

(204101)

Medical Benefit		Effective Date: 10/01/20	Next Review Date: 07/21
Preauthorization	Yes	Review Dates: 07/14, 07/15, 07/16, 07/17, 07/18, 07/19, 07/20	

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.

RELATED PROTOCOL

Preimplantation Genetic Testing

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With suspected Li-Fraumeni syndrome by clinical criteria 	Interventions of interest are: <ul style="list-style-type: none"> Genetic testing for TP53 	Comparators of interest are: <ul style="list-style-type: none"> Standard clinical management without genetic testing 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Test accuracy Test validity Changes in reproductive decision making Resource utilization
Individuals: <ul style="list-style-type: none"> Who are asymptomatic and have a close relative with a known TP53 pathogenic variant 	Interventions of interest are: <ul style="list-style-type: none"> Targeted TP53 familial variant testing 	Comparators of interest are: <ul style="list-style-type: none"> Standard clinical management without genetic testing 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Test accuracy Test validity Changes in reproductive decision making Resource utilization

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.

SUMMARY OF EVIDENCE

For individuals with suspected LFS by clinical criteria who receive genetic testing for TP53, the evidence includes

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

For individuals who are asymptomatic and have a close relative with a known TP53 pathogenic variant who receive targeted TP53 familial variant testing, the evidence includes case series and cross-sectional studies. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, changes in reproductive decision making, and resource utilization. Evidence on the clinical validity of testing comes from the International Agency for Research on Cancer TP53 Database that has compiled records on 891 families with LFS. In asymptomatic individuals who have a close relative with a known TP53 pathogenic variant, targeted familial variant testing can confirm or exclude the presence of the familial variant with high certainty. A positive genetic test will lead to increased surveillance for LFS-associated cancers, and a negative test will eliminate the need for enhanced surveillance. Knowledge of TP53 genetic status may also inform reproductive decision making in individuals considering offspring. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

POLICY

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, or
- In women with early-onset breast cancer (age of diagnosis less than 31 years) (See Background)

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 Background)

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

POLICY GUIDELINES

GENETICS NOMENCLATURE UPDATE

The Human Genome Variation Society 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 protocol review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Genome Project, the HUMAN Genome Organization and the Human Genome Variation Society itself.

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

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

GENETIC COUNSELING

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

BACKGROUND

TP53 GENE

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

LI-FRAUMENI SYNDROME

LFS is a cancer predisposition syndrome associated with a high lifetime cumulative risk of cancer and a tendency for multiple cancers in affected individuals. The syndrome was originally described based on a retrospective analysis of families with aggressive soft tissue sarcomas in young siblings and their biologically related cousins.¹

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

Individuals with LFS are at increased risk of developing multiple primary tumors, with subsequent malignancies, not all being clearly related to the treatment of the previous neoplasms. The risk of developing a second tumor has been estimated at 57%, and the risk of a third malignancy, 38%.² In one study of 322 pathogenic variant carriers from France, Bougeard et al (2015) reported that 43% of individuals had multiple malignancies.³

Individuals with LFS are at increased risk of both bone and soft tissue sarcomas. Sarcomas of various histologies account for 25% of the cancers reported in people with LFS, with the most commonly reported sarcomas in an international database being rhabdomyosarcoma before age five years and osteosarcoma at any age.⁴ Women with LFS are at greatly increased risk of developing premenopausal breast cancer, with the median age of diagnosis being 33 years of age.² Male breast cancer has rarely been reported in LFS families.² Many types of brain tumors have been described in LFS, including astrocytomas, glioblastomas, medulloblastomas, and choroid plexus carcinomas.² The median age of onset of LFS-related brain tumors is 16 years of age. Individuals with LFS are at increased risk of developing adrenocortical carcinoma. For adults, Raymond et al (2013) estimated that 6% of individuals diagnosed with adrenocortical carcinoma after age 18 years have a germline TP53 pathogenic variant.⁵

Data from M.D. Anderson Cancer Center's long-term clinical studies of LFS have shown that the risk of developing soft tissue sarcomas is greatest before the age of 10, brain cancer appears to occur early in childhood with a smaller peak in risk in the fourth to fifth decade of life, risk for osteosarcoma is highest during adolescence, and breast cancer risk among females with LFS starts to increase significantly around age 20 and continues into older adulthood.⁶

Clinical Diagnosis

The diagnosis of LFS is based on an evolving set of clinical classification criteria, established using salient aspects of family history and tumor-related characteristics.¹ 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.¹

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.²

Chompret Criteria

Chompret et al (2001) developed criteria that have the highest positive predictive value, and that, when combined with the classic LFS criteria, provide the highest sensitivity for identifying individuals with LFS.⁷ The Chompret criteria were updated in 2009 to assist in identifying families with milder phenotypes.⁸ The Chompret criteria will also identify individuals with de novo TP53 pathogenic variants, whereas the classic LFS criteria require a family history.

The Chompret criteria are defined as the following:

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

National Comprehensive Cancer Network guidelines recommend TP53 testing for individuals who meet classic LFS criteria and Chompret criteria, or who have been diagnosed with early-onset breast cancer (age of diagnosis <31 years).⁹

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 TP53.² The presence of a TP53 variant is considered diagnostic.

LFS is a highly penetrant cancer syndrome, with the risks of cancer being about 50% by age 30 years, and 90% by age 60 years.² 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.²

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

Management

Treatment

The evaluation of cancer in an individual diagnosed with LFS should be based on personal medical history and, to some degree, the specific pattern of cancer in the family. Women with LFS who develop breast cancer are encouraged to consider bilateral mastectomies to reduce the risk of developing a second primary breast cancer and to avoid exposure to radiotherapy. Preventive measures may include risk-reducing (prophylactic) mastectomy in women, and in all patients with a TP53 pathogenic variant, avoidance of radiotherapy, because the evidence has suggested that TP53 pathogenic variants confer an increased sensitivity to ionizing radiation and the possibility of radiation-induced malignancies.

Surveillance

LFS confers a high risk of multiple different types of cancer, which poses challenges for establishing a comprehensive screening regimen, and many of the cancers associated with LFS do not lend themselves to early detection. There is no international consensus on the appropriate clinical surveillance strategy in individuals with LFS,¹⁰ but, in general, the strategy includes physical examination, colonoscopy, and breast imaging. Other protocols being evaluated include additional imaging techniques and biochemical assessment. National Comprehensive Cancer Network has consensus-based screening guidelines.

Testing Strategy

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

1. Sequencing of the entire TP53 coding region (exons 2-11). Examples of types of pathogenic variants detected by sequence analysis include small insertions and deletions (frameshift), and missense, nonsense, and splice site variants; most are missense variants.
2. Deletion and duplication analysis, which detects large deletions and duplications involving the coding region (exon 1) or promoter; these types of deletions and duplications are not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. These types of pathogenic variants account for less than 1% of those found in individuals with LFS.

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.

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

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