HIGHMARK Delaware
HEALTH OPTIONS

CLINICAL MEDICAL POLICY	
Policy Name:	Genetic Testing for Warfarin Therapy
Policy Number:	MP-063-MD-DE
Responsible Department(s):	Medical Management
Provider Notice Date:	08/15/2019; 10/15/2018; 01/15/2018
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Products:	Highmark Health Options Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 6

DISCLAIMER

Highmark Health Options medical policy is intended to serve only as a general reference resource regarding coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

POLICY STATEMENT

Highmark Health Options does not provide coverage for genetic testing for warfarin therapy initiation.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrant individual consideration, based upon review of applicable medical records.

The qualifications of the policy will meet the standards of the National Committee for Quality Assurance (NCQA) and the Delaware Department of Health and Social Services (DHSS) and all applicable state and federal regulations.

DEFINITIONS

Genetic Testing – Genetic testing requires the analysis of human chromosomes, DNA (deoxyribonucleic acid), RNA (ribonucleic acid), genes, or gene products in order to detect or predict risk of inherited or non-inherited genetic variants related to disease, identify carriers, or establish prenatal and clinical diagnosis or prognosis.

Genetic Counseling – The process in which a specially trained professional evaluates family history, medical records, and genetic test results in the risk assessment of an individual for genetic disease, while understanding the limitations and risks of genetic testing.

Warfarin (Coumadin®) – An anticoagulant therapeutic used to reduce the formation of blood clots. Warfarin is used to treat or prevent blood clots in veins or arteries, which can reduce the risk of stroke, heart attack, or other serious conditions.

International Normalized Ratio (INR) – A calculation based on results of a prothrombin time (PT) and is used to monitor individuals who are being treated with the blood-thinning medication warfarin.

PROCEDURES

1. Medical Necessity Guidelines
   Pharmacogenetic testing of CYP2C9 and VKORC1 alleles are considered experimental and investigational for managing the administration and dosing of warfarin dosing therapy, including use in guiding the initial warfarin dose to decrease time management to a stable INR and to reduce the risk of serious bleeding.

2. Post-payment Audit Statement
   The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Gateway Health℠ at any time pursuant to the terms of your provider agreement.

GOVERNING BODIES APPROVAL

There have been several tests that have been cleared by the U.S. Food and Drug Administration (FDA) to help assess warfarin sensitivity by determining the presence or the absence of the relevant CYP2C9, VKORC1, and CYP4F2 variants.
On August 16, 2007, the FDA approved updated labeling for Coumadin (warfarin), to include information on genetic testing for gene variants that may help "personalize" the starting dose for each patient and reduce the number of serious bleeding events.

Warfarin pharmacogenetic tests cleared by the FDA:

Name of Test	Alleles Tested	Estimated Time to Completion, h
eSensor Warfarin Sensitivity Test (GenMark Dx, Carlsbad, CA)[a]	CYPC9*2 and *3, VKORC1-1639G/A	3-4
Verigene Warfarin Metabolism Nucleic Acid Test (Nanosphere, Northbrook, IL)	CYPC9*2 and *3, VKORC1-1173C/T	≤ 2
Infiniti 2C9-VKORC1 Multiplex Assay for Warfarin (AutoGenomics Inc., Vista, CA)[b]	CYP2C9*2 and *3, VKORC1 -1639G/A	6-8
eQ-PRC LightCycler Warfarin Genotyping Kit (TrimGen, Sparks Glencoe, MD)	CYP2C9*2 and *3, VKORC1 -1639G/A	≤ 2

[a] eSensor Warfarin Plus Test offers testing for CYP2C9*2, *3, *5, *6, *11, *14, *15, and *16, VKORC1 -1639G>A, and CYP4F2.

[b] The expanded Infiniti CYP450 2C9 assay offers testing for CYP2C9*2, *3, *4, *5, *6 and *11, VKORC1 – 1639G.A and six additional VKORC variants.

CODING REQUIREMENTS

Non-covered Procedure Codes

CPT/HCPCS Codes	Description
G9143	Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (e.g., warfarin metabolism), gene analysis, common variant(s) (e.g., -1639G>A, c.173+1000C>T)

*Requests for any of these procedure codes will require Medical Director review.

REIMBURSEMENT

Participating facilities will be reimbursed per their Highmark Health Options contract.

SUMMARY OF LITERATURE

Warfarin is the most commonly prescribed oral anticoagulant and is effective in reducing and preventing thromboembolism or stroke in patients with history of a thromboembolism, recent orthopedic surgery, atrial fibrillation (AF), heart valve replacement, or other diseases that increase the risk for thrombosis (Cavallari, 2011).

Although warfarin plays an integral role in helping patients lower the risk of thromboembolic events, the drug is difficult to manage due to highly variable pharmacological responses in anticoagulant effects and narrow therapeutic ranges. Warfarin dosing varies according to influencing factors such as age, race, body weight, diet, gender, concomitant medications, other drug interference, comorbidities, or genetic factors (CYP2C9 and VKORC1) (Coumadin [prescribing information], 2017). Clinical evidence shows significant variations in dose requirements on the basis of race, with African-Americans averaging higher maintenance doses and Asians averaging lower maintenance doses (Cavallari, 2011). The challenging factors create difficulty in achieving and maintaining levels of time in therapeutic range (TTR) which can lead to adverse drug events (Flockhart, 2008).

The genetic factors consist of two genetic variants: cytochrome p 450 2C9 (CYP2C9) and vitamin K epoxide reductase subunit C1 (VKORC1) genes, contributing to the proportion of inter-individual variability within warfarin responses (Park, 2017). Variants in CYP2C9 and VKORC1 genes result in differences in warfarin metabolism. The variations in genes encoding CYP2C9 and VKORC1 account for 10%-15% and 20%-35%, respectively, of variations in warfarin dose requirements (Park, 2017). In addition to the warfarin inter-individual variability, scientific data shows differences in genetic predisposition among racial groups, leading to the increased prevalence of CYP2C9 AND VKORC1 alleles in specific races (See Attachment C).

Genetic testing for CYP2C9 and VKORC1 genes was developed and is performed using the polymerase chain reaction and a variety of downstream methodologies to detect the specific variants of interest. The results of CYP2C9 and VKORC1 genetic testing provide the ability to predict when to start a warfarin dose that approximates a patient's likely maintenance dose. A genetic test for CYP2C9 and VKORC1 may benefit patients by decreasing the risk of serious bleeding events and improving time management to produce a stable INR (Cavallari, 2011). Pharmacogenetic algorithms have been developed to incorporate genetic

variation and other significant factors to predict the best starting dose (Kimmel, 2015). Most dosing is developed and individually designed by clinical algorithms but it does not incorporate genetic variants. The clinical algorithms do include all pertinent clinical information. The International Warfarin Pharmacogenomics Consortium (IWPC) set forth to publish algorithms for CYP2C9 and VKORC1 genes to calculate average dosing for individuals in each country (Park, 2017). The IWPC consists of 22 research groups from four continents and 11 countries (Kimmel, 2015). The recommendations suggest three ranges of expected maintenance doses observed in subgroups of patients with differing combinations of CYP2C9 and VKORC1 gene variants (Coumadin [prescribing information], 2017). Patients that have CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require a longer amount of time (> 2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen than patients without these CYP variants (Coumadin [prescribing information], 2017).

Rationale

There is insufficient evidence to conclude that testing for CYP2C9 and VKORC1 genetic variants improves the health outcomes of patients taking warfarin. The health outcomes consist of events such as bleeding rates and thromboembolisms. In genotyping, there is a validation multistep process which shows pharmacologic treatment outcomes. In warfarin genotyping, there are three important periods in the validation process, including analytic validity, clinical validity, and clinical utility (Cavallari, 2011).

There are two mechanisms of warfarin pharmacogenetic test introduction into clinical use, including available in-house testing which does not require FDA clearance and assays that are used in laboratories which have received clearance through the FDA in vitro diagnostic devices or “test kits” (Kimmel, 2015). The tests that do not require FDA clearance have infrequent publishing of developed data, contributing to the lack of information that shows analytical validity (Flockhart, 2008). *(See the warfarin pharmacogenetic tests cleared by the FDA in the Procedures section above*.)

The last step in the validation process for the CYP2C9 and VKORC1 genotyping is clinical utility, which had global pharmacogenetic data investigated through the IWPC. The IWPC investigators pooled genotype and phenotype data from more than 5,700 warfarin-treated patients to create a large, geographically and ethnically diverse population to discover the use of genetics to alter dose in practice (Cavallari, 2011). In addition to the IWPC investigation, randomized controlled trial (RCT) remains the gold standard for comparing genetic-based strategies.

There have been ongoing, prospective trials developed to evaluate the clinical utility. Based on the associated RCTs and systematic reviews, there is an unclear clinical utility for using the genetic variant information to guide the therapy and dosing of warfarin (Kimmel, 2015). Although analytical validity and clinical validity demonstrate a relationship between genetic variants and the adverse events of dosing and drugs, there is no evidence that warfarin genetic testing reduces the rate of adverse events experienced by patients taking warfarin (Kimmel, 2015). Even with availability of FDA-cleared devices, there are still several large barriers to clinical adoption of warfarin genetic testing.

Some of the important gaps and barriers to warfarin pharmacogenetic testing for analytical validity include (Flockhart, 2008):

1. A poorly organized evidence base related to the analytical performance of tests targeting rarer variants;
2. There is limited information on the performance of clinical laboratories;
3. There is a lack of comparative information on the performance of the multiple laboratory methods used for testing;
4. There is a gap in knowledge of INR testing related to intralaboratory performance differences;

5. There is a gap in knowledge of INR testing related to the differences between point-of-care and clinical laboratory-based testing;
6. There is a gap in knowledge of INR testing related to the direct comparison of the utility of the INR as compared with molecular testing.

There are several gaps and barriers to warfarin (CYP2C9 and VKORC1) pharmacogenetic testing for clinical validity including (Flockhart, 2008):

1. The clinical sensitivity, clinical specificity, relative risk, and attributable risk of severe bleeding in VKORC1 haplotypes and CYP2C9 and VKORC1 genotypes combined are poorly characterized;
2. The contribution of genetic versus other influences toward bleeding is poorly understood for many populations (i.e. specific races);
3. Positive and negative predictive values for severe bleeding in the VKORC1 halotypes and the CYP2C9 and VKORC1 genotypes combined is poorly understand;
4. Understanding of the clinical performance characteristics in those with rare alleles and the compound heterozygotes with those alleles is less well informed than is the evidence for the common alleles.

There are also several gaps and barriers to warfarin (CYP2C9 and VKORC1) pharmacogenetic testing for clinical utility including (Flockhart, 2008):

1. The lack of adequately powered prospective trials that test whether pharmacogenetically guided therapy is able to reduce the risk of warfarin-associated adverse events during the initiation phase, during the maintenance phase, or during longer periods of therapy;
2. There is a lack of trials that have tested whether does adjustments resulting from the use of genetic testing are associated with changes in the efficacy of warfarin;
3. There is a lack of comprehensive data on cost or cost-effectiveness as to the use of VKORC1 testing alone or in combination with CYP2C9;
4. An examination of the clinically necessary and/or preferred turn-around-time of CYP2C9 and VKORC1 testing as related to the clinical situations in which it is used;
5. There is a lack of validated educational materials for patients and providers;
6. There is a lack of guidelines for the evaluation of program performance.

There are no professional organizations that endorse warfarin pharmacogenetic testing in guidelines due to the lack of clinical utility (Cavallari, 2011). In addition to professional organizations, the Centers for Medicare and Medicaid Services (CMS) and many commercial insurers have deemed the warfarin genetic testing investigational due to the lack of clinical utility. CMS has criteria that supports coverage with evidence development (CED) under §1862(a)(1)(E) of the Social Security Act (the Act) appropriate for pharmacogenomics testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness (CMS, 2009). Genetic testing for Warfarin therapy is only covered when provided to Medicare beneficiaries who are candidates for the CED clinical study (CMS, 2009). Before routine testing can be recommended, evidence for the clinical utility of genotyping for clinical management needs to be developed. Therefore, genotyping for variants to predict initial warfarin dose is considered investigational.

POLICY SOURCE(S)

Cavallari LH, Shin J, Perera MA. Role of pharmacogenomics in the management of traditional and novel oral anticoagulants. Pharmacotherapy. Dec 2011; 31(12):1192-1207. PMID 22122181. Accessed on June 30, 2017.

CMS National Coverage Determination. NCD 90.1, Pharmacogenomic testing for warfarin response; effective August 3, 2009.

Coumadin (warfarin) [prescribing information]. Princeton, NJ: Bristol-Meyers Squibb; May 2017. Accessed on June 27, 2017.

Flockhart, D.A., O'Kane, D., Williams, M.S., et al. Pharmacogenetic testing of CYP2C9 and VKORC1 alleles for warfarin: ACMG Policy Statement. Genetics in Medicine: American College of Medical Genetics 2008; 10:2. Accessed on June 26, 2017.

Kimmel, S.E. Warfarin pharmacogenomics: current best evidence: Invited Review. Journal of Thrombosis and Haemostasis 2015; 13:S266-S271. Accessed on June 29, 2017.

Park, Y.K., Lee, M.J., Kim, J.H., et al. Genetic and Non-Genetic Factors Affecting the Quality of Anticoagulation Control and Vascular Events in Atrial Fibrillation. Journal of Stroke and Cerebrovascular Diseases, April 2017. Accessed on June 29, 2017.

Policy History

Date	Activity
07/03/2017	Initial policy developed
07/19/2017	QI/UM Committee approval
02/15/2018	Provider effective date
09/11/2018	Annual Review Revisions: Attachment C has been titled informational; added CMS position to the summary of literature; operational guidelines updated; updated references
09/11/2018	QI/UM Committee Review Approval
11/15/2018	Provider effective date
06/25/2019	Annual Review Revisions: No criteria changes; no operational changes
07/16/2019	QI/UM Committee Review Approval
09/16/2019	New Provider Effective Date