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NLM Citation: Schneider K, Zelley K, Nichols KE, et al. Li-Fraumeni Syndrome. 1999 Jan 19 [Updated 2019 Nov 21]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Li-Fraumeni Syndrome

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Created: January 19, 1999; Updated: November 21, 2019.

Summary

Clinical characteristics

Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome associated with high risks for a diverse spectrum of childhood- and adult-onset malignancies. The lifetime risk of cancer in individuals with LFS is ≥70% for men and ≥90% for women. Five cancer types account for the majority of LFS tumors: adrenocortical carcinomas, breast cancer, central nervous system tumors, osteosarcomas, and soft-tissue sarcomas. LFS is associated with an increased risk of several additional cancers including leukemia, lymphoma, gastrointestinal cancers, cancers of head and neck, kidney, larynx, lung, skin (e.g., melanoma), ovary, pancreas, prostate, testis, and thyroid. Individuals with LFS are at increased risk for cancer in childhood and young adulthood; survivors are at increased risk for multiple primary cancers.

Diagnosis/testing

The diagnosis of LFS is established in a proband who meets ALL THREE classic clinical criteria and/or has a heterozygous germline pathogenic variant in *TP53*. Classic clinical criteria:

- A proband with a sarcoma diagnosed before age 45 years
- A first-degree relative with any cancer diagnosed before age 45 years
- A first- or second-degree relative with any cancer diagnosed before age 45 years or a sarcoma diagnosed at any age

Management

Treatment of manifestations: Routine oncologic management is recommended for malignancies, with the exception of breast cancer, in which bilateral mastectomy rather than lumpectomy is recommended in order to reduce the risks of a second primary breast cancer and avoid radiation therapy. Concerns about increased risk for radiation-induced second primary tumors has led to more cautious use of therapeutic radiation in general,

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but most experts recommend that treatment efficacy be prioritized above concerns about late effects after careful analysis of risks and benefits.

Prevention of primary manifestations: Prophylactic bilateral mastectomy to reduce the risk for breast cancer is an option for women with a germline *TP53* pathogenic variant. Colonoscopy may be considered surveillance as well as primary prevention of colorectal cancer. Avoidance of sun exposure, tobacco use, and exposure to other known or suspected carcinogens is encouraged.

Surveillance: Comprehensive physical examination and ultrasound of abdomen and pelvis every 3-4 months from birth to age 18 years, annual neurologic exam and whole-body MRI including brain MRI from the time of diagnosis. In individuals 18 years or older, complete physical exam every 6 months, ultrasound of abdomen and pelvis and dermatologic exam annually. Women should have a clinical breast examination every 6-12 months beginning at age 20-25 years, annual breast MRI beginning at age 20-30 years, annual mammogram and breast MRI from age 30 to age 75 years. Upper endoscopy and colonoscopy are recommended every 2-5 years in individuals from age 25 years.

Agents/circumstances to avoid: Minimize exposure to diagnostic and therapeutic radiation; avoid known carcinogens including sun exposure, tobacco use, occupational exposures, and excessive alcohol use.

Evaluation of relatives at risk: It is appropriate to offer genetic counseling and testing to all relatives who are at risk of having a familial *TP53* pathogenic variant.

Genetic counseling

LFS is inherited in an autosomal dominant manner. Most individuals diagnosed with LFS inherited a *TP53* pathogenic variant from a parent. The proportion of individuals with a *de novo* germline *TP53* pathogenic variant is estimated to be between 7% and 20%. Offspring of an individual with an established diagnosis of LFS (i.e., an individual who meets classic LFS criteria and/or has a heterozygous germline *TP53* pathogenic variant) have a 50% risk of inheriting an LFS-causative pathogenic variant and having the cancer risks associated with LFS. Predictive testing for at-risk family members, prenatal testing, and preimplantation genetic testing are possible if a *TP53* germline pathogenic variant in the family has been identified.

Diagnosis

Clinical diagnostic criteria for Li-Fraumeni syndrome (LFS) have been published [Mai et al 2012].

Suggestive Findings

LFS **should be suspected** in individuals who meet the Chrompret criteria [Bougeard et al 2015, Valdez et al 2017], have early-onset hypodiploid acute lymphoblastic leukemia (ALL), or have suggestive findings on somatic tumor tissue testing.

- **2015 Chompret criteria** (~30% will have a germline *TP53* pathogenic variant) [Mai et al 2012]:
  - A proband with a tumor belonging to the LFS tumor spectrum (e.g., premenopausal breast cancer, soft-tissue sarcoma, osteosarcoma, central nervous system (CNS) tumor, adrenocortical carcinoma) before age 46 years **AND** at least one first- or second-degree relative with an LFS tumor (except breast cancer if the proband has breast cancer) before age 56 years or with multiple tumors; **OR**
  - A proband with multiple tumors (except multiple breast tumors), two of which belong to the LFS tumor spectrum and the first of which occurred before age 46 years; **OR**
  - A proband with adrenocortical carcinoma, choroid plexus tumor, or rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of family history; **OR**
  - A female proband with breast cancer before age 31 years.

- **Hypodiploid acute lymphoblastic leukemia (ALL)** diagnosed in a proband <age 21 years (~50% will have a germline *TP53* pathogenic variant) [Holmfeldt et al 2013]

  Note: To date, a germline *TP53* pathogenic variant has not been reported in an individual with adult-onset hypodiploid ALL.

- **Somatic tumor tissue testing** identifies one of the following:
  - A *TP53* pathogenic variant with an allele frequency of ~50% or >50%
  - Absent or decreased staining of p53 by immunohistochemistry

    Note: The LFSPRO prediction tool, based on a Mendelian model, can also be used to estimate the likelihood of identifying a germline *TP53* pathogenic variant [Peng et al 2017].

Establishing the Diagnosis

The diagnosis of LFS **is established** in a proband who meets ALL THREE classic LFS criteria AND/OR has a germline pathogenic (or likely pathogenic) variant in *TP53* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *TP53* variant of uncertain significance does not establish or rule out the diagnosis.

Classic LFS criteria (~60%-80% will have a germline *TP53* pathogenic variant) [Mai et al 2012]:

- A proband with a sarcoma diagnosed before age 45 years
- A first-degree relative with any cancer diagnosed before age 45 years
- A first- or second-degree relative with any cancer diagnosed before age 45 years or a sarcoma diagnosed at any age

Note: Identification of low-level (<20%) mosaicism for a *TP53* pathogenic variant in leukocytes is suggestive of a postzygotic (acquired) pathogenic variant due to clonal hematopoiesis of indeterminate potential (CHIP) related to aging, cytotoxic treatments, underlying hematologic malignancy or premalignancy, or circulating tumor cells [Weitzel et al 2018]. There are no standardized approaches to distinguish a *TP53* pathogenic variant due to CHIP from a germline *TP53* pathogenic variant, but evaluations may include the following [Weitzel et al 2018]:

- Analysis of cultured skin fibroblasts for the identified *TP53* pathogenic variant
- Molecular genetic testing of all offspring to determine if the *TP53* pathogenic variant was transmitted
- Molecular genetic testing of other affected family members to determine if the *TP53* pathogenic variant is segregating with cancer in the family

Molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *TP53* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

- **A multigene panel** that includes *TP53* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by

laboratory and are likely to change over time. (2) Multigene panels typically include additional inherited cancer genes, which are not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Li-Fraumeni Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
TP53	Sequence analysis [3]	91% [4]
	Gene-targeted deletion/duplication analysis [5]	1% [6]
Unknown [7]	NA	8%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Sequence analysis of the entire *TP53* coding region (exons 2-11) detects about 95% of *TP53* pathogenic variants, most of which are missense variants. It is estimated that about 91% of individuals with LFS will have *TP53* pathogenic / likely pathogenic variants detected by sequence analysis [Guha & Malkin 2017].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. LFS can be caused by a deletion involving the coding region of *TP53* or the promoter and noncoding exon [Guha & Malkin 2017].
7. To date, *TP53* is the only gene known to be associated with LFS. However, a germline pathogenic variant is identified in only 92% of individuals with LFS [Guha & Malkin 2017].

Clinical Characteristics

Clinical Description

Li-Fraumeni syndrome (LFS) is associated with high risks for a diverse spectrum of childhood- and adult-onset malignancies. The lifetime risk of cancer in individuals with LFS is ≥70% for men and ≥90% for women [Mai et al 2016, Guha & Malkin 2017]. Five cancer types account for the majority of LFS tumors: adrenocortical carcinomas, breast cancer, central nervous system tumors, osteosarcomas, and soft-tissue sarcomas [Guha & Malkin 2017].

- **Adrenocortical carcinomas (ACC)** develop in 6%-13% of individuals with individuals with LFS with most diagnoses occurring before age five years. ACC also occurs in adults with LFS, typically before age 40 years [Mai et al 2016]. The southern Brazilian *TP53* founder variant, p.Arg337His, is associated with a high risk of ACC, especially in childhood. In one series of individuals with pathogenic variant p.Arg337His, ACC accounted for 55% of the childhood cancers and 23% of the adult-onset cancers observed [Ferreira et al 2019]. For individuals with pathogenic variant p.Arg337His, the penetrance of childhood ACC is one in 30 to 40 [Achatz & Zambetti 2016].
- **Breast cancer.** Female breast cancer accounts for 27%-31% of LFS cancers, making it the most common cancer in women with LFS [Id Said et al 2016]. In one series, the cumulative incidence of breast cancer in

females by age 70 was 54% [Mai et al 2016]. LFS-associated breast cancers occur at a younger age (median age: 33 years), with almost all breast cancers in women with LFS occurring prior to menopause [Bougeard et al 2015]. LFS-associated breast cancers are more likely to be ductal, estrogen receptor and progesterone receptor positive, and show *HER2* amplification [Bougeard et al 2015, Mai et al 2016, Packwood et al 2019]. Malignant phyllodes tumors of the breast are also associated with LFS [Villani et al 2016]. In two series of families with LFS, no instances of male breast cancer were observed [Bougeard et al 2015, Mai et al 2016].

- **Central nervous system (CNS) tumors** account for 9%-14% of LFS cancers [Bougeard et al 2015]. In one series, the cumulative incidence of brain cancer by age 70 was 6% for women and 19% for men [Mai et al 2016]. The age of onset of brain tumors is biphasic with both childhood and adult onset, typically before age 40 years (median age: 16 years) [Valdez et al 2017]. Glioblastomas and astrocytomas are the most common CNS tumor types in individuals with LFS, although many other CNS tumor types have been reported, including ependymomas, choroid plexus carcinomas, and supratentorial primitive neuroectodermal tumors [Bougeard et al 2015, Valdez et al 2017]. Medulloblastomas in individuals with LFS are more likely to be of the sonic hedgehog subtype [Taylor et al 2012] and display chromothripsis (numerous clustered chromosome rearrangements occurring in malignant cells) [Zhukova et al 2013].
- **Osteosarcomas** account for 3%-16% of LFS cancers and typically occur prior to age 30 years (median age: 14 years), although later diagnoses up to age 55 years have been reported [Bougeard et al 2015, Mirabello et al 2015]. In one series, the cumulative incidence of bone cancers by age 70 was 5% for women and 11% for men [Mai et al 2016].
- **Soft-tissue sarcomas.** Rhabdomyosarcomas and other soft-tissue sarcomas are the most common LFS cancers in children and account for 17%-27% of the total cancers occurring in individuals with LFS [Bougeard et al 2015]. In one series, the cumulative incidence of soft-tissue sarcoma was 15% for women and 22% for men [Mai et al 2016]. Rhabdomyosarcomas often occur before age five years [Ognjanovic et al 2012] and are often nonalveolar tumors with diffuse anaplasia [Hettmer et al 2014].

Additional cancers. LFS is associated with an increased risk of several additional cancer types including the following:

- **Leukemias and lymphomas.** Primary and secondary leukemias, especially acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), and myelodysplastic syndrome (MDS) represent about 2%-4% of LFS cancers. In one series, leukemia occurred between ages two and 35 years (median age: 12 years) [Bougeard et al 2015]. ALL often exhibits a low hypodiploid state with 32-39 chromosomes [Holmfeldt et al 2013, Qian et al 2018, Swaminathan et al 2019]. Hodgkin and non-Hodgkin lymphomas account for approximately 2% of cancers reported in individuals with LFS [Bougeard et al 2015]. Lifetime risk estimates for developing leukemia or lymphoma in LFS are not established but are likely to be lower than the risks for developing any of the five most common cancers reported in individuals with LFS.
- **Gastrointestinal cancers.** Colorectal cancers account for about 3% of the cancers diagnosed in individuals with LFS [Guha & Malkin 2017]. A recent series reported that 8.6% of individuals with LFS were diagnosed with colorectal cancer or a polyp with high-grade dysplasia; 3.2% of these occurred before age 25 years and 4.3% before age 35 years [Rengifo-Cam et al 2018]. Additional gastrointestinal cancers have also been reported including gastric cancer [Bougeard et al 2015, Mai et al 2016]. A higher incidence of gastric cancer is reported in individuals younger than age 40 years in Asian kindreds [Ariffin et al 2015]. Lifetime risk estimates for developing gastrointestinal cancer in LFS are not established but are likely to be lower than the risks for developing any of the five most common cancers reported in individuals with LFS.
- **Other cancers.** Additional cancers reported in families with an identified *TP53* pathogenic variant or a clinical diagnosis of LFS have included cancers of the head and neck, kidney, larynx, lung, skin (e.g., melanoma), ovary, pancreas, prostate, testis, and thyroid [Mai et al 2016, Valdez et al 2017].
- **Gestational choriocarcinoma in female partners.** The pregnant mother of a fetus heterozygous for a paternally inherited *TP53* pathogenic variant is at risk for choriocarcinoma or another gestational

trophoblastic disease (i.e., the occurrence of cancer in placental tissue, which may spread to other maternal organs) [Cotter et al 2018].

Excess of early-onset cancers. In one series, the average onset of first cancer for men with LFS was age 17 years; the average onset of first cancer for women was age 28 years when including breast cancer and age 13 years when excluding breast cancer [Bougeard et al 2015]. In another series, it was estimated that 50% of LFS-associated malignancies occurred by age 30-31 years for women and age 46 for men [Mai et al 2016].

Excess of multiple primary cancers. Individuals with LFS have a 40%-49% risk of developing a second cancer (median onset: 10 years after the first cancer diagnosis). Radiation and chemotherapy treatment of an LFS-related cancer may increase the risk for a second malignancy [Bougeard et al 2015, Churpek et al 2016, Mai et al 2016, Schon & Tischkowitz 2018].

Prognosis. In a series of 89 individuals with LFS who either selected or declined surveillance including rapid whole-body MRI, breast imaging, brain imaging, blood tests, and other targeted interventions, including upper and lower endoscopies in adults, the five-year overall survival rate was 88.8% for individuals in the surveillance group and 59.6% for those in the non-surveillance group [Villani et al 2016].

With the utilization of multigene panel testing, the number of individuals identified with a germline *TP53* pathogenic variant has substantially increased. Individuals who had germline *TP53* pathogenic variants identified on multigene panel testing appear to have had cancer diagnoses at older ages and less striking family histories of cancer, and were less likely to meet classic LFS or Chompret criteria compared to individuals who had a *TP53* pathogenic variant identified on single-gene testing [Rana et al 2018]. Thus, there may be a broader phenotypic spectrum in LFS than was previously recognized.

Genotype-Phenotype Correlations

There continues to be debate regarding genotype-phenotype correlations in LFS.

A recent study reported that individuals with germline *TP53* pathogenic variants resulting in p53 loss of function appeared to have a more severe phenotype than individuals with pathogenic variants that caused partial deficiency of p53. Individuals with loss-of-function variants had an earlier onset of first cancer, higher incidences of breast cancer before age 35 and of sarcoma, and greater likelihood of meeting classic LFS and/or Chompret criteria [Rana et al 2019].

These findings are in contrast with another series, which reported that individuals with LFS who carry dominant-negative pathogenic variants (in which the mutated p53 protein interferes with the function of the wild type p53 protein) appeared to have more clinically severe phenotypes than did individuals with other *TP53* pathogenic variants [Bougeard et al 2015]. A laboratory study also reported that dominant-negative pathogenic variants appear to cause a more profound alteration of p53 DNA binding than other pathogenic variants [Zerdoumi et al 2017].

The *TP53* founder variant p.Arg337His common in southern Brazil is associated with a high risk of childhood-onset ACC, up to 55% in one series [Ferreira et al 2019]. This variant is associated with an increased risk of breast cancer, as well as other LFS-associated cancers, although at older ages and with lower lifetime risks (50%-60%) compared to other *TP53* pathogenic variants [Ferreira et al 2019]. Maternal inheritance of p.Arg337His was identified in 72% of individuals, suggesting preferential selection. One individual homozygous for p.Arg337His whose clinical phenotype did not appear to differ from p.Arg337His heterozygotes, has been identified [Ferreira et al 2019].

Penetrance

LFS is typically considered to be a highly penetrant cancer syndrome with a 70% or higher lifetime risk of cancer in men and a 90% or higher lifetime risk of cancer in women [Mai et al 2016, Guha & Malkin 2017]. Another study reported an 80% risk of cancer by age 70, with 22% of the cancers occurring between ages 0 and15 years, 51% between ages 16 and 50 years, and 27% between ages 51 and 80 years [Amadou et al 2018].

However, the penetrance of LFS may be overestimated as more individuals recently identified with a germline *TP53* pathogenic variant do not meet classic LFS or Chompret criteria due to a less striking family and personal history of cancer [Rana et al 2018].

Individuals with *TP53* pathogenic variant p.Arg337His appear to have a lower lifetime risk of cancer than those with other *TP53* pathogenic variants [Ferreira et al 2019].

Genetic Modifiers

Genetic modifiers of LFS-associated cancer risk include the following:

- ***TP53* p.Arg72 polymorphism.** The p.Arg72 polymorphism causes increased affinity toward MDM2, resulting in higher levels of p53 degradation and earlier onset of first cancer [Guha & Malkin 2017].
- ***MDM2* c.14+309T>G variant.** The presence of the NM_002392.2:c.14+309G>T variant (also termed SNP309T>G) in the *MDM2* promoter region (rs2279744) leads to increased MDM2 expression resulting in higher levels of p53 degradation and earlier onset of first cancer [Guha & Malkin 2017, Amadou et al 2018].
- **microRNA R-605 variant.** The presence of a variant in *miR-605*, which regulates the p53-MDM2 loop, resulted in a ten-year accelerated mean age of tumor onset [Guha & Malkin 2017, Amadou et al 2018].
- **16 base pair duplication polymorphism in intron 3 (PIN3).** The presence of the PIN3 polymorphism appears to be protective, with older ages of first cancer compared to individuals who do not have this polymorphism [Guha & Malkin 2017, Amadou et al 2018].
- **Shortened telomere length.** Shortened telomere length over subsequent generations has been associated with accelerated tumor development (anticipation) in families with LFS [Guha & Malkin 2017]. The association between telomere erosion and earlier cancer onset continues to be studied.

Nomenclature

LFS was referred to as SBLA (*s*arcoma, *b*reast, *l*eukemia, and *a*drenal gland) syndrome in earlier publications.

Prevalence

The frequency of germline *TP53* pathogenic variants in the general population is not well established. One group places the prevalence at 1:3,555 to 1:5,476 [de Andrade et al 2019].

TP53 pathogenic variant p.Arg337His is a founder variant in southern Brazil with a prevalence of 0.3% (1:375 individuals) [Achatz & Zambetti 2016, Valdez et al 2017].

Genetically Related (Allelic) Disorders

Sporadic tumors occurring as single tumors in the absence of any other findings of Li-Fraumeni syndrome (LFS) frequently harbor a somatic variant in *TP53* that is **not** present in the germline. Somatic *TP53* pathogenic variants are found in approximately 50% of all tumors, making it one of the most frequently altered genes in human cancers. For more information see Cancer and Benign Tumors.

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *TP53*.

Differential Diagnosis

Table 2. Other Genes of Interest in the Differential Diagnosis of Li-Fraumeni Syndrome

Gene(s)	Disorder	MOI	Core Cancer(s)	Age at Cancer Onset	Comments
BRCA1 *BRCA2*	*BRCA1*- and *BRCA2*-associated hereditary breast and ovarian cancer	AD	Breast; ovary; pancreas; prostate; melanoma	Typically in adulthood	*A BRCA1* or *BRCA2* pathogenic variant is more likely in individuals w/: • Premenopausal breast cancer, especially ER/PR/*HER2*-negative tumors • Personal or family history of ovarian, pancreatic, male breast, or prostate cancer • Ashkenazi Jewish ancestry • No family history of adrenocortical carcinomas, CNS tumors, osteosarcomas, or soft-tissue sarcomas
CHEK2	*CHEK2* cancer susceptibility (OMIM 609265)	AD	Breast; colorectal; prostate	Typically in adulthood	*CHEK2* pathogenic variants are more likely to explain personal & family histories of predominantly breast, colon, prostate, or other adult-onset cancers.
MLH1 *MSH2* *MSH6* *PMS2*	Constitutional mismatch repair deficiency (a variant of Lynch syndrome)	AR	Colorectal; small bowel; hematologic; brain	Early childhood	CMMRD should be considered in individuals w/childhood-onset gastrointestinal cancer or polyps, malignant brain tumor, hematologic cancer, &/or café au lait macules.

AD = autosomal dominant; AR = autosomal recessive; CMMRD = constitutional mismatch repair deficiency; CNS = central nervous system; ER = estrogen receptor; MOI = mode of inheritance; PR = progesterone receptor

Somatic mosaicism for *TP53* pathogenic variant. Low-level (<20%) mosaicism for a *TP53* pathogenic variant due to clonal hematopoiesis of indeterminate potential (CHIP) can be identified in leukocytes of individuals due to aging, cytotoxic treatments, underlying hematologic malignancy or premalignancy, or circulating tumor cells [Weitzel et al 2018]. Medical history should include assessment of exposure to cigarette smoke or cytotoxic chemotherapy, the possibility of circulating malignant clones (leukemia, lymphoma, or other tumor), and allelic fraction [Weitzel et al 2018]. It is important to distinguish individuals with CHIP from those with Li-Fraumeni syndrome (LFS), as screening for LFS-related tumors is not recommended for individuals with CHIP [Weitzel et al 2018].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Li-Fraumeni syndrome (LFS), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Due to the lifelong increased cancer risk and the diversity of tumors associated with LFS, evaluations for cancer in individuals with LFS need to be ongoing and comprehensive. Cancer monitoring can include physical examinations, blood counts, imaging studies, endoscopies, and/or biopsies (see Surveillance). Individuals with

or suspected of having LFS based on clinical or molecular criteria should seek a cancer genetics consultation to review the diagnosis and medical management recommendations.

Treatment of Manifestations

In individuals with LFS, radiation therapy is avoided if possible to reduce the risk of secondary malignancies. However, treatment efficacy should be prioritized above concerns regarding risk of subsequent malignancies (e.g., radiation treatment may be necessary to provide the best chance of cure).

Women with LFS who develop breast cancer are encouraged to consider bilateral mastectomy (rather than lumpectomy) in order to reduce the risk of developing a second primary breast cancer and avoid exposure to radiation therapy [Schon & Tischkowitz 2018].

Aside from avoiding radiation therapy if possible, LFS tumors are typically treated according to standard protocols.

Prevention of Primary Manifestations

Women with LFS have the option of bilateral mastectomy to reduce the risk of breast cancer [Schon & Tischkowitz 2018].

Adults with LFS should have screening colonoscopy examinations, which can be considered surveillance as well as primary prevention of colorectal cancer [MacFarland et al 2019].

Avoidance of sun exposure, tobacco use, and exposure to other known or suspected carcinogens is encouraged.

Surveillance

Surveillance guidelines for adults and children with LFS have been developed, largely based on the "Toronto protocol" [Villani et al 2016, Kratz et al 2017, NCCN 2019].

Table 3. Recommended Surveillance for Individuals with Li-Fraumeni Syndrome

System/Concern	Evaluation	Frequency
All cancers	Complete physical exam w/high index of suspicion for cancer [1]	• Every 3-4 mos, birth to 18 yrs • Every 6 mos, ≥18 yrs
	Whole-body MRI [2, 3]	Annually, all ages
ACC	Ultrasound of abdomen & pelvis	Every 3-4 mos, birth to age 18 yrs (not on same visit as whole-body MRI)
	Serum total testosterone, dehydroepiandrosterone sulfate, & androstenedione	If ultrasound is unsatisfactory [4]
Breast cancer	Clinical breast exam	Every 6-12 mos, age ≥20-25 yrs
	Breast MRI w/& w/o contrast	Annually, age 20-30 yrs
	Mammogram + breast MRI w/ & w/o contrast	Annually, age 30-75 yrs
CNS tumors	Neurologic exam	Annually, all ages
	Brain MRI [5]	Annually
Gastrointestinal cancers	Upper endoscopy & colonoscopy	Every 2-5 yrs, age ≥25 yrs [6]
Leukemia/ Lymphoma	None recommended [7]	NA

Table 3. continued from previous page.

System/Concern	Evaluation	Frequency
Melanoma	Dermatologic exam	Annually, age ≥18 yrs
Sarcomas	Whole-body MRI	Annually, all ages
	Ultrasound of abdomen & pelvis	Annually, age ≥18 yrs

NA = not applicable
1. Complete physical examination should include blood pressure, full neurologic exam, and assessment of growth, sudden weight gain or loss, Cushingoid appearance, or signs of virilization in a child [Kratz et al 2017].
2. MRI preferably within a clinical trial [NCCN 2019]. A meta-analysis of baseline whole-body (WB)-MRI reported cancers in 7% of individuals screened [Ballinger et al 2017]. Risks of WB-MRI include the high false positive rate (requiring further evaluation to rule out malignancy) and the need for sedation in young children.
3. Participants with LFS in a WB-MRI screening program reported significant reductions in anxiety following WB-MRI exam. Some individuals with LFS reported an increased sense of control and hope due to participation in a surveillance program, while others reported an increased burden due to multiple visits, extra surveillance, and concerns regarding false positive results [McBride et al 2017].
4. Kratz et al [2017]
5. The first brain MRI should be done with contrast, and subsequent brain MRIs may be done without contrast if the previous MRI was normal and there is no new abnormality [Kratz et al 2017].
6. Colonoscopy examinations starting at age 25 or five years prior to earliest case of colorectal cancer in the family [NCCN 2019]
7. Periodic blood tests, such as complete blood count, erythrocyte sedimentation rate, and lactate dehydrogenase, are not generally recommended for individuals with LFS, but can be considered in those at increased risk for MDS or leukemia due to prior cancer treatments [Kratz et al 2017].

Agents/Circumstances to Avoid

There is some evidence that *TP53* pathogenic variants confer an increased sensitivity to ionizing radiation [Churpek et al 2016, Schuler et al 2017, Kasper et al 2018]. Thus, when possible, individuals with a germline *TP53* pathogenic variant should avoid or minimize exposure to diagnostic and therapeutic radiation. Radiation-induced tumors and leukemias have been reported among individuals with LFS [Churpek et al 2016, Schuler et al 2017]. However, there remains limited information regarding the extent of risk posed by radiation in terms of the dosage, age of the person, or other factors [Valdez et al 2017].

Individuals with LFS are also encouraged to avoid or minimize exposures to known or suspected carcinogens, including sun exposure, tobacco use, occupational exposures, and excessive alcohol use, because the effects of carcinogenic exposures and germline *TP53* pathogenic variants may be cumulative.

Cytotoxic chemotherapy agents may also increase the risk of treatment-related leukemias or other cancers in individuals with LFS [Churpek et al 2016, Kasper et al 2018].

Evaluation of Relatives at Risk

If a *TP53* pathogenic variant has been identified in a family, molecular genetic testing of at-risk relatives can identify those family members who also have LFS and thus need increased cancer monitoring with attention to symptoms or signs of cancer and early intervention when a cancer or precancer is identified. Since the risks of LFS-related cancers are increased at all ages, including infancy and childhood, it is recommended that predictive testing be offered to individuals at birth (via cord blood analysis) or soon after birth.

If a *TP53* pathogenic variant has not been identified in a family but the family meets classic criteria for LFS, all at-risk family members should be counseled regarding their potential increased risks for LFS-related cancers and options for surveillance and risk reduction.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Female with LFS. Women with LFS who are pregnant should bring any potential signs or symptoms of cancer to the attention of their physicians. Women with LFS who are pregnant can continue to have clinical breast exams and/or breast imaging studies if indicated.

Heterozygous fetus. There are no special recommendations for screening a fetus identified as having a germline *TP53* pathogenic variant. Once the infant is born, he or she should begin screening for cancer (see Surveillance).

Reproductive partner of a male with LFS. The pregnant mother of a fetus heterozygous for a paternally inherited *TP53* pathogenic variant is at risk for choriocarcinoma or another gestational trophoblastic disease (i.e., the occurrence of cancer in placental tissue, which may spread to other maternal organs) [Cotter et al 2018].

Therapies Under Investigation

There are efforts to identify medications that can reduce the risk of cancer in individuals with LFS. The National Cancer Institute plans to begin a clinical trial with metformin based on encouraging preclinical models, which demonstrated lower cancer incidence when mitochondrial metabolism was inhibited [Wang et al 2017].

Several trials utilizing cell-free DNA for early cancer detection are also under way in LFS cohorts.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Other

The Li-Fraumeni Exploration (LiFE) Research Consortium, formed in 2010, is a collaborative group of clinicians, scientists, genetic counselors, and psychologists who work with individuals and families with LFS [Mai et al 2012].

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Li-Fraumeni syndrome (LFS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with LFS inherited a *TP53* pathogenic variant from a parent.
- Some individuals diagnosed with LFS have the disorder as the result of a *de novo* pathogenic variant. The frequency of *de novo* pathogenic variants is estimated at between 7% and 20%; a recent series reported a 14% *de novo* rate with about one fifth of the cases being mosaic [Renaux-Petel et al 2018].
- If a *TP53* pathogenic variant has been identified in a proband and a diagnosis of LFS has not already been established in one of the parents, molecular genetic testing is recommended for the parents of the proband. If one parent has a significant personal and/or family history of cancer, that parent should be

tested first. Otherwise, the parents can be tested simultaneously. If a *TP53* pathogenic variant is identified in a parent, the parent should be followed by appropriate medical surveillance (see Surveillance).
    - If the pathogenic variant found in the proband is not detected in the leukocyte DNA of either parent, it is likely that the pathogenic variant occurred *de novo* in the proband; another possible explanation is germline mosaicism in a parent [Khincha et al 2019].
    - The family history of some individuals diagnosed with LFS may appear to be negative because of failure to recognize the disorder in family members, a small family size, variable expressivity, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate molecular genetic testing has been performed on the parents of the proband.
- If a *TP53* pathogenic variant has not been identified in a proband who meets classic criteria for LFS and a diagnosis of LFS has not already been established in one of the parents, both parents should be counseled regarding their potential increased risks for LFS-related cancers and the options for surveillance and risk reduction.

Sibs of a proband. The risk to sibs of the proband depends on the status of the proband's parents:

- If a parent of the proband is heterozygous for the *TP53* pathogenic variant, each sib has a 50% risk of having the same variant and the cancer risks associated with LFS.
- If neither parent of the proband is heterozygous for the *TP53* pathogenic variant identified in the proband (i.e., the pathogenic variant cannot be detected in parental leukocyte DNA), the pathogenic variant most likely occurred *de novo* in the proband and the recurrence risk to sibs is low. However, because of the possibility of parental germline mosaicism, the recurrence risk to sibs is slightly greater than that of the general population [Khincha et al 2019].
- If the family meets clinical criteria for LFS but a *TP53* pathogenic variant is not identified in the proband, it is assumed that one parent of the proband is heterozygous for an LFS-causative pathogenic variant and, consequently, each sib has a 50% risk of having LFS. Sibs should be counseled regarding their potential increased risks for LFS-related cancers and the options for surveillance and risk reduction.

Offspring of a proband. Each child of an individual with an established diagnosis of LFS (i.e., an individual who meets classic LFS criteria and/or has a heterozygous germline *TP53* pathogenic variant) has a 50% risk of inheriting an LFS-causative pathogenic variant and having the cancer risks associated with LFS.

Other family members

- The risk to other family members depends on the status of the proband's parents: if a parent has an established diagnosis of LFS or is at risk of being heterozygous for an LFS-causative pathogenic variant, the parent's family members are at increased risk.
- Family history or molecular genetic testing can help determine whether maternal or paternal relatives are at risk.

Related Genetic Counseling Issues

Testing of at-risk asymptomatic individuals. Consideration of molecular genetic testing of young, at-risk family members is appropriate for guiding medical management (see Management, Evaluation of Relatives at Risk).

Molecular genetic testing can be used with certainty to clarify the genetic status of at-risk family members if a clinically diagnosed relative has undergone molecular genetic testing and is found to have a pathogenic variant in *TP53*.

The use of molecular genetic testing for determining the genetic status of at-risk relatives when a clinically diagnosed relative is not available for testing is problematic, and test results need to be interpreted with caution. A positive test result in the at-risk family member indicates the presence of a *TP53* pathogenic variant and also indicates that the same molecular genetic testing method can be used to assess the genetic status of other, at-risk family members. In contrast, when genetic testing is offered to an at-risk family member prior to testing a family member known to be affected, the failure to identify a pathogenic variant in the at-risk family member does not eliminate the possibility that a *TP53* pathogenic variant is present in other members of the family.

Because cancer screening for individuals with LFS begins in infancy, molecular genetic testing is offered to at-risk children and adolescents.

Parents often want to know the genetic status of their children prior to initiating cancer monitoring in order to avoid unnecessary procedures in a child who has not inherited the pathogenic variant. Special consideration should be given to education of the children and their parents prior to genetic testing and older children and adolescents should be given the option of assenting to the test. A plan should be established for the manner in which results are to be given to the parents and their children. Although most children do not show evidence of clinically significant psychological problems after learning they have LFS, ongoing genetic counseling and psychological support should be available to these families [Druker et al 2017, McBride et al 2017, Valdez et al 2017].

Collecting a cancer history. Collecting a cancer history for a family suspected of having LFS involves obtaining information on all childhood- and adult-onset malignancies among first-, second-, and third-degree relatives. This includes information about the age of onset and the type and site of each cancer diagnosis.

Details about relatives may be incorrect or incomplete for a variety of reasons. For example, cancer may be a topic that the family avoids, or a parent's death may have led to estrangement from relatives on that side of the family. In addition, collecting a cancer history for a family with possible LFS is often emotionally charged because of the number of cancer-related illnesses and deaths among close relatives.

Genetic cancer risk assessment and counseling. For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling - for health professionals (part of PDQ®, National Cancer Institute).

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo* [Renaux-Petel et al 2018]. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

If a *TP53* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Individuals with LFS who are of childbearing age should be made aware of their reproductive choices [Druker et al 2017].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Li-Fraumeni Syndrome Association**
  Phone: 833-469-5372
  www.lfsassociation.org
- **Living LFS**
  Phone: 844-537-2255
  www.livinglfs.org
- **MedlinePlus**
  Li-Fraumeni syndrome
- **National Cancer Institute (NCI)**
  Phone: 800-422-6237 (toll-free)
  Email: cancergovstaff@mail.nih.gov
  Genetics of Breast and Gynecologic Cancers (PDQ®): Li-Fraumeni Syndrome
- **American Cancer Society**
  Phone: 800-227-2345
  cancer.org
- **CancerCare**
  Phone: 800-813-4673
  Email: info@cancercare.org
  cancercare.org
- **National Cancer Institute (NCI)**
  Phone: 800-422-6237
  Email: NCIinfo@nih.gov
  www.cancer.gov
- **National Coalition for Cancer Survivorship (NCCS)**
  Phone: 877-NCCS-YES
  Email: info@canceradvocacy.org
  www.canceradvocacy.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Li-Fraumeni Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TP53	17p13.1	Cellular tumor antigen p53	p53 Mutations and Cancer IARC TP53 Mutation Database TP53 @ LOVD Database of Germline p53 Mutations	TP53	TP53

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Li-Fraumeni Syndrome (View All in OMIM)

151623	LI-FRAUMENI SYNDROME; LFS
191170	TUMOR PROTEIN p53; TP53

Molecular Pathogenesis

TP53 encodes p53, which has been termed the guardian of the genome and has many important functions including DNA replication and repair, epigenetic patterning of the genome, cell cycle arrest, apoptosis, autophagy, senescence, differentiation, antioxidant stress responses, and cellular energy metabolism [Schuler et al 2017, Zerdoumi et al 2017].

In normal (unstressed) cells, p53 protein levels are kept low by a negative-regulatory feedback mechanism that is mediated by the MDM2 protein. MDM2 binds to p53, marking it for degradation. However, following the exposure to genotoxic stressors, such as ionizing radiation or other carcinogens, p53 and MDM2 become phosphorylated, which weakens the MDM2-p53 bond. The weakened MDM2-p53 interaction lessens the degradation of p53, which allows p53 to accumulate in the cell. The absence of normal p53 and/or the accumulation of abnormal p53 adversely effects the expression of many downstream genes that regulate critical cellular processes including cell cycle arrest, DNA repair, apoptosis, and senescence and ultimately leads to genomic instability and malignant transformation [Valdez et al 2017, Zerdoumi et al 2017].

Mechanism of disease causation. Germline *TP53* pathogenic variants create a constitutive defect of p53 DNA binding and transcriptional response to DNA damage. According to Zerdoumi et al [2017], "germline *TP53* mutations represent a genetic permissive context facilitating malignant transformation of cells in which DNA damage has occurred."

***TP53*-specific laboratory technical considerations.** *TP53* missense variants are the variants most commonly identified in tumors and they present challenges in germline interpretation. Recent efforts have utilized loss-of-function screens in human cancer cell lines with *TP53* saturation mutagenesis screens, and integrated the DNA with the COSMIC database. One such effort reports development of a statistical model that estimates the percent transcriptional activity in yeast, and the creation of a database for examination (mutantp53.broadinstitute.org); however, variants such as p.Arg337His (which scores in the wild type range) highlight the challenges of such systems [Giacomelli et al 2018].

Table 4. Notable *TP53* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000546.5 NP_000537.3	c.1010G>A	p.Arg337His	High risk of adrenocortical carcinoma; a low-penetrance allele for other LFS cancers; founder variant in Southern Brazil [Ferreira et al 2019].

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Cancer and Benign Tumors

TP53 is the most frequently mutated gene in human cancer. In *ERBB2* (previously known as *Her2*) amplified breast cancers and lung cancers with *EGFR* pathogenic variants, the presence of somatic *TP53* pathogenic variants appears to confer a poorer prognosis, and in aggressive cancers *TP53* pathogenic variants are so ubiquitous that they may not have any prognostic value [Hainaut & Pfeifer 2016].

Chapter Notes

Acknowledgments

We wish to acknowledge Dr Frederick P Li and Dr Joseph F Fraumeni for their contributions.

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Revision History

- 21 November 2019 (sw) Comprehensive update posted live
- 11 April 2013 (me) Comprehensive update posted live
- 9 February 2010 (me) Comprehensive update posted live
- 12 October 2004 (me) Comprehensive update posted live
- 3 October 2002 (me) Comprehensive update posted live
- 19 January 1999 (me) Review posted live
- 24 July 1998 (ks) Original submission

References

Published Guidelines / Consensus Statements

- PDQ Cancer Genetics Editorial Board. Cancer Genetics Risk Assessment and Counseling (PDQ®): Health Professional Version. In: PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002-. Available online. 2019. Accessed 10-6-22.
- National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2018. Accessed 10-6-22.

Literature Cited

Achatz MI, Zambetti GP. The inherited p53 mutation in the Brazilian population. Cold Spring Harb Perspect Med. 2016;6(12)

Amadou A, Waddington Achatz MI, Hainaut P. Revisiting tumor patterns and penetrance in germline TP53 mutation carriers: temporal phases of Li-Fraumeni syndrome. Curr Opin Oncol. 2018;30:23–9. PubMed PMID: 29076966.

Ariffin H, Chan AS, Oh L, Abd-Ghafar S, Ong GB, Mohamed M, Razali H, Juraida E, Teo SH, Karsa M, Shamsani J, Hainaut P. Frequent occurrence of gastric cancer in Asian kindreds with Li-Fraumeni syndrome. Clin Genet. 2015;88:450–5. PubMed PMID: 25318593.

Ballinger ML, Best A, Mai PL, Khincha PP, Loud JT, Peters JA, Achatz MI, Chojniak R, Balieiro da Costa A, Santiago KM, Garber J, O'Neill AF, Eeles RA, Evans DG, Bleiker E, Sonke GS, Ruijs M, Loo C, Schiffman J, Naumer A, Kohlmann W, Strong LC, Bojadzieva J, Malkin D, Rednam SP, Stoffel EM, Koeppe E, Weitzel JN, Slavin TP, Nehoray B, Robson M, Walsh M, Manelli L, Villani A, Thomas DM, Savage SA. Baseline surveillance in Li-Fraumeni syndrome using whole-body magnetic resonance imaging. JAMA Oncol. 2017;3:1634–9. PubMed PMID: 28772291.

Bougeard G, Renaux-Petel M, Flaman JM, Charbonnier C, Fermey P, Belotti M, Gauthier-Villars M, Stoppa-Lyonnet D, Consolino E, Brugieres L, Caron O, Benusiglio PR, Bressac-de-Paillerets B, Bonadona V, Bonaiti-Pellie C, Tinat J, Baert-Desurmont S, Frebourg T. Revisiting Li-Fraumeni syndrome from *TP53* mutation carriers. J Clin Oncol. 2015;33:2345–52. PubMed PMID: 26014290.

Churpek JE, Marquez R, Neistadt B, Claussen K, Lee MK, Churpek MM, Huo D, Weiner H, Bannerjee M, Godley LA, Le Beau MM, Pritchard CC, Walsh T, King MC, Olopade OI, Larson RA. Inherited mutations in cancer susceptibility genes are common among survivors of breast cancer who develop therapy-related leukemia. Cancer. 2016;122:304–11. PubMed PMID: 26641009.

Cotter JA, Szymanski L, Karimov C, Boghossian L, Margol A, Dhall G, Tamrazi B, Varaprasathan GI, Parham DM, Judkins AR, Biegel JA. Transmission of a *TP53* germline mutation from unaffected male carrier associated with pediatric glioblastoma in his child and gestational choriocarcinoma in his female partner. Cold Spring Harb Mol Case Stud. 2018;4:a002576. PubMed PMID: 29581140.

de Andrade KC, Frone MN, Wegman-Ostrosky T, Khincha PP, Kim J, Amadou A, Santiago KM, Fortes FP, Lemonnier N, Mirabello L, Stewart DR, Hainaut P, Kowalski LP, Savage SA, Achatz MI. Variable population prevalence estimates of germline TP53 variants: a gnomAD-based analysis. Hum Mutat. 2019;40:97–105. PubMed PMID: 30352134.

Druker H, Zelley K, McGee RB, Scollon SR, Kohlmann WK, Schneider KA, Wolfe Schneider K. Genetic counselor recommendations for cancer predisposition evaluation and surveillance in the pediatric oncology patient. Clin Cancer Res. 2017;23:e91–7. PubMed PMID: 28674117.

Ferreira AM, Brondani VB, Helena VP, Charchar HLS, Zerbini MCN, Leite LAS, Hoff AO, Latronico AC, Mendonca BB, Diz MDPE, de Almeida MQ, Fragoso MCBV. Clinical spectrum of Li-Fraumeni syndrome/Li-Fraumeni-like syndrome in Brazilian individuals with the TP53 p.R337H mutation. J Steroid Biochem Mol Biol. 2019;190:250–5. PubMed PMID: 30974190.

Giacomelli AO, Yang X, Lintner RE, McFarland JM, Duby M, Kim J, Howard TP, Takeda DY, Ly SH, Kim E, Gannon HS, Hurhula B, Sharpe T, Goodale A, Fritchman B, Steelman S, Vazquez F, Tsherniak A, Aguirre AJ, Doench JG, Piccioni F, Roberts CWM, Meyerson M, Getz G, Johannessen CM, Root DE, Hahn WC. Mutational processes shape the landscape of *TP53* mutations in human cancer. Nat Genet. 2018;50:1381–7. PubMed PMID: 30224644.

Guha T, Malkin D. Inherited *TP53* mutations and the Li-Fraumeni syndrome. Cold Spring Harb Perspect Med. 2017;7:a026187. PubMed PMID: 28270529.

Hainaut P, Pfeifer GP. Somatic *TP53* mutations in the era of genome sequencing. Cold Spring Harb Perspect Med. 2016;6:a026179. PubMed PMID: 27503997.

Hettmer S, Archer NM, Somers GR, Novokmet A, Wagers AJ, Diller L, Rodriguez-Galindo C, Teot LA, Malkin D. Anaplastic rhabdomyosarcoma in TP53 germline mutation carriers. Cancer. 2014;120:1068–75. PubMed PMID: 24382691.

Holmfeldt L, Wei L, Diaz-Flores E, Walsh M, Zhang J, Ding L, Payne-Turner D, Churchman M, Andersson A, Chen SC, McCastlain K, Becksfort J, Ma J, Wu G, Patel SN, Heatley SL, Phillips LA, Song G, Easton J, Parker M, Chen X, Rusch M, Boggs K, Vadodaria B, Hedlund E, Drenberg C, Baker S, Pei D, Cheng C, Huether R, Lu C, Fulton RS, Fulton LL, Tabib Y, Dooling DJ, Ochoa K, Minden M, Lewis ID, To LB, Marlton P, Roberts AW, Raca G, Stock W, Neale G, Drexler HG, Dickens RA, Ellison DW, Shurtleff SA, Pui CH, Ribeiro RC, Devidas M, Carroll AJ, Heerema NA, Wood B, Borowitz MJ, Gastier-Foster JM, Raimondi SC, Mardis ER, Wilson RK, Downing JR, Hunger SP, Loh ML, Mullighan CG. The genomic landscape of hypodiploid acute lymphoblastic leukemia. Nat Genet. 2013;45:242–52. PubMed PMID: 23334668.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Id Said B, Kim H, Tran J, Novokmet A, Malkin D. Super-transactivation TP53 variant in the germline of a family with Li-Fraumeni syndrome. Hum Mutat. 2016;37:889–92. PubMed PMID: 27297285.

Kasper E, Angot E, Colasse E, Nicol L, Sabourin JC, Adriouch S, Lacoume Y, Charbonnier C, Raad S, Frebourg T, Flaman JM, Bougeard G. Contribution of genotoxic anticancer treatments to the development of multiple primary tumours in the context of germline TP53 mutations. Eur J Cancer. 2018;101:254–62. PubMed PMID: 30072235.

Khincha PP, Jones K, Teshome K, Hicks B, Mai PL, Savage SA. Gonadal mosaicism in a family with TP53-associated Li-Fraumeni syndrome [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2019 Mar 29-Apr 3; Atlanta, GA. Cancer Res. 2019;79:4159A.

Kratz CP, Achatz MI, Brugieres L, Frebourg T, Garber J, Greer MLC, Hansford JR, Janeway KA, Kohlmann WK, McGee R, Mullighan CG, Onel K, Pajtler KW, Pfister SM, Savage SA, Schiffman JD, Schneider KA, Strong LC, Evans DGR, Wasserman JD, Villani A, Malkin D. Cancer screening recommendations for individuals with Li-Fraumeni syndrome. Clin Cancer Res. 2017;23:e38–45. PubMed PMID: 28572266.

MacFarland SP, Zelley K, Long JM, McKenna D, Mamula P, Domchek SM, Nathanson KL, Brodeur GM, Rustgi AK, Katona BW, Maxwell KN. Earlier colorectal cancer screening may be necessary in patients with Li-Fraumeni syndrome. Gastroenterology. 2019;156:273–4. PubMed PMID: 30243621.

Mai PL, Best AF, Peters JA, DeCastro R, Khincha PP, Loud JT, Bremer RC, Rosenberg PS, Savage SA. Risks of first and subsequent cancers among TP53 mutation-carriers in the NCI LFS cohort. Cancer. 2016;122:3673–81. PubMed PMID: 27496084.

Mai PL, Malkin D, Garber JE, Schiffman JD, Weitzel JN, Strong LC, Wyss O, Locke L, Means V, Achatz MI, Hainaut P, Frebourg T, Evans DG, Bleiker E, Patenaude A, Schneider K, Wilfod B, Peters JA, Hwang PM, Ford J, Tabori U, Ognjanovic S, Dennis PA, Wentzensen IM, Greene MH, Fraumeni JF Jr, Savage SA. Li-Fraumeni syndrome: report of a clinical research workshop and creation of a research consortium. Cancer Genet. 2012;205:479–87. PubMed PMID: 22939227.

McBride KA, Ballinger ML, Schlub TE, Young MA, Tattersall MHN, Kirk J, Eeles R, Killick E, Walker LG, Shanley S, Thomas DM, Mitchell G. Psychosocial morbidity in TP53 mutation carriers: is whole-body cancer screening beneficial? Fam Cancer. 2017;16:423–32. PubMed PMID: 28124295.

Mirabello L, Yeager M, Mai PL, Gastier-Foster JM, Gorlick R, Khanna C, Patino-Garcia A, Sierrasesumaga L, Lecanda F, Andrulis IL, Wunder JS, Gokgoz N, Barkauskas DA, Zhang X, Vogt A, Jones K, Boland JF, Chanock SJ, Savage SA. Germline TP53 variants and susceptibility to osteosarcoma. J Natl Cancer Inst. 2015;107(7)

NCCN. The National Comprehensive Cancer Network Clinical Practice Guidelines® in Oncology: Li-Fraumeni syndrome (Version 1.2015). ©2015 National Comprehensive Cancer Network, Inc. 2019.

Ognjanovic S, Olivier M, Bergemann TL, Hainaut P. Sarcomas in TP53 germline mutation carriers: a review of the IARC TP53 database. Cancer. 2012;118:1387–96. PubMed PMID: 21837677.

Packwood K, Martland G, Sommerlad M, Shaw E, Moutasim K, Thomas G, Bateman AC, Jones L, Haywood L, Evans DG, Birch JM, Alsalmi OA, Henderson A, Poplawski N, Eccles DM. Breast cancer in patients with germline TP53 pathogenic variants have typical tumour characteristics: the Cohort study of TP53 carrier early onset breast cancer (COPE study). J Pathol Clin Res. 2019; 2019;5:189–98. PubMed PMID: 31041842.

Peng G, Bojadzieva J, Ballinger ML, Li J, Blackford AL, Mai PL, Savage SA, Thomas DM, Strong LC, Wang W. Estimating TP53 mutation carrier probability in families with Li-Fraumeni syndrome using LFSPRO. Cancer Epidemiol Biomarkers Prev. 2017;26:837–44. PubMed PMID: 28137790.

Qian M, Cao X, Devidas M, Yang W, Cheng C, Dai Y, Carroll A, Heerema NA, Zhang H, Moriyama T, Gastier-Foster JM, Xu H, Raetz E, Larsen E, Winick N, Bowman P, Martin PI, Mardis ER, Fulton R, Zambetti G, Borowitz M, Wood B, Nichols KE, Carroll WL, Pui CH, Mullighan CG, Evans WE, Hunger SP, Relling MV, Loh ML, Yang JJ. TP53 germline variations influence the predisposition and prognosis of B-cell acute lymphoblastic leukemia in children. J Clin Oncol. 2018;36:591–9. PubMed PMID: 29300620.

Rana HQ, Clifford J, Hoang L, LaDuca H, Black MH, Li S, McGoldrick K, Speare V, Dolinsky JS, Gau CL, Garber JE. Genotype-phenotype associations among panel-based TP53+ subjects. Genet Med. 2019; 2019;21:2478–84. PubMed PMID: 31105275.

Rana HQ, Gelman R, LaDuca H, McFarland R, Dalton E, Thompson J, Speare V, Dolinsky JS, Chao EC, Garber JE. Differences in *TP53* mutation carrier phenotypes emerge from panel-based testing. J Natl Cancer Inst. 2018;110:863–70. PubMed PMID: 29529297.

Renaux-Petel M, Charbonnier F, Thery JC, Fermey P, Lienard G, Bou J, Coutant S, Vezain M, Kasper E, Fourneaux S, Manase S, Blanluet M, Leheup B, Mansuy L, Champigneulle J, Chappe C, Longy M, Sevenet N, Bressac-de Paillerets B, Guerrini-Rousseau L, Brugieres L, Caron O, Sabourin JC, Tournier I, Baert-Desurmont S, Frebourg T, Bougeard G. Contribution of de novo and mosaic *TP53* mutations to Li-Fraumeni syndrome. J Med Genet. 2018;55:173–80. PubMed PMID: 29070607.

Rengifo-Cam W, Shepherd HM, Jasperson KW, Samadder NJ, Samowitz W, Tripp SR, Schiffman JD, Kohlmann W. Colon pathology characteristics in Li-Fraumeni syndrome. Clin Gastroenterol Hepatol. 2018;16:140–1. PubMed PMID: 28624650.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Schon K, Tischkowitz M. Clinical implications of germline mutations in breast cancer: *TP53*. Breast Cancer Res Treat. 2018;167:417–23. PubMed PMID: 29039119.

Schuler N, Palm J, Schmitz S, Lorat Y, Rube CE. Increasing genomic instability during cancer therapy in a patient with Li-Fraumeni syndrome. Clin Transl Radiat Oncol. 2017;7:71–8. PubMed PMID: 29594232.

Swaminathan M, Bannon SA, Routbort M, Naqvi K, Kadia TM, Takahashi K, Alvarado Y, Ravandi-Kashani F, Patel KP, Champlin R, Kantarjian H, Strong L, DiNardo CD. Hematologic malignancies and Li-Fraumeni syndrome. Cold Spring Harb Mol Case Stud. 2019;5(1)

Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC, Eberhart CG, Parsons DW, Rutkowski S, Gajjar A, Ellison DW, Lichter P, Gilbertson RJ, Pomeroy SL, Kool M, Pfister SM. Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol. 2012;123:465–72. PubMed PMID: 22134537.

Valdez JM, Nichols KE, Kesserwan C. Li-Fraumeni syndrome: a paradigm for the understanding of hereditary cancer predisposition. Br J Haematol. 2017;176:539–52. PubMed PMID: 27984644.

Villani A, Shore A, Wasserman JD, Stephens D, Kim RH, Druker H, Gallinger B, Naumer A, Kohlmann W, Novokmet A, Tabori U, Tijerin M, Greer ML, Finlay JL, Schiffman JD, Malkin D. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. Lancet Oncol. 2016;17:1295–305. PubMed PMID: 27501770.

Wang PY, Li J, Walcott FL, Kang JG, Starost MF, Talagala SL, Zhuang J, Park JH, Huffstutler RD, Bryla CM, Mai PL, Pollak M, Annunziata CM, Savage SA, Fojo AT, Hwang PM. Inhibiting mitochondrial respiration prevents cancer in a mouse model of Li-Fraumeni syndrome. J Clin Invest. 2017;127:132–6. PubMed PMID: 27869650.

Weitzel JN, Chao EC, Nehoray B, Van Tongeren LR, LaDuca H, Blazer KR, Slavin T, Pesaran T, Rybak C, Solomon I, Niell-Swiller M, Dolinsky JS, Castillo D, Elliott A, Gau CL, Speare V, Jasperson K I. Somatic TP53 variants frequently confound germline testing results. Genet Med. 2018;20:809–16. PubMed PMID: 29189820.

Zerdoumi Y, Lanos R, Raad S, Flaman JM, Bougeard G, Frebourg T, Tournier I. Germline TP53 mutations result into a constitutive defect of p53 DNA binding and transcriptional response to DNA damage. Hum Mol Genet. 2017;26:2591–602. PubMed PMID: 28369373.

Zhukova N, Ramaswamy V, Remke M, Pfaff E, Shih DJ, Martin DC, Castelo-Branco P, Baskin B, Ray PN, Bouffet E, von Bueren AO, Jones DT, Northcott PA, Kool M, Sturm D, Pugh TJ, Pomeroy SL, Cho YJ, Pietsch T, Gessi M, Rutkowski S, Bognar L, Klekner A, Cho BK, Kim SK, Wang KC, Eberhart CG, Fevre-Montange M, Fouladi M, French PJ, Kros M, Grajkowska WA, Gupta N, Weiss WA, Hauser P, Jabado N, Jouvet A, Jung S, Kumabe T, Lach B, Leonard JR, Rubin JB, Liau LM, Massimi L, Pollack IF, Shin Ra Y, Van Meir EG, Zitterbart K, Schuller U, Hill RM, Lindsey JC, Schwalbe EC, Bailey S, Ellison DW, Hawkins C, Malkin D, Clifford SC, Korshunov A, Pfister S, Taylor MD, Tabori U. Subgroup-specific prognostic implications of TP53 mutation in medulloblastoma. J Clin Oncol. 2013;31:2927–35. PubMed PMID: 23835706.

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