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# Li-Fraumeni Syndrome

**Approved by the Cancer.Net Editorial Board (http://www.cancer.net/about-us/cancernet-editorial-board), 01/2020**

## What is Li-Fraumeni Syndrome?

The Li-Fraumeni Syndrome (LFS) is a hereditary cancer predisposition syndrome first reported in 1969 by Drs. Frederick Li and Joseph Fraumeni from the National Cancer Institute. What caught their attention was the wide range of cancers found in affected families, the inherited higher risk of developing cancer across several generations, and the relatively early age of the cancer diagnosis with nearly half of affected individuals having a cancer diagnosis before age 30.

The most common types of cancer found in families with LFS include **osteosarcoma** (http://www.cancer.net/node/31389) (bone cancer), **soft tissue sarcoma** (http://www.cancer.net/node/31379), **acute leukemia** (http://www.cancer.net/node/31280), **breast cancer** (http://www.cancer.net/node/31322), **brain cancer** (http://www.cancer.net/node/31327), and **adrenal cortical tumors** (http://www.cancer.net/node/31341), which involves an organ on the top of the kidney. An increased risk for **melanoma** (http://www.cancer.net/node/31265), **Wilms' tumor** (http://www.cancer.net/node/31257), which is a type of kidney cancer, and cancers of the **stomach** (http://www.cancer.net/node/31376), **colon** (http://www.cancer.net/node/31317), **pancreas** (http://www.cancer.net/node/31388), **esophagus** (http://www.cancer.net/node/31310), **lung** (http://www.cancer.net/node/31273), and **gonadal germ cells** (http://www.cancer.net/node/31298) (sex organs) have also been reported.

## What causes LFS?

LFS is a hereditary genetic condition. This means that the cancer risk can be passed from generation to generation in a family. This condition is most commonly caused by a mutation (alteration) in a gene called *TP53*, which is the genetic blueprint for a protein called p53. The mutation takes away the gene's ability to function correctly. Approximately 70% of families with LFS will have a mutation in the *TP53* gene.

Mutations in the *TP53* gene are also found in 22% of families who have Li-Fraumeni-like Syndrome (LFL) by Definition 1 and in 8% of families who have LFL by Definition 2 (see full definitions, below).

Mutations in another gene, called *CHEK2*, have been found in some families with LFS. It is not known whether the cancer risks are the same in families that have *TP53* mutations and *CHEK2* mutations. However, with the increase in multiple-gene panel testing, many carriers of *CHEK2* mutations are being identified, most with far less incidence of cancer in their family histories than with LFS. Research is ongoing to identify other genes associated with LFS and LFL.

## How is LFS inherited?

Normally, every cell has 2 copies of each gene: 1 inherited from the mother and 1 inherited from the father. LFS follows an autosomal dominant inheritance pattern. That means that even if a mutation happens in only 1 of the 2 copies of the *TP53* gene, that person will have LFS. When a person

inherits a mutation from a parent, it is called a germline mutation.

Most people with LFS have 1 normal copy of *TP53* and 1 mutated (altered) copy of *TP53*, most often because they have inherited the mutated copy of *TP53* from a parent who was also affected by LFS. However, it is estimated that 25% of people with LFS do not have any family history of the condition; they have a *de novo* (new) mutation in the *TP53* gene. Regardless of whether a person inherits a mutation or it is a *de novo* mutation, that person has a 50% chance of passing on the normal copy of the *TP53* gene and a 50% chance of passing on the mutated copy of the gene to any children. A brother, sister, or parent of a person who has a mutation also has a 50% chance of having the same mutation. However, if the parents test negative for the mutation (meaning each person's test results found no mutations), the risk to the sibling significantly decreases but their risk may still be higher than an average risk. Learn more about **genetics** (http://www.cancer.net/node/24864) .

Options exist for people interested in having a child when a prospective parent carries a gene mutation that increases the risk for this hereditary cancer syndrome. Preimplantation genetic diagnosis (PGD) is a medical procedure done in conjunction with in-vitro fertilization (IVF). It allows people who carry a specific known genetic mutation to reduce the likelihood that their children will inherit the condition. A woman’s eggs are removed and fertilized in a laboratory. When the embryos reach a certain size, 1 cell is removed and is tested for the hereditary condition in question. The parents can then choose to transfer embryos that do not have the mutation to the woman’s uterus. PGD has been in use for over 2 decades and has been used for several hereditary cancer predisposition syndromes. However, this is a complex procedure with financial, physical, and emotional factors to consider before starting. For more information, talk with an assisted reproduction specialist at a fertility clinic.

## How common is LFS?

LFS is rare, but with the introduction of the Chompret Criteria (see below), more families with LFS have been identified. It was previously estimated that less than 400 families had been diagnosed with LFS worldwide. Now, LFS is thought to be as frequent as 1 in 5,000 families to 1 in 20,000 families.

As testing for hereditary cancer expands to include multi-gene panels, the classical definition of syndromes such as LFS may change. Some individuals may have a mutation in the *TP53* and *CHEK2* gene but do not meet any of the criteria listed below for LFS. It is not known if these people will have the same risks for developing cancer.

### How is LFS diagnosed?

**Classic LFS** is diagnosed when a person has **all** of the following criteria:

- A sarcoma diagnosed before age 45
- A first-degree relative, meaning a parent, sibling or child, with any cancer before age 45
- A first-degree relative or second-degree relative, meaning a grandparent, aunt/uncle, niece/nephew, or grandchild, with any cancer before age 45 or a sarcoma at any age

**Chompret Criteria for Clinical Diagnosis of Li-Fraumeni Syndrome** is a recent set of criteria that has been proposed to identify affected families beyond the Classic criteria listed above. A diagnosis of LFS and performing *TP53* gene mutation testing is considered for anyone with a personal and family history that meets **1** of the following 3 criteria:

Criterion 1

- A tumor belonging to the LFS tumor spectrum, before the age of 46. This means any of the following diseases: soft tissue sarcoma, osteosarcoma, pre-menopausal breast cancer, brain

tumor, adrenal cortical carcinoma, leukemia, or lung cancer, **and**
- At least 1 first-degree or second-degree family member with an LFS-related tumor, except breast cancer if the individual has breast cancer, before the age of 56 or with multiple tumors

Criterion 2

- A person with multiple tumors (except multiple breast tumors), 2 of which belong to the LFS tumor spectrum and the first of which occurred before age 46

Criterion 3

- A person who is diagnosed with adrenal cortical carcinoma or a tumor in the choroid plexus, meaning a membrane around the brain, regardless of family history

**Li-Fraumeni-like Syndrome (LFL)** is another, similar set of criteria for affected families who do not meet Classic criteria (see above). There are 2 suggested definitions for LFL:

LFL Definition 1, called the Birch definition:

- A person diagnosed with any childhood cancer, sarcoma, brain tumor, or adrenal cortical tumor before age 45 **and**
- A first-degree or second-degree relative diagnosed with a typical LFS cancer, such as sarcoma, breast cancer, brain cancer, adrenal cortical tumor, or leukemia, at any age **and**
- A first-degree or second-degree relative diagnosed with any cancer before age 60

LFL Definition 2, called the Eeles definition:

- 2 first-degree or second-degree relatives diagnosed with a typical LFS cancer, such as sarcoma, breast cancer, brain cancer, adrenal cortical tumor, or leukemia, at any age

## Other risk factors to consider, specific to breast cancer:

- A woman who has a personal history of breast cancer at a younger age and **does not** have an identifiable mutation in breast cancer genes 1 or 2, called *BRCA1* or *BRCA2*.
  - A woman who is diagnosed with breast cancer before age 30 and is not found to have a *BRCA* mutation has an estimated 4% to 8% likelihood of having a *TP53* mutation
  - Women with breast cancer diagnosed between ages 30 and 39 may also have a small increased risk of having a *TP53* mutation

- Possible *TP53* mutation in younger women with breast cancer is also increased with any of the following features:
  - A family history of cancer, especially LFS-related cancers
  - A personal history of a breast tumor that is positive for estrogen (ER), progesterone (PR), and HER2/neu markers, also known as “triple-positive” breast cancer. Learn more about these markers in this **website’s main section on breast cancer** (http://www.cancer.net/node/18624) .
  - A personal history of an additional LFS-related cancer

## Can I have *TP53* genetic testing?

In the past, the diagnosis of LFS was made by clinical criteria, meaning it was based on the signs and symptoms the patient and family had. Now, genetic testing is available for people to learn whether they carry a copy of the *TP53* mutation before any physical signs of LFS appear.

The decision to test is highly personal. People considering *TP53* genetic testing are strongly encouraged to receive professional genetic counseling first, so they can gain the knowledge they need to make an informed decision. This can also help with the serious emotional effects that may occur when people learn that they are a carrier. Genetic counseling, as a part of considering genetic testing, is important not only for the patient but also for that person's relatives.

Testing a child in a family with LFS is a complex situation since the decision to do testing must made by the child's parents, with the help of medical experts. However, since cancers occur often among children in families with LFS, testing at-risk children, rather than delaying testing until young adulthood, must also be strongly considered when the goal is to find LFS-related cancers early and treat them more effectively.

If genetic testing shows that a person has a *TP53* mutation, this may mean that their doctor could recommend surveillance, which means being monitored (screened) regularly for LFS-related types of cancer. This is an in-depth, lifelong process. More about the surveillance process is outlined below.

Knowing whether there is a *TP53* mutation may help a doctor to make appropriate and effective medical recommendations. Specifically, some data suggests people with LFS are very sensitive to radiation. This means that affected people may be advised to avoid or minimize radiation exposure in some types of screening scans and cancer treatments, if other options are available.

Genetic testing for a *CHEK2* mutation is also available, but at this time little is known about the potential benefits of detailed surveillance if a mutation is identified. However, screening for common cancers, such as those in the breast and colon, has the potential to find cancers earlier and at a more curable stage.

## What are the estimated cancer risks associated with LFS?

The lifetime risk for a person with LFS to develop any type of cancer is 90%. Approximately 50% of these cancers will be diagnosed before age 30. In a study of 200 people with a *TP53* gene mutation who had a previous diagnosis of cancer, 15% developed a second cancer, 4% developed a third cancer, and 2% developed a fourth cancer, with the highest risk of additional cancers being in those diagnosed with their first cancer during childhood. However, some people with LFS will never develop cancer.

## What is the surveillance/monitoring strategy for people with *TP53* mutations, to watch for the development of cancer?

There is increasing research showing that an intensive screening plan improves survival of individuals with a *TP53* mutation who do not have any signs or symptoms of cancer. People following this screening protocol have regular cycles of testing on a yearly basis, including: whole-body magnetic resonance imaging (**MRI** (http://www.cancer.net/node/24578) ), brain MRI, abdominal **ultrasound** (http://www.cancer.net/node/24714) , and biochemical markers of adrenal cortical function. If this plan is followed, it may be important to work with specialists to complete the recommended screening because some tests, such as rapid whole-body MRI, may only be available at specific centers. Additional studies are needed to demonstrate the effectiveness of this surveillance strategy in both affected adults and children.

Individuals in families with LFS have been surveyed regarding their attitudes toward cancer surveillance, given there is not complete data about its overall effectiveness. In a 2010 study, most individuals believed in the value of surveillance in order to find tumors at an early stage and also reported psychological benefits, including a better to sense of control and security, when they participated in a regular surveillance program.

Children and adults should undergo comprehensive annual physical examinations, including careful skin and neurologic examinations. Other screening tools are outlined below for more common LFS-related cancers.

## Children:

*Adrenocortical carcinoma*

- **Ultrasound** (http://www.cancer.net/node/24714) of abdomen and pelvis every 3 to 4 months
- Complete urinalysis every 3 to 4 months
- Blood tests every 4 months: β-human chorionic gonadotropin, alpha-fetoprotein, 17-OH-progesterone, testosterone, dehydroepiandrosterone sulfate, and androstenedione

*Brain tumor*

- Annual brain **MRI** (https://www.cancer.net/navigating-cancer-care/diagnosing-cancer/tests-and-procedures/magnetic-resonance-imaging-mri)

*Soft tissue and bone sarcoma*

- Annual, rapid whole-body MRI, meaning an MRI with fast imaging times

*Leukemia or lymphoma*

- Blood test every 4 months: complete blood count (CBC), erythrocyte sedimentation rate, lactate dehydrogenase

## Adults:

Individuals should pay close attention to any lingering symptoms and illnesses, particularly headaches, bone pain, or abdominal discomfort. If a person experiences such signs, that person is encouraged to talk with their doctor as soon as possible.

*Breast cancer*

- Monthly breast self-examination, starting at age 18
- Clinical breast examination twice a year, starting at age 20 to 25, or 5 to 10 years before the earliest known breast cancer diagnosis in the family

Women should undergo breast cancer monitoring, with annual breast MRI and twice-yearly clinical breast examination, which is an examination by a health professional, beginning at age 20 to 25. The use of mammograms, which is an x-ray of the breast, has been controversial because of radiation sensitivity concerns (see below). Mammograms should not be started younger than age 30, given evidence that the breast is more sensitive to cancer caused by radiation when women are in their 20s. If performed, annual mammograms should alternate with breast MRI every 6 months. Women with LFS should talk with their doctor about other options to **reduce future risk of breast cancer** (http://www.cancer.net/node/18621).

*Brain tumor*

- Annual brain MRI

*Soft tissue and bone sarcoma*

- Annual, rapid whole-body MRI

- Ultrasound of abdomen and pelvis every 6 months

*Colon cancer*

- **Colonoscopy** (http://www.cancer.net/node/24481) every 2 years, beginning at age 25 to 30 or 10 years before the earliest known colon cancer in the family

*Melanoma*

- Annual dermatology (skin) examination

*Leukemia or lymphoma*

- Complete blood count every 4 months
- Erythrocyte sedimentation rate, lactate dehydrogenase every 4 months

**These screening tools should be used in addition to regular check-ups with the person's physician and with close attention to any medical concerns or complaints. Additional testing should be done as needed.** A person with LFS should talk with his or her doctors about their experience with LFS, as doctors who are monitoring people with LFS should be aware of the high risks for uncommon types of cancers, the earlier-than-usual development of more common cancers, and also for second cancerous tumors in cancer survivors with LFS.

Learn more about **what to expect when having common tests, procedures, and scans** (http://www.cancer.net/node/24959).

## Radiation sensitivity

As mentioned above, there is some evidence that a *TP53* genetic mutation can cause a person to have an increased sensitivity to ionizing (therapeutic) radiation. When possible, people with a germline *TP53* mutation should avoid or minimize exposure to diagnostic radiation, such as certain scans, and treatments that use radiation to treat the cancer, such as radiation therapy. For instance, in order to reduce their exposure to radiation, some women with a diagnosis of breast cancer may choose to have a mastectomy, meaning the surgical removal of the entire breast, instead of having the combination of lumpectomy, meaning the surgical removal of the tumor and surrounding breast tissue, and radiation therapy together. However, there is strong medical agreement that there are times when radiation therapy for specific types of tumors will still be the most effective treatment plan to recommend. Radiation-induced second cancers (generally sarcoma) have been reported among people with a germline *TP53* mutation.

## Questions to ask the health care team

If you are concerned about your risk of cancer, talk with your health care team. It can be helpful to bring someone along to your appointments to take notes. Consider asking your health care team the following questions:

- What is my risk of developing cancer?
- Should I receive a risk assessment, genetic counseling, and discuss genetic testing? If so, how can I do that?
- What can I do to reduce my risk of cancer?
- What are my options for cancer screening and prevention?

If you are concerned about your family history and think your family may have LFS, consider asking the following questions:

- Does my family history increase my risk of cancer?
- Could my family have LFS?
- Will you refer me to a hereditary cancer clinic to meet with a genetic counselor and other genetics specialists?
- Should I consider **genetic testing** (http://www.cancer.net/node/24895)?

## Related Resources

**The Genetics of Cancer** (http://www.cancer.net/node/24897)

**Genetic Testing** (http://www.cancer.net/node/24864)

**What to Expect When You Meet With a Genetic Counselor** (http://www.cancer.net/node/24907)

**Collecting Your Family Cancer History** (http://www.cancer.net/node/30761)

**Sharing Genetic Test Results with Your Family** (http://www.cancer.net/node/36141)

## More Information

**National Comprehensive Cancer Network (NCCN) Version 1.2020: Li-Fraumeni** (http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf) (PDF; free registration required)

**Li-Fraumeni Syndrome Association** (https://www.lfsassociation.org/)

**Facing Our Risk of Cancer Empowered (FORCE)** (https://www.facingourrisk.org)

**National Cancer Institute** (https://www.cancer.gov)

To find a genetic counselor in your area, ask your health care team or visit the following website:

**National Society of Genetic Counselors** (https://www.nsgc.org)