2.04.38	Cytochrome P450 Genotype-Guided Treatment Strategy		
Original Policy Date:	October 1, 2010	**Effective Date:**	August 1, 2023
Section:	2.0 Medicine	**Page:**	Page 1 of 27

Policy Statement

Note: Cytochrome P450 is a family of proteins (enzymes) including several genes (CYPs). The letters that follow CYP indicate a subfamily of gene.

I. Cytochrome P450 2D6 (CYP2D6) genotyping to determine drug metabolizer status may be considered **medically necessary** for individuals with **either** of the following conditions:
   A. Gaucher disease being considered for treatment with eliglustat
   B. Huntington disease being considered for treatment with tetrabenazine in a dosage greater than 50 mg per day

II. Cytochrome P450 *2C9* (CYP2C9) genotyping to determine drug metabolizer status may be considered **medically necessary** for individuals:
   A. 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

III. Cytochrome P450 (CYP450) genotyping for the purpose of aiding in the choice of clopidogrel (Plavix®) versus alternative antiplatelet agents, or in decisions on the optimal dosing for clopidogrel (Plavix®), is considered **investigational**.

IV. CYP450 genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for the following drugs is considered **investigational** for **all** of the following (see Policy Guidelines):
   A. Selection or dosage of codeine
   B. Dosing of efavirenz and other antiretroviral therapies for HIV infection
   C. Dosing of immunosuppressants for organ transplantation
   D. Selection or dosing of β-blockers (e.g., metoprolol)
   E. Dosing and management of antitubercular medications

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

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

This policy does not address the use of genetic or panel testing that include tests for genes other than CYP450-related genes (e.g., the Genecept Assay). Testing related to mental health drugs (see below) and the broader panel testing, which are discussed in Blue Shield of California Medical Policy: Genetic Testing for Mental Health Conditions:

- Selection or dosing of selective serotonin reuptake inhibitors (SSRIs)
- Selection or dosing of selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Selection or dosing of tricyclic antidepressants
- Selection or dosing of antipsychotic drugs

The Food and Drug Administration maintains a database of pharmacogenomic biomarkers in drug labeling. See section "Regulatory Status" for details.

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Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

The following are specific CPT coding for this testing:

- **81225:** *CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19)* (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)
- **81226:** *CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6)* (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
- **81227:** *CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9)* (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)

The following CPT codes are specific to CYP450 genotyping. CYP3A4 and CYP3A5 were previously reported under code 81401:

- **81230:** CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (e.g., drug metabolism), gene analysis, common variant(s) (e.g., *2, *22)
- **81231:** CYP3A5 (cytochrome P450, family 3, subfamily A member 5) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *7)

There following are tier 2 CPT codes that include cytochrome P450 testing:

- **81402:** Molecular pathology procedure, Level 3 (e.g., >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD]) includes –
  - *CYP21A2 (cytochrome P450, family 21, subfamily A, polypeptide 2)* (e.g., congenital adrenal hyperplasia, 21-hydroxylase deficiency), common variants (e.g., IVS2-13G, P30L, I172N, exon 6 mutation cluster [I235N, V236E, M238K], V281L, L307FfsX6, Q318X, R356W, P453S, G110VfsX21, 30- kb deletion variant)
- **81404**: Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) includes –
  - *CYP1B1 (cytochrome P450, family 1, subfamily B, polypeptide 1)* (e.g., primary congenital glaucoma), full gene sequence
- **81405** Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) includes –
  - *CYP11B1 (cytochrome P450, family 11, subfamily B, polypeptide 1)* (e.g., congenital adrenal hyperplasia), full gene sequence
  - *CYP17A1 (cytochrome P450, family 17, subfamily A, polypeptide 1)* (e.g., congenital adrenal hyperplasia), full gene sequence
  - *CYP21A2 (cytochrome P450, family 21, subfamily A, polypeptide 2)* (e.g., steroid 21-hydroxylase isoform, congenital adrenal hyperplasia), full gene sequence

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PLA codes include:

- **0029U:** Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (i.e., CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823) (Focused Pharmacogenomics Panel)
- **0031U:** CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(e.g., drug metabolism) gene analysis, common variants (i.e., *1F, *1K, *6, *7) (Cytochrome P450 1A2 Genotype)

PLA codes include:

- **0070U**: CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, common and select rare variants (i.e., *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN)
- **0071U**: CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure)
- **0072U**: CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D6-2D7 hybrid gene)
- **0073U**: CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure)
- **0074U**: CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., non-duplicated gene when duplication/multiplication is trans)
- **0075U**: CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 5′ gene duplication/multiplication)
- **0076U**: CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 3′ gene duplication/ multiplication)

Description

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

Related Policies

- Genetic Testing for Diagnosis and Management of Mental Health Conditions
- Genotype-Guided Tamoxifen Treatment
- Genotype-Guided Warfarin Dosing
- Pharmacogenomic and Metabolite Markers for Patients Treated With Thiopurines

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 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 the 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 I030c0300 (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 diagnostic genotyping panel tests for *CYP450* genes, such as the YouScript Panel (Genelex Corp.), which includes *CYP2D6*, *CYP2C19*, *CYP2C9*, *VKORC1*, *CYP3A4*, and *CYP3A5*. Other panel tests include both *CYP450* and other non-*CYP450* genes involved in drug metabolism, such as the GeneSight Psychotropic panel (Assurex Health) and PersonaGene Genetic Panels (AIBioTech). These tests are beyond the scope of this evidence review.

Food and Drug Administration 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, the 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

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CYP2D6 metabolizer 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. The 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 per day 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,]

The FDA does not recommend genotyping before prescribing codeine. The 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 years 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,]

Rationale

Background

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 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 studies how an individual's genetic inheritance affects the body's response to drugs. It may be possible to predict therapeutic failures or severe adverse drug reactions in individual patients by testing for important DNA variants (genotyping) in genes related to the metabolic pathway (pharmacokinetics) or signal transduction pathway (pharmacodynamics) of the drug. Potentially, test results could be used to optimize drug choice and/or dose for more effective therapy, avoid serious adverse events, 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, β-blockers, antiarrhythmics, antidepressants, morphine derivatives), including most prescribed drugs. CYP2C19 metabolizes several important types of drugs, including proton pump inhibitors, diazepam, propranolol, imipramine, and amitriptyline.

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

Individuals with 2 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 (EMs; normal). Poor metabolizers (PMs) lack active enzyme gene alleles, and intermediate metabolizers, who have 1 active and 1 inactive enzyme gene allele, may experience to a lesser degree some of the consequences of PMs. Ultrarapid metabolizers (UMs) are individuals with more than 2 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 events, and PMs may not respond.

Many drugs are metabolized to varying degrees by more than one enzyme, either within or outside of the CYP450 superfamily. Also, the interaction between different metabolizing genes, the interaction between genes and environment, and interactions among different nongenetic 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 interindividual 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 for drugs with a very narrow therapeutic range and/or potentially serious adverse events outside that range. However, therapeutic drug monitoring 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 patient outcomes) may be favored when the drug under consideration has a narrow therapeutic dose range, 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. The potential severity of the disease condition may call for immediate and sufficient therapy; genotyping might speed up the process of achieving a therapeutic dose and avoiding significant adverse events.

Literature Review

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

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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 technology improves the net health outcome. Broadly defined, health outcomes are the 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 managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance, and 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Cytochrome P450 Genotype-guided Treatment Strategy

Clinical Context and Therapy Purpose

The purpose of a cytochrome P450 (*CYP450*) genotype-guided strategy is to tailor selection and dosing of drugs based on gene composition for drug metabolism. In theory, this should lead to early selection and optimal dosing of the most effective drugs, while minimizing treatment failures or toxicities.

The following PICO was used to select literature to inform this review.

Populations

The relevant populations of interest is individuals being considered for treatment with clopidogrel, eliglustat, tetrabenazine, selective serotonin 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 antitubercular medications.

Interventions

Commercial tests for individual genes or gene panels are available and are listed in the Regulatory Status section. Only those panels that include *CYP450* genes are listed in that section.

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Comparators
The following practice is currently being used: standard clinical management without genetic testing.

Outcomes
Specific outcomes of interest are listed in 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

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 hypothesized 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. However, evidence of publication bias has been reported in these studies where smaller studies have reported larger benefits than larger studies which have reported no effect or smaller effect.[7,] Wang et al (2016) reported a post hoc analysis of the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events 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 versus aspirin alone was associated with statistical significant reduction in the risk of stroke (6.7% vs. 12.4%; hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.35 to 0.75) but not among those who carried loss of function alleles (9.4% vs. 10.8%; HR,

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0.93; 95% CI, 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. However, only a few trials of genotype-directed dosing or drug choice have been conducted; they 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) reported on the results of an RCT that allocated patients undergoing PCI for acute coronary syndrome or stable angina to genotype-guided management to select for treatment with prasugrel (carriers) or clopidogrel (noncarriers) or to standard treatment with clopidogrel.[9,] Among those who received prasugrel and clopidogrel based on genotyping test, 0% and 10%, respectively, exhibited high on-treatment platelet reactivity while 17% of patients who received standard treatment with clopidogrel without any genotypes testing exhibited high on-treatment platelet reactivity. This difference was not statistically significant. So et al (2016) reported on the results of an RCT that randomized patients with ST-elevation myocardial infarction who were carriers of *CYP2C19*2*, *ABCB1* TT, and *CYP2C19*17* alleles to prasugrel 10 mg daily or an augmented dosing strategy of clopidogrel (150 mg per day for 6 days and subsequently 75 mg per day).[10,] Results showed that (1) carriers did not respond to augmented clopidogrel as well as they did to prasugrel (24% patients with high platelet reactivity vs. 0%) and (2) among noncarriers, physician-directed clopidogrel was effective for most patients (95% did not have high platelet reactivity).

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. However, the trial results do not inform whether using genotype based strategy for prescribing clopidogrel results in any incremental net health benefit versus standard treatment with clopidogrel. Furthermore, there was no difference in the incidence of PLATelet inhibition and patient Outcomes (PLATO) major bleeding between the genotype-guided group and the standard-treatment group (2.3% in both groups; HR, 0.97; 95% CI, 0.58 to 1.63). The statistically 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.[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=.06). None of the 11 prespecified secondary end points showed significant

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differences, including major or minor bleeding in *CYP2C19* carriers in the genotype-guided group (1.9%) versus the conventional therapy group (1.6%) at 12 months (HR, 1.22; 95% CI, 0.60 to 2.51; p=.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=.16). The trial failed to meet the pre-specified end point 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 relative risk reduction was 34% instead of the estimated 50%, hence a borderline p value of.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 Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
So et al (2016)[10]; RAPID STEMI	Canada	1	2011-2012	18 to 75 y who had PCI for STEMI who received POC testing for *CYP2C19*2*, *ABCB1* TT, and *CYP2C19*17* alleles (N=102)	Carriers randomized to prasugrel 10 mg/d (n=30) or augmented clopidogrel (150 mg/d for 6 d and then 75 mg/d) (n=29)	Noncarriers given clopidogrel with dosing as per treating physician (n=43)
Roberts et al (2012)[9]; RAPID GENE	Canada	1	2010-2011	18 to 75 y undergoing PCI for acute coronary syndrome or stable angina (N=200)	POC testing for *CYP2C19*2* allele (n=102). Of these, 23 carriers were given prasugrel 10 mg/d, and 74 noncarriers were given clopidogrel 75 mg/d.	No genetic testing and clopidogrel 75 mg/d

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Study	Countries	Sites	Dates	Participants	Interventions	
Claassens et al (2019);[11] 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)[12]; TAILOR PCI	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).
Wang et al (2021)[13]; CHANCE-2	China	202	2019-2021	Individuals (median age, 64.8 years; 33.8% female; 98% Chinese) with minor ischemic stroke or TIA who carried *CYP2C19* LOF alleles (N=6412)	Ticagrelor (180 mg loading dose on day 1, followed by 90 mg twice daily on days 2 through 90) and aspirin for the first 21 days (n=3205)	Clopidogrel (300 mg loading dose on day 1, followed by 75 mg daily on days 2 through 90) and aspirin for the first 21 days (n=3207)

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 Randomized Controlled Trial 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%			

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Study	Outcome			
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

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

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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.

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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* poor metabolizers 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*.[19,20,] *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

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dose-adjusted trough concentrations of tacrolimus, possibly delaying achievement of target blood concentrations compared with those who are *CYP3A5* nonexpressers (poor metabolizers) 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 includes RCTs by Thervet et al (2010)[22,] and Min et al (2018).[23,] 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 al (2010).[22,]

b-Blockers

Several reports have indicated that lipophilic b-blockers (e.g., metoprolol), used in treating hypertension, may exhibit impaired elimination in patients with *CYP2D6* variants.[24,25,] 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.[26,] 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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input 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, input was received from 4 physician specialty societies and 4 academic medical centers while this policy was under review in 2012. Opinions on use of genotype testing of patients being considered for clopidogrel treatment were mixed, with 5 suggesting the test be considered investigational and 3 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.

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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 the selection and dosing of clopidogrel was published in 2010.[27,] The recommendations for practice included the following statements:

1. "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…
2. 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.
3. The specific impact of the individual genetic polymorphisms on clinical outcome remains to be determined….
4. 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.
5. The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time….
6. 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 whome 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]
***CYP2C19* ultrarapid metabolizer**	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	No recommendation
***CYP2C19* rapid metabolizer**	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	No recommendation
***CYP2C19* normal metabolizer**	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	Strong
***CYP2C19* 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]
***CYP2C19* intermediate metabolizer**	Avoid standard dose clopidogrel (75 mg) if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong	No recommendation
***CYP2C19* likely poor metabolizer**	Avoid clopidogrel if possible. Use prasugrel or ticagrelor at	Strong[d]	Moderate[d]

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CYP2C19 phenotype	Therapeutic recommendation	Classification of recommendation[a] - ACS and/or PCI[b]	Classification of recommendation[a] - non-ACS, non-PCI CV indications[c]
	standard dose if no contraindication		
***CYP2C19* 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
***CYP2C19* ultrarapid metabolizer**	No recommendation	No recommendation	
***CYP2C19* rapid metabolizer**	No recommendation	No recommendation	
***CYP2C19* normal metabolizer**	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	
***CYP2C19* likely intermediate metabolizer**	Consider an alternative $P2Y_{12}$ inhibitor at standard dose if clinically indicated and no contraindication	Moderate[c]	
***CYP2C19* 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 *CYP2C19* genetic variants include ticagrelor and ticlopidine. Prasugrel is contraindicated in patients with a history of stroke or TIA.[d]
***CYP2C19* likely poor metabolizer**	Avoid clopidogrel if possible. Consider an alternative $P2Y_{12}$ inhibitor at standard dose if clinically indicated and no contraindication	Moderate[c]	
***CYP2C19* 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-

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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

CPIC: Clinical Pharmacogenetics Implementation Consortium; CYP: cytochrome P450.
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	Strong

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CYP3A5 phenotype[a]	Therapeutic recommendation[b]	Classification of recommendation[c]
	monitoring to guide dose adjustments.	
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

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.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing or unpublished trials that might influence this review are listed in Table 11.

Table 11. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04072705[a]	A Multicenter Prospective observationaL Study to evAluate the effecT of Clopidogrel on the prEvention of Major vascuLar Events According to the gEnotype of Cytochromem P450 2C19 in Ischemic Stroke paTients; PLATELET Study	2927	June 2023

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

References

1. United States Food and Drug Administration: Table of Pharmacogenetic Associations. Updated October 26, 2022. Available at https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations. Accessed on April 28, 2023.

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2. Prescribing Label: Cerdelga (eliglustat). 2022; Available at https://products.sanofi.us/cerdelga/cerdelga.html. Accessed April 25, 2023.
3. Prescribing Label: Xenazine (tetrabenazine). 2019; Available at https://www.lundbeck.com/content/dam/lundbeck-com/americas/united-states/products/neurology/xenazine_pi_us_en.pdf. Accessed April 25, 2023.
4. 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. Published April 20, 2017. Updated February 28, 2019; https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm553285.htm. Accessed April 25, 2023.
5. Prescribing Label: Mayzent (siponimod) tablets, for oral use. 2023; Available at https://www.novartis.us/sites/www.novartis.us/files/mayzent.pdf Accessed April 28, 2023.
6. 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): 317-23. PMID 23698643
7. 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): 2704-14. PMID 22203539
8. 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 05 2016; 316(1): 70-8. PMID 27348249
9. 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 05 2012; 379(9827): 1705-11. PMID 22464343
10. 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): 71-8. PMID 25850030
11. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A Genotype-Guided Strategy for Oral P2Y 12 Inhibitors in Primary PCI. N Engl J Med. Oct 24 2019; 381(17): 1621-1631. PMID 31479209
12. 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
13. Wang Y, Meng X, Wang A, et al. Ticagrelor versus Clopidogrel in CYP2C19 Loss-of-Function Carriers with Stroke or TIA. N Engl J Med. Dec 30 2021; 385(27): 2520-2530. PMID 34708996
14. Montalescot G, Rangé G, Silvain J, et al. High on-treatment platelet reactivity as a risk factor for secondary prevention after coronary stent revascularization: A landmark analysis of the ARCTIC study. Circulation. May 27 2014; 129(21): 2136-43. PMID 24718568
15. Collet JP, Cuisset T, Rangé G, et al. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med. Nov 29 2012; 367(22): 2100-9. PMID 23121439
16. King J, Aberg JA. Clinical impact of patient population differences and genomic variation in efavirenz therapy. AIDS. Sep 12 2008; 22(14): 1709-17. PMID 18753940
17. 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): 782-7. PMID 18503405
18. 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 01 2007; 45(9): 1230-7. PMID 17918089
19. 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): 2092-8. PMID 21715435

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20. 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): 246-57. PMID 21288825
21. 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): 1909-16. PMID 23774940
22. Thervet E, Loriot MA, Barbier S, et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. Clin Pharmacol Ther. Jun 2010; 87(6): 721-6. PMID 20393454
23. Min S, Papaz T, Lafreniere-Roula M, et al. A randomized clinical trial of age and genotype-guided tacrolimus dosing after pediatric solid organ transplantation. Pediatr Transplant. Nov 2018; 22(7): e13285. PMID 30178515
24. 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
25. 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. 2008; 36(6): 1354-62. PMID 19094446
26. 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): 334-40. PMID 27062377
27. Holmes DR, 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): 321-41. PMID 20633831
28. Lee CR, Luzum JA, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. Clin Pharmacol Ther. Nov 2022; 112(5): 959-967. PMID 35034351
29. Desta Z, Gammal RS, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2B6 and Efavirenz-Containing Antiretroviral Therapy. Clin Pharmacol Ther. Oct 2019; 106(4): 726-733. PMID 31006110
30. ENCORE1 Study Group. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. Lancet. Apr 26 2014; 383(9927): 1474-1482. PMID 24522178
31. Birdwell KA, Decker B, Barbarino JM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. Clin Pharmacol Ther. Jul 2015; 98(1): 19-24. PMID 25801146

Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Reason for performing test
  - Signs/symptoms/test results related to reason for genetic testing
  - How test result will impact clinical decision making including but not limited to specific drugs being considered for treatment
  - Diagnosis being considered for treatment
  - Name and description of genetic test
  - Name of laboratory that will perform or performed the test
  - CPT codes billed for the particular genetic test

Post Service (in addition to the above, please include the following):

- Laboratory report including: specific name and test requested

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Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (i.e., CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823)
	0031U	CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(e.g., drug metabolism) gene analysis, common variants (i.e., *1F, *1K, *6, *7)
	0070U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, common and select rare variants (i.e., *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN)
	0071U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure)
	0072U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D6-2D7 hybrid gene)
	0073U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure))
	0074U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., non-duplicated gene when duplication/multiplication is trans)
	0075U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 5' gene duplication/multiplication)
	0076U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 3' gene duplication/ multiplication)
	81225	*CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19)* (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)
	81226	*CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6)* (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
	81227	*CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9)* (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)
	81230	CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (e.g., drug metabolism), gene analysis, common variant(s) (e.g., *2, *22)

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Type	Code	Description
	81231	CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *7)
	81402	Molecular Pathology Procedure Level 3
	81404	Molecular Pathology Procedure Level 5
	81405	Molecular Pathology Procedure Level 6
	81418	Drug metabolism (e.g., pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
10/01/2010	New policy Combined the following BSC policies: • Cytochrome p450 Genotyping • Genetic Testing for Initial Warfarin Dose with BCBSA Medical Policy adoption
03/12/2012	Coding Update
02/22/2013	Coding Update
04/04/2014	Policy revision with position change Coding Update
05/29/2015	Coding update
03/01/2016	Policy title change from Pharmacogenomics Policy revision with position change effective 5/1/2016
05/01/2016	Policy revision with position change
08/01/2017	Policy revision without position change
02/01/2018	Coding update
05/01/2018	Coding update
08/01/2018	Policy title change from Cytochrome p450 Genotyping Policy revision without position change
10/01/2018	Coding update
08/01/2019	Policy revision without position change
03/01/2020	Coding update
08/01/2020	Annual review. No change to policy statement. Literature review updated.
08/01/2021	Annual review. No change to policy statement. Literature review updated.
08/01/2022	Annual review. Policy statement, guidelines and literature review updated.
08/01/2023	Annual review. Policy statement and literature review updated. Coding update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent

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therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

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Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
Cytochrome P450 Genotype-Guided Treatment Strategy 2.04.38 **Policy Statement:** **Note**: Cytochrome P450 is a family of proteins (enzymes) including several genes (CYPs). The letters that follow CYP indicate a subfamily of gene. I. Cytochrome P450 2D6 (CYP2D6) genotyping to determine drug metabolizer status may be considered **medically necessary** for individuals with **either** of the following conditions: A. Gaucher disease being considered for treatment with eliglustat B. Huntington disease being considered for treatment with tetrabenazine in a dosage greater than 50 mg per day C. 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 II. Cytochrome P450 (CYP450) genotyping for the purpose of aiding in the choice of clopidogrel (Plavix®) versus alternative antiplatelet agents, or in decisions on the optimal dosing for clopidogrel (Plavix®), is considered **investigational** III. CYP450 genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for the following drugs is considered **investigational** for **all** of the following (see Policy Guidelines): A. Selection or dosage of codeine	**Cytochrome P450 Genotype-Guided Treatment Strategy 2.04.38** **Policy Statement:** **Note**: Cytochrome P450 is a family of proteins (enzymes) including several genes (CYPs). The letters that follow CYP indicate a subfamily of gene. I. Cytochrome P450 2D6 (CYP2D6) genotyping to determine drug metabolizer status may be considered **medically necessary** for individuals with **either** of the following conditions: A. Gaucher disease being considered for treatment with eliglustat B. Huntington disease being considered for treatment with tetrabenazine in a dosage greater than 50 mg per day II. Cytochrome P450 *2C9* (CYP2C9) genotyping to determine drug metabolizer status may be considered **medically necessary** for individuals: A. 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 III. Cytochrome P450 (CYP450) genotyping for the purpose of aiding in the choice of clopidogrel (Plavix®) versus alternative antiplatelet agents, or in decisions on the optimal dosing for clopidogrel (Plavix®), is considered **investigational**. IV. CYP450 genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for the following drugs is considered **investigational** for **all** of the following (see Policy Guidelines): A. Selection or dosage of codeine

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POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
B. Dosing of efavirenz and other antiretroviral therapies for HIV infection C. Dosing of immunosuppressants for organ transplantation D. Selection or dosing of β-blockers (e.g., metoprolol) E. Dosing and management of antitubercular medications IV. The use of genetic testing panels that include multiple CYP450 variants is considered **investigational**.	B. Dosing of efavirenz and other antiretroviral therapies for HIV infection C. Dosing of immunosuppressants for organ transplantation D. Selection or dosing of β-blockers (e.g., metoprolol) E. Dosing and management of antitubercular medications V. The use of genetic testing panels that include multiple CYP450 variants is considered **investigational**.

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