Li-Fraumeni Syndrome [1]

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 were the wide range of cancers found in affected families, the inherited higher risk of developing cancer among 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 [2] (bone cancer), soft-tissue sarcoma [3], acute leukemia [4], breast cancer [5], brain cancer [6], and adrenal cortical tumors [7] (an organ on the top of the kidney). An increased risk for melanoma [8] , Wilms' tumor [9] (a type of kidney cancer), and cancers of the stomach [10], colon [11], pancreas [12], esophagus [13], lung [14], and gonadal germ cells [15] (sex organs) have also been reported.

What causes LFS syndrome?

LFS is a 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 if the cancer risks are the same in families that have *TP53* mutations and *CHEK2* mutations. Research is ongoing to identify other genes associated with LFS and LFL.

How is LFS inherited?

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

have LFS.

Most individuals with LFS have one normal copy of *TP53* and one 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 an individual inherits a mutation or the mutation occurs for the first time in an individual, that individual 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 his/her child. A brother, sister, or parent of a person who has a mutation also has a 50% chance of having the same mutation. Learn more about genetics [16].

Options exist for couples interested in having a child when they know that one of them 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 have children who do not carry the mutation. A woman?s eggs are removed and fertilized in a laboratory. When the embryos reach a certain size, one cell is removed and is tested for the hereditary condition in question. The parents can then choose to transfer embryos which do not have the mutation. PGD has been in use for over a decade, and more recently has been used for several hereditary cancer predisposition syndromes. However, this is a complex procedure with financial, physical, and emotional factors for couples 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 may be as frequent as one in 5,000 to one in 20,000.

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 above 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 Li-Fraumeni Syndrome Clinical Diagnosis 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 **one** of the following three 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 one 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, two of which belonging 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 not included in the Classic criteria (see above). There are two 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 (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:

- Two first-degree or second-degree relatives diagnosed with a typical LFS cancer (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/or HER2/neu markers. Learn more about these markers in this website?s main section on breast cancer [17].
- 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 a highly personal one. People considering *TP53* genetic testing are strongly encouraged to first receive professional genetic counseling, so they can gain knowledge they need to make an informed decision. This can also help with the serious emotional effects that can occur when people learn that they are a carrier. Genetic counseling, as a part of considering genetic testing, is important not only for the individual 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 will need to be made by the child?s parents, with the help of medical experts. However, since cancers occur with high frequency among children in families with LFS, testing at-risk children, rather than delaying it until young adulthood, must also be strongly considered when the goal is to find LFS-related cancers early and treat them.

If genetic testing shows a person has a *TP53* mutation, this may mean your 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 your doctor with future 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 therapy in screening scans and cancer treatments if other options are available.

Genetic testing for *CHEK2* mutations 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 detect 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, 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 some data that suggests that an intensive screening strategy may improve survival of individuals with a *TP53* mutation who do not have any signs or symptoms of cancer. In this strategy, the person would have regular cycles of testing on an ongoing basis, including: whole-body magnetic resonance imaging (MRI [18]), brain MRI, abdominal ultrasound [19], and biochemical markers of adrenal cortical function. If this strategy 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 not be available at many 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 to detect tumors at an early stage and also reported psychological benefits, including a better 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 [19] of abdomen and pelvis every three to four months
- Complete urinalysis every three to four months
- Blood tests every four months: ?-human chorionic gonadotropin, alpha-fetoprotein, 17-OH-progesterone, testosterone, dehydroepiandrosterone sulfate, and androstenedione

Brain tumor

- Annual brain MRI [18]

Soft-tissue and bone sarcoma

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

Leukemia or lymphoma

- Blood test every four 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 his/her 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 five 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 (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. If available, annual mammograms should alternate with breast MRI every six months. Women with LFS should talk with their doctor about other options to reduce future risk of breast cancer [20].

Brain tumor

- Annual brain MRI

Soft-tissue and bone sarcoma

- Annual, rapid whole-body MRI
- Ultrasound of abdomen and pelvis every six months

Colon cancer

- Colonoscopy [21] every two years, beginning at age 40 or 10 years before the earliest known colon cancer in the family

Melanoma

- Annual dermatology (skin) examination

Leukemia or lymphoma

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

These screening tools should be used in addition to regular check-ups with the person?s general physician and with close attention to any medical concerns or complaints. Additional testing should be done as needed. Talk with your doctors about their experience with LFS, as doctors monitoring people with LFS should be aware of the high risks for rarer types of cancers, the earlier than usual development of more common cancers, and also for second malignancies (cancerous tumors) in cancer survivors with LFS.

Learn more about what to expect when having common tests, procedures, and scans [22].

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. Individuals with germline *TP53* mutations should avoid or minimize exposure to diagnostic and therapeutic radiation when possible. For instance, some women with a diagnosis of breast cancer 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 in order to reduce their exposure to radiation. 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 malignancies have been reported among individuals with germline *TP53* mutations.

Questions to ask the doctor

If you are concerned about your risk of cancer, talk with your doctor. Consider asking the following questions:

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

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?

More Information

The Genetics of Cancer [23]

Genetic Testing [24]

What to Expect When You Meet With a Genetic Counselor [25]

Collecting Your Family Cancer History [26]

Sharing Genetic Test Results with Your Family [27]

Additional resources

National Comprehensive Cancer Network (NCCN) 2013: Li-Fraumeni (PDF; free registration required)
http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf [28]

Li-Fraumeni Syndrome Association
http://www.lfsassociation.org/

[29]

Facing Our Risk of Cancer Empowered (FORCE)
Information for women who are at a high risk of developing breast cancer or ovarian cancer.
www.facingourrisk.org [30]

National Cancer Institute
www.cancer.gov [31]

American Cancer Society
www.cancer.org [32]

To find a genetic counselor in your area, ask your doctor or visit the following websites:

National Society of Genetic Counselors
www.nsgc.org [33]

National Cancer Institute: Cancer Genetics Services Directory
www.cancer.gov/cancertopics/genetics/directory [34]

Links:
[1] http://www.cancer.net/cancer-types/li-fraumeni-syndrome
[2] http://www.cancer.net/node/31389
[3] http://www.cancer.net/node/31379
[4] http://www.cancer.net/cancer-types
[5] http://www.cancer.net/node/31322
[6] http://www.cancer.net/node/31327
[7] http://www.cancer.net/node/31341
[8] http://www.cancer.net/node/31265
[9] http://www.cancer.net/node/31257
[10] http://www.cancer.net/node/31376
[11] http://www.cancer.net/node/31317
[12] http://www.cancer.net/node/31388
[13] http://www.cancer.net/node/31310
[14] http://www.cancer.net/node/31273
[15] http://www.cancer.net/node/31298
[16] http://www.cancer.net/node/24864
[17] http://www.cancer.net/node/18624
[18] http://www.cancer.net/node/24578
[19] http://www.cancer.net/node/24714
[20] http://www.cancer.net/node/18621
[21] http://www.cancer.net/node/24481
[22] http://www.cancer.net/node/24959
[23] http://www.cancer.net/node/24897
[24] http://www.cancer.net/node/24895
[25] http://www.cancer.net/node/24907
[26] http://www.cancer.net/node/30761
[27] http://www.cancer.net/node/24906
[28] http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf
[29] http://www.lfsassociation.org/
[30] http://www.facingourrisk.org/
[31] http://www.cancer.gov/

[32] http://www.cancer.org/
[33] http://www.nsgc.org/
[34] http://www.cancer.gov/cancertopics/genetics/directory