Genetic testing for TP53 (p53) mutation is **COVERED** for individuals with suspected or known clinical diagnosis of Li-Fraumeni syndrome or Li-Fraumeni-Like syndrome, or a known family history of a TP53 mutation, or in women with early-onset breast cancer (less than age 31).

Genetic testing for germline TP53 mutation for all other indications, including general screening of healthy individuals with no family history, is investigative and unproven, and therefore **NOT COVERED**. There is insufficient reliable evidence in the form of high quality peer-reviewed medical literature to establish the efficacy or effects on health care outcomes.

**Note:** See also related coverage policy, *Genetic Testing*.

**Description**

Li-Fraumeni syndrome (LFS), also known as SBLA syndrome (Sarcoma, Breast, Leukemia, and Adrenal Gland) is an inherited cancer syndrome associated with a variety of malignancies. Cancers most often associated with LFS are premenopausal breast cancer, soft tissue sarcomas, osteosarcomas, brain tumors, and adrenocortical carcinomas. However, leukemia, colorectal cancer, lung cancer, choroid plexus carcinomas, among others, have also been associated with the syndrome. It is estimated that individuals with LFS have a 60% chance of malignancy prior to age 45, and a 95% chance by the age of 70. There are two types of LFS recognized: Li-Fraumeni syndrome and Li-Fraumeni-like syndrome. LFS is associated with germline mutations in the TP53 gene (chromosome 17p13.1), which encodes for a ubiquitous transcription factor that is responsible for a complex set of regulatory functions that promote DNA repair and tumor suppression. TP53 is the only gene in which mutations are known to cause LFS, and no other inherited phenotypes are associated specifically with germline mutations involving TP53. Approximately 70% of individuals with LFS have sequence variants in the tumor protein p53 (TP53) gene, a tumor suppressor gene.

The diagnosis of LFS is based on two sets of clinical classification criteria, Classic LFS and Chompret criteria, established using salient aspects of family history and tumor-related characteristics. Definitive diagnosis requires molecular testing with demonstration of a tumor protein p53 gene (TP53) mutation or exonic/multiexonic rearrangement (deletion or duplication).

1. Classic LFS criteria is defined by the presence of all of the following criteria:
   - An Individual with a sarcoma before 45 years of age
   - A first-degree relative with any cancer before 45 years of age
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- An additional first- or second-degree relative with any cancer before 45 years of age or a sarcoma at any age

2. Chompret Criteria:
- Individual 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 46 years of age, AND at least one first- or second-degree relative with LFS tumor (other than breast cancer if the proband has breast cancer) before age 56 years or with multiple tumors 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 years; OR
- Individual with adrenocortical carcinoma, or choroid plexus tumor or rhabdomyosarcoma of embryonal anaplastic subtype, at any ae of onset, regardless of the family history; OR
- Breast cancer before age 31 years.

3. Molecular Diagnosis:
- Genetic testing for this syndrome is available from numerous laboratories in the United States and generally involves direct sequence analysis of all coding regions of the p53 gene.

FDA Approval
Genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988. Premarket approval from the FDA is not required as long as the assay is performed in a laboratory facility that observes CLIA regulations. There are multiple laboratories in the United States currently testing for TP53 gene mutations, including but not limited to, the University of Minnesota, Transgenomic Labs, Omaha, NE, Prevention Genetics of Marshfield, WI, City of Hope Molecular Diagnostic Laboratory, Duarte, CA, Baylor College of Medicine Medical Genetics Laboratories, Houston, TX, and Ambry Genetics in Aliso Viejo, CA.

Coding Considerations
Use the current applicable CPT/HCPCS code(s). The following codes are included below for informational purposes only, and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

CPT Codes:
- 81404 - Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)…. Includes TP53 (tumor protein 53) (eg, tumor samples), targeted sequence analysis of 2-5 exons.
- 81405 - Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)… Includes TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome, tumor samples), full gene sequence or targeted sequence analysis of >5 exons

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