition of Medical and Other Health Services) of the Act. Pharmacogenomic testing to predict warfarin responsiveness may be considered a benefit under Social Security Act §1861(s)(3), "other diagnostic tests." This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

The Medicare regulations at 42 CFR § 410.32(a) state in part, "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem."

IV. Timeline of Recent Activities

August 4, 2008
CMS opened an internally generated National Coverage Analysis to evaluate coverage of the diagnostic use of pharmacogenomic testing for warfarin response.
The initial 30-day comment period began.

September 3, 2008
The public comment period closed; 73 timely comments were received.

May 4, 2009
CMS posted the proposed decision and opened a 30 day public comment period.

June 3, 2009
The public comment period closed; 6 timely comments were received.

V. FDA Status of Tests for *VKORC1* and *CYP2C9* Variants That Affect Warfarin Response

Several laboratory test manufacturers offer FDA-cleared kits suitable for testing for *VKORC1* and *CYP2C9* variants associated with warfarin metabolism. These tests use oligonucleotide sequences, immobilized onto silicon or plastic film or attached to gold beads to detect multiple variants of both genes with or without polymerase chain reaction (PCR) methods for variant detection or amplification. A peripheral blood sample (or a buccal swab) is required for testing. The following table indicates several of the laboratory test manufacturers and the tests available.

Instrument/Kit Name	Approval or Clearance Status	Manufacturer(s)
Verigene Warfarin Metabolism Nucleic Acid Test	510(k) 09/07	Nanosphere
INFINITI Warfarin (3 genetic variants)	510(k) 01/08	AutoGenomics
Rapid Genotyping Assay – CYP2C9 & VKORC1	510(k) 04/08	ParagonDx
eSensor Warfarin Sensitivity Test	510(k) 07/08	Osmetech

Instrument/Kit Name	Approval or Clearance Status	Manufacturer(s)
eQ-PCR Warfarin Genotyping Kit	510(k) 02/09	TrimGen

Pharmacogenomic testing for warfarin responsiveness is also available as 'home-brew' tests developed by individual clinical laboratories, using in-house methods of various types. In addition, certain laboratories provide direct-to-consumer pharmacogenomic testing for warfarin responsiveness and other genetically-associated personal health information.

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the Agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A.

Public commenters sometimes cite the published clinical evidence and provide CMS with useful information. Public comments that provide information based on unpublished evidence, such as the results of individual practitioners or patients, are less rigorous and, therefore, less useful for making a coverage determination. CMS uses the initial comment period to inform the public of its proposed decision. CMS responds in detail to the public comments that were received in response to the proposed decision when it issues the final decision memorandum.

VII. Evidence

A. Introduction

Below is a summary of the evidence we considered during our review. CMS commissioned an external technology assessment (TA) from the Agency for Healthcare Research and Quality on pharmacogenomic testing in certain conditions. The agency also conducted its own independent search and review of applicable clinical studies, professional society and other group/organization statements, evidence-based practice guidelines, and other relevant sources detailed below. CMS did not hold a MEDCAC meeting to specifically address the evidentiary base for the use of pharmacogenetic testing as part of the workup of patients needing anticoagulation. However, we did hold a MEDCAC panel to address the appropriate evidentiary standards for diagnostic genetic tests in general. We discuss those results below.

B. Discussion of Evidence Reviewed

1. Questions
In Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin:

a. Is the evidence sufficient to determine that pharmacogenomic testing to predict warfarin responsiveness improves patient oriented health outcomes related to the underlying indication for anticoagulation; and

b. Is the evidence sufficient to determine that pharmacogenomic testing to predict warfarin responsiveness reduces the incidence or severity of adverse outcomes related to anticoagulation therapy?

2. External Technology Assessments

CMS commissioned from the Agency for Healthcare Research and Quality (AHRQ) an external technology assessment (TA) on pharmacogenetic testing in selected conditions. Relevant portions of this TA (Raman 2008) are summarized in the following paragraphs. CMS is also aware of other systematic reviews on this topic; they are summarized below.

Tufts-NEMC Review
This technology assessment was based on research conducted by the Tufts-New England Medical Center Evidence-based Practice Center (EPC) under contract to AHRQ (Raman 2008). The findings and conclusions in this document are those of the authors, who are responsible for its contents. This study primarily examined two issues:

- Effect(s) of genetic variants of either *CYP2C9* or of *VKORC1* on warfarin pharmacokinetics (i.e., whether warfarin dosing's effect on warfarin concentration or actions in the patient differ among patients with different genotypes of these genes in a consistent way); and
- Effect(s) of variants of either gene on benefit(s) or risk(s) of warfarin therapy at the patient level (i.e., whether warfarin's preventive effect on thrombus formation or progression, or incidence of bleeding events in warfarin-treated patients, differ among patients with different genotypes in a consistent way).

For *CYP2C9* genetic variants **2* and **3*, the Tufts-NEMC EPC literature search identified 270 citations published between 1995 and 2007. Thirty-three of these, including two recent randomized controlled trials, were included in the systematic review. Studies chosen for this systematic review focused on the induction or maintenance phases of warfarin therapy. For *VKORC1* variants (all of which were single nucleotide polymorphisms, or SNPs), the Tufts-NEMC EPC literature search identified 288 citations. Twenty-eight articles were retrieved and reviewed in full text, and 18 studies reported data on the correlation of common *VKORC1* SNPs with outcomes of interest.

Tufts-NEMC EPC addressed the following questions in its systematic review:

1. Does a pharmacogenomic test diagnosis of being a variant genotype carrier compared to non-carriers among patients who will use warfarin correlate with therapeutic INR?
2. Does a pharmacogenomic test diagnosis of being a variant genotype carrier compared to non-carriers among patients who will use warfarin correlate with adverse outcomes such as serious bleeding events or thrombotic events?
3. What patient characteristics (e.g., age, race/ethnicity) and disease-related relevant factors (e.g., use of adjuvant medications) affect pharmacogenomic test results correlation with clinical or biochemical parameters, and other clinical outcomes among patients who will use warfarin?
4. How does a pharmacogenomic test result impact the therapeutic choice among patients who will use warfarin (i.e., how often does planned warfarin induction therapy change after genetic testing is available to the treating physician)?
5. What are the benefits and harms or adverse effects for patients from their subsequent therapeutic management after pharmacogenomic testing among patients on warfarin?
    a. Does pharmacogenomic testing among patients who are on warfarin and have supratherapeutic PT/INR findings result in better maintenance of therapeutic INR and fewer episodes of serious bleeding?
    b. Does pharmacogenomic testing among patients who are on warfarin and have subtherapeutic PT/INR findings result in better maintenance of therapeutic INR and fewer serious thromboembolic events, e.g., stroke, pulmonary embolus, etc., due to subtherapeutic INR?

Findings of the Tufts-NEMC systematic review included:

1. Carriers of the variant *CYP2C9* alleles **2* or **3* receiving warfarin therapy were associated with lower mean maintenance warfarin dose requirements compared with the non-carriers. There was a lack of studies investigating the role of pharmacogenetic testing (*CYP2C9* or *VKORC1*) and warfarin dose requirements in the induction phase. Carriers of the three relatively common *VKORC1* variants were more likely to need lower maintenance warfarin dose requirements, on average, compared with the non-carriers.
2. Carriers of *CYP2C9* variants **2* and **3* were associated with an increased rate of bleeding complications during warfarin induction phase, but the studies did not report if those patients had normal or supratherapeutic range of PT/INR.

3. Risk of over-anticoagulation (INR results exceeded desired upper limits) was also noted among carriers of *CYP2C9* variants **2* and **3* compared with non-carriers. Significant risk increases were noted in 5 of these 6 studies reviewed.

The Tufts-NEMC researchers also summarize RCTs (see below) of warfarin dosing using pharmacogenomic test results, compared with standard warfarin dosing approaches. Some findings from these studies (among study group participants in comparison to control group participants) included fewer bleeding complication rates, shorter times to reach therapeutic INR range, longer times within therapeutic range, and fewer dosing changes required. One study noted a greater risk of over-anticoagulation among those who carried both *CYP2C9* and *VKORC1* variants. The researchers focused on RCTs in which warfarin induction dosage was algorithmically guided based on pharmacogenomic testing results, as compared to 'standard' dosing protocols.

The Tufts NEMC TA identified three published RCTs on pharmacogenetic testing of *CYP2C9* and/or *VKORC1* and warfarin dosing.

"Hillman (2005) evaluated the impact of pharmacogenetic based dosing compared with standard dosing on bleeding complications. The RCT reported lower bleeding complication rates among patients treated with pharmacogenetic based dosing compared to those treated with standard dosing (11% versus 25%).

"Caraco (2008) randomized 191 adult patients to receive warfarin dosing in the induction phase either by six different *CYP2C9* genotype-adjusted algorithms (study group) or by a validated algorithm (control group). The subjects were followed up for 2 years. The investigators were blinded to the genotype of study subjects until after completion of the induction phase period of 8 weeks. Baseline characteristics were similar for both groups except for the combined indication of warfarin (deep venous thrombosis and pulmonary embolism), and for the clinical characteristics of hyperlipidemia—these were significantly higher in the control group. The proportion of subjects with wild genotype (*CYP2C9 *1/*1*) was higher in study group than in control group. The primary endpoints of the study were time to reach the first therapeutic INR range > 2 and time to reach stable anticoagulation. Compared with the control group, the time to reach first therapeutic INR > 2 and stable anticoagulation was statistically significantly earlier in the study group by 2.7 days and 18.1 days, respectively. Higher proportions of the study group patients were within therapeutic range INR for a longer time period and experienced less minor bleeding compared with the control group. This study did not evaluate the influence of *VKORC1* in the variability of warfarin maintenance dose.

"Anderson (2007) randomized 206 patients to pharmacogenetic-guided dosing compared with standard dosing. The pharmacogenetic guided dosing was derived from a regression equation based on 3 genetic variants (*CYP2C9 *2* and *3, and *VKORC1* C1173T), age, sex, and weight. The subjects were followed up for 3 months. There were baseline differences in the patient characteristics. The study group included older subjects and higher proportion of subjects with hyper-tension, and the control group had a higher proportion of variant genotypes than the study group. The primary end point was per-patient percentage of out-of range INR (< 1.8 or > 3.2) in study group compared with control group. There were no differences between the groups for the primary outcome. However, the study group required statistically significantly fewer dosing changes and fewer INRs compared with control group. Patients who carried both *CYP2C9* and *VKORC1* variants had an increased risk for INR ≥ 4, and total number of adverse events defined as clinical events plus INR ≥ 4 were fewer in the pharmacogenetic dosing group compared with the standard dosing group."

Limitations and Scope: This TA noted that studies of *CYP2C9* and *VKORC1* had significant between-study heterogeneity. Few studies evaluated the questions related to patient- and disease-related factors and their relationship to the pharmacogenetic test results or their predicted response to therapy. No study reviewed in the external TA addressed the questions (their question 5) on therapeutic choice impact and benefits, harms or adverse effects for patients from their subsequent therapeutic management after pharmacogenetic testing for *CYP2C9* and *VKORC1*. The time-frame of included studies in this TA was from 1995 through September 2007.

Sanderson 2005

This systematic review and meta-analysis of studies investigated the effects of *CYP2C9* gene variants on warfarin dose requirements and on bleeding risks. The study used the HuGEnet™ database and other sources including PubMED and the Cochrane Library to include articles up to late January 2003 (Sanderson 2005). The review was based on 11 studies, including 3029 patients, of which nine studies, including 2775 patients, were used for the meta-analysis. This meta-analysis found that:

- Mean daily maintenance warfarin doses were reduced in those with the **2* (0.85 mg/d or 17%) and with the **3* (1.92 mg/d or 37%) variants; and
- Relative bleeding risk for variant **2* was 1.91, and for **3* was 1.77.

This meta-analysis also found that:

- Variant alleles of *CYP2C9* were present in twenty percent of participants: 12% were **2*, and 8% were **3*. The authors noted that these variants were rare among persons of Asian or African-American heritage; and
- In its discussion section, noting the changes in daily dose required and the higher risks of bleeding associated with certain genotypes, the review team suggested that testing for these variants could affect clinical management decisions in patients initiating warfarin therapy. However, the review acknowledged that additional evidence of clinical utility and cost-effectiveness would be needed before routine testing can be recommended.

McClain 2008

This systematic review investigated the association of *CYP2C9* and *VKORC1* genotype information and the incidence of serious adverse events (McClain 2008). Its major findings included:

- Strength of evidence is low for an association between *CYP2C9* testing and severe bleeding events (clinical sensitivity 46% (CI 32-60%), clinical specificity 69% (CI 62-75%)). No evidence was found to demonstrate that *VKORC1* testing and severe bleeding events are associated; and
- No evidence of clinical utility of such testing is available.

McClain 2008 also noted:

- Analytic sensitivity and specificity of *CYP2C9* genotyping are 98% or higher.
- Strength of evidence to establish the analytic sensitivity and specificity of *VKORC1* genotyping is judged less than desirable; and
- Evidence gaps cited by this review included lack of information from external proficiency testing, lack of validated dosing algorithm including both clinical and genetic factors, and reliable economic analysis.

Ongoing clinical studies:
The Tufts-NEMC EPC TA noted nine ongoing clinical trials (registered with the national clinical trials database (www.clinicaltrials.gov) on pharmacogenomic testing of *CYP2C9* and *VKORC1.* Additional information about clinical utility may be expected as these studies are completed and their results are published.

3. Internal technology assessment

Articles from the medical literature were searched on February 27, 2009 for relevant abstracts, using the PubMED (National Library of Medicine, NIH) database and search engine. It was found that almost all of the relevant clinical articles retrieved are a subset of those reviewed by the Tufts-NEMC EPC, except for three clinical studies published since September 2007 (summarized below).

Schwarz 2008
The authors assessed *CYP2C9* genotypes (*CYP2C9 *1*, *2, and *3*), *VKORC1* haplotypes (designated A and non-A), clinical characteristics, response to therapy (as determined by the INR), and bleeding events in 297 patients starting warfarin therapy (Schwarz 2008). The median age of participants was 61, with an M:F ratio of 54:46. Indications for warfarin therapy in participants included joint replacement (41%), atrial fibrillation/flutter (36%), thrombosis or embolus (13%), and other or combined indications (10%). The study outcomes were:

- time to first PT/INR within the therapeutic range;
- time to first INR > 4;
- time above therapeutic INR range;
- PT/INR response over time; and
- warfarin dose requirement.

As compared with patients with the non-A/non-A haplotype, patients with the A/A haplotype of *VKORC1* had a decreased time to the first PT/INR within the therapeutic range ($p = 0.02$) and to the first PT/INR > 4 ($p = 0.003$). In contrast, the *CYP2C9* genotype was not a significant predictor of the time to the first PT/INR within the therapeutic range ($p = 0.57$) but was a significant predictor of the time to the first PT/INR > 4 ($p = 0.03$). Both *CYP2C9* genotype and *VKORC1* haplotype had a significant influence on the required warfarin dose after the first 2 weeks of therapy. Eight major and five minor bleeding events were noted, with 9/13 bleeding events occurring in the first 28 days after initiation of warfarin therapy. Patients with bleeding events tended to be older (median age of 71 years of age) than other participants, and were associated with INR values ranging from 1.7 to 12.3. The authors concluded that initial variability in the PT/INR response to warfarin was more strongly associated with genetic variability in the gene for the pharmacologic target of warfarin, *VKORC1*, than with *CYP2C9*.

Wen 2008

The authors studied the effects on INR of genetically-guided warfarin dosing algorithms including information on *CYP2C9* and *VKORC1* variants in 108 Han Chinese patients in Taiwan without prior warfarin treatments (Wen 2008). The mean age of participants was 64 years. Fifty-eight percent of participants were males. There was no comparison group. Using genotype-based warfarin dosing, eighty-three percent of patients reached stable, therapeutic INR within 2 weeks of treatment initiation and none of the patients developed clinical bleeding or a thromboembolic event. The study noted that 11 patients developed INR > 4 without signs of clinical bleeding during the study period. At 12 weeks, sixty-nine percent of patients' maintenance doses matched the dose predicted by the algorithm. Dosing algorithms incorporating genetic factors, age, and body surface area were developed, which could explain up to 62% of the total variation (R^2 of 0.62). The authors concluded that pharmacogenetics-based dosing could improve time to stable, therapeutic INR, reduce adverse events, and achieve high sensitivity.

Wadelius 2008

This clinical study noted that harms (bleeding events) occurred more frequently among those with certain *CYP2C9* genotypes, in particular **3/*3* homozygous persons. Among 1542 recruited participants, the mean age was 66 years, with about a 2:1 M:F proportion. Pharmacogenomic testing results were available (retrospectively) on 1496 participants. Warfarin dosing was initiated using various standard loading protocols. A serious bleeding event occurred in one of the eight persons in the **3/*3* subgroup in the first five weeks of therapy (12.5%); in contrast, the 1488 persons with other genotypes had only a 0.27% chance of such an event during the first five weeks. A graph of PT/INR response by week for all *CYP2C9* genotypes (Figure 3b in that article) shows a large initial rise in PT/INR in the *CYP2C9 *3/*3* homozygous groups. The study also noted no significant differences in the serious bleeding event rates among the *VKORC1* genotypes studied during the first five weeks. A multiple regression model was developed for initial warfarin dosage based on *CYP2C9* and *VKORC1* genetic test results, age, gender, and drug interactions. The authors stated that this model accounted for 59% of the interindividual variation in the study population, and 53% of interindividual variation in a separate sample of 181 Swedish individuals. However, the authors recognized that the regression model was limited by lack of data on participants' weight and height, and its consideration of only one ethnic group.

Additional Evidence

We reviewed evidence that has come to our attention after our earlier review. Articles from the medical literature were searched on 5/28/2009 for relevant abstracts, using the PubMED (National Library of Medicine, NIH) database and search engine. The additional evidence is summarized below.

International Warfarin Pharmacogenetics Consortium 2009

The authors describe results from an international, multi-center study designed to derive and subsequently validate an algorithm in which genetic variables were added to clinical variables to derive initial warfarin dose. Clinical information was collected by 21 research groups from 9 countries; genotyping of *VKORC1* and *CYP2C9* was performed in a blinded manner by a single laboratory. The 5052 participants were grouped randomly into either into a 'derivation' cohort, from whose clinical and genetic variables a multiple regression model for initial warfarin dosage was calculated, and a 'validation' cohort used to assess the predictive ability of the model. Demographic and genetic features of these two cohorts were not statistically significant. Of the three models (fixed-dose, clinical algorithm, and pharmacogenetic ('PG') algorithm) the lowest mean absolute error in weekly warfarin dose was found in the PG (8.5 +/- 1.7 mg/week) with higher errors found in the clinical algorithm (9.9 +/- 1.9 mg/week) and the fixed-dose approach (13.0 +/- 2.3 mg/week). In particular, for the groups requiring low (21 mg/week or less) or high (49 mg/week or more) doses, the PG algorithm was a better predictor of dose than either other approach. Limitations of this study included insufficient data across the 21 research groups to include potentially important factors including smoking status, vitamin K intake, or alcohol consumption, and other genetic factors such as *CYP4F2* status. Patient inclusion was limited to those whose therapeutic INR range targets were 2-3. In addition, missing data from some patients required imputing missing genotypes for some patients.

Kangelaris 2009

This systematic review and meta-analysis included randomized trials comparing pharmacogenetic dosing of warfarin versus a 'standard' dose control algorithm in adult patients taking warfarin for the first time. Three studies met the inclusion criteria: Hillman 2005, Caraco 2007, and Anderson 2007 (summarized above in the Tufts-NEMC TA). In reviewing these three studies, the authors found "… little randomized trial data available to support the hypothesis that pharmacogenetic dosing at the onset of warfarin therapy reduces major bleeding events." Specific challenges to trial validity were discussed for each of these three articles. The authors, citing a number of ongoing or planned clinical trials, suggest that additional evidence may be forthcoming to support the use of pharmacogenetic testing to guide warfarin therapy.

Li 2009

The authors investigated the relative contribution of CYP2C9 and VKORC1 genotypes and early INR response to predict warfarin responsiveness during the initiation of warfarin therapy in 214 subjects. The demographic characteristics of the subjects are described as 49% female, 92% self-reported European-American, and mean age 61 years (SD 14 years). Joint replacement, atrial fibrillation/atrial flutter, and venous thromboembolism accounted for 92% of the indications for anticoagulation. Results of pharmacogenomic testing along with the results of early (day 4-6) INR testing were entered into a regression model, adjusted for age, sex, ethnicity, use of amiodarone, target INR and cumulative warfarin dose. The authors conclude that pharmacogenomic testing adds little to no predictive value beyond early INR results.

Lindh et al. 2009

In this publication, the authors present the results of a systematic review and meta-analysis focusing on the impact of *CYP2C9* genotype on warfarin dose. 39 studies, including 7907 participants, were included in the meta-analysis. All 39 studies were published between 1999 and 2007, and were performed in Asia (12 studies), the Americas (13) and Europe (14). The mean age was 64 years (range 57-67 years); 59% of participants were males. Average maintenance warfarin dose (relative to that among patients with the *CYP2C9 *1/*1* genotype) was lower by 20% (17-22%) for *CYP2C9 *1/*2* patients (based on data from 31 studies), and lower by 78% (72-84%) among *CYP2C9 *3/*3* patients (based on data from 7 studies). The authors noted that lack of *VKORC1* haplotype data precluded the assessment of that gene's effects on dose requirements.

Millican et al. 2007

This study used retrospectively collected clinical data to derive a multiple regression model for predicting warfarin dose from genetic and clinical factors, based on a retrospective cohort study of warfarin anticoagulation for deep venous thrombosis prophylaxis in 2 cohorts of orthopedic surgery patients enrolled at one university medical center. Inclusion criteria were: age of 18 years or older; no history of prior warfarin therapy or contraindications to warfarin therapy; and referral to the anticoagulation service at least 7 days prior to surgery (to allow time for genotyping). The study's endpoint was reaching a stable warfarin dose in the therapeutic range after 6 or 7 days. The two cohorts were recruited between August 2003 and March 2004 (n = 46), and between February 2006 and July 2006 (n = 72). The mean age of the 'final' combined cohort (i.e., those who reached a stable therapeutic dose) was 58 years (range 21-83 years). The 'final' cohort included 44 females and 48 males; 14% of these participants were African-American. The therapeutic range for INR varied from 2-3 in the first cohort to 1.7-2.7 in the second. Patients who discontinued warfarin therapy before reaching a therapeutic INR level were also excluded (n=26). Using stepwise multiple regression techniques, the authors found that significant variables for predicting the therapeutic dose included: INR after three doses; first warfarin dose (mg); *CYP2C9 *2* and **3* genotypes; and *VKORC1* haplotype A copies. The authors also noted a significant impact of smoking status on the model for warfarin dose (+ 20.1% dose increase, 95% CI (+ 6.0 to + 36.2%)). They also commented on the effect of loss of plasma coagulation factors during surgery, for which the estimated surgical blood loss was used as a surrogate. Their clinical and pharmacogenomic model was found to explain (based on R^2_{adj}) 79.3% of variation between the predicted and observed therapeutic doses in participants. Based on this model, the authors concluded that "… accuracy of dose refinements based solely on INR is inherently limited, heightening the chance of excessive or inadequate warfarin dose adjustments". They noted the following study limitations. All the subjects were anticoagulated for the same indication, which limited the generalizability of their findings. They also acknowledged that their data driven model may reflect "peculiarities within our data rather than causal relationships between the variables and the therapeutic dose", and suggested that prospective confirmatory studies would be needed to validate this model.

4. MEDCAC

A Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) meeting was convened on February 25, 2009 to make recommendations on the desirable characteristics of evidence pertaining to the effect, if any, of diagnostic genomic testing on health outcomes. Additional information about the meeting is available at https://www4.cms.hhs.gov/mcd/viewmcac.asp?id=224. A summary of the MEDCAC meeting announcement is provided below.

The meeting announcement stated that CMS " …wished to obtain the MEDCAC's recommendation regarding the desirable characteristics of evidence that could be used by the Medicare program to determine whether genetic (including genomic) testing as a laboratory diagnostic service improves health outcomes in Medicare beneficiaries". The meeting announcement also states that SACGHS (DHHS 2008) has defined genetic testing as "…any test performed using molecular biology methods to test DNA or RNA, including germline, heritable, and acquired somatic variations."

It was noted that " … Medicare may cover a diagnostic test that is used by the beneficiary's treating physician to guide the physician's diagnosis and treatment of the beneficiary's personal condition. This contrasts with a screening test used to identify an occult condition or state in an asymptomatic person. The questions below should be addressed in the former context, i.e. diagnostic testing."

Note that, after each question Q1-Q6 below, the MEDCAC panel's consensus view is indicated by *italics*.

"Q1. Are the desirable characteristics of evidence for diagnostic genetic testing different from the desirable characteristics of diagnostic testing in general?"

*Response: The MEDCAC consensus was that the desirable characteristics of evidence for diagnostic genetic testing are not different from the desirable characteristics of diagnostic testing in general. The panel felt that the evidence should be rigorous, and noted that genetic testing has potential harms as well as potential benefits, and that the public is served by robust evidence. The panel also noted that, as with other diagnostic testing, determining the acceptable level of evidence may be interpreted within the context of specific diseases, specific treatments and specific tests. The MEDCAC consensus is that the EGAPP-identified ACCE (**A**nalytic and **C**linical validity, **C**linical utility and associated **E**thical, legal, and social implications) criteria are a desirable framework for this use. See Teutsch SM et al. (2009), in particular Tables 3and 4 from that article. Note: EGAPP is the Evaluation of Genetic Applications in Practice and Prevention working group, supported by the Centers for Disease Control and Prevention's National Office of Public Health Genomics .*

"Q2. What are the desirable characteristics of evidence for determining the analytical validity of genetic diagnostic tests?"

Response: The MEDCAC consensus was that the relevant factors in the ACCE criteria adopted by EGAPP are a desirable framework for this use.

"Q3. Beyond aspects of analytical validity considered above, are there meaningful differences in the desirable and/or necessary characteristics of evidence about the effect of genetic testing on outcomes for the three testing paradigms below? If yes, please consider question 4 separately for each paradigm. If not, please consider question 4 to apply equally to all three.

- Diagnostic assessment
- Prognostic assessment
- Pharmacogenomic assessment"

Response: The MEDCAC consensus was that there are no meaningful differences in the desirable and/or necessary characteristics of evidence about the effect of genetic testing on outcomes for the three testing paradigms. The panel noted that evidence related to pharmacogenomic testing is more challenging because of the consequent linkage between a test and a drug.

"Q4. For each type of outcome below, how confident are you that methodologically rigorous evidence on the outcome is sufficient to infer whether or not diagnostic genetic testing improves patient centered health outcomes?"

For each lettered outcome type, assign a number from 1 to 5 to indicate your vote. A lower number indicates lower confidence; a higher number indicates higher confidence.

a. Changes in physician-directed patient management
b. Indirect or intermediate healthcare outcomes e.g., changes in laboratory test results such as hemoglobin or time to achieve a target value
c. Direct patient-centered healthcare outcome e.g., mortality, functional status, adverse events "

Response: The mean of MEDCAC panelists' scores are noted in the table below.

Outcome Type	Voting Members Only	All Panelists
a	2.10	1.79
b	3.30	3.00
c	4.80	4.50

"Q5. Are there ethical issues particular to genetic testing that may alter the methodologic rigor of studies of genetic testing?"

Response: The MEDCAC consensus is that methodologic rigor contributes to ethical rigor and that a lower methodologic standard would actually detract from the ethical generation of evidence for genetic testing.

"Q6. Does the age of the Medicare beneficiary population present particular challenges that may compromise the generation and/or interpretation of evidence regarding genetic testing?"

Response: The MEDCAC discussed this question but did not attempt to reach a consensus. Many genetic conditions, especially Mendelian single gene disorders, are much rarer in the Medicare aged population as contrasted with the pediatric aged population. In the Medicare aged population, competing causes of death may create practical challenges to study of genetic conditions. Pharmacogenomic testing is relevant to the Medicare aged population because older persons are more likely to take multiple drugs and have multiple comorbid conditions that may affect their response to and tolerance of drugs.

Although not in response to a particular question, speakers and panelists described the evidence base on genomic testing as immature. Several suggested that CMS use its CED authority to facilitate the collection of evidence.

5. Evidence-based guidelines

A guideline published by the American College of Chest Physicians recommended against genomic testing for initial warfarin dosage guidance (emphasis added in boldface below):
"… Among the key recommendations in this article are the following: for dosing of VKAs [vitamin K antagonists], we recommend the initiation of oral anticoagulation therapy, with doses between 5 mg and 10 mg for the first 1 or 2 days for most individuals, with subsequent dosing based on the international normalized ratio (INR) response (Grade 1B); **we suggest against pharmacogenetic-based dosing until randomized data indicate that it is beneficial (Grade 2C)**; and in elderly and other patient subgroups who are debilitated or malnourished, we recommend a starting dose of ≤ 5 mg (Grade 1C)"... (Ansell 2008)

6. Professional Society Position Statements:

American Association for Clinical Chemistry (AACC)
AACC believes that a national policy which promotes greater use of personalized medicine, particularly in regards to warfarin dosing levels, is warranted because more appropriate dosing will reduce the risk of bleeding in those receiving the drug. AACC has concluded that an NCD providing coverage for such testing is appropriate. AACC is aware of studies (Caraco 2008, Anderson 2007) that show up to 40 percent of the warfarin dose variation between individuals can be attributed to genetic variation for which tests are available. They also refer to a number of institutions engaged in ongoing research studies. AACC suggests that Medicare coverage would reduce, not only risks of bleeding, but also overall costs of care, given the wide use of warfarin in the population.

Association for Molecular Pathology (AMP)
AMP recommended additional research on this subject.

American Society of Hematology (ASH)
ASH noted that the current evidence base is interesting but insufficient, and recommended further clinical research on the subject. ASH does not support the use of pharmacogenomic testing to guide initial dosing or ongoing treatment of warfarin.

College of American Pathologists (CAP)
CAP believes that there is ample evidence of clinical validity and utility for pharmacogenomic testing for warfarin metabolism.

American College of Chest Physicians (ACCP)
In guidelines (Ansell 2008) on managing anticoagulation with Vitamin K antagonists (VKA) such as warfarin, an ACCP panel concluded: "... 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 ... ".

American College of Medical Genetics (ACMG)
Although noting that initiation of warfarin therapy is associated with highly variable responses between individuals, the ACMG Working Group report (Flockhart 2008) stated that "…there is insufficient evidence at this time to recommend for or against routine *CYP2C9* and *VKORC1* testing in warfarin-naïve patients." However, the report noted that in certain situations, such testing "…may be useful and warranted in determining the cause of unusual therapeutic responses to warfarin therapy."

7. Expert Opinion

We did not receive expert opinions on the use of pharmacogenomic testing to predict warfarin responsiveness. We are however aware that various experts or professional groups have, in other venues, opined on this topic. We note them below.

National Heart, Lung and Blood Institute (NHLBI)
Doctors Shurin and Nabel of NHLBI editorialized in the New England Journal of Medicine that despite increasing evidence of the role of genomics in warfarin metabolism and response, the warfarin story is far from complete (Shurin 2008). They concluded by suggesting:
"…After strong associations between genotype and drug sensitivity have been identified, trials must be conducted to evaluate the clinical efficacy of the gene-based prescribing strategy and to determine whether the increment in efficacy or safety warrants the cost of genetic testing."

Their editorial also noted that NHLBI was providing contract support for a large, multicenter, double-blind, randomized trial of genotype-guided administration of warfarin therapy (See Trial Identifier NCT00839657 at www.clinicaltrials.gov).

The American Medical Association (AMA), the Critical Path Institute (funded by FDA) and Arizona Center for Education and Research on Therapeutics (CERT)

The AMA made a brochure available to clinicians entitled "Personalized health care report 2008: Warfarin and genetic testing" (AMA 2008). This brochure indicates that up to 40% of the inter-individual variation in response to warfarin therapy may be explained by variations of two genes: *CYP2C9* and *VKORC1*. The brochure notes that testing for both variants is available.

However, the brochure also notes that monitoring of PT/INR is still required for optimal dose adjustment; that the value of genetic testing could be negated by drug or food interactions with warfarin; and that more than 300 drugs are known to interact with warfarin and may require a warfarin dosage adjustment. The brochure also cites two useful websites for physicians: and www.warfarindosing.org.

SACGHS

The May 2008 SACGHS report entitled "Realizing the Potential of Pharmacogenomics: Opportunities and Challenges" referred to the use of *CYP2C9* and *VKORC1* testing to guide warfarin dosage as an early application of pharmacogenomics (DHHS 2008). However, the report indicated that

"… much of the valuable evidence about pharmacogenomics is in the form of early scientific discoveries. Although this information has the potential to be useful, its clinical utility is not yet well understood."

Michael Brophy, MS, MT (ASCP), Department of Veterans Affairs (DVA) Diagnostic Services
Brophy's comments appeared in the newsletter VA Research Currents:

" … For example, about five percent of patients carry a gene that makes them very sensitive to the blood thinner warfarin, sold as Coumadin®. But offering the test appears to have little impact on patient care and outcomes. Brophy: 'Most of the clinicians just didn't feel it was going to make much practical difference when looked at from the perspective of real clinical outcomes. Because if you start patients on a low dose as you're supposed to, and then adjust their therapy upward, the genetic predisposition, when considered along with the other variables, is generally not as relevant. It's only one of many factors that determine the appropriate dose.'" (DVA 2008)

California Technology Assessment Forum (CTAF)
In a March 2008 assessment regarding published evidence about using genetic testing to guide the initiation of warfarin therapy, CTAF suggested that due to absent or insufficient evidence for improvement of outcomes, for benefit compared to established alternatives and for improvement attainable outside the investigational setting, the use of *CYP2C9* and *VKORC1* genotyping did not meet its criteria for recommendation. (CTAF 2008)

8. Public Comments

Initial Comment Period: August 4, 2008 – September 3, 2008
CMS received 73 timely public comments during the initial public comment period. Of the public commenters who furnished this information, 10 were from providers and clinicians, 6 were from genetic services or pharmacy management businesses, 5 were from patients, 1 was from a caregiver, 4 were from professional societies, 3 were from advocacy groups, 2 health plans, 12 were from scientists, academic and research organizations and 30 commenters did not identify their title or affiliation.

A number of commenters noted that while available testing methods accurately determine the genetic markers, there is insufficient data to demonstrate that the use of the tests impacts on health outcomes. Several commenters stated that this test should not be held to a more strict review than other tests while a few commenters felt that Medicare should not cover pharmacogenomic testing for warfarin sensitivity.

Comment period on the proposed decision: May 4, 2009 – June 3, 2009

We received 6 timely comments on the proposed decision. Of the comments, 2 were from pharmaceutical and diagnostic companies, 1 was from a health plan, 1 was from a researcher/scientist, and 1 was from a national association of health insurers. One did not identify the commenter's title or affiliation.

All but two commenters agreed with the proposed coverage decision, generally stating that the decision promotes the needed research to provide evidence of the clinical utility of pharmacogenomic testing for warfarin responsiveness. One commenter in agreement suggested that clinical trial designs include additional patient outcomes like time to target INR, number of days spent at excess INR and number of days spent at inadequate INR. However, we note that these are intermediate outcomes that would require additional evidence to establish an effect of pharmacogenomic testing on patient centered health outcomes such as significant bleeding or thromboembolism.

Two comments did not support the proposed decision. One comment questioned the benefit of using warfarin to prevent blood clots, citing evidence of rebound hypercoagulability upon discontinuation of warfarin. Although interesting, this comment did not contest the use of pharmacogenomic testing for warfarin responsiveness or the evidence summarized in the proposed decision memorandum.

The second comment cited additional evidence from an article that CMS reviewed and noted in the decision memorandum "Evidence" section, Section VII(B)3, under the heading 'International Warfarin Pharmacogenetics Consortium 2009' (see Bibliography for complete citation). We appreciate the reference to this source of additional evidence. In addition, this commenter indicated a concern that requiring Medicare patients to be enrolled in a recognized clinical study might tend to discriminate against those who for a variety of reasons cannot enroll in a clinical study, and that coverage should be provide to all Medicare beneficiaries. As we have discussed above, and as many national professional societies agree, the current evidence is not sufficient to recommend national coverage of pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles for warfarin responsiveness as provided for under section 1862(a)(1)(A) of the SSA. Finalizing coverage under Coverage with Evidence Development (CED), provides a means to provide limited coverage, as provided for under section 1862(a)(1)(E) of the SSA. CED allows for coverage by providing support for well -designed, well-executed clinical studies in part to obtain additional evidence, and to establish the value of promising, if unproven, diagnostic technologies. Unfortunately, this may mean that not all Medicare beneficiaries may be eligible to receive coverage of this service. Ultimately, however, this NCD providing for coverage under CED will assist in growing the evidentiary base for the use of pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles for warfarin responsiveness, and if appropriate, provide an opportunity for the agency to reconsider this determination and review such evidence to determine whether broader coverage for such testing would be supported.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1862(l) of the Act). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." See §1862(a)(1)(A)of the Social Security Act.

In addition to §1862(a)(1)(A), a second statutory authority may permit Medicare payment for items and services in certain circumstances. Section 1862(a)(1)(E), provides, in pertinent part, that:

(a)(1) Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—
. . .
(E) in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section[.]
. . .

Section 1142 describes the authority of the AHRQ.

Under the authority of § 1862(a)(1)(E), Medicare may cover under coverage with evidence development/coverage with study participation (CED/CSP) certain items or services for which the evidence is not adequate to support coverage under §1862(a)(1)(A), and where additional data gathered in the context of clinical care would further clarify the impact of these items and services on the health of Medicare beneficiaries. Further guidance on CED/CSP can be found at http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=8. CSP allows CMS to determine that an item or service is only reasonable and necessary when it is provided within a research setting where there are added safety, patient protections, monitoring, and clinical expertise.

Under section 1142, research may be conducted on the outcomes, effectiveness, and appropriateness of health care services and procedures to identify the manner in which diseases, disorders, and other health conditions can be prevented, diagnosed, treated, and managed clinically.

As a general matter CSP is to be used in rare instances. For some items or services, CMS may determine that the evidence is preliminary and not reasonable and necessary for Medicare coverage under section 1862(a)(1)(A), but, if the following criteria are met, CSP might be appropriate:

The evidence includes assurance of basic safety;
The item or service has a high potential to provide significant benefit to Medicare beneficiaries; and
There are significant barriers to conducting clinical trials.

Regarding these three criteria:

1. Testing for the presence of certain genetic variants requires only the collection of venous blood or a buccal swab, both regarded as generally safe procedures. In other aspects, the performance of genetic testing on a blood sample carries no additional risks to the individual tested.
2. Current warfarin dosing recommendations (not guided by genetic testing results) at the time a patient initiates therapy are regarded as inexact starting points in the process of titrating warfarin dose to a patient's needs. There is often wide variation between the initial warfarin daily dose and the eventual 'titrated' dose achieved by a trial-and-error process during the first weeks or months of warfarin therapy. Although we comment elsewhere in this Decision Memorandum about the insufficiency of evidence for coverage, the ability to more effectively treat or prevent blood thrombosis and avoid the risk of hemorrhage due to over-anticoagulation by guiding warfarin dosing based on genetic testing results would be a worthwhile potential benefit for the numerous Medicare beneficiaries, perhaps exceeding one million annually, who are initiating anticoagulant therapy with this drug.
3. Several medical professional societies and federal public health agencies have, citing current levels of evidence, called for additional studies of the actual benefit in net patient health outcomes achieved in practice of such genetic testing to guide warfarin dosing. However, absent conditional coverage (under CED/CSP) such studies would not be available for participation by Medicare beneficiaries in most areas of the country. (Upcoming NHLBI -sponsored clinical trials (e.g., NCT00839657) may be limited to patients able to receive care at selected university medical centers in about a dozen urban areas of the U.S.)

To qualify for reimbursement, such a study must be designed to produce evidence that could be used in a future national coverage decision that would focus on whether the item or service should be covered by Medicare under §1862(a)(1)(A). Payment for the items and services provided in the study will be restricted to the Medicare qualified patients involved as human subjects in the study. These research studies will be rigorously designed and include additional protections and safety measures for beneficiaries.

We have consulted with AHRQ which has agreed that the study questions and requirements outlined above are consistent with section 1142 of the Social Security Act.

Based on the legal framework set forth above, this section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment questions posed above in Section VII, part B. As previously noted, pharmacogenomic testing for warfarin responsiveness is a diagnostic test.

The Medicare regulations at 42 CFR 410.32(a) state in part, "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem." Thus we look for evidence demonstrating how the treating physician uses the result of a pharmacogenomic test to manage the anticoagulation treatment in patients who are candidates for warfarin.

We considered the evidence in the hierarchical framework of Fryback and Thornbury (1991) where Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan and Level 5 measures the effect of the diagnostic information on patient outcomes. Most studies have focused on test characteristics and have not considered health outcomes, such as mortality, morbidity or reduction of invasive angiography. However, we believe that evidence of improved health outcomes is more persuasive than evidence of test characteristics. Please see Appendix A, General Methodological Principles of Study Design.[1]

In evaluating diagnostic tests, Mol and colleagues (2003) reported: "Whether or not patients are better off from undergoing a diagnostic test will depend on how test information is used to guide subsequent decisions on starting, stopping, or modifying treatment. Consequently, the practical value of a diagnostic test can only be assessed by taking into account subsequent health outcomes." When a proven, well established association or pathway is available that demonstrates a virtually certain association between a well-defined, objectively assessed intermediate health outcome and one or more net beneficial patient outcomes of interest, intermediate health outcomes may also be considered. For example, if a particular diagnostic test result can be shown to change patient management and other evidence has demonstrated that those patient management changes improve health outcomes, then those separate sources of evidence may be sufficient to demonstrate positive health outcomes from the diagnostic test.

As a diagnostic test, the pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness would not be expected to directly change health outcomes. Rather, a diagnostic test affects health outcomes through changes in disease management brought about by physician actions taken in response to test results. Such actions may include decisions to treat or withhold treatment, to choose one treatment modality over another, or to choose a different dose or duration of the same treatment. To some extent the usefulness of a test result is constrained by the available management alternatives. As noted in the Background section, the ongoing titration of warfarin remains dependent on testing the PT/INR. A patient whose anticoagulation is not optimal with a particular dosing regimen is likely to be prescribed a different dosing regimen of the same drug. In addressing the question, one of the factors we consider is whether there is sufficient evidence that the incremental information derived from pharmacogenomic testing leads to improved control of warfarin based anticoagulation by causing physicians to prescribe a different warfarin dosing regimen than they would have prescribed without access to pharmacogenomic test results, or to forego warfarin therapy entirely.

Ideally we would see evidence that the systematic incorporation of pharmacogenomic test results into an anticoagulation algorithm leads treating physicians to prescribe different dosing of warfarin than they would otherwise have prescribed, and that patients whose treatment is changed by pharmacogenomic test results remain on the regimen and achieve better long term anticoagulation documented by repeated assessments over time, reduced frequency and severity of adverse drug effects, and improved outcomes related to the primary condition for which the patient is being anticoagulated. Unfortunately the current data are sparse on health outcomes and current guidelines do not establish that the treating physicians currently base patient warfarin management on the pharmacogenomic test results.

Questions

In Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin:
a. Is the evidence sufficient to determine that pharmacogenomic testing to predict warfarin responsiveness improves patient oriented health outcomes related to the underlying indication for anticoagulation; and
b. Is the evidence sufficient to determine that pharmacogenomic testing to predict warfarin responsiveness reduces the incidence or severity of adverse outcomes related to anticoagulation therapy?

Coverage Under §1862(a)(1)(A)

CMS agrees with most professional societies' recommendations, and with the findings of published articles noted in the TA and in CMS' internal evidence review, that the evidence for improved health outcomes attributable to pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness fails (as of this writing) to meet the standards of evidence to establish a basis for coverage of genetic testing for warfarin responsiveness under §1862(a)(1)(A). The conclusions about improved health outcomes that flow from that evidence seem to us premature, even though they are intuitively appealing. We are concerned that there is a paucity of evidence from studies incorporating prospective randomization of patients to either genetic testing for warfarin responsiveness or best current warfarin dose adjustment regimens to support the necessity of use of genetic testing for warfarin dose guidance among subjects representative of the Medicare beneficiary population.

We believe that there is good evidence that the FDA-cleared pharmacogenomic tests accurately identify persons who have the variant *CYP2C9* and *VKORC1* alleles (for example, McClain 2008). We also believe that there is good evidence that persons who have these variant alleles have heightened warfarin responsiveness (for example, Schwarz 2008, Wadelius 2009). However, although such studies suggest indirect evidence of potential clinical benefit from pharmacogenomic testing for these alleles, they do not conclusively establish an actual benefit or risk to a beneficiary's health outcome.

The clinical usefulness of pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness may differ between the typical Medicare beneficiary and younger, generally healthier patients who have lower risks for adverse events related to warfarin. This point is particularly relevant to the questions posed in this National Coverage Analysis. As the 2007 FDA warfarin label notes:

"The lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 and VKORC1 enzymes as well as for elderly and/or debilitated patients and patients with potential to exhibit greater than expected PT/INR responses to COUMADIN…" (*emphasis added by CMS*).

Thus, since the lower initiation dose recommendation is already relevant to Medicare population in general, it is not clear that pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness itself adds additional actionable information to further guide physician management.

In our review, we found that some evidence demonstrates that an algorithmic management of warfarin that used genetic testing results resulted in greater time in INR range, shorter time to therapeutic INR, etc. It is not clear from the evidence, however, if these algorithms incorporated lower starting doses for Medicare aged subjects as would typically be the case. We did not find any evidence that demonstrated that using genetic testing results to guide initial warfarin therapy improved health outcomes, e.g., fewer pulmonary emboli in patients treated for deep vein thrombosis or decreased adverse events, fewer or less serious bleeding episodes.

CMS found no evidence that pharmacogenetic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness can replace PT/INR testing for titrating and monitoring warfarin therapy. Use of PT/INR results to assess an individual's anticoagulant response during warfarin therapy is well established. Target ranges for therapeutic effect (based on INR results) have been established for the major indications for warfarin's use. It is not clear at this time if patients who have variant alleles identified by pharmacogenomic testing should be targeted to lower INR targets. In that instance pharmacogenomic testing could provide a benefit beyond initial titration. However, we have not found such provisions in currently published anticoagulation guidelines.

Experts in the field have commented that based on the evidence available at this time, conclusions cannot be drawn with confidence about clinical benefit to patients (Shurin 2008). Other experts, citing other examples of early, favorable genetic testing trials which could not be reproduced, advise caution in assessing possible benefit or risk due to genetic factors (Ioannidis 2007).

There appears to be no consensus of opinion among the professional societies that expressed positions. Interestingly, societies that represent providers of the test believe that there is sufficient evidence for coverage while, in contrast, societies that represent providers who treat the patients with warfarin therapy note the need for more research on the issue.

Based on the evidence reviewed, we believe 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, we believe 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 we have 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.

Coverage under §1862(a)(1)(E)

As we noted above, we found limited evidence demonstrating that an algorithmic management of warfarin that used pharmacogenomic testing affects intermediate outcomes such as greater time in INR range, shorter time to therapeutic INR, etc. We found good evidence that the FDA cleared pharmacogenomic tests accurately identify persons who have the variant *CYP2C9* and *VKORC1* alleles. We also believe that there is good evidence that persons who have these alleles have heightened warfarin responsiveness. Though promising, the evidence of clinical outcome benefit is not yet conclusive and is not generalizable to the Medicare patient population.

We recognize that warfarin anticoagulation may be especially perilous in Medicare beneficiaries. There is consensus that anticoagulation provides a meaningful clinical benefit, but enthusiasm for treatment is sorely tempered by the known risks associated with warfarin anticoagulation. It is not clear from the available evidence that pharmacogenomic testing will provide the solution to this problem, but we believe that the addition of this technology may present the best available alternative to current practice.

As we have said in section V(B) of the previously published guidance document "National Coverage Determinations with Data Collection of Coverage: Coverage with Evidence Development"

(http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=8),

"(Coverage with study participation) CSP will allow coverage of certain items or services for which the evidence is not adequate to support coverage under section 1862(a)(1)(A) and where additional data gathered in the context of clinical care would further clarify the impact of these items and services on the health of Medicare beneficiaries. In the past, this level of evidence would have prompted non-coverage decisions.

"CSP allows CMS to determine that an item or service is only reasonable and necessary when it is provided within a research setting where there are added safety, patient protections, monitoring, and clinical expertise. If CMS decides that there is limited existing evidence to support a decision to cover the item or service under review and more evidence is needed for CMS to determine whether that item or service meets the evidentiary standards for reasonable and necessary, then the item or service is found to not be reasonable and necessary for Medicare coverage under section 1862(a)(1)(A). CMS may then consider whether coverage of the item or service is reasonable and necessary for Medicare coverage under section 1862(a)(1)(E) of the Act."

The guidance document further notes:
"When the evidence is inadequate to determine that the item or service is reasonable and necessary under section 1862(a)(1)(A), Medicare coverage may be extended to patients enrolled in a clinical research study."

The outcomes of greatest interest occur largely within the first few months of warfarin therapy. These include

- major hemorrhage,
- minor hemorrhage,
- thromboembolism related to the primary indication for anticoagulation,
- other thromboembolic event, and
- mortality.

We believe that prospective randomized clinical studies are required to assure that any differences in outcomes are confidently attributable to the additional information provided by pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness rather than to bias or other factors. Furthermore, enrolled subjects must adequately represent the Medicare beneficiary population that is likely to be tested, specifically elderly persons with comorbidities that include the use of drugs that are known to affect warfarin response.

As we noted above and in the background discussion, the putative uses of pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness fall generally into one of the following categories:

- To guide warfarin dosing in patients who are committed to urgent anticoagulation therapy as treatment for an acute event; and
- To encourage physicians to initiate elective warfarin therapy in patients with certain chronic conditions, who are thought to be at higher risk of adverse events related to anticoagulation.

We restate it here for clarity as we believe it is also relevant to our determination under §1862(a)(1)(E).

The sometimes lengthy turnaround time for pharmacogenomic testing poses challenges for beneficiaries who require urgent anticoagulation, as the test result may not become available until several days to a week or more after warfarin has been initiated and the dose is being titrated based on INR testing. This concern may be lessened if testing can be completed on a same day or next day basis but reservations remain. As several authors have noted, the early (during the first few days of warfarin therapy) INR results have a greater predictive value for the stable warfarin dose than the results of pharmacogenomic testing. We believe that pharmacogenomic testing to determine warfarin responsiveness is not supportable by evidence when the initiation of warfarin therapy has progressed past the early INR results, which we believe is accomplished by the fifth day of therapy.

The turnaround time for pharmacogenomic testing is less problematic for elective anticoagulation. We also note that such warfarin naïve beneficiaries would not have comparable early INR results as they would not be taking warfarin yet.

We therefore conclude that pharmacogenomic testing of *CYP2CP* or *VKORC1* alleles to predict warfarin responsiveness is reasonable and necessary only under section 1862(a)(1)(E) Coverage with Evidence Development, specifically Coverage with Study Participation (CSP), as noted above.

IX. Conclusion

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. Therefore, we have determined that pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act. However, we do believe the available evidence supports that Coverage with Evidence Development (CED) under §1862(a)(1)(E) of the Social Security Act is appropriate. Thus, we are making the following decision:

Pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness is 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. who are enrolled in a prospective,randomized, controlled clinical study when that study meets the following
4. standards:

A clinical study seeking Medicare payment for pharmacogenomic testing to predict warfarin responsiveness provided to the beneficiary pursuant to Coverage with Evidence Development (CED) must address one or more aspects of the following question.

Prospectively, in Medicare aged subjects whose warfarin therapy management includes pharmacogenomic testing 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 Food and Drug Administration (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 three (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 Social Security Act (the Act), the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that the Centers for Medicare and Medicaid Services (CMS) determines meet the above-listed standards and address the above-listed research questions.

Appendix A

General Methodological Principles of Study Design

(Section VI of the Proposed Decision Memorandum)

General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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[1] We also considered the evidence using the framework adopted by EGAPP (See Teutsch SM et al. (2009)), which includes the ACCE criteria. The recent MEDCAC (2/25/2009) on diagnostic uses of genetic testing recommended this approach. Although we are not formally adopting the ACCE framework, MEDCAC's strong endorsement has convinced us of its importance. The EGAPP 2009 framework is conceptually similar to Fryback and Thornbury's 1991 framework, which classified sources of evidence about the efficacy of diagnostic imaging, and which has been cited by CMS in prior DMs related to other forms of diagnostic technology. CMS believes the best current evidence on genetic testing for warfarin responsiveness does not rise to the highest level ('Level 1') of the EGAPP 2009 framework for clinical utility.

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