FEP Medical Policy Manual

FEP 2.04.101 Genetic Testing for Li-Fraumeni Syndrome

Annual Effective Policy Date: October 1, 2025

Original Policy Date: December 2014

Related Policies:

None

Genetic Testing for Li-Fraumeni Syndrome

Description

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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.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing improves the net health outcome in individuals with suspected Li-Fraumeni syndrome and asymptomatic individuals with family members with Li-Fraumeni syndrome.

POLICY STATEMENT

Genetic testing for *TP53* may be considered **medically necessary** to confirm a diagnosis of Li-Fraumeni syndrome under the following conditions:

- In an individual who meets either the classic or the Chompret clinical diagnostic criteria for Li-Fraumeni syndrome, or
- In individuals with early-onset breast cancer (age of diagnosis <31 years), or
- In pediatric hypodiploid acute lymphoblastic leukemia (see Policy Guidelines).

Targeted *TP53* familial variant testing may be considered **medically necessary** in an at-risk relative of a proband with a known *TP53* pathogenic variant.

Genetic testing for a germline *TP53* variant is considered **investigational** for all other indications (see Policy Guidelines).

POLICY GUIDELINES

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

This reference medical policy addresses germline testing for *TP53* and does not address somatic testing. Somatic *TP53* variants found on tumor testing are common across many types of cancers. According to the National Comprehensive Cancer Network (NCCN), the finding of somatic *TP53* variant(s) on tumor testing would support genetic counseling for assessment of risk for germline alterations associated with Li-Fraumeni Syndrome.

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

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-AMPStandards 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

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.
Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. 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.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

RATIONALE

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 pathogenicTP53 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.

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. Recommendations for cancer surveillance were updated and published in 2025.The following surveillance protocols were recommended for children (birth to age 18) and adults.[21,]

For children:

- Complete physical examination with complete blood count every 3 to 4 months ;
- Prompt assessment with primary care physician for any medical concerns;
- Abdominal and pelvic ultrasound every 3 to 4 months;
- Annual skin evaluation;

- Annual brain magnetic resonance imaging (MRI);
- Annual whole-body MRI (WBMRI).

For adults:

- Complete physical examination every 6 months;
- Complete blood count with differential every 3 to 4 months;
- Prompt assessment with primary care physician for any medical concerns;
- Breast awareness and annual self-exam (age 18 years onward);
- Annual breast MRI screening (age 20 onward);
- Annual mammogram (age 30 onward, can consider alternating breast MRI and mammogram);
- Consider risk-reducing bilateral mastectomy;
- Annual brain MRI (age 18 years onward);
- Annual WBMRI;
- Abdominal and pelvic ultrasound every 6 months;
- Upper endoscopy and colonoscopy every 2 to 5 years (age 25 years onward);
- Annual serum prostate-specific antigen (age 35 years onward);
- Annual dermatologic examination.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines on genetic or familial high-risk assessment of breast, ovarian, pancreatic, and prostate cancer (v.3.2025) indicate that, in general, testing criteria for high-penetrance breast and/or ovarian cancer susceptibility genes specifically includes "*BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11*, and *TP53*" (CRIT-2).[3,] 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.

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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2014	New policy	
March 2017	Replace policy	Policy updated with literature review. References 3, 7, and 12-14 added. Policy statements unchanged.
September 2017	Replace policy	Policy updated with literature review through May 25, 2017; reference 12 added. Policy revised with updated genetics nomenclature. Policy statement updated for early-onset breast cancer to align with NCCN age cutoff of "<31 years,. Clinical criteria removed from the Policy Guidelines section as it is repeated in the text.
September 2018	Replace policy	Policy updated with literature review through May 10, 2018; references 9, 13, 15-16, and 18 added. Policy statements unchanged except "at-risk relative, statement removed due to benefit considerations.
September 2019	Replace policy	Policy updated with literature review through May 29, 2019; reference 19 added. Policy statements unchanged.
September 2020	Replace policy	Policy updated with literature review through June 2, 2020; NCCN guideline updated. Policy statements unchanged.
September 2021	Replace policy	Policy updated with literature review through May 20, 2021; references added and updated. Policy statements unchanged.
September 2022	Replace policy	Policy updated with literature review through May 25, 2022; references added. Minor editorial refinements to policy statements; intent unchanged.
September 2023	Replace policy	Policy updated with literature review through May 23, 2023; references added. Policy statement updated to add pediatric hypodiploid acute lymphoblastic leukemia as a criteria for genetic testing for TP53; additional minor editorial refinements to policy statements.
September 2024	Replace policy	Policy updated with literature review through May 10, 2024; references added. No references added. FEP Effective 1/1/2024 Benefits are provided for medically necessary genetic testing for members requesting this service due to susceptibility or possible high-risk of disease once prior approval has been obtained.
September 2025	Replace policy	Policy updated with literature review through May 30, 2025; reference added. Policy statements unchanged.