Mass General Brigham
Mass General Cancer Center

Li-Fraumeni Syndrome (LFS): 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 *may* have "classic" **Li-Fraumeni syndrome**

It is important to know that our understanding of LFS is changing, and we now know that not all people with pathogenic variants in the TP53 gene have the same level of cancer risk. The cancer risks described in this handout apply to people with "classic" LFS. The cancer risks associated with your TP53 pathogenic variant may be lower.

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 their 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 "classic" LFS have one or more of the following features:
    - Early-onset breast cancer in people assigned female at birth
    - 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 for preventing cancer in many different parts of the body. Therefore, individuals with *TP53* pathogenic variants may be at increased risk to develop a variety of different cancer types throughout life.

- The following is a summary of the cancer risks associated with "classic" LFS (The cancer risks associated with your particular *TP53* variant may be lower.):

    - The most common cancers that occur in families with "classic" LFS are sarcomas, breast cancer, brain tumors and adrenal cortical carcinomas.
    - Many other cancers have been seen in families with "classic" LFS such as colorectal, esophageal, stomach, renal cell, leukemia, lymphoma, lung, skin, non-medullary thyroid cancer and neuroblastomas.
    - For people assigned female at birth, the lifetime risk for cancer is >90%, with about 50% developing cancer by age 30. For people assigned male at birth, the lifetime risk for cancer is >70%, with about 50% developing cancer by age 46.
    - Approximately 40-50% of individuals with "classic" 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 "classic" LFS focus mainly on surveillance and surgery. It is important to note there are limitations to screening for many of the cancers associated with "classic" LFS, and that medical recommendations differ for children and adults (see tables below). It is also important to understand that the medical recommendations for your particular *TP53* pathogenic variant may differ from those described below.

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. Surveillance recommendations are available for both adults and children with "classic" LFS.

Cancer type	ADULTS: Surveillance recommendations
Breast cancer (assigned female at birth)	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	Comprehensive physical exam every 6-12 months to include neurological and skin exam. Awareness of signs and symptoms of rare cancers is critical. Yearly dermatologic examination beginning at age 18. Yearly brain MRI. Yearly whole-body MRI, if available. Education regarding sign and symptoms of cancer with prompt response if concerned Pediatricians should be informed of risk of childhood cancers

Adapted from the National Comprehensive Cancer Network Genetic Breast/Ovarian Guideline, Version 3.2023. *Please note that these are general guidelines. Specific guidelines for individual patients and families may differ.*

Cancer type	CHILDREN: Surveillance recommendations (birth to 18 years)
Adrenocortical carcinoma	Ultrasound of abdomen and pelvis every 3-4 months Blood test (testosterone, dehydroepiandrosterone sulfate, and androstenedione) recommended if ultrasound is unsatisfactory
Brain tumor	Yearly brain MRI
Soft tissue and bone sarcoma	Yearly whole-body MRI
Other cancer risks	Comprehensive physical exam every 3-4 months Education regarding sign and symptoms of cancer with prompt response if concerned Pediatricians should be informed of risk of childhood cancers

Adapted from the American Association for Cancer Research, Cancer Screening Recommendations for Individuals with Li-Fraumeni Syndrome, 2017. *Please note that these are general guidelines. Specific guidelines for individual patients and families may differ.*

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.

- **Risk Reducing bilateral mastectomy (RRBM):** This surgery removes the healthy breast tissue to lower the chance for breast cancer by more than 90%. Those considering RRBM 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, people with "classic" LFS may choose surveillance as an acceptable alternative to RRBM. Deciding between RRBM 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.

Other recommendations:

People with pathogenic variants in the*TP53* gene are especially sensitive to the cancer-causing effects of radiation. Therefore, excessive radiation exposure should be avoided when possible, especially for those with "classic" LFS.

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 may be 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 a *TP53* gene pathogenic variant inherited it from one of their parents. Therefore, in most cases, siblings 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 a *TP53* pathogenic variant 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 *TP53* pathogenic variants 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 and support:

MGH Center for Cancer Risk Assessment www.massgeneral.org/ccra (617) 724-1971
American Cancer Society www.cancer.org (800) 227-2345
National Cancer Institute's Cancer Information Service www.cancer.gov/aboutnci/cis (800) 4-CANCER
Li-Fraumeni Syndrome Association www.lfsassociation.org (855) 239-LFSA
Living LFS www.livinglfs.org (844) LFS-CALL

Glossary of cancer genetics terms:

- **Assigned female at birth/Assigned male at birth**: Refers to the sex that a doctor or midwife uses to describe a child at birth based on their external anatomy.
- **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 their 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.