TP53 gene

Associated Syndrome Name: Li-Fraumeni syndrome (LFS)

Important Note: The information below applies only to individuals known to have *TP53* mutations that are germline in nature (mutations present in all cells of the body). Some *TP53* mutations which appear to be germline in nature are actually somatic mutations present in only a subset of blood cells or tissues, or in tumor cells contaminating the sample used for genetic testing. Individuals with somatic *TP53* mutations do not have Li-Fraumeni Syndrome, and the information below regarding cancer risks, medical management options and information for family members may not apply.

TP53 Summary Cancer Risk Table

CANCER	GENETIC CANCER RISK
Breast	High Risk
Colorectal	High Risk
Gastric	High Risk
Lung	High Risk
Other	High Risk
Pancreatic	High Risk
Skin	High Risk
Endometrial	Elevated Risk
Other	Elevated Risk
Prostate	Elevated Risk
Renal	Elevated Risk

TP53 gene Overview

Li-Fraumeni syndrome (LFS) [1, 2, 3]

- Individuals with germline mutations in *TP53* have a condition called Li-Fraumeni syndrome (LFS).
- Individuals with LFS have a high lifetime cumulative risk for a wide spectrum of cancers and for developing multiple primary tumors. Cancer risk is heavily biased towards younger ages, and individuals with LFS often develop cancer at early ages, with the majority of cancers diagnosed under age 45.
- The most common cancers diagnosed in patients with LFS are premenopausal female breast cancer, soft tissue and bone sarcomas, adrenocortical carcinoma and brain tumors. However, the risk for a diverse group of other cancers may also be increased as detailed in the Cancer Risk Table below.
- The overall lifetime cancer risk for women is higher than that for men. This is mostly due to the very high risk for female breast cancer compared with the 12.5% lifetime risk for breast cancer in women in the general population of the United States. Male breast cancer risk is not thought to be increased.
- The ages at which to begin specific cancer screenings should be modified based on personal and family history, typically 5-10 years before the earliest diagnosis of the cancer. Additional cancer screenings may be appropriate based on family history.
- For individuals with a family history of colorectal cancer, colonoscopy screening should begin at 25 years, or 5 years before the earliest diagnosis in the family, whichever comes first. For individuals who have received whole body or abdominal therapeutic radiation therapy, colonoscopy screening should begin at 25 years, or 5 years after treatment of disease, whichever comes first.
- When possible, individuals with LFS are advised to avoid therapeutic radiation therapy for the treatment of cancer, as this can increase the likelihood of additional malignancies.
- Although the risk for cancer in patients with LFS is very high, it may be possible to reduce this risk with appropriate medical management. Guidelines for the management of patients with LFS have been developed by the National Comprehensive Cancer Network (NCCN) and the American Association for Cancer Research (AACR). These are listed below. Since LFS is a rare and complex condition, it is recommended that patients with *TP53* mutations and a diagnosis of LFS be managed by a multidisciplinary team with experience in the prevention and treatment of the many malignancies for which these patients are at risk.

TP53 gene Cancer Risk Table

CANCER TYPE	AGE RANGE	CANCER RISK	RISK FOR GENERAL POPULATION
Overall Cancer Risk	To age 5[4, 5]	3%-6%	0.1%
	To age 20[4, 5]	9%-18%	0.4%
	To age 50[4, 5]	60%-92%	4.7%
	To age 70[4, 5]	92%-98%	19.8%
	Risk for a second primary cancer within 10 years of a first cancer diagnosis[6, 7]	46%	NA
Female Breast	To age 70[4, 5]	71%, with a strong tendency towards very young ages of diagnosis - the large majority of cases occurring before age 45	7.6%
Colorectal	To age 70[5, 8]	18%	1.8%
Melanoma	To age 70[3, 5, 6, 9, 10]	15%	1.0%
Gastric	To age 70[5, 8]	11%	0.4%
Lung	To age 60[4, 5]	7%-9%	0.6%
Pancreatic	To age 70[5, 8]	7%	0.6%
Other - including Adrenocortical Carcinoma, Choroid Plexus Carcinoma, Soft Tissue Sarcoma, Bone Sarcoma, and Brain	To age 80[2, 3, 6, 9]	Greatly increased risk, with a strong tendency towards young ages of diagnosis - sometimes in childhood	NA
Prostate	To age 60[4, 5]	22%	1.8%
Renal	To age 80[3, 5, 6, 9]	Elevated risk	1.4%
Endometrial	To age 80[3, 5, 6, 9]	Possibly elevated	2.7%
Other - Including non-Melanoma Skin, Blood/Bone Marrow (Myelodysplastic Syndromes, Leukemia, Lymphoma), Esophageal, Neuroblastoma, and Thyroid	To age 80[2, 3]	Elevated risk	NA

TP53 Cancer Risk Management Table

The overview of medical management options provided is a summary of professional society guidelines. The most recent version of each guideline should be consulted for more detailed and up-to-date information before developing a treatment plan for a particular patient.

This overview is provided for informational purposes only and does not constitute a recommendation. While the medical society guidelines summarized herein provide important and useful information, medical management decisions for any particular patient should be made in consultation between that patient and his or her healthcare provider and may differ from society guidelines based on a complete understanding of the patient's personal medical history, surgeries and other treatments.

CANCER TYPE	PROCEDURE	AGE TO BEGIN	FREQUENCY (UNLESS OTHERWISE INDICATED BY FINDINGS)
Overall Cancer Risk	Provide education about the signs and symptoms of cancer.[2, 11]	As needed	As needed

CANCER TYPE	PROCEDURE	AGE TO BEGIN	FREQUENCY (UNLESS OTHERWISE INDICATED BY FINDINGS)
Female Breast	Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider. Periodic, consistent breast self-examination (BSE) may facilitate breast awareness.[2, 11]	Individualized	NA
	Clinical breast examination[2, 11]	20 years, or at the age of the earliest diagnosis in the family if under age 20.	Every 6 to 12 months
	Breast MRI with and without contrast[2, 11]	20 years, or at the age of the earliest diagnosis in the family if under age 20.	Annually
	Mammogram[2, 11]	30 years. If MRI unavailable, start at 20 years, or at the age of the earliest diagnosis in the family if under age 20.	Annually
	Consider risk-reducing mastectomy.[2, 11]	Individualized	NA
Colorectal	Colonoscopy[2, 11, 12]	20 to 25 years, or younger based on family history or prior radiation therapy	Every 2 to 5 years
Melanoma	Skin examination[2, 11]	From birth	Annually
Gastric	Upper endoscopy[2, 11, 12]	20 to 25 years, or 5 years younger than the earliest gastric cancer in the family	Every 2 to 5 years
Pancreatic	For patients with a family history of pancreatic cancer, consider endoscopic ultrasound (EUS) and/or contrast-enhanced MRI/magnetic resonance cholangiopancreatography (MRCP). It is recommended that patients who are candidates for pancreatic cancer screening be managed by a multidisciplinary team with experience in screening for pancreatic cancer, preferably within a study setting.[2, 11]	Age 50, or 10 years younger than the earliest age of pancreatic cancer diagnosis in the family	Annually
Other including Lung, Adrenocortical Carcinoma, Sarcomas, Brain tumors, Leukemia, Lymphoma, and other cancers, especially those for which there is a past diagnosis in the family.	Comprehensive physical and neurological examination[2, 11]	From birth	Every 3 to 4 months (from birth to age 18) and every 6 to 12 months from age 18
	Whole body MRI, including brain[2, 11, 13]	From birth	Annually
	Abdominal and pelvic ultrasound[2, 11]	From birth	Every 3 to 4 months (from birth to age 18) and every 6 months from age 18

CANCER TYPE	PROCEDURE	AGE TO BEGIN	FREQUENCY (UNLESS OTHERWISE INDICATED BY FINDINGS)
	Complete blood count (CBC)[2, 11]	From birth	Every 3 to 4 months
Prostate	Recommend prostate cancer screening. Discuss potential benefits and harms of baseline digital rectal examination (DRE) and prostate specific antigen (PSA).[2, 11, 14]	35 to 40 years	Every 1 to 2 years, or adjusted based on PSA
Other including Endometrial and Renal cancer.	Comprehensive physical and neurological examination[2, 11]	From birth	Every 3 to 4 months (from birth to age 18) and every 6 to 12 months from age 18
	Whole body MRI, including brain[2, 11, 13]	From birth	Annually

Information for Family Members

The following information for Family Members will appear as part of the MMT for a patient found to have a mutation in the TP53 gene.

This patient's relatives are at risk for carrying the same mutation(s) and associated cancer risks as this patient. Cancer risks for females and males who have this/these mutation(s) are provided below.

Family members should talk to a healthcare provider about genetic testing. Close relatives such as parents, children, brothers and sisters have the highest chance of having the same mutation(s) as this patient. Other more distant relatives such as cousins, aunts, uncles, and grandparents also have a chance of carrying the same mutation(s). Testing of at-risk relatives can identify those family members with the same mutation(s) who may benefit from surveillance and early intervention.

Approximately 7%-20% of individuals with LFS have not inherited the *TP53* mutation from a parent. In these cases the mutation has developed spontaneously in that individual (a *de novo* mutation). Once this occurs, the children of that individual are each at 50% risk of inheriting the mutation.[3]

Since *TP53* mutations carry a very high risk for cancer in young children, it is important that consideration be given to the possibility of genetic testing and screening at very young ages.

Parents who are concerned about the possibility of passing on a *TP53* mutation to a future child may want to discuss options for prenatal testing and assisted reproduction techniques, such as pre-implantation genetic diagnosis (PGD).[2]

References

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