What is Li-Fraumeni syndrome?
Li-Fraumeni syndrome (LFS) is a hereditary condition which causes a significantly increased risk to develop certain types of cancers. People with Li-Fraumeni syndrome are often diagnosed with cancer at younger than expected ages and may develop multiple different cancers in their lifetime. Not every person with Li-Fraumeni syndrome will develop cancer; however, the risks of developing cancer are much higher than the risk in the general population. In people with LFS, the lifetime risk to develop cancer can be as high as 73% for men and close to 90% for women (mostly due to the associated risk for breast cancer in women with LFS). Therefore, it is very important for people with LFS to be closely monitored for cancer development starting at a very young age.

The most common types of cancers seen in families with LFS include:
- Sarcomas of the soft tissue (such as fat tissue, muscles, or nerves)
- Osteosarcomas (sarcomas of the bone)
- Brain tumors
- Breast cancers
- Adrenocortical carcinomas (cancer of the adrenal gland)

Other cancers that can also be seen in people with LFS include:
- Melanoma (an aggressive type of skin cancer)
- Colon cancer
- Lung cancer
- Leukemia (typically acute myeloid leukemia (AML) in children)

What causes Li-Fraumeni syndrome?
Everyone has thousands of genes in their body that can act like instruction manuals to help direct and control various functions in the body. In fact, some of our genes even help to protect the body from developing cancer. Some people may have a mutation in one of these genes. A mutation is a harmful change in the gene that negatively impacts the function or “instruction” of the gene in the body. Li-Fraumeni syndrome occurs due to a mutation in the TP53 gene. The TP53 gene normally helps to control the growth of cells in our body. When someone has a mutation in the TP53 gene, the gene no longer can control cell growth resulting in an increased risk of uncontrolled growth of cells, which leads to the development of cancer.
How is Li-Fraumeni syndrome inherited?
A person with a mutation in the TP53 gene has a 50% chance, or one-in-two (1 in 2) chance, of passing the mutation on to each of his or her children. Both males and females have an equal risk to inherit the mutation from their parent who has the TP53 mutation. It is important to note that TP53 mutations do NOT skip generations.

Sometimes a mutation in the TP53 gene may occur at the time of conception and is a new mutation, called a “de novo” mutation. This means the mutation randomly developed in that person when he or she was conceived, but was not inherited from either parent. In these cases, the person usually does not have a family history of cancer concerning for LFS. However, this person is at risk to develop LFS-associated cancers and pass the mutation on to children. From our current understanding, de novo mutations in the TP53 gene occur in about 7-20% of people with LFS.

Genetic testing for Li-Fraumeni syndrome
Meeting with a genetic counselor to discuss your personal and family history will help determine whether genetic testing for Li-Fraumeni syndrome is indicated. Genetic testing for LFS is most often recommended when there is a:

- Known family history of Li-Fraumeni syndrome
- Personal or family history of a rare cancer associated with LFS
- Personal or family history of cancer diagnosed at a very young age, including in children
- Personal and/or family history of cancer that meets criteria for LFS

Deciding to have genetic testing for LFS may be complex and challenging for some people. A genetic counselor can help discuss the benefits, risks, and limitations of genetic testing. A confirmed diagnosis of LFS can help in creating a cancer screening and risk-reduction plan. Some people may also use this information in making reproductive decisions. However, some people who have genetic testing may experience depression, anxiety, or fear. Discussing all of these considerations and the possible outcomes of genetic testing with a genetic counselor can assist you in making the decision that is best for you.

If you decide to pursue genetic testing, it is typically performed on a blood or saliva sample. Genetic testing will thoroughly examine the TP53 gene to determine whether or not there is a mutation in the gene.

I was diagnosed with Li-Fraumeni syndrome. What are the next steps?
You and your providers should work together to create a personalized cancer screening and risk-reduction plan. Increased cancer screening helps in detection of
cancer at an early and often more treatable stage. In people with LFS, cancer screening typically begins at a younger age and is performed more often than cancer screening in people in the general population. People with Li-Fraumeni syndrome are strongly encouraged to be followed by a clinic or a physician who is well versed with LFS and its associated cancer risks and management guidelines.

Screening guidelines for men and women with LFS include:

- Yearly comprehensive physical exams and neurologic evaluation
- Yearly dermatological exams
- Yearly whole body MRI and brain MRI
- Colonoscopy screening every 2-5 years starting at age 25

For adult women with LFS, recommendations for breast cancer screening and risk reduction include:

- Yearly clinical breast exams
- Yearly breast MRI staring at age 20
- Yearly mammogram starting at age 30
- Consideration of risk-reducing mastectomy (removal of both breasts)

It is important to note that people with a TP53 mutation should avoid radiation exposure whenever possible, as radiation exposure increases the risk for cancer development. Additionally, people with LFS should avoid tobacco use, excessive sun exposure, and exposure to other known or suspected cancer-causing substances.

People found to have LFS have the option to meet with a physician with LFS expertise in the Smilow Cancer Genetics and Prevention Program at Yale New Haven Hospital to create a personalized screening and prevention plan.

**Support organizations**

Undergoing genetic testing and finding out you have Li-Fraumeni syndrome can be stressful. Some people may benefit from additional resources and support, such as connecting with others who have also been diagnosed with LFS. Some of these LFS resources include:

- Li-Fraumeni Syndrome Association: [www.lfsassociation.org](http://www.lfsassociation.org)
- Living LFS: Living LFS: Li-Fraumeni Syndrome
- National Society of Genetic Counselors: [www.nsgc.org](http://www.nsgc.org)