Genetic Testing for Li-Fraumeni Syndrome

Policy # 00424
Original Effective Date: 07/16/2014
Current Effective Date: 01/01/2023

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.

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 genetic testing for TP53 to confirm a diagnosis of Li-Fraumeni syndrome (LFS) under the following conditions to be eligible for coverage**:

Patient Selection Criteria
Coverage eligibility will be considered when the following criteria are met and requested TP53 genetic testing was not performed before:

- In a patient who meets either the classic or the Chompret clinical diagnostic criteria for Li-Fraumeni syndrome (LFS), or

**Diagnostic criteria for Li-Fraumeni syndrome (LFS):**

**Classic Li-Fraumeni syndrome (LFS):**
- Individual diagnosed at age <45 years with a sarcoma AND
- A first-degree relative diagnosed at age <45 with any cancer AND
- An additional first- or second-degree relative in the same lineage with any cancer diagnosed at age <45 years, or a sarcoma at any age.

**Chompret criteria:**
- Individual with a tumor from LFS tumor spectrum (e.g., soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma) before 46 years of age, AND at least one first- or second-degree relative with LFS tumor (except breast cancer if proband has breast cancer) before the age of 56 years or with multiple primaries at any age; OR
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- Individual with multiple tumors (except multiple breast tumors), 2 of which belong to LFS tumor spectrum and the initial cancer occurring before the age of 46 years; OR
- Individual with adrenocortical carcinoma (ACC), or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of family history; OR
  - Individual with breast cancer diagnosed before 31 years of age; OR
  - Pediatric hypodiploid acute lymphoblastic leukemia diagnosed before 21 years of age; OR
  - Targeted TP53 familial variant testing in an individual from a family with a known TP53 pathogenic or likely pathogenic variant.

Notes:
In an individual with breast cancer diagnosed at young age (age 50 or younger), germline multi-gene small panel testing run on one testing platform that includes other high-penetration breast cancer susceptibility genes (i.e., BRCA 1 and 2, CDH1, PALB2, and PTEN) can be considered when criteria are met for BRCA (see MP 00047) or TP53 gene testing and an individual was not tested before. In this situation procedure code representing smaller panel (i.e., CPT code 81432, with 81433 only if initial sequencing represented by code 81432 did not identify pathogenic or likely pathogenic variants, or if applicable PLA code 0129U) should be reported rather than multiple codes representing individual or sequential gene testing.

Consideration of both maternal and paternal family histories is necessary in the evaluation for risk of carrying a mutation in the TP53 gene; each lineage must be considered separately.

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

The use of genetic testing for a germline TP53 variant when patient selection criteria are not met is considered to be investigational.*

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Based on review of available data, the Company considers direct-to-consumer genetic testing (e.g., mail or online ordering), mRNA sequence analysis, testing for variants of unknown significance, polygenic risk scores (PRS), and testing large panels of genes (e.g., Myriad myRisk®, CancerNext®, Comprehensive Common Cancer Panel, Invitae Multi-Cancer Panel, Invitae Common Hereditary Cancers Panel) to be **investigational.**

**Policy Guidelines**
Somatic TP53 variants found on tumor testing are common across many types of cancers. The finding of somatic TP53 variant(s) on tumor testing would support genetic counseling for assessment of risk for Li-Fraumeni Syndrome.

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

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| 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

<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.

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.

Background/Overview

TP53 Gene
The TP53 gene contains the genetic instructions for the production of tumor protein p53. The p53 protein is a tumor suppressor that functions as a cell cycle regulator to prevent cells from uncontrolled growth and division when there is DNA damage. Somatic (acquired) pathogenic
variants are one of the most frequent alterations found in human cancers. Germline (inherited) pathogenic variants in *TP53* are associated with LFS.

**Li-Fraumeni Syndrome**

Li-Fraumeni syndrome is a cancer predisposition syndrome associated with a high lifetime cumulative risk of cancer and a tendency for multiple cancers in affected individuals. The syndrome was originally described based on a retrospective analysis of families with aggressive soft tissue sarcomas in young siblings and their biologically related cousins.

The tumor types most closely associated with LFS include soft tissue sarcomas, osteosarcomas, premenopausal breast cancer, brain tumors, and adrenal cortical carcinoma. Other malignancies associated with LFS include a wide variety of gastrointestinal tract, lung, skin, and thyroid cancers as well as leukemias and lymphomas.

Individuals with LFS are at increased risk of developing multiple primary tumors, with subsequent malignancies, not all being clearly related to the treatment of the previous neoplasms. The risk of developing a second tumor has been estimated at 40 to 49%. In 1 study of 322 pathogenic variant carriers from France, Bougeard et al (2015) reported that 43% of individuals had multiple malignancies.

Individuals with LFS are at increased risk of both bone and soft tissue sarcomas. Sarcomas of various histologies account for 25% of the cancers reported in people with LFS, with the most commonly reported sarcomas in an international database being rhabdomyosarcoma before age 5 years and osteosarcoma at any age. Women with LFS are at greatly increased risk of developing premenopausal breast cancer, with the median age of diagnosis being 33 years of age. Male breast cancer has rarely been reported in LFS families. Many types of brain tumors have been described in LFS, including astrocytomas, glioblastomas, medulloblastomas, and choroid plexus carcinomas. The median age of onset of LFS-related brain tumors is 16 years of age. Individuals with LFS are at increased risk of developing adrenocortical carcinoma. For adults, Raymond et al (2013) estimated that 6% of individuals diagnosed with adrenocortical carcinoma after age 18 years have a germline *TP53* pathogenic variant.

Data from M.D. Anderson Cancer Center's long-term clinical studies of LFS have shown that the risk of developing soft tissue sarcomas is greatest before the age of 10, brain cancer appears to occur...
early in childhood with a smaller peak in risk in the fourth to fifth decade of life, risk for osteosarcoma is highest during adolescence, and breast cancer risk among females with LFS starts to increase significantly around age 20 and continues into older adulthood.

**Clinical Diagnosis**
The diagnosis of LFS is based on an evolving set of clinical classification criteria, established using salient aspects of family history and tumor-related characteristics. The first formal criteria, the classic LFS criteria, were developed in 1988, and are the most stringent used to make a clinical diagnosis of LFS.

**Classic Li-Fraumeni Syndrome**
Classic LFS is defined by the presence of all of the following criteria:
- A proband with a sarcoma before 45 years of age,
- A first-degree relative with any cancer before 45 years of age, and
- A first- or second-degree relative with any cancer before 45 years of age or a sarcoma at any age.

**Chompret Criteria**
Chompret et al (2001) developed criteria that have the highest positive predictive value, and that, when combined with the classic LFS criteria, provide the highest sensitivity for identifying individuals with LFS. The Chompret criteria were updated in 2009 to assist in identifying families with milder phenotypes. The Chompret criteria will also identify individuals with de novo TP53 pathogenic variants, whereas the classic LFS criteria require a family history.

The Chompret criteria, most recently updated in 2015, are defined as the following:
- Proband with tumor belonging to the LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, brain tumor, premenopausal breast cancer, adrenocortical carcinoma) before age 46 years AND at least 1, first- or second-degree relative with LFS tumor (except breast cancer if the proband has breast cancer) before age 56 years or with multiple tumors; or
- Proband with multiple tumors (except multiple breast tumors), 2 of which belong to the LFS tumor spectrum and the first of which occurred before age 46 years; or
- Patient with adrenocortical carcinoma, rhabdomyosarcoma of embryonal anaplastic subtype, or choroid plexus tumor, irrespective of family history; or...
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• Female proband with breast cancer before age 31 years.

National Comprehensive Cancer Network guidelines recommend TP53 testing for individuals who meet classic LFS criteria and Chompret criteria.

Molecular Diagnosis
Li-Fraumeni syndrome is associated with germline pathogenic variants in the TP53 gene (chromosome 17p13.1), which encodes for a ubiquitous transcription factor that is responsible for a complex set of regulatory functions that promote DNA repair and tumor suppression. TP53 is the only gene in which pathogenic variants are known to cause LFS, and no other inherited phenotypes are associated specifically with germline pathogenic variants involving TP53. The presence of a TP53 variant is considered diagnostic.

Li-Fraumeni syndrome is a highly penetrant cancer syndrome, with the risks of cancer being about 80% by age 70. It is inherited in an autosomal dominant manner. De novo germline TP53 pathogenic variants (no pathogenic variant is identified in either biologic parent) are estimated to be 7% to 20%. Approximately 95% of pathogenic variants detected in the TP53 gene are sequence variants (small intragenic deletions and insertions and missense, nonsense, and splice site variants). Large deletions and duplications not readily detected by sequence analysis account for approximately 1% of the pathogenic variants detected.

Certain genotype-phenotype correlations have been reported in families with LFS and TP53 pathogenic variants. Genotype-phenotype correlations in LFS are predictive of the age of onset of a tumor, level of risk of developing a tumor, and outcome in patients with TP53 germline pathogenic variants.

Management

Treatment
The evaluation of cancer in an individual diagnosed with LFS should be based on personal medical history and, to some degree, the specific pattern of cancer in the family. Women with LFS who develop breast cancer are encouraged to consider bilateral mastectomies to reduce the risk of developing a second primary breast cancer and to avoid exposure to radiotherapy. Preventive measures may include risk-reducing (prophylactic) mastectomy in women, and in all patients with a
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TP53 pathogenic variant, avoidance of radiotherapy, because the evidence has suggested that TP53 pathogenic variants confer an increased sensitivity to ionizing radiation and the possibility of radiation-induced malignancies.

Surveillance
Li-Fraumeni syndrome confers a high risk of multiple different types of cancer, which poses challenges for establishing a comprehensive screening regimen, and many of the cancers associated with LFS do not lend themselves to early detection. There is no international consensus on the appropriate clinical surveillance strategy in individuals with LFS, but, in general, the strategy includes physical examination, colonoscopy, and breast imaging. Other protocols being evaluated include additional imaging techniques and biochemical assessment. National Comprehensive Cancer Network has consensus-based screening guidelines.

Testing Strategy
Given the common germline TP53 variant types associated with LFS, a possible testing strategy to optimize yield would be:

1. Sequencing of the entire TP53 coding region (exons 2 through 11). Examples of types of pathogenic variants detected by sequence analysis include small insertions and deletions (frameshift), and missense, nonsense, and splice site variants; most are missense variants.
2. Deletion and duplication analysis, which detects large deletions and duplications involving the coding region (exon 1) or promoter; these types of deletions and duplications are not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. These types of pathogenic variants account for less than 1% of those found in individuals with LFS.

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. Laboratories that offer laboratory-developed tests must be licensed under the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.
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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.

LFS is a cancer predisposition syndrome associated with the development of several types of tumors. The syndrome is caused by germline pathogenic variants in the $TP53$ gene. Testing for LFS pathogenic variants may be useful in confirming the diagnosis of LFS and/or evaluating genetic status in asymptomatic relatives of an index case.

Summary of Evidence
For individuals with suspected LFS by clinical criteria who receive genetic testing for $TP53$, the evidence includes case series and cross-sectional studies. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, changes in reproductive decision making, and resource utilization. Evidence on the clinical validity of testing comes from the International Agency for Research on Cancer TP53 Database that has compiled records on 891 families with LFS. For patients with suspected LFS based on clinical criteria, the clinical sensitivity ranges from 50% to 80%. No evidence was identified on clinical specificity. In individuals with suspected LFS, a positive genetic test will establish a genetic diagnosis of LFS and facilitate the overall workup for cancer susceptibility syndrome when multiple conditions are considered. Also, the presence of a documented $TP53$ pathogenic variant may aid in decision making for risk-reducing (prophylactic) mastectomy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic and have a close relative with a known $TP53$ pathogenic variant who receive targeted $TP53$ familial variant testing, the evidence includes case series and cross-sectional studies. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, changes in reproductive decision making, and resource utilization. Evidence on the clinical validity of testing comes from the International Agency for Research on Cancer TP53 Database that has compiled records on 891 families with LFS. In asymptomatic individuals who have a close relative with a known $TP53$ pathogenic variant, targeted familial variant testing can...
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confirm or exclude the presence of the familial variant with high certainty. A positive genetic test will lead to increased surveillance for LFS-associated cancers, and a negative test will eliminate the need for enhanced surveillance. Knowledge of TP53 genetic status may also inform reproductive decision making in individuals considering offspring. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Supplemental Information**

**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.

**National Comprehensive Cancer Network**

The National Comprehensive Cancer Network (NCCN) guidelines on genetic or familial high-risk assessment of breast, ovarian, and pancreatic cancer (v. 2.2021) indicate that, in general, testing criteria for high-penetrance breast and/or ovarian cancer susceptibility genes "can include BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53 among others" (CRIT-1). This is followed by more detailed discussions of TP53 testing that are specifically focused on its association with LFS and include the following testing criteria recommendations (CRIT-4):

- Individual from a family with a known TP53 pathogenic/likely pathogenic variant
- Individual who meets either the classic or the Chompret clinical diagnostic criteria for LFS, including those with breast cancer before 31 years of age
- Affected individual with pathogenic/likely pathogenic variant identified on tumor genomic testing that may have implications if also identified on germline testing.

The guidelines further state that somatic pathogenic or likely pathogenic variants in TP53 would not indicate the need for germline testing unless the clinical/family history is consistent with a pathogenic or likely pathogenic variant in the germline.
American Association for Cancer Research
In 2017, the American Association for Cancer Research published recommendations for cancer screening and surveillance for patients with LFS. Genetic counseling and clinical TP53 testing should be strongly considered in the following clinical situations:

"(i) proband with an LFS spectrum tumor … prior to age 46 and at least one first- or second-degree relative with an LFS tumor … before the age of 56 years or with multiple tumors, (ii) … proband with multiple malignancies (except two breast cancers), of which at least 2 belong to the LFS spectrum, before age 46; (iii) … patients with rare tumors such as ACC, choroid plexus carcinoma, or embryonal anaplastic subtype rhabdomyosarcoma independent of family history; and (iv) breast cancer before age 31 years."

Cancer surveillance has been shown to improve overall survival for surveillance and non-surveillance groups and should be offered as soon as either clinical or molecular diagnosis of LFS is established. The following surveillance protocols were recommended for children (birth to age 18) and adults.

For children:
- Complete physical examination every 3 to 4 months and full neurologic assessment
- Prompt assessment with primary care physician for any medical concerns
- Abdominal and pelvic ultrasound every 3 to 4 months
- Annual brain magnetic resonance imaging (MRI)
- Annual whole-body MRI (WBMRI).

For adults:
- Complete physical examination every 6 months
- Prompt assessment with primary care physician for any medical concerns
- Breast awareness (age 18 years onward)
- Clinical breast examination twice per year (age 20 years onward)
- Annual breast MRI screening (ages 20 to 75)
- Consider risk-reducing bilateral mastectomy
- Annual brain MRI (age 18 years onward)
- Annual WBMRI
- Abdominal and pelvic ultrasound every 12 months
- Upper endoscopy and colonoscopy every 2 to 5 years (age 25 years onward)
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- Annual dermatologic examination.

U.S. Preventive Services Task Force Recommendations
No U.S. Preventive Services Task Force recommendations for LFS 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 unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01443468</td>
<td>Clinical, Epidemiologic, and Genetic Studies of Li-Fraumeni Syndrome; An Observational/Prospective Study: (Long-term prospective cohort study to collect data from as many individuals with LFS as permissible in order to precisely evaluate the main aims)</td>
<td>5000</td>
<td>(ongoing)*</td>
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<tr>
<td>NCT04541654</td>
<td>Li-Fraumeni &amp; TP53: Understanding and Progress (LiFT UP)</td>
<td>1500</td>
<td>Dec 2025</td>
</tr>
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</table>

NCT: national clinical trial.
*Ongoing - last update on clinicaltrials.gov website: May 2021

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Policy History
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Current Effective Date: 01/01/2023
07/10/2014 Medical Policy Committee review
07/16/2014 Medical Policy Implementation Committee approval. New policy.
08/06/2015 Medical Policy Committee review
08/19/2015 Medical Policy Implementation Committee approval. No change to coverage.
08/04/2016 Medical Policy Committee review
08/17/2016 Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
09/07/2017 Medical Policy Committee review
09/20/2017 Medical Policy Implementation Committee approval. Policy statement updated for early-onset breast cancer to align with NCCN age cutoff of “<31 years”.
10/04/2018 Medical Policy Committee review
10/17/2018 Medical Policy Implementation Committee approval. No change to coverage.
10/03/2019 Medical Policy Committee review
10/09/2019 Medical Policy Implementation Committee approval. No change to coverage.
10/01/2020 Medical Policy Committee review
10/07/2020 Medical Policy Implementation Committee approval. No change to coverage.
12/11/2020 Coding update
10/07/2021 Medical Policy Committee review
10/13/2021 Medical Policy Implementation Committee approval. No change to coverage.
11/03/2022 Medical Policy Committee review
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Next Scheduled Review Date: 11/2023

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

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<th>Code Type</th>
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<td>No codes</td>
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<tr>
<td>ICD-10 Diagnosis</td>
<td>Z15.01</td>
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*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, 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;
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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.