BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.101 Genetic Testing for Li-Fraumeni Syndrome

Effective Policy Date: October 1, 2023

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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).

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 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.

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. 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 [1,].

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.

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.[2,] 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.[3,1,]

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.[8,] The Chompret criteria were updated in 2009 to assist in identifying families with milder phenotypes.[9,] 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.[4,3,1,]

National Comprehensive Cancer Network guidelines recommend *TP53* testing for individuals who meet classic LFS criteria and Chompret criteria.[1,]

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*.[3,] 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.[3,]

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.[2,3,]

BENEFIT APPLICATION

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.

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 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). [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- 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.

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.

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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.