MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR LI-FRAUMENI SYNDROME
POLICY NUMBER	MP-2.274

Original Issue Date (Created):	**12/1/2014**
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Effective Date:	**9/1/2018**

I. 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 individuals with early-onset breast cancer (age of diagnosis <31 years).

Targeted *TP53* familial variant testing may be considered **medically necessary** in an at-risk relative of a proband with a known *TP53* pathogenic variant.

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

Policy Guidelines

GENETICS NOMENCLATURE UPDATE

Human Genome Variation Society (HGVS) 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). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and 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 uncertian significance	Change in the DNA sequence with uncertian 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

II. PRODUCT VARIATIONS

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This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

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FEP PPO: Refer to FEP Medical Policy Manual MP-2.04.101 Genetic Testing for Li-Fraumeni Syndrome. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

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TP53 GENE

The *TP53* gene contains the genetic instructions for the production of tumor protein p53 (or 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 a high lifetime cumulative risk of cancer and a tendency for multiple cancers in affected individuals. The syndrome was originally described in 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 1 study of 322 pathogenic variant 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 5 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 1

series, it was estimated that 6% of individuals diagnosed with ACC 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 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]

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 CriteriaChompret 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.[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* pathogenic variants, whereas the classic LFS criteria require a family history.

- 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 1 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), 2 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 and Chompret criteria, or who have been diagnosed with early-onset breast cancer (age of diagnosis <31 years).

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 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* 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/insertions and missense, nonsense, and splice site variants). Large deletions/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 tumor, level of risk of developing tumor, and outcome in patients with *TP53* germline pathogenic variants. [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* pathogenic variant, avoidance of radiotherapy, because the evidence suggests 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. 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.

IV. RATIONALE

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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.

V. DEFINITIONS

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NA

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VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

CPT Codes®								
81405	81479							

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ICD-10-CM Diagnosis Code	Description
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
Z15.01	Genetic susceptibility to malignant neoplasm of breast

IX. REFERENCES

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X. POLICY HISTORY

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MP 2.274	**CAC 7/22/14** New policy adopting BCBSA. Previously Li-Fraumeni Syndrome genetic testing was not specifically addressed, now listed as medically necessary with criteria.

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	CAC 7/21/15 Consensus. No change to policy statements. References and rationale updated**.** No coding changes.
	11/2/15 Administrative change. LCD number changed from L34796 to L35396 due to Novitas update to ICD-10.
	CAC 7/26/16 Consensus. No change to policy statements. Background, rationale and references updated. Coding reviewed.
	1/1/17 Administrative update. Variation section reformatted.
	CAC 9/26/17 Minor. Policy revised with updated genetics nomenclature. Policy statement updated for early-onset breast cancer to align with NCCN age cut-off of "<31 years". Coding updated with breast cancer diagnosis.
	7/9/18 Consensus review. No changes to the policy statements. References updated. Rationale revised**.**

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