Preauthorization is required.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

Description

Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome associated with the development of several different types of tumors. The syndrome is caused by germline mutations in the TP53 gene.

Summary of Evidence

The analytic validity of TP53 mutation testing is high, and almost all of these mutations can be identified by sequence analysis; a far smaller number of mutations can be detected by deletion/duplication analysis.

The clinical validity of TP53 mutation testing is high in that a mutation can be identified in up to 80% of patients who meet the clinical criteria for a diagnosis of Li-Fraumeni Syndrome (LFS).

The clinical utility of genetic testing for a TP53 mutation is high in that confirming a diagnosis in a patient with clinical criteria of LFS will lead to changes in clinical management by increasing surveillance to detect cancers known to be associated with LFS at an early and treatable stage, or to address possible prophylactic measures. Most cases of LFS are inherited, and testing of at-risk relatives will identify those who should also undergo increased cancer surveillance.

Therefore, genetic testing for TP53 mutations may be considered medically necessary to confirm a diagnosis of LFS in patients who meet either the classic or the Chompret clinical diagnostic criteria for LFS, in a patient who has been diagnosed with breast cancer at 35 years of age or younger and in at-risk relatives of a proband with a known TP53 mutation.

Policy

Genetic testing for TP53 mutations 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, or
- In women with early-onset breast cancer (age of diagnosis ≤ 35 years) (See Policy Guideline No. 1)
Genetic testing for a TP53 mutation may be considered **medically necessary** in an at-risk relative of a proband with a known TP53 mutation. (See Policy Guideline No. 2)

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

**Policy Guidelines**

Policy Guideline No. 1

*Diagnostic criteria for LFS:*

**Classic LFS**
- A proband with a sarcoma before 45 years of age AND
- 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**
- Proband with tumor belonging to 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 LFS tumor spectrum and first of which occurred before age 46 years; OR
- Patient with adrenocortical carcinoma (ACC) or choroid plexus tumor, irrespective of family history

**Early-onset breast cancer**

NCCN recommends that in patients with breast cancer diagnosed at 35 years or younger, TP53 testing can be ordered concurrently with BRCA1/2 testing, or as a follow-up test after negative BRCA 1/2 testing. It has been estimated that among women with BRCA 1/2 negative, early-onset breast cancer, approximately 5% have a TP53 mutation.

The optimal strategy for confirming a TP53 mutation in a proband would be:

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

Policy Guideline No. 2

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

- 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**

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

If a *TP53* mutation is identified in one of the parents, 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%.

**Background**

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.

The tumor types that are most closely associated with LFS include soft tissue sarcomas, premenopausal breast cancer, brain tumors, and adrenal cortical carcinoma. 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 and leukemias and lymphomas.

Individuals with LFS are at increased risk of developing multiple primary tumors, with subsequent malignancies not all being clearly related to the treatment of the previous neoplasms. The risk of developing a second tumor has been estimated at 57%, and the risk of a third malignancy, 38%.

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. Women with LFS are at greatly increased risk of developing premenopausal breast cancer, with the median age of diagnosis being 33 years of age. Male breast cancer has rarely been reported in LFS families. Many different types of brain tumors have been described in LFS, including astrocytomas, glioblastomas, medulloblastomas, and choroid plexus carcinomas. The median age of onset of LFS-related brain tumors is 16 years of age.

Individuals with LFS are at increased risk of developing ACC. In adults, in one series, it was estimated that 6% of individuals diagnosed with ACC after age 18 years have a germline *TP53* mutation.

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.

**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 set of criteria, the classic LFS criteria, were developed in 1988, and are the most stringent criteria 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
- A first- or second-degree relative with any cancer before 45 years of age or a sarcoma at any age

Chompret et al developed criteria which were shown to have the highest positive predictive value, and which, 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 \textit{TP53} mutations, whereas the classic LFS criteria require a family history.

Chompret Criteria

- Proband with tumor belonging to 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 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 \textit{TP53} analysis for individuals who meet classic LFS criteria, Chompret criteria, or who have been diagnosed with early-onset breast cancer (age of diagnosis ≤ 35 years).

Molecular Diagnosis

LFS is associated with germline mutations in the \textit{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. \textit{TP53} is the only gene in which mutations are known to cause LFS, and no other inherited phenotypes are associated specifically with germline mutations involving \textit{TP53}.

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 \textit{TP53} mutations (no mutation is identified in either biologic parent) are estimated to be 7% to 20%.

Approximately 95% of mutations detected in the \textit{TP53} gene are sequence variants (small intragenic deletions/insertions and missense, nonsense, and splice site mutations). Large deletion/duplications not readily detected by sequence analysis accounts for approximately 1% of the mutations detected.

Certain genotype-phenotype correlations have been reported in families with LFS and \textit{TP53} mutations. 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 \textit{TP53} germline mutations.

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 \textit{TP53} mutation, avoidance of radiotherapy, as there is some evidence to suggest that
TP53 mutations 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 that are being evaluated include additional imaging techniques and biochemical assessment. NCCN has consensus-based screening guidelines.

**Regulatory Status**

No U.S. Food and Drug Administration–cleared molecular diagnostic tests were found. Thus, molecular evaluation is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

**References**

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


