Genetic Testing for Li-Fraumeni Syndrome

Policy # 00424
Original Effective Date: 07/16/2014
Current Effective Date: 10/17/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing for *TP53* to confirm a diagnosis of Li-Fraumeni syndrome (LFS) under the following conditions to be **eligible for coverage:**

Patient Selection Criteria
Coverage eligibility will be considered when the following criteria are met:

- In a patient who meets either the classic or the Chompret clinical diagnostic criteria for Li-Fraumeni syndrome (LFS), or
  Diagnostic criteria for Li-Fraumeni syndrome (LFS):
  Classic Li-Fraumeni syndrome (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 Li-Fraumeni syndrome (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 Li-Fraumeni syndrome (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 Li-Fraumeni syndrome (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
- In women with early-onset breast cancer (age of diagnosis ≤31 years); or
  Note: National Comprehensive Cancer Network 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).
- Genetic testing for a *TP53* mutation in an at-risk relative of a proband with a known *TP53* variant.

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When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

The use of genetic testing for a germline TP53 variant when patient selection criteria are not met is considered to be **investigational.***

Background/Overview

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 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 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.

The tumor types that are most closely associated with LFS include soft tissue sarcomas, premenopausal breast cancer, brain tumors, and adrenal cortical carcinoma. 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.

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 ACC. In adults, in 1

series, it was estimated that 6% of individuals diagnosed with ACC after age 18 years have a germline *TP53* variant.

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 set of criteria, the classic LFS criteria, was developed in 1988, and is the most stringent criteria used to make a clinical diagnosis of LFS. Since the availability of genetic testing, National Comprehensive Cancer Network (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 (2001) 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 pathogenic variants*, whereas the classic LFS criteria require a family history.

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

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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*. 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. LFS is inherited in an autosomal dominant manner. De novo germline *TP53* pathogenic variants (no mutation is identified in either biologic parent) are estimated to be 7% to 20%.

Approximately 95% of pathogenic variants detected in *TP53* gene are sequence variants (small intragenic deletions/insertions and missense, nonsense, and splice site variants). Large deletion/duplications not readily detected by sequence analysis accounts for approximately 1% of the variants detected.

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 variants.

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* mutation, avoidance of radiotherapy, as there is some evidence to suggest that *TP*53 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, 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.

Testing Strategy
Given the common germline *TP53* variant types associated with LFS, a possible testing strategy to optimize yield would be:

1. Sequencing of the entire *TP53* coding region (exons 2-11). Examples of types of pathogenic variants detected by sequence analysis include small insertions and deletions (frameshift), and missense, nonsense, and splice site variants; most are missense variants.
2. Deletion and duplication analysis, which detects large deletions and duplications involving the coding region (exon 1) or promoter; these types of deletions and duplications are not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. These types of pathogenic variants account for less than 1% of those found in individuals with LFS.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

TESTING INDIVIDUALS WITH SUSPECTED LI-FRAUMENI SYNDROME

Clinical Context and Test Purpose
The purpose of genetic testing of individuals with suspected LFS is to establish the genetic diagnosis of LFS to inform management decisions such as prophylactic mastectomies in women, avoidance of radiotherapy, cancer surveillance, and aid in reproductive planning.

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The question addressed in this evidence review is: In individuals with suspected LFS, does the use of genetic testing improve health outcomes, including prophylactic mastectomies in women, avoidance of radiotherapy, necessitate or eliminate the need for increased cancer surveillance, or aid in reproductive decision making?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest includes individuals with suspected LFS.

Interventions
The relevant intervention of interest is genetic testing of *TP53*.

Comparators
The relevant comparator of interest is usual care without genetic testing.

Outcomes
The potential beneficial outcomes of primary interest include changes in management when test results are positive (ie, prophylactic mastectomies in women, avoidance of radiotherapy, increased cancer surveillance).

Timing
The time frame for outcome measures varies from several years for the development of cancers to long-term survival as a result of cancer.

Setting
Patients suspected of LFS are actively managed by medical geneticists or oncologists. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Approximately 80% of families with features of LFS will have an identifiable *TP53* pathogenic variant. Families that have no identifiable *TP53* pathogenic variant but share clinical features of LFS are more likely to have a different hereditary cancer syndrome (eg, hereditary breast-ovarian cancer syndrome).

Cohorts of individuals with adrenocortical carcinoma, which is diagnostic of LFS by the Chompret criteria, have been published. In a 2015 study, 88 consecutive patients with adrenocortical carcinoma were evaluated. Direct sequencing of exons 2 through 11 together with multiplex ligation–dependent probe amplification was used to identify pathogenic variants. For the entire population, 50% of individuals had a pathogenic variant detected. The detection rate varied by age, with 58% of individuals younger than 12 years of age having a pathogenic variant compared with 25% of individuals between ages 12 and 20.

The most comprehensive source of compiled data on the clinical validity of *TP53* pathogenic variants is found in the International Agency for Research on Cancer TP53 Database (R18, April 2016), which has shown tumor types associated with *TP53* germline variants (see Table 1). The main tumor types associated with *TP53* germline variants include breast, soft tissue, brain, adrenal gland, and bone tumor, which comprise 74% of all tumors with confirmed *TP53* germline variants.

Table 1. Tumors Associated With *TP53* Germline Variants (N=1644)

Tumor Type	No. With *TP53* Variant	Percentage With *TP53* Variant
Breast	449	27
Soft tissues	216	13
Brain	203	12
Adrenal gland	190	12
Bones	167	10
Other	142	9
Hematologic	57	3
Colorectal	51	3
Lung	41	2
Skin	41	2
Ovary	27	2
Stomach	20	1
Kidney	17	<0.5
Testis	7	<0.5
Liver	4	<0.5
Prostate	4	<0.5
Larynx	3	<0.5
Head and neck	3	<0.5
Esophagus	1	<0.5
Bladder	1	<0.5

Adapted from Bouaoun et al (2016).

O'Shea et al (2018) retrospectively analyzed 123 individuals (118 women, 5 men) in Ireland undergoing full *TP53* sequencing. Classic criteria for LFS or Li-Fraumeni like syndrome were met by 64 (52%) individuals, none of whom was *TP53*-positive. Of the 59 (48%) individuals who did not meet classic criteria, 2 had pathogenic *TP53* variants (3% detection rate), showing that broadened testing criteria may be beneficial. It

was noted that the detection rate of this study (1.6%) was lower than those of similar studies, but the authors suggested that this might be due to the predominance of patients in this cohort with breast cancer, which has an associated lower detection rate.

Rana et al (2018) published a retrospective, single-laboratory analysis of 38,938 individuals who had undergone *TP53* testing to compare different phenotype manifestations found in *TP53*-positive individuals identified by single-gene testing and multigene panel testing (MGPT). The differences included a significantly lower median age at first cancer for MGPT *TP53*-positive patients (n=126) than single-gene testing *TP53*-positive patients (n=96; women: median age, 36 vs 28 years; p<0.001; men: median age, 40 vs 15 years; p<0.004). For breast cancer specifically, median ages were 40 years and 33 years for MGTP *TP53*-positive and single-gene testing *TP53*-positive women, respectively (p<0.001). Also, fewer MGPT *TP53*-positive patients met LFS testing criteria. The study: (1) lacked complete family histories, (2) enrolled predominantly women with breast cancer in the MGPT cohort, (3) used improved technology permitting detection of lower levels of *TP53* variants, possibly contributing to misclassification, and (4) assessed a sample too small to investigate other possible factors for phenotypic variation.

Tables 2 and 3 summarize key study characteristics and results.

Table 2. Summary of Key Observational Comparative Study Characteristics

Study	Type	Country	Dates	Participants	Treatment
Wasserman et al (2015)	Cohort	U.S., Canada	NR	88	*TP53* testing
O'Shea et al (2018)	Retrospective	Ireland	2012-2014	123	*TP53* testing
Rana et al (2018)	Prospective	U.S.	2010-2014	38,938	*TP53* testing

NR: not reported.

Table 3. Summary of Key Observational Comparative Study Results

Study	*TP53*-Positive, n (%)	LFS-Positive, n (%)	*TP53* Variants Detected (n)
Wasserman et al (2015)	34 (50)		• *TP53* hotspot (2) • c.375G>A (3) • C229R (3) • deletion of exons 10 to 11 (2)
O'Shea et al (2018)		64 (52)	• c.919+1G>A (1) • c.818G>A (1)
Rana et al (2018)	132 (4.1)		• *TP53* VUS (38)

LFS: Li-Fraumeni syndrome; VUS: variants of uncertain significance.

Section Summary: Clinically Valid

Evidence on the clinical validity for testing for *TP53* pathogenic variants is provided by the International Agency for Research on Cancer TP53 Database, which includes a compilation of published studies and 891 families to date. The largest amount of evidence involves patients with breast, soft tissue, brain, and adrenal gland tumors, which represents a 72% of all patients with tumors who have an associated *TP53* germline variant. In patients who meet clinical criteria for LFS, the clinical sensitivity has been reported to range between 50% and 80%. No evidence was identified on the clinical specificity of testing.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Direct evidence for the clinical utility of genetic testing to confirm a diagnosis of LFS is lacking.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.
Diagnostic Testing in Individuals With Suspected LFS
A chain of indirect evidence was developed, which addresses 2 key questions:

1. Does use of *TP53* genetic testing in individuals with suspected LFS lead to change clinical management (eg, increased cancer surveillance, risk-reducing [prophylactic] mastectomy)?
2. Do those management changes improve outcomes?

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. Classic LFS and Chompret criteria, when used in combination, provide the greatest sensitivity to providing a clinical diagnosis of LFS. With the greater availability of genetic testing, National Comprehensive Cancer Network guidelines recommend that a positive genetic test be required for a definitive diagnosis of LFS.

Changes in Management
In most cases, treatment and management will be unaffected by negative results from genetic testing, because individuals with a strong clinical presentation for LFS 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 workup for cancer susceptibility syndromes when multiple conditions are considered. Knowledge of pathogenic variant status may also assist in decision making for risk-reducing mastectomy by providing more definitive risk estimates. If a cancer is detected, knowledge of the presence of a *TP53* variant would lead to avoidance of radiotherapy in the cancer treatment.

Improved Outcomes
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 risk-reducing mastectomy.

Section Summary: Clinically Useful
Direct evidence of the clinical utility of *TP53* testing is limited. One observational study reported improved survival for screened patients. However, the design of this study included self-selection into screening protocols, likely resulting in selection bias. However, an indirect chain of evidence can demonstrate clinical utility of genetic testing for *TP53* variants. For diagnosis, a positive genetic test will increase the certainty of LFS, facilitate the overall workup for cancer susceptibility syndromes, eliminate or necessitate the need for increased cancer surveillance and assist in decision making for prophylactic mastectomy.

TESTING AT-RISK RELATIVES OF A PROBAND WITH LFS
Clinical Context and Test Purpose
The purpose of targeted familial variant testing of at-risk relatives of a proband with LFS is to determine the carrier status of the relative when there is a known *TP53* pathogenic variant in the family. If the relative has a positive test for a known *TP53* familial variant, appropriate management such as risk-reducing (prophylactic) mastectomies in women, avoidance of radiotherapy, and cancer surveillance may be initiated. If the relative has a negative test for a known *TP53* familial variant, then increased cancer surveillance is not necessary.

The question addressed in this evidence review is: In at-risk relatives of a proband with LFS, does the use of targeted familial variant testing result in changes in management or outcome improvements, including, in the case of a positive result, risk-reducing mastectomies in women, avoidance of radiotherapy, necessitating or eliminating the need for increased cancer surveillance, or aid in reproductive decision making?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest includes at-risk relatives of a proband with LFS.

Interventions
The test being considered is targeted *TP53* familial variant testing.

Comparators
The following practice is currently being used: usual care without genetic testing.

Outcomes
The potential beneficial outcomes of primary interest include improved overall or disease-specific survival and reduced morbidity associated with changes in management when test results are positive (eg, risk-reducing mastectomies in women, avoidance of radiotherapy, increased cancer surveillance).

The potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to inappropriate surgeries (eg, risk-reducing mastectomies in women), inappropriate avoidance of radiotherapy, or psychological harm after receiving positive test results. False-negative test results can lead to lack of risk-reducing mastectomies in women, inappropriate use of radiotherapy, or lack of increased cancer surveillance.

Timing
The time frame for outcome measures varies from several years for the development of cancers to long-term survival as a result of cancer.

Setting
Patients suspected of LFS are actively managed by medical geneticists or oncologists. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

See the Clinically Valid section for Testing for Suspected Li-Fraumeni Syndrome.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

There is some direct evidence that enhanced screening protocols may improve outcomes. Villani et al (2011) conducted a prospective, observational study of members of 8 LFS families who were asymptomatic *TP53* carriers. Participants either chose or did not choose to undergo surveillance. Surveillance included biochemical and imaging studies, which included ultrasonography, brain magnetic resonance imaging, and rapid total body magnetic resonance imaging. The primary outcome measure was the detection of new cancers, and the secondary outcome measure was overall survival. Of 33 pathogenic variant carriers 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, 1 benign thyroid tumor, 1 myelodysplastic syndrome), and small, high-grade tumors (2 choroid plexus carcinomas, 2 adrenocortical carcinomas, 1 sarcoma). The 9 solid tumors detected were completely resected, and patients were in complete remission. After a median follow-up of 24 months, all patients who had undergone surveillance were alive. In the group without surveillance, 12 high-grade, high-stage tumors developed in 10 patients, of whom 2 were alive at the end of follow-up (p=0.04 vs 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 had an 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* pathogenic variant carriers.

Tables 4 and 5 summarize key study characteristics and results.

Table 4. Summary of Key Observational Comparative Study Characteristics

Study	Type	Country	Dates	Participants	Treatment	Follow-Up
Villani et al (2011)	Prospective	U.S., Canada	2004-2010	8 families	Comprehensive surveillance protocol	24 mo

Table 5. Summary of Key Observational Comparative Study Results

Study	*TP53* Variant Carriers Identified	Carriers Surveilled (%)	Tumors Detected in Surveilled Group (%)	3-Year OS (%)	3-Year OS in Nonsurveillance Group (%)	p
Villani et al (2011)	33	18 (54.5)	7 (38.9)	18 (100)	2 (20)	0.016

OS: overall survival.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Genetic testing of at-risk relatives who have family members with LFS may have clinical utility in:

- Confirming or excluding the need for cancer surveillance based on the presence or absence of a known *TP53* familial variant.
- Informing the reproductive decision making process in preimplantation testing, prenatal (in utero) testing, or altering reproductive planning decisions when a known *TP53* familial variant is present in a parent. Preimplantation testing is addressed elsewhere.

Testing At-Risk Relatives of Patients With LFS
There is limited direct evidence on the clinical utility of genetic testing in this population. Therefore, a chain of evidence was developed, which addressed 2 key questions:

1. Does use of the targeted *TP53* familial variant testing in individuals with suspected LFS and a proband with confirmed LFS lead to change clinical management (eg, increased cancer surveillance, risk-reducing [prophylactic] mastectomy, reproductive planning)?
2. Do those management changes improve outcomes?

Changes in Management
Genetic testing of close relatives of an index case with a pathogenic variant will confirm or exclude the presence of the variant 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.

TP53 pathogenic variants have high penetrance, indicating high risk for clinical disease when a pathogenic variant is present. The multiple malignancies associated with LFS have presymptomatic phases in which early detection strategies can be implemented. The presence of a pathogenic variant will lead to enhanced screening strategies for LFS-associated malignancies. A negative genetic test will eliminate the need for enhanced screening strategies.

Improved Outcomes
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 uncertain due to the rarity of the conditions and lack of screening trials.

Section Summary: Clinically Useful
Direct evidence of the clinical utility of *TP53* testing is limited. One observational study has reported improved survival for screened patients. However, the design of this study included self-selection into screening protocols, likely resulting in selection bias. A chain of evidence can demonstrate clinical utility of genetic testing for *TP53* variants. For asymptomatic family members who have a close relative with a pathogenic variant, genetic testing can confirm or exclude the presence of a variant, and direct future screening interventions that are likely to improve outcomes.

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.

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Policy History

Original Effective Date: 07/16/2014
Current Effective Date: 10/17/2018

07/10/2014	Medical Policy Committee review
07/16/2014	Medical Policy Implementation Committee approval. New policy.
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. No change to coverage.
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. Policy statement updated for early-onset breast cancer to align with NCCN age cutoff of “<31 years”.
10/04/2018	Medical Policy Committee review
10/17/2018	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 10/2019

Genetic Testing for Li-Fraumeni Syndrome

Policy # 00424
Original Effective Date: 07/16/2014
Current Effective Date: 10/17/2018

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81405, 81479
HCPCS	No codes
ICD-10 Diagnosis	Z15.01

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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