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Li-Fraumeni syndrome: report of a clinical research workshop and creation of a research consortium

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Abstract

Li-Fraumeni syndrome (LFS) is a rare dominantly inherited cancer predisposition syndrome that was first described in 1969. In most families, it is caused by germline mutations in the *TP53* gene and is characterized by early onset of multiple specific cancers and very high lifetime cumulative cancer risk. Despite significant progress in understanding the molecular biology of *TP53*, the optimal clinical management of this syndrome is poorly defined. We convened a workshop on November 2, 2010, at the National Institutes of Health in Bethesda, Maryland, bringing together clinicians and scientists, as well as individuals from families with LFS, to review the state of the science, address clinical management issues, stimulate collaborative research, and engage the LFS family community. This workshop also led to the creation of the Li-Fraumeni Exploration (LiFE) Research Consortium.

Keywords

Li-Fraumeni syndrome; hereditary cancer predisposition syndrome; *TP53* mutations

Li-Fraumeni syndrome (LFS, OMIM#151623) is a dominantly inherited cancer predisposition syndrome associated with a wide variety of childhood- and adult-onset cancers, most notably soft-tissue and bone sarcomas, breast cancer, adrenal cortical carcinoma (ACC), brain tumors, and leukemia (1). Germline mutations in the tumor suppressor gene *TP53* were identified in 1990 as the cause in most families with classic LFS (2,3). The absence of detectable germline *TP53* mutations in some LFS families suggests that other genes might be involved in this syndrome; however, additional other loci in LFS have not been identified. Despite advances in our understanding of the molecular biology of *TP53* and the clinical manifestations of LFS, numerous important questions, such as optimal cancer risk management strategies and genetic testing guidelines for asymptomatic at-risk children in families with LFS, remain unanswered.

In revisiting the existing data on the evaluation and management of this syndrome, we identified several areas that could be addressed through multi-center collaborations. Toward this end, a workshop was held on November 2, 2010, at the National Institutes of Health (NIH) in Bethesda, Maryland, which brought clinicians, scientists, and LFS families together to form an international LFS research consortium as well as a family-based support/advocacy group. This report summarizes the topics presented at the workshop and announces the formation of the LiFE (Li-Fraumeni Exploration) consortium.

A brief history and overview of LFS

LFS was first described in 1969 by Drs. Frederick Li and Joseph F. Fraumeni Jr. in a report of families with a variety of early-onset cancers, including childhood sarcomas and breast cancer in young adults (4). LFS is inherited in an autosomal dominant fashion, with a tendency for multiple primary cancers in affected individuals (5,6). Although bone and soft tissue sarcomas, breast cancer, ACC, brain tumors, and leukemia remain the hallmarks of LFS, subsequent studies showed that the cancer spectrum was more diverse, including

cancers of the lung, colorectum, stomach, prostate, ovary, pancreas, as well as lymphoma, melanoma, and choroid plexus carcinomas (7,8). The diagnostic criteria for the syndrome gradually evolved to include not only classic LFS (Table 1) (9,10) but also Li-Fraumeni-like syndrome (LFL), which shares some features of LFS but does not meet the strict LFS diagnostic criteria (11,12).

Germline mutations in the *TP53* tumor suppressor gene were discovered as the primary cause of LFS in 1990 (2) and are found in approximately 70% of LFS (13,14) and 40% of LFL families (11). To provide guidelines for consideration of *TP53* genetic testing, the Chompret criteria were proposed in 2001 and revised in 2008 and 2009 (Table 1) (15-17). The prevalence of *TP53* mutations in individuals meeting the revised Chompret criteria is approximately 30% (17). The prevalence of germline *TP53* mutations has been estimated for some selected populations, specifically Southeastern Brazil and the United Kingdom (see Clinical aspects of LFS—a global view).

The workshop's keynote address included an overview of data from the M.D. Anderson Cancer Center's long-term clinical studies of LFS. In a study focused on sarcomas, germline *TP53* mutations were present in approximately 10% of families with either an osteosarcoma diagnosed before age 20 or a soft-tissue sarcoma diagnosed before age 16 (5). Cancer penetrance in individuals carrying a *TP53* mutation was less than 20% in children, but was nearly 100% by age 70, with females having an earlier age at cancer onset, mostly due to breast cancer (18). The risk for developing soft-tissue sarcomas was greatest before the age of 10. Brain cancer appeared to occur early in childhood as well, with a smaller peak in risk later in the fourth to fifth decade of life. Risk for osteosarcoma, on the other hand, was highest during adolescence. Breast cancer risk among females with LFS started to increase significantly around age 20 and continued into older adulthood. Other cancers commonly observed included lung cancer, hematopoietic cancer such as leukemia and lymphoma, and gastrointestinal (colon, gastric, pancreatic) cancer. Compared with mutation-negative relatives as well as the general population, individuals with LFS who have had a cancer are at an increased risk of developing a second cancer. In addition, risk for a subsequent cancer increases with younger age at diagnosis of the first cancer and radiation therapy. A second cancer usually occurred approximately 6–12 years after the first cancer (7).

Clinical aspects of LFS—a global view

Recent studies in families from Southeastern Brazil who fulfilled LFS/LFL clinical criteria have identified a founder germline *TP53* mutation that exhibits unusually high population prevalence (~0.3%) (19-22). This mutation, R337H (c.1010G>A, p.Arg337His), is in the oligomerization domain of the gene and was initially recognized to be the underlying cause of the high incidence of childhood ACC in Southern Brazil (23); however, carriers of this mutation appear to have a lifetime cumulative risk of ~50–60% for a wide spectrum of cancer (22). Additionally, thyroid cancer and renal cancer, which are not common in LFS, occur at a higher frequency among the Brazilian families with this mutation. The high prevalence of the R337H mutation and the broad array of cancers pose a difficult public health challenge in this area of Brazil (19).

In France, of the more than 1,000 families referred for evaluation who had genetic testing since 1996, 148 families were found to harbor a *TP53* mutation, most of which were point mutations. Similar to the phenotype described in the International Agency for Research on Cancer (IARC) database (see The *TP53* mutation database), missense mutations were associated with an earlier age at onset compared with other mutations. The spectrum and frequencies of tumors seen in LFS families were also similar to those reported elsewhere.

In the United Kingdom, the *TP53* mutation detection rates among families meeting the classic LFS and LFL criteria were reported as 83% and 25–40%, respectively. Approximately 5–10% of childhood sarcoma patients and 80% of ACC patients have a germline *TP53* mutation, with most of the mutations identified in ACC cases being at codons 152 or 158. Mutations at these two positions are reportedly associated with a lower penetrance compared with other mutations (24). Among women who were diagnosed with breast cancer before age 31, the prevalence of germline *TP53* mutation was 6%. Based on this and other evidence, the estimated prevalence of a deleterious germline *TP53* mutation in the United Kingdom was 1/10,000 to 1/25,000 live births (25). For female mutation carriers, lifetime breast cancer risk was ~70%, with a sharp increase starting in the mid-20s and approximately 25% of cases diagnosed before age 30. The risk of subsequent contralateral breast cancer was ~2% annually after the initial diagnosis.

Cancer screening in LFS

No international consensus on the appropriate clinical surveillance strategies in individuals with LFS has been established. Furthermore, the potential clinical benefits, psychosocial, societal and economic impact of a comprehensive clinical surveillance protocol utilizing frequent biochemical and imaging studies on early cancer detection and overall survival in asymptomatic *TP53* mutation carriers remains unknown.

In the United Kingdom, no standard recommendation exists for LFS cancer screening. In France, the screening recommendations include an annual physical examination, annual breast MRI starting at age 20, avoidance of radiation therapy if at all possible, and a discussion of prenatal/preimplantation genetic diagnosis. In the United States, the National Comprehensive Cancer Network (NCCN) has published a consensus-based set of screening guidelines (Table 2), but uncertainty remains in several major areas. For example, mammography employs ionizing radiation, and its sensitivity as a cancer screening test in young women is limited. MRI plus mammography is reportedly effective among women with an increased risk of developing breast cancer; however, its impact on overall survival is not known. Breast cancer screening with MRI for *TP53* mutation carriers is now included in the American Cancer Society's surveillance recommendations (26). Since the risk of gastrointestinal cancers is increased in LFS and may cluster in some families, NCCN guidelines recommend consideration of colorectal cancer screening with colonoscopy starting before the age of 25.

Pilot studies aimed at systematic cancer screening for individuals with LFS may provide useful guidance for future studies. In the United States, a PET/CT scanning screening study of 15 individuals with LFS identified two thyroid cancers and one gastric cancer in three individuals; false-positive test results occurred in five individuals (27). In Brazil, a PET/CT screening program involving 30 asymptomatic *TP53* mutation carriers identified six abnormal results, of which three had cancer: one lung adenocarcinoma, one papillary ovarian cancer, and one breast cancer with bone metastases (unpublished data). Given the possible risk of radiation-induced second cancers and the finding of an anomalous concentration of 18F-FDG in benign lesions, PET/CT screening should be considered cautiously as a surveillance modality for *TP53* mutation carriers.

A clinical surveillance protocol for *TP53* mutation carriers was implemented at the Hospital for Sick Children in Toronto in 2004. The study included 33 *TP53* mutation carriers from eight families; 15 opted for the surveillance group and 18 elected not to have surveillance. Ten tumors were detected in 7 of 15 screened mutation carriers. All 15 were alive after a mean follow-up time of 47 months compared with 2 of 10 (20%) mutation carriers in whom 12 malignant tumors occurred who did not undergo surveillance ($P = 5.29 \times 10^{-4}$). Among

those diagnosed with a cancer, survival was better in the surveillance group than the non-surveillance group (100% vs. 21.4%, $P = 0.001$) (28). This protocol combines an array of biochemical and hematological blood tests, rapid total body MRI, brain MRI, and abdominal/pelvic ultrasound in all patients, as well as breast MRI and colonoscopy in adults (<http://www.sickkids.ca/pdfs/Cancer-Genetics-Program/35386-TP53TorontoProtocol.pdf>). The results of this study demonstrated that a clinical surveillance protocol for detecting asymptomatic cancers in germline *TP53* mutation carriers is feasible, and lends support for genetic testing and cancer surveillance of patients suspected to have LFS (*Note*: These results represent the final data from this study and are slightly different from the data that were presented at the workshop. The differences do not substantially change the conclusions of the study).

The workshop discussed other screening regimens under evaluation. In France, the Lifscreen Project is being implemented to assess the effectiveness of a screening strategy, including annual whole body MRI, physical examination, brain MRI, abdominal ultrasound, and breast MRI and ultrasound in women age 20 and older (<http://clinicaltrials.gov/ct2/show/NCT01464086>).

Despite the encouraging results to date, the wide cancer spectrum in LFS provides challenges for a comprehensive screening regimen. In addition, concerns exist regarding the potential increased cancer risk associated with radiation exposure, the absence of data regarding the psychological impact of starting early and frequent screening, the issues associated with false-positive screens, and the large number of participants and centers that will be required for a study to adequately evaluate the efficacy of a screening regimen.

TP53 in LFS

The *TP53* gene was localized to chromosome 17p13.1 in 1986 and subsequently identified as the primary cause of LFS. Most deleterious germline mutations occur in the DNA binding domains, and somatic *TP53* mutations are frequently seen in various cancer types. The p53 protein plays a critical role in a variety of cellular processes, including growth arrest, apoptosis or enhanced DNA repair in response to DNA damage and to multiple forms of cellular stress, and regulation of embryo implantation and fertility. Furthermore, the link between p53, mitochondrial respiration, and cell cycle regulation is being evaluated (29-31) because it might provide insights into the mechanisms through which *TP53* mutations may contribute to tumorigenesis.

The complexities of the p53 pathway and relative rarity of LFS have made the search for modifiers of cancer types and age of onset in patients with germline *TP53* mutations challenging. Single nucleotide polymorphisms (SNPs) in both *TP53* and *MDM2*, an integral component of p53 function, appear to influence the age of cancer onset in LFS (6,32). Short telomeres have also been associated with younger age at first cancer diagnosis in individuals with LFS (33,34). The level of genetic instability, as measured by genomic copy number variations (CNV), is higher in individuals with germline *TP53* mutations than in healthy controls and is further elevated in mutation carriers with a history of cancer (35).

Currently, no tools are available to predict for an individual with LFS whether or which cancer(s) will occur and at what age(s). Thus, by combining information derived from the specific *TP53* mutation (genotype–phenotype correlation), a selected set of genetic markers (e.g., the *MDM2* SNP 309; the *TP53* PIN3 duplication), and measures of genetic instability (e.g., telomere length, CNV frequency), it might be possible to stratify individuals with LFS into low-, intermediate-, and high-risk groups, with screening recommendations based on risk level (36).

The *TP53* mutation database

The *TP53* Mutation Database is maintained by the IARC and is updated annually. The database consists of both germline and somatic *TP53* mutations reported in the literature since 1989. It also contains information on the predicted effects on protein structure and function, and the number and type of cancers reported in families. At the time of this workshop, there were 535 germline mutations recorded from 532 families from North America, Europe, Japan, Brazil, and other countries (37). These data provide important information on mutation prevalence and cumulative cancer risks. For instance, the prevalence of *TP53* mutations in women with breast cancer diagnosed before age 30 and no family history of cancer was 3–4%, (16,38), and the cumulative risk for all cancers is approximately 50% by age 30, with no apparent geographical differences (except for Brazil, see Clinical aspects of LFS—a global view). LFS has a bi-phasic distribution in age at first cancer diagnosis, with peaks in the first two years of life and the fourth decade, and with evidence of genetic anticipation, manifested by earlier age at first cancer diagnosis in successive generations.

The data collected and maintained by the IARC should continue to serve as an important resource in efforts to clarify the clinical characteristics of LFS and the underlying carcinogenic mechanisms. Detailed information is available at <http://www-p53.iarc.fr/germline.html>.

Genetic counseling and psychosocial aspects of LFS

During the workshop, the speakers emphasized the importance of a detailed and accurate pedigree, which includes personal cancer history and family history over at least three generations. Counseling about LFS is a lifelong process that goes far beyond issues encountered in the initial counseling session and takes into account the informational and emotional needs of children and teenagers. The counseling process should include a discussion of cancer risk, the uncertainties in estimating risk, the role of reasons for seeking testing, and, if the individual is found to be mutation positive, facilitation of medical and psychological care referral. This process can be challenging to individuals in the setting of unresolved grief related to loss of family members and hesitancy to re-open psychological wounds. The discussion should include not only the medical benefits and limitations of testing, but also the potential for genetic discrimination in insurance and employment, financial concerns, and how to share the information with relatives and other people.

Overall, the uptake of genetic testing among members of families with a known *TP53* mutation is approximately 50% (39). The decision regarding whether to have *TP53* mutation testing and to receive the results can raise complex issues of identity, family interaction, guilt, and uncertainty. Very few studies to date have addressed these issues for LFS families, but in other hereditary syndromes, a consistent minority of participants have reported high levels of cancer-related anxiety and depression (40). In a recent study from the Netherlands, 23% of 70 participants from LFS families reported clinically relevant levels of distress, which was associated mainly with an absence of social support instead of mutation carrier status (41). Since a substantial proportion of individuals undergoing testing may suffer distress, psychological monitoring is important, with special attention paid to ensure an adequate perceived and actual social support mechanism.

A major issue in LFS surrounds the question of genetic testing of children, particularly when the child has not been diagnosed with a cancer. The uncertainties include when testing should be done, whether the child should be informed of the results, how to talk to children about inherited predisposition to cancer, and what surveillance should be implemented. The medical and psychological benefits and risks of learning a child's test result need to be

carefully considered. Moreover, balancing the role of parental authority and adolescent autonomy in this situation is especially challenging. The predisposition to childhood cancer associated with *TP53* mutations suggests that medical benefits may be derived by learning the mutation status of children in LFS families, in contrast to the common guidance against testing children in adult-onset hereditary cancer syndromes. Nonetheless, once the parents decide to test a child, the option is no longer available to that child to later choose to not ever be tested, the timing of testing, or not to have others know the test result. Furthermore, as the test result may impact not only the child but also a parent's sense of guilt or depression, attention must be given to the reasons for or against testing and the availability of follow-up for both psychological and medical considerations following disclosure of test results.

Further research is needed on the psychological, social, and ethical issues in approaches to ascertainment of potential LFS cases, to the nature and timing of genetic counseling and testing of young children in LFS families, and to issues related to re-contact at adulthood for children whose parents consented to inclusion of their DNA in LFS biobanks.

Family support and advocacy

In an effort to bolster peer support, individuals with LFS and their family members were invited to participate in an informal gathering the previous evening as well as to attend the workshop to share their experiences related to LFS and their goals in attending the conference.

Two individuals with LFS and a member of an LFS family gave moving accounts of their experiences with this disorder (Box 1). In addition, a separate session was held in which members of various support and advocacy groups, including the online Li-Fraumeni support group MDJunction.com, the Angioma Alliance, the Genetic Alliance, the Fanconi Anemia Research Fund, Inc., and Special Love, Inc., shared their perspectives and advice in forming disease-focused support and advocacy groups.

The families identified several clinical research priorities: 1) the need for standard screening recommendations; 2) information and recommendations on use of various therapeutic and preventive treatments including hormone and complementary or alternative medicine; 3) a directory of specialty medical practices focused on LFS; 4) how to improve communication with medical professionals about LFS; 5) how to communicate with children about LFS and help them cope with a cancer diagnosis or loss of family members; and 6) ready access to new, LFS-related treatment information, for instance, in the form of periodic newsletters. A newly established advocacy group was created to, among other tasks, facilitate effective communications between LFS families and the clinical and scientific members of the research consortium.

Creation of the LiFE Research Consortium

In an effort to begin addressing the questions related to the complex clinical and basic science issues related to LFS, an international, multi-institution collaboration is needed. A consensus was reached on the key features of the research consortium.

A cooperative biospecimen collection effort

Collecting normal and tumor tissues is a key component of establishing any disease or syndrome-oriented research consortium. Biobanking (i.e., the collection, processing, storage, and disbursement of biological specimens) and a biospecimen's life cycle as detailed by the National Cancer Institute (NCI) Biospecimen Research Network, including a pre-acquisition

phase (patient, medical/surgical procedures, and sample acquisition) and a post-acquisition phase (acquisition, handling/processing, storage, distribution, scientific analysis, and restocking unused sample), were reviewed.

The participants discussed prototypes of a biobank, such as the Tissue Resource and Applications Core (TRAC), which was established as a shared facility for the Huntsman Cancer Institute (HCI) at the University of Utah. The TRAC serves as a biobank for local and national studies to collect, process, and store high-quality biospecimens for use in cancer research. An Oversight Committee meets regularly and is responsible for procurement and usage guidelines as well as working closely with multidisciplinary disease groups at HCI.

The LFS Consortium developed plans to collect and analyze an unprecedented number of specimens from affected families, including both normal and tumor tissue, DNA, RNA, serum, and plasma. This effort will require a commitment to the sharing of data and specimen resources, data management and harmonization, respect for different healthcare, ethical, and legislative guidelines at each center for data and biospecimen sharing, and the need for local and universal informed consent plans/institutional review boards. Other large international consortia have already addressed these challenges and may serve as a model in building a cooperative LFS biobank network.

Development of an LFS Registry

Several countries have developed initiatives to coordinate LFS registration (e.g., France). In North America, one such effort was a proposal through the Children's Oncology Group (COG). The COG's pediatric cancer registry, Childhood Cancer Research Network (CCRN), was implemented nationwide in July 2008. The CCRN registry enrolled individuals with a childhood cancer, regardless of family history or prior genetic evaluation, who consented (or whose parents consented) to be re-contacted for participation in non-therapeutic studies. We discussed the potential for creating an LFS registry from the CCRN by identifying participants in the CCRN with one of the cancers characteristically associated with LFS. At the time of the workshop, a funding application had been submitted to support the LFS registry within the COG.

Surveillance and risk-reduction strategies

Given the high risk of multiple cancers and the understanding of and concerns about different screening methods, further studies are needed to test screening protocols in a variety of countries and contexts, which would be aimed at establishing effective screening regimens that take into account the wide diversity of disease phenotypes in *TP53* mutation carriers. The consortium also will consider pilot studies that explore the potential of chemopreventive agents in reducing the risk of various cancers associated with LFS. Studies of possible environmental risk modifiers may contribute to the development of prevention strategies. Also discussed was the need to identify novel risk-reducing interventions aimed at restoring *TP53* function, compensating for loss of function, or selectively targeting tumor cells that have lost *TP53* expression or function.

At the end of the workshop, the formation of the Li-Fraumeni Exploration (LiFE) consortium was announced. All members present agreed on a resolution to promote the understanding of the syndrome and the improvement of the lives of individuals with LFS (Box 2).

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Box 1**Perspectives from Li-Fraumeni Syndrome Families****Family 1: The story of a family**

I was born in Switzerland and came to the United States at age 19 to play soccer. I was diagnosed with severe aplastic anemia at age 22 for which I had a bone marrow transplant, and have been healthy ever since. After the bone marrow transplant, my wife and I decided to start a family and we were blessed with a baby girl; two years later we welcomed a baby boy.

We were the perfect family and had a very good life until our son was diagnosed at 10 months old with a choroid plexus carcinoma. Subsequently, we were recommended to have genetic testing for LFS and I was found to be a *TP53* mutation carrier, as was our daughter. Our son went through multiple relapses and endured a total of 6 surgeries, 15 different chemotherapy agents, 62 radiation treatments, and multiple clinical trials. He passed away from his relentless brain tumor at age 3.

At age 4 our daughter started baseline screening. She also was found to have a very small choroid plexus carcinoma and a low-grade glioma. Since her initial diagnosis she has done very well, with no recurrence of the choroid plexus carcinoma. However, this past June, after a routine abdominal ultrasound, she was found to have an adrenal cortical carcinoma, which was resected, and she has remained in complete remission.

It is a little surprising to learn today that this syndrome was recognized in 1969, and that it took 41 years to organize this workshop. Meeting and speaking with others here made it clear that this syndrome affects all of us—doctors, scientists, and families—in some way. As I am here today as a father and a husband, I am speaking for all of the families that there is simply not enough going on. We can't be satisfied with screening; we have to find a cure for this genetic disorder. We, the patients and the families, are willing to do more. And while we understand the politics, the financial constraints, and all the other issues involved, it is not good enough and not acceptable where we are today. So we entrust our futures and our families into your hands and ask that you find a way to move forward toward finding a cure for this disorder.

Family 2: Living with LFS

Cancer is not only something I have survived. Rather, it has been a constant presence in my life, since long before my diagnosis with breast cancer exactly 14 years ago.

I have never known a life without that monster called cancer by my side. For other kids there's the fear of imaginary ghosts and goblins hiding under the bed or in a closet, which keeps them lying awake at night with the covers wrapped tightly under their chins, or which makes them come running into their parents' bedroom for protection against the dark. As a child, what kept me lying awake at night, sometimes crying myself to sleep, were the memories of the aftermath this cancer monster left behind when it claimed the lives of my 9-year-old sister and 35-year-old mother, within a 3-year span, and the very real fear of it lurking somewhere in the distance, ready to strike again at any moment.

What I didn't know as a young girl and would not discover until I was 25 years old and pregnant with my first child, was that the repeated occurrences of cancer in my family were not a coincidence. With the science available in 1998, I finally learned that each diagnosis, the 3 before mine and the 2 since then, were, in fact, linked to that which prompted today's gathering of 180 people from different parts of the globe, for the first-ever conference of its kind. This extended family assembled for 2 days to share their

stories, their research, their goals, their questions, their fears and their triumphs related to their work in or plight with LFS.

The reality for those of us living with LFS is that we know the monster that plagued me as a young girl is never far away. Although it is not always actively engaged in battle against us, it continues to be a constant presence in our lives. So, while we learn to cope and approach our situation with a sense of cautious optimism and hope, we can never let our guards down, because the moment we do, we make ourselves vulnerable to the monster's strength and ambition.

While I do my part by being proactive and vigilant in the education and quarterly screening of myself and my children, I know there are doctors and scientists everywhere, who continue in their unflinching endeavour to uncover more effective treatments, better ways to detect cancer earlier and to predict disease onset and its aggressiveness when a cancer occurs, and a cure.

I am certain that through this work and with the support of the LFS families, our deepest desire and wish for the future will be realized, and that the legacy of loss and decimation of families at the hand of the monster we know as cancer will one day end.

Family 3: Perspective from a husband and father

When I was first asked to speak at this meeting, I was a little dumbfounded. After all, I don't have LFS; neither do my parents nor my siblings. My children have it.

I was introduced to my wife many years ago, and we got married shortly afterward. After seven years of marriage, she was diagnosed with breast cancer and underwent treatment with mastectomy and chemotherapy. Later, the cancer was found to have metastasized. That meant there was probably not a lot of time left. We had three small children at the time. How would I help them understand? How would I comfort her? How would I comfort them?

A little while after my wife passed away, several young individuals in her family were diagnosed with various types of cancers. A trip to the Huntsman Institute led to the discovery of LFS in the family. My wife was obviously a carrier.

We did not know a lot about LFS then, and made a decision to hold off on testing for a while. When my oldest son was ready to get married and have a family of his own, we as a family decided to have testing. All three of my children tested positive. My two grandchildren were also positive. My children started screening, and my son was diagnosed with a brain tumor, which was treated with surgery. The treatment left him paralyzed on the left side. He had to learn to walk again, and is making progress. We deal with that, and we deal with other things in life. Our moments together are precious, as we don't know how long they are. The choices we make regarding our health, we don't know if they matter. We take each day and we take each thing that comes in our lives. And we make decisions by our heart, based on what we know now. What we know tomorrow should be greater than what we know today, and what we choose to do with that is up to each of us. Each individual with LFS is different. I have three children with LFS and they have all dealt with it differently. For individuals with LFS, it is your right to make your own choices and decisions. So make them with what you know and with your heart, and do not look back.

Box 2**The LiFE Resolution**

We, the clinicians, researchers, psychologists, genetic counselors, and members of the Li-Fraumeni Syndrome (LFS) research community hereby unite our resources and efforts into an international consortium to understand and combat this disorder and to support the individuals and families it affects. Our goal is to eliminate suffering, morbidity and mortality related to this condition. The Li-Fraumeni Syndrome is a hereditary cancer predisposition disorder which greatly increases the risks of multiple different cancers that may affect persons of all ages, from children to the elderly. Its only known genetic cause is mutation in the tumor suppressor gene *TP53*. Long considered to be a rare syndrome, LFS now appears to be much more common than previously recognized. Despite significant progress in understanding the characteristics of the disease and its molecular mechanisms, a comprehensive cure is still far beyond our grasp. Nonetheless, new methods are emerging to better identify, counsel, test, screen, follow-up and treat individuals with LFS.

Recognizing the complexity of this disorder, we acknowledge that no single research institution or organization has the ability to effectively work on and deliver comprehensive, global and affordable solutions to the problems faced by LFS families or to fully exploit the potential benefits of LFS research to enhance our understanding of the mechanisms of sporadic cancers. Consequently, we hereby commit to pooling our ideas, resources, and energy as the most effective means of addressing these issues together. We have therefore created the LiFE (Li-Fraumeni Exploration) Consortium, which will provide a shared research infrastructure and organizational umbrella to facilitate implementation of a coordinated research strategy. Its name reflects our hope and belief that the cancers associated with LFS are, in many cases, manageable, increasingly curable, and, ultimately, preventable. LiFE will work to understand the mechanisms of this disorder, predict individual cancer risk, detect cancers at their earliest and therefore most treatable stage, develop new therapeutic strategies, and support affected patients and their families. In the upcoming months, LiFE will develop its organizational structure and research agenda. It will operate in partnership with LFS advocacy groups, large international organizations and funding agencies to deliver our promise of improving the LiFE of LFS families on a global scale.

Table 1

Diagnostic criteria for Li-Fraumeni syndrome and Li-Fraumeni-like syndrome, and criteria for *TP53* genetic testing

	Criteria	Reference
Classic Li-Fraumeni syndrome (LFS)	<ul style="list-style-type: none"> • A proband with <ul style="list-style-type: none"> – A sarcoma diagnosed before age 45 years <i>and</i> – A first-degree relative with any cancer before age 45 years <i>and</i> – A first- or second-degree relative with any cancer before age 45 years or a sarcoma at any age 	(9)
Li-Fraumeni- like syndrome	Birch definition: <ul style="list-style-type: none"> • A proband with any childhood cancer or sarcoma, brain tumor, or adrenocortical carcinoma diagnosed before age 45 years <i>and</i> • A first- or second-degree relative with a typical LFS cancer (sarcoma, breast cancer, brain tumor, adrenocortical carcinoma, or leukemia) at any age <i>and</i> • A first- or second-degree relative with any cancer before age 60 years 	(11)
	Eeles definition: <ul style="list-style-type: none"> • Two first- or second-degree relatives with LFS-related malignancies at any age 	(12)
Chompret criteria	<ul style="list-style-type: none"> • A proband who has <ul style="list-style-type: none"> – A tumor belonging to the LFS tumor spectrum (soft tissue sarcoma, osteosarcoma, pre-menopausal breast cancer, brain tumor, adrenocortical carcinoma, leukemia, or bronchoalveolar lung cancer) before age 46 years <i>and</i> – 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 	(15)
	<i>or</i>	
	<ul style="list-style-type: none"> • 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 	(16)
<i>or</i>		
	<ul style="list-style-type: none"> • A proband who is diagnosed with adrenocortical carcinoma or choroid plexus tumor, irrespective of family history 	(17)

Table 2

National Comprehensive Cancer Network: Li-Fraumeni syndrome screening recommendations

Cancer	Recommendations
Breast cancer	<ul style="list-style-type: none">• Breast self-exam (BSE) training and regular monthly BSE starting at age 18y• Clinical breast exam, semi-annually, starting at age 20–25y, or 5–10 years before the earliest known breast cancer in the family (whichever comes first)• Annual mammogram and/or breast MRI screening starting at age 20–25y, or individualized based on earliest age of onset in family• Discuss option of risk-reducing mastectomy on case-by-case basis and counsel regarding degree of protection, degree of cancer risk, and reconstruction options
Other cancers	<ul style="list-style-type: none">• Annual physical exams with a careful skin and neurological assessment• Colonoscopy every 2–5 years• Additional organ-targeted surveillance based on family history