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 or equal to 35 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

- Proband with tumor 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) before age 46 years AND at least one first- or second-degree relative with LFS tumor (except breast cancer if proband has breast cancer) before age 56 years or with multiple tumors
- Proband with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum and first of which occurred before age 46 years
- Patient with adrenocortical carcinoma or choroid plexus tumor, irrespective of family history.

Early-Onset Breast Cancer

The National Comprehensive Cancer Network recommends that in patients with breast cancer diagnosed at 35 years of age or younger, TP53 testing can be ordered concurrently with BRCA1 and BRCA2 testing, or as a follow-up test after negative BRCA1 and BRCA2 testing. It has been estimated that among women with BRCA1- and BRCA2-negative, early-onset breast cancer, approximately 5% have a TP53 mutation.

The 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

At time, there are no specific, evidence-based, standardized guidelines for recommendations of which “at-risk” relatives should be tested. In relatives of an index case, the risk of having a pathologic 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 of 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).

Genetics Nomenclature Update

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). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the Human Genome Organization (HUGO).

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

Table PG1. Nomenclature to Report on Variants Found in DNA

<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>
</tbody>
</table>
### Genetic Testing for Li-Fraumeni Syndrome

#### Genetic Counseling

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

#### Coding

The following CPT code includes 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

- N/A

### 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 (or 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 in 1969 by 2 physician-scientists, Frederick P. Li and Joseph F. Fraumeni, 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 (2015) of 322 pathogenic variant carriers from France, 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.5 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 (ACC). In adults, in a 2013 series, it was estimated that 6% of individuals diagnosed with ACC 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. Since the availability of genetic testing, National Comprehensive Cancer Network (NCCN) guidelines have recommended that a positive genetic test is required for a definitive 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 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.

Chompret Criteria
- 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 ACC or choroid plexus tumor, irrespective of family history.

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 for 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 tumor, level of risk of developing tumor, and outcome in patients with TP53 germline pathogenic variants.
Management

Treatment
The evaluation for 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 prophylactic mastectomy in women, and in all patients with a TP53 pathogenic variant, avoidance of radiotherapy, because the evidence suggests 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, but, in general, the strategy includes physical examination, colonoscopy, and breast imaging. Other protocols being evaluated include additional imaging techniques and biochemical assessment. NCCN has consensus-based screening guidelines.

Literature Review
See Appendix Table 1 for genetic testing categories.

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). The following is a summary of the key literature.

Testing Individuals with 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 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 prophylactic mastectomies in women, avoidance of radiotherapy, necessitate or eliminate the need for increased cancer surveillance, or aid in reproductive decision making?

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

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

Interventions
The relevant intervention of interest is genetic testing of TP53.

Comparators
The relevant comparator of interest is usual care without genetic testing.
Outcomes
The potential beneficial outcomes of primary interest include changes in management when test results are positive (i.e., prophylactic mastectomies in women, avoidance of radiotherapy, increased cancer surveillance).

Timing
The time frame for outcome measures varies from several years for the development of cancers to long-term survival as a result of cancer.

Setting
Patients suspected of LFS are actively managed by medical geneticists or oncologists. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Analytic Validity
Analytic validity is the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent.

According to a large reference laboratory, analytic sensitivity and specificity for polymerase chain reaction sequencing for LFS TP53 testing and deletions and duplications testing by multiplex ligation-dependent probe amplification is greater than 95%.

Compiled data (see Table 1) from the current version of the World Health Organization’s International Agency for Research on Cancer (IARC) TP53 Database (R18, April 2016) have shown that the most common variant types found are missense, nonsense, splice, and frameshift, which account for 96% of all variants found in LFS families. The majority of pathogenic variants are found in exons 2 through 11 (n=1509 [92%]).

Table 1. Variant Types IARC TP53 Database, R18, April 2016 (N=1644)

<table>
<thead>
<tr>
<th>Variant Type</th>
<th>No. of TP53 Variants</th>
<th>Percentage of Total TP53 Variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missense</td>
<td>1205</td>
<td>73</td>
</tr>
<tr>
<td>Nonsense</td>
<td>146</td>
<td>9</td>
</tr>
<tr>
<td>Splice</td>
<td>134</td>
<td>8</td>
</tr>
<tr>
<td>Frameshift</td>
<td>93</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Large deletion</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Intronic</td>
<td>10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Silent</td>
<td>9</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Not applicable</td>
<td>1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

IARC: International Agency for Research on Cancer.

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.

Therefore, sequencing of the TP53 coding region (exon 2-11) is expected to identify 96% of TP53 pathogenic variants in patients with LFS. If initial sequencing is negative, reflex testing for deletion and duplication analysis is expected to identify an additional 1% of variants.
Section Summary: Analytic Validity
There is a lack of published evidence on the analytic validity of testing for TP53 pathogenic variants. It is expected that analytic validity will be high when testing is performed according to optimal laboratory standards. The website of a large laboratory claims analytic validity of greater than 95% but empirical, peer-reviewed data are not available.

Clinical Validity
Clinical validity is the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease.

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

Cohorts of individuals with adrenocortical carcinoma, which is diagnostic of LFS by the Chompret criteria, have been published. In a 2015 study, 88 consecutive patients with adrenocortical carcinoma were evaluated. 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 IARC TP53 Database, which includes a compilation of published studies and 891 families to date. 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 2. 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>1&lt;0.5</td>
</tr>
<tr>
<td>Testis</td>
<td>7</td>
<td>1&lt;0.5</td>
</tr>
<tr>
<td>Liver</td>
<td>4</td>
<td>1&lt;0.5</td>
</tr>
<tr>
<td>Prostate</td>
<td>4</td>
<td>1&lt;0.5</td>
</tr>
<tr>
<td>Larynx</td>
<td>3</td>
<td>1&lt;0.5</td>
</tr>
<tr>
<td>Head and neck</td>
<td>3</td>
<td>1&lt;0.5</td>
</tr>
<tr>
<td>Esophagus</td>
<td>1</td>
<td>1&lt;0.5</td>
</tr>
<tr>
<td>Bladder</td>
<td>1</td>
<td>1&lt;0.5</td>
</tr>
</tbody>
</table>

IARC: International Agency for Research on Cancer.

Section Summary: Clinical Validity
Evidence on the clinical validity for testing for TP53 pathogenic variants is provided by the IARC TP53 Database, which includes a compilation of published studies and 891 families to date. The largest amount of evidence is on 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.

Clinical Utility
Clinical utility is defined as how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Diagnostic Testing in Individuals with Suspected LFS
Direct evidence for the clinical utility of genetic testing to confirm a diagnosis of LFS is lacking. Therefore, a chain of indirect evidence was developed, which addresses 2 key questions:
1. Does use of the genetic testing of TP53 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 prophylactic 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 prophylactic mastectomy.

Section Summary: Clinical Utility
Direct evidence for the clinical utility of TP53 testing is limited. One observational study reported improved survival for screened patients. However, this study had an observational design that 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 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, prophylactic mastectomies in women, avoidance of radiotherapy, necessitating or eliminating the need for increased cancer surveillance, or aid in reproductive decision making?

The following PICOTS 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 relevant intervention of interest is targeted TP53 familial variant testing.

**Comparators**
The relevant comparator of interest is 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., prophylactic 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., prophylactic mastectomies in women), inappropriate avoidance of radiotherapy, or psychological harm after receiving positive test results. False-negative test results can lead to lack of prophylactic mastectomies in women, inappropriate use of radiotherapy, or lack of increased cancer surveillance.

**Timing**
The time frame for outcome measures varies from several years for the development of cancers to long-term survival as a result of cancer.

**Setting**
Patients suspected of LFS are actively managed by medical geneticists or oncologists. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

**Analytic Validity**
See the Analytic Validity section for Testing Individuals with Suspected Li-Fraumeni Syndrome.

**Clinical Validity**
See the Clinical Validity section for Testing Individuals with Suspected Li-Fraumeni Syndrome.

**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 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.

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 (MRI), and rapid total body magnetic resonance imaging. The primary outcome measure was 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, a 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 nonsurveillance group (p = 0.155). 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.

Section Summary: Clinical Utility
Direct evidence of the clinical utility of TP53 testing is limited. One observational study has reported improved survival for screened patients. However, this study had an observational design that 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 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 Li-Fraumeni syndrome (LFS) by clinical criteria who receive genetic testing for TP53, the evidence includes case series and cross-sectional studies. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, changes in reproductive decision making, and resource utilization. Evidence on the clinical validity of testing comes from the International Agency for Research on Cancer TP53 Database that has compiled data 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 familial 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 data 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.2.2017) 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 20-25 y (or at the age of the earliest diagnosed breast cancer in the family, if below 20 y).
- Breast screening
  - Age 20-29 y, annual breast MRI (magnetic resonance imaging) screening (preferred) or mammogram if MRI is unavailable
  - Age 30-75 y, annual mammogram, and breast MRI screening
  - Age >75 y, management considered on an individual basis...
- Discuss option of risk-reducing mastectomy and counsel regarding degree of protection, degree of cancer risk, and reconstruction options.
- Address psychosocial, social, and quality-of-life aspects of risk-reducing mastectomy.”

Other cancer risks:
- “Annual comprehensive physical exam with high index of suspicion for [cancers associated with LFS]
- Therapeutic RT (radiation therapy) for cancer should be avoided when possible.
- Consider colonoscopy 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).”
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.”

**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**

A search of ClinicalTrials.gov in June 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

---

**Appendix**

**Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.101**

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td>X</td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>2b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td>X</td>
</tr>
<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
<td></td>
</tr>
<tr>
<td>5. Reproductive testing</td>
<td></td>
</tr>
<tr>
<td>5a. Carrier testing: preconception</td>
<td></td>
</tr>
<tr>
<td>5b. Carrier testing: prenatal</td>
<td></td>
</tr>
<tr>
<td>5c. In utero testing: aneuploidy</td>
<td></td>
</tr>
<tr>
<td>5d. In utero testing: familial variants</td>
<td></td>
</tr>
<tr>
<td>5e. In utero testing: other</td>
<td></td>
</tr>
<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
<td></td>
</tr>
</tbody>
</table>

**References**


**Documentation for Clinical Review**

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

- History and physical, including:
  - Ancestry
  - Personal and/or family history of cancer (if applicable) including:
    - Family relationship(s): (maternal or paternal), (family member [e.g., sibling, aunt, grandparent]), (living or deceased) ((if applicable)
    - Site(s) of cancer
    - Age at diagnosis (including family members)
  - If breast cancer, indicate if bilateral, premenopausal, or triple negative cancer
    - BRCA1/BRCA2 mutation history (if applicable)
- Genetic counseling/professional results (if applicable)
- Laboratory or Pathology reports demonstrating determined:
  - BRCA1/BRCA2 results
  - TP53 results
  - Proximity of relation to index case (first-, second-, or third-degree)
  - Mode of inheritance of mutation (autosomal dominant versus autosomal recessive)
  - Degree of penetrance of mutation (high, intermediate, or low)
  - Results of detailed pedigree analysis
  - De novo mutation rate
- Reason for testing
2.04.101 Genetic Testing for Li-Fraumeni Syndrome
Page 15 of 16

**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 a procedure, diagnosis or device code(s) 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>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>81405</td>
<td>Molecular Pathology Procedure Level 6</td>
</tr>
<tr>
<td></td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All Diagnoses</td>
<td></td>
</tr>
</tbody>
</table>

**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<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>
<td>09/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</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.