MEDICAL POLICY

Capital BLUE

POLICY TITLE	CYTOCHROME P450 GENOTYPE GUIDED TREATMENT STRATEGY (FORMERLY CYTOCHROME P450 GENOTYPING)
POLICY NUMBER	MP-2.234

Original Issue Date (Created):	**12/1/2007**
Most Recent Review Date (Revised):	**4/18/2020**
Effective Date:	**7/1/2020**

I. POLICY

CYP2D6 genotyping to determine drug metabolizer status may be considered **medically necessary** for patients:

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

CYP450 genotyping for the purpose of aiding in the choice of clopidogrel (Plavix®), versus alternative anti-platelet agents, or in decisions on the optimal dosing for clopidogrel is considered **investigational.** There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this testing for this indication.

(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** aside from determinations in the separate cross-referenced policies:

- Selection or dosing of codeine; **or**
- Dosing of efavirenz and other antiretroviral therapies for HIV (human immunodeficiency virus) infection; **or**
- Dosing of immunosuppressants for organ transplantation; **or**
- Selection or dosing of β blockers (e.g., metoprolol) ; **or**
- Dosing and management of antitubercular medications.

There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this testing for these indications.

The use of genetic testing panels that include multiple *CYP450* variants is considered **investigational**. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with these testing panels.

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Policy Guidelines

This policy does not address the use of genetic panel testing that include tests for genes other than *CYP450*-related genes (e.g., the Genecept Assay), which are discussed in MP- 2.264 Genetic Testing for Mental Health Conditions.

Genetics Nomenclature Update

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial Variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely Pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely Benign	Likely benign change in DNA sequence
Benign	Benign change in the DNA sequence

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ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Cross-references:

MP-2.218 Pharmacogenomic and Metabolite Markers for Patients with Inflammatory Bowel Disease Treated with Thiopurines
MP-2.264 Genetic Testing for Diagnosis and Management of Mental Health Conditions
MP-2.307 Genotype-Guided Tamoxifen Treatment
MP-2.306 Genotype-Guided Warfarin Dosing

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital BlueCross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO: Refer to FEP Medical Policy Manual MP-2.04.38, Cytochrome 450 Genotyping. The FEP Medical Policy Manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines

III. DESCRIPTION/BACKGROUND

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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 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.

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 one active and one inactive enzyme gene allele, may experience to a lesser degree some of the consequences of PMs. Ultrarapid metabolizers (UMs) are individuals with more than two alleles of an active enzyme gene. There is pronounced ethnic variability in the population distribution of metabolizer types for a given CYP enzyme.

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

Many drugs are metabolized to varying degrees by more than 1 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.

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.

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Table 1. Testing Kits for *CYP450* Genotyping Cleared for Marketing by FDA

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

FDA: Food and Drug Administration.

Several manufacturers market 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.

FDA Labeling on CYP450 Genotyping

The FDA has included pharmacogenomics information in the physician prescribing information (drug labels) of multiple drugs. In most cases, this information is general and lacks specific directives for clinical decision making. In the following examples, 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 CYP2D6 metabolizer's status. Further, the label states that the dosing strategy should be 84 mg orally, twice daily for CYP2D6 EMs or intermediate metabolizers and 84 mg orally, once daily for CYP2D6 PMs. The FDA has included a black box to warn about the reduced effectiveness in

PMs and to advise healthcare professionals to consider alternative dosing or to use of other medications in patients identified as potential PMs.

Tetrabenazine

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

Codeine

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

IV. RATIONALE

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SUMMARY OF EVIDENCE

Clopidogrel

For individuals with a need for antiplatelet therapy who are undergoing or being considered for clopidogrel therapy who receive testing for CYP2C19 metabolizer status by CYP2C19 genotyping, the evidence incudes 2, randomized controlled trials (RCTs). Relevant outcomes are overall survival, medication use, and treatment-related morbidity. The 2 RCTs evaluated the impact of CYP2C19 genotyping using an intermediate outcome measure (platelet reactivity). One RCT showed no statistical difference between patients with on-treatment high platelet reactivity between genotype-guided management or standard treatment with clopidogrel. The second RCT showed carriers of loss of function alleles did not respond to augmented clopidogrel as well as they did to prasugrel, and physician-directed clopidogrel was effective for most noncarriers. However, routine testing using platelet reactivity as an outcome measure to predict CYP2C19 metabolic state has not been shown to improve health outcomes. Results of an ongoing RCT (TAILOR-PCI) assessing outcomes in 5270 patients randomized to genotype-based antiplatelet therapy approach or standard care are expected in 2020 and likely to address this gap. The evidence is insufficient to determine the effects of the technology on health outcomes.

Other Drugs

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

V. DEFINITIONS

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GENOTYPE refers to the pair of genes present for a particular characteristic or protein.
POLYMORPHISM refers to the state or quality of existing or occurring in several different forms.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital BlueCross' Provider Services or Member Services.

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Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered:

CPT Codes®								
81225	81227	81230	81231	0031U	0070U	0071U	0072U	0073U
0074U	0075U	0076U						

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Covered when medically necessary:

CPT Codes®								
81226								

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ICD-10-CM Diagnosis Codes	Description
E75.22	Gaucher disease
G10	Huntington's disease

IX. REFERENCES

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2. *Food and Drug Administration. Highlights of Prescribing Information: Xenazine (tetrabenazine). 2015; https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021894s010lbl.pdf. Accessed April 18, 2020.*
3. *FDA statement from Douglas Throckmorton, M.D., deputy center director for regulatory programs, Center for Drug Evaluation and Research, on new warnings about the use of codeine and tramadol in children & nursing mothers. 2017;*

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm553285.htm. *Accessed April 18,2020.*

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X. POLICY HISTORY

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MP-2.234	**CAC 1/30/07**
	CAC 1/29/08
	CAC 1/27/09 Consensus review.
	CAC 5/26/09
	CAC 7/27/10 Minor review. Added medical necessity indication for CYP450 phenotyping in patients with cardiovascular disease undergoing treatment with clopidogrel (Plavix).
	CAC 11/22/11 Minor review. Title changed to Cytochrome p450 Genotyping, formerly Drug Metabolism Genetic and Pharmacologic Testing. Adopting BCBSA for p450 Genotyping. Information related to genetic testing for Warfarin Dose, Tamoxifen Treatment and Helicobacter pylori treatment was extracted from this policy and separate individual policies created. Policy statement related to p450 genotyping remains medically necessary with criteria.
	03/28/13- Administrative update. Code review complete.
	CAC 6/4/13 Minor revision. Wording of medically necessary statement clarified for clopidogrel. Investigational statements added for selective norepinephrine reuptake inhibitors and tricyclic antidepressants. To dose atomoxetine HCl was removed as an example of an investigational indication.

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	References updated. FEP variation revised to refer to the FEP medical policy manual. Codes reviewed 11/21/12
	03/21/2014 Admin update. Coding reviewed.
	CAC 5/20/14. Minor review. Investigational statement added for dosing of anti-tuberculosis medications. References updated. Added Medicare variation to reference LCD L33640 Biomarkers Overview. Coding reviewed.
	CAC 6/2/15 Minor revision. A statement was added that use of genetic testing panels that include multiple *CYP450* mutations is considered investigational. Background, references and rationale updated. Codes unranged.
	11/2/15 Administrative update. LCD number changed from L33640 to L35062 due to Novitas update to ICD-10
	CAC 3/29/16 Minor revision. Medically necessary statements for CYP2D6 genotyping added for patients being considered for eliglustat for Gaucher disease or tetrabenazine therapy for Huntingdon disease. Medically necessary statement for CYP450 genotyping for patients receiving clopidogrel therapy changed to investigational. Background, rationale and references revised. Coding reviewed and updated. CODING: CPT 81401-81405 removed as not pertaining to this policy; 81226 changed from investigational to covered service; 81225 moved to investigational; and multiple Dx codes removed as not pertaining to this policy.
	1/1/17Admin update. Product variation section reformatted
	CAC 3/28/17 Consensus review. No changes to the policy statements. Extraneous sentence in the regulatory status section regarding "Lab X" was removed. References reviewed. Coding reviewed.
	1/1/18 Admin Update. Medicare variations removed from Commercial Policies. Added new codes 81230-81231; effective 1/1/18
	1/19/18 Admin Update: Added new codes 0025U & 0031U; effective 1/1/18.
	2/12/18 Consensus review. No changes to the policy statements. Policy revised with updated genetics nomenclature. Background, rationale, and references updated. Appendix added.
	10/1/2018 Admin update – HCPCs codes updated removed 0028U and added 0070U thru 0076U new PLA codes effective for 10/1/2018
	6/15/18 Minor review. Policy title changed to "Cytochrome P450 Genotype Guided Treatment Strategy". Four criteria to include the following: • Selection or dose of selective serotonin reuptake inhibitor (SSRI) • Selection or dosing of selective norepinephrine reuptake inhibitors and serotonin –norepinephrine reuptake inhibitors • Selection or dosing of antipsychotic drugs; and • Selection or dosing of tricyclic antidepressants

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	were removed from the investigational statement and placed in MP-2.264 Genetic Testing for Diagnosis and Management of Mental Health Conditions. Background and references updated. Rationale revised. Appendix removed. Removed 0025U since it was added in error during new code review, 0028U is now in its place as medically necessary. Effective 3/1/19.
	05/01/2019 Consensus review. No changes to policy statements. Formatting updated for tables.
	4/18/2020 Consensus review. Policy statement unchanged. Background and references updated. Coding reviewed.

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