Genetic Testing for Li-Fraumeni Syndrome

Policy # 00424
Original Effective Date: 07/16/2014
Current Effective Date: 12/11/2023

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

  - 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
  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).
- Pediatric hypodiploid acute lymphoblastic leukemia diagnosed before 21 years of age (see Policy Guidelines); OR
- Targeted TP53 familial variant testing in an individual from a family with a known *TP53* pathogenic or likely pathogenic variant; OR
- Individual with cancer with pathogenic or likely pathogenic TP53 variant identified on tumor-only genomic testing, germline testing can be considered for:
  - Those meeting one or more of the other Li-Fraumeni Syndrome criteria based on personal and family history; or
  - Those diagnosed age <30 years with any cancer; or
  - Those not meeting criteria but warranting germline evaluation per clinician discretion.

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-penetrance 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.

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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.***
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.***

When Services Are Considered Not Covered

Based on review of available data, the Company considers repeat germline testing to be **not covered****.

Note: *Repeat germline testing that investigates the same genetic information is not reasonable and necessary as it is duplicative and not required for medical treatment decisions. Examples of germline tests include, but are not limited to, single gene testing, gene panel tests, and whole exome or whole genome sequencing for inherited disorders.*

Policy Guidelines

The NCCN Pediatric Acute Lymphoblastic Leukemia panel considers "pediatric" to include any patient age ≤18 years, as well as adolescent and young adult (AYA) patients >18 years treated in a pediatric oncology setting; the latter could include patients up to age 30 years.

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.

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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

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 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 premenopausal breast cancer, bone and soft tissue sarcomas, central nervous system (CNS) tumor, adrenocortical carcinoma, hypodiploid acute lymphoblastic leukemia, unusually early onset of other adenocarcinomas, or other childhood cancers. Sarcoma, breast cancer, adrenocortical tumors, and certain brain tumors have been referred to as the "core" cancers of LFS since they account for the majority of cancers observed in individuals with germline *TP53* pathogenic and likely pathogenic variants. 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%.[3,] 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 years, 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 years and continues into older adulthood.

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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
- 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.

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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 years.[3,] 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 *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. The 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.

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.

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.

Summary of Evidence
For individuals with suspected Li-Fraumeni syndrome (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. A frequency of *TP53* alterations upwards of 90% has been identified in individuals with low hypodiploid acute lymphoblastic leukemia (ALL), with nearly half suspected of germline pathogenic alterations; and, nearly 30% of non-subtyped pediatric hypodiploid ALL having germline pathogenic*TP53* alterations. No reports of germline*TP53* pathogenic variants were identified among adult-onset hypodiploid ALL. 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 an 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 an 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.1.2023) indicate that, in general, testing criteria for high-penetrance breast and/or ovarian cancer susceptibility genes specifically includes "BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53 " (CRIT- 2). 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- 7):

- 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
- Pediatric hypodiploid acute lymphoblastic leukemia
- 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.

The NCCN guidelines (v. 2.2024) on hereditary cancer testing criteria for Li-Fraumeni syndrome indicate that testing is clinically indicated in the following scenarios:

- Individual from a family with a known *TP53* P/LP variant
- Classic Li-Fraumeni syndrome (LFS) criteria:
  - Combination of an individual diagnosed at age <45 years with a sarcoma *AND*
  - A first-degree relative diagnosed at age <45 years with cancer *AND*
  - An additional first- or second-degree relative in the same lineage with 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, central nervous system (CNS) tumor, breast cancer, adrenocortical carcinoma [ACC]), before 46 years of age, AND at least one first- or second-degree relative with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) before the age of 56 years or with multiple primaries at any age OR
  - Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 years OR
  - Individual with ACC, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of family history OR
  - Breast cancer before 31 years of age
- Personal or family history of pediatric hypodiploid acute lymphoblastic leukemia
- In individuals with cancer with a P/LP *TP53* variant identified on tumor-only genomic testing, germline testing should be considered for:
  - Those meeting one or more of the other LFS testing criterion above after reevaluation of personal and family history
  - Those diagnosed age <30 years with any cancer
  - Those with clinical scenario not meeting these criteria but warranting germline evaluation per clinician discretion.

American Association for Cancer Research

In 2017, the American Association for Cancer Research published recommendations for cancer screening and surveillance for patients with LFS.[20,] 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 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 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)
- 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

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01443468	Clinical, Epidemiologic, and Genetic Studies of Li-Fraumeni Syndrome	5000	(recruiting)*
NCT04541654	Li-Fraumeni & TP53: Understanding and Progress (LiFT UP)	1500	Dec 2025

NCT: national clinical trial.
*last update on clinicaltrials.gov website: May 2023; no estimated completion date listed.

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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
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
11/09/2022	Medical Policy Implementation Committee approval. Criteria revised due to Senate bill update.
11/02/2023	Medical Policy Committee review

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11/08/2023 Medical Policy Implementation Committee approval. Added the following to patient selection criteria for TP53 genetic testing: Individual with cancer with pathogenic or likely pathogenic TP53 variant identified on tumor-only genomic testing, germline testing can be considered for:

- Those meeting one or more of the other Li-Fraumeni Syndrome criteria based on personal and family history; or
- Those diagnosed age <30 years with any cancer; or
- Those not meeting criteria but warranting germline evaluation per clinician discretion.

Added a When services are not covered section for repeat germline testing and a note to the policy. Also updated policy guidelines and NCCN guidelines.

Next Scheduled Review Date: 11/2024

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 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Genetic Testing for Li-Fraumeni Syndrome

Policy # 00424
Original Effective Date: 07/16/2014
Current Effective Date: 12/11/2023

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	0129U, 81351, 81352, 81353, 81432, 81433, 81479 Delete codes effective 01/01/2023: 0102U, 81404, 81405
HCPCS	No codes
ICD-10 Diagnosis	All related Diagnoses

*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;

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.

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.

NOTICE: 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 eligibility for coverage.