Genetic Testing for Li-Fraumeni Syndrome

Policy # 00424
Original Effective Date: 07/16/2014
Current Effective Date: 10/09/2019

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:

• 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)
- A proband with a sarcoma before 45 years of age AND
- 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
- Proband with tumor belonging to Li-Fraumeni syndrome (LFS) tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, brain tumor, premenopausal breast cancer, adrenocortical carcinoma, leukemia, lung bronchoalveolar cancer) before age 46 years AND at least 1 first- or second-degree relative with Li-Fraumeni syndrome (LFS) tumor (except breast cancer if proband has breast cancer) before age 56 years or with multiple tumors; OR
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- Proband with multiple tumors (except multiple breast tumors), 2 of which belong to Li-Fraumeni syndrome (LFS) tumor spectrum and first of which occurred before age 46 years; OR
- Patient with adrenocortical carcinoma (ACC) or choroid plexus tumor, irrespective of family history

- In women with early-onset breast cancer (age of diagnosis ≤31 years); or

Note: National Comprehensive Cancer Network guidelines recommend TP53 analysis for individuals who meet classic LFS criteria and Chompret criteria, or who have been diagnosed with early-onset breast cancer (age of diagnosis <31 years).
- Targeted TP53 familial variant testing in an at-risk relative of a proband with a known TP53 pathogenic variant.

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.*

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
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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>
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<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td></td>
<td>Change in the DNA sequence</td>
</tr>
<tr>
<td>Familial</td>
<td>Variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
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Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

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<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
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<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>
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</table>
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<table>
<thead>
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<th>Likely benign</th>
<th>Likely benign change in the DNA sequence</th>
</tr>
</thead>
<tbody>
<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 Li-Fraumeni syndrome (LFS).

**Li-Fraumeni Syndrome**
LFS 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, premenopausal breast cancer, brain tumors, and adrenal cortical carcinoma. These core cancers account for approximately 70% to 80% of all LFS-related tumors. There is less agreement about the noncore cancers, which account for the remaining 30% of malignancies in LFS and include a wide variety of gastrointestinal tract, genitourinary 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 57%, and the risk of a third malignancy, 38%. In a 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
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classic LFS criteria, were developed in 1988, and are the most stringent used to make a clinical diagnosis of LFS.

**Classic LFS**

*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 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, leukemia, lung bronchoalveolar cancer) 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), two of which belong to the LFS tumor spectrum and the first of which occurred before age 46 years; or
- Patient with adrenocortical carcinoma or choroid plexus tumor, irrespective of family history.

National Comprehensive Cancer Network guidelines recommend *TP53* testing for individuals who meet classic LFS criteria and Chompret criteria, or who have been diagnosed with early-onset breast cancer (age of diagnosis <31 years).
Molecular Diagnosis

LFS 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.

LFS is a highly penetrant cancer syndrome, with the risks of cancer being about 50% by age 30 years, and 90% by age 60 years. LFS 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 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.
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Surveillance
LFS 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 2-11). 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. Food and Drug Administration has chosen not to require any regulatory review of this test.
Rationale/Source

Li-Fraumeni syndrome (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.

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 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

National Comprehensive Cancer Network guidelines on genetic or familial high-risk assessment of breast and ovarian (v.1.2018) recommend the following for Li-Fraumeni syndrome (LFS) management:

Breast cancer risk, women:
- "Breast awareness starting at age 18 y.
- Clinical breast exam, every 6-12 mo, starting at age 20y.
- Breast screening
  - Age 20-29 y, annual breast MRI [magnetic resonance imaging] screening with contrast (or mammogram with consideration of tomosynthesis, only if MRI is unavailable)…
  - Age 30-75 y, annual mammogram with consideration of tomosynthesis and breast MRI screening contrast
  - Age >75 y, management considered on an individual basis
- For women with a TP53 pathogenic/likely pathogenic variant who are treated for breast cancer and who have not had a bilateral mastectomy, screening with annual breast MRI and mammogram should continue as described above. ref 19
- Discuss option of risk-reducing mastectomy
  - Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and residual breast cancer risk with age and life expectancy should be considered during counseling.
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy…"ref 19

Other cancer risks:
- "Comprehensive physical exam including neurologic examination with high index of suspicion for rare cancers [cancers associated with LFS] and second malignancies in cancer survivors every 6-12 months
- Colonoscopy and upper endoscopy every 2-5 y starting at 25 y of age or 5 y before the earliest known colon cancer in the family (whichever comes first)." ref 19
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- Annual dermatologic examination starting at 18 y.
- Annual whole body MRI (category 2B)
- Annual brain MRI (category 2B) may be performed as part of the whole body MRI or as a separate exam. ref 19

For relatives:
- "Advise about possible inherited cancer risk to relatives, options for risk assessment, and management.
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives."

American Association for Cancer Research
The American Association for Cancer Research (2017) 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 two 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 nonsurveillance 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 3-4 months and full neurologic assessment
- Prompt assessment with primary care physician for any medical concerns
- Abdominal and pelvic ultrasound every 3-4 months
- Annual brain MRI
- Annual whole-body MRI (WBMRI).
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For adults:
- Complete physical examination every six 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 20-75)
- 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)
- 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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<tr>
<td>NCT01443468</td>
<td>Clinical, Epidemiologic, and Genetic Studies of Li-</td>
<td>5000</td>
<td>(ongoing)*</td>
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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)

NCT: national clinical trial.
^a Denotes industry-sponsored or cosponsored trial.
^*=Ongoing—last update on clinicaltrials.gov website: May 2019

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Policy History
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Current Effective Date: 10/09/2019
07/10/2014 Medical Policy Committee review
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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.

Next Scheduled Review Date: 10/20/2020

Coding
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contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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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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*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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.
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**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;
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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