Li-Fraumeni Syndrome

MOL.TS.193.A
v2.0.2021

Introduction

Li-Fraumeni syndrome 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

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 tumor, and adrenocortical carcinomas. People with LFS also have an increased risk of a variety of other cancers.[1-3]

Cause

Historically, there are two forms of LFS: Classic LFS, and Li-Fraumeni-like syndrome (LFL).[1] LFL shares some of the features for LFS, but has less strict clinical diagnostic criteria.[1] LFS/LFL are caused by mutations in the TP53 gene.

Prevalence

Prevalence of inherited p53 mutations is estimated to be 1 in 20,000.[1] The likelihood of detecting a TP53 mutation is about 70% in classic LFS cases and 40-50% in LFL cases.[1]

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Inheritance

This condition is inherited in an autosomal dominant manner.[1] Children of an affected person have a 1 in 2 (50%) chance to be affected. Most TP53 mutations are inherited from an affected parent.[1] The frequency of de novo mutations is not well defined but may be as high as 20%.[1]

Prognosis

About 50% of individuals with LFS/LFL will have cancer by 30 years of age, and 90% of individuals with LFS/LFL will have cancer by 60 years of age.[1]

Test information

Introduction

Testing for Li-Fraumeni may include sequence analysis, deletion/duplication analysis, or known familial mutation analysis.

Sequence analysis

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

Limited sequencing of only certain regions of the TP53 gene is also available. The detection rate of the limited sequencing tests varies between 70-90% depending on which portions of the gene are screened.[1]

Deletion/duplication testing

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.

Known familial mutation analysis

Once a mutation has been identified in the family, known familial mutation testing can be done for at-risk family members.[1,2]

Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to Li-Fraumeni testing.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (2020) guidelines outline the following Li-Fraumeni syndrome testing criteria (quoted directly). These are considered a category 2A recommendation "lower level evidence with uniform NCCN consensus":[2]

- Individuals from a family with a known TP53 mutation, OR
- Classic Li-Fraumeni syndrome 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 version)[4], when ANY of the following are present:
    - Individual with a tumor from LFS tumor spectrum (for example, soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma), 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 adrenocortical carcinoma or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of the family history
- Early onset breast cancer
    - Individual with breast cancer diagnosed before 31 years. TP53 testing can be ordered alone, concurrently with BRCA1/2 testing and/or other gene testing or as a follow up test after negative BRCA1/2 testing.
- Hypodiploid Pediatric Acute Lymphoblastic Leukemia (ALL)
    - The National Comprehensive Cancer Network Guidelines (2020) for the treatment of Pediatric Acute Lymphoblastic Leukemia state that germline TP53 mutations are common in hypodiploid ALL and testing should be considered.[5,6] Approximately 50% of pediatric patients (<21 years) with a diagnosis of hypodiploid ALL will have a germline TP53 mutation. A germline mutation has not been reported in individuals with adult-onset hypodiploid ALL.[1,6]

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Criteria

Introduction

Requests for Li-Fraumeni testing are reviewed using these 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 of TP53, AND
- Diagnostic and Predisposition Testing for Presymptomatic/Asymptomatic Individuals**:
  - Known family mutation in TP53, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

** Includes prenatal testing for at-risk pregnancies.

TP53 Sequencing

- 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 previous duplication/deletion analysis, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Classic Li-Fraumeni syndrome 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, sarcoma, CNS tumor, breast cancer, osteosarcoma, adrenocortical carcinoma, leukemia, or lung bronchoalveolar cancer) 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 are LFS tumor spectrum (eg, sarcoma, CNS tumor, breast cancer, osteosarcoma, adrenocortical carcinoma, leukemia, or lung bronchoalveolar cancer) 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

o Early onset breast cancer

▪ Individual with breast cancer diagnosed before 31 years of age, OR

o 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/LFL (relative meets classic Li-Fraumeni syndrome criteria or Chompret criteria, as listed above) and no known family mutation or no testing to date, OR

o Individual who is less than 21 years of age with hypodiploid acute lymphoblastic leukemia (ALL), OR

- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - One or more biologic relatives (1st, 2nd, or 3rd degree) with a clinical diagnosis of LFS/LFL (relative meets classic Li-Fraumeni syndrome 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 analyses of TP53, and
  - No mutation detected on full sequencing of TP53, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Li-Fraumeni

References

Introduction

These references are cited in this guideline.

1. Schneider K, Garber J. (Updated November 2019). Li-Fraumeni Syndrome. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2020. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1311/.
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6. Holmfeldt L, Wei L, Diaz-Flores E, et al. The genomic landscape of hypodiploid acute lymphoblastic leukemia. *Nat Genet*. 2013;45:242-52.

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