Clinical Policy Title: Pharmacogenetic testing for cardiac meds

Clinical Policy Number: CCP.1181

Effective Date: January 1, 2016
Initial Review Date: August 19, 2015
Most Recent Review Date: October 1, 2019
Next Review Date: February 2021

ABOUT THIS POLICY: AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas’ 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 AmeriHealth Caritas 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. AmeriHealth Caritas’ 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. AmeriHealth Caritas’ clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas’ clinical policies are not guarantees of payment.

Coverage policy

Pharmacogenetic testing for cardiac medications is investigational and, therefore, not medically necessary.

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

Limitations:

All other uses of pharmacogenetic testing for cardiac medications are investigational and, therefore, not medically necessary.

Alternative covered services:

Laboratory testing 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 using at least one prescription drug in the past 30 days, during the period 2011 to 2014:

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Percent</th>
</tr>
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<tr>
<td>High cholesterol</td>
<td>14.3</td>
</tr>
<tr>
<td>Beta-adrenergic blocking agents</td>
<td>7.7</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>7.3</td>
</tr>
<tr>
<td>Other high blood pressure, heart disease</td>
<td>5.6</td>
</tr>
<tr>
<td>Anti-hypertensive combinations</td>
<td>4.1</td>
</tr>
<tr>
<td>Calcium channel blocking agents</td>
<td>4.7</td>
</tr>
<tr>
<td>TOTAL</td>
<td>43.7</td>
</tr>
</tbody>
</table>

While 43.7 percent is probably overstated somewhat 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, and 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.

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 percent of commonly prescribed drugs, including clopidogrel (Plavix®) (Genetics Home Reference, 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 (Munsuru, 2012).

**Searches**

AmeriHealth Caritas searched PubMed and the databases of:
- UK National Health Services Center for Reviews and Dissemination.
- Agency for Healthcare Research and Quality.
- The Centers for Medicare & Medicaid Services.
- The Cochrane library.

We conducted searches on August 9, 2019. Search terms were: "pharmacogenomics," "cardiac medications" and "pharmacogenetic testing."

We included:
- **Systematic reviews,** which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses,** such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

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 so 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).
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).

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:**
Perhaps the first large-scale efficacy comparison of treating patients with warfarin based on genotype results versus non-genetic clinical findings paired 896 and 2,688 patients in the two groups, respectively. After six months, the genotype group had 31 percent fewer hospitalizations ($P < .001$) and 28 percent fewer hospitalizations for bleeding or thromboembolism ($P = .029$) (Epstein, 2010).

A randomized trial of warfarin users, 505 based on genotype information and 1,866 controls, showed superior results (all $P < .001$), including 1) lower (31 versus 42) percent of out-of-range international normalized ratios at one month, and 30 percent versus 42 percent at three months; 2) higher percent of time in therapeutic range (69 percent versus 58 percent and 71 percent versus 59 percent at one and three months; 3) lower serious adverse events at three months (4.5 percent versus 9.4 percent of patients, $P < .001$) (Anderson, 2012).

Pirmohamed (2013) studied pharmacogenetic-based dosing of warfarin and found that foreknowledge of genotype prompted therapeutic levels of anticoagulant faster than a standard blind dosing regimen of warfarin. The median time to reach a therapeutic level was less in the genotype-guided group as compared with the control group by eight days (21 versus 29 days, respectively; $P < .001$).

On the other hand, a large randomized controlled trial of 1015 patients came to the opposite conclusion: genotype control did not improve anticoagulation control over the initial four weeks of therapy (Kimmel 2013).

A meta-analysis of 22 studies (n = 6,272) assessed hemorrhagic complications from warfarin therapy by whether or not dose was selected by genotype data. Both CYP2C9*2 ($P = .01$) and *3 ($P < .001$) are risk factors for over-anticoagulation within 30 days of warfarin treatment, and only the latter showed higher risk after 30 days of treatment ($P = .03$) (Yang, 2013).
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 ($P = .040$) (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 (Stergiopoulou, 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 ($P < .00001$); reduced adverse event risk ($P = 0.03$) and major bleeding ($P = 0.03$). 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 were significantly lower for those in the genotype group (10.8 percent versus 14.7 percent, \(P < .02\)) (Gage, 2017).

In a validation cohort of 1,009 (of 4,043) subjects using anticoagulant medications, the pharmacogenetic algorithm accurately identified larger proportions of patients who required 21 mg or less of warfarin per week (49.4 percent versus 33.3 percent, \(P < .001\)) and of those who required 49 mg per week or more (24.8 percent versus 7.2 percent, \(P < .001\)) (The International Warfarin Pharmacogenetics Consortium, 2009).

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 meta-analysis of 53 studies determined that, in addition to the variation in needed warfarin maintenance dose differing by VKORC1 gene polymorphisms, Caucasians require higher doses of warfarin than do Asians, and thus gene polymorphism detection is suggested (Tang, 2017).

**Clopidogrel:**

A meta-analysis of nine clopidogrel studies (n = 9,685) found that carriers of CYP2C19 alleles suffered a 57 percent increase in risk of cardiovascular death, myocardial infarction or ischemic stroke compared with non-carriers (Mega 2009). The new Food and Drug Administration label for clopidogrel indicates that heterozygosity is associated with diminished response to clopidogrel (i.e., poorer anticoagulation) and that pharmacogenetic testing can identify these genotypes. A systematic review/meta-analysis of 32 studies (n = 42,016) of persons taking clopidogrel determined that there was a link between those with at least one CYP2C19 allele and lower enzyme activity, less platelet inhibition, and lower bleeding risk, but higher risk of cardiovascular disease events (Holmes, 2011).

A meta-analysis looked at CYP2C19 polymorphisms and cardiovascular outcomes. Patients with a loss-of-function allele, mainly CYP2C19*2, did not show an elevated risk of a cardiovascular event, but CYP2C19*2 was linked with risk of a stent thrombosis. The gain-of-function allele, mainly CYP2C19*17, was associated with fewer cardiovascular events greater risk of major bleeding (Zabalza, 2012).

A meta-analysis of 21 studies (n = 23,035) assessed coronary artery disease patients treated with clopidogrel. Carriers had a significantly higher risk than non-carriers of the CYP2C19 variant allele for adverse clinical events (odds ratio 1.50, \(P = .0003\)), myocardial infarction (1.62, \(P < .00001\)), stent thrombosis (2.08, \(P < .00001\)), ischemic stroke (2.14, \(P = .001\)) and repeat revascularization (1.35, \(P = .004\)), but not of mortality (\(P = .50\)) and bleeding events (\(P = .93\)) (Mao, 2013).
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 4762 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 percent versus 5.8 percent; 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 percent versus 9.4 percent; risk ratio 1.51, \( P = .01 \)), whereas bleeding rates were similar (2.4 percent versus 3.1 percent 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).

Asians have a greater prevalence of the CYP2C19 allele. A review of 24 studies (n = 36,076) of Asians and non-Asians undergoing percutaneous coronary intervention revealed a significant \( (P < .001) \) difference between carriage of >1 CYP2C19 loss-of-crown artery intervention, indicative of clopidogrel, and major cardiovascular outcomes for whites without the intervention (relative risk 0.99), whites with the intervention (1.20) and Asians with the intervention (1.91) (Sorich, 2014).

A systematic review of 20 studies (n = 15,056) showed subjects with at least one CYP2C19 allele had an increased risk of a major adverse coronary event compared with non-carriers (10.58 percent versus 6.07 percent, \( P < .001 \)); for stent thrombosis (2.22 percent versus 0.44 percent \( P < .001 \)); but with a lower risk of bleeding \( (P < .001) \) (Xi, 2019).

**Statins:**
Pharmacogenetic tests may predict response to statin therapy, specifically in the presence of the KIF6 (rs20455) gene. Carriers of the KIF6 genome experience greater protection against coronary heart disease with pravastatin therapy than non-carriers (Iakoubova, 2008). Conversely, a study of patients
taking simvastatin, 85 with myopathy and 90 controls, observed a single variant in SLCO1B1 (a hepatic gene) brings with it a 17-fold increased risk of myopathy with high doses of simvastatin (SEARCH Collaborative Group, 2008). A recent government relabeling of simvastatin warns of this risk.

A study to assess if the SLCO1B1 and rs4149056 genotyping could predict the type and dose of statin in individual patients observed sensitivity and specificity rates of 70.4 percent and 73.7 percent to predict definite or incipient myopathy during five years of simvastatin. The authors found no clinical utility of statin prescription guided by SLCO1B1 genotype (Stewart, 2013).

A meta-analysis of nine studies compared 1360 cases and 3082 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 five percent 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 (Leusink, 2016).

Other:
An Agency for Healthcare Research and Quality publication reviewed 124 studies, and concluded no direct evidence exists that testing for mutations is linked with improved clinical outcomes in adults with a history of venous thromboembolism or their adult family members (Segal, 2009).

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 analysis of darapladib efficacy endpoints, despite low power, identified six low frequency loci with main genotype effect (though with borderline imputation scores) and one common locus (minor allele frequency 0.24) with genotype by treatment interaction effect passing the significance threshold. This locus conferred risk in placebo subjects, hazard ratio 1.22 with 95 percent confidence interval 1.11-1.33, but was protective in
darapladib subjects, hazard ratio 0.79. No major loci for tolerability were found. 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 within these two large clinical trials.

Policy updates:
A total of one peer-reviewed reference was added to, and four peer-reviewed references removed from this policy in August 2019.

References

Professional society guidelines/other:


Peer-reviewed references:


**Centers for Medicare & Medicaid Services National Coverage Determinations:**

Cytogenetic studies (190.3).

Pharmacogenomic testing for warfarin response (90.1).

**Local Coverage Determinations:**

No Local Coverage Determinations identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and
bill in accordance with those manuals.

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<th>Description</th>
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**Appendix A.**

No additional information was identified for this section during the writing of this policy.