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TP53 Testing and Li-Fraumeni Syndrome: Current Status of Clinical Applications and Future Directions

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Abstract

Prevalent as an acquired abnormality in cancer, the role of *TP53* as a germline mutation continues to evolve. The clinical impact of a germline *TP53* mutation is often dramatic and affects the full life course, with a propensity to develop rare tumors in childhood and multiple common cancers of unexpectedly early onset in adulthood. We review the clinical relevance of germline mutations in the *TP53* tumor suppressor gene in current healthcare practices, including the optimal ways to identify patients with Li-Fraumeni syndrome (LFS), to recognize the core-cancers associated with LFS and to develop strategies for early detection of LFS-associated tumors. Several *TP53*-targeted approaches to improve outcomes in LFS patients are also reviewed. A case report was used to highlight special *TP53* testing dilemmas and unique challenges associated with genetic testing decisions in our current age of rapidly advancing genomic technologies.

Keywords

TP53; Li-Fraumeni syndrome; genetic testing; cancer risk; genetic counseling

1. Introduction

Li-Fraumeni syndrome (LFS; OMIM 151623) is an autosomal dominant cancer syndrome caused by heterozygous germline mutations in the *TP53* gene. Half of patients with LFS develop at least one LFS-associated cancer by age 30.[1-4] This is in comparison to the 1% chance of developing cancer by age 30 in the general population.[5] Almost one third (15-35%) of cancer survivors with LFS will develop multiple primary cancers over their lifetimes.[6-9] LFS predisposes to radiation-induced malignancies as well.[10-12] Understanding the critical role of *TP53* as the guardian of the genome has long suggested the potential for targeted cancer treatment.

In this review, we will discuss the clinical relevance of *TP53* mutations to modern day healthcare practices. We will review the literature on the clinical picture of LFS, genetic testing criteria, issues related to genetic testing for LFS, and management recommendations.

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We will also review emerging methods for early disease detection and promising *TP53*-targeted approaches to maximize outcomes.

2. Historical Milestones

As we rise to the challenge of merging the explosive number of key findings in the field of cancer biology, it is appropriate to review the medical impact of a gene that has revolutionized the field of cancer biology--*TP53.*

TP53 was first discovered in 1979[13-15] during a period of time when the viral theory of cancer development was held in highest esteem. The viral theory suggested that viruses (such as the Simian virus 40, human papilloma virus, and Epstein Barr virus) were the principal drivers of oncogenesis. The identification and characterization of *TP53* changed this theoretical paradigm, leading us into the current age of genomics and advancing our understanding of the role that oncogenes and tumor suppressor genes play in malignant transformation.[16-19]

Because of *TP53's* key role as the "guardian of the genome,"[20] more than half of all human cancers acquire mechanisms to impede *TP53* function. *TP53* is the most frequently mutated gene in human cancer[19] with the prevalence of acquired *TP53* mutations highest in epithelial ovarian cancers (47%), colorectal (43%), head/neck (42%), and esophageal cancers (41%) (International Agency for Research on Cancer (IARC) database, R15 release).[21] Cancers with acquired *TP53* mutations are also associated with diminished survival rates, increased resistance to chemotherapy and radiation, and elevated relapse rates.[22-24]

TP53 was first detected in simian virus 40-transformed cells[14, 25] with high levels of detectable p53 protein also seen in cells transformed by other biological or physical agents[26, 27] in tumor cell lines[28] and in human cancers (especially leukemia and sarcoma).[29-33]

In 1989, Lavigueur and colleagues accelerated *TP53* research when they reported that 20% of transgenic mice carrying a germline mutant *TP53* gene developed lung adenocarcinomas, osteosarcomas, and lymphomas. They identified variable degrees of disease penetration and the occasional occurrence of simultaneous primary cancers; and the rare development of cancers like rhabdomyosarcoma, skin carcinoma, fibrosarcoma, testicular carcinoma, and adrenal neuroblastoma.[34]

In 1996, Pfeifer et al. showed that *TP53* pathway alterations could directly cause human cancer. Using the active metabolite of benzo[a]pyrene (a byproduct of cigarette smoke), Pfeifer's group induced *TP53* mutagenesis, causing malignant transformation with unique genetic alterations.[35, 36] Pfeifer's work refuted tobacco industry claims by providing the "smoking gun," scientific proof that cigarettes caused human lung cancer and was, therefore, the lynchpin research that changed public health policies and practices in the United States and abroad.[35, 37] During a similar timeframe, Donehower and colleagues showed that *TP53* did not appear to impair normal embryogenesis, growth, or development in genetically engineered mice.[38-40] Donehower's observations confirmed that germline mutations in the *TP53* gene could be present without lethal consequences; making an inherited human disorder a plausible concept.[14, 25, 26, 41]

The original suggestion of a familial cancer syndrome of diverse tumors in humans was first proposed in 1969 by two physician-scientists, Drs. Frederick P. Li and Joseph F. Fraumeni, Jr., after identifying aggressive, soft tissue sarcomas in young siblings and their biologically-related cousins.[42] Over a twenty year period, they defined and refined a clinical syndrome

that was ultimately confirmed, by segregation analysis, to be of genetic etiology and given the moniker “Li-Fraumeni syndrome” (LFS).[3, 9, 43, 44] Molecular genetic testing for *TP53* germline mutations was developed in 1990 by David Malkin and colleagues[45, 46] and was quickly used as a screening tool to identify patients with hereditary forms of cancer.[47-49] In the early 1990s, Louis Strong and colleagues were the first to develop cancer-specific risk estimates, improving clinical care for families with LFS.[50] These major landmarks in *TP53* history have formed the foundation for the modern era of scientific advancements in *TP53*-related research and clinical care.[41]

3. Li-Fraumeni Syndrome Core Cancers

While many tumor types can be seen in patients with LFS, four core cancers (breast, sarcoma, brain, and adrenocortical carcinoma) make up about 80% of LFS associated tumors.[1, 43, 44, 51]

Breast Cancer accounts for about 25-30% of all LFS-associated tumors.[1, 51, 52] This is believed to account for at least part of the difference in lifetime cancer risk between women and men (nearly 100% vs. 73%, respectively).[53] Breast cancer is most predictive of the presence of a germline *TP53* mutation when it is diagnosed before age 30-35 in a woman with a family history of a first- or second-degree relative with a core LFS cancer (other than breast cancer).[1, 54, 55] Women with LFS-associated breast cancer tend to present at an earlier age (in the 20s or early 30s) with more advanced stage disease (i.e., tumors greater than 5 cm and axillary node disease) at the time of initial diagnosis. Recent studies have begun to describe the phenotype of breast cancers in *TP53* mutation carriers.[56-58] All three studies found that the majority of breast tumors were Her2Neu positive, and Melhem-Bertrandt et al. found a significantly greater number of Her2Neu positive tumors among *TP53* carriers than among non-carriers ($p = 0.0001$; table 1).[57] Therefore, the emerging phenotype of a classic LFS-associated breast cancer appears to be ductal in histology, ER, PR, and Her2/neu positive, and diagnosed in the 20s or early 30s.

Sarcomas account for another 25-30% of all LFS-associated tumors.[1, 51, 59, 60] Multiple types of soft tissue sarcomas and osteosarcoma are associated with LFS; but Ewings sarcoma, gastrointestinal stromal cell tumors (GIST), desmoids tumors, and angiosarcomas have not been reported in LFS.[59] A recent study by Ognjanovic et al. compared sarcomas diagnosed in *TP53* mutation carriers in the IARC *TP53* database (n=236) to sarcoma diagnoses in the Surveillance, Epidemiology, and End Results (SEER) database (n=34,671).[59] They found that 67% of sarcomas in *TP53* mutation carriers occurred before the age of 20 compared with only 11.9% in the SEER database; in *TP53* carriers only 4.4% of sarcomas occurred after age 50, while 62.7% were diagnosed after 50 in the SEER data. The age distribution of sarcomas in *TP53* mutation carriers is biphasic, with one peak in childhood and another between ages 20 and 40.[59, 60]

Brain Tumors occur in 9-16% of individuals with *TP53* mutations.[1, 51, 60, 61] Glioblastomas/astrocytomas are the most common but, medulloblastoma, ependymoma, supratentorial primitive neuroectodermal tumors, and choroid plexus tumors may also be seen.[61, 62] Despite limited sample sizes, a compelling body of evidence supports the association between choroid plexus tumors, particularly choroid plexus carcinomas (CPC) and *TP53* germline mutations.[1, 22, 63-65] Gonzalez et al. reported that all 8 individuals in their cohort with choroid plexus tumor (type not specified) and no additional personal or family history reported were positive for a germline *TP53* mutation.[1] Other studies report prevalence rates between 36-44% in patients with choroid plexus carcinomas, many of whom also met the Classic LFS or Li-Fraumeni-Like (LFL) criteria.[22, 65] As with sarcoma,

there appears to be a biphasic age distribution of brain tumors in those with *TP53* mutations, with highest prevalence rates before age 10 and after 20 years of age.[51, 60]

Adrenocortical Carcinoma (ACC) accounts for 10-14% of cancers in *TP53* mutation carriers overall.[1, 60] While ACC has been diagnosed in individuals with LFS at a wide range of ages, it is considered a hallmark of LFS when diagnosed in childhood.[1, 60, 66] The IARC *TP53* database reports a median age of ACC diagnosis among *TP53* mutation carriers of 4.8 years versus 41.9 years among sporadic cases of ACC.[60] Gonzalez et al. found that 80% of individuals in their cohort with ACC diagnosed under 18 had *TP53* mutations.[1] The highest prevalence rates of ACC are reported in carriers of the Brazilian founder mutation, *TP53* R337H. The R337H mutation is present at a high frequency in southern Brazil (about 1 in 300 individuals)[67, 68] and evidence shows it to be a founder mutation.[52, 69] The frequency of this mutation among children with ACC in southern Brazil is 78-97%.[70, 71] Initially, it was thought to be a low penetrance mutation that predisposes only to ACC and not other LFS-associated tumors.[70-72] However, more recent studies have found that the R337H mutation can be found in families with a broad spectrum of LFS-associated cancers.[73, 74]

Other LFS Cancers

Beyond the four core LFS cancers, the next most frequently associated cancers include leukemia, lung, colorectal, skin, gastric, and ovarian.[1, 51, 60, 75-77] All cancer types are diagnosed at younger than average ages. One study on colorectal cancer in LFS families found the average age of diagnosis to be 33, with four individuals diagnosed before age 21.[75] A study of gastric cancer in LFS families found an average age of diagnosis of 43 (range: 24-74), with four diagnosed before age 30.[75, 76]

4. *TP53* Gene and Genotype-Phenotype Correlations

The human *TP53* gene (chromosome 17p13.1) encodes for a ubiquitous transcription factor that is now known to be responsible for a complex set of critical regulatory functions that promote DNA repair and tumor suppression. It contains 11 exons (including 10 coding exons) and encodes for a protein that is 393 amino acids long. The *TP53* gene is comprised of four distinct types of functional domains: two transactivation domains (amino acids 1-42 and 43-62), a centralized DNA binding and mutation hotspot domain (102-292), an oligomerization domain (323-356), and a regulatory domain (363-393) (figure 1).[49, 78] Most *TP53* mutations are clustered in the DNA-binding domain within specific codons, such as 175 and 248 (figure 2). *TP53* mutations are often missense alterations[21] that cause a change in one nucleotide and encode for a different amino acid than the one typically found in that particular location within the protein. Missense mutations are usually transcriptionally inactive; however, some reports have shown gain of function oncogenic effects in *TP53*.[79, 80]

Genotype-phenotype correlations in LFS are predictive of age of tumor onset, highest tumor risks, and outcome in patients with *TP53* germline mutations.[51, 59, 60, 81] Mutations in the DNA binding portion of the gene cause highly penetrant disease with very early onset cancers; mutations outside the core DNA binding domain are associated with slower rates of tumor development.[82-84] Monti and colleagues utilized clinically-annotated *TP53* mutation data contained in the IARC database to correlate the functional properties of 104 *TP53* germline mutations (with single amino acid substitutions) to cancer-related outcomes. They (and others) have used yeast-based functional assays to show that *TP53* mutant alleles with reduced transactivation capability (including dominant negative acting proteins that reduce the transactivation ability of the p53 wild-type protein) are associated with a higher frequency of multiple tumors and are more likely to be found in germline carriers with

strong family histories of cancer.[85] Inherited genetic variations (including single-nucleotide polymorphisms, SNPs) of the *TP53* gene have been reported to impair p53 function in vitro and are associated with worse outcomes in specific subgroups of patients with cancer.[86]

5. Li-Fraumeni Syndrome: Genetic Testing

The diagnosis of LFS is based on an evolving set of clinical classification criteria that have been established using the most salient aspects of family history and tumor-related characteristics. Deleterious (disease causing) mutations in *TP53* are only found in ~70% of the patients who meet the classic diagnostic criteria for LFS,[43] underscoring the importance of clinical suspicion and astute diagnostic skills when trying to identify affected patients and families. *TP53* genotyping is typically performed by DNA Sanger sequence analysis and multiplex ligation-dependant probe assay or other technique to detect large rearrangements of portions of the gene.[87]

5.1. Testing Criteria

The following is a summary of when *TP53* analysis may be recommended, and when personal and family history should be evaluated for LFS and *TP53* genotyping should be considered. The National Comprehensive Cancer Network (NCCN) guidelines recommend *TP53* analysis for individuals who meet either the classic LFS criteria, the Chompret criteria, or who were diagnosed with breast cancer under age 30.[88]

- **Published Criteria** Several sets of criteria have been developed over the past 20 years to help identify individuals with LFS who should be considered for *TP53* testing (table 2). The first formal set of criteria developed (in 1988) is the Classic LFS criteria; these criteria are the most stringent and are the ones used to make a clinical diagnosis of LFS (with or without the identification of a deleterious germline *TP53* mutation).[43] Later, broader criteria were developed by Birch and Eeles to identify families which are Li-Fraumeni-like (LFL).[83, 89] Chompret and colleagues developed another set of criteria which were shown to provide the highest positive predictive value and, when combined with the classic LFS criteria, provided the highest sensitivity for identifying individuals with LFS (table 3).[1, 90] During the 3rd International p53 mutant workshop-LFS symposium in 2007, the Chompret criteria were modified to develop a set of Consensus-based criteria to identify *TP53* carriers.[60] The Chompret criteria were most recently updated in 2009 to better identify families with milder phenotypes.[84, 91]
- **Breast Cancer < 30** Some, including the NCCN, advocate testing all individuals with breast cancer under age 30 who are negative for *BRCA1* and *BRCA2* mutations for *TP53* mutations.[1, 55, 61, 88] However, others do not support this recommendation, stating that without additional family history, the probability of mutation is too low (<5%).[91] Most recently, McCuaig et al. have suggested that a *TP53* mutation is actually more likely than a *BRCA1* or *BRCA2* mutation in women with breast cancer diagnosed under age 30 without contributory family history.[92] They, therefore, propose that testing for *BRCA1, BRCA2,* and *TP53* be performed simultaneously in this subset of patients.
- **Adrenocortical Carcinoma** Well-established criteria recommend *TP53* analysis for any individual with ACC regardless of age at diagnosis or family history.[88, 91] Based on the published literature, however, it appears that the probability of finding a *TP53* mutation is higher in ACC diagnosed <40, especially those diagnosed in childhood.[1, 60, 66]

- **Choroid Plexus Carcinoma** The 2009 Chompret criteria recommend germline *TP53* analysis for any patient with CPT regardless of family history.[1, 91]
- **GI Cancers** *TP53* mutation analysis should also be considered in cases of early onset gastrointestinal (GI) cancer who meet the classic LFS or LFL criteria if other more common hereditary GI syndromes have been ruled out.[75, 76]

5.2. Other *TP53* Genetic Testing Considerations

In an attempt to develop an approach to finding other patients with LFS, Gonzalez and colleagues published the largest single report from a diagnostic testing lab.[1] Using clinical data from a *TP53* clinical testing cohort of 525 patients submitted for testing, with 91 mutations identified, prevalence tables summarizing the individual and family characteristics associated with *TP53* mutations were created. These tables can be used as clinical tools to help guide testing decisions (table 4). Gonzalez and colleagues found that the highest germline *TP53* mutation frequency rate (100%; n=5) was in patients who had at least one core cancer during childhood (prior to 18 years of age) and a positive family history for cancer.

TP53 testing is generally not recommended without a substantial probability of identifying a deleterious mutation. One of the most common and challenging clinical testing dilemmas is determining the most appropriate testing strategy for a woman who has tested negative for *BRCA1* and *BRCA2* mutations, but who has a family history consistent with a hereditary breast cancer syndrome. Indeed the NCCN recommends *TP53* genetic testing for patients with breast cancer diagnosed under age 30, who have already tested negative for *BRCA1* and *BRCA2*. However, in the absence of very early age of breast cancer diagnosis, most families with breast cancer have an exceedingly low probability of carrying a *TP53* mutation.[91] For example, if there are multiple cases of breast cancer in a family, but there are women interspersed between them who have lived past age 50 and not developed breast cancer, *TP53* testing is usually not warranted. Common cancers historically associated with *TP53* (such as leukemia and lung cancer), which are not among the more recently reported core Li-Fraumeni-associated cancers,[44] do not add to the likelihood of detecting a mutation.[1] Similarly, sarcoma patients over age 50 are much less common in Li-Fraumeni families than in the general population.[59] However, like all of medicine, there are rare exceptions to these rules, supporting the need for clinical judgment to navigate the nuances of strategizing the gene testing process.

6. Genetic Counseling for Li-Fraumeni Syndrome

6.1. Pre- and Post-Test Counseling

Decisions regarding germline *TP53* testing should be made by healthcare professionals with specialized training in clinical cancer genetics and experience interpreting complex, and potentially novel, variant gene mutations of uncertain clinical significance. All patients should have cancer genetic counseling, prior to initiating the testing process, and access to long term counseling to support the educational and psychosocial needs of LFS patients and their families.

6.2. Risk for Family Members

Most *TP53* mutations have been inherited from a parent. After identifying a mutation, the proband's parent with any pertinent cancer history or family history should be tested first to establish the lineage of the mutation; otherwise, both parents should be tested. A family history can appear negative due to a limited family structure or incomplete penetrance of the mutation. The frequency of de novo mutations is not well established; however, based on

two studies, the de novo rate has been estimated to be as low as 7% (5 of 75) and as high as 24% (4 of 17).[53, 93]

Siblings and offspring of the proband should also be tested. If one of the proband's parents carries the *TP53* mutation, each sibling has a 50% risk of having the mutation. If neither parent is found to carry the mutation, the risk to siblings is low, but they should be tested due to the possibility of germline mosaicism. Offspring of a proband have a 50% risk of carrying the mutation.

6.3. Testing of At-Risk Unaffected Children

For some time, testing of at-risk minors for identified *TP53* mutations has been controversial, due to the lack of proven surveillance or prevention strategies and concerns about informed consent, stigmatization, and discrimination.[94] However, due to emerging screening protocols showing efficacy in reducing mortality from *TP53*-related malignancies,[95] testing of at-risk children is now considered.

6.4. Preimplantation Genetic Diagnosis (PGD)

PGD is available for high-risk couples seeking to avoid an affected pregnancy. PGD uses a standard in-vitro fertilization procedure, allowing embryos to be tested for an identified disease-causing *TP53* mutation prior to being transferred to the uterus.[96] PGD for LFS is one of the most compelling uses of this technology, among all cancer-predisposing syndromes, due to the early age of onset of cancer and significant risk of death by early adulthood.[97] PGD for *TP53* mutations has been described and successfully performed.[98] Prenatal diagnosis of LFS using amniocentesis or chorionic villus sampling (CVS) is another option for avoiding an affected child. Such an approach has been described but, due to the consideration of termination of an affected pregnancy, is controversial and psychologically difficult for families.[99]

6.5. Psychological Considerations

Psychological functioning in individuals and families considering germline TP53 testing is an understudied but important aspect of clinical decision making and should be addressed throughout the counseling process. Peterson et al studied individual perceptions of cancer risk and psychological distress in 92 members of 15 LFS-families. They found that increased psychological distress was associated with poor quality of life and a higher perceived risk of carrying a *TP53* germline mutation. Interestingly, they also found that study participants with no personal history of cancer reported more psychological distress than those personally affected by cancer. Increased distress was also seen in participants who had a larger number of relatives affected by cancer.[100] Another study of 119 individuals considering *TP53* testing found that study participants who lacked social support were more prone to report clinically relevant levels of distress.[101] TP53 germline carriers did not show higher levels of distress than non-carriers or those who declined testing. A substantial proportion of the overall group (23%) reported clinically relevant levels of distress.[101] Partners of patients with a high probability of carrying a *TP53* germline mutation have been reported to have elevated levels of distress and have expressed a desire for psychosocial support services.[102] Collectively, these reports support the need for comprehensive counseling services, including psychosocial counseling, for individuals and families considering *TP53* germline testing.[100, 101]

6.6. Duty to Warn

When patients are reluctant to share relevant genetic information with family members, physicians may have to consider how to balance the patient's privacy with the interests of at-

risk family members who can benefit from available screening and interventions. However, warning the relatives without the patient's consent is not consistent with the provider's ethical obligation to the patient and could be at odds with state and federal privacy laws. Instead, it is appropriate for providers to encourage patients to share such genetic information with relatives in a manner that is deliberate, but not coercive.[103]

6.7. New Challenges to Informed Consent: *TP53* Mutation Discovery with Genomic Approaches

With the growing availability and use of whole genome sequencing (WGS), whole exome sequencing (WES), whole genome arrays, and multi-gene panels comes the increased likelihood of unintentionally or unexpectedly identifying a *TP53* mutation carrier. There have already been some case reports of this in the literature. One case was discovered through whole genome array CGH done on a child with mental retardation and no family history of cancer.[104] Another case was discovered through WGS performed on a patient with myelodysplastic syndrome and a history of premenopausal breast and ovarian cancer who had normal genotyping for *BRCA1* and *BRCA2* and no family history suggestive of a hereditary cancer syndrome.[105] These cases bring up important and complicated questions about how to ensure an adequate informed consent process for genomic testing, maintain health information privacy, and provide appropriate mechanisms for test result disclosures.[106-108] Employing these molecular strategies especially on a research basis, initially, will help us to gain a broader phenotypic picture of hereditary cancer syndromes like LFS.[77, 106, 109]

7. Management of Li-Fraumeni Syndrome Patients

Guidelines for the management of patients with LFS have been published by the NCCN and include the following recommendations for early detection of disease: (1) children and adults should undergo comprehensive annual physical examination; (2) women should undergo age-specific breast cancer monitoring that is routine for women with an increased inherited risk which includes annual mammograms, breast MRI,[110] and clinical breast examination beginning at age 20-25 years, or even earlier based on the youngest age of onset in the family, and consider the option of risk-reducing mastectomy; and (3) all should see a physician promptly for evaluation of lingering symptoms and illnesses.[88]

Due to the challenges of interpreting results of mammographic images of dense breast tissue in young women and the need to reduce lifetime exposure to radiation, the ACS recommends delaying the use of yearly mammograms in women with LFS until after 25-30 years of age.[111] The NCCN also indicates that MRI-only screening may be sufficient between ages 20 and 30.[88] The NCCN prevention guidelines also include recommendations that adults can consider colonoscopy every 2-5 years beginning no later than age 25, that individuals should undergo organ-targeted surveillance based on the pattern of cancer observed in the family, and that the option to participate in novel screening approaches (such as total body MRI and brain MRI, see below) should be discussed.[88]

7.1. Enhanced Surveillance

Historically, enhanced surveillance for early disease detection in LFS patients beyond what is recommended in the NCCN guidelines has been considered investigational, primarily due to a lack of a proven survival benefit.[112, 113] However, recent reports show that enhanced screening protocols can detect early stage disease and improve outcome in LFS patients.[95, 113, 114]

The first successful LFS-screening study incorporated PET-CT (F18-Fluorodeoxyglucose–Positron Emission Tomography/Computed Tomography) imaging into an enhanced clinical surveillance regimen. The PET-CT study, conducted by Masciari et al, successfully identified cancer in 20% (n=3) of the 15 asymptomatic LFS individuals studied.[113] Two LFS patients had papillary thyroid cancer (stage II and stage III); one LFS patient had stage II esophageal adenocarcinoma. This study laid the foundation for a subsequent study by Villani et al., wherein there was an effort to minimize screening-associated ionizing radiation exposure.

Villani and colleagues conducted a prospective, observational study of eight LFS families.[95] The thirty-three asymptomatic germline *TP53* mutation carriers studied self-selected to be followed with enhanced surveillance (n=18) or routine institutional follow-up care (n=16; one LFS patient was in both groups). The surveillance protocol is published and included physical examinations with targeted biochemical monitoring and radiological imaging (with ultrasounds, brain MRIs, and rapid total body MRI scans).[95] The overall survival at 3 years was excellent (100%) in the surveillance group, but only 21% in the group without enhanced surveillance (95% CI 4-48%; p=0.0155). Ten tumors were identified in 7 members of the surveillance group; the five cancers detected were choroid plexus carcinomas (n=2), Adrenocortical carcinomas (n=2), and one malignant fibrous histiocytoma. Three low grade gliomas and one case of myelodysplastic syndrome were also detected in this group.[95]

This is the first reported data that clearly shows a survival benefit for enhanced surveillance in LFS patients. Due to the rarity of LFS, it is not realistically feasible to conduct outcome studies using large scale, randomized, clinical trial study designs. It is, however, reasonable to utilize well developed prospective studies, such as the one conducted by Villani et al., to inform decisions about advanced clinical care options for LFS patients.

Current biochemical screening tests for LFS-patients include standardized tumor-based assays, such as 17-Hydroxyprogesterone to help detect adenocortical carcinoma. However, several research-based testing methodologies are beginning to show promise as future tools for early disease detection and risk stratification for LFS patients. For instance, genomic assessment of copy number variation (CNV) can yield a pattern associated with LFS-associated cancers compared to other cancers and may identify early stage disease in asymptomatic germline *TP53* mutation carriers.[115] In one study, germline *TP53* mutation carriers had a 4-8 fold increase in CNV, and affected *TP53* carriers had much higher CNV levels than unaffected carriers.[115] Recently, LFS has been associated with shortened telomere length.[116, 117] Telomere length may be a reliable marker for assessing cancer-risk and for determining the most appropriate timeframe to begin enhanced surveillance regimens for LFS carriers.

7.2. Other Considerations in Breast Cancer Risk-Reduction and Screening

As part of individualized preventative care, risk-reducing mastectomy should be offered to women with LFS as an option to reduce primary breast cancer risk.[88] LFS patients with breast cancer should be encouraged to consider mastectomy, rather than lumpectomy, to minimize the risk of developing new primary breast cancers and to avoid developing radiation-induced malignancies.[88, 112]

Mammography has diminished efficacy in women with LFS, predominantly due to the increased mammographic densities seen in these young premenopausal women.[118, 119] In addition to limiting the effectiveness of mammography, increased mammographic densities have been associated with elevated breast cancer risk in women with hereditary and sporadic forms of breast cancer.[120, 121] Because interventions that modify hormone effect (e.g.,

oophorectomy and Tamoxifen) have been shown to reduce mammographic densities and breast cancer risks in younger women, Weitzel et al. developed an open label pilot study to test the efficacy, safety, and tolerability of a novel hormone-based approach to chemoprevention in young women at risk for hereditary breast cancer.[122] Weitzel's hormonal chemoprevention regimen included daily intranasal sprays of the gonadotropin-releasing hormone agonist, deslorelin, combined with ultralow-dose estradiol, replacement testosterone, and intermittent doses of oral medroxyprogesterone acetate. In this small series (n=6) of premenopausal women with germline *BRCA1* mutations, mammographic density was significantly reduced at 12 months (median absolute decrease, 8.3%; P = 0.043; representing a 29.2% median reduction in mammographic percent density). This study suggests that hormone-based chemoprevention options may expand the non-surgical cancer risk reduction options available to women with LFS.

8. Case Example[95, 123]

The proband was a 31-year-old male who had been diagnosed with aplastic anemia at 22 years old for which he received an allogeneic hematopoietic stem cell transplantation (HSCT). His family history (see pedigree, figure 3) was significant for a son who was diagnosed with CPC just before one year of age. The proband's father was diagnosed with lung cancer at age 60 and died at age 62. The proband presented for *TP53* testing after his son was found to have a *TP53* mutation. Due to his prior history of HSCT, a buccal sample was submitted for testing and was found to contain wild-type (normal) *TP53.* His wife was also tested and found to carry wild-type *TP53.* At this point, it was determined that even a buccal specimen would contain mostly donor DNA (due to peripheral blood contamination) and that a tissue biopsy would be needed. A tissue sample from the proband was analyzed and a deleterious *TP53* mutation was identified. The proband had another child, a 4-year-old asymptomatic daughter, who was tested and found to carry the same *TP53* mutation. Given the mutation and her brother's history, she underwent a brain MRI and two tumors were identified: a low grade glioma and a CPC. Since her initial diagnosis she has done very well, with no recurrence of the choroid plexus carcinoma. However, later an abdominal ultrasound detected an adrenal cortical carcinoma, which was resected, and she has remained in complete remission. Unfortunately, the proband's son passed away a short time later. Despite the tragedy, this remarkably resilient family was able to see the potential importance of the genetic approach and became founding members of a new advocacy and support group for families with *TP53* mutations.

(The LFS Association; http://www.lfsassociation.org/)

8.1. Case Discussion

There are many genetic testing and genetic counseling issues to consider in this case example. Since aplastic anemia is not one of the typical LFS malignancies, the only criterion for *TP53* testing that was met was the 2009 Chompret criteria, due to the CPC in the son. As discussed above, testing for *TP53* mutations in children has been quite controversial in the past, but is gaining acceptance due to recent data showing a benefit from screening regimens. This case is an excellent example of how testing the second child for the previously identified mutation allowed for the screening and early detection of malignancy and, ultimately, improved survival. Another important consideration is that of genetic testing in individuals who have had HSCT. While genetic testing is usually performed on DNA isolated from a blood sample, this would not be accurate in individuals who have undergone HSCT as the DNA in their blood would be that of their donors. In these cases, a tissue sample that will provide enough DNA for analysis must be provided, such as a skin biopsy or sperm sample, from which lymphocytes can be cultured. The last issue related to this case

is that of PGD. This particular couple was not interested in having more children, but PGD is an option that should be discussed for families with LFS.

9. Treatment of *TP53*-Related Malignancies

9.1. Choroid Plexus Carcinomas

Choroid plexus carcinomas (CPCs) are associated with extremely poor outcomes in the pediatric patient population. Typically these patients require treatment with aggressive protocols that include myelosuppressive chemotherapy and brain radiation (with significant developmental and intellectual consequences).[65, 124] In a recent study of 64 choroid plexus tumors from children (with and without LFS), more than 90% of CPCs demonstrated *TP53* dysfunction, either due to deleterious *TP53* germline mutations (~50%) or due to somatic *TP53* sequence variants involving *TP53* codon 72 or MDM SNP 309.[125] High-resolution single nucleotide polymorphism (SNP) arrays revealed extremely high total structural variation (TSV) in *TP53*-mutated CPC tumor genomes ($p=0.006$ in mutated vs. *TP53* wild-type tumors; $p=0.004$ in mutated vs. CP papillomas).[125] High TSV levels were predictive of tumor progression ($p< 0.001$).[125]In addition, 14 out of 16 children with *TP53* wild-type tumors had significantly favorable outcomes without radiation with a mean follow-up time of 10.2 years (range, 2.4 to 20 years). This and similar studies[65, 124, 125] show that children with CPCs can be stratified based on *TP53* mutational status into favorable and unfavorable risk groups, allowing a subset of children to benefit from the opportunity to avoid radiation therapy. In addition to advancements in risk stratification, novel therapeutic options are being explored as well. For instance, Poly (ADP-ribose) polymerase-1 (PARP1), a DNA repair protein, has been studied in an assortment of malignancies and may be protective against therapy-induced DNA damage. There is early evidence that PARP inhibition may be a therapeutic target that can trigger selective cell death in high-grade brain cancers (including choroid plexus carcinomas).[126]

9.2. Hematopoietic Malignancies-Stem Cell Transplantation

TP53 mutation carriers are 100 times more likely to develop leukemia; however, only three percent of LFS patients develop a hematopoietic malignancy. LFS-associated leukemia tends to be very aggressive and is associated with a poor prognosis, complex karyotypes, and chromosome abnormalities seen in patients with therapy-related myelodysplastic syndrome.[11] *TP53* alterations were the first biological marker to become incorporated in risk stratification and upfront treatment decisions for chronic lymphocytic leukemia (CLL) patients treated on randomized clinical trials.[127, 128] *TP53* inactivation in CLL predicts for an ultra high-risk group of patients with fludarabine-resistant disease and median survival times of less than 12 months.[128-131] Therefore, the European Research Initiative on CLL, has recommended that *TP53* mutation analysis be performed for all CLL patients and that those with *TP53* mutations be considered for allogeneic stem cell transplantation in first remission. Studies have shown that Alemtuzumab-based regimens may provide complete responses in this treatment-resistant group of patients.[132]

10. Future Directions for Therapies

A number of strategies have been explored to target *TP53*-associated cancers and improve outcomes for patients with somatic and germline *TP53* mutations. For instance, single gene targeting strategies that utilize viral vectors (such as Advexin and ONYX-015) have shown some promise.[4, 133-135] However, current approaches target more generalized *TP53* pathway functions, aiming for low toxicity profiles that could support the possibility of incorporating these therapies into multi-agent combination regimens. A few representative approaches are described below.

10.1. Monoclonal Antibodies

Monoclonal antibodies have been shown to improve outcomes in several disease types, including some promising laboratory and early-phase clinical trials showing an apoptotic affect against *TP53*-associated leukemia.[136, 137] Humanized monoclonal antibodies such as Trastuzumab (Herceptin®) are currently being used to treat several malignancies, including breast and stomach cancer.[138, 139] Trastuzumab binds to the extracellular domain of the human epidermal growth factor receptor type 2 (HER2), inhibiting cell growth, and targeting cancer cells for destruction by the patient's immune system. Trastuzumab has been shown to significantly improve outcomes for the 20-30% of patients with HER2-positive breast cancer; this includes patients with metastatic disease that are unlikely to be cured by any other means.[140, 141] Recent studies have begun to identify a unique LFS-breast cancer phenotype that is ductal in histology with estrogen, progesterone, and HER2 receptor positivity.[56-58] This HER2 positive phenotype suggests that clinical trials, which incorporate Trastuzumab into front-line therapy for young women with LFS-breast cancer, should be considered.

10.2. Small Molecules

Various small molecules are being explored to try to restore normal *TP53* function to deficient cells. Reactivation of wild-type *TP53* activity can be a successful strategy and has caused regression of lymphoma and liver cancer in *TP53* deficient in vivo model systems.[142-144] A number of promising small molecules have been identified using in silico drug screening technologies. These small molecules (currently named PhiKan083, PRIMA-1, CP31398, WR1065, MIRA-1, STIMA-1, RETRA, Nutlin -3, and RITA) reactivate *TP53* functional pathways using mechanisms such as raising the melting temperature of the mutant protein to trigger reactivation of function, normalizing the folding conformation of the mutant protein to restore its ability to bind to DNA, or reactivating *TP53* wild-type function in *TP53*-associated cancers.[145-150] Although promising, the strategy of *TP53* reactivation much be approached with some caution because of reports that increased *TP53* expression is associated with treatment resistance in breast cancer.[151]

10.3. Metabolic Therapy

Autophagy is an evolutionarily conserved process of self-degradation of cellular components such as very long-lived proteins and damaged (or excessive numbers of) organelles. Current research suggests that autophagy has two somewhat contradictory functions. It protects the host by suppressing early stages of tumor development, yet it supports the survival of established tumors that are threatened by starvation or chemotherapy. *TP53* regulates the expression of key genes in the pathways required for both autophagy and adaptive metabolic responses to stressors through the AMPK and mTOR pathways.[78] Metformin is a drug that regulates cellular metabolism by activating the *TP53*-AMPK pathway.

Metformin is a well tolerated, commercially available drug, commonly used to treat type II diabetes mellitus. Epidemiological studies have shown decreased cancers in diabetes patients receiving treatment with Metformin.[152-155] This clinical observation has been supported by preclinical reports showing that Metformin preferentially inhibits growth of cells lacking functional *TP53*.[156] Similarly, studies of *TP53* deficient mice have shown prolonged overall survival of more than 5 months when treated with Metformin. These observations are very encouraging and clinical trials aimed at using Metformin to reduce cancer risk in LFS patients are under consideration by members of the Li-Fraumeni Exploration research Consortium (http://epi.grants.cancer.gov/Consortia/single/life.html).

10.4. Heavy Ion Cancer Therapy

Heavy Ion radiation therapy utilizes charged particles (heavier than helium ions) to give increased dosages of precisely targeted radiation to cancers, achieving good cancer control while minimizing damage to nearby organs. This highly effective form of linear energy transfer has been shown to induce cell death in a *TP53*-independent manner (possibly through a pathway that activates the mitochondrial apoptotic factor, caspase 9). These findings suggest that heavy ion therapy may be a very well tolerated way to improve outcomes for patients with *TP53* mutated or *TP53* null cancers. The practical application of this technology is limited by prohibitive costs and the need for impractical, huge, accelerators; thus, there are only a few heavy-ion facilities available worldwide. Even so, advances in *TP53*-independent apoptosis-related gene pathways could lead to similar, more near-term applications of heavy ion therapies that target aberrant *TP53*-associated pathways.[157]

11. Summary

Although most *TP53* targeted therapies are still in the early phases of testing, the field of *TP53* directed research remains very active and is expanding rapidly. Notably, a workshop on November 2, 2010, at the National Institutes of Health in Bethesda, Maryland, brought 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 patient community. This workshop led to the creation of the Li-Fraumeni Exploration (LiFE) Research Consortium, to promote a better understanding of the syndrome and the improvement of the lives of individuals with LFS.[123] Following that inaugural meeting, the LFS Association (www.lfsassociation.org) was created as a resource designed to provide a wide range of information, advocacy, and support services for individuals and families with Li-Fraumeni Syndrome. The newly established advocacy group was created to facilitate effective communications, among other tasks, between LFS families and the clinical and scientific members of the research consortium. By summarizing these forty years worth of dedicated efforts to advance treatment and cancer prevention options for people with this rare syndrome, we hope to encourage and provide a voice for our international group of research partners and the LFS patients and families who are living each day for a better tomorrow.

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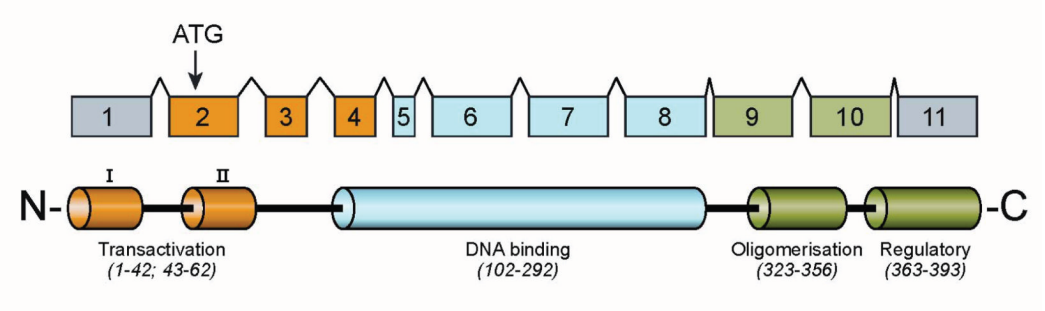

Fig. 1.

A graphic representation of the *TP53* gene (boxes) and protein (cylinders), adapted from the IARC *TP53* database.[21] The *TP53* gene contains 11 exons represented by the numbered boxes. The exons 2-4 (yellow) encode for the two Transactivation domains (I, II) of the protein (amino acids 1 through 42 and 43-62). Exons 5-8 (blue) encode for the DNA binding portion of the protein (amino acids 102-292). Exons 9 and 10 (green) encode for the Oligomerisation (amino acids 323-356) and Regulatory (amino acids 363-393) domains. The approximate location of the initiation codon (ATG) is denoted.

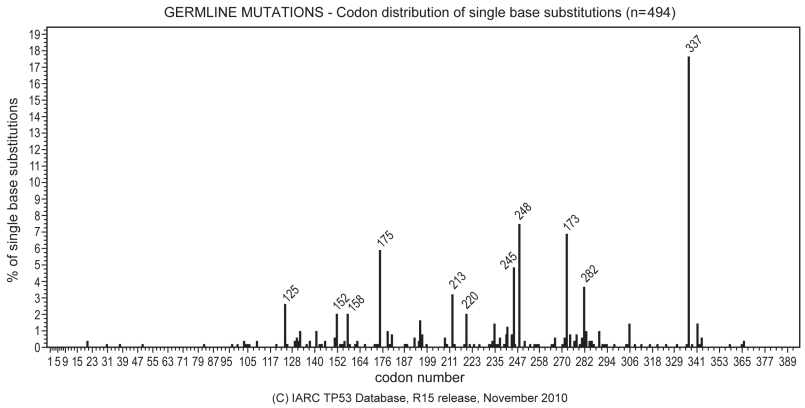

Fig. 2.

Summary of the most frequent *TP53* germline mutations by codon, reproduced from the International Agency for research on Cancer (IARC) *TP53* database.[21] Each vertical line represents the codon location of a *TP53* germline mutation. The codon location for the most frequently reported mutations (based on percentage of base substitutions) are located at the top of the vertical line. For instance, the Brazilian founder mutation, at codon position 337, is the most frequently reported mutation.

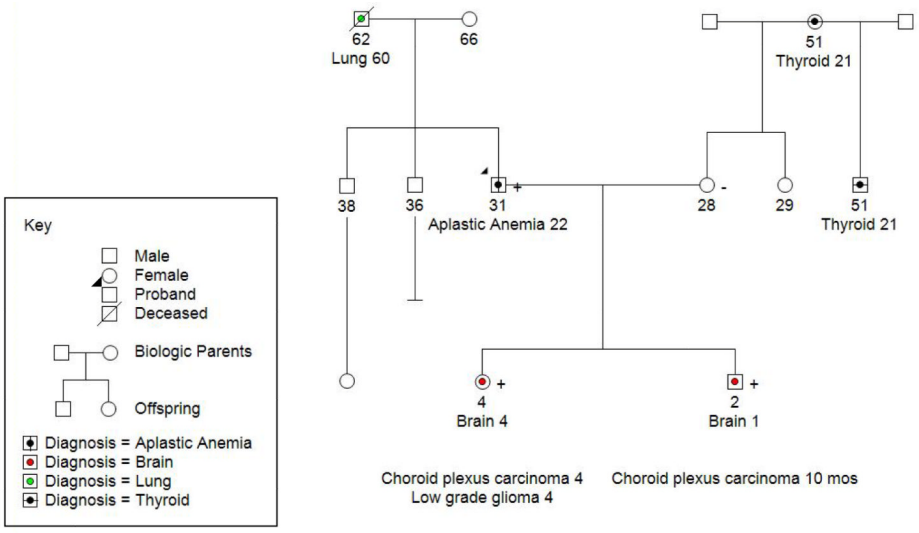

Fig. 3.
Pedigree for the family described in the case example

Table I

Breast Cancer Receptor Phenotype in *TP53* Mutation Carriers

Study Cohort	N	ER+	Her2/neu+
TP53 mutation carriers from the LiFE Consortium[56]	32	84%	63%
TP53 mutation carriers from a UK regional genetics service[58]	9	-	83%
TP53 mutation carriers from MD Anderson Cancer Center and University of Chicago[57]	30	70%	67%
Comparison cohort: women <40 with breast cancer, unselected for family history or *TP53* mutation status[158, 159]	-	52-66%	22-33%

Table II

Diagnostic criteria for Li-Fraumeni Syndrome and Li-Fraumeni Like Syndrome and criteria for *TP53* genetic testing

Criteria	Description

Classic Li-Fraumeni Syndrome[43]	• A proband with
	  • a sarcoma diagnosed before age 45 years, AND
	  • A first-degree relative with any cancer before age 45 years, AND
	  • A first- or second-degree relative with any cancer before age 45 years or a sarcoma at any age

Li-Fraumeni Like Syndrome[83, 89]	Birch definition: • A proband with any childhood cancer or sarcoma, brain tumor, or adrenocortical carcinoma diagnosed before age 45 years, AND • A first- or second-degree relative with a typical LFS cancer (sarcoma, breast cancer, brain tumor, adrenocortical carcinoma, or leukemia) at any age, AND • A first- or second-degree relative with any cancer before age 60 years Eeles definition: • Two first- or second-degree relatives with LFS-related malignancies at any age

Chompret criteria[84, 90, 91]	• A proband with:
	  • a tumor belonging to the LFS tumor spectrum (soft tissue sarcoma, osteosarcoma, brain tumor, pre-menopausal breast cancer, adrenocortical carcinoma, leukemia, or bronchoalveolar lung cancer) before age 46 years, AND
	  • At least one first- or second-degree relative with an LFS tumor (except breast cancer if the proband has breast cancer) before age 56 years or with multiple tumors, OR
	• A proband with multiple tumors (except multiple breast tumors), two of which belong to the LFS tumor spectrum and the first of which occurred before age 46, OR
	• A proband who is diagnosed with adrenocortical carcinoma or choroid plexus tumor, irrespective of family history

Table III

Likelihood of detecting a mutation based on current clinical classification schemes

Criteria:	Families meeting individual criteria		Cumulative (including all criteria above)[a]			
	No. families	With *TP53* mutations	No. of families	With *TP53* mutations	Sensitivity[b]	Specificity[c]
Classic LFS	54	30 (56%)	54	30 (56%)	40%	91%
Chompret criteria	195	69 (35%)	199	71 (36%)	95%	52%
Birch criteria	101[d]	16 (16%)	238	72 (30%)	96%	38%
Eeles criteria	205[d]	29 (14%)	296	73 (25%)	97%	16%
Families meeting no criteria	45	2 (4%)	341	75 (22%)	100%	0%

[a] Each category includes patients from the criteria within that row in addition to all patients from the criteria above.

[b] Sensitivity: No. of positive patients meeting criteria/75 total positive patients

[c] Specificity: 1 - (No. of negative patients meeting criteria/266 total negative patients)

[d] Does not include families that meet Classic LFS

Table IV

Prevalence of *TP53* mutations

Patient tested:	Cancer in 1st and 2nd degree relatives less than 50 years of age			
	No core[a] cancer in any family members	**Only one family member with at least one core cancer, no cancer in any other relatives**	**Only one family member with at least one core cancer and one or more family members with a non-core cancer**	**Two or more family members with core cancers**
No core cancer at any age	0% (0/21)	13% (1/8)	10% (1/10)	13% (2/15)
Only one core cancer, this cancer occurs >40	6% (1/18)	0% (0/12)	0% (0/9)	21% (5/24)
Only one core cancer, this cancer occurs ≥18 & ≤40	5% (2/43)	7% (1/15)	10% (2/21)	57% (16/28)
At least one childhood core cancer (<18)[b]	33% (16/49)	50% (5/10)	100% (5/5)	38% (3/8)
Two or more core cancers, both occurring >40	0% (0/7)	0% (0/3)	67% (2/3)	0% (0/2)
Two or more core cancers, at least one ≤40	21% (3/14)	33% (2/6)	50% (1/2)	88% (7/8)

[a] Core cancers are adrenocortical carcinoma (ACC), breast cancer, brain cancer, and sarcoma

[b] Patients with childhood cancers as well as adult cancers fall into this category