BlueCross BlueShield of Alabama

Name of Policy:

Cytochrome P450 ~~Genotyping~~ Genotype-Guided Treatment Strategy

Policy #: 425
Category: Laboratory/Medicine

Latest Review Date: July 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

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Description of Procedure or Service:

The cytochrome P450 (CYP450) family is involved in the metabolism of many currently administered drugs, and genetic variants in cytochrome P450 are associated with altered metabolism of many drugs. Testing for cytochrome P450 variants may assist in selecting and dosing drugs affected by these genetic variants.

Drug Efficacy and Toxicity

Drug efficacy and toxicity vary substantially across individuals. Because drugs and doses are typically adjusted, if needed, by trial and error, clinical consequences may include a prolonged time to optimal therapy. In some cases, serious adverse events may result.

Multiple factors may influence the variability of drug effects, including age, liver function, concomitant diseases, and nutrition, smoking, and drug-drug interactions. Inherited (germline) DNA sequence variation in genes coding for drug metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways also may have major effects on the activity of those molecules and thus on the efficacy or toxicity of a drug.

Pharmacogenomics is the study of how an individual's genetic inheritance affects the body's response to drugs. It may be possible to predict therapeutic failures or severe adverse drug reactions in individual patients by testing for important DNA variants (genotyping) in genes related to the metabolic pathway (pharmacokinetics) or signal transduction pathway (pharmacodynamics) of the drug. Potentially, test results could be used to optimize drug choice and/or dose for more effective therapy, avoid serious adverse effects, and decrease medical costs.

Cytochrome P450 System

The cytochrome p450 (CYP450) family is a major subset of all drug-metabolizing enzymes; several CYP450 enzymes are involved in the metabolism of a significant proportion of currently administered drugs. CYP2D6 metabolizes approximately 25% of all clinically used medications (e.g., dextromethorphan, beta-blockers, antiarrhythmics, antidepressants, and morphine derivatives), including most prescribed drugs. CYP2C19 metabolizes several important types of drugs, including proton pump inhibitors, diazepam, propranolol, imipramine, and amitriptyline.

Some CYP450 enzyme genes are highly polymorphic, resulting in some enzyme variants that have variable metabolic capacities among individuals, and some with little to no impact on activity. Thus, CYP450 enzymes constitute an important group of drug-gene interactions influencing the variability of effect of some CYP450 metabolized drugs.

Individuals with two copies (alleles) of the most common (wild type) DNA sequence of a particular CYP450 enzyme gene resulting in an active molecule are termed extensive metabolizers (EM's; normal). Poor metabolizers (PM's) lack active enzyme gene alleles, and intermediate metabolizers (IM), who have one active and one inactive enzyme gene allele, may experience to a lesser degree some of the consequences of poor metabolizers. Ultrarapid metabolizers (UM) are individuals with more than two alleles of an active enzyme gene. There is pronounced ethnic variability in the population distribution of metabolizer types for a given CYP enzyme.

UMs administered an active drug may not reach therapeutic concentrations at usual, recommended doses of active drugs, while PMs may suffer more adverse events at usual doses due to reduced metabolism and increased concentrations. Conversely, for administered prodrugs that must be converted by CYP450 enzymes into active metabolites, UMs may suffer adverse effects and PMs may not respond.

Many drugs are metabolized to varying degrees by more than one enzyme, either within or outside of the CYP450 superfamily. In addition, interaction between different metabolizing genes, interaction of genes and environment, and interactions among different non-genetic factors also influence CYP450-specific metabolizing functions. Thus, identification of a variant in a single gene in the metabolic pathway may be insufficient in all but a small proportion of drugs to explain inter-individual differences in metabolism and consequent efficacy or toxicity.

Determining Genetic Variability in Drug Response
Genetically determined variability in drug response has been traditionally addressed using a trial and error approach to prescribing and dosing, along with therapeutic drug monitoring (TDM) for drugs with a very narrow therapeutic range and/or potential serious adverse effects outside that range. However, TDM is not available for all drugs of interest, and a cautious trial and error approach can lengthen the time to achieving an effective dose.

CYP450 enzyme phenotyping (identifying metabolizer status) can be accomplished by administering a test enzyme substrate to a patient and monitoring parent substrate and metabolite concentrations over time (e.g., in urine). However, testing and interpretation are time-consuming and inconvenient; as a result, phenotyping is seldom performed.

The clinical utility of *CYP450* genotyping, i.e., the likelihood that genotyping will significantly improve drug choice/dosing and consequent patient outcomes, is favored when the drug under consideration has a narrow therapeutic dose range (window), when the consequences of treatment failure are severe, and/or when serious adverse reactions are more likely in patients with gene sequence variants. Under these circumstances, genotyping may direct early selection of the most effective drug or dose, and/or avoid drugs or doses likely to cause toxicity. For example, warfarin, some neuroleptics, and tricyclic antidepressants have narrow therapeutic windows and can cause serious adverse events when concentrations exceed certain limits, resulting in cautious dosing protocols. Yet, the potential severity of the disease condition may call for immediate and sufficient therapy; genotyping might speed the process of achieving a therapeutic dose and avoiding significant adverse events.

For CYP450 genotyping related to warfarin dosing, refer to medical policy #525 - *Genetic Testing for Warfarin Dose.*

For CYP450 genotyping related to antidepressant drugs and antipsychotic drugs (e.g. ssri, tricyclic antidepressants, etc.) and the use of panels of genetic testing that includes tests for genes other than CYP450 related genes (e.g. the Genecept Assay), refer to medical policy #550 – *Genetic Testing for Mental Health Conditions.*

Policy:

Effective for dates of service on or after September 24, 2016:

CYP450 genotyping for the purpose of aiding in the choice of clopidogrel **(Plavix)** versus alternative anti-platelet agents, or in decisions on the optimal dosing for clopidogrel **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

CYP2D6 genotyping to determine **drug metabolizer status meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the following members:

- With **Gaucher disease** being considered for treatment with **eliglustat**; **OR**
- With **Huntington disease** being considered for treatment with **tetrabenazine** in a dosage greater than 50mg per day

CYP450 genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for all other drugs **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**. This includes, **but is not limited to**, CYP450 genotyping for the following applications:

- ~~Selection or dosing of selective serotonin reuptake inhibitor (SSRI);~~
- ~~Selection or dosing of antipsychotic drugs;~~
- ~~Selection and dosing of selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors;~~
- ~~Selection and dosing of tricyclic antidepressants;~~
- Dosing of efavirenz and other antiretroviral therapies for HIV (human immunodeficiency virus) infection;
- Selection or dose of beta blockers (e.g., metoprolol);
- Dosing of immunosuppressant for organ transplantation;
- Dosing and management of anti-tuberculosis medications
- Selection or dosage of codeine;

The **use of genetic testing panels** that include **multiple CYP450 ~~mutations~~ variants does not meet** Blue Cross Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Effective for DOS prior to September 24, 2016:

CYP450 genotyping for the purpose of aiding in the choice of clopidogrel **(Plavix)** versus alternative anti-platelet agents, or in decisions on the optimal dosing for clopidogrel **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage.

CYP450 genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for all other drugs **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**. This includes, **but is not limited to**, CYP450 genotyping for the following applications:

- Selection or dosing of selective serotonin reuptake inhibitor (SSRI);

- Selection or dosing of antipsychotic drugs;
- Deciding whether to prescribe codeine;
- Selection and dosing of selective norepinephrine reuptake inhibitors;
- Selection and dosing of tricyclic antidepressants;
- Dosing of efavirenz and other antiretroviral therapies for HIV (human immunodeficiency virus) infection;
- Selection or dose of beta blockers (e.g., metoprolol);
- Dosing of immunosuppressant for organ transplantation;
- Managing the treatment of *H. pylori* infection;
- Dosing and management of anti-tuberculosis medications

The **use of genetic testing panels** that include **multiple CYP450 ~~mutations~~ variants does not meet** Blue Cross Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent review of the literature covered the period through April 9, 2018.

The primary goal of pharmacogenomics testing and personalized medicine is to achieve better clinical outcomes in compared with the standard of care. Drug response varies greatly between individuals, and genetic factors are known to play a role. However, in most cases, the genetic variation only explains a modest portion of the variance in the individual response because clinical outcomes are also affected by a wide variety of factors including alternate pathways of metabolism and patient- and disease-related factors that may affect absorption, distribution, and elimination of the drug. Therefore, assessment of clinical utility cannot be made by a chain of evidence from clinical validity data alone. In such cases, evidence evaluation requires studies that directly demonstrate that the pharmacogenomic test alters clinical outcomes; it is not sufficient to demonstrate that the test predicts a disorder or a phenotype.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

P450 Genotype-Guided Treatment Strategy

Clinical Context and Therapy Purpose

The purpose of P450 genotype-guided strategy is to tailor drug selection and dosing based on gene composition for drug metabolism. In theory, this should lead to early selection and optimal dosing of the most effective drugs, while minimizing treatment failures or toxicities.

The question addressed in this evidence review is: Does P450 genotype-guided strategy change patient management in a way that improves net health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant populations of interest are patients being considered for treatment with clopidogrel, eliglustat, tetrabenazine, codeine, efavirenz and other antiretroviral therapies for HIV infection, immunosuppressants for organ transplantation, β-blockers (e.g., metoprolol) and anti-tuberculosis medications.

Interventions

Commercial testing for individual genes or gene panels are available and listed in the regulatory status section. Only those panels that include *CYP450* genes are listed in that section.

Comparators

The comparator of interest is standard clinical management without genetic testing.

Outcomes

Specific outcomes of interest are listed in the Table 1.

Table 1: Outcomes of Interest for Individuals with Altered Drug Metabolism

Drug	Outcomes
Clopidogrel	• Initial and maintenance dose selection • Decrease in platelet reactivity • Myocardial infarction, cardiovascular or all cause death, revascularization, fatal/nonfatal cerebrovascular accident, aortic event
Highly active antiretroviral agents	• Dose selection • Avoidance of treatment failure • Avoidance or reduction of adverse effects
Immunosuppressant therapy for organ transplantation	• Dose selection • Avoidance of organ failure • Avoidance or reduction of adverse effects
β-blocker(s)	• Dose selection • Superior control of blood pressure • Avoidance or reduction of adverse effects due to over treatment
Anti-tuberculosis medications	• Dose selection • Avoidance or reduction of hepatotoxicity due to over treatment

Timing
Outcomes in the first 3 months are relevant because the interest is in whether P450 genotype-guided strategy reduces adverse events or avoids treatment failure.

Setting
Consultations about choice of drug generally occur in outpatient setting and a variety of specialists may be involved with multiple categories of drugs such as primary care providers (HIV, β-blockers, TB and cough medications), cardiologist (clopidogrel), psychiatrist (anti-depressants and anti-psychotics), neurologist (Huntington) and endocrinologist (Gaucher disease).

Clopidogrel
Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor, (clopidogrel, prasugrel, or ticagrelor) is the standard of care for the prevention of subsequent atherothrombotic events such as stent thrombosis or recurrent acute coronary syndrome in patients who undergo a percutaneous intervention or who have an acute coronary syndrome.

Clopidogrel is a prodrug that is converted to its active form by several CYP450 enzymes (particularly CYP2C19). Individuals with genetic variants that inactivate the CYP2C19 enzyme are associated with lack of response to clopidogrel. There are several variants of CYP2C19 but

the 2 most frequent variants associated with loss of function alleles are CYP2C19*2 and CYP2C19*3. It is hypothesized that such individuals may benefit from other drugs such as prasugrel or ticagrelor or a higher dose of clopidogrel. Approximately 30% of whites and blacks and 65% of Asians carry a nonfunctional CYP2C19 gene variant. While CYP2C19 is the major enzyme involved in the generation of clopidogrel active metabolite, the variability in clinical response seen with clopidogrel may also result from other factors such as variable absorption, accelerated platelet turnover, reduced CYP3A metabolic activity, increased adenosine diphosphate exposure, or upregulation of P2Y12 pathways, drug-drug interactions, comorbidities (eg, diabetes, obesity), and medication adherence.

Multiple observational studies in patients undergoing percutaneous coronary intervention (PCI) have reported associations between the presence of loss of function alleles and lower levels of active clopidogrel metabolites, high platelet reactivity, and increased risk of adverse cardiovascular events. However, evidence of publication bias has been reported in these studies where smaller studies have reported larger benefits than larger studies which have reported no effect or smaller effect. Wang et al (2016) reported post hoc analysis of the CHANCE trial conducted in China; it randomized patients with a transient ischemic attack or minor stroke to clopidogrel plus aspirin or aspirin alone. In a subgroup analysis of patients who did not have the loss of function alleles, clopidogrel plus aspirin vs aspirin alone was associated with statistical significant reduction in the risk of stroke (6.7% vs 12.4%; hazard ratio, 0.51; 95% confidence interval, 0.35 to 0.75) but not among those who carried loss of function alleles (9.4% vs 10.8%; hazard ratio, 0.93; 95% confidence interval, 0.69 to 1.26). Results of this analysis have contributed to the formulation of the hypothesis of a differential effect of clopidogrel in patients with and without loss of function alleles.

Trials are important to validate such hypotheses. However, only a few trials of genotype-directed dosing or drug choice have been conducted; they are summarized in Tables 2 and 3 and discussed next. It is important to note that these trials use "high on-treatment platelet reactivity" as the outcome measure. Patients who exhibit "high on-treatment platelet reactivity" are referred to as being nonresponsive, hyporesponsive, or resistant to clopidogrel in the published literature.

Roberts et al (2012) reported on the results of RCT that allocated patients undergoing PCI for acute coronary syndrome or stable angina to genotype-guided management to select for treatment with prasugrel (carriers) or clopidogrel (noncarriers) or to standard treatment with clopidogrel. Among those who received prasugrel and clopidogrel based on genotyping test, 0% and 10%, respectively, exhibited high on-treatment reactivity while 17% patients who received standard treatment with clopidogrel without any genotypes testing exhibited high on-treatment reactivity. This difference was not statistically significant. So et al (2016) reported on the results of an RCT that randomized ST-elevation myocardial infarction patients who were carriers of CYP2C19*2, ABCB1 TT, and CYP2C19*17 alleles to prasugrel 10 mg daily or an augmented dosing strategy of clopidogrel (150 mg/d for 6 days and subsequently 75 mg/d). Results showed that (1) carriers did not respond to augmented clopidogrel as well as they did to prasugrel (24% patients with high platelet reactivity vs 0%) and (2) among noncarriers, physician-directed clopidogrel was effective for most patients (95% did not have high platelet reactivity).

Table 2. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
So et al (2016); RAPID STEMI	Canada	1	2011-2012	18-75 y who had PCI for STEMI who received POC testing for *CYP2C19*2*, *ABCB1* TT, and *CYP2C19*17* alleles (N=102)	Carriers randomized to prasugrel 10 mg/d (n=30) or augmented clopidogrel (150 mg/d for 6 d and then 75 mg/d) (n=29)	Noncarriers given clopidogrel with dosing as per treating physician (n=43)
Roberts et al (2012); RAPID GENE	Canada	1	2010-2011	18-75 y undergoing PCI for acute coronary syndrome or stable angina (n=200)	POC testing for *CYP2C19*2* allele (n=102). Of these, 23 carriers were given prasugrel 10 mg/d, and 74 noncarriers were given clopidogrel 75 mg/d	No genetic testing and clopidogrel 75 mg/d

PCI: percutaneous coronary intervention; POC: point of care; RCT: randomized controlled trial: STEMI: ST-elevation myocardial infarction.

Table 3. Summary of Key RCT Results

Study; Trial	High Platelet Reactivity[a]
So et al (2016); RAPID STEMI	102
Carriers	
Prasugrel	0%[d]
Augmented clopidogrel	24%[d]
Noncarriers	
Clopidogrel as per treating physician	5%[d]
p	0.0046[b]; 0.507[c]
Roberts et al (2012); RAPID GENE	187
Genotype-guided management	
Prasugrel 10 mg/d	0%
Clopidogrel 75 mg/d	10%
Entire cohort	10%
Standard clinical management	
Clopidogrel 75 mg/d	17%[e]
p	*NS*

a P2Y12 reaction unit >234 (a measure of high on-treatment platelet reactivity).
b Prasugrel vs augmented clopidogrel.
c Prasugrel vs physician-directed clopidogrel.
d At 30 days.
e At 1 week.

The purpose of the gaps tables (see Tables 4 and 5) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement. The studies were, in general, well-designed and -conducted, the major limitation being the use of platelet activity, which is an intermediate outcome measure, and lack of reporting on health endpoints over a longer follow-up.

Platelet reactivity during treatment is an intermediate end point that has been shown to have a limited value in guiding therapeutic decisions based on results of the large ARTIC RCT. Briefly,

the ARCTIC trial randomized 2440 patients scheduled for coronary stenting to platelet-function monitoring or no monitoring. Platelet-function testing was performed in the monitored group both before and 14 to 30 days after PCI. Multiple therapeutic changes, including an additional loading dose of clopidogrel (at a dose ≥600 mg) or a loading dose of prasugrel (at a dose of 60 mg) before the procedure, followed by a daily maintenance dose of clopidogrel 150 mg or prasugrel 10 mg, were made according to a predefined protocol. There was no difference in the rate of the primary composite end point (death, myocardial infarction, stent thrombosis, stroke, or urgent revascularization) at 1 year between the monitoring (34.6%) and no monitoring groups (31.1%). In the absence of results from well-performed randomized trials designed to evaluate this issue, performing routine genetic testing or ex vivo tests of platelet reactivity to predict CYP2C19 metabolic state and identify PMs has not been shown to improve health clinical outcomes. TAILOR-PCI (NCT01742117) is a large ongoing RCT that will randomize 5270 patients undergoing PCI to clopidogrel without prospective genotyping guidance or a prospective CYP2C19 genotype-based antiplatelet therapy approach (ticagrelor 90 mg bid in CYP2C19*2 or CYP2C19*3 reduced function allele patients, clopidogrel 75 mg once daily in non-CYP2C19*2 or -CYP2C19*3 patients). The trial is expected to be completed in March 2020.

Table 4. Relevance Gaps

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
So et al (2016); RAPID STEMI				2. Platelet activity is an intermediate outcome measure 3. CONSORT harms not reported	1, 2. Outcomes assessed at 1 mo
Roberts et al (2012); RAPID GENE				2. Platelet activity is an intermediate outcome measure 3. CONSORT harms no reported	1, 2. Outcomes assessed at 1 wk

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Gaps

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
So et al (2016); RAPID STEMI						
Roberts et al (2012); RAPID GENE	3. Allocation concealment unclear					

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
f Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Clopidogrel

Two RCTs have evaluated the role of genetic testing for CYP2C19 for selecting appropriate antiplatelet treatment and/or amplified dosing of clopidogrel using an intermediate outcome measure of platelet reactivity to predict CYP2C19 metabolic state. One RCT has shown there was no statistical difference in patients with "on-treatment high platelet reactivity" who received genotype-guided management or standard treatment with clopidogrel. The second RCT showed that carriers of loss of function alleles did not respond to augmented clopidogrel as well as they did to prasugrel, while physician-directed clopidogrel was effective for most noncarriers. However, routine testing using platelet reactivity as an outcome measure to predict CYP2C19 metabolic state has not been shown to improve health outcomes. Results of an ongoing RCT (TAILOR-PCI), assessing outcomes in 5270 patients randomized to genotype-based antiplatelet therapy approach or standard care, are expected in 2020 and likely to address this gap.

Selection and Dosing of Other Drugs

Antiretroviral Agents

Efavirenz is a widely used non-nucleoside reverse transcriptase inhibitor component of highly active antiretroviral therapy for patients with HIV infection. However, unpredictable interindividual variability in efficacy and toxicity remain important limitations associated with its use. Forty percent to 70% of patients have reported adverse central nervous system events. While most resolve in the first few weeks of treatment, about 6% of patients discontinue efavirenz due to adverse events. Efavirenz is primarily metabolized by the CYP2B6 enzyme, and inactivating variants such as CYP2B6*6 are associated with higher efavirenz exposure, although plasma levels appear not to correlate with adverse events. On the other hand, CYP2B6 PMs have markedly reduced adverse events while maintaining viral immunosuppression at substantially lower doses. An increased early discontinuation rate with efavirenz has been reported in retrospective cohort studies evaluating multiple CYP450 variants including CYP2B6. CYP2B6 G516T and T983C single nucleotide variants were reported by Ciccacci et al (2013) to be associated with susceptibility to Stevens-Johnson syndrome in a case-control study of 27 patients who received nevirapine-containing antiretroviral treatment. The current evidence documenting the usefulness of CYP450 variant genotyping to prospectively guide antiretroviral medications and assess its impact on clinical outcomes is lacking.

Immunosuppressants for Therapy for Organ Transplantation

Tacrolimus is the mainstay immunosuppressant drug and multiple studies have shown that individuals who express CYP3A5 (extensive and intermediate metabolizers) generally have decreased dose-adjusted trough concentrations of tacrolimus, possibly delaying achievement of

target blood concentrations compared with those who are CYP3A5 nonexpressers (PMs) in whom drug levels may be elevated and possibly result in nephrotoxicity. The current evidence demonstrating the impact of CYP3A5 genotyping to guide tacrolimus dosing and its impact on clinical outcomes is a limited RCT by Thervet et al (2010). This RCT compared the impact of CYP3A5 genotype-informed dosing with standard dosing strategies on tacrolimus drug levels. The trial was not powered to assess any clinical outcomes such as graft function or survival, which otherwise were similar between groups.

Beta Blockers
Several reports have indicated that lipophilic beta blockers (e.g., metoprolol), used in treating hypertension, may exhibit impaired elimination in patients with CYP2D6 variants. The current evidence documenting the usefulness of CYP2D6 genotyping to prospectively guide antitubercular medications and assess its impact on clinical outcomes is lacking.

Antitubercular Medications
A number of studies, summarized in a systematic review by Wang et al (2016), have reported an association between CYP2E1 status and the risk of liver toxicity from antitubercular medications. The current evidence documenting the usefulness of CYP2E1 genotyping to prospectively guide antitubercular medications and assess its impact on clinical outcomes is lacking.

Codeine
Enhanced CYP2D6 activity is associated with risk of accelerated codeine metabolism with high levels of circulating morphine in rapid metabolizers, which is thought to have contributed to deaths in infants of nursing mothers prescribed codeine and in pediatric patients post-tonsillectomy. Few case reports have described the association between CYP2D6 variant status and risk of death. There is little evidence about the clinical utility of testing for CYP2D6 genotype.

Section Summary: Selection and Dosing of Other Drugs
In general, most published CYP450 pharmacogenomic studies for highly active antiretroviral agents, beta blockers, and antitubercular medications are retrospective evaluations of CYP450 genotype associations, reporting intermediate outcomes (e.g., circulating drug concentrations) or less often, final outcomes (e.g., adverse events or efficacy). Many of these studies are small, underpowered, and hypothesis generating. Prospective intervention studies, including RCTs documenting clinical usefulness of CYP450 genotyping to improve existing clinical decision-making to guide dose or drug selection, which will then translate into improvement in patient outcomes, were not identified.

Summary of Evidence
Clopidogrel
For individuals with a need for antiplatelet therapy who are undergoing or being considered for clopidogrel therapy who receive a CYP2C19-guided treatment strategy, the evidence incudes 2 RCTs. Relevant outcomes are overall survival, medication use, and treatment-related morbidity. The 2 RCTs evaluated the impact of CYP2C19 genotyping using an intermediate outcome measure (platelet reactivity). One RCT showed no statistical difference between patients with

on-treatment high platelet reactivity between genotype-guided management or standard treatment with clopidogrel. The second RCT showed carriers of loss of function alleles did not respond to augmented clopidogrel as well as they did to prasugrel, and physician-directed clopidogrel was effective for most noncarriers. However, routine testing using platelet reactivity as an outcome measure to predict CYP2C19 metabolic state has not been shown to improve health outcomes. Results of an ongoing RCT (TAILOR-PCI), assessing outcomes in 5270 patients randomized to genotype-based antiplatelet therapy approach or standard care, are expected in 2020 and likely to address this gap. The evidence is insufficient to determine the effects of the technology on health outcomes.

Other Drugs

For individuals who are undergoing or being considered for treatment with highly active antiretroviral agents, immunosuppressant therapy for organ transplantation, beta blockers, antitubercular medications or codeine who receive a CYP2C19-guided treatment strategy, the evidence includes retrospective studies and case reports. Relevant outcomes are medication use and treatment-related morbidity. In general, most published CYP450 pharmacogenomic studies for these drugs consist of retrospective evaluations of CYP450 genotype associations, reporting intermediate outcomes (eg, circulating drug concentrations) or less often, final outcomes (eg, adverse events or efficacy). Many of these studies are small, underpowered and hypothesis generating. Prospective intervention studies, including RCTs documenting the clinical usefulness of CYP450 genotyping to improve existing clinical decision making to guide dose or drug selection, which may then translate into improvement in patient outcomes, were not identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statement

A consensus statement by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) on genetic testing for selection and dosing of clopidogrel was published in 2010. The recommendations for practice included the following statements:

- Adherence to existing ACCF/AHA guidelines for the use of antiplatelet therapy should remain the foundation for therapy. Careful clinical judgment is required to assess the importance of the variability in response to clopidogrel for an individual patient and its associated risk to the patient.
- Clinicians must be aware that genetic variability in CYP enzymes alter clopidogrel metabolism, which in turn can affect its inhibition of platelet function. Diminished responsiveness to clopidogrel has been associated with adverse patient outcomes in registry experiences and clinical trials.
- The specific impact of the individual genetic polymorphisms on clinical outcome remains to be determined.
- Information regarding the predictive value of pharmacogenomic testing is very limited at this time; resolution of this issue is the focus of multiple ongoing studies. The selection of the specific test, as well as the issue of reimbursement, is both important additional considerations.
- The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time.

- There are several possible therapeutic options for patients who experience an adverse event while taking clopidogrel in the absence of any concern about medication compliance.

U.S. Preventive Services Task Force Recommendations
No U.S. Preventive Services Task Force recommendations for cytochrome p450 have been identified.

Key Words:
Cytochrome p450, CYP450, genotyping, AmpliChip®, CYP2D6, CYP2C19, CYP2B6, clopidogrel, Plavix, SSRI, CYP2C19*2, CYP2C19*3, Helicobacter pylori, H. pylori, CYP2C9, GeneSightRx, PHARMAchip

Approved by Governing Bodies:
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

Table 6. Testing Kits for CYP450 Genotyping Cleared for Marketing by FDA

Device Name	Manufacturer	Approval Date
xTAG Cyp2d6 Kit V3	Luminex Molecular Diagnostics	2017
xTAG Cyp2c19 Kit V3	Luminex Molecular Diagnostics	2013
Spartan Rx Cyp2c19 Test System	Spartan Bioscience	2013
xTAG Cyp2d6 Kit V3 (Including Tdas Cyp2d)	Luminex Molecular Diagnostics	2013
Verigene Cyp2c19 Nucleic Acid Test (2c19)	Nanosphere	2012
Infiniti Cyp2c19 Assay	Autogenomics	2010
xTAG Cyp2d6 Kit V3, Model I030c0300 (96)	Luminex Molecular Diagnostics	2010
Invader Ugt1a1 Molecular Assay	Third Wave Technologies	2005
Roche AmpliChip Cyp450 Test	Roche Molecular Systems	2005

FDA: Food and Drug Administration.

Several manufacturers market panels of diagnostic genotyping tests for *CYP450* genes, such as the YouScript Panel (Genelex Corporation, Seattle, WA), which includes *CYP2D6*, *CYP2C19*, *CYP2C9*, *VKORC1*, *CYP3A4* and *CYP3A5*. Other panel tests include both *CYP450* genes and other non-*CYP450* genes involved in drug metabolism, such as the GeneSight Psychotropic panel (Assurex Health, Inc., Mason, OH) and PersonaGene Genetic Panels (AIBioTech, Richmond, VA). These tests are beyond the scope of this policy.

FDA Labeling on CYP450 Genotyping
FDA has included pharmacogenomics information in the physician prescribing information (drug labels) of multiple drugs. In most cases, this information is general and lacks specific directives for clinical decision making. In the following examples, FDA has given clear and specific directives on either use of a specific dose (eg, eliglustat, tetrabenazine) or when a drug may not

be used at all (e.g., codeine) and therefore evidence in such cases is not reviewed in the Rationale section.

Eliglustat
The FDA has approved eliglustat for treatment of adults with Gaucher disease type 1 who are CYP2D6 EMs, intermediate metabolizers, or PMs as detected by an FDA-cleared test. Further, the label acknowledges the limitation of use among UMs because they may not achieve adequate concentrations and a specific dosage was not recommended for patients with indeterminate CYP2D6 metabolizer's status. Further, the label states that the dosing strategy should be 84 mg orally, twice daily for CYP2D6 EMs or intermediate metabolizers and 84 mg orally, once daily for CYP2D6 PMs. FDA has included a black box to warn about the reduced effectiveness in PMs and to advise healthcare professionals to consider alternative dosing or to use of other medications in patients identified as potential PMs.

Tetrabenazine
FDA has approved tetrabenazine for the treatment of chorea associated with Huntington disease. According to the label, patients requiring doses above 50 mg/d should be genotyped for the drug-metabolizing enzyme CYP2D6 to determine if the patient is a PM or EM. For patients categorized as PMs using an FDA-approved test, the maximum daily dose should not exceed 50 mg, with a maximum single dose of 25 mg.

Codeine
FDA does not recommend genotyping before prescribing codeine. FDA has contraindicated codeine for treating pain or cough in children under 12 years of age and codeine is not recommended for use in adolescents ages 12 to 18 who are obese or have conditions such as obstructive sleep apnea or severe lung disease. There is an additional warning to mothers not to breastfeed when taking codeine.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT codes:

81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g. drug metabolism); gene analysis, common variants (e.g. *2,

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*3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)

81227 CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g. *2, *3, *5, *6)

81230 CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22) **(Effective 01/01/18)**

81231 CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *7) **(Effective 01/01/18)**

81402 Molecular pathology procedure Level 3 (e.g., >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD]) includes-

CYP21A2 (cytochromeP450, family 21, subfamily A, polypeptide 2) (e.g., congenital adrenal hyperplasia, 21-hydroxylase deficiency), common variants (e.g., IVS2-13G, P30L, I172N, exon 6 mutation cluster [I235N, V236E, M238K], V281L, L307FfsX6, Q318X, R356W, P453S, G110VfsX21, 30- kb deletion variant)

81404 Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) includes –

CYP1B1 (cytochrome P450, family 1, subfamily B, polypeptide 1) (e.g., primary congenital glaucoma), full gene sequence

81405 Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) includes –

CYP11B1 (cytochrome P450, family 11, subfamily B, polypeptide 1) (e.g., congenital adrenal hyperplasia), full gene sequence;
CYP17A1 (cytochrome P450, family 17, subfamily A, polypeptide 1) (e.g., congenital adrenal hyperplasia), full gene sequence;
CYP21A2 (cytochrome P450, family 21, subfamily A, polypeptide 2) (e.g., steroid 21-hydroxylase isoform, congenital adrenal hyperplasia), full gene sequence **(effective 01/01/2012)**

81479 Unlisted molecular pathology procedure **(effective 01/01/2013)**

81599	Unlisted multianalyte assay with algorithmic analysis **(effective 01/01/2013)**
0028U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, copy number variants, common variants with reflex to targeted sequence analysis **(Effective 01/01/18)**
0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (i.e., CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823) **(Effective 01/01/18)**
0031U	CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(eg, drug metabolism) gene analysis, common variants (i.e., *1F, *1K, *6, *7) **(Effective 01/01/18)**

Previous Coding:

Prior to 01/01/2018, there was no specific code for CYP3A4 or CYP3A5:

0015U	Drug metabolism (adverse drug reactions), DNA, 22 drug metabolism and transporter genes, real time PCR, blood or buccal swab, genotype and metabolizer status for therapeutic decision support. **(Effective 08/01/17 and Deleted 12/31/17)**

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Policy History:

Medical Policy Group, April 2010 **(1)**
Medical Policy Administration Committee, May 2010
Available for comment May 7-June 21, 2010
Medical Policy Group, April 2011 **(1):** Consolidated all coverage criteria related to cytochrome p450 to this policy and Updated Policy, Key Points, Key Words and References
Medical Policy Administration Committee, May 2011
Available for comment May 11 – June 27, 2011
Medical Policy Group, July 2011 **(1):** Update to Key Points and References for H. pylori
Medical Policy Group, December 2011 **(1):** Update to Codes with 2012 information
Medical Policy Group, February 2012 **(1):** Update to Codes with addition of G9143
Medical Policy Group, March 2012 **(1):** Update to Key Points and References related to MPP update on warfarin dosing
Medical Policy Group, January 2013 **(1):** Codes 88384-88386, 83890-83914 and modifier -9B moved to previous codes due to deletion 01/01/13; addition of codes 81479 and 81599 to current coding effective 01/01/2013
Medical Policy Panel, December 2012
Medical Policy Group, January 2013 **(1):** Update to Key Points and References related to warfarin dosing; update to Key Words with addition of GeneSightRx and PHARMAchip related to dosing of antidepressants; no change in policy statement

Medical Policy Panel, September 2012
Medical Policy Group, May 2013 **(1):** Removal of all CYP450 testing related to warfarin testing and moved to separate policy 525-Genetic testing for warfarin dosing; Update to policy section with addition of more investigational criteria—selection and dosing of tricyclic antidepressants, replaced atomoxetine HCL dosing with broader selective norepinephrine uptake inhibitors, reworded section pertaining to clopidogrel dosing to make more generic in nature without change in criteria; Update to Key Points and References
Medical Policy Administration Committee, May 2013
Available for comment May 21 through July 5, 2013
Medical Policy Panel, October 2013
Medical Policy Group, October 2013 **(1):** Update to Policy with addition of investigational statement for dosing of anti-tuberculosis medications, no other changes to policy statement; update to Key Points and References
Medical Policy Administration Committee, November 2013
Medical Policy Panel, October 2014
Medical Policy Group, October 2014 **(1):** Update to Policy with addition of investigational statement for use of genetic testing panels that include multiple CYP450 mutations. Update to Description, Governing Bodies, Key Points, and References
Medical Policy Group, November 2014: 2015 Coding Updates – Wording change to codes 81402, 81404, & 81405
Medical Policy Group, January 2015 Updated CPT code descriptions for 81402, 81404, and 81405
Medical Policy Group, November 2015: 2016 Annual Coding Update; verified coding
Medical Policy Panel, December 2015
Medical Policy Group, August 2016 **(3)**: Updates to Key Points & References; removed Previous Coding section containing coding prior to December 2013; policy statements updated to reflect removal of coverage criteria related to CYP450 genotyping for the purpose of aiding in the choice of clopidogrel (Plavix) versus alternative anti-platelet agents, or in decisions on the optimal dosing for clopidogrel and addition of coverage criteria related to CYP2D6 genotyping to determine drug metabolizer status for members with Gaucher disease being considered for treatment with eliglustat or with Huntington disease being considered for treatment with
Medical Policy Administration Committee, August 2016
Available for comment August 9 through September 23, 2016
Medical Policy Panel, June 2017
Medical Policy Group, June 2017 **(3):** 2017 Updates to Description, Key Points, Approved by Governing Bodies & References; no change in policy statement.
Medical Policy Group, July 2017: Ad hoc coding update. Added CPT code 0015U to Current coding section.
Medical Policy Group, December 2017: Annual Coding Update 2018. Added new codes 81230, 81231, and 0028U – 0031U effective 01/01/18 to Current Coding. Created Previous Coding section and moved 81401 and deleted code 0015U to this section.
Medical Policy Panel, June 2018
Medical Policy Group, July 2018 **(4):** Updates to Title, Description, Policy, Key Points, Approved by Governing Bodies, Current Coding and References. Removed investigational criteria points related to mental health drugs and moved to MP# 550. Removed CPT code

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0030U. This code is included in MP# 525. Removed Code 81401 deleted effective 12/1/14 in Previous Coding section.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.