



Li-Fraumeni Syndrome

Li-Fraumeni syndrome (LFS) is a rare hereditary cancer syndrome associated with germline *TP53* gene mutations, inherited in an autosomal dominant manner.

Sarcoma, premenopausal breast cancer, adrenocortical carcinoma and brain tumours are the most common cancers observed with LFS. A wide spectrum of malignancies has also been associated with LFS including: leukemia, lung, colon, gastric, melanoma, lymphoma, and pancreatic cancers.

People with LFS often have their first cancer diagnosis at a young age and have increased risk for multiple primary cancer diagnoses over their lifetimes. Confirmation of LFS is, therefore, important both for children or adults with cancer, because of the associated risk for another LFS cancer, and to inform appropriate cancer risk management for their family members.

Hereditary Cancer Program Referral Criteria

Notes:

1. *LFS cancers include: soft tissue sarcoma, osteosarcoma, pre-menopausal breast cancer, brain tumor, adrenocortical carcinoma, leukemia, bronchoalveolar lung cancer*
 2. **close relatives** include children, brothers, sisters, parents, aunts, uncles, grandchildren & grandparents **on the same side of the family**. History of cancer in cousins and more distant relatives from the same side of the family may also be relevant.
- family member with a confirmed *TP53* gene mutation – refer for carrier testing
 - person with low hypodiploid acute lymphoblastic leukemia
 - person with adrenocortical carcinoma or choroid plexus tumour diagnosed at any age
 - person with soft tissue sarcoma (excludes Ewing's sarcoma), osteosarcoma, breast cancer, brain tumour, leukemia or bronchoalveolar lung cancer diagnosed at age 45 or younger who has at least 1 close relative with:
 - multiple primary cancers OR
 - a LFS cancer diagnosis at age 55 or younger
 - person with at least 2 primary LFS cancer diagnoses and the 1st diagnosis at age 45 or younger
 - person with family history as above

Referral of children is appropriate for this syndrome because it may inform their medical management.

Lifetime Cancer Risks for TP53 mutation carriers

Estimating cancer risks for a person with LFS is challenging because of the ranges of risk reported in the literature and the wide variation between and within families. The most common cancers observed per age group are:

- age 0-10: soft-tissue sarcoma, brain tumour, ACC
- age 11-20: osteosarcoma
- after age 20: breast cancer (female), brain tumour

The estimated overall lifetime risk of developing cancer is 73% for males and almost 100% for females. The estimated cancer risk **by age 30** is 20% for males and 49% for females. The median age of female breast cancer diagnosis is reported as 33. People with LFS are also believed to have significantly increased risks to develop multiple primary tumours.

Cancer Risk Management Recommendations for TP53 mutation carriers ****under review****

Note: The wide spectrum of tumours associated with LFS coupled with a lack of evidence to support screening for these specific tumours makes clinical management challenging. The recommendations below are general in nature. Individualized recommendations based on personal and/or family medical histories may be provided through Hereditary Cancer Program assessment and/or by other specialists involved in a person's current care.

General considerations for adults and children

- identify a "managing clinician" (physician or nurse practitioner) to coordinate cancer screening and to provide expedited assessment of new symptoms
- physical exam every 3-4 months from birth to age 18 and every 6 months thereafter, including careful skin and neurologic examinations
- prompt scheduling of diagnostic tests for any ongoing symptoms and illnesses (e.g. headaches, bone/limb pain, abdominal discomfort).
- healthy lifestyle including: smoking cessation, regular physical exercise, maintain healthy body weight, limit alcohol intake, avoid excessive sun exposure.
- avoid or minimize exposure to radiation (including x-ray). However, diagnostic or therapeutic radiation should not be withheld due to concerns about exposure to ionizing radiation.

Breast Cancer

- breast awareness from age of first development
- consider bilateral risk-reducing mastectomy
- annual breast MRI from age 20-65; at age 65 there should be a discussion between a woman and her healthcare provider about continuing MRI based on her personal needs, cancer risks, health history and local access
- consider mammogram and ultrasound as screening tests only if no access to breast MRI
- consider breast ultrasound during pregnancy and lactation
- risk-reducing medication (e.g. tamoxifen, raloxifene, anastrozole, exemestane) can almost halve the risk of developing a hormone-receptor positive breast cancer, but no studies have been reported of its use by women with LFS. The decision to use such medication requires discussion about the relative benefits and the risk of side effects.

Other cancers – consider the following screening tests:

- annual whole body MRI (include brain or book separate brain MRI)
- abdominal ultrasound every 3-4 months from birth to age 18 and annually thereafter
 - ideally ultrasound and whole body MRI are scheduled so that some imaging is done every 6 months
- colonoscopy every 2-5 years beginning at age 25 or 5 years younger than the earliest colorectal cancer in the family (whichever comes first)
- upper GI endoscopy every 2-5 years beginning at age 25 or younger if there is family history of upper GI cancers at young ages
- ongoing periodic CBCs to detect evidence of accelerated myelodysplasia as a precursor for leukemic transformation in people with a prior personal history of cancer (possible exposure to leukemogenic agents). There is no evidence to support screening for leukemia in those without prior personal cancer history.

Additional Information

The following websites offer support and information which may be helpful to people living with LFS:

- <http://www.lfsassociation.org/>
- <http://www.livinglfs.org/>
- <http://listserv.acor.org/archives/li-fraumeni.html>

References available on request.

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