Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 5/1/22**
(See policy history boxes for previous effective dates)

Title: Genetic Testing for Cytochrome P450 Polymorphisms

Note: For genetic testing for mental health conditions using multigene panels, please reference the policy, "Genetic Testing for Specified Conditions Using Panel Testing."

Description/Background

The cytochrome p450 (*CYP450*) family is involved in the metabolism of a significant proportion of currently administered drugs, and genetic variants in cytochrome p450 are associated with altered metabolism of many drugs. Genetic testing for cytochrome p450 variants may assist in selecting and dosing drugs that are impacted 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, nutrition, smoking and drug-drug interactions. Inherited (germline) DNA sequence variation (polymorphisms) 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 polymorphisms (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 many of the 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* enzyme variants constitute one 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; normal). Poor metabolizers (PM) 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 (UMs) 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* super family. 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.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Diagnostic genotyping tests for certain *CYP450* enzymes are now available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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..

Several testing kits for *CYP450* genotyping cleared for marketing by FDA (FDA product code: NTI) are summarized in Table 1.

Table 1. Selected 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 1030c0300 (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 Corp., 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); these tests are beyond the scope of this evidence review.

FDA Labeling on *CYP450* Genotyping

The 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 (e.g., 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.[1]

Tetrabenazine

The 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.[2]

Codeine

The 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.[3]

Medical Policy Statement

The safety and effectiveness of *CYP450* genotyping for the purpose of aiding in the choice of clopidogrel versus alternative antiplatelet agents or determining drug metabolizer status for patient with Gaucher and Huntington's disease have been established. It may be considered a useful diagnostic option for patients who meet specific patient selection criteria.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:

- *CYP450* genotyping for the purpose of aiding in the choice of clopidogrel versus alternative anti-platelet agents, or
- *CYP450* genotyping for the purpose of aiding in decisions on the optimal dosing for clopidogrel
- *CYP2D6* genotyping to determine drug metabolizer status for patients
    - With Gaucher disease being considered for treatment with eliglustat; or
    - With Huntington's disease being considered for treatment with tetrabenazine in a dosage greater than 50mg per day.

Exclusions:

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. This includes, but is not limited to, *CYP450* genotyping for the following applications (list may not be all-inclusive):

- Selection or dosage of codeine
- Dosing of efavirenz and other antiretroviral therapies for HIV (human immunodeficiency virus) infection.
- Dosing of immunosuppressant for organ transplantation
- Selection or dose of beta blockers (e.g., metoprolol)
- Dosing and management of antituberculosis medicines

The use of genetic testing panels that include multiple *CYP450* mutations is considered investigational.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

81225 81226

Other codes (investigational, not medically necessary, etc.):

81227 81401 81402 81404 81405

81230 81231

Rationale

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, two 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 genotyping is to tailor drug selection and dosing to individual patients based on their 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 outcome?

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant populations of interest are patients being considered for treatment with clopidogrel, eliglustat, tetrabenazine, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, antipsychotic drugs, codeine, efavirenz and other antiretroviral therapies for HIV infection, immunosuppressants for organ transplantation, β-blockers (e.g., metoprolol) and anti-tubercular 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 following practice is currently being used: standard clinical management without genetic testing.

Outcomes

Specific outcomes of interest are listed in the Table 2.

Table 2: 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 events
Immunosuppressant therapy for organ transplantation	• Dose selection • Avoidance of organ failure • Avoidance or reduction of adverse events
β-blocker(s)	• Dose selection • Superior control of blood pressure • Avoidance or reduction of adverse events due to overtreatment
Antitubercular medications	• Dose selection • Avoidance or reduction of hepatotoxicity due to overtreatment

Clopidogrel

Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor (clopidogrel, prasugrel, 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 thought 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.[4] 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 (e.g., 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. 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).[6] 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. These trials are summarized in Tables 3 and 4 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) used a point-of-care genetic test to identify carriers of the *CYP2C19*2* allele and aimed to assess a pharmacogenetic approach to dual antiplatelet treatment after percutaneous coronary intervention (PCI). Between Aug 26, 2010, and July 7, 2011, 200 patients were enrolled into this prospective, randomised, proof-of-concept study. Patients undergoing PCI for acute coronary syndrome or stable angina were randomly assigned to rapid point-of-care genotyping or to standard treatment. Individuals in the rapid genotyping group were screened for the *CYP2C19*2* allele. Carriers were given 10 mg prasugrel daily, and non-carriers and patients in the standard treatment group were given 75 mg clopidogrel daily. The primary endpoint was the proportion of *CYP2C19*2* carriers with high on-treatment platelet reactivity (P2Y12 reactivity unit [PRU] value of more than 234) after 1 week of dual antiplatelet treatment, which is a marker associated with increased adverse cardiovascular events. Interventional cardiologists and data analysts were masked to genetic status and treatment. Patients were not masked to treatment allocation. All analyses were by intention to treat. After randomisation, 187 patients completed follow-up (91 rapid genotyping group, 96 standard treatment). Twenty-three individuals in each group carried at least one *CYP2C19*2* allele. None of the 23 carriers in the rapid genotyping group had a PRU value of more than 234 at day 7, compared with seven (30%) given standard treatment (p=0·0092). The point-of-care genetic test had a sensitivity of 100% (95% CI 92·3-100) and a specificity of 99·3% (96·3-100). The authors concluded that point-of-care genetic testing after PCI can be done effectively at the bedside and treatment of identified *CYP2C19*2* carriers with prasugrel can reduce high on-treatment platelet reactivity.

Claassens et al (2019)[9] reported on the results of the CYP2C19 Genotype Guided Treatment With Antiplatelet Drugs in Patients With ST-segment-elevation Myocardial Infarction Undergoing Immediate PCI With Stent Implantation: Optimization of Treatment (POPular Genetics) trial. In this non-inferiority trial, patients with acute coronary syndrome were randomly assigned to receive standard treatment (prasugrel or ticagrelor) or genotype-guided treatment (clopidogrel in those without CYP2C19 loss of-function variants; standard treatment otherwise). Results of the primary combined endpoint met the P value for non-inferiority. Thus, one can conclude that a genotype guided strategy led to outcomes that were at least as good as, if not better than, outcomes with the standard approach of prescribing prasugrel or ticagrelor to all patients. There was no difference in the incidence of PLATO major bleeding between the genotype-guided group and the standard-treatment group (2.3% in both groups;

hazard ratio, 0.97; 95% CI, 0.58 to 1.63). The statistical significant difference observed in the primary bleeding outcome was primarily driven by PLATO minor bleeding events in the genotype-guided group versus standard-treatment group (7.6% vs. 10.5%; HR=0.72; 95% CI, 0.55 to 0.94).

Pereira et al (2021) reported the results of the open-label randomized TAILOR-PCI trial of 5302 patients undergoing PCI for acute coronary syndromes or stable coronary artery disease.[10] The genotype-guided group underwent point-of-care genotyping for detection of CYP2C19 carriers and were prescribed ticagrelor (prasugrel was recommended as an alternative for patients who did not tolerate ticagrelor) and noncarriers were prescribed clopidogrel. Patients randomized to the conventional group were prescribed clopidogrel and underwent genotyping after 12 months. Among 5302 patients randomized (median age, 62 years; 25% women), 94% completed the trial. Of 1849 CYP2C19 carriers, 764 of 903 (85%) assigned to genotype-guided therapy received ticagrelor, and 932 of 946 (99%) assigned to conventional therapy received clopidogrel. The primary end point (a composite of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia at 12 months) occurred in 35 of 903 CYP2C19 carriers (4.0%) in the genotype-guided therapy group and 54 of 946 (5.9%) in the conventional therapy group at 12 months (HR=0.66; 95% CI 0.43 to 1.02; p = 0.06). None of the 11 prespecified secondary end points showed significant differences, including major or minor bleeding in CYP2C19 carriers in the genotype-guided group (1.9%) vs the conventional therapy group (1.6%) at 12 months (HR= 1.22; 95% CI: 0.60 to 2.51; p = 0.58). Among all randomized patients, the primary end point occurred in 113 of 2641 (4.4%) in the genotype-guided group and 135 of 2635 (5.3%) in the conventional group (HR= 0.84; 95% CI: 0.65 to 1.07; p = 0.16). The trial failed to meet the pre-specified endpoint and the authors contend that the trial was underpowered to detect an effect size less than the 50% relative risk after a revised sample calculation. Despite the occurrence of 89 ischemic events observed in this trial, which exceeded the 76 events anticipated to provide adequate power, the observed RR reduction was 34% instead of the estimated 50%, hence a borderline p value of 0.056 was observed. Further, the authors also comment that the potential benefit of genotype-guided oral P2Y12 inhibitor therapy may be important early after PCI rather than 12 months after PCI. A post-hoc analysis of the data from the trial showed that a nearly 80% reduction in the rate of adverse events occurred in the first three months of treatment among patients who received genetically guided therapy compared with those who did not.

Table 3. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
So et al (2016)[8]; RAPID STEMI	Canada	1	2011-2012	18-75 y who had PCI for STEMI who received POC testing for *CYP2C19 *2*, *ABCB1* T T, and *CYP2C1 9*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)[7]; RAPID GENE	Canada	1	2010-2011	18-75 y undergoing PCI for acute	POC testing for *CYP2C19 *2* allele	No genetic testing and clopidogrel 75

				coronary syndrome or stable angina (n=200)	(n=102). Of these, 23 carriers were given prasugrel 10 mg/d, and 74 noncarriers were given clopidogrel 75 mg/d	mg/d
Claassens et al (2019);[9] POPular Genetics	Europe	10	2011-2018	21 y or older with signs and symptoms of STEMI undergoing PCI (n=2488)	Genotype-guided group: Individuals received clopidogrel (non-carriers) or prasugrel/ticagrelor (carriers) for one year	Prasugrel/ticagrelor for one year
Pereira et al (2021)[10]	US, Canada, South Korea, and Mexico	40	2013-2018	Adult undergoing PCI for ACS or stable CAD (n=5302).	Genotype-guided therapy group using POC genotyping. CYP2C19 carriers were prescribed ticagrelor for maintenance therapy, and noncarriers or those with inconclusive results were prescribed clopidogrel. Prasugrel was recommended as an alternative for patients who did not tolerate ticagrelor (n=2653 randomized; n=2641eligible for analysis; n=903 CYP2C19 carriers identified and included in primary analysis).	Conventional therapy group without prospective genotyping. All were prescribed clopidogrel according to drug label (n=2650 randomized; n=2635 eligible for analysis; n=946 CYP2C19 carriers identified and included in primary analysis).

POC; point of care; PCI; Percutaneous coronary intervention; STEMI; ST-elevation myocardial infarction
POPular Genetics: Cost-effectiveness of CYP2C19 Genotype Guided Treatment With Antiplatelet Drugs in Patients With ST-segment-elevation Myocardial Infarction Undergoing Immediate PCI With Stent Implantation: Optimization of Treatment; RAPID GENE: ReAssessment of Anti-Platelet Therapy Using an In Dividualized Strategy Based on GENetic Evaluation; RAPID STEMI: ReAssessment of Anti-Platelet Therapy Using an In Dividualized Strategy in Patients With ST-segment Elevation Myocardial Infarction.

Table 4. Summary of Key RCT Results

Study; Trial	Outcome
	High Platelet Reactivity[a]
So et al (2016)[8]; 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)[7]; 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*
Claassens et al (2019);[9] POPular Genetics	Primary Combined Outcome[f]
Genotype-guided management (n=1242)	63 (5.1%)
Standard-treatment group (n=1246)	73 (5.9%)
Absolute difference (95% CI)	0.7 (−2.0 to 0.7); p<0.001 for noninferiority
	Primary Bleeding Outcome[g]
Genotype-guided management (n=1242)	*122 (9.8%)*
Standard-treatment group (n=1246)	156 (12.5%)
Hazard ratio (95% CI)	0.78 (0.61 to 0.98) p=0.04
Pereira et al (2021)[10]	Primary Combined Outcome[b]
Genotype-guided management (n=903)	35 (4%)
Conventional therapy (n=946)	54 (5.9%)
Difference in 12-month event rates, % (95% CI)	−1.8 (−3.9 to 0.1)
Hazard ratio (95% CI), p value	0.66 (0.43 to 1.02),.06
	Secondary Combined Outcome[i]
Genotype-guided management (n=903)	16 (1.9%)
Conventional therapy (n=946)	14 (1.6%)
Difference in 12-month event rates, % (95% CI)	0.3 (−0.9 to 1.6)
Hazard ratio (95% CI), p value	1.22 (0.60 to 2.51),.58

POPular Genetics: Cost-effectiveness of CYP2C19 Genotype Guided Treatment With Antiplatelet Drugs in Patients With ST-segment-elevation Myocardial Infarction Undergoing Immediate PCI With Stent Implantation: Optimization of Treatment; RAPID GENE: ReAssessment of Anti-Platelet Therapy Using an In Dividualized Strategy Based on GENetic Evaluation; RAPID STEMI: ReAssessment of Anti-Platelet Therapy Using an In Dividualized Strategy in Patients With ST-segment Elevation Myocardial Infarction.
RCT: randomized controlled trial.
[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.
[f] Death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding as defined by Platelet Inhibition and Patient Outcomes (PLATO) criteria at 12-months
[g] PLATO major bleeding (CABG-related and non–CABG-related) or minor bleeding at 12 months (primary bleeding outcome)

Mega et al (2009)[10] reported on the association between functional genetic variants in CYP genes, plasma concentrations of active drug metabolite, and platelet inhibition in response to clopidogrel in 162 healthy subjects. The authors examined the association between these genetic variants and cardiovascular outcomes in a separate cohort of 1477 subjects with acute

coronary syndromes who were treated with clopidogrel in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasurgrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38. In healthy subjects who were treated with clopidogrel, carriers of at least one *CYP2C19* reduced-function allele (approximately 30% of the study population) had a relative reduction of 32.4% in plasma exposure to the active metabolite of clopidogrel, as compared with noncarriers (P<0.001). Carriers also had an absolute reduction in maximal platelet aggregation in response to clopidogrel that was 9 percentage points less than that seen in noncarriers (P<0.001). Among clopidogrel-treated subjects in TRITON-TIMI 38, carriers had a relative increase of 53% in the composite primary efficacy outcome of the risk of death from cardiovascular causes, myocardial infarction, or stroke, as compared with noncarriers (12.1% vs. 8.0%; hazard ratio for carriers, 1.53; 95% confidence interval [CI], 1.07 to 2.19; P=0.01) and an increase by a factor of 3 in the risk of stent thrombosis (2.6% vs. 0.8%; hazard ratio, 3.09; 95% CI, 1.19 to 8.00; P=0.02). The authors concluded that among persons treated with clopidogrel, carriers of a reduced-function *CYP2C19* allele had significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and a higher rate of major adverse cardiovascular events, including stent thrombosis, than did noncarriers.

In 2010, the FDA approved a new label for clopidogrel with a “boxed warning” about the diminished effectiveness of the drug in patients with impaired ability to convert the drug into its active form.[22] The boxed warning is based on the concern that the antiplatelet effect of clopidogrel depends primarily on its activation by the cytochrome P450 system. Patients with decreased *CYP2C19* function because of genetic polymorphisms metabolized clopidogrel poorly and have higher rates of cardiovascular events after acute coronary syndrome and percutaneous coronary interventions than patients with normal *CYP2C19* function. The warning also notes that tests are available to identify patients with genetic polymorphisms, and the alternative treatment strategies should be considered in poor metabolizers of the drug.

The new label emphasizes a single study of 40 healthy subjects (10 each with different degrees of *CYP2C19* function—poor, intermediate, extensive, and Ultrarapid) in a crossover design. Each group was randomized to a 300-mg loading dose (LD) followed by a 75-mg per day maintenance dose (MD), or a 600-mg LD followed by 150-mg per day MD, each for a total of 5 days. After a washout period, subjects were crossed over to the alternate treatment. The chief findings were decreased active metabolite exposure and increased platelet aggregation in the poor metabolizers compared with the other groups. When poor metabolizers received the 600-mg LD followed by 150 mg daily MD, active metabolite exposure and antiplatelet response were greater than with the 300-mg LD and 75 mg per day MD regimen, but remained quantitatively less than the response in the extensive metabolizers when they received the 300 mg and 75 mg regimen. Two different assays for platelet function were used—platelet aggregation stimulated by 5 micromolar adenosine diphosphate and the vasodilator-stimulated phosphoprotein phopsphorylation assay. Improvement in platelet inhibitory responses with higher-dose clopidogrel in poor metabolizers was apparent only with the former assay. There was no comment about statistical significance in the labeling material. Analysis of the final as yet unpublished data set of this study, which played a prominent role in the boxed warning, will be essential to a more complete understanding of the issues.[22]

Section Summary: Clopidogrel
Two RCTs used a point-of-care genetic test to identify carriers of the *CYP2C19*2* allele and aimed to assess a pharmacogenetic approach to dual antiplatelet treatment after percutaneous

coronary intervention (PCI). The authors in both RCTs concluded that point-of-care genetic testing after PCI can be done effectively at the bedside and treatment of identified *CYP2C19*2* carriers with prasugrel can reduce high on-treatment platelet reactivity. In a cohort study the authors found that among persons treated with clopidogrel, carriers of a reduced-function *CYP2C19* allele had significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and a higher rate of major adverse cardiovascular events, including stent thrombosis, than did noncarriers. In a non-inferiority trial, results of the primary combined endpoint met the P value for non-inferiority. Authors concluded that a genotype guided strategy led to outcomes that were at least as good as, if not better than, outcomes with the standard approach. In addition, the FDA approved a new label for clopidogrel with a "boxed warning" about the diminished effectiveness of the drug in patients with impaired ability to convert the drug into its active form. The boxed warning is based on the concern that the antiplatelet effect of clopidogrel depends primarily on its activation by the cytochrome P450 system.

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.[12] 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.[14,15] An increased early discontinuation rate with efavirenz has been reported in retrospective cohort studies evaluating multiple *CYP450* variants including *CYP2B6*.[16,17] *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.[18] 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) and Min et al (2018).[19,20] Both RCTs compared the impact of *CYP3A5* genotype-informed dosing with standard dosing strategies on tacrolimus drug levels. The trials were not powered to assess any clinical outcomes such as graft function or survival, which otherwise were similar between groups in Thervet et (2010).[19]

B-Blockers

Several reports have indicated that lipophilic -blockers (e.g., metoprolol), used in treating hypertension, may exhibit impaired elimination in patients with *CYP2D6* variants.[21,22] 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.[23] The current evidence documenting the usefulness of *CYP2E1* genotyping to prospectively guide antitubercular medications and assess its impact on clinical outcomes is lacking.

Section Summary: Selection and Dosing of Other Drugs

In general, most published *CYP450* pharmacogenomic studies for highly active antiretroviral agents, -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 need for antiplatelet therapy who are undergoing or being considered for clopidogrel therapy managed with testing for *CYP2C19* metabolizer status by *CYP2C19* genotyping, the evidence includes multiple systematic reviews, secondary analyses of a RCT and multiple observational studies. Relevant outcomes are test accuracy and validity, morbid events, and treatment-related morbidity and mortality. Multiple observational studies report that genetic variants associated with *CYP2C19* may be associated with a modest increase in the rate of stent thrombosis and increased incidence of adverse clinical events. Two large meta-analysis that included patients treated with and without percutaneous coronary intervention showed genetic testing after PCI can be done effectively and treatment of identified *CYP2C19*2* carriers with prasugrel can reduce high on-treatment platelet reactivity. A prospective cohort study reported that in patients with a recent acute coronary syndrome or percutaneous coronary intervention who underwent *CYP2C19* genotyping, providers were more likely to increase antiplatelet therapy intensification for carriers than for noncarriers. Given the association between *CYP2C19* metabolizer status and risk of stent thrombosis in patients undergoing cardiac interventions, genotype may be used to consider treatment alternatives (e.g., higher doses of clopidogrel or alternative drug choices). The U.S. Food and Drug Administration (FDA) created a black box warning indicating testing should be considered. The evidence is sufficient 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, b-blockers, or

antitubercular medications who receive a *CYP2C19*-guided treatment strategy, the evidence includes retrospective studies. 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 (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 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.

Ongoing and Unpublished Clinical Trials

No relevant ongoing or unpublished studies that might influence this review were identified.

SUPPLEMENTAL INFORMATION

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, BCBSM received from 4 physician specialty societies and 4 academic medical centers while this policy was under review in 2012. Opinions on use of genotyping for testing in patients being considered for clopidogrel treatment were mixed with five suggesting the test be considered investigational and three suggesting it be considered medically necessary.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Cardiology Foundation et al

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.[24] 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.

Government Regulations
National / Local:

There is no national or local coverage determination on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing for Specified Conditions using Testing Panels
- Genotype-Guided Testing for Warfarin Dosing
- Pharmacogenomic and Metabolite Markers for Patients Who Have Been Treated with Azathioprine (6-MP)

References

1. Genzyme. Highlights of Prescribing Information: Cerdelga (eliglustat). 2014; http://www.cerdelga.com/pdf/cerdelga_prescribing_information.pdf. Accessed May 15, 2020.
2. Food and Drug Administration. Highlights of Prescribing Information: Xenazine (tetrabenazine). 2015; https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021894s010lbl.pdf. Accessed May 15, 2020.
3. FDA statement from Douglas Throckmorton, M.D., deputy center director for regulatory programs, Center for Drug Evaluation and Research, on new warnings about the use of codeine and tramadol in children & nursing mothers. 2017; https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm553285.htm. Accessed May 15, 2020.
4. Scott SA, Sangkuhl K, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther. Sep 2013;94(3):317-323. PMID 23698643
5. Holmes MV, Perel P, Shah T, et al. CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. JAMA. Dec 28, 2011;306(24):2704-2714. PMID 22203539
6. Wang Y, Zhao X, Lin J, et al. Association between CYP2C19 loss-of-function allele status and efficacy of clopidogrel for risk reduction among patients with minor stroke or transient ischemic attack. JAMA. Jul 5 2016;316(1):70-78. PMID 27348249

7. Roberts JD, Wells GA, Le May MR, et al. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. Lancet. May 5 2012;379(9827):1705-1711. PMID 22464343
8. So DY, Wells GA, McPherson R, et al. A prospective randomized evaluation of a pharmacogenomic approach to antiplatelet therapy among patients with ST-elevation myocardial infarction: the RAPID STEMI study. Pharmacogenomics J. Feb 2016;16(1):71-78. PMID 25850030
9. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A Genotype-Guided Strategy for Oral P2Y 12 Inhibitors in PrimaryPCI. N Engl J Med. Oct 24 2019; 381(17): 1621-1631. PMID 31479209
10. Pereira NL, Farkouh ME, So D, et al. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes After Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. JAMA. Aug 25 2020; 324(8): 761-771. PMID 32840598
11. Mega JL, Close SL, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med. 2009 Jan 22;360(4):354-62. doi: 10.1056/NEJMoa0809171. Epub 2008 Dec 22. PMID: 19106084.
12. King J, Aberg JA. Clinical impact of patient population differences and genomic variation in efavirenz therapy. AIDS. Sep 12 2008;22(14):1709-1717. PMID 18753940
13. Torno MS, Witt MD, Saitoh A, et al. Successful use of reduced-dose efavirenz in a patient with human immunodeficiency virus infection: case report and review of the literature. Pharmacotherapy. Jun 2008;28(6):782-787. PMID 18503405
14. Gatanaga H, Hayashida T, Tsuchiya K, et al. Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 *6 and *26. Clin Infect Dis. Nov 1 2007;45(9):1230-1237. PMID 17918089
15. Wyen C, Hendra H, Siccardi M, et al. Cytochrome P450 2B6 (CYP2B6) and constitutive androstane receptor (CAR) polymorphisms are associated with early discontinuation of efavirenz-containing regimens. J Antimicrob Chemother. Sep 2011;66(9):2092-2098. PMID 21715435
16. Lubomirov R, Colombo S, di Iulio J, et al. Association of pharmacogenetic markers with premature discontinuation of first-line anti-HIV therapy: an observational cohort study. J Infect Dis. Jan 15 2011;203(2):246-257. PMID 21288825
17. Ciccacci C, Di Fusco D, Marazzi MC, et al. Association between CYP2B6 polymorphisms and Nevirapine-induced SJS/TEN: a pharmacogenetics study. Eur J Clin Pharmacol. Nov 2013;69(11):1909-1916. PMID 23774940
18. Thervet E, Loriot MA, Barbier S, et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. Clin Pharmacol Ther. Jun 2010;87(6):721-726. PMID 20393454
19. Min S, Papaz T, Lafreniere-Roula M, et al. A randomized clinical trial of age and genotype-guided tacrolimusdosing after pediatric solid organ transplantation. Pediatr Transplant. Nov 2018; 22(7): e13285. PMID 30178515
20. Bijl MJ, Visser LE, van Schaik RH, et al. Genetic variation in the CYP2D6 gene is associated with a lower heart rate and blood pressure in beta-blocker users. Clin Pharmacol Ther. Jan 2009;85(1):45-50. PMID 18784654
21. Yuan H, Huang Z, Yang G, et al. Effects of polymorphism of the beta(1) adrenoreceptor and CYP2D6 on the therapeutic effects of metoprolol. J Int Med Res. Nov-Dec 2008;36(6):1354-1362. PMID 19094446
22. Wang FJ, Wang Y, Niu T, et al. Update meta-analysis of the CYP2E1 RsaI/PstI and DraI polymorphisms and risk of antituberculosis drug-induced hepatotoxicity: evidence from 26 studies. J Clin Pharm Ther. Jun 2016;41(3):334-340. PMID 27062377

23. Holmes DR, Jr., Dehmer GJ, Kaul S, et al. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the American Heart Association endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol. Jul 20, 2010;56(4):321-341. PMID 20633831
24. Blue Cross Blue Shield Association. Cytochrome p450 Genotyping. Medical Policy Reference Manual. Policy #2.04.38, Issue 6:2017, original policy date 4/1/04, last review date June 2021.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2022, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/06	8/30/06	9/18/06	Joint policy established
1/1/08	10/16/07	11/18/07	Routine maintenance
11/1/08	8/19/08	10/30/08	Routine maintenance
5/1/10	2/16/10	2/16/10	Routine maintenance
9/1/11	6/21/11	6/21/11	• Policy status changed; Cyp450 testing may be considered a useful diagnostic option for patients with cardiovascular disease undergoing treatment with clopidogrel (Plavix®) in order to identify those who are poor metabolizers of the drug (patients with CYP2C19*2/2,*3/3, and *2/3 genotypes) and who are, therefore, likely to exhibit poor response to the drug. • Testing for under- or over-metabolizers for any other drug is still considered experimental and investigational. • Additional references added.
1/1/13	10/16/12	10/16/12	• No change in policy status. • Policy updated with literature search, references 32, 46, 53-62, 70-72, 78, 79, 86 added. Wording of established indications statement clarified for clopidogrel. Investigational statements added for selective norepinephrine reuptake inhibitors and tricyclic antidepressants.
7/1/14	4/8/14	5/1/14	Routine maintenance. Added new codes 81401, 81402, 81404 and 81405 to policy
9/1/15	6/19/15	7/16/15	Routine maintenance. Updated rationale and references; no change to policy position.
1/1/17	10/11/16	10/11/16	Routine policy maintenance. Added Gaucher and Huntington disease to inclusion section. Moved code 81226 to the established code section.

1/1/18	10/19/17	10/19/17	Updated rationale section, added reference # 17, 30, 31, 76, 77, 90, 106, 110 and 111. No change to policy status.
5/1/18	2/20/18	2/20/18	Code update, added codes 81230 and 81231 as E/I.
5/1/19	5/1/19		Several references and subsections of the rationale section were deleted/revised. Information on pharmacologic treatments used to treat mental health disorders removed and added to policy for genetic testing for specified conditions.
5/1/20	2/18/20		Routine policy maintenance. No change in policy status.
5/1/21	2/16/21		Routine maintenance.
5/1/22	2/15/22		Routine policy maintenance, added reference #10, no change in policy status.

Next Review Date: 1st Qtr. 2023

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR CYTOCHROME P450 POLYMORPHISMS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.