

Genetic Testing for Li-Fraumeni Syndrome

Policy Number: AHS – M2081 – Genetic Testing for Li-Fraumeni Syndrome	Policy Revision Date: 10/15/2025 Initial Policy Effective Date: 12/01/2024
---	---

[POLICY DESCRIPTION](#) | [RELATED POLICIES](#) | [INDICATIONS AND/OR LIMITATIONS OF COVERAGE](#) | [TABLE OF TERMINOLOGY](#) | [SCIENTIFIC BACKGROUND](#) | [GUIDELINES AND RECOMMENDATIONS](#) | [APPLICABLE STATE AND FEDERAL REGULATIONS](#) | [APPLICABLE CPT/HCPCS PROCEDURE CODES](#) | [EVIDENCE-BASED SCIENTIFIC REFERENCES](#) | [REVISION HISTORY](#)

I. Policy Description

Li-Fraumeni syndrome (LFS) is an autosomal dominant cancer predisposition syndrome characterized by a wide range of malignancies that appear at an unusually early age and is generally associated with defects in the tumor protein p53 gene (*TP53*).¹⁻³

II. Related Policies

Policy Number	Policy Title
AHS-M2003	Genetic Testing for Breast, Ovarian, Pancreatic, and Prostate Cancers

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the “Applicable State and Federal Regulations” section of this policy document.

- 1) For individuals who have received genetic counseling and who have a close blood relative (see Note 1) with a *TP53* mutation (see Note 2), the following germline testing **MEETS COVERAGE CRITERIA**:
 - a) Testing restricted to the known familial mutation.
 - b) Comprehensive *TP53* gene sequencing when the specific *TP53* mutation is unknown.
- 2) For individuals who have received genetic counseling, germline testing for *TP53* mutations (single gene or multi-gene panel testing) **MEETS COVERAGE CRITERIA** under **any** of the following conditions:
 - a) For an individual who meets either the classic or the Chompret clinical diagnostic criteria for LFS:
 - i) Classic LFS is defined by the presence of **all** of the following criteria:
 - (a) An individual with a sarcoma before 45 years of age.
 - (b) Having a first-degree relative (see Note 1) with any cancer before 45 years of age.
 - (c) Having an additional first- or second-degree relative (see Note 1) with any cancer before 45 years of age, or a sarcoma at any age.
 - ii) Chompret clinical diagnostic criteria is defined by the presence of any **one** of the following:
 - (a) Individual with a tumor belonging to the LFS tumor spectrum (e.g., soft tissue sarcoma, osteosarcoma, central nervous system (CNS) tumor, breast cancer, adrenocortical

carcinoma) before 46 years of age **AND** at least one first- or second-degree relative (see Note 1) with a LFS tumor (except breast cancer if proband has breast cancer) before 56 years of age or with multiple tumors at any age.

- (b) Individual with multiple tumors (except multiple breast tumors), two of which belong to the LFS tumor spectrum described above, with the first tumor having occurred before 46 years of age.
 - (c) Individual with adrenocortical carcinoma (ACC), or choroid plexus tumor or rhabdomyosarcoma of embryonal anaplastic subtype, at any age, irrespective of family history.
 - (d) Individual was diagnosed with breast cancer before 31 years of age.
- b) For an individual with a personal or family history of pediatric hypodiploid acute lymphoblastic leukemia.
 - c) For individuals who have been diagnosed with any cancer before 30 years of age and for whom a pathogenic or likely pathogenic *TP53* variant has been identified on tumor-only genomic testing.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

- 3) For all other situations not addressed above, single gene testing for a germline *TP53* mutation **DOES NOT MEET COVERAGE CRITERIA.**

NOTES:

Note 1: Close blood relatives include first-degree relatives (e.g., parents, siblings, and children), second-degree relatives (e.g., grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings), and third-degree relatives (great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins).

Note 2: At the present time, there are no specific, evidence-based, standardized guidelines for recommendations of which “at risk” relatives should be tested. In relatives of an index case, the risk of having a pathologic mutation, and developing disease, is influenced by numerous factors that should be considered in evaluating risk:

1. Proximity of relation to index case (first-, second-, or third-degree)
2. Mode of inheritance of mutation (autosomal dominant versus autosomal recessive)
3. Degree of penetrance of mutation (high, intermediate or low)
4. Results of detailed pedigree analysis
5. De novo mutation rate

If a proband has a *TP53* mutation, the risk to the proband's offspring of inheriting the mutation is 50 percent. If a proband has a *TP53* mutation, the risk to other relatives may depend on the genetic status of the proband's parents (that is, it is not a de novo mutation in the proband). Most *TP53* mutations are inherited from one of a proband's parents. After a mutation has been identified in a proband, the

proband’s parent with any pertinent cancer history of family history should be tested first to establish the lineage of the mutation; otherwise, both parents should be tested. A family history could appear to be negative because of incomplete penetrance of the mutation, limited family members available for testing, early death of a parent, etc.

IV. Table of Terminology

Term	Definition
ACC	Adrenocortical carcinoma
ACMG	American College of Medical Genetics and Genomics
ASBRS	American Society of Breast Surgeons
<i>BAX</i>	<i>BCL2 associated x gene</i>
BC	Breast cancer
<i>BCL10</i>	<i>BCL10 immune signaling adaptor gene</i>
<i>BRCA 1</i>	<i>Breast cancer 1 gene</i>
<i>BRCA 2</i>	<i>Breast cancer 2 gene</i>
<i>CDKN2A</i>	<i>Cyclin dependent kinase inhibitor 2A gene</i>
<i>CHEK2</i>	<i>Checkpoint kinase 2 gene</i>
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid Services
CNS	Central nervous system
DNA	Deoxyribonucleic acid
ERN	European Reference Network
FDA	Food and Drug Administration
GIST	Gastrointestinal stromal cell tumors
LDT	Laboratory-developed test
LFL	Li-Fraumeni-like syndrome
LFS	Li-Fraumeni syndrome
LFSA	Li-Fraumeni Syndrome Association
NCCN	National Comprehensive Cancer Network
NORD	National Organization of Rare Diseases
<i>PALB2</i>	<i>Partner and localizer of BRCA2 gene</i>
PGV	Pathogenic germline variant
<i>PTEN</i>	<i>Phosphatase and tensin homolog gene</i>
PV	Pathogenic variant
<i>STK11</i>	<i>Serine/threonine kinase 11 gene</i>
<i>STS</i>	<i>Soft tissue sarcomas</i>
<i>TP53</i>	<i>Tumor protein p53 gene</i>
<i>TP63</i>	<i>Tumor protein p63 gene</i>

V. Scientific Background

Li-Fraumeni syndrome (LFS) is a rare cancer predisposition syndrome associated with a germline mutation in the tumor suppressor gene TP53 (tumor protein p53) on chromosome 17p13.1.⁴ This genetic mutation has an autosomal dominant pattern of inheritance with high penetrance. TP53 encodes for a ubiquitous transcription factor that is responsible for a complex set of critical regulatory functions that promote DNA repair and tumor suppression during episodes of cellular stress and DNA damage.⁵ Most TP53 mutations are clustered in the DNA-binding domain within specific codons, such as 175 and 248.⁶ TP53 mutations are often missense alterations⁷ that cause a change in one nucleotide and encode for a different amino acid than the one typically found in that location within the protein. Missense mutations are usually transcriptionally inactive leading to downstream events permissive for development of various malignancies throughout life; however, some reports have shown gain of function oncogenic effects in TP53.^{8,9}

Li-Fraumeni syndrome is characterized clinically by the development of cancers arising in multiple organ systems, often at a young age.¹⁰⁻¹⁷ These patients have a very high lifetime cumulative risk of developing malignancies and early-onset malignancies; around 50% of the individuals carrying mutations in TP53 will develop cancer by the age of 30 years.¹⁸⁻²⁰ While many tumor types can be seen in patients with LFS, four cancers (breast, sarcoma, brain, and adrenocortical carcinoma) comprise about 80% of LFS associated tumors.^{10,21-23}

Breast Cancer accounts for about 30% of all LFS-associated tumors.^{21,23} Individuals with LFS-associated breast cancer tend to present at an earlier age (in the 20s or early 30s) with more advanced stage disease at the time of initial diagnosis.²⁴ The ability to distinguish between a germline TP53 mutation (LFS) and a somatic TP53 pathogenic variant (TP53 mosaicism or clonal hematopoiesis) is very important for breast cancer patients and relatives and may help to determine the best method of treatment; “For PV [pathogenic variant] carriers in high-penetrance genes like BRCA1, BRCA2, and TP53, prophylactic mastectomy is often recommended and radiation therapy avoided when possible.”²⁵

Sarcomas account for about 30% of all LFS-associated tumors.^{21,23,26,27} Multiple types of soft tissue sarcomas and osteosarcoma are associated with LFS; but Ewing’s sarcoma, gastrointestinal stromal cell tumors (GIST), desmoid tumors, and angiosarcomas have not been reported in LFS patients.²³

Brain Tumors occur in approximately 14% of individuals with TP53 mutations.^{15,21,23,27} Glioblastomas/astrocytomas are the most common, but medulloblastoma, ependymoma, supratentorial primitive neuroectodermal tumors, and choroid plexus tumors may also be seen.^{15,28}

Adrenocortical Carcinoma (ACC) accounts for about seven percent of cancers in TP53 mutation carriers overall.^{21,27} While ACC has been diagnosed in individuals with LFS at a wide range of ages, it is considered a hallmark of LFS when diagnosed in childhood.^{21,27,29}

Other LFS Cancers

Beyond the four core LFS cancers, the next most frequently associated cancers include leukemia, lung, colorectal, skin, gastric, and ovarian.^{21,23,27,30-32} All cancer types are diagnosed at younger than average ages.

Over the years, several types of classifying systems have been developed for LFS diagnostic purposes (shown below in table 1). The classic LFS phenotype was clinically defined before the identification of

germline mutations in TP53; these criteria are the most stringent and are the ones used to make a clinical diagnosis of LFS (with or without the identification of a deleterious germline TP53 mutation).¹⁰ Further studies revealed that, although highly specific for TP53 germline mutations, these criteria fail to include many mutation-positive families. Broader criteria were developed by Birch and Eeles to identify families which are Li-Fraumeni-like (LFL).^{11,33} The most robust analysis of TP53 mutation carriers to date was performed in France by Bougeard, et al. (2008); these analyses helped to develop the most recent version of the Chompret criteria which can better identify families with milder phenotypes.^{21,35-37} The Chompret criteria for clinical diagnoses of LFS was shown to provide the highest positive predictive value and, when combined with the classic LFS criteria, provided the highest sensitivity for identifying individuals with LFS.^{34,37,38}

Table 1: Types of LFS classifying systems

Clinical criteria	Description
Classical LFS ¹⁰	I -sarcoma diagnosed in childhood/young adulthood (≤ 45 years) and II -first-degree relative with any cancer in young adulthood (≤ 45 years) and III -first- or second-degree relative with any cancer diagnosed in young adulthood (≤ 45 years) or sarcoma diagnosed at any age.
LFL – Birch ¹¹	I -childhood cancer (at any age) or sarcoma, CNS tumor, or ACC in young adulthood (≤ 45 years) and II -first- or second-degree relative with LFS-spectrum cancer (sarcoma, BC, CNS tumor, ACC, leukemia) at any age and III -first- or second-degree relative with any cancer diagnosed at age < 60 years.
LFL – Eeles 1 and 2 ³³	I -at least two first- or second-degree relatives with LFS-spectrum cancer (sarcoma, BC, CNS tumor, ACC, leukemia, melanoma, prostate cancer, pancreatic cancer) diagnosed at any age I -sarcoma diagnosed at any age and II -at least two other tumors diagnosed in one or more first- or second-degree relatives: BC at age < 50 years; CNS tumor, leukemia, ACC, melanoma, prostate cancer, pancreatic cancer at age < 60 years; or sarcoma at any age.
LFL – Chompret ³⁵	I -diagnosis of sarcoma, CNS tumor, BC, ACC at age < 36 years and II -first- or second-degree relative with any of the above cancers (except BC if proband had BC) or relative with multiple primary tumors at any age or III -multiple primary tumors, including two of the following: sarcoma, CNS tumor, BC, or ACC, with the first tumor diagnosed at age < 36 years regardless of family history; or IV -ACC at any age, regardless of family history.
LFL – Modified Chompret ^{34,38}	I -index case with LFS-spectrum cancer (sarcoma, BC, CNS tumor, ACC, leukemia, bronchioloalveolar carcinoma) occurring at age < 46 years and II -a first- or second-degree relative with LFS-spectrum cancer occurring at age < 56 years (except BC if the index case has BC as well), or multiple tumors; or III -index patient with multiple tumors, at least two of which are in the LFS spectrum, the first occurring at age < 46 years; or IV -ACC or choroid plexus carcinoma occurring at any age or BC occurring at age < 36 years without <i>BRCA1</i> or <i>BRCA2</i> mutations.
LFL – Revisiting Li-Fraumeni Syndrome	Familial presentation: proband with tumor belonging to LFS tumor spectrum (eg, premenopausal breast cancer, soft tissue sarcoma, osteosarcoma, CNS tumor, adrenocortical carcinoma) before age 46 yr, AND at least on first or

Clinical criteria	Description
from TP53 Mutation Carriers ³⁷	second-degree relative with LFS tumor (except breast cancer if proband has breast cancer) before age 56 yr or with multiple tumors; Multiple primitive tumors: Proband with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum and first of which occurred before age 46 yr. Rare tumors: patient with adrenocortical carcinoma, choroid plexus tumor or rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of family history; Early-onset breast cancer: Breast cancer before age 31 yr

ACC: adrenocortical carcinoma; BC: breast cancer; CNS: central nervous system; LFS: Li-Fraumeni syndrome; LFL: Li-Fraumeni-like syndrome.

As noted above, the TP53 gene has an autosomal dominant pattern of inheritance.¹ Mutations such as this can be studied with a pedigree, which is a genetic based family tree. Pedigrees begin with the “proband,” which is the subject being studied or tested. If one of the proband’s parents carries the TP53 mutation, each sibling has a 50% risk of having the mutation. If neither parent is found to carry the mutation, the risk to siblings is low, but they should be tested due to the possibility of germline mosaicism. Offspring of a proband have a 50% risk of carrying the mutation. Phenotypes of families carrying TP53 mutations can be highly variable.^{2,39}

Additionally, mutations in TP53 can lead to different consequences on gene function. A locus is a fixed position on a chromosome where a gene is located. The possibility of a second locus involved in LFS is an additional issue in the etiology of the syndrome since approximately 20% of LFS and up to 80% of LFL families do not exhibit TP53 mutations.^{2,39} However, no association was found with p53 partners in tumor suppressor pathways, including BAX (BCL2 Associated X),⁴⁰ CDKN2A (Cyclin Dependent Kinase Inhibitor 2A),⁴¹ TP63 (tumor protein p63),³⁶ CHEK2 (Checkpoint kinase 2),³⁶ BCL10 (BCL10 Immune Signaling Adaptor),⁴² or PTEN (Phosphatase and tensin homolog)⁴³ in TP53-negative families. Although a few studies have linked other loci to LFS,^{44,45} TP53 remains the only gene conclusively associated to the syndrome.¹

Large panels or single gene tests can be used to identify a TP53 pathogenic variant. For example, Invitae has developed a test which analyzes only the TP53 gene with a three mL whole blood sample; this test has a turnaround time of 10-21 days.⁴⁶ Blueprint Genetics has developed a similar one gene panel test which also analyzes the TP53 gene in three to four weeks.⁴⁷

It is common to find TP53 mutations during tumor profiling, but germline mutations are very rare. Germline testing is not recommended if somatic mutations in TP53 are found unless there is a defined personal or family history indicative of Li-Fraumeni syndrome.⁴⁸

Clinical Utility and Validity

The reported percentage of LFS due to TP53 mutation varies between studies and criteria used. According to Schneider, et al. (2013), approximately 80 percent of individuals with features of LFS will have an identifiable TP53 mutation. Families that have clinical features of LFS without TP53 mutation are more likely to have a different hereditary cancer syndrome.²⁰ Some studies have reported that 70% to 80% of families meeting the classic LFS criteria have the TP53 mutation.^{49,50} However, Gonzalez, et al. (2009) reported that a slightly lower positive predictive value for the p53 mutation rate using the classic criteria among 341 patients (56%), with high specificity of 91% but low sensitivity (40%). Chompret, et

al. (2001) reported TP53 mutations can be found in 20% of cases using the Chompret criteria. Gonzalez, et al. (2009) reported a higher positive predictive value for LFL syndrome using Chompret criteria (35%) than Birch (16%) or Eeles (14%).

Gonzalez, et al. (2009) used a clinical testing cohort to understand the spectrum of tumors associated with germline p53 mutations. Mutations were identified in 17% (91 of 525) of patients submitted for testing. All families with a p53 mutation had at least one family member with a sarcoma, breast, brain, or adrenocortical carcinoma. Overall, 75 patients with a p53 mutation had an adequate family history, and out of these 75, 71 fulfilled the classic LFS or Chompret criteria. When the classic LFS and Chompret criteria were used together, the testing sensitivity was 95%, and the specificity was 52%.²¹

Villani, et al. (2011) assessed the feasibility and clinical impact of a comprehensive surveillance protocol in asymptomatic TP53 mutation carriers in eight families with LFS. A total of 33 TP53 mutation carriers were identified, 18 of whom underwent surveillance. In the surveillance group, 10 tumors developed in seven patients, and all seven patients were alive after a median follow-up of 24 months. In the non-surveillance group, 12 tumors developed in 10 patients, and only two were alive after 24 months. The authors reported a three-year overall survival of 100% in the surveillance group compared to 21% in the non-surveillance group.⁵¹

Bougeard, et al. (2015) evaluated the genetic spectrum of LFS. The authors identified 415 TP53 mutation carriers with 133 different TP53 mutations. A total of 322 of these carriers were affected and eventually developed 552 tumors. In childhood, the LFS tumor spectrum was as follows: “osteosarcomas, adrenocortical carcinomas, central nervous system (CNS) tumors, and soft tissue sarcomas (STS) observed in 30%, 27%, 26%, and 23% of the patients, respectively.” Adults presented with breast carcinomas in 79% of females and with soft tissue sarcomas in 27% of overall patients. Age of onset varied according to type of mutation; carriers with dominant-negative missense mutations had a mean onset of 21.3 years, carriers with loss of function mutations had a mean onset of 28.5 years, and carriers with genomic rearrangements had a mean onset of 35.8 years. The authors suggested that stratifying clinical management of LFS by class of mutation may be useful.³⁷

In 2016, Villani, et al. (2016) updated their assessment of a prospective observational study and modified the surveillance protocol. Out of the 89 carriers of TP53 pathogenic variants in 39 unrelated families, 40 (45%) agreed to surveillance and 49 (55%) declined surveillance. The authors reported a five-year overall survival was 88.8% in the surveillance group and 59.6% in the non-surveillance group.⁶

Rana, et al. (2018) compared the histories of patients whose TP53 mutations (TP53+) were identified by panel testing to those whose mutations were identified by single-gene testing. A total of 126 TP53+ patients were identified with panel testing, and 96 were identified with single-gene testing. The patients who were identified with panel testing were older at “first cancer identification” and at cancer diagnosis. Established LFS testing criteria were met less often in patients in the panel testing cohort, and phenotypes of the panel testing cohort were often different from those in the single-gene cohort.⁵²

Bakhuizen, et al. (2019) completed a nation-wide analysis in the Netherlands which measured TP53 germline mutations in early-onset breast cancer cases. This study included data from 370 individuals diagnosed with breast cancer between 2005 and 2016 who were younger than 30 years at the time of diagnosis. All individuals included in the study were tested for TP53 genetic mutations. A total of eight of these individuals were found to carry a likely pathogenic TP53 sequence (less than one percent), showing the rarity of a TP53 mutation in breast cancer cases. However, the researchers note that TP53

mutation prevalence was similar or greater in other studies which included patients with an older age of onset, questioning whether an early age of onset is necessary as a TP53 genetic testing criterion.⁵³

Lincoln, et al. (2020) studied the yield and utility of germline genetic testing following tumor DNA sequencing in patients with cancer. Germline testing was performed on 2023 patients and the prevalence of pathogenic germline variants (PGVs) was calculated. PGVs were found in 617 of the 2023 patients associated with cancers of the breast, colorectal, renal, lung, and bladder. About 82% of the patients identified with a PGV met the criteria for follow-up testing and 8.1% of PGVs were missed by tumor sequencing. Only four percent of pathogenic TP53 variants were germline, but 64% of the germline TP53 carriers did not meet the Chompret criteria for germline TP53 testing. It was found that genes which frequently acquire somatic mutations were a challenge because clinicians assumed TP53 to be somatic, so TP53 variants identified by tumor germline sequencing were underreported. The authors conclude that although the yield of germline findings of the TP53 gene is relatively low, the clinical impact can be substantial. Therefore, they recommend broader germline testing for these genes despite the low yield.⁵⁴

Terradas, et al. (2021) studied TP53 variants that were detected in colorectal cancer patients without a LFS phenotype. A total of 473 patients with colorectal cancer were assessed for TP53 pathogenic variants. Pathogenic variants were identified in 0.05% of the control and 0.26% of the colorectal cancer patients, none of whom fulfilled the clinical criteria for TP53 testing. The authors conclude that "TP53 pathogenic variants should not be unequivocally associated with LFS. Prospective follow-up of carriers of germline TP53 pathogenic variants in the absence of LFS phenotypes will define how surveillance and clinical management of these individuals should be performed."⁵⁵

Yamamoto, et al. (2020) performed an analysis of 194 patients with advanced cancer who had undergone next-generation sequencing (NGS) performed only on tumor specimens. The goal was to identify variants that had the potential to be secondary findings. Out of 194 patients, 120 were identified with possible secondary findings. The gene with the highest incidence was TP53, with a total of 97 variants identified among 91 patients. Of these patients, nine had additional germline testing performed, with 14 variant genes involved (BRCA1, n = 1; BRCA2, n = 2; PTEN, n = 2; RB1, n = 1; SMAD4, n = 1; STK11, n = 1; TP53, n = 6). Those persons identified with TP53 variants were confirmed as somatic variants, as opposed to germline. The authors concluded, "We analyzed 24 patients with TP53 variants who underwent a paired tumor–normal NGS assay. As expected, all TP53 variants were confirmed to be somatic variants. A total of 30 patients were tested for germline variants in TP53, but none of them resulted in true SFs, suggesting the low prevalence of SFs in this gene."⁵⁶

Patel, et al. (2022) studied the clinical utility of widespread germline testing of cancer patients outside of guidelines. The goal of the study was to diversify the research area, as past studies on cancer screening have "skewed towards wealthier socioeconomic populations that lack ethnic diversity." The authors conducted a single center prospective study on germline testing, aiming to "understudied real-world populations." The study included 67 patients, reported as "African American (14), White (50), or Asian American (3)." All patients were outside of guideline concordance for genetic testing due to either young age, rare tumors, or recurrent or multiple malignancies. There were 11 pathogenic or likely pathogenic variants that increased susceptibility to cancer, including rare germline findings and LFS. The authors concluded that "current practice of guidelines and genetic counselor recommended testing should be re-examined for broader testing for all incoming cancer patients in a more inclusive manner."⁵⁷

VI. Guidelines and Recommendations

National Comprehensive Cancer Network (NCCN)

The NCCN maintains guidelines for the diagnosis and management of Li-Fraumeni Syndrome.²⁴

NCCN recommends testing for Li-Fraumeni Syndrome in the following situations:

- Individual from a family with a known *TP53* pathogenic/likely pathogenic variant
- Classic Li-Fraumeni syndrome criteria
- Chompret criteria
- Personal or family history of pediatric hypodiploid acute lymphoblastic leukemia
- In individuals with cancer with a pathogenic/likely pathogenic *TP53* variant identified on tumor only genomic testing, germline testing should be considered for:
 1. Those meeting one or more of the other LFS testing criterion above after reevaluation of personal and family history
 2. Those diagnosed age <30 with any cancer
 3. Those with clinical scenario not meeting these criteria but warranting germline evaluation per clinician discretion

The classic Li-Fraumeni syndrome criteria are as follows:

- “Combination of an individual diagnosed age <45 y with a sarcoma AND
- A first-degree relative diagnosed age <45 y with cancer AND
- An additional first- or second-degree relative in the same lineage with cancer diagnosed <45 y, or a sarcoma at any age.”²⁴

The Chompret criteria are as follows:

- “Individual with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma [ACC]) before 46 y 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) at age <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 at age <46 years OR
- Individual with adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of family history OR
- Breast cancer diagnosed at age <31 years”²⁴

If these criteria are fulfilled, the *TP53* gene may be tested. If the familial pathogenic variant of *TP53* is known, that variant may be tested for. If it is unknown, a comprehensive *TP53* test may be done.

Reproductive options:

- “For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic diagnosis and donor gametes. Discussion should include known risks, limitations, and benefits of these technologies.”²⁴

For relatives:

- “Advise about possible inherited cancer risk to relatives, and options for risk assessment, testing, and management.
- Counselor should discuss the importance of genetic counseling and testing for relatives who also may be at increased risk.”²⁴

Children (under 18 years):

“Genetic testing is generally not recommended when results would not impact medical management.”²⁴

American College of Medical Genetics and Genomics (ACMG)

The ACMG has noted *TP53* as a gene whose secondary findings should be reported if found.⁵⁸ In 2021, a joint ACMG/AMP variant interpretation guideline was published for germline *TP53* variants; the authors note that “intense” cancer surveillance for those patients with *TP53* germline pathogenic variants can lead to “reduced cancer-related mortality.”⁵⁹

Li-Fraumeni Syndrome Association (LFSA)

The LFSA notes certain criteria that can be used to determine if genetic testing should be performed. The classic LFS criteria, Chrompret criteria, Birch definition of Li-Fraumeni-like syndrome, and Eeles definition of Li-Fraumeni-syndrome may all be fulfilled to consider genetic testing.⁶⁰ The association goes on to add that the potential of genetic testing (and the implications of the results) should always involve discussions with a genetic counselor, medical providers, and family.⁶⁰

National Organization of Rare Diseases (NORD)

The NORD states that “Li-Fraumeni syndrome is diagnosed based on the presence of a so called pathogenic or likely pathogenic variant in the *TP53* gene.”; further, “The potential of genetic testing (and the implications of the results) should always involve discussions with a genetic counselor, medical providers, and family.”⁶¹ The NORD also notes that genetic testing can be considered based on classic LFS criteria, Chrompret criteria, the Birch definition of Li-Fraumeni-like syndrome, and the Eeles definition of Li-Fraumeni-syndrome.⁶¹

American Society of Breast Surgeons (ASBrS)

The ASBrS have published consensus guidelines on genetic testing for hereditary breast cancer. These guidelines state that “Increased access to testing would likely lead to more patients pursuing testing and improving rates of identification of gene carriers. Breast surgeons are well positioned to be a resource for patients who may benefit from testing. Breast surgeons can identify individuals who are suitable for testing, inform patients of the risks and benefits, provide access to genetic testing, and discuss risk management strategies for those patients who test positive. For patients with less common mutations, strong consideration should be given to consultation with cancer genetics specialists. Hereditary mutations to be considered include *BRCA 1&2*, *PALB2*, and other hereditary breast cancer syndromes, which include but are not limited to Li-Fraumeni syndrome (*TP53* pathogenic variant), Cowden syndrome (*PTEN* pathogenic variant), hereditary diffuse gastric cancer syndrome (*CDH1* pathogenic variant), and Peutz-Jeghers syndrome (*STK11* pathogenic variant).”⁶²

European Reference Network (ERN) GENTURIS

The ERN provides recommendations on cancer patients who should be tested for *TP53* germline mutations. They recommend testing the following patients:

- Patients who meet the Chompret Criteria. These include those with familial presentation, multiple primitive tumors, rare tumors such as adrenocortical carcinoma, choroid plexus carcinoma, or rhabdomyosarcoma, or very early-onset breast cancer (Breast cancer before 31 years, irrespective of family history)
- Patients who are children or adolescents presenting with hypodiploid acute lymphoblastic leukemia, unexplained sonic hedgehog-driven medulloblastoma, or Jaw osteosarcoma.
- Patients who develop a second primary tumour, within the radiotherapy field of a first core *TP53* tumor which occurred before 46 years, should be tested for germline *TP53* variants
- Children with any cancer from southern and south-eastern Brazilian families should be tested for the p.R337H Brazilian founder germline *TP53* variant.⁶³

The ERN does not recommend testing “patients older than 46 years presenting with breast cancer without personal or familial history fulfilling the ‘Chompret Criteria’.” If a patient with isolated breast cancer does not fulfill the Chompret Criteria but has a *TP53* variant, the patient should be referred to an expert multidisciplinary team for discussion.⁶³

The ERN also provides testing recommendations for pre-symptomatic individuals. They recommend that:

- “Adult first-degree relatives of individuals with germline disease causing *TP53* variants should be offered testing for the same germline *TP53* variant.
- Testing in childhood of first-degree relatives of individuals with germline disease-causing *TP53* variants should be systematically offered, if database shows that the variant can be considered as a high cancer risk *TP53* variant conferring a high cancer risk in childhood.”⁶³

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <http://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81351	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence

81352	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)
81353	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; known familial variant
81479	Unlisted molecular pathology procedure

Current Procedural Terminology[®] American Medical Association. All Rights reserved.

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Evidence-based Scientific References

1. Evans DG, Hanson H. Li-Fraumeni syndrome. Updated March 13, 2024. <https://www.uptodate.com/contents/li-fraumeni-syndrome>
2. Malkin D. Li-fraumeni syndrome. *Genes & cancer*. Apr 2011;2(4):475-84. doi:10.1177/1947601911413466
3. Mai PL, Best AF, Peters JA, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. *Cancer*. Dec 01 2016;122(23):3673-3681. doi:10.1002/cncr.30248
4. Correa H. Li-Fraumeni Syndrome. *Journal of pediatric genetics*. Jun 2016;5(2):84-8. doi:10.1055/s-0036-1579759
5. Sorrell AD, Espenschied CR, Culver JO, Weitzel JN. TP53 Testing and Li-Fraumeni Syndrome: Current Status of Clinical Applications and Future Directions. *Mol Diagn Ther*. Feb 2013;17(1):31-47. doi:10.1007/s40291-013-0020-0
6. Villani A, Shore A, Wasserman JD, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. *The Lancet Oncology*. Sep 2016;17(9):1295-305. doi:10.1016/s1470-2045(16)30249-2
7. Petitjean A, Mathe E, Kato S, et al. Impact of mutant p53 functional properties on TP53 mutation patterns and tumor phenotype: lessons from recent developments in the IARC TP53 database. *Human mutation*. Jun 2007;28(6):622-9. doi:10.1002/humu.20495
8. Sigal A, Rotter V. Oncogenic mutations of the p53 tumor suppressor: the demons of the guardian of the genome. *Cancer research*. Dec 15 2000;60(24):6788-93.
9. Brosh R, Rotter V. When mutants gain new powers: news from the mutant p53 field. *Nature reviews Cancer*. Oct 2009;9(10):701-13. doi:10.1038/nrc2693
10. Li FP, Fraumeni JF, Jr., Mulvihill JJ, et al. A cancer family syndrome in twenty-four kindreds. *Cancer research*. Sep 15 1988;48(18):5358-62.
11. Birch JM, Hartley AL, Tricker KJ, et al. Prevalence and diversity of constitutional mutations in the p53 gene among 21 Li-Fraumeni families. *Cancer research*. Mar 01 1994;54(5):1298-304.
12. Garber JE, Goldstein AM, Kantor AF, Dreyfus MG, Fraumeni JF, Jr., Li FP. Follow-up study of twenty-four families with Li-Fraumeni syndrome. *Cancer research*. Nov 15 1991;51(22):6094-7.
13. Birch JM, Blair V, Kelsey AM, et al. Cancer phenotype correlates with constitutional TP53 genotype in families with the Li-Fraumeni syndrome. *Oncogene*. Sep 03 1998;17(9):1061-8. doi:10.1038/sj.onc.1202033
14. Malkin D, Li FP, Strong LC, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science (New York, NY)*. Nov 30 1990;250(4985):1233-8. doi:10.1126/science.1978757
15. Ruijs MW, Verhoef S, Rookus MA, et al. TP53 germline mutation testing in 180 families suspected of Li-Fraumeni syndrome: mutation detection rate and relative frequency of cancers in different familial phenotypes. *J Med Genet*. 2010:421-8. vol. 6.

16. Olivier M, Hollstein M, Hainaut P. TP53 mutations in human cancers: origins, consequences, and clinical use. *Cold Spring Harbor perspectives in biology*. Jan 2010;2(1):a001008. doi:10.1101/cshperspect.a001008
17. Mai PL, Malkin D, Garber JE, et al. Li-Fraumeni syndrome: report of a clinical research workshop and creation of a research consortium. *Cancer genetics*. Oct 2012;205(10):479-87. doi:10.1016/j.cancergen.2012.06.008
18. Hwang SJ, Lozano G, Amos CI, Strong LC. Germline p53 mutations in a cohort with childhood sarcoma: sex differences in cancer risk. *American journal of human genetics*. Apr 2003;72(4):975-83. doi:10.1086/374567
19. Lustbader ED, Williams WR, Bondy ML, Strom S, Strong LC. Segregation analysis of cancer in families of childhood soft-tissue-sarcoma patients. *American journal of human genetics*. Aug 1992;51(2):344-56.
20. Schneider K, Zelle K, Nichols KE, Garber J. Li-Fraumeni Syndrome. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. *GeneReviews*. University of Washington, Seattle; 2013. <https://www.ncbi.nlm.nih.gov/books/NBK1311/>
21. Gonzalez KD, Noltner KA, Buzin CH, et al. Beyond Li Fraumeni Syndrome: clinical characteristics of families with p53 germline mutations. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Mar 10 2009;27(8):1250-6. doi:10.1200/jco.2008.16.6959
22. Lynch HT, Mulcahy GM, Harris RE, Guirgis HA, Lynch JF. Genetic and pathologic findings in a kindred with hereditary sarcoma, breast cancer, brain tumors, leukemia, lung, laryngeal, and adrenal cortical carcinoma. *Cancer*. May 1978;41(5):2055-64.
23. Olivier M, Goldgar DE, Sodha N, et al. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. *Cancer research*. Oct 15 2003;63(20):6643-50.
24. NCCN. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 3.2025. Updated March 6, 2025. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf
25. Batalini F, Peacock EG, Stobie L, et al. Li-Fraumeni syndrome: not a straightforward diagnosis anymore-the interpretation of pathogenic variants of low allele frequency and the differences between germline PVs, mosaicism, and clonal hematopoiesis. *Breast Cancer Res*. Sep 18 2019;21(1):107. doi:10.1186/s13058-019-1193-1
26. Ognjanovic S, Olivier M, Bergemann TL, Hainaut P. Sarcomas in TP53 germline mutation carriers: a review of the IARC TP53 database. *Cancer*. Mar 01 2012;118(5):1387-96. doi:10.1002/cncr.26390
27. Palmero EI, Achatz MI, Ashton-Prolla P, Olivier M, Hainaut P. Tumor protein 53 mutations and inherited cancer: beyond Li-Fraumeni syndrome. *Current opinion in oncology*. Jan 2010;22(1):64-9. doi:10.1097/CCO.0b013e328333bf00
28. Farrell CJ, Plotkin SR. Genetic causes of brain tumors: neurofibromatosis, tuberous sclerosis, von Hippel-Lindau, and other syndromes. *Neurologic clinics*. Nov 2007;25(4):925-46, viii. doi:10.1016/j.ncl.2007.07.008
29. Herrmann LJ, Heinze B, Fassnacht M, et al. TP53 germline mutations in adult patients with adrenocortical carcinoma. *The Journal of clinical endocrinology and metabolism*. Mar 2012;97(3):E476-85. doi:10.1210/jc.2011-1982
30. Walsh T, Casadei S, Lee MK, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proceedings of the National Academy of Sciences of the United States of America*. Nov 01 2011;108(44):18032-7. doi:10.1073/pnas.1115052108
31. Masciari S, Dewanwala A, Stoffel EM, et al. Gastric cancer in individuals with Li-Fraumeni syndrome. *Genetics in medicine : official journal of the American College of Medical Genetics*. Jul 2011;13(7):651-7. doi:10.1097/GIM.0b013e31821628b6

32. Wong P, Verselis SJ, Garber JE, et al. Prevalence of early onset colorectal cancer in 397 patients with classic Li-Fraumeni syndrome. *Gastroenterology*. Jan 2006;130(1):73-9. doi:10.1053/j.gastro.2005.10.014
33. Eeles RA. Germline mutations in the TP53 gene. *Cancer surveys*. 1995;25:101-24.
34. Bougeard G, Sesboue R, Baert-Desurmont S, et al. Molecular basis of the Li-Fraumeni syndrome: an update from the French LFS families. *J Med Genet*. 2008;45(8):535-8. doi:10.1136/jmg.2008.057570
35. Chompret A, Abel A, Stoppa-Lyonnet D, et al. Sensitivity and predictive value of criteria for p53 germline mutation screening. *J Med Genet*. Jan 2001;38(1):43-7.
36. Bougeard G, Limacher JM, Martin C, et al. Detection of 11 germline inactivating TP53 mutations and absence of TP63 and HCHK2 mutations in 17 French families with Li-Fraumeni or Li-Fraumeni-like syndrome. *J Med Genet*. Apr 2001;38(4):253-7. doi:10.1136/jmg.38.4.253
37. Bougeard G, Renaux-Petel M, Flaman JM, et al. Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 20 2015;33(21):2345-52. doi:10.1200/jco.2014.59.5728
38. Tinat J, Bougeard G, Baert-Desurmont S, et al. 2009 version of the Chompret criteria for Li Fraumeni syndrome. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009;27(26):e108-9; author reply e110. doi:10.1200/jco.2009.22.7967
39. McBride KA, Ballinger ML, Killick E, et al. Li-Fraumeni syndrome: cancer risk assessment and clinical management. *Nature reviews Clinical oncology*. May 2014;11(5):260-71. doi:10.1038/nrclinonc.2014.41
40. Barlow JW, Mous M, Wiley JC, et al. Germ line BAX alterations are infrequent in Li-Fraumeni syndrome. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. Aug 2004;13(8):1403-6.
41. Portwine C, Lees J, Verselis S, Li FP, Malkin D. Absence of germline p16(INK4a) alterations in p53 wild type Li-Fraumeni syndrome families. *J Med Genet*. Aug 2000;37(8):E13. doi:10.1136/jmg.37.8.e13
42. Stone JG, Eeles RA, Sodha N, Murday V, Sheriden E, Houlston RS. Analysis of Li-Fraumeni syndrome and Li-Fraumeni-like families for germline mutations in Bcl10. *Cancer letters*. Dec 01 1999;147(1-2):181-5. doi:10.1016/S0304-3835(99)00291-8
43. Brown LT, Sexsmith E, Malkin D. Identification of a novel PTEN intronic deletion in Li-Fraumeni syndrome and its effect on RNA processing. *Cancer genetics and cytogenetics*. Nov 2000;123(1):65-8. doi:10.1016/S0165-4608(00)00303-4
44. Bachinski LL, Olufemi SE, Zhou X, et al. Genetic mapping of a third Li-Fraumeni syndrome predisposition locus to human chromosome 1q23. *Cancer research*. Jan 15 2005;65(2):427-31.
45. Aury-Landas J, Bougeard G, Castel H, et al. Germline copy number variation of genes involved in chromatin remodelling in families suggestive of Li-Fraumeni syndrome with brain tumours. *European journal of human genetics : EJHG*. Dec 2013;21(12):1369-76. doi:10.1038/ejhg.2013.68
46. Invitae. Invitae Li-Fraumeni Syndrome Test. <https://www.invitae.com/us/providers/test-catalog/gene-20572>
47. Blueprint. TP53 single gene test. <https://blueprintgenetics.com/tests/single-gene-tests/tp53-single-gene-test-2/>
48. Peshkin BNI, Claudine, . Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes. Updated Oct 31, 2024. <https://www.uptodate.com/contents/genetic-testing-and-management-of-individuals-at-risk-of-hereditary-breast-and-ovarian-cancer-syndromes>
49. Nagy R, Sweet K, Eng C. Highly penetrant hereditary cancer syndromes. *Oncogene*. Aug 23 2004;23(38):6445-70. doi:10.1038/sj.onc.1207714

50. Varley JM. Germline TP53 mutations and Li-Fraumeni syndrome. *Human mutation*. Mar 2003;21(3):313-20. doi:10.1002/humu.10185
51. Villani A, Tabori U, Schiffman J, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study. *The Lancet Oncology*. Jun 2011;12(6):559-67. doi:10.1016/s1470-2045(11)70119-x
52. Rana HQ, Gelman R, LaDuca H, et al. Differences in TP53 Mutation Carrier Phenotypes Emerge From Panel-Based Testing. *Journal of the National Cancer Institute*. Feb 26 2018;doi:10.1093/jnci/djy001
53. Bakhuizen JJ, Hogervorst FB, Velthuisen ME, et al. TP53 germline mutation testing in early-onset breast cancer: findings from a nationwide cohort. *Fam Cancer*. Apr 2019;18(2):273-280. doi:10.1007/s10689-018-00118-0
54. Lincoln SE, Nussbaum RL, Kurian AW, et al. Yield and Utility of Germline Testing Following Tumor Sequencing in Patients With Cancer. *JAMA Netw Open*. Oct 1 2020;3(10):e2019452. doi:10.1001/jamanetworkopen.2020.19452
55. Terradas M, Mur P, Belhadj S, et al. TP53, a gene for colorectal cancer predisposition in the absence of Li-Fraumeni-associated phenotypes. *Gut*. 2021;70(6):1139-1146. doi:10.1136/gutjnl-2020-321825
56. Yamamoto Y, Kanai M, Kou T, et al. Clinical significance of TP53 variants as possible secondary findings in tumor-only next-generation sequencing. *Journal of Human Genetics*. 2020/02/01 2020;65(2):125-132. doi:10.1038/s10038-019-0681-6
57. Patel KB, Oh WK, Jun T, et al. Clinical utility of widespread germline testing of cancer patients in a diverse community cancer clinic. *Journal of Clinical Oncology*. 2022;40(16_suppl):e18537-e18537. doi:10.1200/JCO.2022.40.16_suppl.e18537
58. Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genetics in medicine : official journal of the American College of Medical Genetics*. Feb 2017;19(2):249-255. doi:10.1038/gim.2016.190
59. Fortuno C, Lee K, Olivier M, et al. Specifications of the ACMG/AMP variant interpretation guidelines for germline TP53 variants. *Human mutation*. Mar 2021;42(3):223-236. doi:10.1002/humu.24152
60. LFSA. Criteria for LFS. Li-Fraumeni Syndrome Association. <https://www.lfsassociation.org/criteria-for-lfs/>
61. NORD. Li-Fraumeni Syndrome. Updated March 14, 2025. <https://rarediseases.org/rare-diseases/li-fraumeni-syndrome/>
62. Manahan ER, Kuerer HM, Sebastian M, et al. Consensus Guidelines on Genetic Testing for Hereditary Breast Cancer from the American Society of Breast Surgeons. *Ann Surg Oncol*. Oct 2019;26(10):3025-3031. doi:10.1245/s10434-019-07549-8
63. Frebourg T, Bajalica Lagercrantz S, Oliveira C, Magenheimer R, Evans DG. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes. *European journal of human genetics : EJHG*. Oct 2020;28(10):1379-1386. doi:10.1038/s41431-020-0638-4

X. Review/Revision History

Effective Date	Summary
10/15/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following changes were made for clarity and consistency: CC2.a.ii.a., changed “age 46 years” to “46 years of age” for consistency within and among criteria.

	Note 1, wrote out “first”, “second”, and “third” for consistency. Added CPT code 81479
12/01/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review necessitated the following changes to coverage criteria: Addition of “or family history” to CC2.b., now reads: “b) For an individual with a personal or family history of pediatric hypodiploid acute lymphoblastic leukemia.” Based on NCCN guideline updates, new CC2.c.: “c) For individuals who have been diagnosed with any cancer before 30 years of age and for whom a pathogenic or likely pathogenic TP53 variant has been identified on tumoronly genomic testing.”
12/01/2024	Initial Policy Implementation