Cytochrome P450 Genotype-Guided Treatment Strategy

Policy # 00169
Original Effective Date: 07/15/2005
Current Effective Date: 09/12/2022

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines is addressed separately in medical policy 00237.

Note: Genetic Testing for Warfarin Dose is addressed separately in medical policy 00245.

Note: Genetic Testing for Tamoxifen Treatment is addressed separately in medical policy 00269.

Note: Genetic Testing for Diagnosis and Management Mental Health Conditions is addressed separately in medical policy 00402.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider CYP2C9 genotyping to determine drug metabolizer status to be eligible for coverage.**

Patient Selection Criteria
Coverage eligibility for CYP2C9 genotyping to determine drug metabolizer status will be met for patients:

- 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.

Based on review of available data, the Company may consider CYP2D6 genotyping to determine drug metabolizer status to be eligible for coverage.**
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Patient Selection Criteria
Coverage eligibility for CYP2D6 genotyping to determine drug metabolizer status will be met 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.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers cytochrome P450 (CYP450) genotyping for the purpose of aiding in the choice of clopidogrel versus alternative anti-platelet agents, or in decisions on the optimal dosing for clopidogrel to be investigational.*

Based on review of available data, the Company considers 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, aside from determinations in the separate policies noted above to be investigational.*

This includes, but is not limited to, CYP450 genotyping for the following applications:
- Selection or dosing of codeine;
- Dosing of efavirenz and other antiretroviral therapies for human immunodeficiency virus (HIV) infection;
- Dose of immunosuppressants for organ transplantation;
- Selection or dosing of beta blockers (e.g., metoprolol);
- Dosing and management of antitubercular medications.

Based on review of available data, the Company considers the use of genetic testing panels that include multiple CYP450 variants to be investigational.*
Policy Guidelines
This policy does not address the use of genetic panel tests for genes other than CYP450-related genes (e.g., the Genecept Assay), which are discussed in medical policy 00402.

Background/Overview
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.

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,
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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 (eg, in urine). However, testing and interpretation are time-consuming and inconvenient; as a result, phenotyping is seldom performed.

The clinical utility of CYP450 genotyping (ie, 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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. Selected Testing Kits for CYP450 Genotyping Cleared for Marketing by the Food and Drug Administration

<table>
<thead>
<tr>
<th>Device Name</th>
<th>Manufacturer</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>xTAG Cyp2c19 Kit V3</td>
<td>Luminex Molecular Diagnostics</td>
<td>2013</td>
</tr>
<tr>
<td>Spartan Rx Cyp2c19 Test System</td>
<td>Spartan Bioscience</td>
<td>2013</td>
</tr>
<tr>
<td>Verigene Cyp2c19 Nucleic Acid Test (2c19)</td>
<td>Nanosphere</td>
<td>2012</td>
</tr>
<tr>
<td>Infiniti Cyp2c19 Assay</td>
<td>Autogenomics</td>
<td>2010</td>
</tr>
<tr>
<td>xTAG Cyp2d6 Kit V3, Model I030c0300 (96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invader Ugt1a1 Molecular Assay</td>
<td>Third Wave Technologies</td>
<td>2005</td>
</tr>
<tr>
<td>Roche AmpliChip Cyp450 Test</td>
<td>Roche Molecular Systems</td>
<td>2005</td>
</tr>
</tbody>
</table>

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 medical policy.

Food and Drug Administration Labeling on CYP450 Genotyping

The FDA maintains online compendia of pharmacogenetic associations online 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.

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
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directives on either use of a specific dose (eg, eliglustat, tetrabenazine) or when a drug may not be used at all (eg, codeine).

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 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 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.

Codeine
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.

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.
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Rationale/Source
This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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.

Summary of Evidence
For individuals with a need for antiplatelet therapy who are undergoing or being considered for clopidogrel therapy who receive a CYP2C19-guided treatment strategy, the evidence includes 4 randomized controlled trials (RCTs). Relevant outcomes are overall survival, medication use, and treatment-related morbidity. 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 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 percutaneous coronary intervention (PCI), genotype-guided selection of an oral P2Y12 inhibitor compared with conventional clopidogrel therapy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 a CYP2C19-guided treatment strategy, the evidence includes retrospective studies. Relevant outcomes are medication use and treatment-related morbidity. In general, most published CYP450 pharmacogenomic studies for these drugs consist of retrospective evaluations of CYP450 genotype associations, reporting intermediate outcomes (eg, circulating drug concentrations) or less often, final outcomes (eg, adverse events or efficacy). Many of these studies are small, underpowered and hypothesis generating. Prospective intervention studies, including RCTs documenting the clinical usefulness of CYP450 genotyping to improve existing clinical decision making to guide dose or drug selection, which may then translate into improvement in patient outcomes, were not identified. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Supplemental Information**

**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.

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
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representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Cardiology Foundation
A consensus statement by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) on genetic testing for the selection and dosing of clopidogrel was published in 2010. 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 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."

U.S. Preventive Services Task Force Recommendations
No U.S. Preventive Services Task Force recommendations for cytochrome P450 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.

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Ongoing and Unpublished Clinical Trials
No relevant ongoing or unpublished studies that might influence this review were identified.

References
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infarction: the RAPID STEMI study. Pharmacogenomics J. Feb 2016; 16(1): 71-8. PMID 25850030
15. 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

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Policy History
Original Effective Date: 07/15/2005
Current Effective Date: 09/12/2022
06/07/2005 Medical Director Review
06/21/2005 Medical Policy Committee review
07/15/2005 Managed Care Advisory Council approval
07/07/2006 Medical Policy Committee approval. Format revision including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
05/02/2007 Medical Director Review
05/07/2009 Medical Director Review

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05/20/2009 Medical Policy Committee approval. Added a statement with seven bulleted applications for clarification of CYP450 genotyping to, “Services Are Considered Investigational” section. Coverage eligibility unchanged.

06/03/2010 Medical Policy Committee review
06/16/2010 Medical Policy Implementation Committee approval. Policy statement regarding cytochrome p450 genetic testing to guide selection or dose of beta blockers added as investigational criteria.

05/05/2011 Medical Policy Committee review
05/18/2011 Medical Policy Implementation Committee approval. Changed the use of CYP450 genotyping with clopidogrel (Plavix) from investigational to eligible for coverage.

05/03/2012 Medical Policy Committee review
05/16/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

05/02/2013 Medical Policy Committee review
05/22/2013 Medical Policy Implementation Committee approval.
05/01/2014 Medical Policy Committee review
05/21/2014 Medical Policy Implementation Committee approval. Added “dosing and management of antituberculosis medications” to the investigational applications.

05/07/2015 Medical Policy Committee review
05/20/2015 Medical Policy Implementation Committee approval. Added INV statement for the use of genetic testing panels that include multiple CYP450 mutations. Updated existing INV bullet “dosing of codeine” and “dose of efavirenz and other antiretroviral therapies”.

02/04/2016 Medical Policy Committee review
02/17/2016 Medical Policy Implementation Committee approval. Policy statements for CYP2B6 genotyping added. CYP450 genotyping in choosing or dosing clopidogrel changed to INV. Serotonin-norepinephrine reuptake inhibitors added to existing INV indication for CYP450 genotyping.

01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
02/02/2017 Medical Policy Committee review
02/15/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

01/01/2018 Coding update
02/01/2018 Medical Policy Committee review

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02/21/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/01/2018 Coding update
08/09/2018 Medical Policy Committee review
08/15/2018 Medical Policy Implementation Committee approval. Policy title changed from “Cytochrome P450 Genotyping” to “Cytochrome P450 Genotype-Guided Treatment Strategy”. Four criteria removed from the third investigational statement; the intent of statements otherwise unchanged. Information on pharmacologic treatments used to treat mental health disorders were removed from this policy and added to policy 00402.
08/30/2018 Coding update
08/01/2019 Medical Policy Committee review
08/14/2019 Medical Policy Implementation Committee approval. Coverage changes, coverage eligibility statement added to Patient Selection Criteria for CYP2C9 genotyping to determine drug metabolizer status will be met for patients with Multiple Sclerosis being considered for treatment with Siponimod. Addition to FDA labeling section to include label guidelines for siponimod (Mayzent) for patients with CYP2C9 genotypes.
08/06/2020 Medical Policy Committee review
08/12/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/05/2021 Medical Policy Committee review
04/05/2022 Coding update
08/04/2022 Medical Policy Committee review
08/10/2022 Medical Policy Implementation Committee approval. Revised the criteria language for CYP2C9 genotyping. Coverage intent unchanged.
09/20/2022 Coding update
12/07/2022 Coding update
03/19/2023 Coding update

Next Scheduled Review Date: 08/2023

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment,
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would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

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

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.