Ambry Genetics®

Understanding Your Positive *TP53* Genetic Test Result

INFORMATION FOR PATIENTS WITH A PATHOGENIC OR LIKELY PATHOGENIC VARIANT

3 Things To Know

1	Result	Your testing shows that you have a pathogenic or likely pathogenic (P/LP) variant in the *TP53* gene.
2	Reason for *TP53* P/LP variant	A *TP53* P/LP variant may already be in a person's body at birth (germline), or may have occurred at some point during a person's lifetime (somatic). ▪ People with a germline P/LP *TP53* variant have Li Fraumeni syndrome ▪ People with a somatic P/LP *TP53* variant do NOT have Li Fraumeni syndrome
3	What this means for you	It is important to discuss your result in detail with your healthcare provider. Your report will indicate whether your *TP53* P/LP variant may have occurred during your lifetime (somatic) or if your result is consistent with a diagnosis of Li Fraumeni syndrome. ▪ If your report has a COMMENT about the possibility of somatic origin, see "Pathogenic or Likely Pathogenic Variants of Unknown Origin in the *TP53* Gene" OR ▪ If your report states you have a pathogenic or likely pathogenic *TP53* variant with a diagnosis of Li Fraumeni syndrome, see "Li Fraumeni syndrome" table on page 2

Pathogenic or Likely Pathogenic Variants of Unknown Origin in the *TP53* Gene

Your test report includes a COMMENT about the possibility of somatic origin

Result	▪ Sometimes *TP53* P/LP variants occur naturally in a person's blood later in life. These types of variants can be observed even in healthy people, especially when they are over 65 years of age. ▪ Somatic *TP53* P/LP variants can also be seen in blood as a result of chemotherapy or radiation treatments. ▪ If your *TP53* P/LP variant is somatic, you do not have the same cancer risks associated with Li Fraumeni syndrome. It is important to discuss your specific management with your healthcare provider. ▪ **It is not always possible to distinguish definitively between germline and somatic variants. It is important to discuss next steps with your healthcare provider and decide on a plan that works for you.**
Other Medical Concerns	Somatic *TP53* P/LP variants are often detected in healthy people. However, some people with *TP53* P/LP variants in blood may be at an increased risk for heart disease or blood cancers. It is important to discuss your management and screening options with your healthcare provider.
Family	Testing your siblings, parents, and/or children can help determine if your *TP53* P/LP variant is germline or somatic. If it is somatic, then neither you nor your family are at increased risk for the types of cancers that are seen more often in people with Li Fraumeni syndrome.

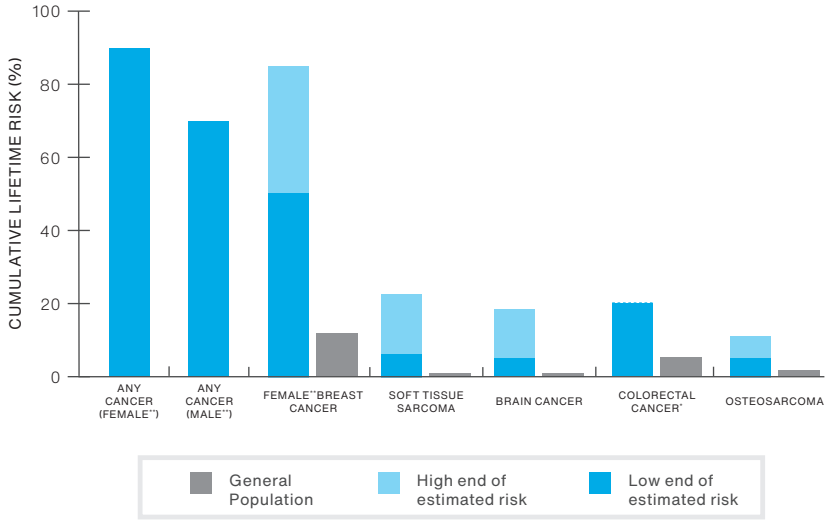
Li Fraumeni Syndrome

Your test report states that the result is consistent with a diagnosis of Li Fraumeni syndrome (LFS), which is caused by germline pathogenic or likely pathogenic variants in the *TP53* gene

Li-Fraumeni syndrome	People with germline *TP53* P/LP variants have classic Li Fraumeni syndrome (LFS) or attenuated LFS. The attenuated form of LFS means that the risk of cancer may not be as high as in classic LFS.
Cancer Risk	People with LFS due to germline *TP53* P/LP variants have an increased chance to develop adrenocortical carcinoma (ACC)†, female** breast cancer, brain tumors, choroid plexus carcinoma†, leukemia , medulloblastoma†, osteosarcoma, rhabdomyosarcoma†, soft tissue sarcoma, and potentially other types of cancer. The lifetime risk for cancer may be as high as 90%†† for females** or 70% for males**. Cancer risks can vary widely, even within the same family.
Risk Management	Risk management decisions are very personal. There are options to detect cancer early or lower the risk to develop cancer. It is important to discuss these options with your healthcare provider and decide on a plan that works for you.
Family	Up to 20% of the time, a person is born with a *TP53* variant that was not inherited from either parent. Testing family members for the P/LP *TP53* variant found in you could help to determine who in your family may or may not be at increased risk. It is recommended that you share this information with your family members so they can learn more and discuss with their healthcare providers.

† These cancers are often diagnosed in childhood (<15 years).
†† Cumulative risk by age 60 years.

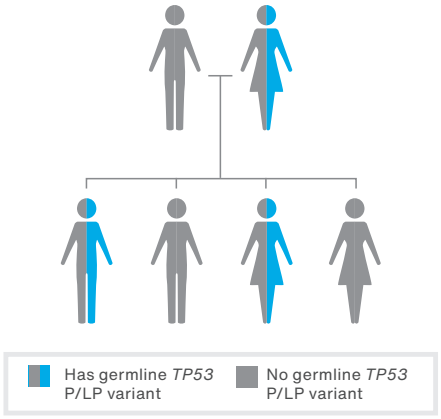
Cancer Risks Associated with Classic LFS



* Colon cancer risk estimates are 20% or higher.
** Refers to sex assigned at birth

Germline *TP53* Variants in the Family^

There is up to a 50/50 random chance to pass on a germline P/LP *TP53* variant to each of your children.



^ People with somatic *TP53* variants cannot pass them on to their children.

RESOURCES

- Bright Pink brightpink.org
- FORCE facingourrisk.org
- Imerman Angels imermanangels.org
- Li-Fraumeni Syndrome Association lfsassociation.org
- Living LFS livinglfs.blogspot.com
- Susan G. Komen Foundation komen.org
- National Society of Genetic Counselors nsgc.org
- Canadian Association of Genetic Counsellors cagc-accg.ca

Please discuss this information with your healthcare provider. The cancer genetics field is continuously evolving, so updates related to your *TP53* result, medical recommendations, and/or potential treatments may be available over time. This information is not meant to replace a discussion with a healthcare provider, and should not be considered or interpreted as medical advice.

Clinician Management Resource for *TP53*

This overview of clinical management guidelines is based on this patient's positive test result for a pathogenic or likely pathogenic variant in the *TP53* gene. Unless otherwise stated, medical management guidelines used here are limited to those issued by the National Comprehensive Cancer Network® (NCCN®)[1] in the U.S. Please consult the referenced guideline for complete details and further information. Clinical correlation with the patient's past medical history, treatments, surgeries and family history may lead to changes in clinical management decisions; therefore, other management recommendations may be considered. Genetic testing results and medical society guidelines help inform medical management decisions but do not constitute formal recommendations. Discussions of medical management decisions and individualized treatment plans should be made in consultation between each patient and his or her healthcare provider, and may change over time.

NOTE:

- **If the patient's report has a COMMENT about the possibility of acquired (somatic) origin, refer to the "Pathogenic or Likely Pathogenic Variants of Unknown Origin in the *TP53* Gene" table below for management guidelines. See the NCCN Guidelines pages LIFR-A 1 through 3 for a more detailed discussion of causes and management of atypical *TP53* findings.**
- **If the patient's report states that the pathogenic or likely pathogenic *TP53* variant is consistent with a diagnosis of Li Fraumeni syndrome, refer to the "Li Fraumeni syndrome" table on the next page for management guidelines.**

Pathogenic or Likely Pathogenic Variants of Unknown Origin in the *TP53* Gene

The patient's test report includes a COMMENT about the possibility of somatic origin

Clinical correlation	*TP53* variants found in blood, saliva, or buccal samples may be present from birth (germline) or acquired later in life (somatic). • Your patient's test report will indicate if the pathogenic or likely pathogenic *TP53* variant is of uncertain origin • It is not always possible to distinguish definitively between germline and acquired (somatic) variants. Clinical presentation may help guide management of these patients.
Reasons for somatic *TP53* variants identified in blood or saliva	Aberrant clonal expansion (ACE) due to clonal hematopoiesis (CHiP) • Common in healthy older age populations (over 65 years) Chemotherapy treatment Radiation treatment
Management and Next Steps	Management of individuals with pathogenic or likely pathogenic *TP53* variants will differ markedly depending on if the *TP53* variant is germline or acquired (somatic). • Testing of family members (such as siblings, parents, and/or children) can help distinguish between germline and acquired (somatic) variants, although it is not always possible to do so.[1,2] • Acquired (somatic) *TP53* variants: these individuals do not have Li Fraumeni syndrome (LFS) and are not at increased risk for LFS cancers. Management is based on personal and family history. • These individuals may be at risk for heart disease or blood cancers.[1] Careful examination of the patient's complete blood count (CBC) and peripheral blood smear may be warranted in all individuals with identified *TP53* variants and testing of non-hematopoietic tissue(s) may help confirm true mosaic involvement across different germ layers.[1,2]

1. Weitzel J, et al. *Genet Med* 2018;20:809 816.
2. Chao E, et al. *Genet Med* 2021 Jul;23(7):1179 1184.

Li Fraumeni Syndrome

The patient's test report states that the result is consistent with a diagnosis of Li Fraumeni syndrome (LFS), which is caused by germline pathogenic or likely pathogenic variants in the *TP53* gene

SCREENING/SURGICAL CONSIDERATIONS[1]		AGE TO START	FREQUENCY
Female Breast Cancer			
Breast Awareness Women should be familiar with their breasts and promptly report changes to their healthcare provider		18 years old	Periodic and consistent
Clinical Breast Exam		20 years old (or at the age of earliest diagnosed breast cancer in the family), whichever comes first	Every 6-12 months
Breast Screening	Breast MRI with and without contrast	20-29 years old (or at the age of earliest diagnosed breast cancer in the family), whichever comes first, including women treated for breast cancer and who have not had bilateral mastectomy	Every 12 months, Individualized after 75 years old
	Breast MRI with and without contrast and mammogram	30-75 years old, including women treated for breast cancer and who have not had bilateral mastectomy	
Discuss option of risk-reducing mastectomy		Individualized	N/A
Brain Tumors			
Brain MRI as part of whole body MRI (see below, Other Cancers), or a separate exam		Individualized	Every 12 months
Neurologic exam**		Individualized	Every 6-12 months
Colorectal and Intestinal Cancer			
Colonoscopy and upper endoscopy		25 years old, or 5 years before earliest known colon or gastric cancer in the family (whichever comes first)	Every 2-5 years
For patients who have received whole body or abdominal therapeutic radiation treatment, colonoscopy screening is recommended		5 years after treatment of disease	Every 2-5 years
Melanoma			
Dermatologic exam		18 years old	Every 12 months
Pancreatic Cancer			
For individuals with exocrine pancreatic cancer in ≥1 first-or second-degree relative on the same side of the family as the identified pathogenic/likely pathogenic germline variant, consider pancreatic cancer screening using contrast-enhanced MRI/ MRCP and/or EUS.^		50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family)	Every 12 months (with consideration of shorter intervals if worrisome abnormalities seen on screening)
Prostate Cancer			
Prostate-specific antigen (PSA) testing		40 years old	Individualized
Pediatric Surveillance			
Comprehensive physical exam including neurologic examination with high index of suspicion for rare cancers and second malignancies in cancer survivors		Infancy	Every 6-12 months
Whole body MRI. Brain MRI may be performed as part of the whole body MRI or as a separate exam.		Infancy	Every 12 months
Ultrasound for adrenocortical carcinoma		Infancy	Every 3-4 months

Other Aspects of Managing LFS		
The screening and management of LFS is complex and LFS is rare; it is preferred that individuals with LFS be followed at centers with expertise in the management of this syndrome.	N/A	N/A
Address limitations of screening for many cancers associated with Li-Fraumeni syndrome (LFS). Screening should be considered for cancer survivors with LFS and a good prognosis from their prior tumor(s).	N/A	N/A
Screening recommendations should take into account personal and family history of cancer. Provide additional surveillance based on family history of cancer.	5-10 years before the earliest diagnosis	Individualized
Therapeutic radiation treatment for cancer should be avoided when possible unless locoregional risk reduction or overall survival from radiation treatment is greater than the risk of downstream secondary malignancies; diagnostic radiation should be minimized to the extent feasible without sacrificing accuracy.	N/A	N/A
Provide education regarding signs and symptoms of cancer.	N/A	N/A
Address psychosocial and quality-of-life aspects of management	N/A	N/A

** This may be done as part of the comprehensive physical exam

^ For individuals considering pancreatic cancer screening, the Guidelines recommends that screening be performed in experienced high-volume centers. The Guidelines recommends that such screening only take place after an in-depth discussion about the potential limitations to screening, including cost, the high incidence of benign or intermediate pancreatic abnormalities, and uncertainties about the potential benefits of pancreatic cancer screening. The Guidelines recommends that screening be considered using annual contrast-enhanced MRI/MRCP and/or EUS, with consideration of shorter screening intervals for individuals found to have worrisome abnormalities on screening. The Guidelines emphasizes that most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any other intervention.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate. v2.2025. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed November 7, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. v3.2024.© National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed October 31, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.