CLINICAL MEDICAL POLICY	
Policy Name:	Genetic Testing for Warfarin and Clopidogrel Therapy
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Responsible Department(s):	Medical Management
Provider Notice/Issue Date:	07/01/2023; 09/01/2022; 08/20/2021; 07/20/2020; 08/12/2019; 09/15/2018
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Products:	Highmark Wholecare℠ Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 11

Policy History

Date	Activity
08/01/2023	Provider Effective date
06/06/2023	PARP Approval
05/17/2022	QI/UM Committee review
05/17/2023	Annual Review: No changes to clinical criteria. Updated 'Summary of Literature' and 'Reference Sources' sections.
10/01/2022	Provider Effective date
08/01/2022	PARP Approval
05/18/2022	QI/UM Committee review
05/18/2022	Annual Review: Per DHS guidance, added the following guidance to the 'Procedures' section, #2: "*Pharmacogenomic testing of CYP2C19 may be considered medically necessary for individuals undergoing treatment of acute ischemic stroke or transient ischemic attack (TIA)*". Added TAG determination information. Updated Reference Sources section.
09/20/2021	Provider Effective Date
07/23/2021	PARP Approval
05/19/2021	QI/UM Committee Review
05/19/2021	Annual Review: Updated Governing Bodies Approvals, Summary of Literature, and Reference section.
08/17/2020	Provider effective date

07/09/2020	PARP approval
05/20/2020	QI/UM Committee Review
05/20/2020	Annual Review; No criteria changes for warfarin. Title changed as coverage was added for genetic testing for clopidogrel therapy; revised operational guidelines to include 81225 as a covered procedure code and added code to covered code section under attachment B. Updated Governing Bodies' Approval, Summary of Literature, and References sections; removed table from Summary of Literature. Removed Informational Attachment C, changed Attachment C to Diagnosis Codes.
08/12/2019	Provider Effective Date
06/07/2019	PARP Approval
05/15/2019	QI/UM Committee Review
05/15/2019	Annual Review: Formatting updates; no criteria changes
07/03/2017	Initial policy developed

Disclaimer

Highmark Wholecare℠ 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 Wholecare℠ does not provide coverage for genetic testing for warfarin therapy initiation, however coverage may be provided for clopidogrel genetic testing.

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.

Current applicable Pennsylvania HealthChoices Agreement Section V. Program Requirements, B. Prior Authorization of Services, 1. General Prior Authorization Requirements.

Definitions

Prior Authorization Review Panel (PARP) – A panel of representatives from within the Pennsylvania Department of Human Services who have been assigned organizational responsibility for the review, approval and denial of all PH-MCO Prior Authorization policies and procedures.

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.

Clopidogrel (Plavix®) – A platelet inhibitor indicated for use in acute coronary syndrome (ACS), recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease. Plavix has been shown to reduce the rate of MI and stroke.

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. PharmacogenomicPharmacogenomic testing of CYP2C19 may be considered medically necessary for individuals with acute coronary syndrome (ACS) undergoing percutaneous coronary interventions (PCI) who are initiating or reinitiating clopidogrel (Plavix) therapy. Testing more than once per lifetime is considered not medically necessary.

2. PharmacogenomicPharmacogenomic testing of CYP2C19 may be considered medically necessary for individuals undergoing treatment of acute ischemic stroke or transient ischemic attack (TIA).

3. PharmacogenomicPharmacogenomic testing of CYP2C9 and VKORC1 alleles are considered experimental and investigational for managing the administration and dosing of warfarin 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.

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

Governing Bodies Approval

Warfarin
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 pharmacogenomic 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.

Clopidogrel

The U.S. Food and Drug Administration (FDA) determined in 2009 that the available data have "provided compelling evidence that genetic variation in CYP2C19 is a significant and independent predictor of clopidogrel pharmacokinetics, pharmacodynamics and clinical response", which prompted the FDA to change clopidogrel prescribing information. In March 12, 2010, the FDA issued a black box warning for clopidogrel due to the reduced effectiveness of the drug in poor metabolizers. The FDA recommended that health professionals be aware that some patients may be poor metabolizers of clopidogrel because of low CYP2C19 activity and to also "be aware that tests are available to determine patients' CYP2C19 status".

The Centers for Medicare and Medicaid Services (CMS) have published the following guidance:

- National Coverage Determination (NCD) Pharmacogenomic Testing for Warfarin Response (90.1)
- Local Coverage Determination (LCD) Biomarkers Overview (L35062)

The Pennsylvania Department of Human Services Technology Assessment Group (TAG) workgroup meets quarterly to discuss issues revolving around new technologies and technologies or services that were previously considered to be a program exception. During this meeting, decisions are made as to whether or not certain technologies will be covered and how they will be covered. TAG's decisions are as follow:

- Option #1: Approved - Will be added to the Fee Schedule
- Option #2: Approved as Medically Effective - Will require Program Exception
- Option #3: Approved with (or denied due to) Limited/Minimal Evidence of Effectiveness - Will require Program Exception
- Option #4: Denied - Experimental/Investigational

As of December 2020, the TAG workgroup assigned genetic testing for warfarin metabolism an Option #4, specifically for CPT codes 81355 and 81227.

As of September 2013, the TAG workgroup assigned genetic testing for Clopidogrel drug metabolism an Option #2, specifically for CPT code 81225.

Program Exception - Genetic testing for Clopidogrel drug metabolism requires a program exception. The ordering physician must provide a supporting statement indicating why the requested therapy or device is medically necessary, and the alternative options have been or are likely to be ineffective, adversely affect patient compliance, or cause an adverse reaction.

Summary of Literature

Warfarin
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. 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. 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 (Park, 2017).

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). Pharmacogenomic 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 pharmacogenomic 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 pharmacogenomic 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 pharmacogenomic 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. In addition to the IWPC investigation, randomized controlled trial (RCT) remains the gold standard for comparing genetic-based strategies (Cavallari, 2011).

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. 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. Even with availability of FDA-cleared devices, there are still several large barriers to clinical adoption of warfarin genetic testing (Kimmel, 2015).

Some of the important gaps and barriers to warfarin pharmacogenomic testing for analytical validity include:

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 (Flockhart, 2008)

There are several gaps and barriers to warfarin (CYP2C9 and VKORC1) pharmacogenomic testing for clinical validity including:

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 (Flockhart, 2008)

There are also several gaps and barriers to warfarin (CYP2C9 and VKORC1) pharmacogenomic testing for clinical utility including:

1. The lack of adequately powered prospective trials that test whether pharmacogenomically 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 (Flockhart, 2008)

There are no professional organizations that endorse warfarin pharmacogenomic 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. Genetic testing for Warfarin therapy is only covered when provided to Medicare beneficiaries who are candidates for the CED clinical study. 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 (CMS, 2009).

Clopidogrel

The effectiveness of clopidogrel depends on its conversion to an active metabolite by CY2C19. Individuals who carry 2 non-functional copies of the CYP2C19 gene are classified as CYP2C19 poor metabolizers. They have no enzyme activity and cannot activate clopidogrel via the CYP2C19 pathway, which means the drug will have no effect. Approximately 2% of Caucasians, 4% of African Americans, and 14% of Chinese are CYP2C19 poor metabolizers.

Several studies have reported an increase in adverse cardiovascular events in patients who carry one or 2 non-functional copies of the CYP2C19 gene (“intermediate metabolizers” and “poor metabolizers”, respectively), compared with patients with 2 normal copies of the CYP2C19 gene (“normal metabolizers”). These studies focus on patients with ACS undergoing PCI, with carriers of non-functional alleles also being

at a higher risk of stent thrombosis. These patients may require much higher doses of clopidogrel (e.g., 4-fold higher) or an alternative drug (Dean, 2018).

Hayes, Inc.
Clopidogrel

- **D2 Rating** – For use of CYP2C19 pharmacogenomic genotyping to direct clopidogrel therapy for secondary prevention in adult patients who have experienced a stroke or transient ischemic attack (TIA). This Rating reflects an assessment of articles relevant to clinical utility only, and for which a very-low-quality body of evidence for studies looking directly at clinical utility was available. In general, there is insufficient evidence to determine the clinical utility of CYP2C19 pharmacogenomic genotyping to direct clopidogrel therapy for secondary prevention in adult patients who have experienced a stroke or TIA.

- **D2 Rating** – For use of CYP2C19 pharmacogenomic genotyping to direct clopidogrel therapy in adult patients undergoing percutaneous coronary intervention (PCI). This Rating reflects an assessment of articles relevant to clinical utility only; and for which a very low-quality body of evidence for studies looking directly at the clinical utility of CYP2C19 genotyping was available suggesting improvement in clinical outcomes for specific populations undergoing PCI when clopidogrel therapy was directed based upon the patients' CYP2C19 genotyping results. It also suggests uncertainty about how this would apply to the U.S. population.

Coding Requirements

Procedure Codes

CPT Code	Description
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)

Diagnosis Codes for 81225

Diagnosis Code	Description
I25.10	Atherosclerotic heart disease of native coronary artery without angina pectoris
I25.110	Atherosclerotic heart disease of native coronary artery with unstable angina pectoris
I25.111	Atherosclerotic heart disease of native coronary artery with angina pectoris with documented spasm
I25.118	Atherosclerotic heart disease of native coronary artery with other forms of angina pectoris
I25.5	Ischemic cardiomyopathy
I25.6	Silent myocardial ischemia
I25.720	Atherosclerosis of autologous artery coronary artery bypass graft(s) with unstable angina pectoris
I25.721	Atherosclerosis of autologous artery coronary artery bypass graft(s) with angina pectoris with documented spasm
I25.728	Atherosclerosis of autologous artery coronary artery bypass graft(s) with other forms of angina pectoris

I25.760	Atherosclerosis of bypass graft of coronary artery of transplanted heart with unstable angina
I25.761	Atherosclerosis of bypass graft of coronary artery of transplanted heart with angina pectoris with documented spasm
I25.768	Atherosclerosis of bypass graft of coronary artery of transplanted heart with other forms of angina pectoris
I25.790	Atherosclerosis of other coronary artery bypass graft(s) with unstable angina pectoris
I25.791	Atherosclerosis of other coronary artery bypass graft(s) with angina pectoris with documented spasm
I25.798	Atherosclerosis of other coronary artery bypass graft(s) with other forms of angina pectoris
I25.810	Atherosclerosis of coronary artery bypass graft(s) without angina pectoris
I25.812	Atherosclerosis of bypass graft of coronary artery of transplanted heart without angina pectoris
I25.83	Coronary atherosclerosis due to lipid rich plaque
I25.84	Coronary atherosclerosis due to calcified coronary lesion
I25.89	Other forms of chronic ischemic heart disease
I25.9	Chronic ischemic heart disease, unspecified
I63.013	Cerebral infarction due to thrombosis of bilateral vertebral arteries
I63.033	Cerebral infarction due to thrombosis of bilateral carotid arteries
I63.113	Cerebral infarction due to embolism of bilateral vertebral arteries
I63.133	Cerebral infarction due to embolism of bilateral carotid arteries
I63.213	Cerebral infarction due to unspecified occlusion or stenosis of bilateral vertebral arteries
I63.233	Cerebral infarction due to unspecified occlusion or stenosis of bilateral carotid arteries
I63.313	Cerebral infarction due to thrombosis of bilateral middle cerebral arteries
I63.323	Cerebral infarction due to thrombosis of bilateral anterior cerebral arteries
I63.333	Cerebral infarction due to thrombosis of bilateral posterior cerebral arteries
I63.343	Cerebral infarction due to thrombosis of bilateral cerebellar arteries
I63.413	Cerebral infarction due to embolism of bilateral middle cerebral arteries
I63.423	Cerebral infarction due to embolism of bilateral anterior cerebral arteries
I63.433	Cerebral infarction due to embolism of bilateral posterior cerebral arteries
I63.443	Cerebral infarction due to embolism of bilateral cerebellar arteries
I63.511	Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery
I63.512	Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery
I63.513	Cerebral infarction due to unspecified occlusion or stenosis of bilateral middle cerebral arteries
I63.519	Cerebral infarction due to unspecified occlusion or stenosis of unspecified middle cerebral artery
I63.523	Cerebral infarction due to unspecified occlusion or stenosis of bilateral anterior cerebral arteries
I63.533	Cerebral infarction due to unspecified occlusion or stenosis of bilateral posterior cerebral arteries
I63.543	Cerebral infarction due to unspecified occlusion or stenosis of bilateral cerebellar arteries
I63.59	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery

I66.01	Occlusion and stenosis of right middle cerebral artery
I66.02	Occlusion and stenosis of left middle cerebral artery
I66.03	Occlusion and stenosis of bilateral middle cerebral arteries
I66.8	Occlusion and stenosis of other cerebral arteries
Z79.02	Long term (current) use of antithrombotics/antiplatelets

Noncovered Procedure Codes
Requests for any of these procedure codes will require Medical Director Review.

CPT/HCPCS Code	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)

Reimbursement

Participating facilities will be reimbursed per their Highmark Wholecare℠ contract.

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