I. 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 individuals with early-onset breast cancer (age of diagnosis ≤35 years).

(See Policy Guidelines #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 Guidelines #2)

Genetic testing for a germline TP53 mutation is considered not medically necessary for all other indications

Policy Guidelines

Policy Guideline #1
Diagnosis 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 (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 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 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

NCCN recommends that in patients with breast cancer diagnosed at ≤35 years, TP53 testing can be ordered concurrently with BRCA1/2 testing, or as a follow-up test after negative BRCA 1/2 testing. It has been estimated that among women with BRCA 1/2 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 1 percent of mutations in individuals meeting classic LFS criteria.

Policy Guideline #2

At the present time, 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 or 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 1 of a proband’s parents. After a mutation has been identified in a proband, the proband’s parent with any pertinent cancer history of 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 1 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%. (1)

II. PRODUCT VARIATIONS

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

BlueJourney HMO*  BlueJourney PPO*  FEP PPO**

*Refer to Novitas Solutions Local Coverage Determination (LCD) L35396 Biomarkers for Oncology.

** 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: www.fepblue.org

III. DESCRIPTION/BACKGROUND

Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome associated with the development of several different types of tumors. The syndrome is caused by germline mutations in the TP53 gene.

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 2 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 that are 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 and 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%. 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. Women with LFS are at greatly increased risk of developing premenopausal breast cancer, with the median age of diagnosis being 33 years of age. Male breast cancer has rarely been reported in LFS families. Many different types of brain tumors have been described in LFS, including astrocytomas, glioblastomas, medulloblastomas, and choroid plexus carcinomas. 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 a series, it was estimated that 6% of individuals diagnosed with ACC after age 18 years have a germline TP53 mutation.

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.

**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. The first formal criteria, the classic LFS criteria, were developed in 1988, and are the most stringent criteria used to make a clinical diagnosis of LFS. Since the availability of genetic testing, NCCN guidelines have recommended that a positive genetic test is required for a definitive diagnosis of 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

Chompret et al developed criteria which were shown to have the highest positive predictive value, and which, 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 mutations, whereas the classic LFS criteria require a family history.
Medical Policy

<table>
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<td>Policy Number</td>
<td>MP-2.274</td>
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- 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 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 LFS tumor spectrum and the first of which occurred before age 46 years; OR
- Patient with adrenocortical carcinoma (ACC) or choroid plexus tumor, irrespective of family history

National Comprehensive Cancer Network (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 ≤35 years).

**Molecular Diagnosis**

LFS is associated with germline mutations 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 mutations are known to cause LFS, and no other inherited phenotypes are associated specifically with germline mutations involving \( TP53 \). \(^1\)

LFS is a highly penetrant cancer syndrome, with the risks for cancer being ~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 \( TP53 \) gene are sequence variants (small intragenic deletions/insertions and missense, nonsense, and splice site mutations). Large deletion/duplications not readily detected by sequence analysis accounts for approximately 1% of the mutations detected. \(^2\) \(^1\)

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 radiation therapy. Preventive measures may include prophylactic mastectomy in women, and in all patients with a \( TP53 \) mutation, avoidance of radiation therapy, as there is some evidence to suggest 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, but, in general, the strategy includes physical examination, colonoscopy and breast imaging. Other protocols that are 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

Analytic Validity.
Analytic validity (technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent)

According to a large reference laboratory, analytic sensitivity and specificity for polymerase chain reaction sequencing for LFS TP53 testing and deletions/duplications testing by multiplex ligation-dependent probe amplification is greater than 95%.

The order of testing to optimize yield would be:

1) sequencing of the entire TP53 coding region (exons 2-11), which detects about 95% of TP53 mutations in patients with LFS. Examples of types of mutations detected by sequence analysis include small deletions/duplications, and missense, nonsense and splice site mutations; most are missense mutations
2) deletion/duplication analysis, which detects large deletions/duplications involving the coding region, exon 1, or promoter; these types of deletions/duplications are not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. These types of mutations account for less than 1 percent of mutations found in individuals with LFS.

Section Summary: Analytic Validity
There is a lack of published evidence on analytic validity of testing for TP53 mutations. It is expected that analytic validity will be high when testing is performed according to optimal laboratory standards. The website of 1 large laboratory claims analytic validity of greater than 95% but empirical, peer-reviewed data is not available.

Clinical Validity
Clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease)

Approximately 80% of families with features of LFS will have an identifiable TP53 mutation. (1) Families that have no identifiable TP53 mutation but share clinical features of LFS are more likely to have a different hereditary cancer syndrome (e.g., hereditary breast-ovarian cancer syndrome). (2)

Cohorts of individuals with adrenocortical carcinoma, which is diagnostic of LFS by the Chompret criteria, have been published. (12-14) In 1 study, 88 consecutive patients with adrenocortical carcinoma were evaluated. (14) Direct sequencing of exons 2 through 11 together with multiplex ligation-dependent probe amplification was used to identify mutations. For the entire population, 50% of individuals had a pathogenic mutation detected. The detection rate was dependent on age, with 58% of individuals younger than 12 years of age having a mutation compared with 25% of individuals between ages 12 and 20.

Section Summary: Clinical Validity
There is a small amount of evidence on the clinical validity of testing for TP53 mutations. In patients who meet clinical criteria for LFS, the clinical sensitivity has been reported to range between 50% and 80%. The largest amount of evidence is on patients with adrenocortical carcinoma, which represents a subset of all patients with LFS. No evidence was identified on the clinical specificity of testing.

Clinical Utility
Clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes)

The clinical utility of genetic testing can be considered in the following clinical situations: 1) individuals with suspected LFS, and 2) testing of asymptomatic family members to determine future risk of LFS.

Diagnostic Testing in Individuals With Suspected LFA
Direct evidence for the clinical utility of genetic testing to confirm a diagnosis of LFS is lacking. An indirect chain of evidence can provide evidence of clinical utility if all the
The elements contributing to the indirect chain of evidence are derived from evidence review 2.04.91 (general approach to genetic testing). The following series of questions represent the indirect chain of evidence for diagnostic testing to confirm a diagnosis of LFS.

Are there some individuals in which the diagnosis of LFS is uncertain following standard clinical workup without genetic testing?

Yes. There are standardized diagnostic criteria based on personal, clinical and family history. However, there are limitations to these methods of diagnosis. A detailed family history may not be complete or may not be available in many instances. There are different diagnostic instruments that use different criteria, and they may be used alone or in combination with each other. The population identified as having LFS will differ depending on the way the instruments are used. In addition, the available instruments do not have high overall accuracy. Therefore, there may be considerable uncertainty about the diagnosis using clinical criteria alone.

Can genetic testing make the diagnosis of LFS with certainty in patients with an uncertain clinical diagnosis?

Yes, in some patients. A positive genetic test will confirm the diagnosis of LFS with high certainty in individuals who meet clinical criteria. As a result, patients with a positive genetic test will have a high certainty for the diagnosis of LFS, whereas the diagnosis by clinical criteria alone has a high false positive rate of up to 50%.

Does establishment of a definitive diagnosis of LFS lead to management changes?

Yes. In the majority of cases, treatment and management will be unaffected by genetic testing, as individuals with a negative genetic test are likely to be treated as presumed LFS. However, there are some situations in which genetic testing may impact management. A positive test will facilitate the work-up for cancer susceptibility syndromes when multiple conditions are considered. Knowledge of mutation status may also assist in decision-making for prophylactic mastectomy by providing more definitive risk estimates.

Do the management changes result in improved health outcomes?

Yes. Outcomes are improved when a definitive diagnosis is made by avoiding the need for further testing to determine whether a cancer susceptibility syndrome is present. Better estimation of risk for breast cancer improves the capacity for informed decision-making regarding prophylactic mastectomy.

Testing Asymptomatic Individuals to Determine Future Risk of LFS

There is limited direct evidence on the clinical utility of genetic testing in this population. An indirect chain of evidence can provide evidence of clinical utility if all the links in the chain of evidence are intact. The elements contributing to the indirect chain of evidence are derived from evidence review 2.04.91 (general approach to genetic testing). The following series of questions represent the indirect chain of evidence for testing asymptomatic individuals to determine future risk of disease.

When there is a known pathogenic mutation in the family, is risk stratification by genetic testing superior to risk stratification from standard workup alone?

Yes. Genetic testing of close relatives of an index case with a pathogenic mutation will confirm or exclude the presence of the mutation with certainty. A positive test will confer high risk for multiple malignancies, while a negative test will imply that an individual is at average risk, in the absence of other high risk factors.
**MEDICAL POLICY**

<table>
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<th>POLICY TITLE</th>
<th>GENETIC TESTING FOR LI-FRAUMENI SYNDROME</th>
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<td>POLICY NUMBER</td>
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**Does the presence of a pathogenic mutation indicate high risk for clinical disease (high penetrance)?** Yes. The TP53 mutations have high penetrance, indicating high risk for clinical disease when a pathogenic mutation is present.

**Is there a presymptomatic phase during which preventive strategies can be implemented?** Yes. The multiple malignancies associated with LFS have presymptomatic phases in which early detection strategies can be implemented.

**Does the presence of a pathogenic mutation lead to management changes?**

Yes. The presence of a pathogenic mutation will lead to enhanced screening strategies for LFS associated malignancies. A negative genetic test will eliminate the need for enhanced screening strategies.

**Do management changes that occur as a result of genetic testing lead to improved health outcomes?**

Yes. Enhanced screening for breast cancer in high-risk individuals improves outcomes, and enhanced screening for lung cancer is also likely to improve outcomes. For the other LFS associated core cancers, outcomes of screening interventions are not certain due to the rarity of the conditions and lack of screening trials.

There is some direct evidence that enhanced screening protocols may improve outcomes. Villani et al conducted a prospective, observational study of members of 8 LFS families who were asymptomatic TP53 carriers.\textsuperscript{15} The participants either chose to undergo or to not undergo surveillance. Surveillance included biochemical and imaging studies, which included ultrasounds, brain magnetic resonance imaging (MRI) scans and rapid total body MRI scans. The primary outcome measure was detection of new cancers, and the secondary outcome measure was overall survival. Of 33 mutation carriers that were identified, 18 underwent surveillance. The surveillance protocol detected 10 asymptomatic tumors in 7 patients, which included premalignant or low-grade tumors (3 low-grade gliomas, a benign thyroid tumor, 1 myelodysplastic syndrome), and small, high-grade tumors (2 choroid plexus carcinomas, 2 adrenocortical carcinomas, 1 sarcoma). The 9 solid tumors that were detected were completely resected, and the patients were in complete remission. After a median follow-up of 24 months, all of the patients who had undergone surveillance were alive. In the nonsurveillance group, 12 high-grade, high-stage tumors developed in 10 patients, of which 2 were alive at the end of follow-up (p=0.04 for comparison of survival in the surveillance group). Three-year overall survival in the surveillance group was 100% and 21% in the nonsurveillance group (p=0.155). This study is limited by the observational design that included self-selection into screening protocols, likely resulting in selection bias. Further higher-quality evidence is needed to determine whether enhanced screening improves outcomes for TP53 mutations carriers.

**Section Summary: Clinical Utility**

Direct evidence of the clinical utility of TP53 testing is limited. One observational study reported improved survival for screened patients. However, this study is limited by the observational design that included self-selection into screening protocols, likely resulting in selection bias. An indirect chain of evidence can demonstrate clinical utility of genetic testing for TP53 mutations. For diagnosis, a positive genetic test will increase the certainty of LFS, facilitate the overall workup for cancer susceptibility syndromes, and assist in decision-making for prophylactic mastectomy. For
asymptomatic family members who have a close relative with a pathogenic mutation, genetic testing can confirm or exclude the presence of a mutation, and direct future screening interventions that are likely to improve outcomes.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in July 5, 2016 did not identify any ongoing or unpublished trials that would likely influence this policy.

Summary of Evidence
For individuals who meet diagnostic criteria for Li-Fraumeni syndrome or women with early-onset breast cancer who receive genetic testing for \textit{TP53}, 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 a small amount of evidence on the clinical validity of testing, with the most evidence being in the population of patients with adrenocortical carcinoma. For patients with suspected 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 2 following situations:

- Diagnostic testing of individuals with suspected LFS: For patients 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.

- Testing asymptomatic individuals to determine future risk of LFS: For asymptomatic relatives of an index patient with a pathogenic 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.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network guidelines (v.1.2016) \textsuperscript{16} recommend the following for LFS management:
Breast cancer risk, women:

- Breast awareness starting at age 18 years.
- Clinical breast exam every 6-12 months, starting at age 20-25 years or 5-10 years before the earliest known breast cancer in the family.
- Breast screening:
  - Age 20-29 years, annual breast MRI screening (preferred) or mammogram if MRI is unavailable or individualized based on earliest age of onset in family.
  - Age >30-75 years, annual mammogram, and breast MRI screening.
  - Age >75 years, management considered on an individual basis.
- Discuss risk-reducing mastectomy and counsel regarding degree of protection and cancer risk, and reconstruction options.
- Address psychosocial, social, and quality-of-life aspects of risk-reducing mastectomy.

Other cancer risks:
- Annual comprehensive physical exam with high index of suspicion for the cancers associated with LFS.
- Consider colonoscopy every 2-5 years starting no later than 25 years of age.
- Therapeutic radiation therapy for cancer treatment should be avoided when possible.
- Discuss option to participate in novel screening approaches using technologies.

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.

U.S. Preventive Services Task Force (USPSTF) Guidelines
No USPSTF guidelines for Li-Fraumeni syndrome testing have been identified.
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 for benefit information.

VII. DISCLAIMER

Capital’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 considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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:

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<th>CPT Codes®</th>
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<th>81479</th>
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<tr>
<th>ICD-10-CM Diagnosis Code*</th>
<th>Description</th>
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<tr>
<td>Z15.01</td>
<td>Genetic susceptibility to malignant neoplasm of breast</td>
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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

Other Sources:


X. POLICY HISTORY

<table>
<thead>
<tr>
<th>MP 2.274</th>
<th>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.</th>
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<tr>
<td></td>
<td>CAC 7/21/15 Consensus. No change to policy statements. References and rationale updated. No coding changes.</td>
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<tr>
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<td>11/2/15 Administrative change. LCD number changed from L34796 to L35396 due to Novitas update to ICD-10.</td>
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<tr>
<td></td>
<td>CAC 7/26/16 Consensus. No change to policy statements. Background, rationale and references updated. Coding reviewed.</td>
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<td>1/1/17 Administrative-variations reformatted.</td>
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