Policy Statement

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

- In a patient who meets either the classic or the Chompret clinical diagnostic criteria for Li-Fraumeni syndrome (see Policy Guideline 1)
- In women with early-onset breast cancer (age of diagnosis less than 31 years) (see Policy Guideline 1)

Targeted TP53 familial variant testing may be considered medically necessary in an at-risk relative of a proband with a known TP53 pathogenic variant (see Policy Guideline 2).

Genetic testing for a germline TP53 variant is considered not medically necessary for all other indications.

Policy Guidelines

Policy Guideline 1
Diagnostic Criteria for Li-Fraumeni Syndrome

Classic Li-Fraumeni Syndrome

- A proband with a sarcoma before 45 years of age
- A first-degree relative with any cancer before 45 years of age
- A first- or second-degree relative with any cancer before 45 years of age or a sarcoma at any age

Chompret Criteria

Any of the following:

- Proband with tumor before age 46 years belonging to Li-Fraumeni syndrome (LFS) tumor spectrum (e.g., soft tissue sarcoma, osteosarcoma, brain tumor, premenopausal breast cancer, adrenocortical carcinoma, leukemia, lung bronchoalveolar cancer) AND at least one first- or second-degree relative with LFS tumor before age 56 years (except breast cancer if proband has breast cancer) or with multiple tumors; or
- Proband with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum and first of which occurred before age 46 years; or
- Patient with adrenocortical carcinoma or choroid plexus tumor, irrespective of family history.

Early-Onset Breast Cancer

National Comprehensive Cancer Network (NCCN) guidelines recommend TP53 testing for individuals who meet classic LFS criteria and Chompret criteria, or who have been diagnosed with early-onset breast cancer (age of diagnosis less than 31 years). It has been estimated that among women with BRCA1- and BRCA2-negative, early-onset breast cancer, approximately 5% have a TP53 mutation.

An optimal strategy for confirming a TP53 pathogenic variant in a proband would be:

1. Sequencing of the entire TP53 coding region (exons 2-11), which detects about 95% of TP53 pathogenic variant in patients with LFS.
2. If sequencing is negative, then: deletion/duplication analysis, which detects large deletions/duplications. These types of variants account for less than 1% of pathogenic variant in individuals meeting classic LFS criteria.
Policy Guideline 2

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 variant and developing disease is influenced by numerous factors that should be considered in evaluating risk:

- Proximity of relation to index case (first-, second-, or third-degree)
- Mode of inheritance of pathogenic variant (autosomal dominant vs. autosomal recessive)
- Degree of penetrance of pathogenic variant (high, intermediate, low)
- Results of detailed pedigree analysis
- De novo mutation rate

If a proband has a TP53 pathogenic variant, the risk to the proband’s offspring of inheriting the variant is 50%. If a proband has a TP53 pathogenic variant, the risk to other relatives may depend on the genetic status of the proband’s parents (i.e., it is not a de novo pathogenic variant in the proband). Most TP53 pathogenic variant are inherited from one of a proband’s parents. After a pathogenic variant has been identified in a proband, the proband’s parent with any pertinent cancer history or family history should be tested first to establish the lineage of the variant; otherwise, both parents should be tested. A family history could appear to be negative because of incomplete penetrance of the variant, limited family members available for testing, early death of a parent, etc.

If a TP53 pathogenic variant is identified in 1 parent, the risk to the proband’s siblings is 50%, the risk to second-degree relatives (grandparents, aunts, uncles, nieces, nephews, grandchildren) is 25%, and to third-degree relatives (first cousins, great-grandparents, great-aunts, great-uncles) is 12.5% (Schneider et al, 1993).

The presence of a TP53 variant is considered diagnostic for LFS. LFS is a highly penetrant cancer syndrome, with the risks of cancer being about 50% by age 30 years, and 90% by age 60 years. LFS 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%.

Genetics Nomenclature Update

The Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the HUMAN Genome Organization (HUGO), and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
<tr>
<td>Variant Classification</td>
<td>Definition</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
<td></td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
<td></td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

**Genetic Counseling**

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

**Coding**

The following CPT code includes the following testing for Li-Fraumeni syndrome:

- **81405**: Molecular Pathology Procedure Level 6. TP53 (tumor protein 53) (e.g., Li-Fraumeni syndrome, tumor samples), full gene sequence or targeted sequence analysis of more than 5 exons.

Duplication and deletion analysis for TP53 would be reported with the following unlisted CPT code:

- **81479**: Unlisted molecular pathology procedure

**Description**

Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome associated with the development of several types of tumors. The syndrome is caused by germline pathogenic variants in the TP53 gene. Testing for LFS pathogenic variants may be useful in confirming the diagnosis of LFS and/or evaluating genetic status in asymptomatic relatives of an index case.

**Related Policies**

- Preimplantation Genetic Testing

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.
Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed under the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale

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

LFS 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.1

The tumor types most closely associated with LFS include soft tissue sarcomas, premenopausal breast cancer, brain tumors, and adrenal cortical carcinoma.2 These core cancers account for approximately 70% to 80% of all LFS-related tumors. There is less agreement about the noncore cancers, which account for the remaining 30% of malignancies in LFS and include a wide variety of gastrointestinal tract, genitourinary tract, lung, skin, and thyroid cancers as well as leukemias and lymphomas.2

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 57% and the risk of a third malignancy, 38%.2 In 1 study of 322 pathogenic variant carriers from France, Bougeard et al (2015) reported that 43% of individuals had multiple malignancies.3

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.4 Women with LFS are at greatly increased risk of developing premenopausal breast cancer, with the median age of diagnosis being 33 years of age.2 Male breast cancer has rarely been reported in LFS families.2 Many types of brain tumors have been described in LFS, including astrocytomas, glioblastomas, medulloblastomas, and choroid plexus carcinomas.2 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.5

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.6
Clinical Diagnosis
The diagnosis of LFS is based on an evolving set of clinical classification criteria, established using salient aspects of family history and tumor-related characteristics. The first formal criteria, the classic LFS criteria, were developed in 1988, and are the most stringent used to make a clinical diagnosis of LFS.

Classic LFS
Classic LFS is defined by the presence of all of the following criteria:
- A proband with a sarcoma before 45 years of age,
- A first-degree relative with any cancer before 45 years of age, and
- A first- or second-degree relative with any cancer before 45 years of age or a sarcoma at any age.

Chompret Criteria
Chompret et al (2001) developed criteria that have the highest positive predictive value, and that, when combined with the classic LFS criteria, provide the highest sensitivity for identifying individuals with LFS. The Chompret criteria were updated in 2009 to assist in identifying families with milder phenotypes. The Chompret criteria will also identify individuals with de novo TP53 pathogenic variants, whereas the classic LFS criteria require a family history.

The Chompret criteria are defined as the following:
- Proband with tumor belonging to the LFS tumor spectrum (e.g., soft tissue sarcoma, osteosarcoma, brain tumor, premenopausal breast cancer, adrenocortical carcinoma, leukemia, lung bronchoalveolar cancer) 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), two of which belong to the LFS tumor spectrum and the first of which occurred before age 46 years; or
- Patient with adrenocortical carcinoma or choroid plexus tumor, irrespective of family history.

National Comprehensive Cancer Network guidelines recommend TP53 testing for individuals who meet classic LFS criteria and Chompret criteria, or who have been diagnosed with early-onset breast cancer (age of diagnosis <31 years).

Molecular Diagnosis
LFS is associated with germline pathogenic variants in the TP53 gene (chromosome 17p13.1), which encodes for a ubiquitous transcription factor that is responsible for a complex set of regulatory functions that promote DNA repair and tumor suppression. TP53 is the only gene in which pathogenic variants are known to cause LFS, and no other inherited phenotypes are associated specifically with germline pathogenic variants involving TP53. The presence of a TP53 variant is considered diagnostic.

LFS is a highly penetrant cancer syndrome, with the risks of cancer being about 50% by age 30 years, and 90% by age 60 years. LFS is inherited in an autosomal dominant manner. De novo germline TP53 pathogenic variants (no pathogenic variant is identified in either biologic parent) are estimated to be 7% to 20%.

Approximately 95% of pathogenic variants detected in the TP53 gene are sequence variants (small intragenic deletions and insertions and missense, nonsense, and splice site variants). Large deletions and duplications not readily detected by sequence analysis account for approximately 1% of the pathogenic variants detected.

Certain genotype-phenotype correlations have been reported in families with LFS and TP53 pathogenic variants. Genotype-phenotype correlations in LFS are predictive of the age of onset.
of a tumor, level of risk of developing a tumor, and outcome in patients with TP53 germline pathogenic variants.1,2

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
LFS 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 2-11). 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.

Literature Review
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 of individuals with suspected Li-Fraumeni syndrome (LFS) 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 question addressed in this evidence review is: In individuals with suspected LFS, does the use of genetic testing improve health outcomes, including risk-reducing mastectomies in women, avoidance of radiotherapy, necessitate or eliminate the need for increased cancer surveillance, or aid in reproductive decision making?

The following PICO were used to select literature to inform this review.

**Patients**
The relevant population of interest includes individuals with suspected LFS.

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

**Comparators**
The following practice is currently being used: usual care without genetic testing.

**Outcomes**
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.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**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).

Approximately 80% of families with features of LFS will have an identifiable TP53 pathogenic variant.2 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).2

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.

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).14 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=1644)

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. With TP53 Variant</th>
<th>Percentage With TP53 Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>449</td>
<td>27</td>
</tr>
<tr>
<td>Soft tissues</td>
<td>216</td>
<td>13</td>
</tr>
<tr>
<td>Brain</td>
<td>203</td>
<td>12</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>190</td>
<td>12</td>
</tr>
<tr>
<td>Bones</td>
<td>167</td>
<td>10</td>
</tr>
<tr>
<td>Other</td>
<td>142</td>
<td>9</td>
</tr>
<tr>
<td>Hematologic</td>
<td>57</td>
<td>3</td>
</tr>
<tr>
<td>Colorectal</td>
<td>51</td>
<td>3</td>
</tr>
<tr>
<td>Lung</td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td>Skin</td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td>Ovary</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Stomach</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Kidney</td>
<td>17</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Testis</td>
<td>7</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Liver</td>
<td>4</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Prostate</td>
<td>4</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Larynx</td>
<td>3</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Head and neck</td>
<td>3</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Esophagus</td>
<td>1</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Bladder</td>
<td>1</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>


O’Shea et al (2018) retrospectively analyzed 123 individuals (118 women, 5 men) in Ireland undergoing full TP53 sequencing.15 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).16 The differences included a significantly lower 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<0.001; men: median age, 40 vs 15 years; p<0.004). For breast cancer specifically, median ages were 40 years and 33 years for MGPT TP53-positive and single-gene testing TP53-positive women, respectively (p<0.001). 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.

Tables 2 and 3 summarize key study characteristics and results.

### Table 2. Summary of Key Observational Comparative Study Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wasserman et al</td>
<td>Cohort</td>
<td>U.S., Canada</td>
<td>NR</td>
<td>88</td>
<td>TP53 testing</td>
</tr>
<tr>
<td>(2015)13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rana et al (2018)16</td>
<td>Prospective</td>
<td>U.S.</td>
<td>2010-2014</td>
<td>38,938</td>
<td>TP53 testing</td>
</tr>
</tbody>
</table>

NR: not reported.
Section Summary: Clinically Valid

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 to date. The largest amount of evidence involves patients with breast, soft tissue, brain, and adrenal gland tumors, which represents a 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.

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.

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 LFS

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 change 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: Clinically Useful**

Direct evidence of the clinical utility of Tp53 testing is limited. One observational study reported improved survival for screened patients. However, the design of this study included self-selection into screening protocols, likely resulting in selection bias. However, 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 LFS**

**Clinical Context and Test Purpose**

The purpose of targeted familial variant testing of at-risk relatives of a proband with LFS 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 question addressed in this evidence review is: In at-risk relatives of a proband with LFS, does the use of targeted familial variant testing result in changes in management or outcome improvements, including, in the case of a positive result, risk-reducing mastectomies in women, avoidance of radiotherapy, necessitating or eliminating the need for increased cancer surveillance, or aid in reproductive decision making?

The following PICOs were used to select literature to inform this review.

**Patients**
The relevant population of interest includes at-risk relatives of a proband with LFS.

**Interventions**
The test being considered is targeted Tp53 familial variant testing.

**Comparators**
The following practice is currently being used: usual care without genetic testing.

**Outcomes**
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 results. 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.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**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. 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=0.04 vs survival in the surveillance group). Three-year overall survival in the surveillance group was 100% and 21% in the non surveillance group (p=0.155). This study had an observational design that included self-selection into screening protocols, likely resulting in selection bias. Further high-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

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
</table>

Table 5. Summary of Key Observational Comparative Study Results

<table>
<thead>
<tr>
<th>Study</th>
<th>TP53 Variant Carriers Identified</th>
<th>Carriers Surveilled (%)</th>
<th>Tumors Detected in Surveilled Group (%)</th>
<th>3-Year OS (%)</th>
<th>3-Year OS in Nonsurveillance Group (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villani et al (2011)</td>
<td>33</td>
<td>18 (54.5)</td>
<td>7 (38.9)</td>
<td>18 (100)</td>
<td>2 (20)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

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 Blue Shield of California Medical Policy: Preimplantation Genetic Testing).

Testing At-Risk Relatives of Patients With LFS

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 the targeted TP53 familial variant testing in individuals with suspected LFS and a proband with confirmed LFS lead to change 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: Clinically Useful

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 a meaningful 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 a meaningful improvement in the net health outcome.

Supplemental Information
Practice Guidelines and Position Statements
National Comprehensive Cancer Network guidelines on genetic or familial high-risk assessment of breast and ovarian (v.1.2018) recommend the following for Li-Fraumeni syndrome (LFS) management:
Breast cancer risk, women:
- Breast awareness starting at age 18 y.
- Clinical breast exam, every 6-12 mo, starting at age 20y.
- Breast screening
  - Age 20-29 y, annual breast MRI [magnetic resonance imaging] screening with contrast (or mammogram with consideration of tomosynthesis, only if MRI is unavailable)...
  - Age 30-75 y, annual mammogram with consideration of tomosynthesis and breast MRI screening contrast
  - Age >75 y, management considered on an individual basis
- For women with a TP53 pathogenic/likely pathogenic variant who are treated for breast cancer and who have not had a bilateral mastectomy, screening with annual breast MRI and mammogram should continue as described above. ref 19
- Discuss option of risk-reducing mastectomy
  - Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and
residual breast cancer risk with age and life expectancy should be considered during counseling.

- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy.... "ref 19

Other cancer risks:

- "Comprehensive physical exam including neurologic examination with high index of suspicion for rare cancers [cancers associated with LFS] and second malignancies in cancer survivors every 6-12 months
- Colonoscopy and upper endoscopy every 2-5 y starting at 25 y of age or 5 y before the earliest known colon cancer in the family (whichever comes first)." ref 19
- Annual dermatologic examination starting at 18 y.
- Annual whole body MRI (category 2B)
- Annual brain MRI (category 2B) may be performed as part of the whole body MRI or as a separate exam." ref 19

For relatives:

- "Advise about possible inherited cancer risk to relatives, options for risk assessment, and management.
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives."

American Association for Cancer Research

The American Association for Cancer Research (2017) published recommendations for cancer screening and surveillance for patients with LFS. 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 two 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 non-surveillance 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 3-4 months and full neurologic assessment
- Prompt assessment with primary care physician for any medical concerns
- Abdominal and pelvic ultrasound every 3-4 months
- Annual brain MRI
- Annual whole-body MRI (WBMRI).

For adults:

- Complete physical examination every six 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 20-75)
- Consider risk-reducing bilateral mastectomy
- Annual brain MRI (age 18 years onward)
- Annual WBMRI
- Abdominal and pelvic ultrasound every 12 months
- Upper endoscopy and colonoscopy every 2 to 5 years (age 25 years onward)
- Annual dermatologic examination.
U.S. Preventive Services Task Force Recommendations
No U.S. Preventive Services Task Force recommendations for LFS have been identified.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT01443468</td>
<td>Clinical, Epidemiologic, and Genetic Studies of Li-Fraumeni Syndrome; An Observational/Prospective Study: (Long-term prospective cohort study to collect data from as many individuals with LFS as permissible in order to precisely evaluate the main aims)</td>
<td>5000</td>
<td>(ongoing)*</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
*a Denotes industry-sponsored or cosponsored trial.

References


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**Documentation for Clinical Review**

**Please provide the following documentation (if/when requested):**

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/NMN**

The following services may be considered medically necessary when policy criteria are met. Services may be considered not medically necessary when policy criteria are not met.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tr>
<td><strong>CPT®</strong></td>
<td>0131U</td>
<td>Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure) <em>(Code effective 10/1/2019)</em></td>
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<td></td>
<td>81405</td>
<td>Molecular Pathology Procedure Level 6</td>
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<td></td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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<tr>
<td><strong>HCPCS</strong></td>
<td>None</td>
<td>None</td>
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<tr>
<td><strong>ICD-10</strong></td>
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**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.
Genetic Testing for Li-Fraumeni Syndrome

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>10/30/2015</td>
<td>BCBSA Medical Policy Adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>09/01/2016</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
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<td>10/01/2019</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
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<tr>
<td>11/01/2019</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
</tbody>
</table>

Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.