Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: Keystone First	**Submission Date**: 10/27/2023
Policy Number: ccp.1181	**Effective Date:** 1/2016 **Revision Date:** October 1, 2023
Policy Name: Pharmacogenetic testing for cardiac meds	

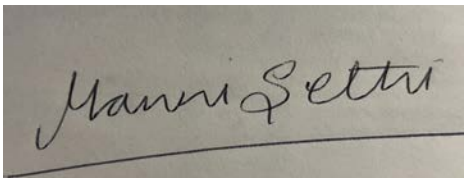
Type of Submission – Check all that apply:

New Policy
x Revised Policy*
Annual Review – No Revisions
Statewide PDL

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

See tracked changes below.

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Pharmacogenetic testing for cardiac meds

Clinical Policy ID: CCP.1181

Recent review date: 10/2023

Next review date: 2/2025

Policy contains: Clopidogrel, CYP2C9 gene, cytochrome p450, pharmacogenetic testing, statins, warfarin.

Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First's clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First's clinical policies are not guarantees of payment.

Coverage policy

Pharmacogenetic testing for cardiac medications is investigational/experimental not clinically proven and, therefore, not medically necessary.

Once-per-lifetime genotyping for cytochrome P450 polymorphisms is clinically proven and, therefore, may be medically necessary for members with acute coronary syndrome undergoing percutaneous coronary intervention, in which clopidogrel (Plavix®) is a treatment option (Scott, 2013).

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

Laboratory therapeutic drug monitoring tests for cardiac medications (e.g., digitalis level) or prothrombin time and international normalized ratio for anticoagulants.

Background

Cardiovascular disease is common among the U.S. population. More than 90 million Americans have a diagnosis of cardiovascular disease, and about one in three (800,000) deaths are due to cardiovascular causes, even though rates have declined steadily in the past several decades (Benjamin, 2017).

Millions of Americans take prescription medications for cardiovascular disorders. The table below lists the percent of the U.S. population using at least one prescription drug in the past 30 days, during the period 2011 to 2014, by type of drug:

High cholesterol	14.3%
Beta-adrenergic blocking agents	7.7%
ACE inhibitors	7.3%
Other high blood pressure, heart disease	5.6%
Anti-hypertensive combinations	4.1%
Calcium channel blocking agents	4.7%
TOTAL	43.7%

While 43.7% is probably an overstatement of the portion of the population on medications for cardiovascular conditions, due to some taking medications in more than one category, between one-third and one-half of Americans used a cardiovascular prescription drug in the past 30 days, a figure that will likely rise given the aging population (National Health and Nutrition Examination Survey, 2017).

Effectiveness of cardiovascular medications is a concern, especially since many are used in the long term, and results of clinical trials rarely exceed several years. Thus, any information on the likelihood of a drug to effectively treat in a particular patient is of great interest to health providers. The rapidly growing knowledge of genetics is a particular area in which the goal of matching a drug to a particular patient can be achieved.

Pharmacogenomics and pharmacogenetics are bodies of science that involve genetics, and at times the terms may be used interchangeably. However, differences exist between the two. Pharmacogenomics pertains to the science of genetic differences that determine drug behavior within the body, while pharmacogenetics is the science that examines the link between an individual's genetic make-up and their response to an exposure to a pharmaceutical product (Dere, 2009).

Cytochrome P450 (CYP2D6) is an enzyme involved in the metabolism of approximately 21% of commonly prescribed medications that include antidepressants; antipsychotics, beta blockers and other cardiac medications, opioids, antiemetics, selective norepinephrine reuptake inhibitors, and antiestrogens. Substantial activity variation is attributed partly due to several individual genetic variants resulting in increased or decreased function of the enzyme or a nonfunctioning CYP2D6 enzyme. This translates to the medication remaining in the body much longer leading to toxicity or being metabolized too quickly providing little therapeutic effect (Pratt, 2021).

The results of a pharmacogenetic test are used to try to predict an individual's response to a specific pharmaceutical before it is used in therapy. For example, an individual may undergo testing of CYP2C19 or VKORC1 alleles to try to predict the individual's response to warfarin prior to the initiation of therapy.

More evidence and outcomes from large prospective clinical trials are needed to link genotype to cardiac medication dosing recommendations before endorsing pharmacogenetic testing for cardiac medications. For example, CYP2C19, an enzyme belonging to the cytochrome P450 mixed-function oxidase system, aids processing or metabolizing of at least 10% of commonly prescribed cardiovascular drugs, including clopidogrel (Plavix®) (Medline Plus, 2015). The enzyme has been linked to adverse clinical outcomes primarily in patients undergoing percutaneous coronary intervention for acute coronary syndromes (Chang, 2015).

Polymorphisms in the genes *CYP2C9* and *VKORC1* account for more than one third of the inter-individual variation in stable therapeutic dosing of warfarin (Jorgensen, 2012).

Findings

A guideline from the American College of Cardiology Foundation and the American Heart Association issued a guideline cautiously recommending pharmacogenetic testing for heart patients' potential use of clopidogrel, based on genetic variability in the patient population (Holmes, 2010). Another subsequent guideline noted that heart patients with "poor metabolizer" alleles may not benefit from clopidogrel (Tantry, 2023).

A 2012 guideline from the American College of Cardiology Foundation and American Heart Association recommended testing for CYP2C19 should be considered on a case-by-case basis, especially for patients taking anti-platelet medications with recurring acute coronary syndrome (Jneid, 2012).

The following year, the National Institutes of Health-supported Clinical Pharmacogenetics Implementation Consortium recommended that persons with acute coronary syndrome undergoing percutaneous coronary intervention be tested for CYP2C19. Extensive/intermediate metabolizers should be given standard clopidogrel, while ultra-rapid/poor metabolizers are given another antiplatelet agent. The guideline stated there is no basis to support clopidogrel dose adjustment based only on CYP2C19 studies. Because no randomized controlled trials had been done, this guideline applies only to acute coronary syndrome only, and not all anti-platelet therapy (Scott, 2013).

Currently, the Consortium has published 25 guidelines, three of which apply to cardiac medications (clopidogrel, warfarin, and simvastatin). The guidelines are not criteria on whether to order pharmacogenetic testing, but recommend how test results can optimize treatment outcomes (Duarte, 2021).

The most recent version of the American College of Chest Physicians Antithrombotic Guidelines recommended against the routine use of genetic testing for guiding doses of Vitamin K Antagonist therapy (Guyatt, 2012; Holbrook, 2012). A British Society for Haematology guideline addressing oral anticoagulation with warfarin concluded that insufficient evidence exists for genotype-guided initiation of therapy for patients with acute thrombosis (Keeling, 2011). A Clinical Pharmacogenomics Implementation Consortium guideline on genetics-driven warfarin recommends that pharmacogenetic warfarin dosing be based on ancestry (Johnson, 2017). The Canadian Pharmacogenetics Committee for Drug Safety recommended persons on warfarin, including children, be tested for VKORC1 (-1639G>A), CYP2C9*2, and CYP2C9*3 within the first two weeks of therapy or after a bleeding event (Shaw, 2015).

A review of cardiovascular-related pharmacogenetic testing of a large, insured, heterogenous population in 2011-2015 matched those treated based on testing with controls. The group with pharmacogenetic testing was significantly more likely to experience ischaemic stroke, pulmonary embolism, deep vein thrombosis, or a composite event. Authors conclude that testing did not improve outcomes (Billings, 2018).

The current evidence generally shows that pharmacogenetics of clopidogrel, warfarin and simvastatin are three examples where pharmacogenetics testing may provide added clinical value, although considerably more research is needed to further understand optimum dose (Tuteja, 2016). Examples of research studies are given below:

Warfarin:
A meta-analysis of nine trials (n = 2,812) analyzing warfarin and vitamin K antagonists with initial doses from genetic and non-genetic data found a significant reduction in risk ratio for major bleeding events in the genetic-guided group (*P* = .04) (Franchini, 2014).

In a meta-analysis of nine randomized controlled trials (n = 2,812), genotype-guided patients taking warfarin, acenocoumarol, or phenprocoumon were compared with those taking similar drugs based on clinical findings and followed from four weeks to six months. Results failed to show superior results for the genotype-guided group, i.e., no greater percentage of time that the international normalized ratio was within the therapeutic range, no fewer patients with a ratio greater than four, or no greater reduction in major bleeding or thromboembolic events (Stergiopoulos, 2014).

A systematic review and meta-analysis of 10 trials (n = 5,299) compared patients taking warfarin based on genetic results versus clinical findings. Nine of the 10 studies were randomized and controlled. The rates of major bleeding was significantly lower for the genotype group ($P = .02$) but not significantly lower for international normalized ratio anticoagulation under four ($P = .60$) (Tang, 2014)

A meta-analysis of 10 studies (n = 2,601) compared persons whose warfarin dose was determined by genotyping versus clinical information. Less major bleeding ($P = .02$) and fewer thromboembolic events ($P = .02$), along with greater percent of time in therapeutic range ($P = .05$) were lower in the genotype group. No difference was observed for international normalized range greater than four (Li, 2015).

A meta-analysis of seven trials (n = 1,910) that assessed patients for initial warfarin dose found the percent of time within the international normalized ratio range improved for the genotype-guided group when the initial standard dose was fixed, but not when the initial dose was not fixed ($P = .647$). Death rates were not significantly different ($P = .328$) between the two groups. Incidence of total adverse events and death rates did not differ between the groups (Liao, 2015).

A meta-analysis of 11 studies (n = 2,678) of patients on warfarin found genetics-based dosing shortened the time to maintenance dose ($P < .00001$) and the time to first therapeutic international normalized ratio ($P < .00001$); and reduced adverse event risk ($P = .03$) and major bleeding ($P = .03$). Genetics-based dosing did not reduce the percent of international normalized ratio > 4.0, risk of thromboembolic events, and death from any cause (Shi, 2015).

A systematic review/meta-analysis of 12 studies (n = 3,217) compared patients initiating anticoagulant (vitamin K antagonist) therapy based on genetic testing versus clinical results. No difference was observed for the primary outcome (mortality), thromboembolic events, and major bleeding ($P = .35$), but the genetic group was associated with a superior time in therapeutic range (Belley-Cote, 2015).

A meta-analysis of 11 studies (n= 2,639) indicated pharmacogenetics-based dosing for warfarin did not significantly improve percent of time in therapeutic range ($P = .08$), but significantly shortened the time to stable therapeutic dose ($P < .00001$), and risk of major bleedings ($P = .04$). No reduction in risks of all-cause mortality, total bleedings, or thromboembolic events were observed (Wang, 2015).

A large (n = 1,650) randomized controlled trial compared warfarin dose in elderly patients after a hip or knee replacement. Groups were assigned warfarin dose based on clinical information, with versus without genotype data for four polymorphisms. After 90 days, the rate of adverse effects was significantly lower for those in the genotype group (10.8% versus 14.7%, $P < .02$) (Gage, 2017).

A systematic review and meta-analysis of 15 studies (n = 5,688) included nine that addressed warfarin. Genotype-guided warfarin dosing was significantly more beneficial in the percent of time in therapeutic

international normalized ratio range and reduction in numbers of warfarin-related minor bleeding, major bleeding and thromboembolisms (Goulding, 2015).

A systematic review/meta-analysis of nine studies (n = 1,393) showed that heart patients with four types of CYP2C19 alleles required 34%, 18%, 16%, and 10% lower doses of warfarin, respectively (Wang, 2019).

Clopidogrel:
Meta-analyses have found that patients undergoing percutaneous coronary intervention for acute coronary syndromes who are poor *CYP2C19* metabolizers (carriers of two reduced-function alleles) and taking clopidogrel have a significantly increased risk of a composite outcome of cardiovascular death, myocardial infarction, or stroke (hazard ratio = 1.76, *P* = .002) or stent thrombosis (hazard ratio = 3.97, *P* = .001). However, meta-analyses show no clinical benefit for testing patients with lower clinical risks (e.g., clopidogrel use in atrial fibrillation) (Chang, 2015).

An overview found sufficient medical evidence of clopidogrel response variability among patients undergoing percutaneous coronary intervention for acute coronary syndrome to ensure the clinical validity of searching for CYP2C19 alleles, particularly among men and women of Asian descent. Although limited prospective trial data is available to support the utility of routine CYP2C19 testing, the increased risks for reduced clopidogrel efficacy among percutaneous coronary intervention acute coronary syndrome patients that carry CYP2C19 loss-of-function alleles should be considered when genotype results are available (Yang, 2015).

A systematic review and meta-analysis examined the association between the CYP2C19 genotype and clopidogrel efficacy for ischemic stroke or transient ischemic attack. Among 15 studies of 4,762 patients with either disorder treated with clopidogrel, carriers of CYP2C19 loss-of-function alleles (*2, *3, and *8) were at increased risk of stroke in comparison with non-carriers (12.0% versus 5.8%; risk ratio, 1.92, *P* < .001). Composite vascular events were also more frequent in carriers of CYP2C19 loss-of-function alleles than in non-carriers (13.7% versus 9.4%; risk ratio 1.51; *P* = .01), whereas bleeding rates were similar (2.4% versus 3.1% risk ratio, 0.89, *P* = .59) (Pan, 2017).

A systematic review/meta-analysis of 20 studies (n = 15,056) in Asian populations showed that while carriers of the CYP2C19 genotype taking clopidogrel were at higher risk for major adverse cardiovascular event and stent thrombosis, they also had lower risk of bleeding (Xi, 2017).

A systematic review of 20 studies (n = 15,056) showed subjects treated with clopidogrel with at least one CYP2C19 allele had an increased risk of a major adverse coronary event compared with non-carriers (10.58% versus 6.07%, *P* < .001); for stent thrombosis (2.22% versus 0.44%, *P* < .001); but with a lower risk of bleeding (*P* < .001) (Xi, 2019).A systematic review/meta-analysis of 21 studies (n = 4,312) of patients with ischaemic stroke or transient ischaemic attack treated with clopidogrel showed non-responders to platelet reactivity had poorer outcomes (*P* = .036). Carriers of CYP2C19*2 or CYP2C19*3 loss of function alleles had a higher risk of high-on clopidogrel platelet reactivity compared to wild type (P < .001). Authors conclude CYP2C19 polymorphisms may potentially influence clopidogrel resistance (Alakbarzade, 2020).

In a meta-analysis of 14 randomized trials (n = 2,351) found after a percutaneous coronary intervention, patients with CYP2C19 loss-of-function alleles had significantly fewer major adverse cardiovascular events after treatment with ticagrelor compared with high-dose clopidogrel. Superior outcomes with ticagrelor included stent thrombosis, myocardial infarction, revascularization, and unstable angina (Sheng, 2023).

Statins:
Pharmacogenetic tests have the potential to predict response to statin therapy, specifically in the presence of the KIF6 (rs20455) gene.

A meta-analysis of nine studies compared 1,360 cases and 3,082 controls and observed that SLCO1B1 gene T521C polymorphism is associated with an increased risk of statin-related myopathy, especially in individuals receiving simvastatin, suggesting a genetic test before statins are administered could be helpful in personalizing treatment (Hou, 2015).

A meta-analysis of 13 studies (n = 11,246) of statin users found that SLCO1B1 -521T>C polymorphism may be a risk factor for statin-induced adverse drug events, especially in simvastatin therapy, with no significant association for the -388A>G polymorphism (Jiang, 2016).

A systematic review revealed only 5% of 141 loci that had claimed to be linked with low-density lipoprotein cholesterol response were positively replicated. No single nucleotide polymorphisms studied consistently affected the risk reduction for cardiovascular events in patients taking statins (Leusink, 2016).

A meta-analysis of 44 articles explored how genetic testing can assess patient risk for statin-induced myopathy. Risk factors significant for myopathy and/or rhabdomyolysis included age, gender, diabetes, renal impairment, cardiovascular disease, certain interacting drugs, and mutations of the SLCO1B1 gene, which encodes a transporter protein in the liver. Factors, such as gender, race, cardiovascular disease, and the GATM gene, which encodes a protein for creatine synthesis, appeared to improve outcomes (Nguyen, 2018).

A meta-analysis of 21 studies (n = 24,365) found certain SLCO1B1 variants can predict effectiveness of statins to reduce low-density lipoprotein cholesterol levels (rs4149056 and rs11045819 in the heterozygote model; and rs4149056, rs2306283, and rs11045819 in the homozygote model) (Nguyen, 2023).

Other:
A meta-analysis of eight studies analyzed the outcomes for patient care based on genetic testing versus from other clinical information for coumarin anticoagulants (acenocoumarol, phenprocoumon, and warfarin). For the primary outcome, the percent of time the international normalized ratio was in the normal range of 2.0 to 3.0, genotype-guided dosing of coumarin improved the outcome (P = .02). A significant reduction occurred in secondary outcomes (international normalized ratio ≥4 events, major bleeding events, and thromboembolic events (P = .04) (Tang, 2015).

Yeo (2017) investigated baseline and change from baseline in Lp-PLA2 activity at two efficacy endpoints (major coronary events and myocardial infarction, n = 13,577 and 10,404 respectively) as well as tolerability parameters at genome-wide and candidate gene level in patients taking darapladib, a lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitor. The authors concluded that genetic analysis confirmed and extended the influence of lipoprotein loci on Lp-PLA2 levels, identified some novel null alleles in the PLA2G7 gene, and only identified one potentially efficacious subgroup.

A meta-analysis of 31 case-control studies reviewed the association of interleukin 10 (gene polymorphisms (-1082G/A) in the progression of cardiovascular disease. This risk with allele G is lower than with allele A for cardiovascular disease (Lu, 2019).

A meta-analysis of six randomized trials (n = 2,371) of patients with coronary artery disease undergoing stent implantation compared efficacy of genotype-guided antiplatelet therapy and standard care. Genotype-guided therapy did not reduce major adverse cardiovascular events (*P* = .22), cardiovascular mortality (*P* = .42), stroke (*P* = .34), stent thrombosis (*P* = .06), or bleeding (*P* = .09). Reductions were in the genotype-guided group were observed in trials with only acute coronary syndromes (*P* < .01) and myocardial infarction (*P* < .01) (Kheiri, 2019).

A recent systematic review found that there is no recommendation with a high level of evidence of the *CES1*, *ABCB1*, *CYP3A4*, *CYP3A5*, and *ABCG2* genes as part of therapeutic optimization for patients undergoing treatment with direct oral coagulants, specifically Dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban (Raymond, 2021).

An incidental finding demonstrated there are no known current diseases or conditions that have been identified to be linked to an isolated cause of cytochrome P450 (CYP2D6) gene variation in drug metabolism (Relling, 2020).

References

On July 24, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "pharmacogenomics,""cytochrome P450," "cardiac medications" and "pharmacogenetic testing." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

8/2015: initial review date and clinical policy effective date: 1/2016

8/2016: Policy references updated.

8/2017: Policy references updated.

8/2018: Policy references updated.

10/2019: Policy references updated. Policy ID changed to CCP.1181.

10/2020: Policy references updated.

10/2021: Policy references updated.

10/2022: Policy references updated.

10/2023: Policy references updated.