Li-Fraumeni Syndrome

What is Li-Fraumeni Syndrome?

Li-Fraumeni syndrome (LFS) is a rare genetic condition, meaning that it can be passed to an individual through their blood relatives. Individuals with LFS are at an increased risk for developing several different types of cancers. The cancers that occur in LFS may be diagnosed during childhood, adolescence or adulthood. The most common types of cancers associated with LFS include:

- Breast cancer, often before the age of 50
- Soft tissue sarcomas - tumors that occur in fat, muscle, nerves, joints, blood vessels, or deep skin tissue
- Osteosarcoma - tumors that occur in the bone
- Brain tumors (cancer)

Other cancers include lung cancer, leukemia (cancer of the bone marrow); cancer of the adrenal gland (a small hormone–producing gland on top of each kidney); and other types of cancer. Individuals with LFS often develop cancer at a younger age than the general population.

What causes LFS?

LFS is caused by an inherited change, or mutation, in a gene called "TP53". Genes are the set of instructions that tell all of the cells in our bodies what to do. We have two copies of every gene, one from our mother and one from our father. Sometimes people inherit a change, or mutation in a gene, and this mutation causes the gene to stop working properly. When it is working properly, the TP53 gene controls cell growth and prevents tumors (cancer) from forming. In the case of LFS, a mutation in the TP53 gene causes the gene to stop working properly.

Although most people with LFS have a mutation passed down to them from one of their parents, occasionally a new mutation (de novo) in TP53 occurs and that person will be the first in the family to have it. In this case, a person can be diagnosed with LFS even if they have little to no family history of cancer. Once there is a new mutation, it can be passed on to future generations as described in the next section.

What are the chances of inheriting LFS?

Each person has two copies of the TP53 gene. One copy is inherited from the mother, and one copy is inherited from the father. If a person inherits one TP53 gene mutation from either his or

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her mother or father, it will cause LFS. There is a 50 percent chance that a person with LFS will pass the mutation to each of their children. LFS does not skip generations.

Why is it important to diagnose LFS?

People who have LFS are at an increased risk of developing several types of cancers. Persons with LFS who have been diagnosed with cancer have an increased risk of developing another type of cancer in a different part of the body, called a second primary cancer. Because of this increased cancer risk, it is important for people with LFS to see their doctors for regular exams, which may include screening tests to detect cancer as early as possible. The screening tests for patients with LFS may be different than screening for cancer in the general population or may be recommended to begin at earlier ages.

Because LFS is an inherited condition, relatives of the person with LFS may also have this condition. LFS may be diagnosed through genetic testing (see following section) or it may be diagnosed based on the pattern of cancers in a family. If the specific TP53 mutation causing LFS in the family can be identified through genetic testing, then other family members can be tested to determine who will need screening and those who will not.

How is LFS diagnosed?

Family History

The first step in diagnosing LFS is to review medical and family history. This includes constructing a multi-generation family tree, or pedigree, that shows who has and has not had cancer. A genetic counselor or doctor usually takes this medical and family history and assesses the family's risk of LFS. Some signs that suggest LFS may run in families include:

- Cancer diagnosed at a young age
- Cancer in multiple family members and in two or more generations
- Family members that have had two or more cancers during their lives
- Family members with rare forms of cancer
- An increased likelihood for new tumors to occur after initial diagnosis

Genetic Testing for LFS

A blood test, conducted through genetic testing, can identify a mutation in the TP53 gene. If a mutation is found, then the LFS diagnosis is confirmed. Next, other family members may have the same test to learn whether or not they carry the same TP53 mutation and have LFS.

Sometimes genetic testing will not find a TP53 mutation in persons with a clinical history that suggests LFS. This is due to the fact that other genes that have not been identified at this time may cause LFS. Therefore, a diagnosis of LFS may depend solely on a patient's personal history of cancer and family history. Patients with LFS are often asked to participate in research to help identify other genes that may cause this condition.

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How is LFS managed?

Because persons with LFS can develop several different types of cancer, often at younger ages than normally expected, it is important to have regular check-ups and cancer screening tests. Cancer screening examinations are medical tests performed when a person has no symptoms. These tests help ensure that cancers are detected at their earliest, most treatable stages. General screening guidelines for LFS include:

Men and Women

- Annual physical exams including urinalysis, complete blood count (CBC) and abdominal ultra sound (US)
- Screening for the specific rare tumors that have occurred in the family (for example, adrenal cortical tumors)
- Evaluation of any symptoms that have persisted for several weeks, such as abdominal pain, bone pain, growths, headaches, etc.
- Education and awareness of the signs and symptoms of cancer

Women

- Semi-annual breast exams starting at 20 to 25 years
- Annual breast screenings using breast ultrasounds and magnetic resonance imaging (MRI) starting at age 20 to 25. Mammograms are usually not recommended before age 25 to 30 because they may not be as effective in young women and because of the radiation involved in the exam.

Men

- Testicular physical exam by a doctor
- Education on testicular self examination

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