Cancer Screening Recommendations for Individuals with Li-Fraumeni Syndrome

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Abstract

Li-Fraumeni syndrome (LFS) is an autosomal dominantly inherited condition caused by germline mutations of the TP53 tumor suppressor gene encoding p53, a transcription factor triggered as a protective cellular mechanism against different stressors. Loss of p53 function renders affected individuals highly susceptible to a broad range of solid and hematologic cancers. It has recently become evident that children and adults with LFS benefit from intensive surveillance aimed at early tumor detection. In October 2016, the American Association for Cancer Research held a meeting of international LFS experts to evaluate the current knowledge on LFS and propose consensus surveillance recommendations. Herein, we briefly summarize clinical and genetic aspects of this aggressive cancer predisposition syndrome. In addition, the expert panel concludes that there are sufficient existing data to recommend that all patients with LFS be offered cancer surveillance as soon as the clinical or molecular LFS diagnosis is established. Specifically, the panel recommends adoption of a modified version of the "Toronto protocol" that includes a combination of physical exams, blood tests, and imaging. The panel also recommends that further research be promoted to explore the feasibility and effectiveness of these risk-adapted surveillance and cancer prevention strategies while addressing the psychosocial needs of individuals and families with LFS. Clin Cancer Res; 23(11); e38–e45. © 2017 AACR.

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Introduction

Li-Fraumeni syndrome (LFS; OMIM #151623) is among the most aggressive cancer predisposition syndromes characterized by a high and early-onset cancer risk. The tumor spectrum is wide and includes brain tumors [choroid plexus carcinoma, Sonic Hedgehog (SHH) subtype medulloblastoma, glioma], adrenocortical carcinoma (ACC), a range of soft tissue sarcomas (STS) and bone tumors, hematologic malignancies, breast cancer (generally very early in onset), and other cancer types, including lung, skin, gastrointestinal tract, kidney, thyroid, as well as neuroblastoma. The tumors most closely associated with LFS are called “core” cancers and include STS, osteosarcoma, premenopausal breast cancer, brain tumors, and ACCs (for review, see refs. 1, 2).

LFS was first described in 1969 by Frederick Li and Joseph Fraumeni Jr based on their observation of a unique spectrum of cancers in four families in whom the index cases presented with rhabdomyosarcoma (3). The original definition of the syndrome was established in 1988 as the result of an analysis of 24 kindreds presenting with an autosomal dominant pattern of transmission of early-onset neoplasms including STS, breast cancers, central nervous system (CNS) tumors, leukemias, and ACCs before the age of 45 years (4). This “classical” definition requires one individual with a sarcoma diagnosed under the age of 45 who has at least one first-degree relative (parent, sibling, or child) with a cancer of any kind diagnosed under the age of 45 and a third family member who is either a first- or second-degree relative in the same parental lineage (grandparent, aunt, uncle, niece, nephew, or grandchild) with any cancer diagnosed under the age of 45, or a sarcoma at any age (4).
In 1990, germline TP53 mutations were discovered as the only cause of LFS (5–7). The identification of germline TP53 mutations in patients not fulfilling the original definition of the syndrome led to periodic updates of operational LFS criteria, designated the "Chompret criteria," to describe four different clinical situations with a high probability of being caused by an underlying TP53 mutation and in which genetic counseling and clinical TP53 mutation testing should be strongly considered and offered: (i) familial presentation: proband with an LFS spectrum tumor (premenopausal breast cancer, STS, brain tumor, ACC) prior to 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 the age of 56 years or with multiple tumors; (ii) multiple tumors: proband with multiple malignancies (except two breast cancers), of which at least two belong to the LFS spectrum, before the age of 46 years; (iii) rare tumors: patients with ACC, chordoid plexus carcinoma, or embryonal anaplastic subtype rhabdomyosarcoma before the age of 56 years or with multiple tumors; (ii) multiple tumors: proband with multiple malignancies (except two breast cancers), of which at least two belong to the LFS spectrum, before the age of 46 years; (iii) rare tumors: patients with ACC, choroid plexus carcinoma, or embryonal anaplastic subtype rhabdomyosarcoma independent of family history; and (iv) breast cancer before the age of 31 years (8–12).

Recent sequencing projects have shown that LFS plays a significant role in the pathogenesis of childhood cancers. Eighty percent of children with rhabdomyosarcoma with diffuse anaplasia (12), 50% of children with ACC (13), 40% of children with choroid plexus carcinoma (11), 40% of children with low-hypodiploid acute lymphoblastic leukemia (ALL; ref. 14), more than 10% of children with SHH medulloblastoma (15, 16), up to 10% of children with osteosarcoma (17–19), and 1% to 2% of children with relapsed ALL have a germline TP53 mutation, often in the absence of an obvious family history (20). Also, rare TP53 germ-line variants contribute to the development of childhood neuroblastoma (21). We expect that future research projects analyzing the germline DNA sequence of children with cancer will reveal a more complete childhood cancer spectrum of LFS. Multigene panel germline testing of adults with cancer or a positive family cancer history may also expand the phenotypic picture of LFS (22). Of note, TP53 germline mutations lead to specific somatic aberrations and mutation signatures in LFS-related cancers (23). Consequently, detection of such signatures, such as excessive chromothripsis in medulloblastoma, should raise the suspicion of an underlying TP53 germline mutation (24).

Penetrance
Ascertainment bias is likely to lead to an overestimation of tumor risk in individuals with LFS, and future studies will be required to provide more accurate cancer risk estimates. It is important to note that individuals with a germline TP53 mutation display great clinical heterogeneity in terms of cancer type and age of onset (25–27). A recent study described 214 LFS families diagnosed between 1993 and 2013 and included 415 constitutional TP53 mutation carriers (11, 28). 322 (78%) of whom developed at least one malignancy. A significant number of cancers occurred at a young age; namely, 22% were diagnosed with a cancer by age 5 years and 41% by age 18 years (11). Notably, 4% of participants developed a malignancy during the first year of life (11). In children and adolescents with LFS, osteosarcoma was the most common tumor (30%), followed by ACC (27%), brain tumors (25%), and STS (23%; ref. 11). Breast cancer was the most frequently encountered malignancy (7% of women), followed by STS (27%) in adults with LFS. Second neoplasms occurred in 40% of patients, often within the radiation field, which is in agreement with previous observations and with the notion that initial antitumor therapy increases the risk of subsequent cancers (29–34).

Investigators from the NCI (Bethesda, Maryland) recently evaluated 286 TP53 mutation–positive individuals from 107 families (35). The cumulative cancer incidence was 50% by age 31 years among females with a TP53 mutation and 50% by 46 years among males, and nearly 100% by age 70 years for the entire cohort (35). Cancer risk was highest after age 20 years for females, mostly due to breast cancer. Among males, the risk was higher in childhood and later adulthood (35). Among females, the cumulative incidence rates by age 70 years were 54% for breast cancer, 15% for STS, 6% for brain tumors, and 5% for osteosarcoma. Among males, the incidence rates were 22% for STS, 19% for brain tumors, and 11% for osteosarcoma (35). After a median of 10 years, almost 50% of those with one cancer developed at least one other cancer (35). As noted above, these estimates also likely suffer from an ascertainment bias, as most of the TP53 analyses have been performed in affected children with familial history of cancer or multiple primaries. With the exponential increase of TP53 tests being performed in cancer patients, germline TP53 mutations are now more frequently identified in patients and families who have developed only adult cancers (22). Notably, however, a pattern of genetic anticipation is frequently observed in individual LFS families. The underlying genetic mechanisms remain unknown (36).

Brazilian founder mutation
In Brazil, a high prevalence of LFS is present due to a founder effect mutation. A germline TP53 mutation (c.1010G>A; p.R337H) is present in 0.3% of individuals from the South/Southeastern regions, and it is estimated that more than 300,000 Brazilian individuals have LFS. The spectrum of cancers occurring in carriers is similar to the cancer spectrum observed in patients who carry other TP53 mutations and includes STS, early-onset breast cancer, cancers of the CNS, and childhood ACC. However, p.R337H carriers have a higher occurrence of young adult papillary thyroid cancer, renal cancer, and lung adenocarcinoma than carriers of other TP53 mutations (37). Assessment of pedigrees and familial cancer patterns shows significant differences between p.R337H and classic TP53 mutation carriers. The penetrance of cancer before age 30 is estimated to be 15% to 20% compared with 50% in carriers of classic mutations (38). Also, tumor patterns are different from those documented in other TP53 mutation carriers. ACCs represent over 8% of all tumors in p.R337H carriers (compared with 4% for classic mutations). Furthermore, adult tumor onset is later in p.R337H carriers. Breast cancers occur at a mean age of 40 years—later than in classic carriers in whom the mean age of onset is 32 years. Although the familial presentation of cancer risk in p.R337H mutation carriers is within the LFS spectrum, the occurrence of specific traits that are unique to the carriers of the Brazilian founder mutation may suggest it represents a variant form of LFS (39, 40).

Genetic Summary
TP53 function and phenotype–genotype correlation
The TP53 gene encodes a transcription factor that is activated in response to a variety of cellular stress factors and controls the expression of multiple genes that govern cellular processes crucial for tumor suppression (41). More than 250 different TP53 germ-line alterations have been reported, and the types of mutations...
Cancer Screening/Surveillance Protocols

In recent years, with the aim of early tumor detection and reduction of cancer and treatment-related morbidity and mortality, suggestions for clinical surveillance of TP53 missense mutations have been proposed from Australia, the United States [National Comprehensive Cancer Network (NCCN) Guidelines], and Canada (Table 1; refs. 52–56). Over an 11-year period, investigators in Toronto, Salt Lake City, and Los Angeles (subsequently Columbus) prospectively followed and reported on the feasibility and outcomes of screening children and adults using a multimodality protocol that has been coined the “Toronto protocol”. These modifiers include the MDM2 polymorphism rs2279744 (44); TP53 polymorphisms, such as a duplication within intron 3 (PIN3; refs. 45, 46); telomere length (47); differential methylation or variant alleles in miRNAs that modify p53-mediated cell regulation (48–50); and the accumulation of copy number variations (CNV; ref. 51).

Key issues related to psychosocial and other impacts on children undergoing surveillance and parents/family members who may be at risk

There is a paucity of data on the psychosocial impact (to both affected individuals and relatives) of LFS testing and a clear need for future research in this field, performed in conjunction with prospective surveillance programs (61–69). Traditionally, LFS families with a history of multiple malignancies have been felt to carry a significant psychological burden given their exposure to multiple experiences of grief and threats to personal well-being (70). Many families undergoing surveillance believe in the value of this approach to detect tumors at an early stage or grade, performing enhanced sense of control, security, and empowerment (71). However, intense cancer surveillance schedules may be a burden to other families: Not all LFS patients choose to participate in the screening, and some find it too anxiety provoking. As is the case with the management of patients with any cancer predisposition syndrome, screening and surveillance strategies impose physical, psychosocial, and financial challenges to patients and families. With the widespread adoption of next-generation sequencing (NGS) panels, many individuals with TP53 mutations lack classic personal or family history of LFS-related cancers. This may create a different set of psychosocial issues. As described in more detail by Druker and colleagues (72) in this CCR Pediatric Oncology Series, these challenges are best explored and managed in the context of multidisciplinary care teams, including physicians, nurses, psychologists, and genetic counselors, with the added support of family/patient advocates and stakeholder communities.

Summary of surveillance studies recommended by the authors

Who should have surveillance? Data strongly indicate that surveillance leads to early detection of cancer and significantly improves OS (55, 56). Therefore, the expert panel recommends that surveillance should be offered to the following: (i) individuals
### Li-Fraumeni Syndrome Cancer Screening

**Table 1. Published surveillance protocols for individuals with LFS**

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Australia (52, 53)</th>
<th>NCCN (54)</th>
<th>Toronto (55, 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC</td>
<td>AUS q 3-4 m: birth–10 y</td>
<td>No screening described</td>
<td>AUS q 3-4 m: birth–40 y</td>
</tr>
<tr>
<td>Breast cancer</td>
<td><strong>BSE: from 18 y</strong></td>
<td><strong>Breast awareness: from 18 y</strong></td>
<td><strong>BSE monthly: from 18 y</strong></td>
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<tr>
<td></td>
<td><strong>CBE q 6–12 m: from 20–25 y</strong></td>
<td><strong>CBE q 6–12 m: from 20–25 y</strong></td>
<td><strong>CBE q 6 m: from 20–25 y or 5–10 y before earliest case of breast cancer in family</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Breast MRI annually: 20/25–50 y</strong></td>
<td><strong>Breast MRI with contrast annually (or mammogram if unavailable)</strong></td>
<td><strong>Annual mammography and breast MRI: from age 20–75 y or 5–10 y before earliest case of breast cancer in family</strong></td>
</tr>
<tr>
<td></td>
<td><strong>(Consider annual mammography ± US if not possible)</strong></td>
<td><strong>30–75 y: breast MRI with contrast and mammogram annually</strong></td>
<td><strong>Breast MRI alternates with WBMRI</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Discuss risk-reducing bilateral mastectomy</strong></td>
<td><strong>75 y: individual recommendations</strong></td>
<td><strong>Breast US with mammography as indicated by breast density</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Continue screening breast cancer survivors with mammogram and breast MRI</strong></td>
<td><strong>Discuss risk-reducing mastectomy</strong></td>
<td><strong>Consider risk-reducing bilateral mastectomy</strong></td>
</tr>
<tr>
<td>Brain tumor</td>
<td><strong>Brain MRI included in annual WBMRI:</strong></td>
<td><strong>The brain may be examined as part of WBMRI or as a separate exam</strong></td>
<td><strong>Annual brain MRI: from birth</strong></td>
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<tr>
<td></td>
<td>potentially from childhood</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td><strong>Annual neurologic exam</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td><strong>Prompt reporting of new neurologic symptoms</strong></td>
<td></td>
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<tr>
<td>Sarcoma</td>
<td><strong>Annual WBMRI</strong></td>
<td><strong>Annual WBMRI (or equivalent)</strong></td>
<td><strong>Annual rapid WBMRI: from birth</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Annual comprehensive physical exam</strong></td>
<td></td>
<td><strong>AUS q 3–4 m: from 18 y</strong></td>
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<tr>
<td></td>
<td><strong>Awareness of new symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematopoietic</td>
<td><strong>Annual CBC: from 18 y</strong></td>
<td><strong>No screening described</strong></td>
<td><strong>CBC, ESR, LDH q3-4m: from birth</strong></td>
</tr>
<tr>
<td>CRC</td>
<td><strong>Colonoscopy q 2–5 y: from age 25 or 10 y before earliest onset of CRC in family</strong></td>
<td><strong>Consider colonoscopy q 2–5 y: from age 25 or 5 y before earliest known colon cancer in family</strong></td>
<td><strong>Colonoscopy q 2 y: from age 25 or 10 y before earliest onset of CRC in family</strong></td>
</tr>
<tr>
<td>Gastric cancer</td>
<td><strong>Endoscopy q 2–5 y: from age 25 or 10 y before earliest onset gastric cancer in family</strong></td>
<td></td>
<td><strong>No screening described</strong></td>
</tr>
<tr>
<td>Skin cancer</td>
<td><strong>No screening described</strong></td>
<td><strong>Annual dermatologic exam</strong></td>
<td><strong>Annual dermatologic exam: from 18 y</strong></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td><strong>Annual comprehensive physical exam, including neurologic exam</strong></td>
<td><strong>Complete physical exam q 3–4 m, including comprehensive neurologic exam and anthropometric measurements in children</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>Education regarding signs and symptoms of cancer. Apprise pediatricians of childhood cancer risk</strong></td>
<td><strong>Prompt assessment with primary care physician for any medical concerns</strong></td>
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<td></td>
<td></td>
<td><strong>Additional surveillance based on family history of cancer</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>Therapeutic RT should be avoided when possible</strong></td>
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</tbody>
</table>

Abbreviations: AUS, abdominal US (abdomen and pelvis); BSE, breast self-examination; CBC, complete blood count; CBE, clinical breast examination; CRC, colorectal carcinoma; DHEAS, dehydroepiandrosterone; ESR, erythrocyte sedimentation rate; h, hour; LDH, lactate dehydrogenase; m, months; q, every; RT, radiation therapy; y, years.

carrying a pathogenic TP53 variant and (ii) individuals fitting the "classic clinical definition" of LFS, without a pathogenic TP53 variant.

**What tests and how often?** The expert panel emphasizes the central importance of a targeted history and regular physical examination in the context of potential manifestations of LFS (including glucocorticoid and sex steroid excess and neurologic changes). The expert panel recommends the use of the Toronto protocol with modifications (Table 2) for all patients, recognizing that more reliable phenotype–genotype data may lead to genotype-specific modifications of these recommendations in the future (73). Given the high ACC risk in children with LFS, we recommend US of abdomen and pelvis every 3 to 4 months until age 18 years. ACC-specific blood tests every 3 to 4 months (total testosterone, dehydroepiandrosterone sulfate, and androstenedione) are recommended in case of a technically unsatisfactory US only. The authors suggest omission of specific ACC surveillance in adults, given its low incidence in this age group. The lifelong brain tumor risk justifies annual brain MRI. If the initial MRI performed with a gadolinium-based contrast agent (GBCA) shows normal results, the following MRIs may be conducted without GBCA unless an abnormality is seen. This is to minimize the potential for gadolinium accumulation in the basal ganglia in individuals undergoing multiple enhanced MRIs (74–76). Because of the sarcoma risk, we recommend lifelong annual WBMRI, including limbs (head to toe) and abdominal and pelvic US (every 3–4 months in children and annually in adults; every 6 months WBMRI or US). Annual WBMRI may alternate with annual dedicated brain MRI (every year, two MRIs total). However, in infants and children requiring anesthesia, and to minimize the number of health care visits, performing both MRI
in which there was already a case of breast cancer at or around 20, awareness and screening can be considered to begin 5 to 10 years before the earliest age of onset. Because of gastrointestinal cancer risk, we propose upper endoscopy and colonoscopies every 2 to 5 years (starting at age 25 years or 5 years before the earliest age of onset in the family). Given an increased melanoma risk, annual dermatologic examinations are recommended starting at 18 years of age. Blood work for hematopoietic malignancies [namely complete blood count (CBC), erythrocyte sedimentation rate (ESR), and lactate dehydrogenase (LDH)] can be omitted because of the lack of data suggesting that presymptomatic diagnosis of leukemia leads to improved survival [see article by Porter and colleagues in this CCR Pediatric Oncology Series (77)]. However, for patients who received leukemogenic agents for treatment of their first cancer, consideration may be given to ongoing periodic CBCs for detection of evidence for accelerated myelodysplasia as a precursor for leukemic transformation.

**When to start, when to stop?** With the knowledge accumulated so far, cancer risk in children is still difficult to evaluate. As a measure of precaution, while waiting for more definitive data, the expert panel strongly advocates for proposed lifelong screening, starting as soon as a genetic diagnosis (proven TP53 mutation carrier status) or clinical diagnosis (phenotype fits classic LFS definition) has been established. Where feasible, screening should also continue following diagnosis of a primary malignancy and be integrated with clinically indicated cancer-specific follow-up. In families with a known TP53 germline mutation, presymptomatic testing may be offered soon after birth to begin screening within the first months of life.

**Should surveillance change over time?** The cancer spectrum is, at least in part, age dependent. As per the modified Toronto protocol (Table 2), screening modalities change depending on the sex and age of the patient (e.g., high ACC risk in very young children or high breast cancer risk in young women age 20–40 years).

**Should surveillance be adjusted on the basis of the gene mutation (genotype) and its perceived spectrum of disease (phenotype)?** Phenotype-genotype correlations may become increasingly important for risk-adapted surveillance for LFS patients. The panel is aware that there is evidence for a genotype-phenotype correlation with dominant-negative missense mutations affecting the DNA-binding domain leading to a more aggressive, early-onset phenotype, and other types of mutations being associated with a less penetrant later onset disease (73). However, the group consensus is that it is currently premature to make adjustments to the surveillance protocol based on genotype because of the lack of precise predictions for individual patients. More data from functional assays to measure the consequence of a given mutation, the presence and role of genetic modifiers, as well as clinical (registry) data will be necessary to incorporate new genotype-phenotype data as they are reported and validated. The expert panel recommends that these surveillance recommendations be reevaluated regularly as this new information becomes available, as they might be stratified in the future according to the type of mutation, family history, and other modifiers.

**Conclusions**

LFS is associated with a high lifelong cancer risk. It has been shown that TP53 mutation carriers enrolled in a surveillance
program have an improved survival. Therefore, our international panel recommends that all individuals with LFS (as defined by the identification of a pathologic TP53 germline mutation and/or by meeting the classic clinical LFS criteria) be offered surveillance as soon as the diagnosis of LFS is established. The expert panel recommends the use of the Toronto protocol with modifications, as outlined in Table 2, while being aware of the notion that not all patients will have access to medical systems offering this type of surveillance. Although the suggested surveillance strategy focuses on early cancer detection, future research studies will need to further address psychosocial impacts of such surveillance on LFS patients and possibly the development of newer molecularly based technologies for even earlier detection of the diverse malignancies. Additional data will be needed to validate and refine the surveillance strategies that comprise the Toronto protocol. In addition to simple measures, such as sun protection and avoidance of tobacco products, cancer prevention strategies will need to be explored in this high-risk condition. Notably, individuals with a germline TP53 mutation who smoke cigarettes have been shown to be at significantly higher risk of developing lung cancer than individuals with a germline TP53 pathogenic variant who do not smoke (78). There are no data indicating that the cancer risk is increased through global flying; however, medical radiation exposure should be limited to those investigations that are required for important treatment decisions. Finally, future research may allow us to design genotype-adopted surveillance strategies, because cancer risk may be influenced by mutation type and genetic modifiers. However, it is too early to make precise predictions. Because of the rarity of LFS, we recommend that surveillance should be led by physicians with experience in cancer predisposition. This is also true for the radiologists interpreting the imaging studies. Shared care strategies may also be feasible. To ensure a continuous learning curve, we highly encourage the enrollment of LFS patients in national or international cancer predisposition registries that collect medical and biochemical information, electronic images, and biospecimens (blood and tissue).

Disclosure of Potential Conflicts of Interest
J.E. Garber reports receiving other commercial research support from Novartis and is a consultant/advisory board member for Gtx, Helix, and Novartis. W.K. Kohlmann reports receiving other commercial research support from Myriad. C.G. Mullighan reports receiving commercial research grants from Loxo Oncology and speaks on behalf honoraria from Amgen. No potential conflicts of interest were disclosed by the other authors.

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