Updated December 2019 (NCCN v1.2020)

Li-Fraumeni Syndrome (LFS): *TP53* Mutations

Individuals with Li-Fraumeni Syndrome (LFS) are at increased risk for several different cancers including breast cancer, brain cancer, blood or hematological cancers, sarcomas, and tumors of the adrenal gland (adrenocortical carcinoma). For women with LFS, the lifetime risk of cancer is nearly 100% and is primarily attributable to the high incidence of breast cancer. There are currently no nationally recommended surveillance guidelines for many of these cancer types; however, there are several proposed screening approaches.

Li-Fraumeni syndrome Associated Cancers

- **Breast Cancer:** The median age of breast cancer in women with LFS is approximately 33 years of age.[1] Malignant phyllodes tumors of the breast may also be associated with LFS.[2] To date, male breast cancer has not been reported in families with LFS.
- **Sarcoma:** Individuals with LFS are at increased risk of developing soft tissue (i.e., muscle and connective tissue) sarcomas (e.g., rhabdomyosarcoma, liposarcoma) and sarcomas of the bone (e.g., osteosarcoma, chondrosarcoma). Almost all types of sarcomas have been noted in families with LFS with the exception of Ewing sarcoma, which is not associated with LFS. The median age of soft tissue sarcomas in individuals with LFS is 14 years, and the median age of bone sarcomas is 15 years.[1] Both types of sarcomas can also occur in adulthood, with most LFS-associated sarcomas occurring before age 50 years.
- **Brain Tumor:** Individuals with LFS are at increased risk of developing many types of brain tumors. Examples include astrocytomas, glioblastomas, medulloblastomas, and choroid plexus carcinomas (CPC). LFS-related brain tumors can occur in either childhood or adulthood. The median age of onset is 16 years.[1] Clinicians and families need to be aware that there are currently no monitoring regimens that have been proven to be beneficial for children or adults with LFS. Annual physical examination should include a neurological examination.
- **Adrenocortical Carcinoma:** Individuals with LFS are at increased risk of developing adrenocortical carcinoma (ACC). The median age of onset of ACC in families with LFS is three years; however, adults with LFS may also develop ACC.[1]
- **Other Cancer Risks:** Although consensus holds that sarcomas, breast cancer, brain tumors, and ACCs constitute the core cancers of LFS, the following malignancies have been found to be increased in some families with LFS: colorectal cancer, endometrial cancer, esophageal cancer, gonadal germ cell tumor, hematopoietic malignancies, lung cancer, melanoma and non-melanoma skin cancer, neuroblastoma, ovarian cancer, pancreatic cancer, prostate cancer, stomach cancer, thyroid cancer, and renal cancer.

Li-Fraumeni syndrome Management

It is hard to predict which cancers will develop in children and adults with Li-Fraumeni syndrome (LFS) and when these cancers will occur. By undergoing regular medical check-ups and cancer screening tests, it is thought that at least some cancers may be detected at early and treatable stages. It is important that parents of children with LFS and adults with LFS be on the lookout for any lumps, bumps, bone pain, or signs of illness that cannot otherwise be explained. Individuals should be evaluated promptly by their doctors if such signs develop, as these could be evidence of an underlying cancer.

Several organizations have proposed surveillance protocols for LFS, including the National Comprehensive Cancer Network[3] and the American Association for Cancer Research (AACR)[4]. Surveillance should be considered based on the individual's personal clinical and family history and at physician discretion.

Pediatric Risk Management (birth to 18 years)[4]

General assessment

- Complete physical examination every 3–4 months, including blood pressure, anthropometric measurements plotted on a growth curve (with particular attention to rapid acceleration in weight or height), Cushingoid appearance, signs of virilization (pubic hair, axillary moisture, adult body odor, androgenic hair loss, clitoromegaly, or penile growth), and full neurologic assessment
- Prompt assessment with primary care physician for any medical concerns

Adrenocortical Carcinoma

- Ultrasound of abdomen and pelvis every 3-4 months.
- In case of unsatisfactory ultrasound, blood tests, may be performed every 3–4 months including: total testosterone, dehydroepiandrosterone sulfate, andandrostenedione

Brain Tumor

- Annual brain MRI I (first MRI with contrast; thereafter without contrast if previous MRI normal and no new abnormality).

Soft Tissue and Bone Sarcoma

- Annual whole-body MRI

Adult Risk Management[3-4]

General assessment

- Complete physical exam, including neurological exam, every 6-12 months
- Additional surveillance provided based on the family history of cancer
- Provide education on signs and symptoms of cancer
- Prompt assessment with primary care physician for any medical concerns

Brain Tumor

- Annual brain MRI (as part of whole body MRI or separate exam).

Breast Cancer

- NCCN guidelines (v1.2020) recommend the following high risk breast cancer surveillance/management:[3]
    - Breast awareness (being familiar with ones breasts, with periodic, consistent breast self-exams, reporting any unusual findings to a physician promptly) beginning at age 18.
    - Clinical breast exam every 6-12 months starting at age 20 or at the age of the earliest diagnosed breast cancer in the family if below 20 years of age.
    - Annual breast MRI screening with contrast starting at age 20-29 (or at the age of the earliest diagnosed breast cancer in the family if below 20 years of age); mammogram with consideration of tomosynthesis if MRI is unavailable.
    - Annual mammogram with consideration of tomosynthesis alternating with annual breast MRI screening (such that a breast MRI or mammogram occurs every 6 months) from age 30-75.
    - Management should be considered on an individual basis after age 75.
    - Discuss option of prophylactic risk-reducing mastectomy.

Soft Tissue and Bone Sarcoma

- Annual whole-body MRI (if unavailable then can consider clinical trial to screen for cancer or consider alternate comprehensive imaging methods).

- Ultrasound of abdomen and pelvis every 12 months.

Melanoma

- Annual dermatological examination starting at 18 years old.

Gastrointestinal cancer

- Colonoscopy and upper endoscopy every 2-5 years starting at age 25 or 5 years before the earliest known colon cancer in the family, whichever comes first.

It is important to note that individuals with LFS have increased risks for developing cancer at younger than typical ages. It is estimated that 50% of LFS-associated malignancies occur by age 30 years.[5] Individuals may want to consider organ-targeted surveillance based on the pattern of cancer observed in the family. However, there are no data to support the efficacy of this approach. Additionally, there is controversy over how to manage cancer risk for individuals who do not meet classical LFS criteria. Some data suggest lower cancer risks for individuals who do not have a family history consistent with LFS.

Agents/Circumstances to Avoid

- There is some evidence that *TP53* mutations confer an increased sensitivity to ionizing radiation.[6,7-9] Thus, individuals with LFS should avoid or minimize exposure to radiation whenever possible.[10] Radiation-induced second malignancies have been reported among individuals with LFS.[11]
- Individuals with LFS are also encouraged to avoid or minimize exposures to other known carcinogens because the effects of carcinogenic exposures (e.g. smoking and secondhand smoke) and germline *TP53* mutations may be cumulative. Additionally, they are encouraged to avoid excess sun exposure and always use sun protective strategies when outdoors in the sunlight.

Support Services for Li-Fraumeni Syndrome

- The Li-Fraumeni syndrome association offers family support and resources for patients (www.lfsassocation.org). The George Pantziarka *TP53* Trust helps families with and provides information for individuals with Li-Fraumeni syndrome (www.tp53.co.uk).

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *TP53* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

References

1. Olivier M, et al. 2003. Li-Fraumeni and related Syndromes: correlation between tumor type, family structure, and TP53 genotype. *Cancer Research*. Oct 15; 63(20):6643-6650.
2. Birch JM, et al. 2001. Relative frequency and morphology of cancers in carrier of germline TP53 mutations. *Oncogenetics*. Aug 2; 20(34):4621-4628.
3. National Comprehensive Cancer Network Guidelines. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (v.1.2020). 2019.

4. Kratz CP, et al. 2017. Cancer Screening Recommendations for Individuals with Li-Fraumeni Syndrome. *Clinical Cancer Reseasrch.* June 1: 23(11).
5. Lustbader ED, et al. 1992. Segregation analysis of cancer in families of childhood soft-tissue-sarcoma patients. *American Journal of Human Genetics*. Aug; 51(2):344-356.
6. Cohen RJ, et al. 2005. The risk of developing second cancers among survivors of childhood soft tissue sarcoma. *Cancer*. Jun 1; 103(11):2391-2396.
7. Hisada M, et al. 1998. Multiple primary cancers in families with Li-Fraumeni syndrome. *Journal of the National Cancer Institute*. Apr 15; 90(8):606-611.
8. Varley JM. 2003. Germline TP53 mutations and Li-Fraumeni syndrome. *Human Mutation*. Mar; 21(3):313-320.
9. Wang QE, et al. 2003. Tumor suppressor p53 dependent recruitment of nucleotide excision repair factors XPC and TFIIH to DNA damage. *DNA Repair (Amsterdam)*. May 13; 2(5):482-499.
10. Evans DG, et al. 2006. Malignant transformation and new primary tumors after therapeutic radiation for benign disease: substantial risk in certain tumor prone syndromes. *Journal of Medicine Genetics*. Apr; 43(4):289-294.
11. Limacher JM, T Frebourg, S Natarjan-Ame, and JP Bergerat. 2001. Two metachronous tumors in the radiotherapy fields of a patient with Li-Fraumeni syndrome. *International Journal of Cancer*. Aug 20; 96(4):238-242.