Li-Fraumeni Syndrome Genetic Testing

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Introduction

Li-Fraumeni syndrome (LFS) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
TP53 deletion/duplication analysis	81479
TP53 known familial mutation analysis	81353
TP53 sequencing	81351
TP53 targeted sequence analysis	81352

Criteria

Introduction

Requests for Li-Fraumeni syndrome (LFS) genetic testing are reviewed using the following criteria.

TP53 Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing that would detect the familial mutation, AND
- Diagnostic and Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - Known family mutation in TP53, AND

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- Rendering laboratory is a qualified provider of service per the Health Plan policy.

TP53 Sequence Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy). AND
- Previous Testing:
  - No previous sequencing of TP53, and
  - No known familial mutation, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Classic LFS when **ALL** of the following are present:
    - Combination of an individual diagnosed less than age 45 years of age with a sarcoma, and
    - First-degree relative diagnosed less than 45 years of age with cancer, and
    - An additional first- or second-degree relative in the same lineage with cancer diagnosed less than 45 years of age, or a sarcoma at any age, OR
  - Chompret Criteria (2015) are met when **ANY** of the following are present:
    - Individual with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma) before age 46 years, and
      - at least one first- or second-degree relative with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) under the age of 56 years, or
      - at least one first- or second-degree relative with multiple primary cancers at any age, or
    - Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma) with the initial cancer occurring before the age of 46 years, regardless of the family history, or
    - Individual with adrenocortical carcinoma or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of the family history, OR
  - Early onset breast cancer
    - Individual with breast cancer diagnosed before 31 years of age, OR

  - Individual with a tumor from LFS tumor spectrum and one or more biologic relatives (1st, 2nd, or 3rd degree) with a clinical diagnosis of LFS (relative meets classic LFS criteria or Chompret criteria, as listed above) and no known family mutation or no testing to date, OR
  - Individual who was diagnosed with hypodiploid acute lymphoblastic leukemia (ALL) before age 21 years, OR

- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - One or more biologic relatives (1st, 2nd, or 3rd degree) with a clinical diagnosis of LFS (relative meets classic LFS criteria or Chompret criteria as listed above) and no known family mutation or no testing to date, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

TP53 Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous deletion/duplication analysis of TP53, and
  - No mutation detected on full sequencing of TP53, AND
- Diagnostic or Presymptomatic Testing:
  - Meets clinical criteria for TP53 sequence analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

LFS testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels,* as this testing is not addressed here.

For information on germline testing after somatic testing, please refer to the guideline *Hereditary (Germline) Testing After Tumor (Somatic) Testing*, as this testing is not addressed here.

What is Li-Fraumeni syndrome?

Definition

Li-Fraumeni syndrome (LFS) is a hereditary cancer-predisposition syndrome typically associated with soft tissue sarcoma, osteosarcoma, premenopausal breast cancer,

brain tumors, and adrenocortical carcinomas. People with LFS also have an increased risk of a variety of other childhood and adult-onset cancers.[1-3]

Prevalence

In Brazil, a high prevalence of LFS is present due to a founder mutation. A specific germline TP53 mutation (c.1010G>A; p.R337H) is present in 0.3% of individuals from the South/Southeastern regions, and it is estimated that more than 300,000 Brazilian individuals have LFS.[4]

The prevalence of inherited TP53 mutations is not well established but is estimated to be 1/3,555 to 1/5,476.[1]

Symptoms

Men with LFS have a 70% or higher lifetime risk of cancer while women have a 90% or higher lifetime risk of cancer. However, penetrance may be overestimated as more individuals with non-classic personal and/or family histories of cancer are identified to have TP53 mutations.[1]

Cause

LFS is caused by mutations in the TP53 gene.

Inheritance

LFS is an autosomal dominant disorder.[1]

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Diagnosis

The identification of a pathogenic mutation in the TP53 gene establishes the diagnosis.[1]

Complete TP53 gene sequencing will detect approximately 95% of known mutations.[1]

Deletion/duplication testing may be considered as a reflex test if a mutation is not found by sequencing. This method will identify gene rearrangements in an additional 1% of cases.

Management

The recommended surveillance for individuals with LFS includes whole-body MRI, ultrasound of the abdomen and pelvis, mammogram and breast MRI, clinical breast

exam, brain MRI, upper endoscopy and colonoscopy, dermatologic exam, and complete physical examination.[1,4] The age for initiation of screening and the frequency at which the screenings are repeated are well-defined.[1,2]

Survival

A study followed 89 individuals who pursued or declined recommended surveillance. The five year survival rate was 88.8% and 59.6% for those in the surveillance group versus those who declined, respectively.[1]

Test information

Introduction

Testing for LFS may include known familial mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and evidence

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2024) guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic outlined the following LFS testing criteria. These are considered a category 2A recommendation "lower level evidence with uniform NCCN consensus":[2]

- "Individual from a family with a known TP53 P/LP [pathogenic/likely pathogenic] variant," OR
- Classic LFS when ALL of the following are present:
  - "Combination of an individual diagnosed at age less than 45 years with a sarcoma AND
  - A first-degree relative diagnosed at age less than 45 years with cancer AND
  - An additional first- or second-degree relative in the same lineage with cancer diagnosed at age less than 45 years, or a sarcoma at any age," OR
- Chompret Criteria (2015 version)[5], when ANY of the following are present:
  - "Individual with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, central nervous system (CNS) tumor, breast cancer, adrenocortical carcinoma [ACC]), before 46 years of age, AND at least one first- or second-degree relative with any of the aforementioned cancer (other than breast cancer if the proband has breast cancer) before the age of 56 years or with multiple primaries at any age OR
  - Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 years OR
  - Individual with ACC or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of the family history OR
  - Breast cancer before 31 years of age".
- The presence of a P/LP TP53 variant on tumor only genomic testing "should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing. Somatic TP53 P/LP variants are common in many tumor types in absence of a germline P/LP variant."
- "In individuals with cancer with a P/LP TP53 variant identified on tumor only genomic testing, germline testing should be considered for:
  - (1) Those meeting one or more of the other LFS testing criterion above after reevaluation of personal and family history
  - (2) Those diagnosed age <30 with any cancer

- (3) Those with clinical scenario not meeting these criteria but warranting germline evaluation per clinician discretion."

- Hypodiploid Pediatric Acute Lymphoblastic Leukemia (ALL)

  - The National Comprehensive Cancer Network Guidelines (NCCN, 2024) for the treatment of Pediatric Acute Lymphoblastic Leukemia stated that germline TP53 mutations are common in low hypodiploid ALL and testing should be considered.[6]

Note This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Li-Fraumeni syndrome testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

References

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2. Daly M, Pal T, AlHilli Z, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2024 – February 12, 2024. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, available at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic V3.2024 – February 12, 2024. ©2024 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guideline® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guideline®, go online to NCCN.org

3. Hampel H, Bennett RL, Buchanan A, et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. *Genet Med*. 2015;17(1):70-87. Available at: https://www.acmg.net/docs/gim2014147a.pdf

4. Katz CP, Achatz MI, Brugieres L, et al. Cancer screening recommendations for individuals with Li-Fraumeni syndrome. *Clin Cancer Res*. 2017;23(11):e38-e45.

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6. Inaba H, Teachey D, Annesley C, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 5.2024 – April 3, 2024. Pediatric Acute Lymphoblastic Leukemia available at: https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline®) for Pediatric Acute Lymphoblastic Leukemia V5.2024 – April 3, 2024. ©2024 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guideline® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guideline®, go online to NCCN.org

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