Genetic Testing for Li-Fraumeni Syndrome

Description

Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome associated with the development of several types of tumors. The syndrome 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.

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OBJECTIVE

The objective of this evidence review is to determine whether genetic testing improves the net health outcome in individuals with suspected Li-Fraumeni syndrome.

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, or
- In women with early-onset breast cancer (age of diagnosis <31 years).

POLICY GUIDELINES

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.

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 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. 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.

The Chompret criteria are defined as the following:

- Proband with tumor belonging to the LFS tumor spectrum (eg, 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

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• 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).

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 medical evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by 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.

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<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<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>
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<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
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<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
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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.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA 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

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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network guidelines on genetic or familial high-risk assessment of breast and ovarian (v.1.2018) 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 20y.
- Breast screening
  - Age 20-29 y, annual breast MRI [magnetic resonance imaging] screening with contrast (or mammogram with consideration of tomosynthesis, only if MRI is unavailable))...  
  - Age 30-75 y, annual mammogram with consideration of tomosynthesis and breast MRI screening contrast  
  - Age >75 y, management considered on an individual basis
- For women with a TP53 pathogenic/likely pathogenic variant who are treated for breast cancer and who have not had a bilateral mastectomy, screening with annual breast MRI and mammogram should continue as described above. ref 19
- Discuss option of risk-reducing mastectomy
  - Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and residual breasts cancer risk with age and life expectancy should be considered during counseling.
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy...."ref 19

Other cancer risks:
- "Comprehensive physical exam including neurologic examination with high index of suspicion for rare cancers [cancers associated with LFS] and second malignancies in cancer survivors every 6-12 months
- Colonoscopy and upper endoscopy 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)." ref 19
- Annual dermatologic examination starting at 18 y.
- Annual whole body MRI (category 2B)
- Annual brain MRI (category 2B) may be performed as part of the whole body MRI or as a separate exam." ref 19

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."

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American Association for Cancer Research

The American Association for Cancer Research (2017) published recommendations for cancer screening and surveillance for patients with LFS. Genetic counseling and clinical TP53 testing should be strongly considered in the following clinical situations:

"(i) proband with an LFS spectrum tumor prior to age 46 and at least one first- or second-degree relative with an LFS tumor before the age of 56 years or with multiple tumors, (ii) proband with multiple malignancies (except two breast cancers), of which at least two belong to the LFS spectrum, before age 46; (iii) patients with rare tumors such as ACC, choroid plexus carcinoma, or embryonal anaplastic subtype rhabdomyosarcoma independent of family history; and (iv) breast cancer before age 31 years."

Cancer surveillance has been shown to improve overall survival for surveillance and nonsurveillance groups and should be offered as soon as either clinical or molecular diagnosis of LFS is established. The following surveillance protocols were recommended for children (birth to age 18) and adults.

For children:

- Complete physical examination every 3-4 months and full neurologic assessment
- Prompt assessment with primary care physician for any medical concerns
- Abdominal and pelvic ultrasound every 3-4 months
- Annual brain MRI
- Annual whole-body MRI (WBMRI).

For adults:

- Complete physical examination every six months
- Prompt assessment with primary care physician for any medical concerns
- Breast awareness (age 18 years onward)
- Clinical breast examination twice per year (age 20 years onward)
- Annual breast MRI screening (ages 20-75)
- Consider risk-reducing bilateral mastectomy
- Annual brain MRI (age 18 years onward)
- Annual WBMRI
- Abdominal and pelvic ultrasound every 12 months
- Upper endoscopy and colonoscopy every 2 to 5 years (age 25 years onward)
- Annual dermatologic examination.

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.

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REFERENCES


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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

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<th>Date</th>
<th>Action</th>
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<tr>
<td>March 2017</td>
<td>Replace policy</td>
<td>Policy updated with literature review through May 25, 2017; reference 12 added. Policy revised with updated genetics nomenclature. Policy statement updated for early-onset breast cancer to align with NCCN age cutoff of “&lt;31 years”. Clinical criteria removed from the Policy Guidelines section as it is repeated in the text.</td>
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<tr>
<td>September 2017</td>
<td>Replace policy</td>
<td>Policy updated with literature review through May 10, 2018; references 9, 13, 15-16, and 18 added. Policy statements unchanged except “at-risk relative” statement removed due to benefit considerations.</td>
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<tr>
<td>September 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through May 29, 2019; reference 19 added. Policy statements unchanged.</td>
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