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Corporate Medical Policy

Genetic Testing for Li_Fraumeni Syndrome AHS – M2081

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Description of Procedure or Service

Li-Fraumeni syndrome is an autosomal dominant cancer predisposition syndrome characterized by a wide range of malignancies that appear at an unusually early age generally associated with defects in the tumor protein p53 gene (*TP53*) (Evans, 2019; Mai et al., 2016; Malkin, 2011).

Related Policies
Molecular Panel Testing of Cancers to Identify Targeted Therapy AHS – M2109
General Genetic Testing, Germline Disorders AHS – M2145
General Genetic Testing, Somatic Disorders AHS – M2146

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for genetic testing for Li-Fraumeni syndrome when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Li-Fraumeni Syndrome is covered

1. Reimbursement for genetic counseling for Li-Fraumeni Syndrome is allowed.

2. Genetic testing for TP53 mutations is considered medically necessary to confirm a diagnosis of Li-Fraumeni syndrome under the following conditions:

   A. In a patient who meets either the classic or the Chompret clinical diagnostic criteria for Li-Fraumeni syndrome (LFS)
      i. Classic LFS is defined by the presence of all the following criteria:
         a. A proband with a sarcoma before 45 years of age
         b. A first-degree relative with any cancer before 45 years of age
         c. A first- or second-degree relative with any cancer before 45 years of age or a sarcoma at any age

ii. Chompret clinical diagnostic criteria is defined by one of the following:
   a. 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 at any age; OR
   b. 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
   c. Patient with adrenocortical carcinoma (ACC) or choroid plexus tumor, at any age irrespective of family history

B. In women with early onset breast cancer (diagnosed at ≤30 years). The optimal strategy for confirming a TP53 mutation in a proband would be:
   i. Sequencing of the entire TP53 coding region (exons 2-11). If sequencing is negative, then:
   ii. Deletion/duplication analysis

3. Genetic testing for a TP53 mutation is considered medically necessary in a first, second or third degree relative of a proband with a known TP53 mutation (see Policy Guidelines No. 1).

4. Comprehensive genetic testing for a TP53 mutation (i.e. full sequencing of the genes and detection of large gene rearrangements) or multi-gene testing is considered medically necessary in a patient or, if unaffected, family member with highest likelihood of a mutation if there is no known familial TP53 mutation.

When Genetic Testing for Li-Fraumeni Syndrome is not covered

Genetic testing for a germline TP53 mutation is considered investigational when the above criteria have not been met.

See "**Note**" below in the Billing/Coding/Physician Documentation Information section.

Policy Guidelines

Policy Guideline #1:

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:

1. Proximity of relation to index case (first-, second-, or third degree)
2. Mode of inheritance of mutation (autosomal dominant versus autosomal recessive)
3. Degree of penetrance of mutation (high, intermediate or low)
4. Results of detailed pedigree analysis
5. De novo mutation rate

If a proband has a TP53 mutation, the risk to the proband's offspring of inheriting the mutation is 50 percent. 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.

Background

Li-Fraumeni syndrome (LFS) is a rare cancer predisposition syndrome associated with a germline mutation in the tumor suppressor gene *TP53* (tumor protein p53) on chromosome 17p13.1 (Correa, 2016). This genetic mutation has an autosomal dominant pattern of inheritance with high penetrance. *TP53* encodes for a ubiquitous transcription factor that is responsible for a complex set of critical regulatory functions that promote DNA repair and tumor suppression during episodes of cellular stress and DNA damage (Sorrell, Espenschied, Culver, & Weitzel, 2013).
Most *TP53* mutations are clustered in the DNA-binding domain within specific codons, such as 175 and 248 (Villani et al., 2016). *TP53* mutations are often missense alterations (Petitjean et al., 2007) that cause a change in one nucleotide and encode for a different amino acid than the one typically found in that particular location within the protein. Missense mutations are usually transcriptionally inactive leading to downstream events permissive for development of various malignancies throughout life; however, some reports have shown gain of function oncogenic effects in *TP53* (Brosh & Rotter, 2009; Sigal & Rotter, 2000).

LFS is characterized clinically by the development of cancers arising in multiple organ systems, often at a young age (Birch et al., 1998; Birch et al., 1994; Garber et al., 1991; Li et al., 1988; Mai et al., 2012; Malkin et al., 1990; Olivier, Hollstein, & Hainaut, 2010; Ruijs et al., 2010). These patients have a very high lifetime cumulative risk of developing malignancies and early-onset malignancies; around 50% of the individuals carrying mutations in *TP53* will develop cancer by the age of 30 years (Hwang, Lozano, Amos, & Strong, 2003; Lustbader, Williams, Bondy, Strom, & Strong, 1992; Schneider, Zelley, Nichols, & Garber, 2013b), with a lifetime risk of up to 70% in men and almost 100% in women (Chompret et al., 2000). While many tumor types can be seen in patients with LFS, four cancers (breast, sarcoma, brain, and adrenocortical carcinoma) comprise about 80% of LFS associated tumors (Gonzalez et al., 2009; Li et al., 1988; Lynch, Mulcahy, Harris, Guirgis, & Lynch, 1978; Olivier et al., 2003).

Breast Cancer accounts for about 30% of all LFS-associated tumors (Gonzalez et al., 2009; Olivier et al., 2003). Women with LFS-associated (NCCN, 2019, 2021) breast cancer tend to present at an earlier age (in the 20s or early 30s) with more advanced stage disease at the time of initial diagnosis. The ability to distinguish between a germline *TP53* mutation (LFS) and a somatic *TP53* pathogenic variant (*TP53* mosaicism or clonal hematopoiesis) is very important for breast cancer patients and relatives and may help to determine the best method of treatment; "For PV [pathogenic variant] carriers in high-penetrance genes like *BRCA1*, *BRCA2*, and *TP53*, prophylactic mastectomy is often recommended and radiation therapy avoided when possible (Batalini et al., 2019)."

Sarcomas account for about 30% of all LFS-associated tumors (Gonzalez et al., 2009; Ognjanovic, Olivier, Bergemann, & Hainaut, 2012; Olivier et al., 2003; Palmero, Achatz, Ashton-Prolla, Olivier, & Hainaut, 2010). Multiple types of soft tissue sarcomas and osteosarcoma are associated with LFS; but Ewing's sarcoma, gastrointestinal stromal cell tumors (GIST), desmoid tumors, and angiosarcomas have not been reported in LFS patients (NCCN, 2019, 2021; Olivier et al., 2003).

Brain Tumors occur in approximately 14% of individuals with *TP53* mutations (Gonzalez et al., 2009; Olivier et al., 2003; Palmero et al., 2010; Ruijs et al., 2010). Glioblastomas/astrocytomas are the most common, but medulloblastoma, ependymoma, supratentorial primitive neuroectodermal tumors, and choroid plexus tumors may also be seen (Farrell & Plotkin, 2007; Ruijs et al., 2010).

Adrenocortical Carcinoma (ACC) accounts for about 7% of cancers in *TP53* mutation carriers overall (Gonzalez et al., 2009; Palmero et al., 2010). While ACC has been diagnosed in individuals

with LFS at a wide range of ages, it is considered a hallmark of LFS when diagnosed in childhood (Gonzalez et al., 2009; Herrmann et al., 2012; Palmero et al., 2010).

Other LFS Cancers
Beyond the four core LFS cancers, the next most frequently associated cancers include leukemia, lung, colorectal, skin, gastric, and ovarian (Gonzalez et al., 2009; Masciari et al., 2011; Olivier et al., 2003; Palmero et al., 2010; Walsh et al., 2011; Wong et al., 2006). All cancer types are diagnosed at younger than average ages.

Over the years, several types of classifying systems have been developed for LFS diagnostic purposes (shown below in table 1). The classic LFS phenotype was clinically defined before the identification of germline mutations in *TP53*; these criteria are the most stringent and are the ones used to make a clinical diagnosis of LFS (with or without the identification of a deleterious germline *TP53* mutation) (Li et al., 1988). Further studies revealed that, although highly specific for *TP53* germline mutations, these criteria fail to include many mutation-positive families. Broader criteria were developed by Birch and Eeles to identify families which are Li-Fraumeni-like (LFL) (Birch et al., 1994; Eeles, 1995). The most robust analysis of *TP53* mutation carriers to date was performed in France by Bougeard et al. (2008); these analyses helped to develop the most recent version of the Chompret criteria which can better identify families with milder phenotypes (Chompret et al., 2001; Gonzalez et al., 2009). The Chompret criteria for clinical diagnoses of LFS was shown to provide the highest positive predictive value and, when combined with the classic LFS criteria, provided the highest sensitivity for identifying individuals with LFS (Bougeard et al., 2008; Tinat et al., 2009).

Table 1: Types of LFS classifying systems

Clinical criteria	Description
Classical LFS (Li, Fraumeni et al., 1988)	**I-**sarcoma diagnosed in childhood/young adulthood (≤ 45 years) **and**
	II-first-degree relative with any cancer in young adulthood (≤ 45 years) **and**
	III-first- or second-degree relative with any cancer diagnosed in young adulthood (≤ 45 years) **or** sarcoma diagnosed at any age.
LFL – Birch (Birch, Hartley et al., 1994)	**I-**childhood cancer (at any age) or sarcoma, CNS tumor, or ACC in young adulthood (≤ 45 years) **and**
	II-first- or second-degree relative with LFS-spectrum cancer (sarcoma, BC, CNS tumor, ACC, leukemia) at any age **and**
	III-first- or second-degree relative with any cancer diagnosed at age < 60 years.
LFL – Eeles 1 and 2 (Eeles, 1995)	**I-**at least 2 first- or second-degree relatives with LFS-spectrum cancer (sarcoma, BC, CNS tumor, ACC, leukemia, melanoma, prostate cancer, pancreatic cancer) diagnosed at any age **I-**sarcoma diagnosed at any age **and II-**at least 2 other tumors diagnosed in one or more first- or second-degree relatives: BC at age < 50 years; CNS tumor, leukemia, ACC, melanoma, prostate cancer, pancreatic cancer at age < 60 years; **or** sarcoma at any age.
LFL – Chompret (Chompret et al., 2001)	**I-**diagnosis of sarcoma, CNS tumor, BC, ACC at age < 36 years **and II-**first- or second-degree relative with any of the above cancers (except BC if proband had BC) **or**relative with multiple primary tumors at any age **or III-**multiple primary tumors, including two of the following: sarcoma, CNS tumor, BC, or ACC, with the first tumor diagnosed at age < 36 years regardless of family history; **or IV-**ACC at any age, regardless of family history.
LFL – Modified Chompret (Bougeard et al 2008; Tinat,et al., 2009)	**I-**index case with LFS-spectrum cancer (sarcoma, BC, CNS tumor, ACC, leukemia, bronchioloalveolar carcinoma) occurring at age < 46 years **and II-**a first- or second-degree relative with LFS-spectrum cancer occurring at age < 56 years (except BC if the index case has BC as well), **or** multiple tumors; **or III-**index patient with multiple tumors, at least two of which are in the LFS spectrum, the first occurring at age < 46

years; **or IV-**ACC or choroid plexus carcinoma occurring at any age or BC occurring at age < 36 years without *BRCA1*or*BRCA2*mutations.

ACC: adrenocortical carcinoma; BC: breast cancer; CNS: central nervous system; LFS: Li-Fraumeni syndrome; LFL: Li-Fraumeni-like syndrome.

As noted above, the *TP53* gene has an autosomal dominant pattern of inheritance (Evans, 2021). Mutations such as this can be studied with a pedigree, which is essentially a genetic based family tree. Pedigrees begin with the "proband," which is the subject being studied or tested. If one of the proband's parents carries the *TP53* mutation, each sibling has a 50% risk of having the mutation. If neither parent is found to carry the mutation, the risk to siblings is low, but they should be tested due to the possibility of germline mosaicism. Offspring of a proband have a 50% risk of carrying the mutation. Phenotypes of families carrying *TP53* mutations can be highly variable (Malkin, 2011; McBride et al., 2014).

Additionally, mutations in *TP53* can lead to different consequences on gene function. A locus is a fixed position on a chromosome where a gene is located. The possibility of a second locus involved in LFS is an additional issue in the etiology of the syndrome since approximately 20 % of LFS and up to 80 % of LFL families do not exhibit *TP53* mutations (Malkin, 2011; McBride et al., 2014). However, no association was found with p53 partners in tumor suppressor pathways, including *BAX* (BCL2 Associated X) (Barlow et al., 2004), *CDKN2A* (Cyclin Dependent Kinase Inhibitor 2A) (Portwine, Lees, Verselis, Li, & Malkin, 2000), *TP63* (tumor protein p63) (Bougeard et al., 2001), *CHEK2* (Checkpoint kinase 2) (Bougeard et al., 2001), *BCL10* (BCL10 Immune Signaling Adaptor) (Stone et al., 1999), or *PTEN* (Phosphatase and tensin homolog) (Brown, Sexsmith, & Malkin, 2000) in *TP53*-negative families. Although a few studies have linked other loci to LFS (Aury-Landas et al., 2013; Bachinski et al., 2005), *TP53* remains the only gene conclusively associated to the syndrome (Evans, 2021).

Large panels or single gene tests can be used to identify a *TP53* pathogenic variant. For example, Invitae has developed a test which analyzes only the *TP53* gene with a 3 mL whole blood sample; this test has a turnaround time of 10-21 days (Invitae, 2020). Blueprint Genetics has developed a similar one gene panel test which also analyzes the *TP53* gene in 3-4 weeks (BluePrint, 2020).

Clinical Validity and Utility

The reported percentage of LFS due to *TP53* mutation varies between studies and criteria used. According to Schneider et al. (2013b), approximately 80 percent of individuals with features of LFS will have an identifiable *TP53* mutation. Families that have clinical features of LFS without *TP53* mutation are more likely to have a different hereditary cancer syndrome (Schneider, Zelley, Nichols, & Garber, 2013a). Some studies have reported that approximately 70% to 80% of families meeting the classic LFS criteria have the *TP53* mutation (Nagy, Sweet, & Eng, 2004; Varley, 2003). However, Gonzalez et al. (2009) reported that a slightly lower positive predictive value for the p53 mutation rate using the classic criteria among 341 patients (56%), with high specificity of 91% but low sensitivity (40%). Chompret et al. (2001) reported *TP53* mutations can be found in 20% of cases using the Chompret criteria. Gonzalez et al (2009) reported a higher positive predictive value for LFL syndrome using Chompret criteria (35%) than Birch (16%) or Eeles (14%) (Gonzalez et al., 2009).

Gonzalez et al. (2009) used a clinical testing cohort to understand the spectrum of tumors associated with germline *p53* mutations. Mutations were identified in 17% (91 of 525) of patients submitted for testing. All families with a *p53* mutation had at least one family member with a sarcoma, breast, brain, or adrenocortical carcinoma. Overall, 75 patients with a *p53* mutation had

an adequate family history, and out of these 75, 71 fulfilled the classic LFS or Chompret criteria. When the classic LFS and Chompret criteria were used together, the testing sensitivity was 95%, and the specificity was 52% (Gonzalez et al., 2009).

Villani et al. (2011) assessed the feasibility and clinical impact of a comprehensive surveillance protocol in asymptomatic *TP53* mutation carriers in eight families with LFS. A total of 33 *TP53* mutation carriers were identified, 18 of whom underwent surveillance. In the surveillance group, 10 tumors developed in 7 patients, and all 7 patients were alive after a median follow-up of 24 months. In the non-surveillance group, 12 tumors developed in 10 patients, and only 2 were alive after 24 months. The authors reported a 3-year overall survival of 100% in the surveillance group compared to 21% in the non-surveillance group (Villani et al., 2011).

Bougeard et al. (2015) evaluated the genetic spectrum of LFS. The authors identified 415 *TP53* mutation carriers with 133 different *TP53* mutations. A total of 322 of these carriers were affected and eventually developed 552 tumors. In childhood, the LFS tumor spectrum was as follows: "osteosarcomas, adrenocortical carcinomas, central nervous system (CNS) tumors, and soft tissue sarcomas (STS) observed in 30%, 27%, 26%, and 23% of the patients, respectively." Adults presented with breast carcinomas in 79% of females and with soft tissue sarcomas in 27% of overall patients. Age of onset varied according to type of mutation; carriers with dominant-negative missense mutations had a mean onset of 21.3 years, carriers with loss of function mutations had a mean onset of 28.5 years, and carriers with genomic rearrangements had a mean onset of 35.8 years. The authors suggested that stratifying clinical management of LFS by class of mutation may be useful (Bougeard et al., 2015).

In 2016, Villani et al. (2016) updated their assessment of a prospective observational study and modified the surveillance protocol. Out of the 89 carriers of *TP53* pathogenic variants in 39 unrelated families, 40 (45%) agreed to surveillance and 49 (55%) declined surveillance. The authors reported a 5-year overall survival was 88.8% in the surveillance group and 59.6% in the non-surveillance group (Villani et al., 2016).

Rana et al. (2018) compared the histories of patients whose *TP53* mutations (*TP53+*) were identified by panel testing to those whose mutations were identified by single-gene testing. A total of 126 *TP53+* patients were identified with panel testing, and 96 were identified with single-gene testing. The patients who were identified with panel testing were older at "first cancer identification" and at cancer diagnosis. Established LFS testing criteria were met less often in patients in the panel testing cohort, and phenotypes of the panel testing cohort were often different from those in the single-gene cohort (Rana et al., 2018).

Bakhuizen et al. (2019) completed a nation-wide analysis in the Netherlands which measured *TP53* germline mutations in early-onset breast cancer cases. This study included data from 370 women diagnosed with breast cancer between 2005 and 2016 who were younger than 30 years at the time of diagnosis. All women included in the study were tested for *TP53* genetic mutations. A total of eight of these women were found to carry a likely pathogenic *TP53* sequence (< 1%), showing the rarity of a *TP53* mutation in breast cancer cases. However, the researchers note that *TP53* mutation prevalence was similar or greater in other studies which included patients with an older age of onset, questioning whether an early age of onset is necessary as a *TP53* genetic testing criterion (Bakhuizen et al., 2019).

Lincoln et al. (2020) studied the yield and utility of germline genetic testing following tumor DNA sequencing in patients with cancer. Germline testing was performed on 2023 patients and the prevalence of pathogenic germline variants (PGVs) was calculated. PGVs were found in 617 of the 2023 patients associated with cancers of the breast, colorectal, renal, lung, and bladder. About 82% of the patients identified with a PGV met the criteria for follow-up testing and 8.1% of PGVs were missed by tumor sequencing. Only 4% of pathogenic TP53 variants were germline, but 64% of the germline TP53 carriers did not meet the Chompret criteria for germline TP53 testing. It was found that genes which frequently acquire somatic mutations were a challenge because clinicians assumed TP53 to be somatic, so TP53 variants identified by tumor germline sequencing were underreported. The authors conclude that although the yield of germline findings of the TP53 gene is relatively low, the clinical impact can be substantial. Therefore, they recommend broader germline testing for these genes despite the low yield (Lincoln et al., 2020).

Terradas et al. (2021) studied *TP53* variants that were detected in colorectal cancer patients without a LFS phenotype. 473 patients with colorectal cancer were assessed for *TP53* pathogenic variants. Pathogenic variants were identified in 0.05% of the control and 0.26% of the colorectal cancer patients, none of whom fulfilled the clinical criteria for *TP53* testing. The authors conclude that "*TP53* pathogenic variants should not be unequivocally associated with LFS. Prospective follow-up of carriers of germline *TP53* pathogenic variants in the absence of LFS phenotypes will define how surveillance and clinical management of these individuals should be performed (Terradas et al., 2021)."

Guidelines and Recommendations

National Comprehensive Cancer Network (NCCN) (NCCN, 2019, 2020, 2021)
The NCCN maintains guidelines for the diagnosis and management of Li-Fraumeni Syndrome (NCCN, 2021)

NCCN recommends testing for Li-Fraumeni Syndrome in the following situations:

- Individual from a family with a known *TP53* pathogenic/likely pathogenic variant
- Classic Li-Fraumeni syndrome criteria
- Chompret criteria

The classic Li-Fraumeni syndrome criteria are as follows:

- Combination of an individual diagnosed age < 45 years with a sarcoma AND
- A first-degree relative diagnosed age < 45 years with cancer AND
- An additional first- or second-degree relative in the same lineage with cancer diagnosed < 45 years, or a sarcoma at any age (NCCN, 2021)"

The Chompret criteria are as follows:

- "Individual with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma [ACC]) before 46 y of age, 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) before the age of 56 y 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 y OR
- Individual with adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma or embryonal anaplastic subtype, at any age of onset, regardless of family history OR

- Breast cancer before age 31 years (NCCN, 2021)"

If these criteria are fulfilled, the *TP53* gene may be tested. If the familial pathogenic variant of *TP53* is known, that variant may be tested for. If it is unknown, a comprehensive *TP53* test may be done.

Reproductive options:

- "For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies (NCCN, 2019, 2021)."

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 . (NCCN, 2019, 2021)."

Children:

- "Genetic testing is generally not recommended when results would not impact medical management (NCCN, 2019)."

American College of Medical Genetics and Genomics (ACMG) (Kalia et al., 2017)

The ACMG has noted *TP53* as a gene whose secondary findings should be reported if found (Kalia et al., 2017).

Li-Fraumeni Syndrome Association (LFSA) (LFSA, 2021)

The LFSA notes certain criteria that can be used to determine if genetic testing should be performed. The classic LFS criteria, Chrompret criteria, Birch definition of Li-Fraumeni-like syndrome, and Eeles definition of Li-Fraumeni-syndrome may all be fulfilled to consider genetic testing (LFSA, 2021).

National Organization of Rare Diseases (NORD) (NORD, 2021)

The NORD states that "Li-Fraumeni syndrome is diagnosed based on clinical criteria and/or genetic testing for the mutation in the *TP53* gene"; further, "The potential of genetic testing (and the implications of the results) should always involve discussions with a genetic counselor, medical providers, and family (NORD, 2017)." The NORD also notes that genetic testing can be considered based on classic LFS criteria, Chrompret criteria, the Birch definition of Li-Fraumeni-like syndrome, and the Eeles definition of Li-Fraumeni-syndrome.

American Society of Breast Surgeons (ASBrS) (Manahan et al., 2019)

The ASBrS have published consensus guidelines on genetic testing for hereditary breast cancer. These guidelines state that "Increased access to testing would likely lead to more patients pursuing testing and improving rates of identification of gene carriers. Breast surgeons are well positioned to be a resource for patients who may benefit from testing. Breast surgeons can identify individuals who are suitable for testing, inform patients of the risks and benefits, provide access to genetic testing, and also discuss risk management strategies for those patients who test positive. For patients with less common mutations, strong consideration should be given to consultation with

cancer genetics specialists. Hereditary mutations to be considered include *BRCA* 1&2, *PALB2*, and other hereditary breast cancer syndromes, which include but are not limited to Li-Fraumeni syndrome (*TP53* pathogenic variant), Cowden syndrome (*PTEN* pathogenic variant), hereditary diffuse gastric cancer syndrome (*CDH1* pathogenic variant), and Peutz-Jegher syndrome (*STK11* pathogenic variant) (Manahan et al., 2019)."

European Reference Network GENTURIS (Frebourg, Bajalica Lagercrantz, Oliveira, Magenheim, & Evans, 2020)

ERN provides recommendations on cancer patients who should be tested for *TP53* germline mutations. They recommend testing the following patients:

- "Patients who meet the Chompret Criteria. These include those with familial presentation, multiple primitive tumors, rare tumors such as adrenocortical carcinoma, choroid plexus carcinoma, or rhabdomyosarcoma, or very early-onset breast cancer (Breast cancer before 31 years, irrespective of family history)
- Patients who are children or adolescents presenting with hypodiploid acute lymphoblastic leukemia, unexplained sonic hedgehog-driven medulloblastoma, or Jaw osteosarcoma.
- Patients who develop a second primary tumour, within the radiotherapy field of a first core *TP53* tumour which occurred before 46 years, should be tested for germline *TP53* variants
- Children with any cancer from southern and south-eastern Brazilian families should be tested for the p.R337H Brazilian founder germline *TP53* variant."

ERN does not recommend testing "patients older than 46 years presenting with breast cancer without personal or familial history fulfilling the 'Chompret Criteria'." If a patient with isolated breast cancer does not fulfill the Chompret Criteria but has a *TP53* variant, the patient should be referred to an expert multidisciplinary team for discussion.

ERN also provides testing recommendations for pre-symptomatic individuals. They recommend that:

- "Adult first-degree relatives of individuals with germline disease causing TP53 variants should be offered testing for the same germline TP53 variant.
- Testing in childhood of first-degree relatives of individuals with germline disease-causing TP53 variants should be systematically offered, if database shows that the variant can be considered as a high cancer risk TP53 variant conferring a high cancer risk in childhood."

Federal Applicable Regulations

No FDA-approved tests were found for the assessment of TP53 specifically for LFS. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Note: For 5 or more gene tests being run on a tumor specimen (i.e. non-liquid biopsy) on the same platform, such as multi-gene panel next generation sequencing, please refer to Laboratory Procedures Medical Policy AHS – R2162.

Applicable service codes: 81404, 81405, 81407, 81351, 81352, 81353, 96040, S0265

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Specialty Matched Consultant Advisory Panel review 3/2020

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Policy Implementation/Update Information

1/1/2019	BCBSNC will provide coverage for genetic testing for Li-Fraumeni syndrome when it is determined to be medically necessary because criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

8/27/2019 Reviewed by Avalon 2nd Quarter 2019 CAB. Added "Related Policies" section, policy guidelines updated, and coding table removed from the Billing/Coding section of the policy. References updated. No change to policy intent. Medical Director reviewed 8/2019. (jd)

10/29/2019 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed.

4/14/2020 Added the following to the When Not Covered section: "when the above criteria have not been met." Specialty Matched Consultant Advisory Panel review 3/2020. Medical Director review 3/2020. (jd)

7/28/20 Reviewed by Avalon 2nd Quarter 2020 CAB. The following note added to Billing/Coding section: "For 5 or more gene tests being run on a tumor specimen (i.e. non-liquid biopsy) on the same platform, such as multi-gene panel next generation sequencing, please refer to Laboratory Procedures Reimbursement Policy AHS – R2162." Policy guidelines and references updated. Medical Director review 7/2020. (jd)

3/31/21 Specialty Matched Consultant Advisory Panel review 3/2021. Medical Director review 3/2021. (jd)

8/24/21 Reviewed by Avalon 2nd Quarter 2021 CAB. Policy guidelines and Billing/Coding section updated. Medical Director review 7/2021. (jd)