



Louisiana

Genetic Testing for Li-Fraumeni Syndrome

Policy # 00424

Original Effective Date: 07/16/2014

Current Effective Date: 11/09/2020

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

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

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

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

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

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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 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

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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

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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), 2 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.

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Louisiana

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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.

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.

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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.

Rationale/Source

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.

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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

The National Comprehensive Cancer Network (NCCN) guidelines on genetic or familial high-risk assessment of breast and ovarian (v.1.2020) indicate that, in general, testing criteria for high-penetrance breast and/or ovarian cancer susceptibility genes "often includes 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 Li-Fraumeni syndrome (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 Li-Fraumeni syndrome, 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.

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:

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"(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 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).

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 20-75)
- 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.

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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

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT01443468	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)	5000	(ongoing)*

NCT: national clinical trial.

*Ongoing-last update on clinicaltrials.gov website: May 2020

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Louisiana

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- 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
- Next Scheduled Review Date: 10/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of

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Louisiana

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descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	0102U, 81404, 81405, 81479 Codes added 1/1/2021: 81351, 81352, 81353
HCPCS	No codes
ICD-10 Diagnosis	Z15.01

*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

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Louisiana

Genetic Testing for Li-Fraumeni Syndrome

Policy # 00424

Original Effective Date: 07/16/2014

Current Effective Date: 11/09/2020

- 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.

****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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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.

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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.

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