Ambry Genetics®

Understanding Your Positive *TP53* Genetic Test Result

INFORMATION FOR PATIENTS WITH A PATHOGENIC MUTATION OR VARIANT, LIKELY PATHOGENIC

3 Things To Know

1	*TP53* mutation	Your testing shows that you have a pathogenic mutation or a variant that is likely pathogenic in the *TP53* gene.
2	Reason for *TP53* Mutation	*TP53* mutations may either be present from birth (germline), or they may also be acquired during one's lifetime (somatic). • People with germline *TP53* mutations have Li Fraumeni syndrome (LFS). • People with acquired somatic *TP53* mutations do NOT have LFS.
3	What this means for you	It is important to discuss your result in detail with your healthcare provider. Your report will indicate if your *TP53* mutation may be of acquired (somatic) origin: • If your report has a COMMENT with the possibility of acquired (somatic) origin, see "*TP53* Mutations of unknown origin" table below • If your report states you have a *TP53* mutation with a diagnosis of Li Fraumeni syndrome, see "Li Fraumeni syndrome" table below

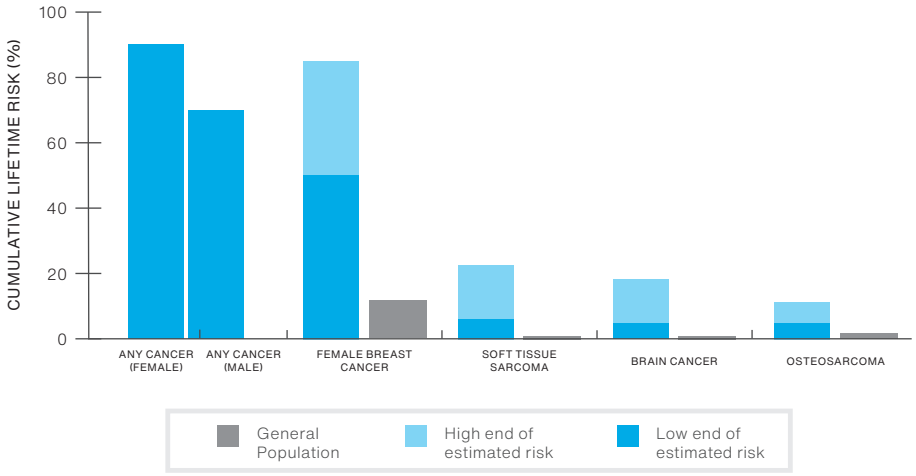
***TP53* Mutations of unknown origin: test report includes a COMMENT with the possibility of somatic origin**	
Your Result	Sometimes, people acquire *TP53* mutations later in life. This is most often due to something called aberrant clonal expansions (ACE) in blood. • ACE is observed in healthy people and occurs more often in individuals over 65 years of age. Acquired (somatic) *TP53* mutations can also been seen in blood as a result of chemotherapy or radiation treatments. Acquired (somatic) *TP53* mutations can be detected in blood samples or saliva samples. • If your *TP53* mutation is acquired (somatic), you do not have the same cancer risks associated with LFS. It is important to discuss your specific management with your doctor. • **It is not always possible to distinguish definitively between germline and acquired (somatic) variants. It is important to discuss next steps with your doctor and decide on a plan that works for you.**
Other Medical Concerns	Acquired (somatic) *TP53* mutations are often detected in healthy people. However, some people with *TP53* mutations in blood due to ACE may be at an increased risk for heart disease or blood cancers. It is important to discuss with your healthcare provider management and screening for these health concerns to determine if you may be at risk.
Family	Testing family members can help determine if your *TP53* mutation is germline or acquired (somatic). If it is determined your mutation is somatic, then you cannot pass this mutation to any of your sons or daughters, and your family and you are not at risk for LFS.

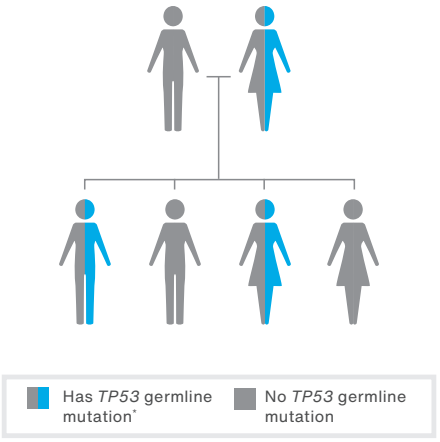
Li Fraumeni syndrome: *TP53* Mutations of Germline Origin	
Li-Fraumeni syndrome	People with germline *TP53* mutations have classic Li Fraumeni syndrome (LFS) or attenuated LFS. The attenuated form of LFS means that the risk of cancer may not be as high as in classic LFS.
Cancer Risk	People with LFS due to germline *TP53* mutations 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 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 doctor and decide on a plan that works for you.
Family	Family members may also be at risk if you have a germline *TP53* mutation - they can be tested for the *TP53* mutation that was identified in you. 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)

TP53 Germline Mutation in the Family*

There is a 50/50 random chance to pass on a germline *TP53* mutation to your sons and daughters. The image to the right shows that both men and women can carry and pass on these mutations.





* People with acquired *TP53* mutations cannot pass these mutations on to sons and daughters.

Reach Out	RESOURCES	

- Ambry's Hereditary Cancer Site for Families patients.ambrygen.com/cancer
- FORCE facingourrisk.org
- Li-Fraumeni Syndrome Association lfsassociation.org
- Living LFS livinglfs.blogspot.com
- Genetic Information Nondiscrimination Act (GINA) ginahelp.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 *TP53* gene mutation. 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 your test report does NOT include a comment with the possibility of somatic origin, please refer only to the "*TP53* Mutations of germline origin" table**

TP53 Mutations of unknown origin: test report includes a COMMENT with 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 test report will indicate if the identified *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* mutations 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 identified *TP53* mutations will differ markedly depending on if the *TP53* mutation is germline versus acquired (somatic). • Testing of family members 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 cases reporting the discovery of a *TP53* P/LP variant, and testing of non lymphoid ancillary tissues may help to delineate bona fide mosaic involvement of 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.

TP53 Mutations of Germline Origin: test report states result is consistent with a diagnosis of Li Fraumeni syndrome (LFS)

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	20-29 years old (or at the age of earliest diagnosed breast cancer in the family), whichever comes first: breast MRI with contrast 30-75 years old: breast MRI with contrast and mammogram Women treated for breast cancer and who have not had bilateral mastectomy, screening continued as described above	Every 12 months
	>75 years old	Individualized
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
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)
Other Cancers and 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
Comprehensive physical exam with high index of suspicion for rare cancers and second malignancies in cancer survivors	Individualized	Every 6-12 months
Whole body MRI*	Individualized	Every 12 months
Address limitations of screening for many cancers associated with Li-Fraumeni syndrome (LFS). Screening may be considered for cancer survivors with LFS and a good prognosis from their prior tumor(s).	N/A	N/A
Pediatricians: Be aware of the risk of childhood cancers and screening recommendations	N/A	N/A
Additional surveillance based on family history of cancer	Individualized	Clinician's discretion
Therapeutic radiation treatment for cancer should be avoided when possible; 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

* Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

** This may be done as part of the comprehensive physical exam (see Other Cancers)

^ 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, and Pancreatic. V2.2023. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed January 11, 2023. 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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