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Genetic Testing for Li-Fraumeni Syndrome

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I. Policy Description

Li-Fraumeni syndrome (LFS) is an autosomal dominant cancer predisposition syndrome characterized by a wide range of malignancies that appear at an unusually early age and is generally associated with defects in the tumor protein p53 gene (TP53) (Evans, 2023; Mai et al., 2016; Malkin, 2011).

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) For individuals who have received genetic counseling and who have a close blood relative (see Note 1) with a TP53 mutation (see Note 2), the following germline testing **MEETS COVERAGE CRITERIA**
   a) Testing restricted to the known familial mutation.
   b) Comprehensive TP53 gene sequencing when the specific TP53 mutation is unknown.
2) For individuals who have received genetic counseling, germline testing for TP53 mutations (single gene or multi-gene panel testing) **MEETS COVERAGE CRITERIA** under any of the following conditions:
   a) For an individual who meets either the classic or the Chompret clinical diagnostic criteria for LFS:
      i) Classic LFS is defined by the presence of all of the following criteria:
         (a) An individual with a sarcoma before 45 years of age.
         (b) Having a first-degree relative (see Note 1) with any cancer before 45 years of age.
         (c) Having an additional first- or second-degree relative (see Note 1) with any cancer before 45 years of age, or a sarcoma at any age.
      ii) Chompret clinical diagnostic criteria is defined by the presence of any one of the following:
         (a) Individual with a tumor belonging to the LFS tumor spectrum (e.g., soft tissue sarcoma, osteosarcoma, central nervous system (CNS) tumor, breast cancer, adrenocortical carcinoma) before age 46 years AND at least one first- or second-degree relative (see Note 1) with a LFS tumor (except breast cancer if proband has breast cancer) before 56 years of age or with multiple tumors at any age.
         (b) Individual with multiple tumors (except multiple breast tumors), two of which belong to the LFS tumor spectrum described above, with the first tumor having occurred before 46 years of age.

(c) Individual with adrenocortical carcinoma (ACC), or choroid plexus tumor or rhabdomyosarcoma of embryonal anaplastic subtype, at any age, irrespective of family history.
(d) Individual was diagnosed with breast cancer before 31 years of age.

b) For an individual with a personal history of pediatric hypodiploid acute lymphoblastic leukemia.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

3) For all other situations not addressed above, single gene testing for a germline TP53 mutation **DOES NOT MEET COVERAGE CRITERIA**.

NOTES:

Note 1: Close blood relatives include 1st-degree relatives (e.g., parents, siblings, and children), 2nd-degree relatives (e.g., grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings), and 3rd-degree relatives (great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins).

Note 2: At the present time, there are no specific, evidence-based, standardized guidelines for recommendations of which "at risk" relatives should be tested. In relatives of an index case, the risk of having a pathologic mutation, and developing disease, is influenced by numerous factors that should be considered in evaluating risk:

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.

III. Table of Terminology

Term	Definition
ACC	Adrenocortical carcinoma
ACMG	American College of Medical Genetics and Genomics
ASBRS	American Society of Breast Surgeons

BAX	*BCL2 associated x* gene
BC	Breast cancer
BCL10	*BCL10 immune signaling adaptor* gene
BRCA 1	*Breast cancer 1* gene
BRCA 2	*Breast cancer 2* gene
CDKN2A	*Cyclin dependent kinase inhibitor 2A* gene
CHEK2	*Checkpoint kinase 2 gene*
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid Services
CNS	Central nervous system
DNA	Deoxyribonucleic acid
ERN	European Reference Network
FDA	Food and Drug Administration
GIST	Gastrointestinal stromal cell tumors
LDT	Laboratory-developed test
LFL	Li-Fraumeni-like syndrome
LFS	Li-Fraumeni syndrome
LFSA	Li-Fraumeni Syndrome Association
NCCN	National Comprehensive Cancer Network
NORD	National Organization of Rare Diseases
PALB2	*Partner and localizer of BRCA2* gene
PGV	Pathogenic germline variant
PTEN	*Phosphatase and tensin homolog* gene
PV	Pathogenic variant
STK11	*Serine/threonine kinase 11* gene
STS	Soft tissue sarcomas
TP53	*Tumor protein p53* gene
TP63	*Tumor protein p63* gene

IV. Scientific 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 et al., 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 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).

Li-Fraumeni syndrome 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 et al., 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 et al., 2003; Lustbader et al., 1992; Schneider et al., 2013a). 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 et al., 1978; Olivier et al., 2003).

Breast Cancer accounts for about 30% of all LFS-associated tumors (Gonzalez et al., 2009; Olivier et al., 2003). Individuals with LFS-associated 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 (NCCN, 2023). 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 et al., 2012; Olivier et al., 2003; Palmero et al., 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 (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 (Bougeard et al., 2001; Bougeard, Renaux-Petel, Flaman, Charbonnier, Fermey, Belotti, Gauthier-Villars, Stoppa-Lyonnet, Consolino, Brugières, et al., 2015; 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, Renaux-Petel, Flaman, Charbonnier, Fermey, Belotti, Gauthier-Villars, Stoppa-Lyonnet, Consolino, Brugieres, et al., 2015; Bougeard et al., 2008; Tinat et al., 2009).

Table 1: Types of LFS classifying systems

Clinical criteria	Description
Classical LFS (Li 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 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 two 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 two 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.
LFL – Revisiting Li-Fraumeni Syndrome from TP53 Mutation Carriers (Bougeard, Renaux-Petel, Flaman, Charbonnier, Fermey, Belotti, Gauthier-Villars, Stoppa-Lyonnet, Consolino, Brugières, et al., 2015)	**Familial presentation:** proband with tumor belonging to LFS tumor spectrum (eg, premenopausal breast cancer, soft tissue sarcoma, osteosarcoma, CNS tumor, adrenocortical carcinoma) before age 46 yr, AND at least on first or second-degree relative with LFS tumor (except breast cancer if proband has breast cancer) before age 56 yr or with multiple tumors; **Multiple primitive tumors:** Proband with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum and first of which occurred before age 46 yr. **Rare tumors:** patient with adrenocortical carcinoma, choroid plexus tumor or rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of family history; **Early-onset breast cancer:** Breast cancer before age 31 yr

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, 2023). Mutations such as this can be studied with a pedigree, which is 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 et al., 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 et al., 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, 2023).

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 three mL whole blood sample; this test has a turnaround time of 10-21 days (Invitae, 2023). Blueprint Genetics has developed a similar one gene panel test which also analyzes the TP53 gene in three to four weeks (BluePrint, 2022).

It is common to find TP53 mutations during tumor profiling, but germline mutations are very rare. Germline testing is not recommended if somatic mutations in TP53 are found unless there is a defined personal or family history indicative of Li-Fraumeni syndrome (Peshkin, 2023).

Clinical Utility and Validity

The reported percentage of LFS due to TP53 mutation varies between studies and criteria used. According to Schneider et al. (2013a), 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 et al., 2013b). Some studies have reported that 70% to 80% of families meeting the classic LFS criteria have the TP53 mutation (Nagy et al., 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 seven patients, and all seven patients were alive after a median follow-up of 24 months. In the non-surveillance group, 12 tumors developed in 10 patients, and only two were alive after 24 months. The authors reported a three-year overall survival of 100% in the surveillance group compared to 21% in the non-surveillance group (Villani et al., 2011).

Bougeard, Renaux-Petel, Flaman, Charbonnier, Fermey, Belotti, Gauthier-Villars, Stoppa-Lyonnet, Consolino, Brugieres, 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, Renaux-Petel, Flaman, Charbonnier, Fermey, Belotti, Gauthier-Villars, Stoppa-Lyonnet, Consolino, Brugieres, 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 individuals diagnosed with breast cancer between 2005 and 2016 who were younger than 30 years at the time of

diagnosis. All individuals included in the study were tested for TP53 genetic mutations. A total of eight of these individuals 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. A total of 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).

Yamamoto et al. (2020) performed an analysis of 194 patients with advanced cancer who had undergone next-generation sequencing (NGS) performed only on tumor specimens. The goal was to identify variants that had the potential to be secondary findings. Out of 194 patients, 120 were identified with possible secondary findings. The gene with the highest incidence was TP53, with a total of 97 variants identified among 91 patients. Of these patients, nine had additional germline testing performed, with 14 variant genes involved (BRCA1, n = 1; BRCA2, n = 2; PTEN, n = 2; RB1, n = 1; SMAD4, n = 1; STK11, n = 1; TP53, n = 6). Those persons identified with TP53 variants were confirmed as somatic variants, as opposed to germline. The authors concluded, "We analyzed 24 patients with TP53 variants who underwent a paired tumor–normal NGS assay. As expected, all TP53 variants were confirmed to be somatic variants. A total of 30 patients were tested for germline variants in TP53, but none of them resulted in true SFs, suggesting the low prevalence of SFs in this gene" (Yamamoto et al., 2020).

Patel et al. (2022) studied the clinical utility of widespread germline testing of cancer patients outside of guidelines. The goal of the study was to diversify the research area, as past studies on cancer screening have "skewed towards wealthier socioeconomic populations that lack ethnic diversity." The authors conducted a single center prospective study on germline testing, aiming to "understudied real-

world populations." The study included 67 patients, reported as "African American (14), White (50), or Asian American (3)." All patients were outside of guideline concordance for genetic testing due to either young age, rare tumors, or recurrent or multiple malignancies. There were 11 pathogenic or likely pathogenic variants that increased susceptibility to cancer, including rare germline findings and LFS. The authors concluded that "current practice of guidelines and genetic counselor recommended testing should be re-examined for broader testing for all incoming cancer patients in a more inclusive manner" (Patel et al., 2022).

V. Guidelines and Recommendations

National Comprehensive Cancer Network (NCCN)

The NCCN maintains guidelines for the diagnosis and management of Li-Fraumeni Syndrome (NCCN, 2023).

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
- Pediatric hypodiploid acute lymphoblastic leukemia
- Affected individual with pathogenic/likely pathogenic variant identified on tumor genomic testing that may have implications if also identified on germline testing.

The classic Li-Fraumeni syndrome criteria are as follows:

- "Combination of an individual diagnosed age <45 y with a sarcoma AND
- A first-degree relative diagnosed age <45 y with cancer AND
- An additional first- or second-degree relative in the same lineage with cancer diagnosed <45 y, or a sarcoma at any age" (NCCN, 2023).

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 of embryonal anaplastic subtype, at any age of onset, regardless of family history OR
- Breast cancer before age 31 years" (NCCN, 2023).

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, 2023).

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, 2023).

Children (under 18 years):

- "Genetic testing is generally not recommended when results would not impact medical management"(NCCN, 2023).

American College of Medical Genetics and Genomics (ACMG)

The ACMG has noted *TP53* as a gene whose secondary findings should be reported if found (Kalia et al., 2017). In 2021, a joint ACMG/AMP variant interpretation guideline was published for germline *TP53* variants; the authors note that "intense" cancer surveillance for those patients with *TP53* germline pathogenic variants can lead to "reduced cancer-related mortality" (Fortuno et al., 2021).

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 Eeles definition of Li-Fraumeni-syndrome may all be fulfilled to consider genetic testing (LFSA, 2023).

National Organization of Rare Diseases (NORD)

The NORD states that "Li-Fraumeni syndrome is diagnosed based on the presence of a so called pathogenic or likely pathogenic variant 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, 2021). 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)

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-Jeghers syndrome (*STK11* pathogenic variant)" (Manahan et al., 2019).

European Reference Network (ERN) GENTURIS

The ERN provides recommendations on cancer patients who should be tested for *TP53* germline mutations. They recommend testing the following patients (Frebourg et al., 2020):

- 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* tumor 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.

The 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 (Frebourg et al., 2020).

The 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" (Frebourg et al., 2020).

VI. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: http://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.
Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. Evidence-based Scientific References

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IX. Policy History

Action Date	Action
06/01/2023	Initial policy implementation
11/21/2023	Policy approved by Medical Directors
12/15/2023	Policy approved at UMC
2/01/2025	Policy effective date following notification period