

Understanding Your Moderate Risk *TP53* Genetic Test Result

INFORMATION FOR PATIENTS WITH A MODERATE RISK PATHOGENIC OR LIKELY PATHOGENIC VARIANT

3 Things To Know

1	Result	Your testing shows that you have a moderate risk pathogenic or likely pathogenic (P/LP) variant in the <i>TP53</i> gene. Moderate risk variants may increase cancer risks, but less than typical variants do.
2	Reason for <i>TP53</i> moderate risk P/LP variant	<p>A <i>TP53</i> moderate risk 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).</p> <ul style="list-style-type: none"> • People with a germline <i>TP53</i> moderate risk P/LP variant may have attenuated Li Fraumeni syndrome or an increased risk for <i>TP53</i>-related cancers. The attenuated form of Li Fraumeni syndrome means that the risk of cancer may not be as high as in classic Li Fraumeni syndrome. • People with a somatic <i>TP53</i> moderate risk P/LP variant do NOT have Li Fraumeni syndrome or attenuated Li Fraumeni syndrome.
3	What this means for you	<p>It is important to discuss your result in detail with your healthcare provider. Your report will indicate whether your <i>TP53</i> moderate risk P/LP variant may have occurred during your lifetime (somatic) or if your result is consistent with a diagnosis of attenuated Li Fraumeni syndrome:</p> <ul style="list-style-type: none"> • If your report has a COMMENT about the possibility of somatic origin, see Table 1: "Moderate Risk P/LP Variants of Unknown Origin in the <i>TP53</i> Gene" below. <p>OR</p> <ul style="list-style-type: none"> • If your report states you have a <i>TP53</i> moderate risk pathogenic or likely pathogenic variant with an increased risk for <i>TP53</i>-related cancers, see Table 2: "Attenuated Li Fraumeni syndrome" on page 2.

Table 1: Moderate Risk P/LP Variants of Unknown Origin in the *TP53* Gene

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

Result	<ul style="list-style-type: none"> • Sometimes <i>TP53</i> moderate risk P/LP variants occur naturally in a person's blood later in life. These types of genetic changes can be observed even in healthy people, especially when they are over 65 years of age. • Somatic <i>TP53</i> moderate risk P/LP variants can also be seen in blood as a result of chemotherapy or radiation treatments. • If your <i>TP53</i> moderate risk 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 <i>TP53</i> moderate risk P/LP variants are often detected in healthy people. However, some people with <i>TP53</i> moderate risk 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 <i>TP53</i> moderate risk 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 attenuated Li Fraumeni syndrome.

Table 2: Attenuated Li Fraumeni Syndrome

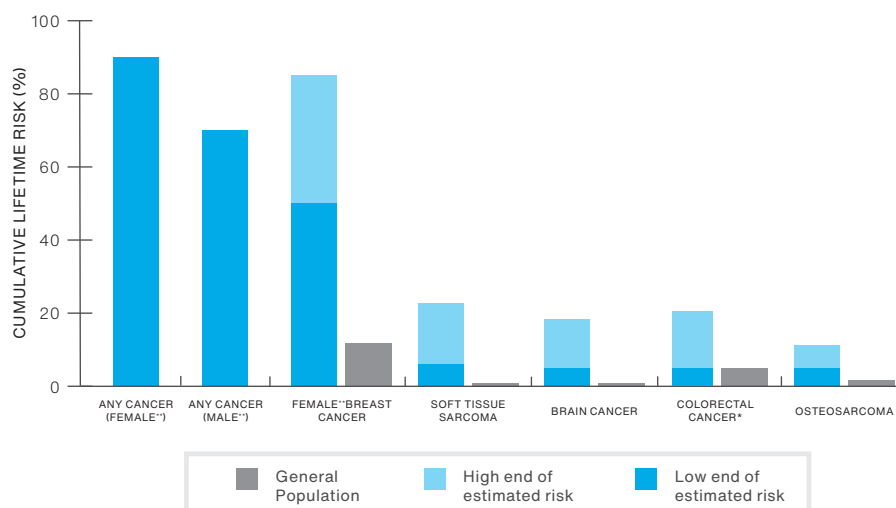
Your test report states that the result is consistent with attenuated Li Fraumeni syndrome (LFS), which is caused by germline *TP53* moderate risk P/LP variants

Attenuated Li Fraumeni syndrome	People with germline <i>TP53</i> moderate risk P/LP variants are more likely to have attenuated Li Fraumeni syndrome (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 classic LFS due to germline <i>TP53</i> 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. If you have a moderate risk P/LP variant, the risks for cancer may not be as high as in classic LFS.
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 <i>TP53</i> variant that was not inherited from either parent. Testing family members for the P/LP <i>TP53</i> 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

[^] Cancer risks associated with attenuated LFS may be lower than in classic LFS, but are not currently well defined

^{^^} People with somatic *TP53* moderate risk P/LP variants cannot pass them on to their children.

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.



RESOURCES

- FORCE facingourrisk.org
- Li-Fraumeni Syndrome Association lfsassociation.org
- Living LFS livinglfs.blogspot.com
- 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 moderate risk 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®) 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 "Moderate Risk P/LP 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 *TP53* Moderate Risk pathogenic or likely pathogenic variant is consistent with attenuated Li Fraumeni syndrome, refer to the "Attenuated Li Fraumeni syndrome" table on the next page for management guidelines.

Moderate Risk P/LP Variants of Unknown Origin in the *TP53* Gene

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

Clinical correlation	<p><i>TP53</i> variants found in blood, saliva, or buccal samples may be present from birth (germline) or acquired later in life (somatic).</p> <ul style="list-style-type: none">• Your patient's test report will indicate if the identified <i>TP53</i> 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 <i>TP53</i> moderate risk variants identified in blood or saliva	<p>Aberrant clonal expansion (ACE) due to clonal hematopoiesis (CHiP)</p> <ul style="list-style-type: none">• Common in healthy older age populations (over 65 years) <p>Chemotherapy treatment</p> <p>Radiation treatment</p>
Management and Next Steps	<p>Management of individuals with identified <i>TP53</i> moderate risk variants will differ markedly depending on if the <i>TP53</i> variant is germline or acquired (somatic).</p> <ul style="list-style-type: none">• 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) <i>TP53</i> 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.<ul style="list-style-type: none">• These individuals may be at risk for heart disease or blood cancers.¹ <p>Careful examination of the patient's complete blood count (CBC) and peripheral blood smear may be warranted in all individuals with identified <i>TP53</i> pathogenic or likely pathogenic variants and testing of non-hematopoietic tissue(s) may help confirm true mosaic involvement across different germ layers.^{1,2}</p>

1. Weitzel J, et al. *Genet Med* 2018;20:809-816.

2. Chao E, et al. *Genet Med* 2021 Jul;23(7):1179-1184.

Attenuated Li Fraumeni Syndrome

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

SCREENING/SURGICAL CONSIDERATIONS ^{1,2}		AGE TO START	FREQUENCY
Female Breast Cancer			
Breast Awareness Women should be familiar with their breasts and promptly report changes to their healthcare provider		Individualized	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 or a separate exam		Individualized	Every 12 months
Neurologic exam**		Individualized	Every 6-12 months
Colorectal and Gastric Cancer			
Colonoscopy and upper endoscopy		20-25 years old, or 5 years before the earliest known colorectal or gastric cancer in the family	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		At time of diagnosis	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 cancer screening		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 3-4 months
Complete blood count with differential in patients with prior cytotoxic chemotherapy or radiation exposures		Individualized	Every 3-4 months

Whole body MRI including upper and lower extremities, whenever feasible, for osteosarcoma risk. 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
Dermatologic exam	Infancy	Every 12 months
Breast Awareness: Young women should be familiar with their breasts and promptly report changes to their healthcare provider	Individualized	Periodic and consistent
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 that should be reported promptly to the care team for evaluation.	N/A	N/A
Address psychosocial and quality-of-life aspects of management. Consider mental health screening at each visit and offer assistance with finding an appropriate mental health provider.	N/A	N/A

* While there are no specific management recommendations for individuals with a moderate risk pathogenic or likely pathogenic variant, a cautious approach would be to follow the same management guidelines as for individuals with a typical *TP53* pathogenic or likely pathogenic variant. NCCN guidelines do not specify management for individuals with a moderate risk pathogenic or likely pathogenic variant.

** 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.

[†] Blood chemistry (total testosterone, dehydroepiandrosterone sulfate, and androstenedione) should be performed if unsatisfactory ultrasound quality.

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. v1.2026. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed July 14, 2025. 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.
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