Update on Cancer Screening Recommendations for Individuals with Li–Fraumeni Syndrome

Maria Isabel Achatz[1], Anita Villani[2], Alison A. Bertuch[3], Gaëlle Bougeard[4], Vivian Y. Chang[5], Andrea S. Doria[6,7], Bailey Gallinger[8,9], Lucy A. Godley[10], Mary-Louise C. Greer[6,7], Junne Kamihara[11], Payal P. Khincha[12], Wendy K. Kohlmann[13,14], Christian P. Kratz[15], Suzanne P. MacFarland[16], Luke D. Maese[17], Kara N. Maxwell[18,19,20], Sarah G. Mitchell[21], Yoshiko Nakano[2], Stefan M. Pfister[22], Jonathan D. Wasserman[23,24], Emma R. Woodward[25], Judy E. Garber[26], and David Malkin[2]

ABSTRACT

Li–Fraumeni syndrome (LFS) is an autosomal dominant cancer predisposition condition characterized by a high lifetime risk for a wide spectrum of malignancies associated with germline pathogenic/likely pathogenic variants in the *TP53* tumor suppressor gene. Secondary malignant neoplasms are particularly common. Early cancer detection through surveillance enables early intervention and leads to improved clinical outcomes with reduced tumor-related mortality and treatment-related morbidity. Since the 2017 publication of LFS tumor surveillance guidelines from the inaugural American Association for Cancer Research Childhood Cancer Predisposition Workshop, understanding the genotype–phenotype relationships in LFS has evolved, and adaptations of the guidelines have been implemented in institutions worldwide. The "Toronto Protocol" remains the current standard for lifelong surveillance; however, as outlined in this perspective, modifications should be considered about the use of certain modalities to target organs in an age-dependent manner. The Working Group's recommendations have also been extended to include a more detailed outline for surveillance in the adult *TP53* pathogenic/likely pathogenic variant carrier population, based on the recognition that early education of both practitioners and patients on what to expect after the transition from childhood/adolescence to young adulthood is important in preparing them for changes in surveillance strategies. In this perspective, we provide an up-to-date clinical overview of LFS and present our updated consensus tumor surveillance recommendations from the 2023 American Association for Cancer Research Childhood Cancer Predisposition Workshop.

Introduction

Li–Fraumeni syndrome (LFS; OMIM #151623) is a cancer predisposition syndrome (CPS) caused by pathogenic or likely pathogenic (P/LP) variants in the *TP53* tumor suppressor gene and is characterized by a high risk of diverse early-onset cancers. Core LFS tumors include soft-tissue sarcomas (STS) and bone sarcomas, early-onset breast cancer, central nervous system (CNS) tumors (glioma, choroid plexus carcinoma, Sonic hedgehog subgroup medulloblastoma), and adrenocortical tumors (ACT). Other malignancies are increasingly described in carriers of *TP53* P/LP variants, including carcinomas of the lung, prostate, gastrointestinal tract,

[1]Centro de Oncologia, Hospital Sírio-Libanês, Sao Paulo, Brazil. [2]Division of Hematology/Oncology, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Canada. [3]Pediatrics, Baylor College of Medicine, Houston, Texas. [4]Department of Genetics, Univ Rouen Normandie, Inserm U1245, Normandie Univ, CHU Rouen, Rouen, France. [5]Pediatric Hematology-Oncology, University of California, Los Angeles, Los Angeles, California. [6]Department of Diagnostic and Interventional Radiology, The Hospital for Sick Children, University of Toronto, Toronto, Canada. [7]Department of Medical Imaging, University of Toronto, Toronto, Canada. [8]Clinical and Metabolic Genetics, The Hospital for Sick Children, Toronto, Canada. [9]Department of Molecular Genetics, The University of Toronto, Toronto, Canada. [10]Division of Hematology/Oncology, Department of Medicine, Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, Illinois. [11]Dana-Farber Cancer Institute, Boston, Massachusetts. [12]Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland. [13]VA Medical Center, National TeleOncology Program, Clinical Cancer Genetics Service, Durham, North Carolina. [14]University of Utah Huntsman Cancer Institute, Salt Lake City, Utah. [15]Department of Pediatric Hematology and Oncology, Hannover Medical School, Hannover, Germany. [16]Division of Oncology, Department of Pediatrics, Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania. [17]University of Utah-Huntsman Cancer Institute, Primary Children's Hospital, Salt Lake City, Utah. [18]Department of Medicine-Hematology/Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania. [19]Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania. [20]Medicine Service, Corporal Michael Crescenz Veterans Affairs Medical Center, Philadelphia, Pennsylvania. [21]Department of Pediatric Hematology/Oncology, Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Emory University School of Medicine, Atlanta, Georgia. [22]Division Pediatric Neurooncology, Hopp Children's Cancer Center Heidelberg (KiTZ), German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg University Hospital and National Center for Tumor Diseases (NCT), Heidelberg, Germany. [23]Division of Endocrinology, The Hospital for Sick Children, Toronto, Canada. [24]Department of Paediatrics, University of Toronto, Toronto, Canada. [25]Faculty of Biology, Medicine and Health, University of Manchester, Manchester Centre for Genomic Medicine, Manchester, United Kingdom. [26]Division of Cancer Genetics and Prevention, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts.

M.I. Achatz and A. Villani contributed equally to this article.

Corresponding Author: David Malkin, Division of Hematology/Oncology, The Hospital for Sick Children, 686 Bay Street, Room 18-9705, Toronto M5G 0A4, Ontario, Canada. E-mail: david.malkin@sickkids.ca

Clin Cancer Res 2025;31:1831–40

doi: 10.1158/1078-0432.CCR-24-3301

Translational Relevance

This article details the updated consensus guidelines for tumor surveillance in Li–Fraumeni syndrome (LFS) as developed by an international gathering of experts at the 2023 American Association for Cancer Research Childhood Cancer Predisposition Workshop. To create these guidelines, the group considered available published data about the development of the wide spectrum of cancers in LFS. Particular attention was given to those instances in which guidelines have evolved or changed from our original consensus publication in 2017. In addition, we have provided guidance for tumor surveillance in the young adult LFS population, recognizing the need to alert practitioners to the continuum of cancer risk beyond the traditional pediatric age range. These guidelines are presented to provide practitioners with the rationale on which to explore early interventions in the context of early tumor detection in LFS in an attempt to improve clinical outcomes as measured by enhanced survival and reduced treatment-related morbidity.

kidney, and thyroid, as well as leukemia, lymphoma, melanoma, and neuroblastoma (1–5). The birth prevalence of individuals with a germline *TP53* P/LP variant is estimated to be ~1:3,000 to 1:20,000 (6–8).

Across all ages, overall cancer incidence is almost 24 times greater than that of the general population (1). The median age at first cancer diagnosis is reported to be 33.7 years for women and 45 years for men (1). The risk of cancer before the age of 20 is high, ranging from 20% to 40%, with sarcomas, CNS tumors, and ACT predominating (1, 9). Breast cancer is the most frequent malignancy in female adults, accounting for 57% of all first cancers by age 60. In males, STS and CNS tumors are the most common first cancers with a 20% lifetime cumulative incidence (1). Antineoplastic therapy may confer additional risks to carriers, including sarcomas arising in the radiation field, therapy-related hematologic malignancies, and other secondary tumors (10).

Regardless of the ascertainment of cohorts to determine age-related cancer risk, cancer risks are high, and appropriate surveillance to enable early cancer detection is indicated. This can be challenging, reflecting the wide range of tumors and the variable incident risks associated with age, sex, and *TP53* variant type. The first American Association for Cancer Research (AACR) Childhood Cancer Predisposition Workshop was convened in 2016, and consensus surveillance recommendations were published by an international group of LFS experts (11). These recommendations were based in large part on two seminal articles by Villani and colleagues (12, 13) that described the first evidence-based approach to tumor surveillance in LFS (coined the "Toronto Protocol"). In this perspective, also based on expert review, we present updates to these consensus recommendations—with additional focus on adult cancer surveillance approaches—and review developments in the field of LFS. Readers are directed to the previous article for detailed background and considerations for tumor surveillance in LFS (11). Readers are also directed to other LFS surveillance recommendations published by UK and European groups (14, 15).

TP53 Variant Spectrum and Penetrance

The impact of germline *TP53* variants on protein function in part contributes to the penetrance of the cancer phenotype in LFS. Kratz and colleagues analyzed the phenotypes of individuals and families reported in the International Agency for Research on Cancer *TP53* database in order to describe the phenotypic spectrum and to search for phenotype–genotype correlations. Individuals with P/LP *TP53* variants who met or did not meet Chompret criteria, respectively, were classified as LFS and attenuated LFS (16). Despite the fact that there were differences in the variant spectrum in patients who met versus did not meet LFS testing criteria, several hotspot variants were present in both the LFS and attenuated LFS groups. Hence, in individual patients or families, it is currently impossible to predict the phenotype based on the genotype alone. Notably, limited family history or *de novo* variants may hinder the phenotypic classification of individual families as LFS versus attenuated LFS (17). A follow-up study based on data accrued in the LFS registry in Germany showed that genotype–phenotype correlations enable an appreciation of the evolving phenotypic variability of the condition (18). P/LP variants grouped as "partially functional" in the yeast-based Kato assay were associated with a lower overall childhood cancer risk, with the exception of adrenocortical carcinoma (ACC), and NULL variants were statistically significantly enriched among patients with LFS versus attenuated LFS. Two newer studies used a sophisticated cluster analysis approach to group known variants into functional clusters based on published functional data. Both articles revealed significant genotype–phenotype correlations (medRxiv 2024.01.06.23300162; ref. 19).

Using machine learning algorithms, Subasri and colleagues (20) demonstrated that epimutations influenced and could predict cancer risk in patients with LFS. Findings from Pinto and colleagues (21) suggest that cosegregation of the *XAF1*-E134* and *TP53*-R337H variants may be related to increased penetrance for this otherwise low-penetrance variant. The observations from both studies are provocative but should not be used for clinical purposes without further validation in larger patient cohorts.

Despite the significant progress in defining the LFS spectrum and elucidating the determinants of LFS penetrance, the updated Toronto Protocol should be performed for all carriers, and surveillance should not be adjusted on the basis of the gene variant (genotype) and its perceived spectrum of disease (phenotype) until additional evidence supports modifications.

Both constitutional mosaicism and clonal hematopoiesis (CH; a form of acquired mosaicism) involving *TP53* PVs are increasingly recognized through high-depth next-generation sequencing. Patients who have developed a hematologic cancer or have been diagnosed with an apparent germline *TP53* variant at a later age with no LFS phenotype in the family pose a unique challenge in that the genotype could, in fact, represent CH with only increased hematologic cancer risk (7). However, because the frequency of CH increases with age, younger patients are much less likely to have clinically significant white blood cell mosaic *TP53* clones. Risk factors for CH include prior chemotherapy, cigarette smoking, and advanced age (22–29).

Germline *TP53* P/LP variants are the only known cause of LFS. Of note, some individuals and families with a clinical diagnosis of LFS [i.e., "phenotypic LFS" as per Kratz and colleagues (16)] may not have an identifiable *TP53* P/LP variant by standard-of-care testing or may have a variant of uncertain significance (VUS) by current clinical variant interpretation criteria (ACMG, or ClinGen

TP53 guidance, and UK guidance; refs. 16, 30). Patients with a clinical diagnosis of LFS should be offered clinical cancer prevention and cancer early detection strategies (i.e., standard surveillance), with the opportunity to enroll in research studies where appropriate.

Updates to Surveillance Recommendations

Where a clinical and/or molecular diagnosis of LFS has been established, clinical surveillance ought to be offered to facilitate early cancer detection with various guidance having been published (11, 13–15). Although there are differences mainly around age- and variant-specific recommendations, the core features are annual imaging with clinical review.

The National Comprehensive Cancer Network (NCCN) recently updated its LFS surveillance recommendations to better align with the previously published AACR Cancer Screening Recommendations for Individuals with Li-Fraumeni Syndrome consensus (2017) and subsequent validating studies (11, 31). The European Reference Network, GENTURIS, provided recommendations on screening and suggested adaptations to the "Toronto Protocol" (14). It suggested stratification of pediatric testing and surveillance based on high-/low-risk alleles although there is no evidence yet published for modifications based on such terms. Furthermore, it recommends discontinuing abdominal ultrasound at age 18, brain MRI at age 50, and breast MRI at age 65 although no evidence is provided to support these modifications. As such, we endorse caution with both limiting and supplementing established guidelines until further evidence is available addressing potential modifications (11). Some examples of modifications based on data are discussed below.

Pediatric Guidelines

The 2017 guidelines are fully endorsed by the authors of this article who convened in July 2023 as part of the AACR-sponsored update on cancer surveillance in pediatric CPSs. Some modifications, points of clarification, and emphasis on the prior guidelines are also proposed based on recently published evidence. Cancer screening/surveillance strategies should be initiated as soon as a germline (or postzygotic mosaic) *TP53* P/LP variant is identified—whether that is based on the particular cancer diagnosis in a child (e.g., choroid plexus carcinoma, ACC, Sonic hedgehog medulloblastoma, hypodiploid acute lymphoblastic leukemia, anaplastic rhabdomyosarcoma) or discovered incidentally through broad paired tumor/germline sequencing of a pediatric oncology patient or through cascade testing of children based on family history (i.e., parent or sibling *TP53* P/LP carrier). Genetic testing can be offered at any age from birth or prenatally/before conception. Whole-body MRI (WBMRI) scans without contrast should be performed yearly from birth in carriers, using institutional WBMRI protocols optimized for oncologic indications, balancing the need for diagnostic quality images and study duration. Further details about WBMRI acquisition with sample pediatric WBMRI protocols are provided in an accompanying article in this series (**Table 1**; ref. 32).

Special Considerations

Considerations on physical examination

Physical examination has been shown to be valuable in the cancer surveillance of children and adults with LFS. It is a low-cost, effective early detection strategy, and physicians who participate in the care of patients with LFS should be educated on relevant potential findings (**Table 2**). A complete physical exam should be conducted every 3 to 4 months (**Table 1**) and include careful dermatologic exams, which may be performed by trained pediatricians or general practitioners from birth. Given that many patients continue to be followed at pediatric centers until age 25, it is important to point out that breast awareness with instruction on self-breast exams should be discussed at age 18 in individuals assigned female sex at birth, and formal clinical breast exams with breast MRI should begin yearly at age 20 (see below).

Considerations for harmonized surveillance for patients with cancer

We emphasize the need for continued surveillance during and after cancer treatment as synchronous or closely metachronous tumors may arise in *TP53* P/LP variant carriers. Harmonization of tumor-related surveillance and postcancer diagnosis follow-up imaging may optimize care for these patients. Shared decision-making with the patient, their family, and the primary oncology team should occur in circumstances in which the current cancer has a predicted poor prognosis.

Considerations for radiotherapy and chemotherapy

Although the risks of primary or treatment-induced malignancies as a result of exposure to diagnostic or therapeutic radiation or genotoxic chemotherapy have not been fully elucidated and are likely confounded by factors including treatment dose, field of exposure, and age at exposure, specific *TP53* variant, and tissue exposed, efforts should be made to avoid exposure where feasible in *TP53* P/LP variant carriers. However, diagnostic imaging and therapies needed for optimal assessment and survival outcomes from a current cancer should not be omitted. The use of fewer fractions but with a high dose per fraction (hypofractionation), as is usually done with stereotactic body radiotherapy, might modify repair mechanisms in the tumor area, with a low dose in fewer fractions to the surrounding normal tissue than that associated with or after intensity-modulated radiotherapy. Simulations and experimental data are warranted to address this theory. Preliminary *in vitro* experiments have shown little or no fractionation sensitivity in Li–Fraumeni fibroblasts, suggesting that the use of smaller doses per fraction (with hyperfractionation or stronger constraints or smaller doses per fraction to normal tissues during intensity-modulated radiotherapy) does not better protect normal tissues with dysfunctional p53. Similarly, there have been no data to show a better response with hypofractionation than with conventional fractionation in tumors with *TP53* mutations. Therefore, no arguments exist in favor of altering radiotherapy fractionation in patients with heritable *TP53*-related cancer syndromes compared with patients with wild-type *TP53* (10). It has been suggested that proton therapy may reduce secondary cancer risk, but these observations have yet to be validated. Although further robust clinical data are needed to define the presence and magnitude of the subsequent cancer risk secondary to genotoxic exposures, preclinical studies provide some insight. *Trp53*-mutant mouse models of LFS by Kasper and colleagues suggest accelerated tumor formation upon exposure to genotoxic agents, and platinum-induced genomic signatures have been observed in secondary tumor tissues of patients with LFS previously treated with these agents (33, 34). Regardless of the treatment plan ultimately used for patients with LFS-associated cancers, the risk of multiple subsequent primary cancers should be

Table 1. Recommended complete pediatric LFS screening protocol (birth to age 18; based on the Toronto Protocol).

Tumor/cancer type	Screening/management method	Starting age	Frequency	Comment
General assessment	Complete physical exam	Birth[a]	Every 3–4 months	In addition, prompt assessment with a primary care physician for any medical concerns (**Table 2**)
STSs/ osteosarcomas	WBMRI without contrast[b,c,d]	Birth[a]	Every year	In centers where WBMRI is not feasible (poorly resourced countries, etc.), modifications to the protocol to be considered
CNS	Dedicated brain MRI[c,e]	Birth[a]	Every year	Initial brain MRI with intravenous contrast; thereafter without contrast if previous MRI is normal (and high quality, nonmotion degraded)
Leukemia	CBC with differential	Birth[a]	Every 3–4 months	In patients with prior exposure to leukemogenic agents, to monitor for evidence of transformation
ACC	Abdominal and pelvic ultrasound	Birth[a]	Every 3–4 months	- Blood biochemistry[f] if unsatisfactory ultrasound quality - Ultrasound may be omitted when timing overlaps with annual WBMRI
Melanoma	Skin evaluation	Birth[a]	Every year	Dermatologic screening to be performed by a pediatrician or family physician, with a low threshold for formal dermatology assessment for uncertain or suspicious nevi or for children who have been exposed to radiotherapy
Breast	Breast awareness	18	Every year	Breast awareness and self-exam to be taught by a health professional at age 18 to individuals assigned female gender at birth

[a]Or at the time of detection of germline *TP53* P/LP variant.
[b]Modification of the protocol may be considered in jurisdictions where WBMRI is not feasible due to limitations relating to technical factors (multistation acquisition) and/or the availability of experienced technologists or radiologists with experience in acquiring/interpreting WBMRI for CPS.
[c]Annual WBMRI, performed yearly, may be performed 6 months apart from the annual dedicated brain MRI. However, in children requiring general anesthesia and to minimize the number of healthcare visits, performing both MRI studies concurrently every 12 months may be more appropriate.
[d]Should include upper and lower extremities.
[e]Brain MRI should be done using the standard institutional protocol for dedicated brain MRI scans (high quality and not motion-degraded).
[f]Blood biochemistry includes total testosterone, dehydroepiandrosterone sulfate, and androstenedione. Serial specimens should be obtained at the same time of day and processed in the same laboratory.

made clear when discussing the management plan with the patient and their parents/guardians. Increased risks of treatment-associated malignancies must be weighed against the increased chance of a good outcome from the current tumor. Additional surveillance in previously radiated areas, especially for gastrointestinal cancers, should be considered for patients with LFS. For instance, for patients who have received total body or abdominal therapeutic radiation, colonoscopy screening should be initiated earlier and may be considered starting 5 years after treatment (35). Cancer screening strategies may continue throughout life, and there is no recommended age limit to discontinue surveillance; however, a discussion with patients as they

Table 2. Specific clinical features of interest for common LFS tumors in children.

Childhood tumor/cancer type	Physical exam features and clinical symptoms
General	Including anthropometrics
STSs/osteosarcomas	Palpable masses, increased girth/swelling, limp/abnormal gait Persistent or worsening pain
ACC	Specific attention to growth velocity, as growth acceleration (i.e., a significant increase from the patient's baseline) to precede signs of virilization or imaging findings (abdominal mass, cushingoid appearance, virilization [pubic hair, axillary moisture, adult body odor, androgenic hair loss or growth, clitoromegaly, or penile growth])
CNS	Full neurologic exam Frequent headaches, seizures, personality or behavior changes, weakness, numbness or paralysis in part or side of the body, loss of balance, nausea, dizziness, loss of hearing or vision changes, and macrocephaly
Leukemia	Pallor, bruising/petechiae, enlarged lymph nodes, hepatosplenomegaly, limp, and constitutional symptoms such as prolonged fevers, night sweats, unintentional weight loss, and/or bony pain
Melanoma	Full-body skin exam for new or growing nevi with concerning features Digital dermatoscopy via a dermatologist if atypical, growing lesion

reach a more mature age about their goals of surveillance may be warranted.

Considerations for modifications based on penetrance and mosaic carriers

At this time, we do not endorse modification of surveillance recommendations for carriers of hypomorphic variants or individuals in families who have clear incomplete penetrance or attenuated LFS along the LFS spectrum. Recent studies on lower penetrance/partially functional variants are generally based on smaller case series and may not be sufficiently robust to change recommendations until they are validated in other larger cohorts or through data linkage studies (36–38). The ClinGen *TP53* variant curation expert panel has not yet developed criteria for hypomorphic variants, including the determination of which assays/approaches to use for variant classification as this often drives genotype–phenotype associations. Surveillance recommendations should also not be modified for moderate/lower penetrance or mosaic carriers. Where low-level mosaicism is identified following testing of white blood cell–derived DNA, particularly when an individual is cancer-unaffected, we recommend that this be confirmed by testing other tissues to ensure a diagnosis of somatic mosaicism rather than clonal hematopoiesis of indeterminate potential (39).

Considerations for resource-constrained settings

In a resource-constrained setting, access to care and surveillance may be limited. Not all centers have the capability to implement diffusion-weighted imaging sequences in their WBMRI protocols. WBMRI acquisition challenges can also relate to the availability of suitable MRI scanner table and coil configurations, postprocessing software, experienced MRI technologists, and radiologists with expertise in WBMRI interpretation. Also, in some countries, MRI of each station (body part) has a different billing code, making the entire WBMRI examination extremely costly to patients/healthcare systems. In resource-rich settings, it remains difficult to manage issues with billing codes or other financial limitations. Although no evidence exists as yet comparing the effect of alternative or modified protocols on early cancer detection in LFS, we stress the recommendation for physical examination in low-resource or resource-constrained settings, in addition to whatever nonradiation-based imaging modalities can be performed in a cost-efficient way (**Table 2**).

Considerations of novel screening strategies

Liquid biopsy via the detection of ctDNA is an emerging technology that may ultimately provide an effective alternative or complementary surveillance tool. Wong and colleagues (40) demonstrated the utility of a multiomic ctDNA platform in detecting a range of cancers in a retrospective study in *TP53* P/LP variant carriers with changes in ctDNA levels being observed months prior to cancer detection by conventional WBMRI. The sensitivity and specificity of this approach, compared with conventional LFS surveillance, are being evaluated in a large-scale prospective study and may inform surveillance strategies in the future.

Considerations on hormonal therapy

Individuals with LFS who are transgender, nonbinary, or gender diverse may wish to pursue gender-affirming hormonal and/or surgical treatments at some point in their lives, which may affect their cancer risk and risk reduction options. As cited in the NCCN guidelines (31), no prospective data exist to guide appropriate cancer risk reduction and/or screening options for these individuals. Therefore, consideration for risk reduction options should be made at an individual patient level, taking into account a wide range of variables. Risk reduction and screening choices should focus on organs at risk based on biologic sex at birth, as well as those potentially affected by additional hormone exposures. Some complexities in care may arise with surgical options as well. For example, individuals undergoing bilateral risk-reducing mastectomies who wish to have a more male chest contour afterward may opt for top surgery, which generally requires more retained breast tissue. This decision may then affect subsequent chest surveillance strategies (31). The risks associated with the use of growth hormone or other hormone therapies (e.g., birth control pills, estrogen replacement, testosterone supplements) have also not been clearly defined. However, the use of these therapies should be considered individually in the context of the potential benefits and risks. Collaboration between a cancer predisposition clinic and providers prescribing and managing these health concerns is optimal.

Psychosocial considerations

The 2017 AACR recommendations for childhood CPSs included a discussion of the psychosocial implications of disease surveillance/screening in both the LFS-specific article as well as the articles on recommendations for genetic counselors managing these syndromes (11, 41, 42). The 2024 AACR update on genetic counselor practice and recommendations for pediatric CPS once again includes a discussion of psychosocial issues related to LFS and, more specifically, emerging literature on the psychosocial impact of cancer surveillance in adolescents with CPS (11, 41, 42). In the interim, further literature has emerged on this critical topic. Screening has been found to provide psychologic benefits measured by a reduction in anxiety scores after WBMRI (43, 44). Bancroft and colleagues (44) report a high degree of acceptance and satisfaction with screening and would recommend surveillance to at-risk family members. Other common perceived benefits include the reduction of uncertainty, understanding causation, the ability to understand risk, and the option to pursue surveillance. The intensity of surveillance is burdensome on patients, caregivers, and the healthcare system with poor compliance due to the frequency of visits, fear of abnormal results, and concerns over insurance sustainability (45–48). Emotional challenges and logistical complexities of surveillance, implications for privacy, insurance risk, and risk to current or future employment opportunities are all important concerns associated with the implementation and continuation of surveillance. The perceived lack of benefit of screening by some patients and physicians highlights the importance of educating clinicians, caregivers, patients, and families. Some studies of *TP53* P/LP variant carriers report higher levels of disease-related worry and depression compared with noncarriers, whereas others have shown this is more common in patients already diagnosed with cancer rather than based solely on carrier status (46). Psychosocial support during surveillance helps patients feel empowered, proactive, and positive and can improve symptoms of anxiety (49).

Cancer Screening/Surveillance Protocols in Adults

This article focuses on the recommendations for the surveillance of children (<18 years of age) who are carriers of *TP53* P/LP variants. In counseling these young patients and their parents, it will also become important to prepare them for the transition to follow

Table 3. Recommended complete adult LFS screening protocol (based on the Toronto Protocol).

Adult tumor/cancer type	Screening/management method	Starting age	Frequency	Comment
General assessment	Complete physical exam including extremities (**Table 4**)	Birth	Every 6 months	In addition, prompt assessment with a primary care physician for any medical concerns (**Table 4**)
Breast cancer	MRI	20 years	Every year	May consider alternating breast MRI and mammogram
	Mammogram	30 years	Every year	None
STSs/osteosarcomas	WBMRI without contrast	Birth	Every year	In centers where WBMRI is not feasible (poorly resourced countries, etc.), modifications of the protocol to be considered
CNS	Dedicated brain MRI	Birth	Every year	Initial brain MRI with intravenous contrast; thereafter without contrast if the previous MRI is normal (and high quality, nonmotion degraded)
ACC	Abdominal and pelvic ultrasound	Birth	Every 6 months	Blood biochemistry if unsatisfactory ultrasound quality Ultrasound may be omitted when timing overlaps with annual WBMRI
Melanoma	Skin evaluation	Birth	Every year	Dermatologic screening to be performed by a family physician, with a low threshold for formal dermatology assessment for uncertain or suspicious nevi or for individuals who have been exposed to RT
Prostate	Serum PSA	35 years	Every year	A rapid increase to prompt assessment with a urologist
GI cancers	Colonoscopy and endoscopy	25 years	Every 2–5 years	Earlier screening being recommended for patients who have received total body or abdominal therapeutic RT
Leukemia	CBC with differential	Birth	Every 3–4 months	In patients with prior exposure to leukemogenic agents, to monitor for evidence of transformation

Abbreviations: ACC, adrenocortical carcinoma; CNS, central nervous system; GI, gastrointestinal; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; RT, radiotherapy; WBMRI, whole-body MRI.

up in adult cancer predisposition or adult oncology centers so that they have knowledge of the changes in surveillance strategies as adults. The following section summarizes the rationale and recommendations for adults with LFS to be considered in educating patients, parents, and practitioners (**Tables 3** and **4**). Transition to adult surveillance includes many possible strategies.

Breast cancer

Breast cancer is the most common malignancy in females with LFS, and the lifetime risk of breast cancer has been estimated at 85% by age 60 (49). The median age of first breast cancer diagnosis varies from 32 to 40 years but has been reported in late teenagers and very young women and may vary depending on

Table 4. Specific clinical features of interest for common LFS tumors in adults.

Adult tumor/cancer type	Physical exam features and clinical symptoms
General	Heavy night sweats or fever, fatigue, unexplained bruising or bleeding, unexplained pain or ache, unusual lump and swelling
STSs/osteosarcomas	Palpable masses, increased girth/swelling, limp/abnormal gait Persistent or worsening pain
ACC	Abdominal mass or cushingoid appearance
CNS	Comprehensive neurologic exam Frequent headaches, seizures, personality or behavior changes, weakness, numbness or paralysis in part or side of the body, loss of balance, nausea, dizziness, loss of hearing or vision changes
Leukemia	Pallor, bruising/petechiae, enlarged lymph nodes, hepatosplenomegaly, limp, constitutional symptoms such as prolonged fevers, unintentional weight loss, bony pain
Melanoma	Full body skin exam for new or growing nevi with concerning features Digital dermatoscopy via dermatologist if atypical, growing lesion
Breast	Breast and axillary palpation to detect lumps or other changes. Nipple pressure to check for any discharge
GI	Blood in stool, changes in fecal color and aspect, thin or stringy stool, abrupt changes in the frequency of bowel movements
Prostate	DRE by a urologist from age 35

Abbreviations: ACC, adrenocortical carcinoma; CNS, central nervous system; DRE, digital rectal examination; GI, gastrointestinal; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; RT, radiotherapy; WBMRI, whole-body MRI.

the *TP53* gene variant domain (9). There is an increased risk of second primary breast cancers. Prophylactic total mastectomy should be discussed with all *TP53* germline P/LP variant female carriers. The optimal timing for this discussion is early adulthood, and patients should receive adequate counseling about its degree of protection. For patients who have been diagnosed with breast cancer, total mastectomy should be regarded as an option and compared with breast-conserving surgery. It may also allow patients with LFS early-stage breast cancer to avoid adjuvant radiotherapy in specific cases (10, 50). Furthermore, surveillance imaging with breast magnetic resonance, even after bilateral mastectomy, should be offered for female TP53 P/LP variant carriers. It is important to stress that risk-reducing mastectomy is the only prophylactic surgery indicated in LFS, and risk-reducing bilateral salpingo-oophorectomy is not a standard recommendation for patients with LFS.

Most breast cancers in LFS are hormone receptor–positive and overexpression of HER2 may direct specific systemic therapies (51–54).

The expert panel emphasizes the central importance of starting annual breast MRI at age 20 and mammograms with tomosynthesis yearly starting at age 30 for females with LFS though many guidelines omit mammography because of concerns about cancer initiation. There is no evidence showing the benefit of performing both techniques on a 6-month interval, but it remains an option that provides more frequent imaging and may be reassuring or relieve anxiety for some patients. A physical exam of the breast should be performed by a trained physician or nurse practitioner every 6 months. Patients should be educated to perform self-examinations monthly beginning at age 18. Ensuring a smooth transition from pediatric to adult surveillance programs should be made an absolute priority, given the importance of breast cancer risk management and patient education for this young adult population.

Hormone replacement in menopausal LFS carriers may provide a similar risk and benefit consideration as in women from the general population. However, there are no data to determine if there are unique cancer risks associated with hormone replacement therapy (HRT) in people with LFS. Patients should discuss the management of menopause and options for HRT with an experienced provider, and factors including age, symptoms, prior cancer history, presence of a uterus if estrogen-only replacement, and whether or not the patient has had risk-reducing mastectomies or a previous breast cancer should be considered.

STS and bone sarcomas

One main reason to perform annual WBMRI is the early detection of sarcomas. Annual abdominal/pelvic ultrasounds in adults with LFS should be considered in addition to annual WBMRI (6 months apart from annual WBMRI), especially after abdominal/pelvic radiation (55).

ACC

Although less frequent than in childhood, adults with LFS are at risk for ACT. A yearly abdominal ultrasound should be considered as a screening strategy, and it may be performed 6 months apart from the annual WBMRI. Abdominal ultrasound would aid in the interpretation of WBMRI findings, given that false-positive/additional imaging findings may be observed in adults that are not cancers. Thus, the abdominal ultrasound would aid in specificity, but WBMRI needs to be retained for sensitivity.

Brain cancer

The majority of adult CNS tumors are gliomas, mostly high-grade gliomas (glioblastomas) at the time of diagnosis. Annual brain MRI is an adequate screening strategy that may be done at the same time or 6 months apart from annual WBMRI.

Gastrointestinal cancers

Colorectal cancer is associated with LFS, but studies have highlighted the complexity in understanding this association and true risk estimates. It has been demonstrated that individuals with colon cancer and germline *TP53* PV do not consistently show an LFS phenotype (56), whereas other recent studies of patients with LFS emphasize an increased lifetime risk of colorectal cancer (57). The UK and GENTURIS guidelines referred to above do not recommend colorectal cancer surveillance (14, 15). Following careful discussion, the AACR Working Group aligned on continuing to recommend surveillance with colonoscopy beginning at age 25, or 5 years younger than the earliest diagnosis in a family, to be repeated every 2 to 3 years (31). Earlier screening is recommended for patients who have received total body or abdominal therapeutic radiotherapy. In the presence of an adenomatous polyp, colonoscopy should be repeated annually. Upper gastrointestinal cancer screening with upper endoscopy should start at age 25 or 5 years younger than the earliest diagnosis.

Pancreatic cancer screening is not routinely suggested in LFS and is not a component of UK and GENTURIS guidelines. Nevertheless, as evidence continues to emerge, this committee endorses the NCCN guidelines, which suggest that when there is a first- or second-degree relative with LFS and pancreatic cancer, screening is recommended to begin at age 50 (or 10 years younger than the earliest exocrine pancreatic cancer in the family; ref. 31). Screening should be performed annually with endoscopic ultrasound or magnetic resonance cholangiopancreatography. Pancreatic cancer screening is ideally done at a center that conducts a high volume of pancreatic cancer screenings (58).

Prostate cancer

Because of the risk of prostate cancer in LFS, management should include annual PSA testing and digital rectal examination starting at age 35 for early detection of prostate cancer (4).

Other adult-onset cancers

Lung cancer

Lung cancer, mostly adenocarcinoma, with somatic variants in *EGFR*, has been reported to occur at a higher frequency in LFS carriers (59). However, screening with standard-of-care imaging is CT, which utilizes ionizing radiation and should not be performed as a screening strategy in LFS carriers. Low-dose chest CT scans have been developed for the screening of tobacco smokers but have not been assessed in LFS. Although WBMRI is not optimal for pulmonary nodule detection, radiologists should nevertheless be vigilant for lung lesions. The addition of dedicated lung MRI sequences will, in the near future, aid nodule detection and characterization, with recent evidence showing the potential for WBMRI in staging lung cancer (40). For now, low- and ultralow-dose CT may be used as a dedicated exam following lung lesion detection (60, 61).

Hematologic malignancies

Non-Hodgkin lymphoma and acute and chronic myeloid leukemia, as well as therapy-related acute myeloid leukemia and

myelodysplastic syndrome, have been reported in adult patients with LFS. Nevertheless, imaging strategies and biochemical exams have not been shown to be effective for early diagnosis in adults. Physical examination for the diagnosis of hematologic malignancies is often predated by symptomatology in adults, making this approach to surveillance likely noninformative (62). It may be reasonable to screen those with prior exposure to leukemogenic agents using regular complete blood count (CBC)/differential. Although absolute hematologic parameters may not be informative, trends pointing to aberrations in hematopoiesis should be noted (**Table 3**).

Thyroid cancer

Most thyroid cancers in LFS are micropapillary/papillary. It has been shown to be more frequent in carriers of the R337H variant, but there is no evidence of a greater risk than in the general population. Nevertheless, isolated single-institution studies suggest that an annual thyroid ultrasound could be included in a cancer surveillance protocol in certain populations (5); however, high false-positive rates preclude endorsing this recommendation. Thyroid nodules may be detected on surveillance WBMRI, and these would warrant further characterization with thyroid ultrasound.

Considerations on physical examination

Physical examination should be performed every 6 months in all adult patients (**Table 4**).

Conclusions

LFS is caused by P/LP in the *TP53* tumor suppressor gene. *TP53* P/LP variant carriers can manifest a wide range of cancers throughout their lifetime, making surveillance recommendations particularly challenging. These surveillance strategies evolve with the patient's age to target organs in an age-dependent manner. The "Toronto Protocol" remains the current standard for lifelong surveillance; however, as outlined in this perspective, modifications should be considered about the use of certain modalities. Furthermore, the Working Group's recommendations have been extended to include a more detailed outline for the adult population of *TP53* P/LP variant carriers than had been published in the 2017 report. This information is provided based on the recognition that early education of both practitioners and patients on what to expect after the transition from childhood/adolescence to young adulthood is important in preparing them for changes in surveillance strategies based on differences in the target organs that must be observed as the patient ages.

Authors' Disclosures

A.S. Doria reports grants from the Terry Fox Foundation, PSI Foundation, Society of Pediatric Radiology, Radiological Society of North America, CARRA Foundation, and Novonordisk Access to Insight Grant outside the submitted work. M.-L.C. Greer reports grants from AbbVie and other support from Alimentiv outside the submitted work. J. Kamihara reports that spouse has received consulting fees from ROME Therapeutics, Sonata Therapeutics, Leica Biosystems Imaging, PanTher Therapeutics, 65 Therapeutics, and abrdn; is a founder and has equity in ROME Therapeutics, PanTher Therapeutics, and TellBio, Inc.; is on the advisory board with equity for ImproveBio, Inc. and 65 Therapeutics; has received honoraria from Astellas, AstraZeneca, Moderna, and Ikena Oncology; and receives research support from ACD Bio-Techne, AVA LifeScience GmbH, Incyte Pharmaceuticals, Sanofi, and Astellas. None of the above are related to this work. C.P. Kratz reports grants from Deutsche Kinderkrebsstiftung during the conduct of the study. L.D. Maese reports grants from St. Baldrick's Foundation during the conduct of the study as well as other support from Jazz Pharmaceuticals and Servier Pharmaceuticals outside the submitted work. S.M. Pfister reports nonfinancial support from Epignostix GbmH, personal fees from BioSkryb, and other support from PMC outside the submitted work. A patent is held by S.M. Pfister, David TW Jones, David Capper, Andreas von Deimling, Martin Sill, and Volker Hovestadt at DKFZ, University Hospital Heidelberg for a DNA Methylation based method for classifying tumor species (European Patent 16 710700.2). S.M. Pfister also reports unpaid membership at GPOH, SIOP, DGNN, and DKG. J.D. Wasserman reports personal fees from Ipsen Pharmaceuticals outside the submitted work. E.R. Woodward reports personal fees from Cancer Research UK outside the submitted work. D. Malkin is supported in part by the CIBC Children's Foundation Chair in Child Health Research. No disclosures were reported by the other authors.

Received October 4, 2024; revised January 5, 2025; accepted March 11, 2025; posted first March 12, 2025.

References

1. de Andrade KC, Khincha PP, Hatton JN, Frone MN, Wegman-Ostrosky T, Mai PL, et al. Cancer incidence, patterns, and genotype-phenotype associations in individuals with pathogenic or likely pathogenic germline TP53 variants: an observational cohort study. Lancet Oncol 2021;22:1787–98.
2. Malkin D. Li-Fraumeni syndrome. Genes Cancer 2011;2:475–84.
3. Kamihara J, Rana HQ, Garber JE. Germline TP53 mutations and the changing landscape of Li-Fraumeni syndrome. Hum Mutat 2014;35:654–62.
4. Maxwell KN, Cheng HH, Powers J, Gulati R, Ledet EM, Morrison C, et al. Inherited TP53 variants and risk of prostate cancer. Eur Urol 2022;81:243–50.
5. Formiga MNDC, de Andrade KC, Kowalski LP, Achatz MI. Frequency of thyroid carcinoma in Brazilian TP53 p.R337H carriers with Li Fraumeni syndrome. JAMA Oncol 2017;3:1400–2.
6. de Andrade KC, Frone MN, Wegman-Ostrosky T, Khincha PP, Kim J, Amadou A, et al. Variable population prevalence estimates of germline TP53 variants: a gnomAD-based analysis. Hum Mutat 2019;40:97–105.
7. de Andrade KC, Strande NT, Kim J, Haley JS, Hatton JN, Frone MN, et al. Genome-first approach of the prevalence and cancer phenotypes of pathogenic or likely pathogenic germline TP53 variants. HGG Adv 2024;5:100242.
8. Lalloo F, Varley J, Ellis D, Moran A, O'Dair L, Pharoah P, et al. Prediction of pathogenic mutations in patients with early-onset breast cancer by family history. Lancet 2003;361:1101–2.
9. Bougeard G, Renaux-Petel M, Flaman J-M, Charbonnier C, Fermey P, Belotti M, et al. Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. J Clin Oncol 2015;33:2345–52.
10. Thariat J, Chevalier F, Orbach D, Ollivier L, Marcy P-Y, Corradini N, et al. Avoidance or adaptation of radiotherapy in patients with cancer with Li-Fraumeni and heritable TP53-related cancer syndromes. Lancet Oncol 2021;22:e562–74.
11. Kratz CP, Achatz MI, Brugières L, Frebourg T, Garber JE, Greer M-LC, et al. Cancer screening recommendations for individuals with Li-Fraumeni syndrome. Clin Cancer Res 2017;23:e38–45.
12. Villani A, Tabori U, Schiffman J, Shlien A, Beyene J, Druker H, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study. Lancet Oncol 2011;12:559–67.
13. Villani A, Shore A, Wasserman JD, Stephens D, Kim RH, Druker H, et al. 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.
14. Frebourg T, Bajalica Lagercrantz S, Oliveira C, Magenheim R, Evans DG, European Reference Network GENTURIS. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes. Eur J Hum Genet 2020;28:1379–86.
15. Hanson H, Brady AF, Crawford G, Eeles RA, Gibson S, Jorgensen M, et al. UKCGG Consensus Group guidelines for the management of patients with constitutional TP53 pathogenic variants. J Med Genet 2020;58:135–9.

16. Kratz CP, Freycon C, Maxwell KN, Nichols KE, Schiffman JD, Evans DG, et al. Analysis of the Li-Fraumeni spectrum based on an international germline TP53 variant data set: an international agency for research on cancer TP53 database analysis. JAMA Oncol 2021;7:1800–5.
17. Kato S, Han S-Y, Liu W, Otsuka K, Shibata H, Kanamaru R, et al. Understanding the function-structure and function-mutation relationships of p53 tumor suppressor protein by high-resolution missense mutation analysis. Proc Natl Acad Sci U S A 2003;100:8424–9.
18. Penkert J, Strüwe FJ, Dutzmann CM, Doergeloh BB, Montellier E, Freycon C, et al. Genotype-phenotype associations within the Li-Fraumeni spectrum: a report from the German Registry. J Hematol Oncol 2022;15:107.
19. Montellier E, Lemonnier N, Penkert J, Freycon C, Blanchet S, Amadou A, et al. Clustering of TP53 variants into functional classes correlates with cancer risk and identifies different phenotypes of Li-Fraumeni syndrome. iScience 2024;27:111296.
20. Subasri V, Light N, Kanwar N, Brzezinski J, Luo P, Hansford JR, et al. Multiple germline events contribute to cancer development in patients with Li-Fraumeni syndrome. Cancer Res Commun 2023;3:738–54.
21. Pinto EM, Figueiredo BC, Chen W, Galvao HCR, Formiga MN, Fragoso M, et al. XAF1 as a modifier of p53 function and cancer susceptibility. Sci Adv 2020;6:eaba3231.
22. Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med 2014;371:2488–98.
23. Weeks LD, Niroula A, Neuberg D, Wong W, Lindsley RC, Luskin M, et al. Prediction of risk for myeloid malignancy in clonal hematopoiesis. NEJM Evid 2023;2:2–21.
24. Weber-Lassalle K, Harter P, Hauke J, Ernst C, Kommoss S, Marmé F, et al. Diagnosis of Li-Fraumeni Syndrome: differentiating TP53 germline mutations from clonal hematopoiesis: results of the observational AGO-TR1 trial. Hum Mutat 2018;39:2040–6.
25. Weitzel JN, Chao EC, Nehoray B, Van Tongeren LR, LaDuca H, Blazer KR, et al. Somatic TP53 variants frequently confound germ-line testing results. Genet Med 2018;20:809–16.
26. Batalini F, Peacock EG, Stobie L, Robertson A, Garber J, Weitzel JN, et al. Li-Fraumeni syndrome: not a straightforward diagnosis anymore-the interpretation of pathogenic variants of low allele frequency and the differences between germline PVs, mosaicism, and clonal hematopoiesis. Breast Cancer Res 2019;21:107.
27. Slavin TP, Coffee B, Bernhisel R, Logan J, Cox HC, Marcucci G, et al. Prevalence and characteristics of likely-somatic variants in cancer susceptibility genes among individuals who had hereditary pan-cancer panel testing. Cancer Genet 2019;235–236:31–8.
28. Coffee B, Cox HC, Bernhisel R, Manley S, Bowles K, Roa BB, et al. A substantial proportion of apparently heterozygous TP53 pathogenic variants detected with a next-generation sequencing hereditary pan-cancer panel are acquired somatically. Hum Mutat 2020;41:203–11.
29. Franch-Expósito S, Mehine M, Ptashkin RN, Bolton KL, Bandlamudi C, Srinivasan P, et al. Associations between cancer predisposition mutations and clonal hematopoiesis in patients with solid tumors. JCO Precis Oncol 2023;7:e2300070.
30. Fortuno C, Lee K, Olivier M, Pesaran T, Mai PL, de Andrade KC, et al. Specifications of the ACMG/AMP variant interpretation guidelines for germline TP53 variants. Hum Mutat 2021;42:223–36.
31. Network NCC. Genetic/familial high-risk assessment: breast, ovarian pancreatic and prostate v2.2025. [cited 2024 Dec 30]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf.
32. Greer M-LC, States LJ, Malkin D, Voss SD, Doria AS. Update on whole-body MRI surveillance for pediatric cancer predisposition syndromes. Clin Cancer Res 2024;30:5021–33.
33. Light N, Layeghifard M, Attery A, Subasri V, Zatzman M, Anderson ND, et al. Germline TP53 mutations undergo copy number gain years prior to tumor diagnosis. Nat Commun 2023;14:77.
34. Kasper E, Angot E, Colasse E, Nicol L, Sabourin J-C, Adriouch S, et al. 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.
35. MacFarland SP, Zelley K, Long JM, McKenna D, Mamula P, Domchek SM, et al. Earlier colorectal cancer screening may Be necessary in patients with Li-Fraumeni syndrome. Gastroenterology 2019;156:273–4.
36. Jeffers JR, Pinto EM, Rehg JE, Clay MR, Wang J, Neale G, et al. The common germline TP53-R337H mutation is hypomorphic and confers incomplete penetrance and late tumor onset in a mouse model. Cancer Res 2021;81:2442–56.
37. Evans DG, Harkness EF, Woodward ER. TP53 c.455C>T p.(Pro152Leu) pathogenic variant is a lower risk allele with attenuated risks of breast cancer and sarcoma. J Med Genet 2023;60:1057–60.
38. Powers J, Pinto EM, Barnoud T, Leung JC, Martynyuk T, Kossenkov AV, et al. A rare TP53 mutation predominant in ashkenazi jews confers risk of multiple cancers. Cancer Res 2020;80:3732–44.
39. Evans DG, Woodward ER. New surveillance guidelines for Li-Fraumeni and hereditary TP53 related cancer syndrome: implications for germline TP53 testing in breast cancer. Fam Cancer 2021;20:1–7.
40. Wong D, Luo P, Oldfield LE, Gong H, Brunga L, Rabinowicz R, et al. Early cancer detection in Li-Fraumeni syndrome with cell-free DNA. Cancer Discov 2024;14:104–19.
41. Druker H, Zelley K, McGee RB, Scollon SR, Kohlmann WK, Schneider KA, et al. Genetic counselor recommendations for cancer predisposition evaluation and surveillance in the pediatric oncology patient. Clin Cancer Res 2017;23:e91–7.
42. Zelley K, Schienda J, Gallinger B, Kohlmann WK, McGee RB, Scollon SR, et al. Update on genetic counselor practice and recommendations for pediatric cancer predisposition evaluation and surveillance. Clin Cancer Res 2024;30:3983–9.
43. McBride KA, Ballinger ML, Schlub TE, Young M-A, Tattersall MHN, Kirk J, et al. Psychosocial morbidity in TP53 mutation carriers: is whole-body cancer screening beneficial?. Fam Cancer 2017;16:423–32.
44. Bancroft EK, Saya S, Brown E, Thomas S, Taylor N, Rothwell J, et al. Psychosocial effects of whole-body MRI screening in adult high-risk pathogenic TP53 mutation carriers: a case-controlled study (SIGNIFY). J Med Genet 2020;57:226–36.
45. Ross J, Bojadzieva J, Peterson S, Noblin SJ, Yzquierdo R, Askins M, et al. The psychosocial effects of the Li-Fraumeni Education and Early Detection (LEAD) program on individuals with Li-Fraumeni syndrome. Genet Med 2017;19:1064–70.
46. Young JL, Pantaleao A, Zaspel L, Bayer J, Peters JA, Khincha PP, et al. Couples coping with screening burden and diagnostic uncertainty in Li-Fraumeni syndrome: connection versus independence. J Psychosoc Oncol 2019;37:178–93.
47. Lammens CR, Bleiker EM, Aaronson NK, Wagner A, Sijmons RH, Ausems MG, et al. Regular surveillance for Li-Fraumeni Syndrome: advice, adherence and perceived benefits. Fam Cancer 2010;9:647–54.
48. Rippinger N, Fischer C, Haun MW, Rhiem K, Grill S, Kiechle M, et al. Cancer surveillance and distress among adult pathogenic TP53 germline variant carriers in Germany: a multicenter feasibility and acceptance survey. Cancer 2020;126:4032–41.
49. Mai PL, Best AF, Peters JA, DeCastro RM, Khincha PP, Loud JT, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. Cancer 2016;122:3673–81.
50. Sandoval RL, Polidorio N, Leite ACR, Cartaxo M, Pisani JP, Quirino CV, et al. Breast cancer phenotype associated with Li-Fraumeni syndrome: a Brazilian cohort enriched by TP53 p.R337H carriers. Front Oncol 2022;12:836937.
51. Tung NM, Boughey JC, Pierce LJ, Robson ME, Bedrosian I, Dietz JR, et al. Management of hereditary breast cancer: American society of clinical oncology, American society for radiation oncology, and society of surgical oncology guideline. J Clin Oncol 2020;38:2080–106.
52. Wilson JR, Bateman AC, Hanson H, An Q, Evans G, Rahman N, et al. A novel HER2-positive breast cancer phenotype arising from germline TP53 mutations. J Med Genet 2010;47:771–4.
53. Melhem-Bertrandt A, Bojadzieva J, Ready KJ, Obeid E, Liu DD, Gutierrez-Barrera AM, et al. Early onset HER2-positive breast cancer is associated with germline TP53 mutations. Cancer 2012;118:908–13.
54. Khincha PP, Best AF, Fraumeni JF Jr., Loud JT, Savage SA, Achatz MI. Reproductive factors associated with breast cancer risk in Li-Fraumeni syndrome. Eur J Cancer 2019;116:199–206.
55. Kagami LAT, Du YK, Fernandes CJ, Le AN, Good M, Duvall MM, et al. Rates of intervention and cancer detection on initial versus subsequent whole-body MRI screening in Li-Fraumeni syndrome. Cancer Prev Res (Phila) 2023;16:507–12.
56. Terradas M, Mur P, Belhadj S, Woodward ER, Burghel GJ, Munoz-Torres PM, et al. TP53, a gene for colorectal cancer predisposition in the absence of Li-Fraumeni-associated phenotypes. Gut 2021;70:1139–46.

57. Fortuno C, Feng B-J, Carroll C, Innella G, Kohlmann W, Lázaro C, et al. Cancer risks associated with TP53 pathogenic variants: maximum likelihood analysis of extended pedigrees for diagnosis of first cancers beyond the Li-Fraumeni syndrome spectrum. JCO Precis Oncol 2024;8:e2300453.
58. Sawhney MS, Calderwood AH, Thosani NC, Rebbeck TR, Wani S, Canto MI, et al. ASGE guideline on screening for pancreatic cancer in individuals with genetic susceptibility: summary and recommendations. Gastrointest Endosc 2022;95:817–26.
59. Hatton JN, Kucera J, Seastedt KP, de Andrade KC, Savage SA, Khincha PP, et al. Characterizing lung cancer in Li-Fraumeni syndrome. JAMA Oncol 2024;10:1284–7.
60. Caron O, Frebourg T, Benusiglio PR, Foulon S, Brugières L. Lung adenocarcinoma as part of the Li-Fraumeni syndrome spectrum: preliminary data of the LIFSCREEN randomized clinical trial. JAMA Oncol 2017;3:1736–7.
61. Taylor SA, Mallett S, Miles A, Morris S, Quinn L, Clarke CS, et al. Whole-body MRI compared with standard pathways for staging metastatic disease in lung and colorectal cancer: the Streamline diagnostic accuracy studies. Health Technol Assess 2019;23:1–270.
62. Swaminathan M, Bannon SA, Routbort M, Naqvi K, Kadia TM, Takahashi K, et al. Hematologic malignancies and Li-Fraumeni syndrome. Cold Spring Harb Mol Case Stud 2019;5:a003210.