Genotyping to determine cytochrome P450 2D6 (CYP2D6) variants is considered investigational for the purpose of managing treatment with tamoxifen for women at high risk for or with breast cancer.

Policy Guidelines

Genetics Nomenclature Update
The Human Genome Variation Society 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). The Society’s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to 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

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Disease-associated change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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

Coding
There is a specific CPT code for this testing:

Description
Tamoxifen is prescribed as a component of adjuvant endocrine therapy to prevent endocrine receptor–positive breast cancer recurrence, to treat metastatic breast cancer, and to prevent disease in high-risk populations and in women with ductal carcinoma in situ. Tamoxifen is a prodrug that undergoes extensive metabolism to yield its active form: 4-hydroxy tamoxifen and
endoxifen (primary active form) via the CYP2D6 enzyme. Variants in the CYP2D6 gene are associated with significant alterations in endoxifen concentrations leading to the hypothesis that CYP2D6 variation may affect the clinical outcomes of women treated with tamoxifen but not with drugs not metabolized by CYP2D6 such as anastrozole.

**Related Policies**

- Cytochrome P450 Genotype-Guided Treatment Strategy

**Benefit Application**

Benefit determinations should be based 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.

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. CYP2D6 genotyping assays are available under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by 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 through the 510(k) process (FDA product code: NTI) are summarized in Table 2.

<table>
<thead>
<tr>
<th>Device Name</th>
<th>Manufacturer</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>xTAG CYP2D6 Kit V3</td>
<td>Luminex Molecular Diagnostics</td>
<td>2017</td>
</tr>
<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>xTAG CYP2D6 Kit V3 (including TDAS CYP2D6)</td>
<td>Luminex Molecular Diagnostics</td>
<td>2013</td>
</tr>
<tr>
<td>Verigene CYP2C19 Nucleic Acid Test (CYP2C19)</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 1030C0300</td>
<td>Luminex Molecular Diagnostics</td>
<td>2010</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>

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 panel tests are beyond the scope of this evidence review.
Rationale

Background

Tamoxifen Metabolism

Tamoxifen is a pro-drug that undergoes extensive metabolism to yield its active form: 4-hydroxytamoxifen (4-OH tamoxifen) and 4-hydroxy-N-desmethyltamoxifen (endoxifen). Among these 2 metabolites, endoxifen is thought to be the major metabolite that exerts the pharmacodynamic effect of tamoxifen. The metabolism of tamoxifen into 4-OH tamoxifen is catalyzed by multiple enzymes while endoxifen is formed predominantly by the CYP2D6 enzyme. Plasma concentrations of endoxifen exhibit high interindividual variability, as described in breast cancer patients. Because CYP2D6 enzyme activity is known to vary across individuals, variants in the CYP2D6 gene are of great interest for understanding tamoxifen metabolism variability and variation in levels of circulating active metabolites. Moreover, known variability in endoxifen levels has been hypothesized to result in variable response to tamoxifen treatment.

Metabolic Enzyme Genotypes

The CYP2D6 gene exhibits a high degree of polymorphism, with more than 100 allelic variants identified. The relations among genotype, phenotype, and clinical implications are summarized in Table 1.

Table 1. Relation among the CYP2D6 Genotype, Phenotype, and Clinical Implications

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
<th>Potential Clinical Implications With Use of Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3 copies of functional alleles</td>
<td>Ultrafast metabolizer</td>
<td>None</td>
</tr>
<tr>
<td>Any one of the following scenarios:</td>
<td>Intermediate metabolizer</td>
<td>• Increased risk for relapse of breast cancer</td>
</tr>
<tr>
<td>• 1 active allele and 1 inactive allele</td>
<td></td>
<td>• Avoid concomitant use of CYP2D6 inhibitors</td>
</tr>
<tr>
<td>• 2 decreased activity alleles</td>
<td></td>
<td>• Consider aromatase inhibitor for postmenopausal women</td>
</tr>
<tr>
<td>• 1 decreased activity allele and 1 inactive allele</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 inactive alleles</td>
<td>Poor metabolizer</td>
<td>• Increased risk for relapse of breast cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consider aromatase inhibitor for postmenopausal women</td>
</tr>
</tbody>
</table>

Adapted from Swen et al (2011).^3^ The prevalence of CYP2D6 poor metabolizers is approximately 7% to 10% in whites of Northern European descent, 1.9% to 7.3% in blacks, and 1% or less in most Asian populations studied. The poor metabolizer phenotype in whites is largely accounted for by CYP2D6*3 and *4 nonfunctional variants, and in black and Asian populations, by the *5 nonfunctional variant. Some poor metabolizers may have 1 nonfunctional allele and 1 reduced-function allele. Among reduced-function variants, CYP2D6*17, *10, and *8 are the most important in blacks, Asians, and whites, respectively. Few studies have investigated the frequency of CYP2D6-variant alleles or poor metabolizers in the Hispanic population.^4^

Endocrine Therapy Regimens

Tamoxifen has several labeled indications:^5^  
- chemoprevention of invasive breast cancer in high-risk women without current disease or with ductal carcinoma in situ;
- adjuvant treatment of primary breast cancer; and
- treatment of metastatic disease.

In women with breast cancer, endocrine receptor-positive disease predicts a likely benefit from tamoxifen treatment. Tamoxifen is currently the most commonly prescribed adjuvant treatment to prevent recurrence of the endocrine receptor-positive breast cancer in pre- or perimenopausal women.
For postmenopausal women with osteoporosis or at high-risk for invasive breast cancer, raloxifene is an alternative treatment for invasive cancer risk reduction. Currently, raloxifene is indicated for the treatment of reduction in the “risk of invasive breast cancer in postmenopausal women with osteoporosis” or those at “high risk for invasive breast cancer.”

Pharmacologic Inhibitors of Metabolic Enzymes
CYP2D6 activity may be affected not only by genotype but also by coadministered drugs that block or induce CYP2D6 function. Studies of selective serotonin reuptake inhibitors, in particular, have shown that fluoxetine and paroxetine, but not sertraline, fluvoxamine, or venlafaxine, are potent CYP2D6 inhibitors. Some individuals treated with fluoxetine or paroxetine have changed from extensive metabolizer phenotype to poor metabolizer. The degree of inhibition may depend on selective serotonin reuptake inhibitors dose.

Thus, CYP2D6 inhibitor use must be considered in assigning CYP2D6 functional status, and potent CYP2D6 inhibitors may need to be avoided when tamoxifen is administered.

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 variation only explains a modest portion of the variance in the individual response because clinical outcomes are also affected by a wide variety of factors including alternate pathways of metabolism and patient- and disease-related factors that may affect absorption, distribution, and elimination of the drug. Therefore, assessment of clinical utility cannot be made by a chain of evidence from clinical validity data alone. In such cases, evidence evaluation requires studies that directly demonstrate that the pharmacogenomic test alters clinical outcomes; it is not sufficient to demonstrate that the test predicts a disorder or a phenotype.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, two domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials 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.

Genotype-Guided Tamoxifen Treatment
Clinical Context and Therapy Purpose
The purpose of genotype-guided tamoxifen treatment is to tailor drug selection (e.g., tamoxifen or an aromatase inhibitor) or dose selection (e.g., tamoxifen 40 mg/d instead of the standard 20 mg/d dose) or strategy (e.g., ovarian ablation in premenopausal women) while minimizing treatment failures or toxicities based on a patient’s genotype.
The question addressed in this evidence review is: Does a genotyping-guided treatment strategy change patient management in a way that it improves net health outcome?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is patients receiving or being considered for tamoxifen therapy:
- Treatment of breast cancer in the adjuvant setting to prevent recurrence (alone or preceding aromatase inhibitor therapy) or for metastatic disease.
- Prevention of breast cancer in high-risk women or women with ductal carcinoma in situ; and absence of contraindications to aromatase inhibitors (for treatment) or raloxifene (for disease prevention).

**Interventions**
The test being considered is CYP2D6 genotype-guided tamoxifen treatment. Commercial tests for individual genes or gene panels are available and listed in the Regulatory Status section.

**Comparators**
The following practice is currently being used: clinically managed tamoxifen treatment.

**Outcomes**
The general outcomes of interest are overall survival, disease-specific survival, medication use, and treatment-related morbidity. Specific outcomes are listed in Table 3.

**Table 3. Outcomes of Interest for Individuals With or at High Risk for Breast Cancer**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication use</td>
<td>Change to alternative treatment (aromatase inhibitor) or strategy (ovarian ablation in premenopausal women)</td>
</tr>
<tr>
<td>Treatment-related morbidity</td>
<td>Reduction in adverse events</td>
</tr>
</tbody>
</table>

The potential beneficial outcomes of primary interest would be a reduction in the rate of recurrence and improvement in disease-free survival or overall survival.

**Timing**
Follow-up to determine whether genotype-guided tamoxifen treatment reduces adverse events or avoids treatment failure is during the first 10 years after treatment initiation.

**Setting**
Patients requiring treatment for prevention or treatment for breast cancer are managed by an oncologist.

**Prospective Cohort Studies**
Multiple retrospective and prospective cohort studies have investigated the association between CYP2D6 genotype and tamoxifen effectiveness and reported contradictory results with relative risks ranging from 0.08 to 13.1 for the association between variant CYP2D6 genotypes and breast cancer recurrence or mortality. The contradictory results may be due to differences in the types of additional therapies patients received, how many and which CYP2D6 alleles were tested, tissue type examined (tumor or germline DNA), and coadministration with CYP2D6 inhibitors. Many of these studies have also been summarized in multiple systematic reviews and meta-analyses with inconsistent results. Data in most of these studies derived from a convenient sample, which was further limited by relatively small numbers of patients, lack of comprehensive genotype data and patient data (e.g., concomitant medications), and detailed clinical outcomes data. Among the most influential studies of the association between CYP2D6 genotype and tamoxifen effectiveness are 3 nonconcurrent prospective studies nested within...
large prospective, randomized double-blind trials that compared tamoxifen with anastrozole, letrozole, or combination tamoxifen and anastrozole in postmenopausal women with hormone receptor-positive early-stage breast cancer. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial and Breast International Group 1-98 (BIG 1-98) trial, a subset of patients who received tamoxifen and were genotyped for CYP2D6 variants (n=588 and n=1243, respectively) did not show any statistically significant associations between phenotype (patients classified as poor, intermediate, or extensive metabolizer) and breast cancer recurrence. In the Austrian Breast and Colorectal Cancer Study Group trial, a case-control study was done using a subset of patients where cases were defined as those with disease recurrence, contralateral breast cancer, second non-breast cancer, or died and controls were identified from the same treatment arm of similar age, surgery/radiation, and stage. Results showed that patients with 2 poor metabolizer alleles had higher likelihood of recurrence than women with 2 extensive metabolizer alleles. Concerns about the substantial departure from Hardy-Weinberg equilibrium for the CYP2D6 allele, *4 and analyses not meeting the Simon-Paik-Hayes criteria for nonconcurrent prospective studies have been raised to explain the lack of effect in the ATAC and BIG 1-98 trials.

Trials are important to validate such hypotheses. However, no trials of genotype-directed dosing or drug choice that assessed outcomes of breast cancer recurrence were identified. Ruddy et al (2013) implemented a tamoxifen adjustment algorithm for 99 patients treated at a cancer treatment institute. Recommendations to modify tamoxifen therapy were made for 18 (18%) patients, all of whom had low endoxifen levels (<6 ng/mL), and 2 of whom also were identified as CYP2D6 poor metabolizers. Breast cancer recurrence or survival outcomes were not reported.

Summary of Evidence
For individuals who are treated with tamoxifen for breast cancer or are high risk for breast cancer who receive CYP2D6 genotype-guided tamoxifen treatment, the evidence includes multiple retrospective and prospective cohort studies and nonconcurrent prospective studies. Relevant outcomes include overall survival, disease-specific survival, medication use, and treatment-related morbidity. Published data on the association between CYP2D6 genotype and tamoxifen treatment outcomes have yielded inconsistent results. Data in most of these studies derived from a convenient sample, which was further limited by relatively small numbers of patients and lack of comprehensive genotype data, patient data (e.g., concomitant medications), and detailed clinical outcomes data. Three influential nonconcurrent prospective studies nested within large prospective, randomized double-blind clinical trials in postmenopausal women with hormone receptor-positive early-stage breast cancer also reported contradictory results, with 2 larger studies failing to show statistically significant associations between phenotype (patients classified as poor, intermediate, or extensive metabolizer) and recurrence of breast cancer. No trials of genotype-directed dosing or drug choice that compared health outcomes for patients managed with and without the test were identified. It is not known whether CYP2D6 genotype-guided tamoxifen treatment results in the selection of a treatment strategy that would reduce the rate of breast cancer recurrence, improve disease-free survival or overall survival, or reduce adverse events. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements

National Comprehensive Cancer Network
Regarding the use of CYP2D6 genotyping before prescribing tamoxifen, the National Comprehensive Cancer Network breast cancer guidelines (v.1.2018) state: "The panel recommends against CYP2D6 genotype testing for women being considered for tamoxifen treatment."
American Society of Clinical Oncology
The 2016 guidelines from the American Society of Clinical Oncology on the use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer stated the following for CYP2D6 variants to guide adjuvant endocrine therapy selection:

- “The clinician should not use CYP2D6 polymorphisms to guide adjuvant endocrine therapy selection (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).
- The ability of polymorphisms in CYP2D6 to predict tamoxifen benefit has been extensively studied. The results of these pharmacogenomics studies have been controversial, with more recent studies being negative. At this point, data do not support the use of this marker to select patients who may or may not benefit from tamoxifen therapy.”17

U.S. Preventive Services Task Force Recommendations
Not applicable.

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 unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01357772</td>
<td>Randomized Placebo-controlled Phase III Trial of Low-dose Tamoxifen in Women With Breast Intraepithelial Neoplasia</td>
<td>1400</td>
<td>Dec 2023</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

References


**Documentation for Clinical Review**

- No records required

**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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**IE**

The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>0028U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, copy number variants, common variants with reflex to targeted sequence analysis (Deleted code effective 10/1/2018)</td>
</tr>
</tbody>
</table>
### Type | Code | Description
--- | --- | ---
| 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) | **(Code effective 10/1/2018)**
| 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) | **(Code effective 10/1/2018)**
| 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) | **(Code effective 10/1/2018)**
| 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) | **(Code effective 10/1/2018)**
| 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) | **(Code effective 10/1/2018)**
| 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) | **(Code effective 10/1/2018)**

**HCPCS** | None
--- | ---
**ICD-10 Procedure** | None

### Policy History

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/02/2016</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>09/01/2016</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>08/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>05/01/2018</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>09/01/2018</td>
<td>Policy title change from Genetic Testing for Tamoxifen Treatment Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>10/01/2018</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
</tbody>
</table>

### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**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 (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. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

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.