IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome associated a high lifetime cumulative risk of cancer and a tendency for multiple cancers in affected individuals. The purpose of genetic testing of individuals with suspected 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.

MEDICAL POLICY CRITERIA

Note: Please refer to the Cross References section below for genetic testing not addressed in this policy, including but not limited to TP53 testing unrelated to Li-Fraumeni syndrome.

I. Genetic testing for TP53 may be considered medically necessary to confirm a diagnosis of Li-Fraumeni syndrome or Li-Fraumeni-like syndrome when any of the following criteria are met:
   A. In a patient who meets either the classic or the Chompret clinical diagnostic criteria, (See Policy Guidelines), or
   B. Early-onset breast cancer (age of diagnosis <31 years), or
   C. In a patient who meets either the Eeles or Birch criteria (See Policy Guidelines)
II. Genetic testing for TP53 associated with Li-Fraumeni or Li-Fraumeni-like syndrome may be considered **medically necessary** when a relative (See Policy Guidelines) is known to have a TP53 pathogenic variant and when testing is for the targeted TP53 variant.

III. Genetic testing for a TP53 variant associated with Li-Fraumeni or Li-Fraumeni-like syndrome is considered **not medically necessary** for all other indications.

**NOTE:** A summary of the supporting rationale for the policy criteria is at the end of the policy.

**POLICY GUIDELINES**

**SUBMISSION OF DOCUMENTATION**

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
   - History and physical exam including any relevant diagnoses related to the genetic testing
   - Conventional testing and outcomes
   - Conservative treatments, if any

**DEFINITIONS**

**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
- A first- or second-degree relative with any cancer before 45 years of age or a sarcoma at any age.[1]

Chompret 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.[2] The Chompret criteria were updated in 2009 to assist in identifying families with milder phenotypes.[3] 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 proband has breast cancer) before age 56 years or with multiple tumors; OR
- Proband with multiple tumors (except multiple breast tumors), 2 of which belong to the LFS tumor spectrum and the first of which occurred before age 46 years; OR
- Patient with ACC or choroid plexus tumor, irrespective of family history.

Li-Fraumeni-like syndrome

Eeles Criteria

- Two different tumors that are part of extended LFS tumor spectrum in first- or second-degree relatives at any age

Birch Criteria

- Proband with any childhood cancer or sarcoma, brain tumor, or adrenal cortical tumor diagnosed under the age of 45; AND
- A first- or second-degree relative with LFS spectrum cancers diagnosed at any age; AND
- A first- or second-degree relative in the same genetic lineage with any cancer diagnosed under the age of 60

Family Members

Close blood relatives include 1st-, 2nd-, and 3rd-degree relatives from the same lineage as follows:
- 1st-degree relatives are parents, siblings, and children of an individual;
- 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren and half-siblings (siblings with one shared biological parent) of an individual; and
- 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first-cousins.

A child of a patient with a TP53 variant has a 50% risk of inheriting the variant. The risk to other relatives depends on whether the variant is de novo or inherited. Most TP53 variants are inherited. After a variant has been identified in a patient, the patient’s parent with any pertinent cancer history of family history should be tested first; 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 variant is identified in a parent, the risk to the patient’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%.¹

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.\textsuperscript{[4]} HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO). The terms “variant” and “disease-associated variant” are recommended in place of “mutation” to describe a change in the DNA sequence and a disease-associated change in the DNA sequence, respectively.

CROSS REFERENCES

1. Genetic Testing for Hereditary Breast and/or Ovarian Cancer, Genetic Testing, Policy No. 02
2. Genetic Testing for Inherited Susceptibility to Colon Cancer, Genetic Testing, Policy No. 06
3. Preimplantation Genetic Testing, Genetic Testing, Policy No. 18
4. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
5. Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer, Genetic Testing, Policy No. 42
6. Molecular Markers in Fine Needle Aspirates of the Thyroid, Genetic Testing, Policy No. 49
7. Genetic Testing for Myeloid Neoplasms and Leukemia, Genetic Testing, Policy No. 59
8. Genetic Testing for PTEN Hamartoma Tumor Syndrome, Genetic Testing, Policy No. 63

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**

Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome associated a high lifetime cumulative risk of cancer and a tendency for multiple cancers in affected individuals. The syndrome was originally described in 1969 by two 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.\textsuperscript{[5]}

The tumor types most closely associated with LFS include soft tissue sarcomas, premenopausal breast cancer, brain tumors, and adrenal cortical carcinoma.\textsuperscript{[1]} 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.\textsuperscript{[1]}

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%.\textsuperscript{[1]} In one study of 322 pathogenic variant carriers from France, 43% of individuals had multiple malignancies.\textsuperscript{[6]}

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 five years and osteosarcoma at any age.\textsuperscript{[7]} Women with LFS are at greatly increased risk
of developing premenopausal breast cancer, with the median age of diagnosis being 33 years of age.\[^1\] Male breast cancer has rarely been reported in LFS families.\[^1\] Many types of brain tumors have been described in LFS, including astrocytomas, glioblastomas, medulloblastomas, and choroid plexus carcinomas.\[^1\] 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 one series, it was estimated that 6% of individuals diagnosed with ACC after age 18 years have a germline TP53 pathogenic variant.\[^8\]

Data from M.D. Anderson Cancer Center's long-term clinical studies of LFS showed 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.\[^9\]

**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.\[^5\] 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.\[^5\] 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.\[^10\]

**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
- A first- or second-degree relative with any cancer before 45 years of age or a sarcoma at any age.\[^11\]

Chompret 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.\[^2\] The Chompret criteria were updated in 2009 to assist in identifying families with milder phenotypes.\[^3\] 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 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; 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.
NCCN guidelines recommend TP53 analysis 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).

In two separate publications, Eeles and Birch further defined populations at risk for TP53 variants, termed Li-Fraumeni-like (LFL) families.[11,12] A recent publication including over 300 families meeting these combined LFL criteria suggest that as many as 14-16% of these additional families may be positive for TP53 variants.[13]

**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.[1] 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.[1] 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/insertions and missense, nonsense, and splice site variants). Large deletions/duplications not readily detected by sequence analysis account for approximately 1% of the pathogenic variants detected.[1]

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.[1,5]

**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,[14] 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.

**REGULATORY STATUS**

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

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**EVIDENCE SUMMARY**

Validation of the clinical use of any genetic test focuses on three 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, which refers to 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 focus of this review is on evidence from well-designed studies related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention; and
- Improve health outcomes as a result of those decisions.

**TESTING INDIVIDUALS WITH SUSPECTED LI-FRAUMENI SYNDROME**

**Clinical Context and Test Purpose**

The purpose of genetic testing of individuals with suspected 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 result in improvement in health outcomes, including prophylactic mastectomies in women, avoidance of radiotherapy, necessitating or eliminating the need for increased cancer surveillance or aid in reproductive decision making?

**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.

Compiled data (see Table 1) from the WHO International Agency for Research on Cancer (IARC) TP53 Database, R18, April 2016 showed that the most common types of variant types found are missense, nonsense, splice and frameshift variants, account for 96% of all variants found in LFS families.\(^{[15]}\) The majority of pathogenic variants are found in exons 2 to 11 (n=1509 [92%]).
Table 1. Variant Types IARC TP53 Database, R18, April 2016 (N=1644)[15]

<table>
<thead>
<tr>
<th>Variant Type</th>
<th>No. of TP53 Variants</th>
<th>Percent 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>

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), which detects about 96% of TP53 pathogenic variants in patients with LFS. Examples of types of pathogenic variants detected by sequence analysis include small insertions/deletions (frameshift), and missense, nonsense, and splice site variants; most are missense variants.
2. Deletion/duplication analysis, which detects large deletions/duplications involving the coding region, exon 1, or promoter; these types of deletions/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 variants 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 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 1 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).[1] Whether the remaining patients have undetected TP53 variants or variants in other, unidentified genes, is not known.

Cohorts of individuals with adrenocortical carcinoma, which is diagnostic of LFS by the Chompret criteria, have been published.[16-18] In one study, 88 consecutive patients with adrenocortical carcinoma were evaluated.[18] 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 WHO International Agency for Research on Cancer (IARC) TP53 Database, R18, April 2016 showed tumor types associated with TP53 germline variants (see Table 2).[15] The main tumor types associated with TP53 germline variants include breast, soft tissue, brain, adrenal gland, and bone tumor that comprise 74% of all tumors with confirmed TP53 germline variants.

Table 2. Tumors Associated With TP53 Germline Variants (N=1644)[15]

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. With TP53 Variant</th>
<th>Percent 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>

Section Summary: Clinical Validity

Evidence on the clinical validity for testing for TP53 is provided by the WHO IARC TP53 Database, R18, April 2016 that includes a compilation of published studies and includes 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 with 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.

The clinical utility of genetic testing can be considered in the following clinical situations:
1. Diagnostic testing in individuals with suspected LFS, and
2. Testing of asymptomatic family members to determine future risk of LFS.

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 two key questions:

1. Does use of the genetic testing of \(TP53\) in individuals with suspected LFS lead to change clinical management (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 genetic testing, because individuals 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 of the clinical utility of \(TP53\) testing is limited. One observational study reported improved survival for screened patients. However, this study is limited by the observational design that included self-selection into screening protocols, likely resulting in selection bias. 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, and assist in decision making for prophylactic mastectomy.

TESTING AT-RISK RELATIVES OF PATIENTS 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. The question addressed in this evidence review is: When a relative is known to have LFS, does the use of targeted familial variant testing result in changes in management or outcome improvements?

The potential beneficial outcomes when test results are positive include prophylactic mastectomies in women, avoidance of radiotherapy, and increased cancer surveillance. Additionally, genetic testing of at-risk relatives with family members with LFS may have clinical utility in 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 the evidence review in Genetic Testing, Policy No. 18, linked in Cross References above). The potential beneficial outcome of a negative test is the elimination of the need for enhanced surveillance.

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.

**Analytic Validity**

The analytic validity of testing at-risk relatives of patients with LFS is based on the WHO IARC TP53 Database as for patients with suspected LFS, discussed above (see Table 1).

**Clinical Validity**

As discussed above for patients with suspected LFS, 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).[1]

**Clinical Utility**

**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. 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 not certain 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 (2011) conducted a prospective, observational study of members of eight LFS families who were asymptomatic TP53 carriers.[19] Participants either chose to or not undergo surveillance. Surveillance included biochemical and imaging studies, which included ultrasounds, brain magnetic resonance imaging (MRI) scans, and rapid total body MRI scans. 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 seven patients, which included premalignant or low-grade tumors (three low-grade gliomas, a benign thyroid tumor, one myelodysplastic syndrome), and small, high-grade tumors (two choroid plexus carcinomas, two adrenocortical carcinomas, one sarcoma). The nine 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 two 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 is limited by the 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 reported improved survival for screened patients. However, this study is limited by the observational design that included self-selection into screening protocols, likely resulting in selection bias. 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 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 WHO IARC TP53 Database that has compiled data on 891 families with LFS. For patients with suspected LFS by 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 familial variant in \textit{TP53} who receive targeted 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 WHO IARC \textit{TP53} Database that has compiled data on 891 families with LFS. In asymptomatic individuals who have a close relative with a known \textit{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 \textit{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.

**PRACTICE GUIDELINE SUMMARY**

**NATIONAL COMPREHENSIVE CANCER NETWORK**

National Comprehensive Cancer Network guidelines on genetic/familial high-risk assessment of breast and ovarian (v.2.2017)[20] 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.”
SUMMARY

There is enough research to show that TP53 genetic testing improves health outcomes for individuals suspected of having Li-Fraumeni syndrome (LFS) or Li-Fraumeni-like syndrome (LFL) and relatives of individuals with TP53 variants. Clinical guidelines based on research recommend TP53 genetic testing for individuals that meet the requirements listed in the policy criteria. Therefore, TP53 genetic testing may be considered medically necessary when policy criteria are met.

There is enough research to show that TP53 genetic testing does not improve health outcomes for individuals who do not meet the policy criteria. Therefore, TP53 genetic testing is considered not medically necessary when policy criteria are not met.

REFERENCES


**CODES**

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*Date of Origin: August 2017*