Li-Fraumeni syndrome is caused by pathogenic (or harmful) variants in the *TP53* gene. Individuals with Li-Fraumeni syndrome generally have a considerably high risk for several types of cancer (lifetime cumulative cancer risk is nearly 100%), can generally be diagnosed at significantly younger ages, and have an increased risk to get more than one type of cancer in their lifetime.

TP53 pathogenic variants are inherited in an autosomal dominant pattern, meaning that children of someone who carries a pathogenic variant each have a 50% risk to inherit the variant and associated cancer risks. Notably, women and men both have the TP53 gene and have the same chances to inherit and pass down variants in these genes. Therefore, both sides of the family are important when assessing inherited risk. However, the associated cancers and lifetime risks are different between men and women.

Cancers commonly associated with Li-Fraumeni syndrome include:

- Breast cancer
- Sarcoma (cancer of the soft tissue or bone)
- Adrenocortical cancer
- Brain cancer
- Colon cancer
- Lung cancer
- Leukemia
- Thyroid
- Others

Genetic testing for TP53

Genetic testing for pathogenic variants in TP53 are currently available, but there are a few different ways to approach testing:

- *Single site analysis*: Testing specific to a known pathogenic variant in the family
- Full gene sequencing and rearrangement analysis: Comprehensive testing to search for all currently detectable variants in the gene
- Gene panels: Newer, more broadly based gene tests that would include not only the TP53 gene, but other genes known or suspected to be associated with increased cancer risks

Whether or not someone meets criteria for genetic testing for Li-Fraumeni syndrome can be determined by a couple different methods. The ‘classic’ Li-Fraumeni criteria include:

- A combination of an individual diagnosed with a sarcoma before age 45, *AND*
- A first-degree relative (sibling, parent, or child) diagnosed with cancer before age 45, *AND*
- An additional first- or second-degree (aunts/uncles, nieces/nephews, grandchildren) relative in the same lineage with cancer diagnosed before age 45, or who was diagnosed with a sarcoma at any age.

Another set of criteria, called Chompret criteria, is a little more complicated. It says that individuals should consider genetic testing for Li-Fraumeni syndrome:

- Individual diagnosed before age 46 with a Li-Fraumeni-associated tumor (soft-tissue sarcoma, osteosarcoma, central nervous system tumor, breast cancer, adrenocortical carcinoma, etc) *AND* at least one first- or second-degree relative with any of the Li-Fraumeni-associated tumor (other than breast cancer if the primary individual has breast cancer) before the age of 56 or with multiple primaries at any age, *OR*
- Individual with multiple tumors (except multiple breast tumors), two of which are one of the above associated tumor types, with the initial cancer being diagnosed before age 46, *OR*
- Individual with adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of the family history, *OR*
- Breast cancer before the age of 31

These criteria are very complex, which is why a genetic counselor or other healthcare professional can help you determine if you meet this criteria and may have an increased risk for Li-Fraumeni syndrome.

Cancer Screening and Management for Li-Fraumeni syndrome

If you are tested and found to have a pathogenic variant in the TP53 gene, it is recommended to discuss your management plan with your healthcare team, and if available, to seek consultation through a specialized high-risk clinic. General recommendations are included here based on updated guidelines of the NCCN, but may be tailored to your specific medical and family history.

Breast cancer screening recommendations for women:

- Breast awareness starting at age 18
- Clinical breast exam every 6-12 months, starting at age 20-25, or at the age of earliest

diagnosed breast cancer in the family if below age 20
- Breast screening:
  - Age 20-29 (or at the age of earliest diagnosed breast cancer in the family if below age 20): annual breast MRI screening with contrast (preferred) or mammogram if MRI is unavailable
  - Age 30-75: annual mammogram and breast MRI screening with contrast
  - Over age 75: management should be considered on an individual basis
  - For women with Li-Fraumeni who have been treated for breast cancer, screening of the remaining breast tissue with annual mammograms and breast MRI should continue
- Discuss option of risk-reducing mastectomy, including the psychosocial, social, and quality-of-life aspects of the procedure

To address the risk for other cancers:

- Annual comprehensive physical exam, including a neurologic exam, paying extra attention for signs or symptoms of rare cancers
- Therapeutic radiation treatment for cancer should be avoided when possible
- Consider colonoscopy screening every 2-5 years starting at age 25, or 5 years before the earliest known colon cancer in the family (whichever comes first)
- Annual dermatologic examination
- Annual whole body MRI; the brain may be examined as part of this or as a separate exam
- Additional surveillance based on family history of cancer
- Provide education regarding signs and symptom of cancer

Click here to learn more about scheduling a genetic counseling appointment for questions about hereditary cancer predisposition.