Medical Policy

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Title: Genetic Testing for Li-Fraumeni Syndrome

Description/Background

TP53 Gene

The *TP53* gene contains the genetic instructions for the production of tumor protein p53. The p53 protein is a tumor suppressor that functions as a cell cycle regulator to prevent cells from uncontrolled growth and division when there is DNA damage. Somatic (acquired) pathogenic variants are one of the most frequent alterations found in human cancers. Germline (inherited) pathogenic variants in *TP53* are associated with Li-Fraumeni syndrome (LFS).

Li-Fraumeni Syndrome

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.[2.]

The tumor types most closely associated with LFS 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..[3.]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 1

study of 322 pathogenic variant carriers from France, Bougeard et al (2015) reported that 43% of individuals had multiple malignancies.[4]

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.[5] Women with LFS are at greatly increased risk of developing premenopausal breast cancer, with the median age of diagnosis being 33 years of age.[3] 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.[6]

Data from M.D. Anderson Cancer Center's long-term clinical studies of LFS have shown that the risk of developing soft tissue sarcomas is greatest before the age of 10, brain cancer appears to occur early in childhood with a smaller peak in risk in the fourth to fifth decade of life, risk for osteosarcoma is highest during adolescence, and breast cancer risk among females with LFS starts to increase significantly around age 20 and continues into older adulthood.[7]

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]

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.[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]

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,[10] but, in general, the strategy includes physical examination, colonoscopy, and breast imaging. Other protocols being evaluated include additional imaging techniques and biochemical assessment. National Comprehensive Cancer Network has consensus-based screening guidelines.

Testing Strategy

Given the common germline *TP53* variant types associated with LFS, a possible testing strategy to optimize yield would be:

1. Sequencing of the entire *TP53* coding region (exons 2 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.

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.

Medical Policy Statement

The safety and effectiveness of genetic testing for TP53 to confirm a diagnosis of Li-Fraumeni syndrome and pediatric hypoliploid acute lymphoblastic leukemia has been established. Genetic testing may be considered a useful diagnostic tool when indicated and should be performed in conjunction with appropriate pre-and post-test genetic counseling.

Inclusionary and Exclusionary Guidelines

Inclusions:

- 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
  - Pediatric hypodiploid acute lymphoblastic leukemia*
- For carrier or presymptomatic testing in relatives of individuals with known TP53 gene variants.

*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.

Exclusions:

Genetic testing for a germline *TP53* variant for all other indications.

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 (e.g., soft tissue sarcoma, osteosarcoma, CNS 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
- proband with breast cancer before age 31 years.[4,3]

TESTING CRITERIA FOR LI-FRAUMENI SYNDROME[a]

Testing is clinically indicated in the following scenarios:*
General Testing Criteria
• Individual from a family with a known TP53[cc] P/LP variant • Classic Li-Fraumeni syndrome (LFS) criteria:[dd] ◦ Combination of an individual diagnosed at age <45 years with a sarcoma[ee] **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:[gg,hh,ii] 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 years with any cancer 3. Those with clinical scenario not meeting these criteria but warranting germline evaluation per clinical discretion

[a] For further details regarding the nuances of genetic counseling and testing,
[cc] When this gene is included as part of a multi-gene panel, an individual does not need to meet these testing criteria if testing criteria on other testing criteria pages are met.
[dd] Li FP, et al. Cancer Res 1988;48:5358-5362.
[ee] In contrast to other types of sarcoma, germline TP53 P/LP variants are rare in those with Ewing sarcoma, gastrointestinal stromal tumor (GIST), desmoid tumor, or angiosarcoma.
* Other cancers associated with LFS but not in the testing criteria include: melanoma, colorectal, gastric, and prostate.
[ff] Chompret A, et al. J Med Genet 2001;38:43-47; Bougeard G, et al. J Clin Oncol 2015;33:2345-2352.
[gg] For testing in the pediatric setting, see Frebourg T, et al. Eur J Hum Genet 2020;28:1379-1386.
[hh] This should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing. Somatic TP53 P/LP variants are common in many tumor types in absence of a germline P/LP variant.
[ii] Mandelker D, et al. Ann Oncol 2019;30:1221-1231.

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

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81351 81352 81353 81432

Other codes (investigational, not medically necessary, etc.):

0102U* 0131U* 81479

*Proprietary panels are considered experimental/investigational until the laboratory test the code represents is formally documented as established in an interim Medical Policy or Joint Uniform Medical Policy document. Covered CPT codes may be used to represent and reimburse testing for incremental codes or multi-target codes.

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Testing for Suspected Li-Fraumeni Syndrome

Clinical Context and Test Purpose
The purpose of genetic testing for *TP53* in individuals with suspected Li-Fraumeni syndrome (LFS) by clinical criteria is to establish the genetic diagnosis of LFS to inform management decisions such as risk-reducing (prophylactic) mastectomies in women, avoidance of radiotherapy, cancer surveillance, and aid in reproductive planning.

The following **PICO** was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with suspected LFS by clinical criteria.

Interventions
The test being considered is genetic testing for *TP53*.

Comparators
The following practice is currently being used: standard clinical management without genetic testing.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, test accuracy and validity, changes in reproductive decision making, and resource utilization. The potential beneficial outcomes of primary interest include changes in management when test results are positive (i.e., risk-reducing mastectomies in women, avoidance of radiotherapy, increased cancer surveillance). The time frame for outcome measures varies from several years for the development of cancers to long-term survival as a result of cancer.

Study Selection Criteria
For the evaluation of clinical validity of the test, studies that meet the following eligibility criteria were considered:

- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
Approximately 80% of families with features of LFS will have an identifiable *TP53* pathogenic variant.[3,] Families that have no identifiable *TP53* pathogenic variant but share clinical features of LFS are more likely to have a different hereditary cancer syndrome (e.g., hereditary breast-ovarian cancer syndrome).

Observational Studies
Cohorts of individuals with adrenocortical carcinoma, which is diagnostic of LFS by the Chompret criteria, have been published.[11,12,13,] In a 2015 study, 88 consecutive patients with adrenocortical carcinoma were evaluated.[13,] Direct sequencing of exons 2 through 11 together with multiplex ligation-dependent probe amplification was used to identify pathogenic variants. For the entire population, 50% of individuals had a pathogenic variant detected. The detection rate varied by age, with 58% of individuals younger than 12 years of age having a pathogenic variant compared with 25% of individuals between ages 12 and 20.

Holmfeldt et al (2013) performed a genomic analysis of 124 cases of hypodiploid acute lymphoblastic leukemia (ALL) and identified 2 distinct subtypes of this malignancy: near haploid ALL and low hypodiploid ALL.[14,] Near haploid cases were defined as having 24–31 chromosomes, and low hypodiploid cases with 32–39 chromosomes. A high frequency of *TP53* alterations was identified in both pediatric and adult cases of low hypodiploid ALL (91.2% and 90.9%, respectively). Almost half (43.3%) of the *TP53* mutations in pediatric low hypodiploid ALL were present in non-tumor cells with many of the mutations previously reported as LFS associated mutations. All of the *TP53* mutations observed in adult cases were somatic.

The most comprehensive source of compiled data on the clinical validity of *TP53* pathogenic variants is found in the International Agency for Research on Cancer *TP53* Database (R18, April 2016), which has shown tumor types associated with *TP53* germline variants (see Table 1).[15] The main tumor types associated with *TP53* germline variants include breast, soft tissue, brain, adrenal gland, and bone tumor, which comprise 74% of all tumors with confirmed *TP53* germline variants.

Table 1. Tumors Associated With *TP53* Germline Variants (N=3034)

Tumor Type	No. With *TP53* Variant	Percentage With *TP53* Variant
Breast	700	27.55
Soft tissues	303	11.92
Brain	360	14.17
Adrenal gland	166	6.53
Bones	279	10.98
Hematopoietic/lymph nodes	129	5.08

Tumor Type	No. With *TP53* Variant	Percentage With *TP53* Variant
Colorectal	81	3.19
Lung	79	3.11
Ovary	30	1.18
Liver	27	1.07
Prostate	33	1.30
Skin	31	1.22
Stomach	77	3.03
Kidney	11	0.44
Pancreas	19	0.75
Not specified	136	5.35
Fibrosarcoma	13	4.3
Leiomyosarcoma	41	13.5
Liposarcoma	18	5.9
Rhabdomyosarcoma	116	38.3
Malignant fibrous histiocytoma	13	43
Other sarcoma	26	8.6
Sarcoma not otherwise specified	76	25.1
Astrocytoma	43	11.9
Choroid plexus carcinoma	46	12.8
Ependymoma	5	1.4
Glioblastoma/glioma	45	12.5
Medulloblastoma	41	11.4
Peripheral primitive neuroectodermal tumor	10	2.8
Other brain tumor	17	4.7
Cancer not otherwise specified	153	42.5

Adapted from Kratz et al (2021).[14,]

O'Shea et al (2018) retrospectively analyzed 123 individuals (118 women, 5 men) in Ireland undergoing full *TP53* sequencing.[16] Classic criteria for LFS or Li-Fraumeni like syndrome were met by 64 (52%) individuals, none of whom was *TP53*-positive. Of the 59 (48%) individuals who did not meet classic criteria, 2 had pathogenic *TP53* variants (3% detection rate), showing that broadened testing criteria may be beneficial. It was noted that the detection rate of this study (1.6%) was lower than those of similar studies, but the authors suggested that this might be due to the predominance of patients in this cohort with breast cancer, which has an associated lower detection rate.

Rana et al (2018) published a retrospective, single-laboratory analysis of 38,938 individuals who had undergone *TP53* testing to compare different phenotype manifestations found in *TP53*-positive individuals identified by single-gene testing and multigene panel testing (MGPT).[17] The differences included a significantly higher median age at first cancer for MGPT *TP53*-positive patients (n=126) than single-gene testing *TP53*-positive patients (n=96; women: median age, 36 vs 28 years; p<.001; men: median age, 40 vs 15 years; p<.004). For breast cancer specifically, median ages were 40 years and 33 years for MGTP *TP53*-positive and single-gene testing *TP53*-positive women, respectively (p<.001). Also, fewer MGPT *TP53*-positive patients met LFS testing criteria. The study: (1) lacked complete family histories, (2) enrolled predominantly women with breast cancer in the MGPT cohort, (3) used improved technology permitting detection of lower levels of *TP53* variants, possibly contributing to

misclassification, and (4) assessed a sample too small to investigate other possible factors for phenotypic variation.

Qian et al (2018) investigated germline *TP53* variants in childhood ALL.[18] Targeted sequencing of TP53 coding regions was performed for 3801 children participating in 2 ALL clinical trials. Within this cohort, 77 patients (2.0%) were found to have 49 unique nonsilent rare *TP53* coding variants, with 22 of these variants classified as pathogenic. Children with *TP53* pathogenic variants were more likely to have hypodiploid ALL 17/26 (65.4% vs. 1.2%; p<.001). Among the 64 hypodiploid ALL, 17 (27%) were found to have a pathogenic germline *TP53* alteration, versus 9/3737 (0.24%) of the non-hypodiploid ALL.

Tables 2 and 3 summarize key study characteristics and results.

Table 2. Summary of Key Observational Comparative Study Characteristics

Study	Type	Country	Dates	Participants	Treatment
Wasserman et al (2015)[13]	Cohort	United States, Canada	NR	88	*TP53* testing
O'Shea et al (2018)[16]	Retrospective	Ireland	2012-2014	123	*TP53* testing
Rana et al (2018)[17]	Retrospective	United States	2010-2014	38,938	*TP53* testing
Qian et al (2018)[18]	NR	NR	NR	3801	*TP53* testing

NR: not reported.

Table 3. Summary of Key Observational Comparative Study Results

Study	*TP53*-Positive, n (%)	LFS-Positive, n (%)	*TP53* Variants Detected (n)
Wasserman et al (2015)[13]	34 (50)		• *TP53* hotspot (2) • c.375G>A (3) • C229R (3) • deletion of exons 10 to 11 (2)
O'Shea et al (2018)[16]		64 (52)	• c.919+1G>A (1) • c.818G>A (1)
Rana et al (2018)[17]	132 (4.1)		• *TP53* VUS (38)
Qian et al (2018)[18]	77 (2)		• Pathogenic (22) • VUS (27)

LFS: Li-Fraumeni syndrome; VUS: variants of uncertain significance.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive

correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Direct evidence for the clinical utility of genetic testing to confirm a diagnosis of LFS is lacking.

Qian et al (2018), introduced above, investigated *TP53* variants in childhood ALL.[18] When comparing children with ALL to non-ALL controls, the investigators found a significantly higher prevalence of *TP53* pathogenic variants in the ALL group (odds ratio, 5.2; p<.001). Furthermore, the presence of *TP53* pathogenic variants in children with ALL was associated with several significant findings. These children were more likely to have hypodiploid ALL compared to those without pathogenic variants (65.4% vs. 1.2%; p<.001). Additionally, they exhibited inferior event-free survival and overall survival rates (hazard ratio, 4.2 and 3.9, respectively; both p<.001). Moreover, children with *TP53* pathogenic variants had a higher risk of developing secondary cancers, with a 5-year cumulative incidence of 25.1% versus 0.7% in those without such variants (p<.001).

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Diagnostic Testing in Individuals With Suspected Li-Fraumeni Syndrome
A chain of indirect evidence was developed, which addresses 2 key questions:

1. Does use of *TP53* genetic testing in individuals with suspected LFS lead to changes in clinical management (e.g., increased cancer surveillance, risk-reducing [prophylactic] mastectomy)?
2. Do those management changes improve outcomes?

There are standardized diagnostic criteria based on personal, clinical, and family history. However, there are limitations to these methods of diagnosis. A detailed family history may not be complete or may not be available in many instances. Classic LFS and Chompret criteria, when used in combination, provide the greatest sensitivity to providing a clinical diagnosis of LFS. With the greater availability of genetic testing, National Comprehensive Cancer Network guidelines recommend that a positive genetic test be required for a definitive diagnosis of LFS.

Changes in Management
In most cases, treatment and management will be unaffected by negative results from genetic testing, because individuals with a strong clinical presentation for LFS with a negative genetic test are likely to be treated as presumed LFS. However, there are some situations in which genetic testing may impact management. A positive test will facilitate the workup for cancer susceptibility syndromes when multiple conditions are considered. Knowledge of pathogenic variant status may also assist in decision making for risk-reducing mastectomy by providing more definitive risk estimates. If a cancer is detected, knowledge of the presence of a *TP53* variant would lead to avoidance of radiotherapy in the cancer treatment.

Improved Outcomes
Outcomes are improved when a definitive diagnosis is made by avoiding the need for further testing to determine whether a cancer susceptibility syndrome is present. Better estimation of risk for breast cancer improves the capacity for informed decision making regarding risk-reducing mastectomy.

Section Summary: Testing for Suspected Li-Fraumeni Syndrome
Evidence on the clinical validity for testing for *TP53* pathogenic variants is provided by the International Agency for Research on Cancer *TP53* Database, which includes a compilation of published studies and 891 families. The largest amount of evidence involves patients with breast, soft tissue, brain, and adrenal gland tumors, which represents 72% of all patients with tumors who have an associated *TP53* germline variant. In patients who meet clinical criteria for LFS, the clinical sensitivity has been reported to range between 50% and 80%. No evidence was identified on the clinical specificity of testing. Direct evidence of the clinical utility of *TP53* testing is limited. Children with *TP53* pathogenic variants are prone to developing hypodiploid ALL and experiencing unfavorable treatment outcomes. An indirect chain of evidence can demonstrate clinical utility of genetic testing for *TP53* variants. For diagnosis, a positive genetic test will increase the certainty of LFS, facilitate the overall workup for cancer susceptibility syndromes, eliminate or necessitate the need for increased cancer surveillance and assist in decision making for prophylactic mastectomy.

Testing At-Risk Relatives of a Proband with Li-Fraumeni Syndrome
Clinical Context and Test Purpose
The purpose of targeted *TP53* familial variant testing of individuals who are asymptomatic and have a close relative with a known *TP53* pathogenic variant is to determine the carrier status of the relative when there is a known *TP53* pathogenic variant in the family. If the relative has a positive test for a known *TP53* familial variant, appropriate management such as risk-reducing (prophylactic) mastectomies in women, avoidance of radiotherapy, and cancer surveillance may be initiated. If the relative has a negative test for a known *TP53* familial variant, then increased cancer surveillance is not necessary.

The following **PICO** was used to select literature to inform this review.

Populations
The relevant population of interest is individuals who are asymptomatic and have a close relative with a known TP53 pathogenic variant.

Interventions
The test being considered is targeted TP53 familial variant testing.

Comparators
The following practice is currently being used: standard clinical management without genetic testing.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, test accuracy and validity, changes in reproductive decision making, and resource utilization. The potential beneficial outcomes of primary interest include improved overall or disease-specific survival and reduced morbidity associated with changes in management when test results are positive

(e.g., risk-reducing mastectomies in women, avoidance of radiotherapy, increased cancer surveillance).

The potential harmful outcomes are those resulting from a false-positive or false-negative test result. False-positive test results can lead to inappropriate surgeries (e.g., risk-reducing mastectomies in women), inappropriate avoidance of radiotherapy, or psychological harm after receiving positive test results. False-negative test results can lead to lack of risk-reducing mastectomies in women, inappropriate use of radiotherapy, or lack of increased cancer surveillance. The time frame for outcome measures varies from several years for the development of cancers to long-term survival as a result of cancer.

Study Selection Criteria
For the evaluation of clinical validity of the test, studies that meet the following eligibility criteria were considered:

- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

See the Clinically Valid section for Testing for Suspected Li-Fraumeni Syndrome.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

There is some direct evidence that enhanced screening protocols may improve outcomes. Villani et al (2011) conducted a prospective, observational study of members of 8 LFS families who were asymptomatic *TP53* carriers.[19] Participants either chose or did not choose to undergo surveillance. Surveillance included biochemical and imaging studies, which included ultrasonography, brain magnetic resonance imaging, and rapid total body magnetic resonance imaging. The primary outcome measure was the detection of new cancers, and the secondary outcome measure was overall survival. Of 33 pathogenic variant carriers identified, 18 underwent surveillance. The surveillance protocol detected 10 asymptomatic tumors in 7 patients, which included premalignant or low-grade tumors (3 low-grade gliomas, 1 benign thyroid tumor, 1 myelodysplastic syndrome), and small, high-grade tumors (2 choroid plexus carcinomas, 2 adrenocortical carcinomas, 1 sarcoma). The 9 solid tumors detected were completely resected, and patients were in complete remission. After a median follow-up of 24 months, all patients who had undergone surveillance were alive. In the group without surveillance, 12 high-grade, high-stage tumors developed in 10 patients, of whom 2 were alive at the end of follow-up (p=.04 vs survival in the surveillance group). Three-year overall survival

in the surveillance group was 100% and 21% in the nonsurveillance group (p=.155). This study had an observational design that included self-selection into screening protocols, likely resulting in selection bias. Further higher quality evidence is needed to determine whether enhanced screening improves outcomes for *TP53* pathogenic variant carriers.

Tables 4 and 5 summarize key study characteristics and results.

Table 4. Summary of Key Observational Comparative Study Characteristics

Study	Type	Country	Dates	Participants	Treatment	Follow-Up
Villani et al (2011)[19]	Prospective	United States, Canada	2004-2010	8 families	Comprehensive surveillance protocol	24 mo

Table 5. Summary of Key Observational Comparative Study Results

Study	*TP53* Variant Carriers Identified	Carriers Surveilled (%)	Tumors Detected in Surveilled Group (%)	3-Year OS (%)	3-Year OS in Nonsurveillance Group (%)	p
Villani et al (2011)[19]	33	18 (54.5)	7 (38.9)	18 (100)	2 (20)	.016

OS: overall survival.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Genetic testing of at-risk relatives who have family members with LFS may have clinical utility in:

- Confirming or excluding the need for cancer surveillance based on the presence or absence of a known *TP53* familial variant.
- Informing the reproductive decision making process in preimplantation testing, prenatal (in utero) testing, or altering reproductive planning decisions when a known *TP53* familial variant is present in a parent. Preimplantation testing is addressed elsewhere (see evidence review 4.02.05).

Testing At-Risk Relatives of Patients With Li-Fraumeni Syndrome

There is limited direct evidence on the clinical utility of genetic testing in this population. Therefore, a chain of evidence was developed, which addressed 2 key questions:

1. Does use of targeted *TP53* familial variant testing in individuals with a close relative with a known *TP53* pathogenic variant lead to changes in clinical management (e.g., increased cancer surveillance, risk-reducing [prophylactic] mastectomy, reproductive planning)?
2. Do those management changes improve outcomes?

Changes in Management

Genetic testing of close relatives of an index case with a pathogenic variant will confirm or exclude the presence of the variant with certainty. A positive test will confer high risk for

multiple malignancies, while a negative test will imply that an individual is at average risk, in the absence of other high-risk factors.

TP53 pathogenic variants have high penetrance, indicating high risk for clinical disease when a pathogenic variant is present. The multiple malignancies associated with LFS have presymptomatic phases in which early detection strategies can be implemented. The presence of a pathogenic variant will lead to enhanced screening strategies for LFS-associated malignancies. A negative genetic test will eliminate the need for enhanced screening strategies.

Improved Outcomes
Enhanced screening for breast cancer in high-risk individuals improves outcomes, and enhanced screening for lung cancer is also likely to improve outcomes. For the other LFS-associated core cancers, outcomes of screening interventions are uncertain due to the rarity of the conditions and lack of screening trials.

Section Summary: Testing At-Risk Relatives of a Proband with Li-Fraumeni Syndrome
Evidence on the clinical validity for testing for *TP53* pathogenic variants is provided by the International Agency for Research on Cancer *TP53* Database, which includes a compilation of published studies and 891 families. The largest amount of evidence involves patients with breast, soft tissue, brain, and adrenal gland tumors, which represents 72% of all patients with tumors who have an associated *TP53* germline variant. In patients who meet clinical criteria for LFS, the clinical sensitivity has been reported to range between 50% and 80%. No evidence was identified on the clinical specificity of testing. Direct evidence of the clinical utility of *TP53* testing is limited. One observational study has reported improved survival for screened patients. However, the design of this study included self-selection into screening protocols, likely resulting in selection bias. A chain of evidence can demonstrate clinical utility of genetic testing for *TP53* variants. For asymptomatic family members who have a close relative with a pathogenic variant, genetic testing can confirm or exclude the presence of a variant, and direct future screening interventions that are likely to improve outcomes.

SUMMARY OF EVIDENCE
For individuals with suspected LFS by clinical criteria who receive genetic testing for *TP53*, the evidence includes case series and cross-sectional studies. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, changes in reproductive decision making, and resource utilization. Evidence on the clinical validity of testing comes from the International Agency for Research on Cancer*TP53* Database that has compiled records on 891 families with LFS. For patients with suspected LFS based on clinical criteria, the clinical sensitivity ranges from 50% to 80%. No evidence was identified on clinical specificity. In individuals with suspected LFS, a positive genetic test will establish a genetic diagnosis of LFS and facilitate the overall workup for cancer susceptibility syndrome when multiple conditions are considered. Also, the presence of a documented *TP53* pathogenic variant may aid in decision making for risk-reducing (prophylactic) mastectomy. The evidence is sufficient to determine that the technology results in 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 among others" (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.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

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

NCT: national clinical trial.

Government Regulations

National:

There is no national coverage determination.

Local:

Local Coverage Determination: (L39040), MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer. Effective on or after 07/03/2022.

Criteria for Coverage
All the following must be present for coverage eligibility:

- The patient must have:
  - Any cancer diagnosis
  - AND a clinical indication for germline (inherited) testing for hereditary cancer
  - AND a risk factor for germline (inherited) cancer
  - AND has not been previously tested with the same germline test using NGS for the same germline genetic content.
- The test has satisfactorily completed a Technical Assessment (TA) by MolDX for the stated indications of the test.
- The assay performed includes **at least** the minimum genetic content (genes or genetic variants) required for clinical decision making for its intended use that can be reasonably detected by the test.
  - Because these genes and variants will change as the literature and drug indications evolve, they are listed separately in associated documents, such as the MolDX TA forms.
  - A single gene may be tested if it is the only gene considered to be reasonable and necessary for a cancer type.
- If a previous NGS test was performed with a similar/duplicative intended use, a subsequent test is only reasonable and necessary if the non-duplicative genetic content of the second test is reasonable and necessary.

Situations in which Test should not be used or coverage is denied:
The test in question will be non-covered if:

- It does not fulfill all the criteria set forth in the NCD 90.2
- A previous test was performed for the same genetic content
- It is used to identify a known familial variant(s) that could be identified with a more specific test
- It is used to confirm a variant(s) detected by somatic tumor testing that can be confirmed by a more specific test
- A satisfactory Technical Assessment is not completed
- For tests that are currently covered but a TA submission has not been made, providers must submit complete TA materials by the original effective date of the policy or coverage will be denied.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing—Preimplantation
- Genetic Testing—Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer
- Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

References

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through August 2023, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/22	10/19/21		Joint policy established
1/1/23	10/18/22		Routine policy maintenance, no change in policy status.
1/1/24	10/17/23		Added covered indication for pediatric hypodiploid acute lymphoblastic leukemia. Updated rationale, added references 14 & 18. No change in policy status. Vendor managed: N/A (ds)

Next Review Date: 4th Qtr. 2024

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR LI-FRAUMENI SYNDROME

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	According to policy
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
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