Corporate Medical Policy

Genetic Testing for Li_Fraumeni Syndrome AHS – M2081

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

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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 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.

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**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.

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**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.

**Literature Review**
Li-Fraumeni syndrome is a rare cancer predisposition syndrome associated with germline mutation in the tumor suppressor gene *TP53* on chromosome 17p13 (Correa, 2016). It has an autosomal dominant pattern of inheritance with high penetrance. The human *TP53* gene (chromosome 17p13.1) 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).

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, 2013a), 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) 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.

**Sarcomas** account for another 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), desmoids tumors, and angiosarcomas have not been reported in LFS (NCCN, 2019; 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.
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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). The classic 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 this date was performed in France by Bougeard et al., in developing the most recent version of the Chompret criteria to better identify families with milder phenotypes(Chompret et al., 2001; Gonzalez et al., 2009) 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).

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<tr>
<th>Clinical criteria</th>
<th>Description</th>
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<tr>
<td>Classical LFS (Li, Fraumeni et al., 1988)</td>
<td>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.</td>
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<td>LFL – Birch (Birch, Hartley et al., 1994)</td>
<td>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 &lt; 60 years.</td>
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<td>LFL – Eeles 1 (Eeles, 1995) Eeles 2 (Eeles, 1995)</td>
<td>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 &lt; 50 years; CNS tumor, leukemia, ACC, melanoma, prostate cancer, pancreatic cancer at age ≤ 60 years; or sarcoma at any age.</td>
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<td>LFL – Chompret (Frebourg, Abel et al., 2001)</td>
<td>I-diagnosis of sarcoma, CNS tumor, BC, ACC at age &lt; 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 &lt; 36 years regardless of family history; or IV-ACC at any age, regardless of family history.</td>
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<td>LFL – Modified Chompret (Bougeard, Sesboüé et al., 2008; Tinat, Bougeard et al., 2009)</td>
<td>I-index case with LFS-spectrum cancer (sarcoma, BC, CNS tumor, ACC, leukemia, bronchioloalveolar carcinoma) occurring at age &lt; 46 years and II-a first- or second-degree relative with LFS-spectrum cancer occurring at age &lt; 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 &lt; 46 years; or IV-ACC or choroid plexus carcinoma occurring at any age or BC occurring at age &lt; 36 years without BRCA1orBRCA2mutations.</td>
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ACC: adrenocortical carcinoma; BC: breast cancer; CNS: central nervous system; LFS: Li-Fraumeni syndrome; LFL: Li-Fraumeni-like syndrome.

As the mutation is autosomal dominant (Evans, 2019), 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. 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 (Barlow et al., 2004), CDKN2A (Portwine, Lees, Verselis, Li, & Malkin, 2000), TP63 (Bougeard et al., 2001), CHEK2 (Bougeard et al., 2001), BCL10 (Stone et al., 1999), or PTEN (Brown, Sexsmith, & Malkin, 2000) in TP53-negative families. Although a few studies have linked other loci to LFL (Aury-Landas et al., 2013; Bachinski et al., 2005), TP53 remains the only gene conclusively associated to the syndrome (Evans, 2019).

**Clinical Validity and Utility**

The reported percentage of LFS due to TP53 mutation varies between studies and criteria used. According to Schneider et al approximately 80 percent of individuals with features of Li-Fraumeni Syndrome 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, 2013b). Some studies have reported that approximately 70% to 80% of families meeting the classic Li-Fraumeni syndrome criteria have TP53 mutation (Nagy, Sweet, & Eng, 2004; Varley, 2003). However, Gonzalez et al (Gonzalez et al., 2009) reported that a slightly lower positive predictive value for the classic criteria (56%), with high specificity but low sensitivity (40%). Chompret et al (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 Li-Fraumeni-like 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 Li-Fraumeni Syndrome or Chompret criteria. When the classic Li-Fraumeni syndrome and Chompret criteria were used together, the testing sensitivity was 95% and the specificity was 52% (Gonzalez et al., 2009).

Villani et al, assessed the feasibility and clinical impact of a comprehensive surveillance protocol in asymptomatic TP53 mutation carriers in eight families with Li-Fraumeni syndrome. 33 TP53 mutation carriers were identified, 18 of whom underwent surveillance. 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, evaluated the genetic spectrum of LFS. The authors identified 415 TP53 mutation carriers with 133 different TP53 mutations. 322 of these carriers were affected and eventually developed 552 tumors. In childhood, the LFS tumor spectrum was as follows: “osteosarcomas, adrenocortical carcinomas (ACC), 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...
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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 update their assessment of 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 compared the histories of patients whose TP53 mutations (TP53+) were identified by panel testing to those whose mutations were identified by single-gene testing. 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).

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.

Guidelines and Recommendations

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

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

- Individual from a family with a known TP53 mutation
- 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.

The Chompret criteria are as follows:

- Individual case with LFS-spectrum cancer (soft tissue sarcoma, breast cancer, CNS tumor, adrenocortical carcinoma [ACC], osteosarcoma) occurring at age < 46 years AND
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- A first- or second-degree relative with LFS-spectrum cancer occurring at age < 56 years (except breast cancer if the individual has breast cancer as well) or with multiple primaries at any age OR
- Individual with multiple tumors (except breast tumors), at least two of which are in the LFS spectrum, the first occurring at age < 46 years; OR
- Individual with ACC or choroid plexus carcinoma or rhabdomyosarcoma or embryonal anaplastic subtype occurring at any age regardless of family history OR
- Breast cancer before age 31 years.

If these criteria are fulfilled, the TP53 gene may be tested. If they familial pathogenic variant of TP53 is known, that variant may be tested. 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.

For relatives:
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives.

Children:
- Genetic testing is generally not recommended when results would not impact medical management.

American College of Medical Genetics and Genomics (ACMG, 2016)
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)
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 Eelse definition of Li-Fraumeni-syndrome may all be fulfilled to consider genetic testing (LFSA, 2019).

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.

Applicable service codes: 81404, 81405, 81407, 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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Genet, 21(12), 1369-1376. Retrieved from http://dx.doi.org/10.1038/ejhg.2013.68. doi:10.1038/ejhg.2013.68


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doi:https://www.ncbi.nlm.nih.gov/books/NBK1311/


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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)

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