Clinical Policy Title: Genetic testing for cytochrome P450 polymorphisms

Clinical Policy Number: 00.01.03

Effective Date: October 1, 2015
Initial Review Date: June 17, 2015
Most Recent Review Date: July 20, 2016
Next Review Date: July 2017

Policy contains:
- Pharmacogenetics.
- Genotype.
- Clopidogrel.
- Cytochrome P450 2C19 (CYP2C19).

Related policies:

CP# 02.01.08 Familial polyposis gene testing
CP# 02.01.14 Gene expression profile testing for breast cancer
CP# 11.04.02 Genetic testing for autism spectrum disorders
CP# 02.01.02 Genetic testing for breast and ovarian cancer
CP# 02.01.07 Genetic testing for cystic fibrosis
CP# 05.01.03 Genetic testing for G1691A polymorphisms Factor V Leiden
CP# 04.01.02 Genetic testing for Long QT syndrome (LQTS)
CP# 02.01.04 Genetic testing for primary autosomal recessive microcephaly
CP# 02.01.09 Genetic testing for rare diseases
CP# 13.01.01 Genetic testing for prostate cancer prognosis
CP# 09.01.09 Genetic testing in neurology
CP# 02.01.18 Genetic testing in sensorineural hearing loss
CP# 05.01.04 Molecular analysis for targeted therapy of non-small cell lung cancer
CP# 05.01.05 Molecular targeted therapy
CP# 02.01.03 Array comparative genomic hybridization testing
CP# 02.01.04 Pharmacogenetic testing for cardiac meds
CP# 02.01.04 Pharmacogenetic testing for warfarin (Coumadin®) sensitivity

ABOUT THIS POLICY: 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**

Keystone First considers once-per-lifetime genotyping for cytochrome P450 polymorphisms to be clinically proven and, therefore, medically necessary for people with acute coronary syndrome (ACS), undergoing percutaneous coronary intervention (PCI), in whom clopidogrel (Plavix®) is a treatment option.

**Limitations:**

Keystone First considers the routine use of pharmacogenetic testing for cardiac medications to be investigational and, therefore, not medically necessary.

All other uses of cytochrome P450 genotyping are considered investigational and, therefore, not medically necessary.

Repeat cytochrome P450 genotyping has no proven value.

Note: The following CPT/HCPCS code is not listed in the Pennsylvania Medicaid fee schedule:

81225 - CYP2C19 (cytochrome P450 family2, subfamily C, polypeptide 19) (eg, drug metabolism, gene analysis, common variants)

**Alternative covered services:**

- Primary care and specialty care physician evaluation and management.
- Laboratory testing for cardiac medications (e.g., dig level) or prothrombin time (PT) and International Normalized Ratio (INR) for anticoagulants.
- Pharmaceutical therapy with unfractionated heparin or low-molecular-weight heparin, IV platelet glycoprotein IIb/IIIa complex blockers (e.g., tirofiban, eptifibatide).

**Background**

In the late 2000’s observation suggested that clopidogrel (Plavix), given in the context of ACS and percutaneous coronary stenting, could be associated with perverse clotting of the stent (incidence 1 – 2 percent) and subsequent myocardial ischemia in treated patient populations. Research suggests that a genetic abnormality of the cytochrome P450 enzyme (i.e., CYP2C19), which is quite prevalent in Asian populations (incidence 50 percent), inhibits metabolism of clopidogrel from its precursor form to an active anti-coagulant metabolite. Tests are available to determine a patient’s cytochrome P450 genotype and identify individuals at-risk for inadequate anticoagulation.
The results of this research are included in the Food and Drug Administration’s prescription labeling requirements for clopidogrel. The label indicates that reduced CYP2C19 metabolism in intermediate and poor metabolizers is associated with diminished response to clopidogrel and pharmacogenetic testing can identify genotypes associated with variability in CYP2C19 activity.

**Searches**

Keystone First searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality Guideline Clearinghouse and evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on June 20, 2016. Search terms were: “genotype (MeSH),” “pharmacogenetics (MeSH)” and “clopidogrel.”

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**

Sorich (2014) in a systematic review of 36,076 patients assessed genotype at risk and found that greater than 50 percent of Asians carry the CYP2C19 “loss-of-function” allele. Significant differences in therapeutic response to the intervention (i.e., stent plus clopidogrel) were demonstrated between control (non-PCI patients) versus whites with PCI on clopidogrel and Asians with PCI on clopidogrel.

Jian (2013) in a systematic review of 23,035 patients showed an increased risk of adverse events in CYP2C19 variant-allele carriers (e.g., myocardial infarction, stent thrombosis, ischemic stroke and repeat revascularization).

The Clinical Pharmacogenetics Implementation Consortium guidelines (Scott 2013) for CYP2C19 recommend that if a patient’s genotype is unknown, the decision to perform CYP2C19 testing is up to the individual clinician.
The Society of Thoracic Surgeons guidelines (Ferraris 2012) suggest that genetic testing early after cardiac procedures might be considered to optimize antiplatelet drug effect and minimize thrombotic risk to vein grafts.

A randomized controlled trial (RCT) inclusive of 416 patients found platelet aggregation by multiple electrode aggregometry (MEA), predicted stent thrombosis better than cytochrome P450 polymorphism analysis Delle-Karth (2012). ACS at hospitalization and diabetes mellitus were the best discriminators for clopidogrel responder status.

American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines for PCI (Levine 2011) also suggest that genetic testing might be considered to identify whether a patient at high risk for poor clinical outcomes is predisposed to inadequate platelet inhibition with clopidogrel. However, the routine clinical use of genetic testing to screen patients treated with clopidogrel who are undergoing PCI was not recommended.

Mega (2009) in a systematic review of 9,685 patients associated the “loss-of-function” allele to stent thrombosis. Among patients treated with clopidogrel for PCI, carriage of even one reduced-function CYP2C19 allele was associated with a significantly increased risk of major adverse cardiovascular events, particularly stent thrombosis. Carriers of at least one CYP2C19 reduced-function allele had a relative reduction of 32.4 percent in plasma levels of the active metabolite of clopidogrel.

O’Connell (2009) found the reduced-function allele tied to ischemia and mortality postintervention. An RCT (n=429) found among patients following coronary intervention with CYP2C19 variant allele, twice as many suffered an ischemic event or death at one year.

Policy updates:

Selective serotonin reuptake inhibitors (SSRIs) are primary treatment options for major depressive and anxiety disorders. Hicks (2015) noted in an update to the Clinical Pharmacogenetics Implementation Consortium 2013 guidelines that both CYP2D6 and CYP2C19 variations can influence the metabolism of SSRIs, thereby affecting drug efficacy and safety. Some studies have reported an association between CYP2D6 and CYP2C19 genetic variants and risk for depression or suicide; however, at present CYP2D6 and CYP2C19 are not considered to be clinically useful predictors of depression or suicide risk, and as such carry interest as a genetic finding but not one of clinical importance.

Summary of clinical evidence

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Hicks (2015)</td>
<td>Key points:</td>
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<tr>
<td>Clinical Pharmacogenetics Implementation</td>
<td>- Guidelines for dosing concurrent with CYP2D6 and CYP2C19 allelic variations that can influence the metabolism of SSRIs.</td>
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<tr>
<td></td>
<td>- Research has suggested an association between CYP2D6 and CYP2C19 genetic variants and</td>
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Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors

- risk for depression or suicide
- At present CYP2D6 and CYP2C19 variations are not considered to be clinically useful predictors of depression or suicide risk.

Sorich (2014)
CYP2C19 genotype has a greater effect on adverse cardiovascular outcomes following percutaneous coronary intervention and in Asian populations treated with clopidogrel: a meta-analysis

**Key points:**
- Systematic review of 36,076 patients assessed genotype at risk
- Greater than 50% of Asians carry the loss of function allele.
- Significant differences in therapeutic response to clopidogrel exist between control (non-PCI patients) versus whites with PCI on clopidogrel and Asians with PCI on clopidogrel.
- Includes substudy of 200 patients with stent-specific indication.

Jian (2013)
Cytochrome CYP2C19 polymorphism and risk of adverse clinical events in clopidogrel-treated patients: a meta-analysis based on 23,035 subjects

**Key points:**
- Systematic review of 23,035 patients shows increased risk of adverse events
- CYP2C19 variant allele carriers had an increased risk of adverse clinical events: myocardial infarction, stent thrombosis, ischemic stroke and repeat revascularization.

Scott (2013)
Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update

**Key points:**
- Guidelines for clopidogrel in presence of CYP2C19 loss of function.
- If a patient’s genotype is unknown, the decision to perform CYP2C19 testing is up to the individual clinician.
- These recommendations apply predominantly to ACS patients undergoing PCI.

Ferraris (2012)
2012 update to the Society of Thoracic Surgeons guideline on use of antiplatelet drugs in patients having cardiac and noncardiac operations

**Key points:**
- Guidelines for antiplatelet therapy in cardiac/noncardiac care.
- Genetic testing early after cardiac procedures might be considered to optimize antiplatelet drug effect and minimize thrombotic risk to vein grafts.

Delle-Karth (2012)
Phenotyping vs. genotyping for prediction of clopidogrel efficacy and safety: the PEGASUS-PCI study

**Key points:**
- Contrarian findings of test efficiency
- RCT (n=416) found platelet aggregation by MEA, predicted stent thrombosis better than CYP2C19 polymorphism analysis.
- ACS at hospitalization and diabetes mellitus were the best discriminators for clopidogrel responder status.

Levine (2011)

**Key points:**
Genetic testing might be considered to identify whether a patient at high risk for poor clinical outcomes is predisposed to inadequate platelet inhibition with clopidogrel.

The routine clinical use of genetic testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended.

**Key points:**

- Systematic review of 9,685 patients links loss of function allele to stent thrombosis
- Among patients treated with clopidogrel for PCI, carriage of even one reduced-function CYP2C19 allele appears to be associated with a significantly increased risk of major adverse cardiovascular events, particularly stent thrombosis.
- Carriers of at least one CYP2C19 reduced-function allele had a relative reduction of 32.4% in plasma levels of the active metabolite of clopidogrel.

**Key points:**

- Loss of function allele tied to ischemia and mortality postintervention
- RCT (n=429) found among patients following coronary intervention with CYP2C19 variant allele, twice as many suffered an ischemic event or death at one year.

**Glossary**

**Pharmacogenetics** — The broad area of pharmacology as it intersects with genetics, i.e., allele variants that impact metabolism, excretion and disposition of a drug in vivo.

**Genotype** — The specific character of the human genetic code in a particular individual.

**Clopidogrel (Plavix)** — A widely prescribed oral anticoagulant.

**CYP2C19** — A specific location on the cytochrome P450 enzyme’s genetic code, which is prone to variations that diminish the in vivo metabolism of clopidogrel.

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


**Clinical trials:**

Searched clinicaltrials.gov on June 21, 2016 using terms “genetic testing” and “cytochrome p450 polymorphism” | Open Studies: 6 studies found, 3 relevant.


**CMS National Coverage Determinations (NCDs):**


**Local Coverage Determinations (LCDs):**


L35332. Pathology and Laboratory: CYP2C19, CYP2D6, CYP2C9, and VKORC1 GENETIC TESTING. CMS Medicare Coverage Database Web site. https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35332&ver=3&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=genetic+testing&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAAABAAAAA%3d%3d&. Accessed June 21, 2016.

L35660. Pathology and Laboratory: CYP2C19, CYP2D6, CYP2C9, and VKORC1 GENETIC TESTING. CMS Medicare Coverage Database Web site. https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35660&ver=3&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=genetic+testing&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAAABAAAAA%3d%3d&. Accessed June 21, 2016.


L36309. MolDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 GENETIC TESTING. CMS Medicare Coverage Database Web site. https://www.cms.gov/medicare-coverage-database/details/lcd-
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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