Protocol

Genetic Testing for Li-Fraumeni Syndrome

(204101)

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

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.

Populations	Interventions	Comparators	Outcomes
Individuals: • With suspected Li-Fraumeni syndrome by clinical criteria	Interventions of interest are: • Genetic testing for the *TP53* gene	Comparators of interest are: • Usual care without genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Changes in reproductive decision making • Resource utilization
Individuals: • Who are asymptomatic and have a close relative with a known pathogenic *TP53* mutation	Interventions of interest are: • Targeted genetic testing for the*TP53* gene	Comparators of interest are: • Usual care without genetic testing	Relevant outcomes include: • 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 mutations in the *TP53* gene. Testing for LFS associated mutations may be useful in confirming the diagnosis of LFS and/or evaluating mutation status in asymptomatic relatives of an index case.

Summary of Evidence

For individuals who have suspected LFS by clinical criteria or who are asymptomatic and have a close relative with a known pathogenic *TP53* mutation or women with early-onset breast cancer who receive genetic testing for the *TP53* gene, the evidence includes case series and cross-sectional studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, changes in reproductive decision making, and resource utilization. There is a lack of evidence on analytic validity of testing, but the analytic validity is likely to be high if performed under optimal laboratory conditions. There is scant evidence on the clinical validity of testing, with the most being in the population of patients with adrenocortical carcinoma. For patients with suspect-

ed LFS by clinical criteria, the clinical sensitivity ranges from 50% to 80%. No evidence was identified on clinical specificity. Clinical utility is considered in the two following situations:

- Individuals with suspected LFS to confirm the diagnosis: For individuals with suspected LFS by clinical criteria, a positive genetic test will confirm the diagnosis of LFS with higher certainty than can be attained by clinical criteria alone. Confirmation of the diagnosis will facilitate the overall workup for cancer susceptibility syndrome when multiple conditions are considered. Also, the presence of a documented mutation may aid in decision making for prophylactic mastectomy. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.
- Asymptomatic individuals to determine future risk of LFS: For asymptomatic individuals who have a close relative with a known pathogenic *TP53* mutation, targeted testing can confirm or exclude a mutation 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 mutation status may also inform reproductive decision making in individuals considering offspring. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

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

The National Comprehensive Cancer Network recommends that in patients with breast cancer diagnosed at 35 years or younger, *TP53* testing can be ordered concurrently with BRCA1 and BRCA 2 testing, or as a follow-up test after negative BRCA1 and BRCA 2 testing. It has been estimated that among women with BRCA1 and BRCA 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 times, 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, 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% Schneider et al, 1993).

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.

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.[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 mutations 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 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 (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.[5]

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.[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] 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.[7]

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.[2]

Chompret et al 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.[8] The Chompret criteria were updated in 2009 to assist in identifying families with milder phenotypes.[9] The Chompret criteria will also identify individuals with de novo *TP53* mutations, 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, Chompret criteria, or who have been diagnosed with early-onset breast cancer (age of diagnosis ≤ 31 years).

Molecular Diagnosis

LFS is associated with germline mutations in the *TP53* gene (chromosome 17p13.1), which encodes for an 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 mutations are known to cause LFS, and no other inherited phenotypes are associated specifically with germline mutations involving *TP53*.[2]

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.[2] LFS is inherited in an autosomal dominant manner. De novo germline *TP53* mutations (no mutation is identified in either biologic parent) are estimated to be 7% to 20%.

Approximately 95% of mutations detected in the *TP53* gene are sequence variants (small intragenic deletions/insertions and missense, nonsense, and splice site mutations). Large deletions/duplications not readily detected by sequence analysis account for approximately 1% of the mutations detected.[2]

Certain genotype-phenotype correlations have been reported in families with LFS and *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 *TP53* germline mutations.[1, 2]

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* mutation, avoidance of radiotherapy, because the evidence suggests 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,[10] 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.

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.

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17. National Government Services, Inc. (Primary Geographic Jurisdiction - Illinois, New York - Entire State, Connecticut, Massachusetts, Maine, New Hampshire, Rhode Island, Vermont, Wisconsin, Minnesota) Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000), Revision Effective Date for services performed on or after 02/01/2017.