Li-Fraumeni syndrome FAQs

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Glossary

(Genetic) Variant: A change in a gene (as compared to the normal sequence of the gene). The change may or may not affect the function of the gene and/or cause disease.

Pathogenic Variant: A variant in a gene that causes disease. The term “mutation” is commonly used, although “pathogenic variant” is currently the preferred term.

Variant of Uncertain Significance (VUS): A variant in a gene that may cause disease or may be benign. A genetic variant is classified as a VUS when there is not enough information to determine if the variant is disease-causing or not. As more information becomes available over time, a VUS may be re-classified as either pathogenic or benign.

Pre-implantation Genetic Testing (PGT): PGT is a method of performing genetic testing on embryos obtained using in-vitro fertilization (IVF).

Prenatal Diagnosis: Prenatal diagnosis refers to genetic testing performed on cells from the embryo during pregnancy. Prenatal diagnosis can be performed using amniotic fluid obtained from amniocentesis or cells from the placenta obtained from chorionic villi sampling (CVS).

Clonal Hematopoiesis of Indeterminate Potential (CHIP): CHIP occurs when a population of blood cells acquire one or more genetic variants. These genetic variants are not present in the rest of the blood cells or any other cells of the body. CHIP can occur for a variety reasons, including aging and prior chemotherapy treatment. Alternatively, clonal hematopoiesis is sometimes an indication of a blood disorder or blood cancer. Sometimes the term “aberrant clonal expansion (ACE)” is used to describe a population of non-cancerous blood cells that acquire one or more genetic variants.

Q1: I have been recommended to have genetic testing for LFS. Is genetic testing covered by insurance? Is there financial assistance available?

Many insurance companies will approve coverage of genetic testing when testing is medically warranted. As with other medical tests, the exact out-of-pocket cost you may pay will vary based on your particular plan, deductible, and whether the testing lab is in-network with your insurance. If you would like to get an out-of-pocket estimate before testing is performed, your healthcare provider can request a pre-authorization from your insurance. If your insurance does not agree to cover your testing, your deductible is high, or you do not have insurance, discuss potential financial assistance or alternative payment options with your provider. Many medical institutions and laboratories have assistance programs available. In some countries, genetic testing may be covered by public health systems for individuals that meet certain criteria.

Q2: Should I have my children tested for LFS?

If you have LFS, or if your child meets criteria for LFS (see Criteria for LFS: **https://bit.ly/3ekaxDP**), genetic testing may be recommended for your child to determine whether or not they have LFS. Whether and when to have your child tested for LFS is a very personal decision. You should discuss this decision with your doctor, genetic counselor, and/or your family prior to testing. Depending on your child's age and maturity level, you may also want to talk to your child before testing and include them in the decision-making process (see below for resources). Your healthcare team can help you decide how much information to share with your child before and after testing.

You might not be sure at what age your child should be tested for LFS. Since cancers can develop at young ages, it is appropriate to test children for LFS at any age, but you can discuss the potential benefits, risks, and timing of testing with your doctor, genetic counselor, and/or family to make the best decision for you and your child.

If you decide not to pursue genetic testing for your child right now, you should still discuss your child's cancer risk with a health care provider familiar with LFS. Cancer screening may still be recommended for your child if he or she is considered to have LFS based on clinical criteria (see the link for Criteria for LFS above) or if he or she is at 50% risk to have LFS (based on a parent having LFS).

For other considerations, see Who Should Be Tested? (**https://bit.ly/3xUi6sy**)

Resources for discussing LFS with children:

- Talking to kids about LFS: **https://bit.ly/2QUMm5E**
- "Robot Music: A Story for Kids with Li-Fraumeni Syndrome and other Cancer Predispositions." Sponsored by your LFS Association, A book about Li-Fraumeni Syndrome designed for children aged 4-plus: **https://bit.ly/3uihzOT**

Q3: Can I get tested for LFS using a direct-to-consumer test? What does it mean if I had a direct-to-consumer test and found out I have a variant in the *TP53* gene?

In recent years, many people have undergone or considered genetic testing through direct-to-consumer testing companies to learn more about their ancestry and/or their health. Direct-to-consumer genetic tests are genetic tests that can be ordered (often online) and completed from home without necessarily involving your doctor or health insurance company. You may be wondering if these tests can tell you if you have LFS, or you may have questions about a result you received from one of these tests.

If you have already had a direct-to-consumer genetic test performed that identified a variant in the *TP53* gene, you should meet with a genetic counselor or other health care provider specializing in cancer genetics to review and interpret your result. Direct-to-consumer testing is very different from a clinical genetic test. It may use a different technology and is not always designed to find or report on variants in the *TP53* gene that might be indicative of LFS. It is important to know that even if your result shows a variant in the *TP53* gene, this doesn't always mean that you have LFS. This would need to be confirmed with a clinical genetic test. Also, if your result does not show a variant in the *TP53* gene, this doesn't mean that you don't have LFS. A genetic counselor or other genetic specialist can review your result as well as your personal and family history to determine if you have LFS or not, or if you should have additional genetic testing.

If you are interested in being tested for LFS, it is recommended that you meet with a genetic counselor and/or health care provider with experience in cancer genetics to determine the appropriate testing approach for you.

Q4: I have been diagnosed with LFS. Are screening tests covered by insurance? Is there financial assistance available?

Unfortunately, this is not a straightforward answer. Different insurance companies have different policies about coverage for cancer screening. It is best to ask your insurance company directly whether or not the screening tests will be covered. Sometimes, the billing department in the healthcare center may also be able to help you clarify costs and coverage. In most cases, your physician or genetic counselor can help you identify the specific codes that will be used in the billing for specific tests. These codes are needed by your insurance company to determine whether or not the test is covered. It is also important to be aware that screening recommendations and insurance coverage for screening vary depending on where you live. You should talk to your doctor, genetic counselor, and/or insurance company for details on screening recommendations and coverage where you live.

It is important to mention that cancer screening may also be recommended for people who meet clinical criteria for LFS but have negative/normal genetic testing, or people who are at 50% risk (based on having a parent with LFS) but have not yet undergone genetic testing. It is difficult to predict if insurance will cover screening tests in these situations. For individuals at 50% risk who have not undergone genetic testing, it is possible that the insurance company may only cover screening tests if genetic testing is performed and is positive for the familial *TP53* variant. As reviewed above, it is best to ask your insurance company, the billing department at the healthcare center, and/or your physician or genetic counselor for assistance in finding out if insurance will cover the screening tests.

Q5: Where can I go to have screening done? Where do they do whole body MRI?

You can find a list of medical centers that offer screening for individuals with LFS in the Resources section of the website, under "Medical Resources" (**https://www.lfsassociation.org/medical-resources/**)

Q6: Where can I find a genetic counselor?

You can find an in-person or by phone genetic counselor in the United States and Canada by using the "Find a Genetic Counselor" feature at the National Society of Genetic Counselors website: **https://www.nsgc.org/**

For genetic counseling services outside the United States and Canada, check with your nearest LFSA international chapter at the homepage (**https://www.lfsassociation.org/**), or check the LFSA Genetic Counselor Directory, (**https://bit.ly/3eORFLX**). A table listing international genetic services and resources is also available here: https://bit.ly/3vEIsg9

If you are seeking *TP53* testing and someone else in your family has already had a *TP53* pathogenic variant identified, be sure to get a copy of your family member's genetic test report if you can. If you are having difficulty speaking with your family member about this, we encourage you to discuss this with your genetic counselor.

Q7: Can LFS be cured? Can the cancers be prevented? Are there any foods, medications, etc. that I can take to reduce the risk of cancer?

There is currently no cure for LFS, nor any direct way to prevent all cancers from occurring, and evidence regarding the impact of diet and exercise on cancer development is limited. However, following a healthy, active, and balanced lifestyle has many benefits, and evidence supports that such a lifestyle improves our overall physical and mental health and longevity. Everyone, including individuals with LFS, should avoid tobacco and heavy alcohol use, and follow safe practices such as sunscreen use. While a healthy lifestyle should be encouraged, cancer screening and risk reducing procedures and surgeries (such as risk reducing bilateral mastectomy and colonoscopy) offer more evidenced-based cancer prevention strategies for individuals with LFS and should be discussed with a physician or genetics professional familiar with LFS.

For information on specific ingredients (like sugar!) and their impact on cancer development, please visit the American Cancer Society at **https://www.cancer.org**.

For more nutrition information from LFSA, please see: **https://bit.ly/339uN4z**.

Researchers are also studying medications that may reduce the risk of cancer in people with LFS. You can refer to question #8 ("I'm interested in participating in research studies on LFS. How can I learn about research and clinical trial opportunities?") to find out how to search for research and clinical trial opportunities for people with LFS.

Q8: I'm interested in participating in research studies on LFS. How can I learn about research and clinical trial opportunities?

You can find information on LFS studies at the Resources section of the LFSA website under Research and Trials, Studies, Surveillance. You can also search for studies at **https://www.clinicaltrials.gov** using "Li-Fraumeni syndrome" as a search term. You can also ask your genetic counselor or other health care providers about research opportunities.

Q9: It's recommended that people with LFS avoid radiation exposure, where possible. Is it still OK to have x-rays done if recommended? What if radiation therapy is recommended to treat my or my family member's cancer diagnosis? Are there other types of radiation exposure that should be avoided?

If you or a family member is diagnosed with cancer and radiation therapy is recommended, you should talk with your doctors about the diagnosis of LFS and ask if radiation therapy can be minimized or avoided. Certain types of medical imaging also involve radiation exposure, while others do not. MRI and ultrasound do not involve radiation exposure. X-rays, PET scans, and CT scans do involve radiation exposure. X-rays generally involve a lower dose of radiation compared to PET scans, and CT scans generally have the highest amount of radiation exposure. When medical imaging is recommended, you should talk with your doctors about the diagnosis of LFS and determine if an imaging test that involves no radiation or a lower level of radiation can be used. Routine dental x-rays involve a very low level of radiation exposure, and it is fine to have these done as needed, but you can talk to your dentist to see if it is OK to do them less frequently than normally recommended. **https://www.imagegently.org/** is a helpful resource if you are looking for more information on imaging tests and radiation exposure.

It is important to know that radiation exposure from treatment or medical imaging can't always be avoided completely, and the benefit of the treatment or the imaging test may outweigh the risk of the radiation exposure in some situations.

Some families also have questions about other potential sources of radiation exposure, including cell phones, fitness trackers, and airport scanners and air travel. These all generally involve low levels of radiation exposure. The NIH has a fact sheet that reviews the currently available evidence on cell phone use and cancer risk: **https://bit.ly/3h4RHCp**.

Q10: I have LFS. What are the chances of my children having LFS?

LFS is an autosomal dominant condition. This means that a parent with LFS has a 50% (or 1 in 2) chance of passing the *TP53* pathogenic variant on to each child.

In a few people with LFS, some of their cells carry the *TP53* pathogenic variant, but not all. This is known as 'mosaicism'. In this case, children have up to a 50% chance of inheriting the *TP53* variant, as it may be unclear whether the egg or sperm cells from the parent carry it.

Additionally, some people meet clinical diagnostic criteria for LFS, but their *TP53* genetic test results are negative/normal. In this case, their children likely also have a 50% chance of having LFS, but it is not possible to test children if the genetic cause has not been identified in a family member with LFS.

Q11: I have LFS and I want to have children. What are my options for future pregnancies?

Often a diagnosis of LFS is made before or during childbearing years. For people with LFS, deciding whether or not to have children can be difficult due to the possibility of passing LFS on to the next generation. However, people with LFS can (and do!) have children, and there are several reproductive options to choose from.

If a parent with a *TP53* pathogenic variant conceives naturally, there is a 50% chance that any child he or she has will also have the same *TP53* variant. There are also options available to try to prevent LFS from being passed on, or to determine during pregnancy or after birth if the baby has LFS. Some of these options occur before conception occurs (such as using a sperm/egg donor), before pregnancy occurs (called preimplantation genetic testing or PGT), or during pregnancy (called prenatal diagnosis). Alternatively, a child can have genetic testing after birth to determine if they have LFS. Some people with LFS may also choose to adopt children. There are many qualified experts including genetic counselors and fertility specialists that can help provide valuable information and guidance when making these decisions.

Q12: I (or my child) have LFS and cancer. Will my/my child's fertility be affected?

Individuals with LFS do not have fertility problems associated with having a *TP53* pathogenic variant. However, receiving treatment for LFS-related cancer can affect fertility. For that reason, it is important to ask your/your child's oncologist about possible options for fertility preservation. Fertility preservation is a process of saving healthy egg or sperm cells, ideally before cancer treatment is started. If fertility can be preserved, options of PGT or other reproductive testing options can be used (see question #11: "I have LFS and I want to have children. What are my options for future pregnancies?").

Q13: What does it mean to be mosaic for LFS?

When someone is mosaic for LFS, it means that they have a *TP53* pathogenic variant in some of the cells of their body, but not all of the cells of their body. This can occur when someone is the first person in their family to have LFS. Mosaicism happens when one cell "acquires" a *TP53* pathogenic variant early in embryonic development, but after the egg and sperm join to form a single cell. Individuals with mosaic LFS may have lower cancer risks than those without mosaicism, as not all the tissues in their body have a *TP53* pathogenic variant. There is currently no way to fully predict what tissues in the body are affected with a pathogenic variant as mosaicism can vary from cell to cell, even within the same tissue. Because of this, individuals with mosaic LFS are often screened using the same protocol as those with a *TP53* gene variant in all the cells of his or her body.

If someone has a *TP53* pathogenic variant in their egg or sperm cells, but that variant is not identifiable in other tissues of their body (like blood or skin cells), they are considered a "germline mosaic". These individuals may not have an increased risk of cancer themselves but have up to a 50% chance of passing on LFS to a child, who would have an increased cancer risk.

When a genetic test suggests that a person may have a mosaic form of LFS, it is important to do further testing to determine whether this truly is mosaic LFS. Sometimes, this type of result can be caused by a *TP53* variant present in the blood cells that is NOT present within any of the other cells. This is called Clonal Hematopoiesis of Indeterminate Potential, or CHIP. CHIP can develop as people get older, or after someone receives chemotherapy or radiation treatment. Rarely, CHIP can indicate that a person has an underlying blood disorder or blood cancer. CHIP does NOT cause the cancer risks present in LFS, but individuals with CHIP may have other health risks that are important for their health care providers to know about. If you have a mosaic test result, you should work with your health care provider to determine the underlying cause of your mosaic result. If you have further questions about the complexities of germline mosaicism, please reach out to a genetics professional.

Q14: Can someone be the first person in their family with LFS?

It is possible for someone to be the first person in their family with LFS, in fact, this happens up to 20% of the time. When someone is the first person in their family to have LFS, they are said to have a "de novo" *TP53* pathogenic variant, meaning a variant that is new in them (not inherited from a parent). While it is not currently known how or why some cells "acquire" a *TP53* pathogenic variant, this can happen either at conception when the egg and sperm join, or after conception when an embryo is forming (in which case, an individual would have mosaic LFS). If someone is the first person in their family to have LFS, they still have the same risk to pass LFS on to any of their biological children, which is 50% (or up to 50% if they have mosaic LFS). It is important to know that if the parents of an individual with a *TP53* pathogenic variant both test negative for the variant, there is a small chance that one parent could be mosaic for the variant (see question #13: "What does it mean to be mosaic for LFS?"). This means that if your child has an apparently "de novo" *TP53* pathogenic variant, genetic testing should still be considered for your other children as there is a small chance for more than one child to inherit the *TP53* variant even when both parents test negative.

Q15: What does it mean to have a variant of uncertain significance in *TP53*?

We have two copies of *TP53*, one from our mother, and one from our father. *TP53*, like all the other genes in our bodies, is made up of different combinations of DNA base pairs (represented by the letters A, T, C, and G). When someone is found to have LFS, it means that they have a harmful spelling mistake, or pathogenic variant, in this combination of letters. When someone has a variant of uncertain significance (VUS) in the *TP53* gene, it means that they were found to have a spelling mistake, but that it is currently unknown whether the mistake is harmful to the gene, or whether the body can "tolerate" the mistake, and *TP53* can still work as it should. Having a VUS in *TP53* does not diagnose someone with LFS on its own, and it is important to interpret the genetic result in the context of someone's personal and family medical history to determine appropriate medical management.

Q16: What is the difference between a “somatic” and a “germline” genetic variant?

A “germline” genetic variant refers to a genetic variant that is present in every cell of the body, including the germ cells (the egg and sperm cells). Germline variants are often, but not always, inherited from a parent. People with LFS are born with a germline *TP53* pathogenic variant and therefore would have the variant in every cell of the body (unless they have mosaic LFS). A “somatic” genetic variant refers to a variant that is acquired later (usually after birth), which can occur in a tumor, or in the blood due to CHIP (see question #13: “What does it mean to be mosaic for LFS?”).

Somatic variants are not present in the egg or sperm cells, and therefore cannot be inherited. Individuals who have cancer may have genetic testing performed on their cancer, which is commonly referred to as “somatic testing” or “tumor testing.” Somatic testing can identify genetic variants that may assist the oncologist in determining the type of cancer and the best way to treat the cancer. Genetic variants identified by somatic testing are usually only present in the tumor cells and not in the normal cells of the body. However, in some cases there may be reasons to suspect that a variant present in the tumor is also present in the normal cells of the body (in other words, a germline variant). Therefore, a doctor or genetic counselor may recommend germline testing based on the results of somatic genetic testing. If you have had testing performed on your cancer and have questions about the results, you should talk to your health care provider who ordered the testing.

Have a suggestion for a question or topic? Contact us at: Info@lfsassociation.org

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