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The Benefit and Burden of Cancer Screening in Li-Fraumeni Syndrome: A Case Report

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Li-Fraumeni syndrome is a rare cancer predisposition syndrome classically associated with remarkably early onset of cancer in families with a typical spectrum of malignancies, including sarcoma, breast cancer, brain tumors, and adrenocortical carcinoma. Because the risks of cancer development are strikingly high for Li-Fraumeni syndrome, aggressive cancer surveillance is often pursued in these individuals. However, optimal screening methods and intervals for Li-Fraumeni syndrome have yet to be determined. In addition, there may be a significant psychosocial burden to intensive cancer surveillance and some prevention modalities. Here, we describe a case of a young woman with a *de novo* mutation in *TP53* and multiple malignancies, with her most recent cancers found at early, curable stages due to aggressive cancer screening. The potential benefits and risks of intensive cancer surveillance in hereditary cancer syndromes is discussed.

INTRODUCTION

Li-Fraumeni syndrome is a rare cancer predisposition disorder that dramatically increases the risk of developing cancer, especially at an early age. The cancers most often associated with Li-Fraumeni syndrome include sarcoma, breast cancer, brain tumors, and adrenocortical carcinoma, although the spectrum of associated cancers can be quite broad. Li-Fraumeni syndrome is known to be linked to germline mutations of the *TP53* tumor suppression gene, located on chromosome 17p13. P53 is a transcription factor that normally regulates the cell cycle and prevents genomic mutations. When individuals harbor a defective copy of the *TP53* gene, they become prone to cancer development if the cell can no longer utilize a functional p53 protein to repair DNA or initiate normal apoptosis. While mutations in *TP53* are typically inherited in an autosomal dominant manner, some families with Li-Fraumeni cancer phenotypes do not harbor an identifiable mutation or, on other occasions, *TP53* mutations can arise *de novo* in an individual without a remarkable family history.

Observations of multiple, early-onset cancers in families led to the description of Li-Fraumeni syndrome in 1969 [1,2]. In 2009, DNA sequencing of 525 patients with clinical suspicion of Li-Fraumeni syndrome found mutations in 91 patients. All families with a *TP53* mutation had at least one family member with a sarcoma, breast, brain, or adrenocortical carcinoma, and these were identified as "core cancers" in this syndrome [3]. Melanoma, gastric cancer, lymphoma, Wilms tumor, leukemia, and colorectal carcinoma are also associated with this syndrome [4].

Risks of cancer development in individuals with Li-Fraumeni syndrome are strikingly high. For female carriers of a *TP53* mutation, lifetime risk of cancer by age 60 approaches 90 percent, with average age of first cancer diagnosis reported to be 28 [3,5]. Male carriers face a slightly lower lifetime risk of 73 percent, though age of onset of first cancer has been reported to be lower as well, at age 21 [3,6]. Risks of developing a second malignancy are high as well, described to be as high as 60 percent in the 30 years following initial cancer diagnosis [7]. Despite these risks, precise cancer screening guidelines for

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†Abbreviations: NCCN, National Comprehensive Cancer Network.

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those with Li-Fraumeni syndrome have yet to be defined. Individuals affected by Li-Fraumeni syndrome may be offered a battery of screening tests, which can include frequent physical exams, blood tests, breast MRI, colonoscopy, and body imaging with CT, ultrasound, and/or body MRI starting as young as age 20 — or even earlier in some cases.

Here, we report a case of a young woman with *de novo* Li-Fraumeni syndrome who initially presented with sarcoma at age 11 and has gone on to develop a total of five different malignancies by the age of 28. We present her case as a noteworthy example of Li-Fraumeni syndrome, illustrating both the potential benefit and the potential burden of cancer screening and subsequent management for these patients.

CASE PRESENTATION

An 11-year-old girl presented in 1998 with a "bump" on her left calf that gradually increased in size. A biopsy was performed, which revealed a rhabdomyosarcoma. The patient was treated with combination chemotherapy that included cyclophosphamide, ifosfamide, doxorubicin, actinomycin D, vincristine, and carboplatin along with radiation therapy to the left calf. She initially did well, but developed a local recurrence 1 year later, which ultimately required a below-the-knee limb amputation at the age of 12. Later that year, she developed a palpable "bump" on one of her right lower ribs. This was resected and found to be a chondrosarcoma. She had a local recurrence at the rib surgical bed within 18 months, requiring wider surgical resection of the rib and adjacent lung. At the age of 18, she developed what appeared to be a cyst on one of her vulva. This was resected and found to be a small Stage I leiomyosarcoma.

Because of her history of three separate, early-onset sarcomas, she started annual surveillance MRI of chest, abdomen, and pelvis at the age of 18. She did well until the age of 22, at which time she was found to have a new, small left renal mass on MRI. She underwent left partial nephrectomy, with pathology showing a Stage I, 0.9 cm clear cell renal carcinoma.

Though she was originally referred at the age of 18 for genetic counseling at the time of her third sarcoma diagnosis, she declined specific testing for *TP53* mutations at that time. Her family history was notable only for a maternal grandfather with bladder cancer at age 85, a maternal great aunt with uterine cancer around age 40, and a paternal great uncle with lung cancer at an unknown age. Neither her parents nor her brother were ever diagnosed with cancer. She was followed closely by her physicians for possible Li-Fraumeni syndrome with body imaging and colonoscopy. At age 27, she underwent germline genetic testing with whole exome analysis for a wide panel of genes that might be relevant to the patient's phenotype including: MUTYH, MSH2, EPCAM, MSH6, MLH1, APC, PMS2, CDKN2A, BMPR1A, PTEN, CDK4, CDH1, PALB2, *TP53*, SMAD4, STK11, CHEK2, SDHB, SDHC, FH, VHL, MET, TSC1, PTEN, SDHD, TSC2, and FLCN. Testing revealed a heterozygous splice site mutation in *TP53*, IVS6-2A>G, and no other mutations in cancer-related genes. Both parents tested negative for the mutation, indicating that it either arose *de novo* in a sperm or egg cell or that one parent was a gonadal mosaic. Genetic testing in the patient's brother was recommended because of the possibility of gonadal mosaicism in a parent. The patient has no children of her own at this time, but she was counseled that as a confirmed *TP53* germline mutation carrier, she has a 50 percent chance of passing the mutation on to her future children.

Shortly following her formal diagnosis of Li-Fraumeni syndrome, she underwent her first routine screening breast MRI at the age of 27. The breast MRI revealed a 5 mm abnormality in the left breast. Biopsy of this area revealed an invasive ductal carcinoma, ER positive, PR positive, HER2 positive (3+ on immunohistochemistry). She initially underwent lumpectomy, with pathology revealing a Stage I invasive ductal carcinoma measuring 4 mm, grade 3, negative margins with no lymph node involvement. She was treated with adjuvant paclitaxel and trastuzumab, followed by trastuzumab alone to complete 1 year of therapy. She underwent bilateral prophylactic mastectomies and was subsequently started on endocrine therapy with a 5- to 10-year course of tamoxifen planned.

She is currently undergoing aggressive ongoing cancer surveillance as per published guidelines, comprised of annual brain MRI, annual total body MRI, colonoscopy every 2 years, annual dermatologic exam, and complete blood counts and LDH screening every 3 months. She no longer requires breast imaging due to her choice of bilateral mastectomies. She soon will undergo an additional 3-month short interval chest MRI based on a new, small rib abnormality seen on total body MRI.

DISCUSSION

The case above illustrates several fundamental lessons, including the importance of recognizing hereditary cancer syndromes and the profound benefit of cancer screening and early detection, as well as the potential heavy burden for patients to be under constant surveillance for future cancers.

This patient's specific presentation of Li-Fraumeni syndrome was notable in several ways. The diagnosis of her initial cancer at an early age, the multiple cancer diagnoses, and the types of cancers she developed (sarcoma, breast) are classic features of Li-Fraumeni syndrome. While the lack of a strong family history in this case is unusual for Li-Fraumeni syndrome, *de novo TP53* mutations are felt to arise in 7 to 20 percent of all cases. As such, providers should maintain a high level of suspicion for the possibility of Li-Fraumeni syndrome in individuals with early onset cancers, even in the absence of a strong family history. In addition, while patients with Li-Fraumeni

Table 1. General criteria for genetic counseling referrals.

• A personal or family history of early-onset cancer (e.g., younger than 45 years for breast cancer; younger than 50 years for colon or uterine cancer)
• Multiple family members on the same side of the family with the same or related cancers
• A family member with a diagnosis of more than one type of cancer
• A personal or family history of breast, ovarian, or pancreatic cancer who are of Jewish ancestry
• A personal or family history of a rare type of cancer/tumor (e.g., breast cancer in a male, medullary thyroid cancer, a sebaceous carcinoma or adenoma)

Table 2. Li-Fraumeni syndrome testing criteria.

Li-Fraumeni Syndrome Testing Criteria	Description
Individual from a family with a known *TP53* mutation	
Classic LFS [2]	• Proband diagnosed with sarcoma before 45 years AND • first-degree relative with cancer before 45 years AND • another first- or second-degree relative with any cancer diagnosed under 45 years of age or with sarcoma at any age
Chompret [6,10]	• Proband with sarcoma, brain tumor, breast cancer, or adrenocortical carcinoma before age 36 years AND at least one first- or second-degree relative with cancer (other than breast cancer if the proband has breast cancer) under the age of 46 years OR • a relative with multiple primaries at any age OR • a proband with multiple primary tumors, two of which are sarcoma, brain tumor, breast cancer, and/or adrenocortical carcinoma, with the initial cancer occurring before the age of 36 years, regardless of the family history OR • a proband with adrenocortical carcinoma at any age of onset, regardless of the family history
Early-age-onset breast cancer	Individual with breast cancer < 35 years, *TP53* testing can be ordered concurrently with *BRCA 1/2* testing or as a follow-up test after negative *BRCA 1/2* testing

syndrome often develop multiple cancers, this patient's cancer history is unusually strong with five separate cancers diagnosed by the age of 27. As a comparison, in a case series of 200 individuals diagnosed with cancer from 24 different Li-Fraumeni kindreds, 15 percent of individuals developed a second cancer, 4 percent had a third cancer, and 2 percent had a fourth cancer [7]. Her specific germline *TP53* mutation, namely IVS6-2A>G, might be predicted to yield a mild phenotype. In general, splice site mutations and other mutations that completely inactivate the gene are felt to produce a milder phenotype than missense mutations in the DNA-binding domain [8], but clearly the genotype-phenotype correlation in this disease is not precise. The specific mutation found in this patient was previously reported in a patient with milder features [9]. It should be noted, however, that the daughter of the reported patient had two sarcomas diagnosed before age 18. Our patient's genetic testing included whole exome analysis, and no additional oncogenic mutations or alterations were found; thus, we reason that her aggressive cancer phenotype is attributed primarily to the single splice site mutation identified in *TP53*.

This patient has been fortunate to have all of her cancers diagnosed at early stages. This has allowed for the benefit of long-term, disease-free survival intervals, but also has provided the opportunity for new cancers to develop during those times. Indeed, as the recognition of hereditary cancer syndromes improves in parallel with enhanced cancer diagnosis and treatment, there may be an increasing number of Li-Fraumeni patients who go on to develop high numbers of serial primary malignancies.

Though this patient's case was unusual in some ways for Li-Fraumeni syndrome, the fact that this patient developed multiple cancers of any kind, especially starting at a young age, would be important red flags for the clinician to recognize and should prompt referral for genetic counseling. The differential diagnosis of Li-Fraumeni syndrome includes other inherited cancer syndromes, including hereditary breast and ovarian cancer syndrome, typically characterized by mutations in *BRCA 1* and *2*, and

Table 3. Adult cancer surveillance guidelines for Li-Fraumeni syndrome.

Cancer Type	NCCN Guidelines [2,3,10,11]	Villani et al. [15]
Breast cancer	• Breast cancer awareness and periodic self breast exams starting age 18 • Clinical breast exam every 6-12 months • Annual breast MRI (preferred) or mammogram starting age 20-29 or based on earliest age of onset in family • Annual mammogram AND breast MRI ages 30-75, then individualized >75y • Discuss risk-reducing mastectomy	• Monthly self-breast exams starting age 18 • Clinical breast exam every 6 months starting age 20-25 years of 5-10 years before earliest known breast cancer in family • Annual mammogram and breast MRI starting age 20-25 years, or at earliest age of onset in family • Consider risk reducing bilateral mastectomy
Brain tumors	• Annual careful neurologic exam • Discuss option of brain MRI	• Annual brain MRI
Soft tissue and bone sarcoma	• Annual careful physical exam • Discuss option of total body MRI and abdominal ultrasound	• Annual rapid total body MRI • Ultrasound of abdomen and pelvis every 6 months
Colon cancer	• Consider colonoscopy every 2-5 years, starting no later than age 25	• Colonoscopy every 2 years, beginning age 40, or 10 years prior to earliest diagnosis in family
Melanoma	• Annual careful skin exam	• Annual dermatologic examination
Leukemia/Lymphoma	• No guidelines	• Complete blood count every 4 months • Erythrocyte sedimentation rate, lactate dehydrogenase every 4 months

hereditary non-polyposis colorectal carcinoma (Lynch) syndrome. Both syndromes can overlap with Li-Fraumeni syndrome in terms of cancer types and age of onset and, in fact, are more prevalent in the general population than Li-Fraumeni syndrome. As such, these syndromes should also be considered in any patient with a strong personal and/or family history of cancer. General criteria for referral for cancer genetic counseling are listed in Table 1.

If mutations in *BRCA 1/2* and/or Lynch syndrome-associated genes have been considered and not found, screening for Li-Fraumeni syndrome may be appropriate. Table 2 lists guidelines regarding whom to test specifically for Li-Fraumeni syndrome. In general, the Classic and Chompret criteria can help identify families at risk for germline p53 mutation, though it is important to remember that negative results do not rule out a diagnosis of Li-Fraumeni syndrome if the personal or family history is suggestive of the syndrome [2,10]. While most guidelines generally suggest testing for *TP53* mutations in families with classic tumor types (sarcoma, breast, adrenocortical carcinoma, and brain tumors) and with cancer onset < age 45, an important independent testing criteria for clinicians to recognize is that all women with early-onset breast cancer (age of diagnosis < 35), regardless of family history, should also be considered for *TP53* mutation testing, particularly if the breast tumor is Her2-positive [3,11]. Thus, our patient would still have qualified for *TP53* testing even if her only cancer diagnosis had been her breast cancer at age 27. Before genetic testing is performed, risk assessment and counseling should be performed by a certified genetic counselor and informed consent should be obtained [12]. Reproductive options and counseling regarding possible inherited cancer risk to relatives should also be addressed [13].

A major goal in recognition and prompt diagnosis of a hereditary cancer syndrome is to provide the opportunity for patients and families to undergo aggressive cancer screening and pursue cancer prevention strategies so that the impact of a cancer diagnosis can be minimized or avoided altogether. In our patient, aggressive cancer screening specifically led to early diagnoses of her renal cell carcinoma and her breast cancer. Though both diseases are ultimately fatal when found at advanced stages, the prognosis for Stage I disease in both renal cell carcinoma and breast cancer is excellent, with cure rates exceeding 90 percent. Early cancer detection also can help minimize the need for aggressive treatment. For example, in our patient, her renal cell carcinoma was treated with curative intent with surgery alone, and her breast cancer chemotherapy regimen was less rigorous than would have been needed for a larger tumor. Knowing she carried a *TP53* mutation, she then opted to pursue bilateral mastectomies, not only to avoid radiation treatment but primarily to prevent future breast cancers from developing.

Despite these seemingly clear benefits, optimal screening methods and intervals for Li-Fraumeni syndrome have yet to be determined. Though periodic surveillance and risk-reducing interventions have been shown in more common

hereditary syndromes such as BRCA 1/2 and Lynch syndrome to reduce morbidity and mortality [14], similar medical benefits from screening and aggressive cancer prevention modalities remain unclear and unproven. There has been only one small observational study regarding screening for patients with Li-Fraumeni syndrome. In 33 asymptomatic TP53 mutation carriers, Villani et al. described aggressive cancer screening, including whole-body MRI and other biochemical tests such as complete blood counts and blood chemistries, to be feasible [15]. Meanwhile, the National Comprehensive Cancer Network (NCCN†) cancer surveillance consensus guidelines for Li-Fraumeni syndrome include consideration of breast and colon cancer screening starting at age 20 and an annual comprehensive physical exam, as well as discussion of other screening modalities such as brain MRI and total body MRI. After discussion of her screening options, our patient desired aggressive surveillance and is being followed per Villani et al. [12] guidelines as described in Table 3.

While the intent of aggressive cancer screening is to help patients enjoy a prolonged, healthy life with minimal cancer burden, there may be significant trade-off in psychosocial burden for some patients related to aggressive surveillance. The common occurrences of incidental findings on repeated screenings, associated "false positive" scans leading to biopsy, and the anxiety of a possible cancer diagnosis can lead to significant psychosocial distress and screening fatigue in some patients with hereditary cancer syndromes. At the time of the discovery of her deleterious *TP53* mutation, this patient expressed a sense of "exhaustion" about her clinical course thus far and indicated her worry about how many times she would have to go through cancer diagnosis and treatment before "enough was enough." This patient was appropriately referred to a therapist by her genetic counselor and later reported that she found this very helpful in coping with her fears and frustrations. Very little exists in the literature specifically addressing psychosocial distress in Li-Fraumeni syndrome, though one small study reported that 36 percent of *TP53* carriers report unnecessary worry as a barrier to screening adherence [14]. However, no significant difference in psychosocial distress was found between those undergoing aggressive surveillance compared to those who were not [14]. It is essential that all patients diagnosed with a hereditary cancer syndrome be counseled by their providers about the potential benefits and the potential burden of cancer surveillance and be offered support and counseling around potential psychosocial distress.

CONCLUSIONS

Here, we present a case of *de novo* Li-Fraumeni syndrome in a young woman with multiple malignancies and her subsequent management. Though rare, a diagnosis of Li-Fraumeni syndrome has significant implications for cancer screening and prevention. Clinicians must be vigilant about recognizing potential hereditary cancer syndromes and refer for appropriate genetic counseling. Individualized risks and benefits and specific attention to the potential for psychosocial distress must be taken into account when managing such patients.

REFERENCES

1. Li FP, Fraumeni JF Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann Intern Med. 1969;71(4):747-52.
2. Li FP, Fraumeni JF Jr., Mulvihill JJ, Blattner WA, Dreyfus MG, Tucker MA, et al. A cancer family syndrome in twenty-four kindreds. Cancer Res. 1988;48(18):5358-62.
3. Gonzalez KD, Noltner KA, Buzin CH, Gu D, Wen-Fong CY, Nguyen VQ, et al. Beyond Li Fraumeni Syndrome: Clinical Characteristics of Families With p53 Germline Mutations. J Clin Oncol. 2009;27(8):1250-6.
4. Malkin D. Li-fraumeni syndrome. Genes Cancer. 2011;2(4):475-84.
5. Chompret A, Brugieres L, Ronsin M, Gardes M, Dessarps-Freichey F, Abel A, et al. P53 germline mutations in childhood cancers and cancer risk for carrier individuals. Br J Cancer. 2000;82(12):1932-7.
6. Wu CC, Shete S, Amos CI, Strong LC. Joint effects of germline p53 mutation and sex on cancer risk in Li-Fraumeni syndrome. Cancer Res. 2006;66:8287.
7. Hisada M, Garber JE, Li FP, Fung CY, Fraumeni JF. Multiple Primary Cancers in Families With Li-Fraumeni Syndrome. J Natl Cancer Inst. 1998;90(8):606-11.
8. Ognjanovic S, Olivier M, Bergemann TL, Hainaut P. Sarcomas in TP53 germline mutation carriers: a review of the IARC TP53 database. Cancer. 2012;118:1387-96.
9. Heymann S, Delaloge S, Rahal A, Caron O, Frebourg T, Barreau L, et al. Radio-induced malignancies after breast cancer postoperative radiotherapy in patients with Li-Fraumeni syndrome. Radiat Oncol. 2010;5:104.
10. Chompret A, Abel A, Stoppa-Lyonnet D, Brugieres L, Pages S, Feunteun J, et al. Sensitivity and predictive value of criteria for p53 germline mutation screening. J Med Genet. 2001;38(1):43-7.
11. Tinat J, Bougeard G, Baert-Desurmont S, Vasseur S, Martin C, Bouvignies E, et al. 2009 version of the Chompret criteria for Li Fraumeni syndrome. J Clin Oncol. 2009;27(26):e108-9; author reply e10.
12. Lammens CR, Aaronson NK, Wagner A, Sijmons RH, Ausems MG, Vriends AH, et al. Genetic testing in Li-Fraumeni syndrome: uptake and psychosocial consequences. J Clin Oncol. 2010;28(18):3008-14.
13. Offit K, Kohut K, Clagett B, Wadsworth EA, Lafaro KJ, Cummings S, et al. Cancer genetic testing and assisted reproduction. J Clin Oncol. 2006;24(29):4775-82.
14. Lammens C, Bleiker E, Aaronson N, Wagner A, Sijmons R, Ausems M, et al. Regular surveillance for Li-Fraumeni Syndrome: advice, adherence and perceived benefits. Fam Cancer. 2010;9(4):647-54.
15. Villani A, Tabori U, Schiffman J, Shlien A, Beyene J, Druker H, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study. Lancet Oncol. 2011;12(6):559-67.