
Medical Policy



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***Current Policy Effective Date: 5/1/24**
(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 the Food and Drug Administration

Device Name	Manufacturer	Approval Date
Genomadix Cube CYP2C19 System	Genomadix Inc.	2023
xTAG Cyp2c19 Kit V3	Luminex Molecular Diagnostics	2013
Spartan Rx Cyp2c19 Test System	Spartan Bioscience	2013
Verigene Cyp2c19 Nucleic Acid Test (2c19)	Nanosphere	2012
Infiniti Cyp2c19 Assay	Autogenomics	2010
xTAG Cyp2d6 Kit V3, Model 1030c0300 (96)	Luminex Molecular Diagnostics, Inc	2010
Invader Ugt1a1 Molecular Assay	Third Wave Technologies	2005
Roche AmpliChip Cyp450 Test	Roche Molecular Systems	2005

CYP450: cytochrome P450.

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 maintains online compendia of pharmacogenetic associations under 3 categories: 1. pharmacogenetic associations for which the data support therapeutic management recommendations; 2. pharmacogenetic associations for which the data indicate a potential impact on safety or response and 3. pharmacogenetic associations for which the data demonstrate a potential impact on pharmacokinetic properties only.¹

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 boxed warning 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.²

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.³

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.⁴

Siponimod

The FDA has approved siponimod for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. The recommended maintenance dosage is 2 mg. The recommended maintenance dosage in patients with a *CYP2C9**1/*3 or *2/*3 genotype is 1 mg. Siponimod is contraindicated in patients with a *CYP2C9**3/*3 genotype.⁵

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 multiple sclerosis, 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

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, OR
 - With relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, being considered for treatment with siponimod. (please see pharmacy policy on Genetic Testing for dosage information)

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

81227

81418

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

81230	81231	81401	81402
81404	81405	0380U	

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.

Cytochrome P450 (CYP450) 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 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Dose selection • Avoidance of treatment failure • Avoidance or reduction of adverse events
Immunosuppressant therapy for organ transplantation	<ul style="list-style-type: none"> • Dose selection • Avoidance of organ failure • Avoidance or reduction of adverse events
β-blocker(s)	<ul style="list-style-type: none"> • Dose selection • Superior control of blood pressure • Avoidance or reduction of adverse events due to overtreatment
Antitubercular medications	<ul style="list-style-type: none"> • Dose selection • Avoidance or reduction of hepatotoxicity due to overtreatment

Review of Evidence

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 coronary intervention (PCI) 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 White and Black individuals and 65% of Asians carry a nonfunctional *CYP2C19* gene variant.⁶ 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 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 (TIA) 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).⁸ 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.

Randomized Controlled Trials

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).⁹ 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)¹¹ 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 statistically significant difference observed in the primary bleeding outcome was primarily driven by PLATelet inhibition and patient Outcomes (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.¹² 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.

Wang et al (2021) published results of the Ticagrelor versus Clopidogrel in CYP2C19 Loss-of-Function Carriers with Stroke or TIA (CHANCE-2) trial.¹³ This double-blind, multicenter RCT in China compared ticagrelor and clopidogrel for the secondary prevention of stroke in individuals with minor ischemic stroke or TIA who were CYP2C19 loss of function carriers. Overall, 6412 individuals (98% Chinese) with ischemic stroke or TIA were determined to be loss of function carriers and were included and randomized 1:1 to receive either ticagrelor or clopidogrel for 90 days duration. All patients received aspirin for the first 21 days. The median time from symptom onset to randomization was 14 hours and the average turnaround time of point-of-care testing was 80.3 minutes. Of those included, 5001 (78%) were intermediate metabolizers and 1411 (22%) were poor metabolizers. A primary-outcome event of new ischemic or hemorrhagic stroke within 90 days occurred in 191 (6.0%) patients in the ticagrelor group and 243 (7.6%) patients in the clopidogrel group (HR, 0.77; 95% CI, 0.64 to 0.94). Severe or moderate bleeding occurred in 9 (0.3%) patients on ticagrelor and 11 (0.3%) on clopidogrel. Any bleeding event occurred in 170 (5.3%) patients and 80 (2.5%) patients in the ticagrelor and clopidogrel groups, respectively. In subgroup analysis, the primary outcome benefit with ticagrelor was consistent in individuals who were intermediate metabolizers (150 vs. 191 events; HR, 0.78; 95% CI, 0.63 to 0.97), but not in poor metabolizers (41 vs. 52 events; HR, 0.77; 95% CI, 0.50 to 1.18). The risk of recurrent stroke within 90 days among Chinese loss of function carriers was modestly lower with ticagrelor than with clopidogrel, without an increased risk of severe or moderate bleeding. Ticagrelor was associated with more total bleeding events compared to clopidogrel. This study is limited by its homogenous study population, making generalizability to populations other than Han Chinese patients difficult. Additionally, no patients with delayed presentation after stroke, receipt of thrombolysis, or cardioembolic stroke were included.

Table 3. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
So et al (2016) RAPID STEMI	Canada	1	2011-2012	18 to 75 y who had PCI for STEMI who received POC testing for <i>CYP2C19</i> *2, <i>ABCB1</i> T, and <i>CYP2C1</i> 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) RAPID GENE	Canada	1	2010-2011	18 to 75 y undergoing PCI for acute coronary syndrome or stable angina (N=200)	POC testing for <i>CYP2C19</i> *2 allele (n=102). Of these, 23 carriers were given prasugrel 10 mg/d, and 74 noncarriers were given	No genetic testing and clopidogrel 75 mg/d

					clopidogrel 75 mg/d	
Claassens et al (2019) 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); TAILOR PC	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=2641 eligible 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).
Wang et al (2021); CHANCE-2	China	202	2019-2021	Individuals (median age, 64.8 years; 33.8% female; 98% Chinese) with minor	Ticagrelor (180 mg loading dose on day 1, followed by 90 mg twice daily on days	Clopidogrel (300 mg loading dose on day 1, followed by 75 mg daily on days 2

ischemic stroke or TIA who carried CYP2C19 LOF alleles (N=6412)	2 through 90) and aspirin for the first 21 days (n=3205)	through 90) and aspirin for the first 21 days (n=3207)
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ACS: acute coronary syndrome; CAD: coronary artery disease; CHANCE-2: Ticagrelor or Clopidogrel with Aspirin in High-Risk Patients with Acute Nondisabling Cerebrovascular Events II trial; CYP: cytochrome P450; LOF: loss-of-function; PCI: Percutaneous coronary intervention; POC: point of care; 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 Individualized Strategy Based on GENetic Evaluation; RAPID STEMI: ReAssessment of Anti-Platelet Therapy Using an Individualized Strategy in Patients With ST-segment Elevation Myocardial Infarction ; STEMI; ST-elevation myocardial infarction; TIA: transient ischemic attack.

Table 4. Summary of Key RCT Results

Study	Outcome			
	High Platelet Reactivity ^a	New stroke within 90 days, n (%)	Severe or moderate bleeding within 90 days, n (%)	Any bleeding, n (%)
So et al (2016)¹⁰; RAPID STEMI	N=102	NA	NA	NA
Carriers				
Prasugrel	0% ^d			
Augmented clopidogrel	24% ^d			
Noncarriers				
Clopidogrel as per treating physician	5% ^d			
p	.0046 ^b ; .507 ^c			
Roberts et al (2012)⁹; RAPID GENE	N=187	NA	NA	NA
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)¹¹; POPular Genetics	Primary Combined Outcome ^f	NA	NA	NA
Genotype-guided management (n=1242)	63 (5.1%)			
Standard-treatment group (n=1246)	73 (5.9%)			
Absolute difference (95% CI); p	0.7 (-2.0 to 0.7); <.001 for noninferiority			

	Primary Bleeding Outcome ^g			
Genotype-guided management (n=1242)	122 (9.8%)			
Standard-treatment group (n=1246)	156 (12.5%)			
HR (95% CI); p	0.78 (0.61 to 0.98);.04			
Pereira et al (2021)¹²; TAILOR PC	Primary Combined Outcome ^h	NA	NA	NA
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)			
HR (95% CI); p	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)			
HR (95% CI); p	1.22 (0.60 to 2.51) ;.58			
Wang et al (2021)¹³; CHANCE-2	NA			
Ticagrelor (n=3205)		191 (6.0)	9 (0.3)	170 (5.3%)
Clopidogrel (n=3207)		243 (7.6)	11 (0.3)	80 (2.5)
HR (95% CI); p		0.77 (0.64 to 0.94);.008		

CI: confidence interval; CHANCE-2: Ticagrelor or Clopidogrel with Aspirin in High-Risk Patients with Acute Nondisabling Cerebrovascular Events II trial; HR: hazard ratio; NA: not applicable; NS: not significant; 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 InDividualized Strategy Based on GENetic Evaluation; RAPID STEMI: ReAssessment of Anti-Platelet Therapy Using an InDividualized Strategy in Patients With ST-segment Elevation Myocardial Infarction.

^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 (coronary artery bypass graft [CABG]-related and non-CABG-related) or minor bleeding at 12 months (primary bleeding outcome).

^h Cardiovascular death, myocardial infarction, stroke, severe recurrent ischemia, stent thrombosis.

ⁱ Major or minor bleeding as defined by the Thrombolysis in Myocardial Infarction (TIMI) criteria.

The purpose of the limitation tables (see Tables 5 and 6) is to display notable limitations 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 endpoint that has been shown to have a limited value in guiding therapeutic decisions based on results of the large Assessment by a Double Randomization of a Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption Versus Continuation One Year After Stenting (ARCTIC) RCT.^{14,15} 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 endpoint (death, myocardial infarction, stent thrombosis, stroke, or urgent revascularization) at 1 year between the monitoring (34.6%) and no monitoring groups (31.1%). Further, an adequately powered TAILOR-PCI RCT reported no statistically significant difference in a composite end point of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia among patients with *CYP2C19* loss-of-function alleles who underwent PCI, genotype-guided selection of an oral P2Y12 inhibitor compared with conventional clopidogrel therapy. Limitations of this trial included the possibility of being underpowered when sample size calculations were revised, some patients not receiving designated antiplatelet therapy and the open-label nature of the trial. However, the adjudication of all events was blinded.

Table 5. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
So et al (2016) ¹⁰ ; 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) ⁹ ; RAPID GENE				2. Platelet activity is an intermediate outcome measure 3. CONSORT harms no reported	1, 2. Outcomes assessed at 1wk
Claassens et al (2019); ¹¹ ; POPular Genetics	2. Clinical context is unclear	2. Not standard or optimal			
Pereira et al (2021) ¹² ; TAILOR PC		2. Version used unclear (some patients not receiving designated antiplatelet			

		therapy)			
	4. 98% of				
	patients				
	included were				
	Chinese				
	5. Exclusion				
	criteria				
Wang et al	included				
(2021)¹³;	stroke,				
CHANCE-2	moderate or				
	severe				
	stroke,				
	delayed				
	presentation				
	after stroke,				
	and those				
	who				
	received				
	thrombolysis				

CHANCE-2: Ticagrelor or Clopidogrel with Aspirin in High-Risk Patients with Acute Nondisabling Cerebrovascular Events II trial; 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 InDIvidualized Strategy Based on GENetic Evaluation; RAPID STEMI: ReAssessment of Anti-Platelet Therapy Using an InDIvidualized Strategy in Patients With ST-segment Elevation Myocardial Infarction.

The evidence limitations 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. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

^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 6. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^d	Data Completeness ^e	Power ^d	Statistical ^f
So et al (2016)¹⁰; RAPID STEMI						
Roberts et al (2012)⁹; RAPID GENE	3. Allocation concealment unclear					
Claassens et al (2019);¹¹; POPular Genetics		1. Not blinded to treatment assignment;				
Pereira et al (2021)¹²; TAILOR PC		1. Not blinded to treatment assignment				
Wang et al (2021)¹³; CHANCE-2						

CHANCE-2: Ticagrelor or Clopidogrel with Aspirin in High-Risk Patients with Acute Nondisabling Cerebrovascular Events II trial; 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 InDIvidualized Strategy Based on GENetic Evaluation; RAPID STEMI: ReAssessment of Anti-Platelet Therapy Using an InDIvidualized Strategy in Patients With ST-segment Elevation Myocardial Infarction.

The evidence limitations 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

Four 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. The third non-inferiority RCT compared showed that 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. Results of this trial do not inform whether using genotype based strategy for prescribing clopidogrel results in any incremental net health benefit versus standard treatment with clopidogrel. Furthermore, the statistical significant difference observed in favor of genotype guided strategy for bleeding outcome was primarily driven by minor bleeding events. There was no difference in the incidence of major bleeding between the 2 groups. Results of TAILOR-PCI reported no statistically significant difference in a composite end point of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia among patients with *CYP2C19* loss-of-function alleles who underwent PCI, genotype-guided selection of an oral P2Y12 inhibitor compared with conventional clopidogrel therapy. In a trial comparing ticagrelor and clopidogrel use in individuals with stroke, results of the CHANCE-2 RCT reported a statistically significant decrease in risk of recurrent stroke in *CYP2C19* LOF carriers taking ticagrelor compared to clopidogrel in the first 90 days after presentation, without an increased risk of significant bleeding. Ticagrelor was associated with a higher number of total bleeding events compared to clopidogrel. These results are limited, however, by the homogenous Han Chinese population, lack of inclusion of those with delayed presentation, receipt of thrombolysis, or cardioembolic stroke, and majority of patients genotyped as intermediate metabolizers, limiting generalizability.

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.¹⁶ 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, based on a case report of 1 patient (Torno et al [2008]) and a case series of 12 patients (Gatanaga et al [2007])^{17,18} An increased early discontinuation rate with efavirenz has been reported in retrospective cohort studies evaluating multiple *CYP450* variants including *CYP2B6*.^{18,19} *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.²¹ However, no RCTs or large observational studies have been identified indicating that genetic testing prior to treatment initiation results in an avoidance of treatment failure, reduction of adverse events, or guides dose selection. 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).^{21,22} 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).²¹

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.^{23,24} 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.²⁵ 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, immunosuppressants, b-blockers, and antitubercular medications are retrospective evaluations of *CYP450* genotype associations, or underpowered RCTs, 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 who receive a cytochrome P450 (CYP) 2C19 guided treatment strategy, 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 (PCI) 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 boxed 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 CYP450-guided treatment strategy, the evidence includes retrospective studies and underpowered RCTs. 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.

2012 Input

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

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Cardiology Foundation

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 [cytochrome P450] 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.

Clinical Pharmacogenetics Implementation Consortium

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is an international consortium interested in facilitating use of pharmacogenetic tests for patient care. Their guidelines are designed to guide clinician understanding on how available genetic test results can be used to optimize drug therapy, rather than to recommend in whom pharmacogenetic testing should be conducted.

The CPIC published updated guidelines for CYP2C19 genotyping and clopidogrel therapy in 2022.²⁸ These guidelines provide recommended indications for CYP2C19 genotype-guided antiplatelet therapy based on a systematic review. Tables 7 and 8 summarize recommendations from these CPIC guidelines.

Table 7. CPIC Antiplatelet Therapy Recommendations Based on CYP2C19 Phenotype When Considering Clopidogrel for Cardiovascular Indications

CYP2C19 phenotype	Therapeutic recommendation	Classification of recommendation^a - ACS and/or PCI^b	Classification of recommendation^a - non-ACS, non-PCI CV indications^c
<i>CYP2C19</i> ultrarapid metabolizer	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	No recommendation
<i>CYP2C19</i> rapid metabolizer	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	No recommendation
<i>CYP2C19</i> normal metabolizer	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	Strong
<i>CYP2C19</i> likely intermediate metabolizer	Avoid standard dose clopidogrel (75 mg) if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong ^d	No recommendation ^d
<i>CYP2C19</i> intermediate metabolizer	Avoid standard dose clopidogrel (75 mg) if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong	No recommendation
<i>CYP2C19</i> likely poor metabolizer	Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong ^d	Moderate ^d
<i>CYP2C19</i> poor metabolizer	Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong	Moderate

ACS: acute coronary syndrome; CPIC: Clinical Pharmacogenetics Implementation Consortium; CV: cardiovascular; CYP: cytochrome P450; PCI: percutaneous coronary intervention.

Adapted from Lee et al (2022).²⁸,

a Strong: the evidence is high-quality and the desirable effects clearly outweigh the undesirable effects; Moderate: there is a close or uncertain balance as to whether the evidence is high quality and the desirable effects clearly outweigh the undesirable effects; Optional: the desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action; No recommendation: there is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

b ACS and/or PCI includes patients undergoing PCI for an ACS or non-ACS (elective) indication.

c Non-ACS, non-PCI CV indications include peripheral arterial disease and stable coronary artery disease following a recent myocardial infarction outside the setting of PCI.

d The strength of recommendation for "likely" phenotypes are the same as their respective confirmed phenotypes. "Likely" indicates the uncertainty in the phenotype assignment, but it is reasonable to apply the recommendation for the confirmed phenotype to the corresponding "likely" phenotype.

Table 8. CPIC Antiplatelet Therapy Recommendations Based on CYP2C19 Phenotype When Considering Clopidogrel for Neurovascular Indications^a

CYP2C19 phenotype	Therapeutic recommendation	Classification of recommendation^b	Other considerations
<i>CYP2C19</i> ultrarapid metabolizer	No recommendation	No recommendation	
<i>CYP2C19</i> rapid metabolizer	No recommendation	No recommendation	
<i>CYP2C19</i> normal metabolizer	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	
<i>CYP2C19</i> likely intermediate metabolizer	Consider an alternative P2Y ₁₂ inhibitor at standard dose if clinically indicated and no contraindication	Moderate ^c	
<i>CYP2C19</i> intermediate metabolizer	Consider an alternative P2Y ₁₂ inhibitor at standard dose if clinically indicated and no contraindication	Moderate	Alternative P2Y ₁₂ inhibitors not impacted by <i>CYP2C19</i> genetic variants include ticagrelor and ticlopidine. Prasugrel is contraindicated in patients with a history of stroke or TIA. ^d
<i>CYP2C19</i> likely poor metabolizer	Avoid clopidogrel if possible. Consider an alternative P2Y ₁₂ inhibitor at standard dose if clinically indicated and no contraindication	Moderate ^c	
<i>CYP2C19</i> poor metabolizer	Avoid clopidogrel if possible. Consider an alternative P2Y ₁₂ inhibitor at standard dose if clinically indicated and no contraindication	Moderate	

CPIC: Clinical Pharmacogenetics Implementation Consortium; CYP: cytochrome P450; TIA: transient ischemic attack. Adapted from Lee et al (2022).²⁸

^a Neurovascular disease includes acute ischemic stroke or TIA, secondary prevention of stroke, or prevention of thromboembolic events following neurointerventional procedures, such as carotid artery stenting and stent-assisted coiling of intracranial aneurysms.

^b Strong: the evidence is high-quality and the desirable effects clearly outweigh the undesirable effects; Moderate: there is a close or uncertain balance as to whether the evidence is high quality and the desirable effects clearly outweigh the undesirable effects; Optional: the desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action; No recommendation: there is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

^c The strength of recommendation for "likely" phenotypes are the same as their respective confirmed phenotypes. "Likely" indicates the uncertainty in the phenotype assignment, but it is reasonable to apply the recommendation for the confirmed phenotype to the corresponding "likely" phenotype.

^d Given limited outcomes data for genotype-guided antiplatelet therapy for neurovascular indications, selection of therapy should depend on individual patient treatment goals and risks for adverse events.

In 2019, the CPIC published guidelines for CYP2B6 considerations and efavirenz-containing antiretroviral therapy.²⁹ Table 9 summarizes efavirenz dosing recommendations based on CYP2B6 phenotype.

Table 9. CPIC Efavirenz Dosing Recommendations Based on CYP2B6 Phenotype in Children ≥40 kg and Adult Patients

CYP2B6 phenotype	Therapeutic recommendation	Classification of recommendation^a
CYP2B6 ultrarapid metabolizer	Initiate efavirenz with standard dosing (600 mg/day)	Strong
CYP2B6 rapid metabolizer	Initiate efavirenz with standard dosing (600 mg/day)	Strong
CYP2B6 normal metabolizer	Initiate efavirenz with standard dosing (600 mg/day)	Strong ^d
CYP2B6 intermediate metabolizer	Consider initiating efavirenz with decreased dose of 400 mg/day ^{b,c}	Moderate
CYP2B6 poor metabolizer	Consider initiating efavirenz with decreased dose of 400 or 200 mg/day ^{b,c}	Moderate

Adapted from Desta et al (2019).²⁹

a Strong: the evidence is high-quality and the desirable effects clearly outweigh the undesirable effects; Moderate: there is a close or uncertain balance as to whether the evidence is high quality and the desirable effects clearly outweigh the undesirable effects; Optional: the desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action; No recommendation: there is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

b If therapeutic drug monitoring is available and a decreased efavirenz dose is prescribed, consider obtaining steady-state plasma efavirenz concentrations to ensure concentrations are in the suggested therapeutic range (~1 to 4 µg/mL).

c To prescribe efavirenz at a decreased dose of 400 mg/day or 200 mg/day in a multidrug regimen may require prescribing more than 1 pill once daily. If so, the provider should weigh the potential benefit of reduced dose against the potential detrimental impact of increased pill number.

d The ENCORE study showed that in treatment-naive patients randomized to initiate efavirenz-based regimens (combined with tenofovir and emtricitabine), 400 mg/day was noninferior to 600 mg/day regardless of CYP2B6 genotype.³⁰

In 2015, the CPIC published guidelines for CYP3A5 genotype and tacrolimus dosing.³¹

Table 10 summarizes tacrolimus dosing recommendations based on CYP3A5 phenotype.

Table 10. CPIC Tacrolimus Dosing Recommendations Based on CYP3A5 Phenotype

CYP3A5 phenotype^a	Therapeutic recommendation^b	Classification of recommendation^c
Extensive metabolizer (CYP3A5 expresser)	Increase starting dose 1.5 to 2 times recommended starting dose. ^d Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Intermediate metabolizer (CYP3A5 expresser)	Increase starting dose 1.5 to 2 times recommended starting dose. ^a Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong

Poor metabolizer (CYP3A5 nonexpresser)	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.	Strong
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CPIC: Clinical Pharmacogenetics Implementation Consortium; CYP: cytochrome P450.

Adapted from Birdwell et al (2019).³¹,

a Typically, with other CYP enzymes, an extensive metabolizer would be classified as a "normal" metabolizer, and, therefore, the drug dose would not be changed based on the patient's genotype. However, in the case of CYP3A5 and tacrolimus, a CYP3A5 expresser (i.e., CYP3A5 extensive metabolizer or intermediate metabolizer) would require a higher recommended starting dose and the CYP3A5 nonexpresser (i.e., poor metabolizer) would require the standard recommended starting dose.

b This recommendation includes the use of tacrolimus in kidney, heart, lung, and hematopoietic stem cell transplant patients, and liver transplant patients in which the donor and recipient genotypes are identical.

c Strong: the evidence is high-quality and the desirable effects clearly outweigh the undesirable effects; Moderate: there is a close or uncertain balance as to whether the evidence is high quality and the desirable effects clearly outweigh the undesirable effects; Optional: the desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.

d Further dose adjustments or selection of alternative therapy may be necessary because of other clinical factors (e.g., medication interactions, or hepatic function).

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for cytochrome P450 testing have been identified.

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 Warfarin Dosing
- Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

References

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through December 2023, 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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.
5/1/23	3/29/23		Added to MPS- With relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, being considered for treatment with siponimod. Added code 81418 as established. Moved code 81227 to established. Added code 0380U as E/I. (ds)
5/1/24	2/20/24		Routine maintenance. Added references 13, 28-31. Vendor: N/A. (ky)

Next Review Date: 1st Qtr. 2025

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.