



## Li-Fraumeni Syndrome: Information for families with a pathogenic variant in the *TP53* gene

*The purpose of this handout is to give you detailed information about your genetic test result which you may read and discuss with your medical providers. Researchers will continue to study the *TP53* gene, so please check in with your medical providers once a year to learn of any new information that may be important for you and your family members. (Please see the last page for a glossary of medical terms which are underlined in this document.)*

**You have a pathogenic variant in the *TP53* gene.** This means you have **Li-Fraumeni syndrome** (also known as **LFS**).

### What is hereditary cancer?

- Cancer is a common disease. One out of every 3 people in the United States will develop some type of cancer in his or her lifetime.
- About 5-10% of cancers (up to 1 in 10) are hereditary. A hereditary cancer occurs when a person is born with a pathogenic variant (also known as a mutation) in a gene that increases the chance to develop certain types of cancer. A pathogenic variant can be passed on from one generation to the next.
- Typically, families with LFS have one or more of the following features:
  - Early-onset breast cancer in women
  - Bone and soft-tissue sarcomas
  - Brain tumors
  - Adrenal cortical carcinoma
  - Childhood-onset cancers
  - Individuals with more than one cancer diagnosis (for example, two early-onset breast cancers, or sarcoma and breast cancer)
  - Multiple family members on the same side of the family affected with these cancers

### What is a pathogenic variant?

- DNA is our genetic material which is passed on from parent to child. It contains the instructions for how our bodies develop, grow, and function. A gene is a small piece of DNA which has a specific job to do in the body. Some genes determine features like eye color or height, while other genes are involved with our health.
- We all have variations in our genes that make us different from one another. Most of these variations do not change the way our genes work. However, some variations do prevent a gene from working correctly. This type of variation is called a pathogenic variant or mutation.

### Why does having this pathogenic variant cause an increased risk for cancer?

- The job of the *TP53* gene is to prevent cancer. It is called a tumor suppressor gene. When working correctly, tumor suppressor genes help to prevent cancer by controlling the growth and division of cells.
- People born with a *TP53* pathogenic variant have only one working copy of the *TP53* gene, so their risk for cancer is higher than average.

## What are the cancer risks linked to this pathogenic variant?

- *TP53* is a gene that is important in regulating cell growth and division in many different parts of the body. Therefore, individuals with a *TP53* pathogenic variant are at increased risk to develop a variety of different cancer types.
- Some families with a *TP53* pathogenic variant do not have “classic” LFS and may have cancer risks lower than those listed below.
- The following is a summary of the cancer risks associated with LFS:
  - The most common cancers that occur in families with LFS are sarcomas, female breast cancer, brain tumors and adrenal cortical carcinomas.
  - Many other cancers have been seen in families with LFS such as colorectal, esophageal, stomach, renal cell, leukemia, lymphoma, lung, skin, non-medullary thyroid cancer and neuroblastomas.
  - There is an estimated 50% risk of cancer by age 30 for women and 50% risk of cancer by age 46 for men, The lifetime risk for cancer is >90% for women and >70% for men.
  - Approximately 40-50% of individuals with LFS will develop a 2nd cancer. Some individuals have been reported to have three or more cancers.
- The numbers above are shown as a range. This is because not all families/individuals have the exact same degree of risk. Risks may also be affected by the environmental factors, lifestyle, personal medical history, family cancer history, and other genetic or unknown factors.

## Is it possible to fix the pathogenic variant?

Unfortunately, it is not yet possible to fix a pathogenic variant in the *TP53* gene. However, it is possible to change your medical care and certain things in your lifestyle. Your provider(s) will work with you to discuss these options and create a medical care plan that is right for you.

## What are the medical care recommendations?

The medical care recommendations for people with LFS focus mainly on surveillance and surgery. It is important to note there are limitations to screening for many of the cancers associated with LFS.

### Surveillance:

The purpose of surveillance (also referred to as ‘screening’) is to diagnose cancer at as early a stage as possible. Although scientists and physicians can’t prevent a cancer from developing, early detection is important. When a cancer is detected early, it is more likely to be treated successfully. There are very good surveillance methods for some, but not for all types of cancer.

The table below outlines surveillance recommendations for individuals with LFS (adapted from the National Comprehensive Cancer Network Genetic Breast/Ovarian Guideline, Version 2.2021). *Please note that these are general guidelines. Specific guidelines for individual patients and families may differ.*

Cancer type	Surveillance recommendations
Breast cancer (females)	Breast awareness beginning at age 18 and report changes to your health care provider Clinical breast exams every 6-12 months, beginning at age 20 (or earlier, based on family history) Age 20-29: Yearly breast MRI screening with contrast (or earlier, based on family history). Age 30-75: Yearly mammogram with consideration of tomosynthesis and breast MRI screening with contrast Age >75: Management should be considered on an individual basis
Gastrointestinal cancer	Colonoscopy and upper endoscopy every 2-5 years, beginning at age 25 (or earlier, based on family history).

Other cancer risks	<p>Comprehensive physical exam every 6-12 months to include neurological and skin exam.</p> <p>Awareness of signs and symptoms of rare cancers is critical.</p> <p>Yearly dermatologic examination beginning at age 18.</p> <p>Yearly brain MRI.</p> <p>Yearly whole body MRI, if available.</p> <p>Education regarding sign and symptoms of cancer with prompt response if concerned</p> <p>Pediatricians should be informed of risk of childhood cancers</p>
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**Risk-reducing surgery options:**

The goal of risk-reducing surgery is to reduce the risk of cancer by removing healthy tissue before cancer develops. This is also called prophylactic surgery. Risk-reducing surgery does not eliminate the chance to get cancer, but it does greatly lower the chance.

- **Prophylactic bilateral mastectomy (PBM):** This surgery removes the healthy breast tissue to lower the chance for breast cancer by more than 90%. Women considering PBM may have questions about their options for breast reconstruction (the rebuilding of the breast mounds through implants or tissue) which can be discussed with a specially trained breast surgeon. Because there are effective breast cancer surveillance tools, women who have LFS may choose surveillance as an acceptable alternative to PBM. Deciding between PBM and surveillance is a very personal decision, so it is important to carefully consider the benefits and drawbacks of each option, which may be discussed with specially trained medical providers.

**Who should I see for my medical care?**

It is important to find health care providers you trust for long-term follow-up care. Your primary care providers may be able to provide some of this care. In some cases, you may need to see specially trained medical providers. We are happy to provide you with referrals to specialists at Mass General as needed.

**How can I live a healthy lifestyle to lower my risk of developing cancer?**

Everyone should follow a healthy lifestyle, but this may be even more important for someone with an increased risk of cancer. According to the American Cancer Society, a healthy lifestyle includes:

- Avoiding tobacco.
- Maintaining a healthy weight.
- Participating in regular physical activity.
- Keeping a healthy diet with plenty of fruits and vegetables.
- Limiting yourself to no more than 1-2 alcoholic drinks per day.
- Protecting your skin and eyes from the sun.
- Knowing your own body and medical history, your family history, and your risks.
- Having regular check-ups and cancer screening tests.

**What are the chances that my family members also have the pathogenic variant?**

- **Your children:** Each of your children has a 50% chance to inherit the normal (working) copy of the *TP53* gene and a 50% chance to inherit the *TP53* pathogenic variant (the non-working copy). Because a *TP53* pathogenic variant is associated with an increased risk of childhood-onset cancers, genetic testing for minors should be considered. Your genetic counselor will discuss genetic testing of your children with you.
- **Your siblings and other relatives:** Most individuals with LFS inherited the *TP53* gene pathogenic variant from one of their parents. Therefore, in most cases, brothers and sisters of a person with a *TP53* pathogenic variant have a 50% chance to have the same pathogenic variant. Additionally, other family members (such as parents, cousins, aunts, uncles) may also be at risk to have the pathogenic variant.

- Up to 20% of individuals with LFS have a *de novo* (or “new”) pathogenic variant, meaning that they are the first in the family to have the pathogenic variant. Siblings of individuals who have a *de novo* pathogenic variant have only a small risk to have the *TP53* pathogenic variant. However, even if a *de novo* pathogenic variant is suspected, genetic counseling and testing is still recommended for siblings.
- **Family planning:** Some patients may have concerns about passing a *TP53* pathogenic variant to a child. There are reproductive options that can be used to lower the chance of passing a *TP53* pathogenic variant to a child. If you are interested in learning more about these options, please contact your genetic counselor for a referral.

The letter you received from your genetic counselor will give more specific recommendations about which relatives are candidates for genetic testing. However, please feel free to contact us with any further questions.

### **Where can I find additional information?**

Feel free to contact us if you have any questions or would like additional resources. Some people find it useful to speak with other people with LFS who have similar concerns. We would be happy to arrange this for you if you are interested.

The following is a list of additional sources of information:

MGH Center for Cancer Risk Assessment  
[www.massgeneral.org/ccra](http://www.massgeneral.org/ccra)  
(617) 724-1971

American Cancer Society  
[www.cancer.org](http://www.cancer.org)  
(800) 227-2345

National Cancer Institute’s Cancer Information Service  
[www.cancer.gov/aboutnci/cis](http://www.cancer.gov/aboutnci/cis)  
(800) 4-CANCER

Li-Fraumeni Syndrome Association  
[www.lfsassociation.org](http://www.lfsassociation.org)  
(855) 239-LFSA

## **Glossary of cancer genetics terms:**

- **Cell:** The basic structural and functional unit of any living thing. Each cell is a small container of chemicals and water wrapped in a membrane. The human body is made up of 100 trillion cells forming all parts of the body such as the organs, bones, and blood.
- **DNA:** Deoxyribonucleic acid, or DNA, is the genetic material that is passed on from parent to child, which gives the instructions for how our bodies develop, grow, and function on a daily basis.
- **Early detection:** The process of finding cancer when it is just starting to develop.
- **Gene:** A gene is a small piece of DNA that gives instructions for a specific trait.
- **Inherited trait:** A character or feature that is passed on from a parent to a child.
- **Lifetime cancer risk:** The chance that a person will develop cancer in his or her life. This is sometimes defined as the chance of developing cancer by the age of 75 or 80.
- **Pathogenic variant:** A change in a gene that prevents it from working correctly. Also called mutation.
- **Risk-reducing surgery:** Surgery to remove healthy tissue or organs before cancer develops. Also called prophylactic surgery.
- **Surveillance:** Screening tests or procedures to look for early signs of cancer development or cancer returning (recurrence).
- **Syndrome:** A set of signs and symptoms that appear together and characterize a disease or medical condition.
- **Tumor suppressor gene:** When working correctly, tumor suppressor genes prevent cancers from developing by controlling the growth of cells.