**Medical Policy**

**Title:** Genetic Testing for Warfarin Dose

**Professional**
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Revision Date(s): May 20, 2011; February 14, 2012; January 15, 2013; March 19, 2013; March 17, 2015; January 1, 2016; February 24, 2016; September 1, 2017
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Current Effective Date: January 1, 2016

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*Contains Public Information*
**DESCRIPTION**

Variants in *CYP2C9* and *VKORC1* genes result in differences in warfarin metabolism. Using information about an individual's *CYP2C9* and *VKORC1* genotypes may help in personalizing warfarin dosing and could reduce the time to dose stabilization and selection of appropriate maintenance dose that might avoid consequences of too much or too little anticoagulation.

**Objective**

The objective of this evidence review is to evaluate whether genetic testing for variants in *CYP2C9* and *VKORC1* guides selection of starting or maintenance dose of warfarin to improve net health outcome (eg, to prevent or treat thromboembolic events).

**Background**

Warfarin is administered to prevent and treat thromboembolic events in high-risk patients; warfarin dosing is a challenging process, due to the narrow therapeutic window, variable response to dosing, and serious bleeding events in 5% or more of patients (depending on definition). Patients are typically given a starting dose of 2 to 5 mg and monitored frequently with dose adjustments until a stable International Normalized Ratio (INR) value (a standardized indicator of clotting time) between 2 and 3 is achieved. During this adjustment period, a patient is at high risk of bleeding.

Stable or maintenance warfarin dose varies among patients by more than an order of magnitude. Factors influencing stable dose include body mass index (BMI), age, interacting drugs, and indication for therapy. Warfarin, which is primarily metabolized in the liver by the CYP2C9 enzyme, exerts an anticoagulant effect by inhibiting the protein vitamin K epoxide reductase complex, subunit 1 (*VKORC1*). Three single-nucleotide variants (SNVs), two in the *CYP2C9* gene and one in the *VKORC1* gene play key roles in determining the effect of warfarin therapy on coagulation. *CYP2C9*\^1 metabolizes warfarin normally, *CYP2C9*\^2 reduces warfarin metabolism by 30%, and *CYP2C9*\^3 reduces warfarin metabolism by 90%. Because warfarin given to patients with *\^2* or *\^3* variants will be metabolized less efficiently, the drug will remain in circulation longer, so lower warfarin doses will be needed to achieve anticoagulation. Recent genome-wide association studies have also identified that a SNV in the *CYP4F2* gene has been reported to account for a small proportion of the variability in stable dose (the *CYP4F2* gene encodes a protein involved in vitamin K oxidation).

Using the results of *CYP2C9* and *VKORC1* genetic testing to predict a warfarin starting dose that approximates a likely maintenance dose may benefit patients by decreasing the risk of serious bleeding events and the time to stable INR. Algorithms have incorporated not only genetic variation but also other significant patient characteristics and clinical factors to predict the best starting dose.
Regulatory Status
Several tests to help assess warfarin sensitivity, by determining the presence or absence of the relevant \textit{CYP2C9}, \textit{VKORC1}, and \textit{CYP4F2} variants, have been cleared by the U.S. Food and Drug Administration (FDA) for marketing (see Table 1). Similar tests also may be available as laboratory-developed services; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The tests are not identical in terms of the specific variants and number of variants detected. Generally, such tests are not intended as stand-alone tools to determine optimum drug dosage, but should be used with clinical evaluation and other tools, including the INR, to predict the initial dose that best approximates the maintenance dose for patients.

**Table 1. FDA-Cleared Warfarin Tests**

<table>
<thead>
<tr>
<th>Test (Laboratories)</th>
<th>Alleles Tested</th>
<th>Estimated Time to Completion, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>eSensor® Warfarin Sensitivity Test (GenMark Dx, Carlsbad, CA\textsuperscript{a})</td>
<td>\textit{CYP2C9}*2 and *3, \textit{VKORC1} 1639G&gt;A</td>
<td>3-4</td>
</tr>
<tr>
<td>Rapid Genotyping Assay (ParagonDx, Morrisville, NC)</td>
<td>\textit{CYP2C9}*2 and *3, \textit{VKORC1} 1173 C&gt;T</td>
<td>Not reported \textsuperscript{b}</td>
</tr>
<tr>
<td>Verigene® Warfarin Metabolism Nucleic Acid Test (Nanosphere, Northbrook, IL)</td>
<td>\textit{CYP2C9}*2 and *3, \textit{VKORC1} 1173C&gt;T</td>
<td>≤2</td>
</tr>
<tr>
<td>Infiniti® 2C9-VKORC1 Multiplex Assay for Warfarin (AutoGenomics, Vista, CA\textsuperscript{c})</td>
<td>\textit{CYP2C9}*2 and *3, \textit{VKORC1} 1639G&gt;A</td>
<td>6-8</td>
</tr>
<tr>
<td>eQ-PCR™ LightCycler® Warfarin Genotyping Kit (TrimGen, Sparks Glencoe, MD)</td>
<td>\textit{CYP2C9}*2 and *3, \textit{VKORC1} 1639G&gt;A</td>
<td>≤2</td>
</tr>
</tbody>
</table>


\textsuperscript{b} Langley et al (2009) reported a turnaround time of 1.5 hours for the ParagonDx SmartCycler, which may be a precursor assay.\textsuperscript{2}

\textsuperscript{c} The expanded Infiniti \textit{CYP450} 2C9 assay offers testing for \textit{CYP2C9} *2, *3, *4, *5, *6, and *11, \textit{VKORC1} 1639G>A, and 6 additional \textit{VKORC} variants.

In August 2007, FDA approved updated labeling for Coumadin\textsuperscript{®}, to include information on testing for gene variants that may help “personalize” the starting dose for each patient and reduce the number of serious bleeding events. The label was updated again in January 2010. With each update, manufacturers of warfarin (generic for Coumadin\textsuperscript{®}) were directed to add similar information to their products’ labels. The 2010 update added information on personalizing initial dose by genotyping results for \textit{CYP2C9} and \textit{VKORC1}, providing a table for genotypes, and suggested initial dose ranges for each. However, suggested starting doses are also provided for when genotyping information is unavailable, indicating that genetic testing is not required. Furthermore, FDA did not include information on genetic variation in the label’s black box warning on bleeding risk.
**POLICY**

Genotyping to determine cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase subunit C1 (VKORC1) genetic variants is considered experimental / investigational for the purpose of managing the administration and dosing of warfarin, including use in guiding the initial warfarin dose to decrease time to stable international normalized ratio (INR) and reduce the risk of serious bleeding.

Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**Policy Guidelines**

**Genetics Nomenclature Update**

Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (Table PG1). Human Genome Variation Society nomenclature is recommended by Human Genome Variation Society, the Human Variome Project, and the HUman Genome Organization.

The American College of Medical Genetics and Genomics and Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from the American College of Medical Genetics and Genomics, the Association for Molecular Pathology, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

**Table PG1. Nomenclature to Report on Variants Found in DNA**

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
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</table>

**Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification**

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.
Genetic Counseling
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

RATIONALE
This evidence review has been updated with searches of the MEDLINE database. The most recent literature review was performed through April 25, 2017. This evidence review addresses BCBSA genetic testing category 1c (therapeutic testing of an affected individual’s germline to benefit the individual; see Appendix Table 1 for genetic testing categories).

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (ie, how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). Following is a summary of the key literature.

Genetic Testing for CYP2C9 and VKORC1 Variants
Clinical Context and Test Purpose
The purpose of genetic testing for CYP2C9 and VKORC1 is to predict an individual’s initiation and maintenance dose of warfarin by incorporating demographic, clinical, and genotype data. In theory, this should lead to a predicted dose that will decrease the probability of over- or undercoagulation thereby avoiding the downstream consequences of thromboembolism or bleeding.

The questions addressed in this evidence review are: (1) Is there evidence that genetic testing for CYP2C9 and VKORC1 genotyping has clinical validity?; and (2) Does CYP2C9 and VKORC1 genotyping change patient management in a way that improves outcomes as a result of genetic testing?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients being considered for treatment with warfarin.
**Interventions**
A number of commercial tests for individual genes or panel testing are available and listed in Table 1.

**Comparators**
The comparator of interest is standard clinical management without genetic testing.

**Outcomes**
The general outcomes of interest are test accuracy, test validity, other test performance measures, morbid events, medication use and treatment-related morbidity. Specific outcomes are listed in the Table 2.

**Table 2. Outcomes of Interest for Individuals Undergoing CYP2C9 and VKORC1 Genotyping**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
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<tr>
<td>Morbid events</td>
<td>Bleeding, thromboembolism</td>
</tr>
<tr>
<td>Medication use</td>
<td>Initial and maintenance dose selection</td>
</tr>
<tr>
<td>Treatment-related mortality</td>
<td>Death due to under- or overtreatment</td>
</tr>
<tr>
<td>Treatment-related morbidity</td>
<td>Time to achieve therapeutic INR, time in therapeutic INR, bleeding, thromboembolism</td>
</tr>
</tbody>
</table>

INR: international normalized ratio.

The potential harmful outcomes are those resulting from a false-test result. False-positive or -negative test results can lead to under- or overtreatment and, consequently, adverse effects from under- or overtreatment.

**Timing**
Genetic testing may be used for dose selection before treatment initiation.

**Setting**
Patients requiring treatment with warfarin are managed by multiple specialists, including but not limited to cardiologists, cardiovascular surgeons, pulmonologists, internists, critical care physicians, and neurologists based on the clinical indication. Warfarin is used in both inpatient and outpatient settings.

**Analytic Validity**
Genetic testing for CYP2C9 and VKORC1 is available at a number of laboratories that have developed in-house tests; these labs tests do not require U.S. Food and Drug Administration (FDA) clearance, and information on analytic validity may not be generally available. Some laboratory-developed assays use commercially available reagents individually cleared by FDA as analyte-specific reagents. Test kits cleared for marketing by FDA include eSensor Warfarin Sensitivity Test (GenMark); Rapid Genotyping Assay (ParagonDx); Verigene Warfarin Metabolism Nucleic Acid Test (Nanosphere); Infiniti 2C9-VKORC1 Multiplex Assay for Warfarin (AutoGenomics); and eQ-PCR LightCycler Warfarin Genotyping Kit (TrimGen) (see Table 1). Inserts for FDA-cleared test kits summarize the extensive analytic validity data required for FDA clearance. Two studies have compared kits with FDA clearance and laboratory-developed assays using commercially available reagents and assay platforms; in each, the authors concluded that the assays provided accurate and rapid genotype information for the most common variants.
evaluated.2,3 However, a 2009 review noted that due to a lack of standardization, tests may
detect as few as 2 CYP2C9 variants or as many as 6.2 A 2013 review indicated that 7 CYP2C9
alleles are important for warfarin response (CYP2C9*2, *3, *5, *6, *8, *11, and *13), and the
frequencies vary across ethnic groups.4 For VKORC1, several known variants are in strong linkage
disequilibrium with one another; thus haplotypes (a combination of variants at nearby locations)
formed from various combinations can be used to assess status. Whether specific haplotypes can
improve predictive value is unknown.5

Turnaround times for these assays range from 1.5 to 8 hours, not including sample
transportation, processing, and delays due to assay scheduling. It is unknown how soon test
results might be needed during the warfarin initiation phase should outcome studies indicate net
benefit of testing.

Section Summary: Analytic Validity
Currently, 5 genotype assays for reduced function CYP2C9 and VKORC1 variants are FDA-cleared.
Evidence for the analytic validity of these tests is provided in the product labels. Although
information on analytic validity of laboratory-developed tests is generally unavailable, 2 studies
have reported comparable analytic validity for FDA-cleared and laboratory-developed tests.

Clinical Validity
Warfarin is metabolized by the cytochrome P450 enzyme CYP2C9; genetic variants of CYP2C9
result in enzymes with decreased activity, increased serum warfarin concentration at standard
doses, and a higher risk of serious bleeding. Information on cytochrome P450 pharmacogenetics
was summarized in a 2004 TEC Assessment6; application to warfarin dosing and important
nongenetic influences are discussed in several publications.7-10 VKORC1 genetic variants alter the
degree of warfarin effect on its molecular target and are associated with differences in
maintenance doses.11-15 CYP2C9 and VKORC1 genetic variations accounts for approximately 55%
of the variability in warfarin maintenance dose.15,16 In 2009, a genome-wide association study
identified a single-nucleotide variant (SNV), found in the CYP4F2 gene, that is also associated
with warfarin dose17; this association was confirmed in a separate, candidate gene study.18
Subsequent studies have predicted that CYP4F2 variants explain 2% to 7% of the variability in
warfarin dose in models including other genetic and nongenetic factors.18,19 Other factors
influencing dosage include body mass index, age, interacting drugs, and indication for therapy.

A 2008 systematic review, commissioned by the American College of Medical Genetics (ACMG),
evaluated CYP2C9 and VKORC1 genetic testing before warfarin dosing and concluded the
following20:

“Clinical validity: CYP2C9 and VKORC1 genotypes contribute significant and independent
information to the stable warfarin dose and, compared to the most common combination,
some individuals with other genotype combinations will need more than the usual dose, while
others will require less.”

Authors of several studies of clinical validity, mainly in white patients already at maintenance
doses evaluated retrospectively, have developed algorithms that incorporate VKORC1 and
CYP2C9 genetic variant information, as well as patient characteristics and other clinical
information.21-28 These studies have evaluated the extent to which these algorithms predicted
various outcomes such as maintenance dose, time to stable international normalized ratio (INR),
time spent in target INR range, and serious bleeding events. These algorithms vary in the
nongenetic variables included and, in general, account for up to approximately 60% of warfarin maintenance dose variance. CYP4F2 genotyping was also added to a retrospective evaluation of several algorithms that already included CYP2C9 and VKORC1; CYP4F2 variants, however, added only 4% to the fraction of the variability in stable dose explained by the best performing algorithms.29 A 2012 systematic review and meta-analysis by Liang et al suggested a more substantial contribution of CYP4F2 variants. Compared with wild-type patients, carriers of CYP4F2 variants required warfarin doses 11% and 21% higher for heterozygous and homozygous patients, respectively.30

Cohort studies have evaluated algorithm-guided dosing in patients starting warfarin and reported that algorithms explained 69% to 79% of the variance in maintenance dose.31,32 In 2009, the International Warfarin Pharmacogenetics Consortium (IWPC) compared an algorithm based only on clinical variables with one that also included genetic factors in a validation cohort of 1009 patients treated with warfarin.33 The pharmacogenetic algorithm was significantly more accurate at predicting an initial dose that was close to the maintenance dose in the 46% of patients who required low (≤21 mg/wk) or high (≥49 mg/wk) warfarin doses. The analysis did not address whether a more precise initial dose of warfarin resulted in improved clinical end points. Avery et al (2011) found that 42% of the variability in maintenance dose on days 4 to 7 was explained by the algorithm and that 40% of maintenance dose variability was explained on days 8 to 15.34

Other cohort studies also have evaluated the initiation phase of warfarin treatment, reporting the impact of genetic factors on different outcomes, including time to therapeutic INR, time to first supratherapeutic (overcoagulation) INR, and time above therapeutic range.35-37 In 2009, Limdi et al estimated that CYP2C9 and VKORC1 variants explained 6.3% of the variance in dose change over the first 30 days of therapy.38 Pautas et al (2010) reported that, in elderly patients with multiple comorbidities and polypharmacy who were starting warfarin, individuals with multiple variant alleles were at highest risk for overanticoagulation, with an odds ratio of 12.8 (95% confidence interval [CI], 2.8 to 60.0).39 Ferder et al (2010) reported that the predictive ability of CYP2C9 and VKORC1 variants in patients from the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial gradually diminished over time, from 43% at day 0 (warfarin initiation) to 12% at day 7, 4% at day 14, and 1% at day 21.40 Moreau et al (2011) studied 187 elderly patients starting warfarin using a “geriatric dosing-algorithm.”41 Adding CYP2C9 and VKORC1 genotype variants to the initial dosing model improved the explained variance in maintenance dose by 21%, from less than 10% to 31%. By day 3, VKORC1 was no longer a significant predictor of maintenance dose; however, CYP2C9 genotype remained a significant predictor. By day 6, neither CYP2C9 nor VKORC1 genotype variants was predictive of maintenance dose. These studies indicated that if genotyping results are clinically useful, it is likely only within the first week of beginning warfarin therapy.

Gong et al (2011) conducted a prospective cohort study of patients requiring warfarin therapy for atrial fibrillation or venous thromboembolism using a novel pharmacogenetic warfarin initiation protocol.42 Practical daily loading doses were prescribed for 2 days and were dependent on VKORC1 and CYP2C9 genotypes and, as necessary, on patient weight. Maintenance dose was determined in a regression model by combining key patient clinical parameters known to influence warfarin dose requirement with genotype. When VKORC1 and CYP2C9 genotypes were incorporated into warfarin initial dose determinations, they had no additional significant effect on time required to reach the first INR within therapeutic range, on risk of overcoagulation (INR ≥4), or on time to stable anticoagulation.
A 2012 study by Horne et al assessed whether pharmacogenetic algorithms can contribute to dose refinements after INR response to warfarin is known. Based on a population (N=1684) drawn from 3 continents and 16 study sites, an algorithm for determining warfarin dose was derived and included a novel treatment response index, comprising previous warfarin dose and INR measurements. The pharmacogenetic warfarin dose-refinement algorithm explained more variability in dosing ($R^2=71.8\%$) compared with the clinical algorithm ($R^2=64.8\%$). In addition to these patients, a prospective external validation cohort (n=43) was recruited to determine the safety and accuracy of the clinical algorithm. The pooled pharmacogenetic algorithm explained 58% to 79% of the variation in therapeutic dose, and the time in therapeutic range during days 11 to 30 was 62%. This pooled clinical algorithm was significantly more accurate than previously validated algorithms.

A 2012 prospective study by Perlstein et al assessed the validity of 3 warfarin-dosing algorithms to predict time in therapeutic range and time to first therapeutic INR in a predominantly white population (N=344). Dosing algorithms were developed sequentially to select both an initial warfarin dose and a titration scheme intended to maximize the likelihood of achieving and maintaining the target INR. Algorithm A determined initial dosing with a decision tree including both clinical and genetic factors based on best practices in the hospital’s anticoagulation management service and the published literature. Algorithm B was generated from an analysis of warfarin dose, INR, genetic factors, demographic factors, and concomitant drug therapy from a group of 74 patients treated with algorithm A. Algorithm C updated algorithm B, with a revision of the half maximal inhibitory concentration for VKORC1 haplotypes. The authors found a significant ($p=0.04$) progressive improvement in mean percentage time in therapeutic range over the entire study period for algorithm A (58.9%), algorithm B (59.7%), and algorithm C (65.8%). The secondary end point of per-patient percentage of INRs outside of the therapeutic range had a similar statistically significant trend across algorithms ($p=0.004$) with algorithm A reporting 21.6%, algorithm B, 22.8%; and algorithm C, 16.8%. Time to stable therapeutic anticoagulation decreased significantly across algorithms ($p<0.001$), but time to first therapeutic INR did not vary significantly subgroups. No differences in rates of adverse events were observed during this study.

Several studies have compared the ability of different algorithms to accurately predict stable warfarin dose. Currently, there does not appear to be consensus for a single algorithm. Rather, it may be necessary to select the algorithm best suited to the treatment population due to differences. For example, not all algorithms include the use of drugs that interact with warfarin; in fact, some studies have excluded patients taking interacting drugs. Hatch et al (2008) applied an algorithm developed in patients not taking interacting drugs and showed that when applied to a small number of patients taking interacting drugs, the proportion of dose variance explained by the algorithm decreased by approximately 10 percentage points.

Several authors have examined associations between CYP2C9 and VKORC1 variants and warfarin dosing requirements in children. Findings are preliminary. Proposed dosing algorithms require evaluation in large, prospective, randomized trials using current standard-of-care comparators to determine net health benefit.

**Ethnicity**

Several studies have included ethnically diverse populations, but it is unclear whether one or several algorithms are needed to address ethnicity. The algorithm developed by Gage et al...
(2008) explained 55% of the variance in a validation cohort of white populations but only 40% of the variation in a small cohort of African Americans. Schelleman et al (2008) developed separate predictive algorithms for white and African American populations, which explained 42% of the variance in white, but only 28% in African Americans. Wu et al (2008) included several different ethnicities in developing their predictive algorithm, which included an ethnicity variable, which overall explained 59% of warfarin dose variation. Schelleman et al (2008) developed separate predictive algorithms for white and African American populations, which explained 42% of the variance in white, but only 28% in African Americans. Wu et al (2008) included several different ethnicities in developing their predictive algorithm, which included an ethnicity variable, which overall explained 59% of warfarin dose variation. Limdi et al (2010) reported that the contribution of the VKORC1 variant to dose requirement is higher in whites than in nonwhites but that genotype predicts similar dose requirements across white, African American, and Asian populations; genotyping for additional VKORC1 variants (ie, other than 1639G>A and 1173C>T, the most commonly tested variants) did not improve dose prediction in any group.

Cavallari et al (2011) tested the performance of published warfarin dosing algorithms derived from non-Hispanic cohorts in the Hispanic population. The combination of the VKORC1 and CYP2C9 genotypes and clinical factors explained 56% of patient variability in warfarin dose. The predicted dose was within 1.0 mg/d of the therapeutic dose for 40% to 50% of patients. Gan et al (2011) studied Asian populations and found that patients from India, compared with Chinese and Malay patients, required a dose of 4.9 mg/d versus 3.5 mg/d and 3.3 mg/d, respectively. The higher warfarin doses correlated with particular VKORC1 genotypes found more commonly in the Indian population.

Perera et al (2011) identified novel genetic markers in VKORC1 and CYP2C9 associated with higher warfarin dosing in African Americans. A regression model, encompassing both genetic and clinical variables, explained 40% of the variability in warfarin maintenance dose. In 2013, Perera et al reported another novel marker in the CYP2C cluster (on chromosome 10) associated with reduced warfarin dosing in African Americans. The proportion of variability in warfarin maintenance dosing explained by adding this novel marker to the IWPC algorithm increased from 21% to 26%. Ramirez et al (2012) developed a predictive algorithm for calculating dose variation in African Americans that included variants in CYP2C9*6 and CALU (which encodes calumenin, a cofactor in the vitamin K epoxide reductase complex). The authors validated an expanded pharmacogenomic dosing algorithm and compared it with the IWPC algorithm with the 2 algorithms explaining 41% and 29% of variation, respectively. Other studies have identified new genetic variants and/or evaluated clinical genetic algorithms for warfarin dose in Thai, Egyptian, Chinese, Japanese, Arabic, Turkish, and Scandinavian populations. In general, genetic factors helped models explain 30% to 54% of the overall variance but were not always statistically significant.

Valentin et al (2012) examined a retrospective cohort of Puerto Rican patients (N=97) to determine the influence of CYP2C9 and VKORC1 variants on warfarin dose in this population. Blood samples were collected during routine INR testing and were analyzed with the HILoMet PhyxioType assay to detect 5 SNVs in CYP2C9 and 7 SNVs in VKORC1. Median actual effective warfarin doses were compared across CYP2C9 and VKORC1 carrier status (wild type/noncarriers, single, double, triple, and quadruple carriers). Significant differences (p<0.001) in warfarin dose were observed between wild type (5.71 mg/d), single carrier (4.64 mg/d), double carrier (3.43 mg/d), triple carriers (2.36 mg/d), and quadruple carriers (1.86 mg/d). No significant difference in time to target INR was identified between groups (p=0.34). Predicted daily warfarin dose was assessed by comparing IWPC pharmacogenomic-guided algorithm, clinical algorithm, and the fixed-dose approach. In the low-dose subgroup, the pharmacogenetic algorithm provided dose estimates that were more accurate, and closer to the actual doses required, than the estimates...
derived from the fixed-dose or clinical algorithms (p<0.001 for both comparisons). No differences were detected among the intermediate-dose patients between algorithms, and in the high-dose subgroup, a marginal difference between pharmacogenetic algorithm and clinical algorithm was found (p<0.042). This study is the first to describe the association between SNVs in CYP2C9 and VKORC1 genes and effective warfarin dose in Puerto Rican patients.

**Section Summary: Clinical Validity**
In primarily white populations, several retrospective and prospective cohort studies have documented that pharmacogenomic algorithms can explain 6% to 79% of the variance in warfarin maintenance dosing. In ethnically diverse populations, such algorithms can explain 40% to 59% of the variance. Accuracy of the algorithms appears to depend on the alleles tested; number of reduced function alleles present; use of interacting drugs; ethnicity; time of warfarin dosing after initiation; and maintenance dose eventually required (high or low). Evidence for the ability of pharmacogenomic algorithms to predict maintenance warfarin dose and to increase time in the therapeutic INR range comes from retrospective and cohort studies and is inconsistent. A single dosing algorithm readily generalizable to a diverse population and prospectively tested in a large, representative validation cohort has not been developed.

**Clinical Utility**

**Systematic Reviews**
In 2014 and 2015, 4 systematic reviews with meta-analyses compared genotype-guided warfarin dosing with other dose selection strategies.69-72 Meta-analyses used random-effects models or fixed-effects models when statistical heterogeneity ($I^2$) was 0%. Two systematic reviews69,70 included the same 9 randomized controlled trials (RCTs) comparing genotype-guided with clinically guided warfarin dosing (n=2812 patients); several RCTs reviewed below73-77 were included, all of which were rated high quality. Range of follow-up duration was 4 to 24 weeks (median, 12 weeks). Publication bias was not detected.69 With 1 exception, pooled results from both systematic reviews were consistent: There was no statistical difference between dosing strategies in the percentage of time that the INR was in therapeutic range ($I^2=89$%), the proportion of INRs that exceeded 4 ($I^2=0$%), or thromboembolic events ($I^2=0$%). However, Stergiopoulos et al (2014)69 found no difference in major bleeding events (pooled relative risk [RR], 0.60; 95% CI, 0.29 to 1.22; $I^2=0$%), and Franchini et al (2014)70 found reduced major bleeding events with genotype-guided warfarin dosing (pooled RR=0.48; 95% CI, 0.23 to 0.97; $I^2=0$%). This inconsistency may be attributed to the exclusion of the EU-PACT trial (reviewed below; N=455) from the Franchini systematic review. EU-PACT reported no major bleeding events in either warfarin dosing group.

A 2015 systematic review by Goulding et al reported improved clinical outcomes with genotype-guided versus other (ie, fixed or clinically guided) warfarin dosing.71 Literature was reviewed through December 2013; 9 RCTs were included, 7 of which overlapped with the systematic reviews previously described, and 6 of which were rated high or very high quality. Range of follow-up duration was 2 to 12 weeks. Pooled mean difference in the percentage of time within the therapeutic range was 6.67 percentage points (95% CI, 1.34 to 12.00; $I^2=80$%). However, this meta-analysis only included 1 trial that showed benefit of genotype-guided dosing compared with fixed initial warfarin dosing (2.5 mg/d)78 and excluded 2 trials (described below) that showed no benefit of genotype-guided dosing compared with clinically guided dosing.74,75 Meta-analysis also showed decreased risk of bleeding or thromboembolic events with genotype-guided dosing (pooled relative risk, 0.57; 95% CI, 0.33 to 0.99; $I^2=60$%).
A 2015 systematic review by Liao et al reported increased time in the therapeutic range with genotype-guided dosing compared with fixed initial warfarin dosing (3 RCTs; $I^2=48\%$) but not compared with clinically guided dosing (2 RCTs; $I^2=0\%$).\textsuperscript{72} Reviewers also found no overall difference between pooled groups in adverse events (major bleeding [defined as a decrease in hemoglobin $\geq 2$ g/dL], clinically relevant nonmajor bleeding, thromboembolism, myocardial infarction, death from any cause, or other conditions requiring emergency medical management; 4 RCTs; $I^2=0\%$) or mortality (3 RCTs; $I^2=10\%$).

The ACMG’s 2008 systematic review of \textit{CYP2C9} and \textit{VKORC1} genetic testing before warfarin dosing (cited earlier) concluded the following\textsuperscript{20}:

“Clinical utility: The purpose of genetic testing in this clinical scenario is to predict an individual’s likely stable warfarin dose by incorporating demographic, clinical, and genotype data (\textit{CYP2C9} and \textit{VKORC1}), and initiate warfarin at that predicted dose as a way to limit high International Normalized Ratio (INR) values (overanticoagulation) that are associated with an increased risk of serious bleeding events. No large study had at the time shown this to be acceptable or effective. Based on limited clinical data, the number needed to treat to avoid 1 serious bleeding event was estimated to range from 48 to 385.”

\textbf{Randomized Controlled Trials}

Few large, well-designed RCTs addressing clinical utility have been published. Such studies would evaluate the net benefit of using genetic factors, or algorithms that include genetic factors, to guide initial dosing compared with empirical initial dosing or dosing guided by clinical factors, such as age and body mass index. Additionally, such trials should address the degree to which INR must continue to be monitored to ensure that physicians do not overly rely on dosing algorithms and monitor patients less frequently, potentially increasing adverse events.

Two larger RCTs of pharmacogenetic dosing algorithms were published in 2013.\textsuperscript{76,77} The larger of these, the Clarification of Optimal Anticoagulation through Genetics (COAG) trial, was conducted in the U.S. by the National Heart, Lung, and Blood Institute,\textsuperscript{76} and the smaller trial was conducted in Sweden and England by the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) consortium.\textsuperscript{77} In both trials, the intervention period was the first 5 days of dosing; genotyping comprised the \textit{CYP2D6}*2 and *3 and \textit{VKORC1} 1639G$>$A alleles; and the primary outcome was the mean percentage of time in the therapeutic INR range of 2.0 to 3.0. Neither trial reported an intention-to-treat analysis.

In the COAG trial, 1015 individuals, 6 to 70 years old, 51\% male, and 27\% African American, were randomized to warfarin doses for the first 5 days of therapy based on their clinical and genetic characteristics or on their clinical characteristics alone.\textsuperscript{76} Patients were followed for 4 additional weeks during which time their drug doses were adjusted based on standard protocols. Ninety-four percent ($n=955$) of patients completed the 5-day intervention period and were included in efficacy analyses. Results showed that INR was within a desired range 45\% ($p=0.91$) of the time in both groups during the 28-day monitoring period, based on standardized blood clotting tests. The principal secondary outcome (a composite of INR $\geq 4$, major bleeding [fatal hemorrhage, intracranial bleeding, or symptomatic bleeding requiring overnight hospitalization, transfusion, angiographic intervention, or surgery], or thromboembolism) was also similar in the 2 groups (20\% vs 21\%, respectively; $p=0.93$). Subgroup analysis of 255 black patients showed that clinically guided group fared better than the genotype-guided group (INR was within a desired range 43.5\% vs 35.2\%, respectively; $p=0.01$).
In the EU-PACT trial, 455 individuals, 24 to 90 years old, 99% white, were randomized to warfarin doses for the first 3 days based on their clinical and genetic characteristics or on their clinical characteristics alone. Patients were followed for 12 additional weeks during which time their drug doses were adjusted based on standard protocols. Ninety-four percent of patients had 13 or more days of INR data and were included in efficacy analyses. Results showed that INR was within a desired range 67% of the time in the genotyped-guided dosing group compared to 60% in clinically guided group (p<0.001). There were no differences in secondary outcomes assessed (bleeding or thromboembolism events). However, the percentage of patients with INR greater than 4 was lower in genotype-guided group (27%) than in the clinically guided group (37%). Note that INRs greater than 4 can lead to serious bleedings. The time to achieving therapeutic INR in fact was also shorter in the genotyped-guided group (21 days) than in the clinically guided group (29 days).

Notable differences between the 2 trials included the EU PACT trial’s use of a fixed-dose control arm while the COAG trial did not. Instead, multiple clinical variables such as age, sex, African American race, and concomitant drug use were used to guide warfarin dosing in the control arm. Further, African American patients made up almost one-third of the COAG trial population, unlike the EU-PACT trial population. The distribution of patients with a genotype associated with a greater impact on warfarin metabolism such as homozygous for VKORC1 or CYP2C9 was more prevalent in the EU-PACT trial than in the COAG trial (17% vs 11% and 3.4% vs 1%, respectively).

Other RCTs are summarized briefly below. Burmester et al (2011) reported results of prospective, blinded, randomized trial that compared genetic plus clinically guided dosing with clinically guided dosing only in 230 hospitalized patients. The median percent time in therapeutic INR range was the same (28.6% in each group) and the median time to stable therapeutic dose also was similar in both arms (≈30 days). The proportion of patients with INR greater than 4.0 was similar (p=0.94).

A blinded RCT (CoumaGen-II) by Anderson et al (2012) investigated whether 2 pharmacogenetic-guided testing algorithms (1-step IWPC algorithm and 3-step modified IWPC algorithm) were better than standard empirical warfarin dosing. Primary end points were the percentage of out-of-therapeutic range INRs and time in therapeutic INR range during the first month and through the third month of warfarin therapy. Both approaches were equivalent at 1 and 3 months for all outcomes, with a stable maintenance dose determined in 444 (88%) patients. There was an inverse relation between the number of reduced function alleles and stable maintenance dose (p<0.001). Pharmacogenomic guidance was more accurate in wild-type patients and in those with multiple variants (p<0.001). Both approaches arms were pooled and observed to be superior to the standard dosing approach with significant (p<0.001) reductions in percentage of time out of the INR range and percentage of time in the therapeutic range at 1 and 3 months after controlling for relevant variables. Adverse events (hemorrhagic events, thromboembolic events, or other serious adverse events) were greater in the control group (9.4%) compared with the pharmacogenetic-guided group (4.5%), with an adjusted relative risk of 0.44 (95% CI, 0.28 to 0.70; p<0.001).

Mega et al (2015) published a supplemental analysis to the ENGAGE AF-TMI 48 trial that examined the clinical response to warfarin among patients with genetic variants. All patients taking warfarin were classified by genetic status as normal (62%), sensitive (35%), or highly
sensitive (3%). Sensitive or highly sensitive responders had higher risks of bleeding than normal responders. For sensitive responders, the hazard ratio was 1.31 (95% CI, 1.05 to 1.61) compared with normal responders, and for highly sensitive responders, the hazard ratio was 2.66 (95% CI, 1.7 to 4.2).

In 2007, Anderson et al reported on an RCT comparing algorithm-guided initial warfarin dosing (including genetic variable; n=101) with empirical dosing (n=99). The primary outcome measure was “per-patient percentage of out-of-range INRs.” Algorithm-predicted doses more accurately approximated maintenance doses, resulting in significantly fewer dose changes, but the primary end point was not achieved (p=0.47); the secondary outcome of serious adverse events also did not differ between study groups (p=0.71).

Jonas et al (2013) reported on a double-blind RCT of 109 adults initiating long-term warfarin therapy. Patients were randomized to warfarin dosing by an algorithm that contained both genetic (specifically, CYP2D6*2 and *3 and VKORC1 1639G>A [also known as VKORC1 3673G>A]) and clinical factors or clinical factors only. Most patients (70%) were white; 30% were African American. Primary efficacy outcomes were the mean number of anticoagulation visits (to clinic or physician) in 90 days and time in the therapeutic range. The trial was powered to detect a difference of 2 visits and a 10% difference in time in the therapeutic range. There were no statistically significant differences between intervention groups for any primary or secondary outcome. (Secondary outcomes included emergency visits, hospitalizations, minor [not requiring hospitalization or transfusion] and major hemorrhagic events, thrombotic events and deaths, but the trial was not powered to detect differences in these outcomes.)

Cohort Studies
In association with Medco, a pharmacy benefits management organization, Epstein et al (2010) conducted a cohort study with historical control in patients initiating warfarin therapy who were invited to participate and receive free genotyping. Hospitalization rates (the primary outcome) during the next 6 months were compared with those of a historical control group of similar patients who had initiated warfarin therapy the previous year. The authors reported that the genotyped cohort had 31% fewer hospitalizations overall compared with controls (adjusted hazard ratio [HR], 0.69; 95% CI, 0.58 to 0.82; p=0.001) and 28% fewer hospitalizations for bleeding or thromboembolism (HR=0.72; 95% CI, 0.53 to 0.97; p=0.029). However, the number of patients who were offered but declined enrollment was omitted from publication, making it impossible to discern selection bias. A high patient refusal rate could produce a highly selected population, not comparable to unselected historical controls. Additionally, hospitalizations related to bleeding or thromboembolism were reduced by 2.2% in absolute terms, and all-cause hospitalizations had a much larger reduction of 7.1%. The latter is more than triple that expected if only due to reductions in hospitalizations from bleeding or thromboembolism by improved warfarin dosing. In the absence of selection bias, changes in warfarin dosing would not be expected to impact hospitalizations for nonhematologic reasons. The question of selection bias could have been avoided in this study if genotyping results had been sent randomly to only half of the physicians caring for patients tested.

Section Summary: Clinical Utility
Multiple randomized trials and meta-analyses of these trials have examined the use of pharmacogenomic algorithms to guide initial warfarin dosing and yielded inconsistent results. Two, large, adequately powered RCTs conducted to resolve the conflicting evidence generated by
smaller RCTs, reported contrasting results. However, the 2 trials, conducted in the United States or in Europe, differed in control arms used. The U.S. trial used standard clinical variables to guide warfarin dosing in the control arm, had a large proportion of African American, and was double-blind: it showed no difference when dosing by genotype. The European trial used a fixed-dose control arm, largely included white patients, and was open-labelled: it showed a difference favoring warfarin dose guided by a genetic testing strategy. Because the findings of the U.S. trial are largely applicable to the U.S. population and more influential than the European trial (owing to its larger sample size, use of double-blind design, and more appropriate control arm), the current evidence does not demonstrate clinical utility in adding genetic testing to a clinical dosing algorithm.

Summary of Evidence
For individuals with conditions requiring warfarin treatment who are being managed with genetic testing for CYP2C9 and VKORC1 variants to determine warfarin dose, the evidence includes multiple randomized controlled trial (RCTs), systematic reviews of the RCTs, and cohort studies. Relevant outcomes are test accuracy and validity, other test performance measures, morbid events, medication use, and treatment-related morbidity. The evidence on clinical validity from several retrospective and prospective cohort studies has shown that algorithms incorporating genetic variants and clinical factors explain greater variance in warfarin dosing over that predicted by clinical factors alone. However, the incremental gain using genetic testing depends on multiple factors, including ethnicity. Further, there is no consensus on a single algorithm that could be generalized to a diverse population. Multiple smaller randomized trials and meta-analyses of these trials have examined the clinical utility of genetic tests to guide warfarin dose and reported inconsistent results. Two large adequately powered RCTs attempted to address this inconsistency but reported contrasting results. Of these 2 trials, the larger U.S.-based RCT found no utility in adding genetic testing to a clinical dosing algorithm. The percentage of time in the therapeutic international normalized ratio range was similar when genetic testing was and was not added. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements
American College of Medical Genetics
The 2008 American College of Medical Genetics policy statement on pharmacogenetic testing concluded: “There is insufficient evidence, at this time, to recommend for or against routine CYP2C9 and VKORC1 testing in warfarin-naive patients.”

American College of Chest Physicians
The 9th edition of the American College of Chest Physicians’ evidence-based clinical practice guidelines on antithrombotic therapy and prevention of thrombosis, published in 2012, stated: “For patients initiating VKA [vitamin K antagonist] therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B).”

Conference in Biomedicine on Pharmacogenetics and Pharmacogenomics
In 2011, the 3rd European Science Foundation–University of Barcelona Conference in Biomedicine on Pharmacogenetics and Pharmacogenomics published a summary on CYP2C9 and VKORC1 genotyping for warfarin dosing. The report noted the Food and Drug Administration’s addition of genetic information to the warfarin label but stated that the European Medicines Agency has not yet decided whether to include this information in European drug labels.
**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

In August 2009, the Centers for Medicare & Medicaid Services (CMS) published a national coverage determination on pharmacogenomic testing for warfarin response. CMS stated that “the available evidence does not demonstrate that pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness improves health outcomes in Medicare beneficiaries outside the context of CED, and is therefore not reasonable and necessary under §1862(a)(1)(A) of the Act.”

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

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

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 3.

**Table 3. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
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<tr>
<td>NCT01633957</td>
<td>A Trial of Genotype-based Warfarin Initiation in Patients With Mechanical Prosthetic Heart Valve (SYSU-WARFA)</td>
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<td>Aug 2016 (ongoing)</td>
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<tr>
<td>NCT00700895</td>
<td>A Randomized Controlled Trial to Assess the Clinical Benefits of a Pharmacogenetics-Guided Dosing Regimen for Calculating Warfarin Maintenance Dose</td>
<td>320</td>
<td>Aug 2017</td>
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<tr>
<td>NCT00964353</td>
<td>The Hospital and Economics CERT: Project 1: The Clinical and Economic Implications of Genetic Testing for Warfarin Management</td>
<td>268</td>
<td>Dec 2018</td>
</tr>
</tbody>
</table>

| **Unpublished** |                                                                        |                    |                 |
| NCT01318057    | Pharmacogenetics of Warfarin in Puerto Rican Patients Using a Physiogenomics Approach | 350                | Jul 2014 (completed) |
| NCT01305148a   | Warfarin Adverse Event Reduction For Adults Receiving Genetic Testing at Therapy Initiation (WARFARIN) | 3800               | Dec 2015 (suspended) |
| NCT01006733    | Genetics Informatics Trial (GIFT) of Warfarin to Prevent Deep Venous Thrombosis (DVT)27 | 1598               | Nov 2016 (completed) |

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.
CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

81355  VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, 1639G>A, c.173+1000C>T)
G9143  Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)

- There are CPT codes that are specific to this testing: 81227, 81355.

Diagnoses

Experimental / investigational for all diagnoses codes related to this medical policy.

REVISIONS

<table>
<thead>
<tr>
<th>Date</th>
<th>Changes</th>
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<tr>
<td>02-24-2012</td>
<td>Description section updated, Rationale section updated, References updated</td>
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<tr>
<td>01-15-2013</td>
<td>In Coding section: Removed CPT codes: 88384, 88385, 88386 (effective 12-31-2012).</td>
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<tr>
<td>03-19-2013</td>
<td>Description section updated, In Coding section: Added CPT code: 81355 (effective 01-01-2012), Updated CPT code notations, Rationale section updated, References updated</td>
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<td>03-17-2015</td>
<td>Description section updated, Rationale section updated, In Coding section: Updated Coding informational bullets, In Revision section: Removed detailed information for: 10-26-2010, 05-20-2011, 02-14-2012, References updated</td>
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<td>01-01-2016</td>
<td>In Coding section: Revised CPT Code: 81355</td>
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<td>02-24-2016</td>
<td>Description section updated, In Policy section: Added &quot;international normalized ratio&quot; to provide nomenclature for &quot;INR&quot;, Rationale section updated, In Coding section: Added CPT code: G9143, References updated</td>
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In Policy section:
• Replaced "polymorphisms" with "variants" to read "Genotyping to determine cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase subunit C1 (VKORC1) genetic variants is considered experimental / investigational..."
• Policy Guidelines updated with addition of Human Genome Variation Society nomenclature and American College of Medical Genetics and Genomics and Association for Molecular Pathology standards and guidelines.

Rationale section updated

References updated

REFERENCES


Appendix Table 1. Categories of Genetic Testing

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>1a. Diagnostic</td>
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<tr>
<td>1b. Prognostic</td>
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<tr>
<td>1c. Therapeutic</td>
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<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
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<tr>
<td>2a. Diagnostic</td>
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</tr>
<tr>
<td>2b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td></td>
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<tr>
<td>3. Testing an asymptomatic patient to determine future risk of disease</td>
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<tr>
<td>4. Testing of an affected individual's germline to benefit family members</td>
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<tr>
<td>5. Reproductive testing</td>
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<td>5a. Carrier testing: preconception</td>
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<tr>
<td>5b. Carrier testing: prenatal</td>
<td></td>
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<tr>
<td>5c. In utero testing: aneuploidy</td>
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<tr>
<td>5d. In utero testing: mutations</td>
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</tr>
<tr>
<td>5e. In utero testing: other</td>
<td></td>
</tr>
<tr>
<td>5f. Preimplantation testing with IVF</td>
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