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Evaluation Of Current Clinical Criteria For Li-Fraumeni Syndrome In A Diverse Sample Of Tp53 Mutation Carriers

Emily A. Parham

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EVALUATION OF CURRENT CLINICAL CRITERIA FOR LI-FRAUMENI SYNDROME IN A DIVERSE SAMPLE OF
TP53 MUTATION CARRIERS

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TP53 MUTATION CARRIERS

A

THESIS

Presented to the Faculty of
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by

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EVALUATION OF CURRENT CLINICAL CRITERIA FOR LI-FRAUMENI SYNDROME IN A DIVERSE SAMPLE OF *TP53* MUTATION CARRIERS

Emily Parham, BA

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Li-Fraumeni syndrome (LFS) is a hereditary cancer predisposition syndrome caused by heterozygous germline mutations in the *TP53* gene and characterized by an excess of early-onset cancers, high lifetime risk of cancer, and a wide range of tumor types. Recent studies suggesting a benefit in comprehensive screening protocols for both children and adults make the timely identification of individuals with LFS increasingly important.

A number of criteria have been proposed to identify patients with LFS. The National Comprehensive Cancer Network (NCCN) combines several in its Clinical Practice Guidelines for *TP53* genetic testing. Prior studies have shown that the cumulative sensitivity of criteria included in these guidelines approaches 100% in populations referred for testing due to clinical suspicion based on personal and family histories at the time of test requisition. Because NCCN guidelines are created and revised by panels of experts and are commonly utilized by both providers and insurance companies, we choose to evaluate these guidelines in order to assess the performance of current of *TP53* genetic testing criteria.

By retrospectively analyzing the cancer histories of positive and negative families within the M.D. Anderson Cancer Center *TP53* Research database, estimates of the individual and cumulative sensitivities and specificities of criteria schemes included in the NCCN guidelines were made at the time of the index patient's initial cancer diagnosis and again at the time of last contact with each family. Out of 122 *TP53* positive families in our sample, 22% (27/122) were missed by NCCN guidelines at the time of the index patient's initial cancer diagnosis. 'De novo' mutations and inherited mutations exhibiting incomplete penetrance were particularly likely to be missed, indicating a need for additional criteria able to identify *TP53* mutation carriers in the absence of significant family history. Interestingly, in 22 of the 27 families missed by NCCN guidelines, the index patient had sarcoma diagnosed ≤ 25 as their initial diagnosis, suggesting that *TP53* genetic testing should be considered in any individual with early-onset sarcoma, regardless of family history.

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INTRODUCTION

Li-Fraumeni syndrome (LFS) is a hereditary cancer predisposition syndrome characterized by an excess of early-onset cancers, high lifetime risk of cancer, and a wide range of tumor types. The only known cause of LFS is heterozygous germline mutation in the gene *TP53*, which encodes the tumor suppressor protein p53. The prevalence of these mutations may be as high as 1:5000 in the general population, 1:300 in founder geographic areas, and 1:20 among women diagnosed with breast cancer at or before 35 years of age (Lalloo et al., 2003; Lee et al., 2012; Palmero et al., 2008). In contrast to other, more common cancer predisposition syndromes, such as Hereditary Breast and Ovarian Cancer (HBOC) and Lynch syndrome (LS), the portion of LFS cases attributable to new or '*de novo*' mutations (i.e. mutations starting new in a proband, rather than inherited from a parent) is significant, accounting for an estimated 7-20% of cases (Gonzalez et al., 2009a). Also in contrast to HBOC and LS, the optimal clinical management of LFS patients remains uncertain due to the wide range of associated cancer susceptibilities and marked inter- and intra-familial variation in disease penetrance (Hwang et al., 2003; Mai et al., 2012; Mitchell et al., 2013). Though several promising modifier mechanisms have been proposed, few robust genotype-phenotype associations have been established, and no clinically-applicable model exists for risk stratification of LFS patients by genotype (Fang et al., 2010; Marcel et al., 2009; Ribeiro et al., 2001; Shlien et al., 2008; Silva et al., 2012; Tabori and Malkin, 2008; Tabori et al., 2007; Zerdoumi et al., 2013). For these reasons, predictive testing of at-risk, unaffected individuals, and in particular children, has been approached cautiously by the medical community (Evans et al., 2010; Frebourg et al., 2001; Fresneau et al., 2013). In light of recent studies suggesting a benefit in using comprehensive screening protocols for both children and adults, as well as potential impact on treatment decisions (e.g. consideration of prophylactic surgeries, avoidance of radiation when possible), the timely identification of individuals with LFS has become increasingly important (Masciari et al., 2008; McBride et al., 2014; Villani et al., 2011).

Several criteria exist for use in the identification of patients with LFS. The Classic LFS criteria were developed in 1988 as a diagnostic tool and are largely based on the original clinical description of Li-Fraumeni syndrome (Li and Fraumeni, 1969; Li et al., 1988). These criteria are very specific to individuals diagnosed with sarcoma and do not allow for patients without significant family history to be considered for testing. To address this limitation, the Chompret criteria were developed as a less stringent tool to identify patients appropriate for *TP53* germline testing (Chompret et al., 2001; Tinat et al., 2009). More recently, the National Comprehensive Cancer Network (NCCN) has recommended that testing be offered to any individual who meets either of the aforementioned criteria, has had a diagnosis of breast cancer at or before 35 years of age, or is from a family with a known *TP53* mutation (Table 1) (NCCN, 2014).

Table 1. Guidelines proposed by the NCCN for *TP53* genetic testing

Any individual meeting one of the following criteria:	
1.	Individual from a family with a known <i>TP53</i> mutation.
2.	Classic LFS (<i>within the same lineage</i>): Proband diagnosed with sarcoma before 45 years of age, AND A first-degree relative with cancer before 45 years of age, AND Another first or second-degree relative with any cancer diagnosed under 45 years of age or with sarcoma at any age.
3.	Chompret: Proband with tumor belonging to the LFS tumor spectrum (e.g., soft tissue sarcoma, osteosarcoma, brain tumor, premenopausal breast cancer, adrenocortical carcinoma, leukemia, lung bronchoalveolar cancer) before age 36 years AND at least one first-or second degree relative with LFS tumor (except breast cancer) before age 56 years or with multiple tumors; OR Proband with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum and first of which occurred before 46 years; OR Patient with adrenocortical carcinoma or choroid plexus tumor, irrespective of family history.
4.	Early-onset breast cancer: Individual with breast cancer at or before 35 years (<i>TP53</i> testing may be ordered concurrently with <i>BRCA1/2</i> testing or as a follow-up after negative <i>BRCA1/2</i> results).
Abbreviations: LFS, Li-Fraumeni syndrome	

In populations referred for *TP53* genetic testing subsequent to clinical suspicion, the individual positive predictive values of the Classic LFS and revised Chompret criteria are 56%-73% and 21% respectively, and cumulative sensitivity approaches 100% based on personal and family history at the time of test requisition (Bougeard et al., 2008; Gonzalez et al., 2009b; Ruijs et al., 2010). However, populations referred following clinical suspicion, especially in the context of rare diseases, may represent the most severe presentations and therefore the families most likely to meet testing criteria. Additionally, given that one of the primary goals in identification of hereditary cancer syndrome patients is prevention and/or early detection of associated malignancies, an assessment of clinical testing criteria not only at

the time of genetic testing, but rather at the time of a patient's first cancer diagnosis, provides an additionally useful measure of utility. The *TP53* Research Database at M.D. Anderson Cancer Center (MDACC) contains comprehensive clinical data on the personal and family histories of patients who have previously undergone germline *TP53* testing on research and/or clinical bases and offers a unique opportunity for the evaluation of LFS clinical testing criteria. In contrast to prior studies performed on populations referred subsequent to clinical suspicion, it is likely that a portion of the LFS families in the MDACC database, particularly among those ascertained through systematic studies of pediatric cancer, might not have been detected clinically. Importantly, research funding allowed for testing of multiple family members beyond the index patients (probands), irrespective of cancer affection status. This permitted identification of confirmed *de novo* mutations, as well as inherited cases displaying decreased disease penetrance. Lastly, a concerted effort is made to follow the research families over time, allowing for the recognition of individuals and families that failed to meet LFS criteria at the time of the index patient's first cancer diagnosis and would have gone undetected, but with additional cancers developing over time, evolved to meet testing criteria years later.

Given the previously underestimated prevalence, unappreciated *de novo* rate, and variable penetrance of *TP53* mutations, it is likely that a substantial portion of individuals with LFS are not identified by current genetic testing guidelines in the absence of remarkable personal and/or family cancer history. We aim to provide a comprehensive evaluation of the current NCCN guidelines for *TP53* genetic testing and a characterization of the mutation-positive families in our cohort that they fail to detect.

METHODS

Patients and *TP53* genetic testing

The Genetics Research Database at MDACC is comprised of families identified on the basis of systematically ascertained rare childhood sarcoma patients, individuals with multiple primary cancers, individuals with cancers at unusually early ages, or familial clustering of cancers including but not

limited to the LFS spectrum. The study has a long-standing, IRB-approved research protocol aimed at understanding the genetic basis of cancer predisposition. The methods for patient identification, data and sample collection, and mutation analysis of *TP53* have been described previously (Strong and Williams, 1987; Bondy et al., 1992; Lustbader et al., 1992; Hwang et al 2003; Wu et al 2006). Only families with mutations considered to be deleterious are categorized as 'mutation-positive.'

The majority of patients included in the database have had genetic testing of *TP53* completed on a research basis by DNA sequencing of the coding exons only. A portion have had large gene deletions detected by deletion/duplication testing through outside clinical laboratories.

Clinical Data

The database was queried for cancer histories of all probands and their first and second-degree relatives. The proband in this dataset is defined as the first individual in each family who underwent *TP53* genetic testing (the index patient). Information queried for each family included year of and reason for ascertainment as outlined in the following paragraph. Information queried for each individual (proband and all first- and second-degree relatives) included relationship to the proband, mutation status, gender, cancer history (type, site, pathology, age at diagnosis, treatment information), current age or age at death, date of last contact, and smoking history.

All families in the MDACC database have been previously grouped into cohorts based on reason for ascertainment of the index patient as follows: osteosarcoma in the index patient (OST), soft tissue sarcoma in the index patient (STS), adrenocortical carcinoma in the index patient (ACC), brain tumor in the index patient (BTX), multiple primary cancers in the index patient (SMN, second malignant neoplasm), or some other form of clinical suspicion not fitting into one of the aforementioned categories, such as early-onset breast cancer or familial cancer aggregation identified through referral from the medical genetics clinic at MDACC (MGC). Due to time constraints and in order to maintain equal representation by reason for ascertainment, mutation-negative families were randomly selected within each of the ascertainment cohorts to achieve a 2:1 ratio to the corresponding mutation-positive

cohort, with the exception of the ACC cohort, which had an equal number of negative and positive families and is therefore represented by a 1:1 ratio.

Exclusion criteria included absence of cancer in the index patient.

Evaluation of families

All positive and negative families were analyzed to determine whether or not they would have been detected by Classic LFS, revised Chompret, and/or cumulative NCCN criteria at the time of the initial cancer diagnosis of the index patient. Those not meeting criteria initially were analyzed again based on family history at the time of last contact with each to determine whether the family evolved to fulfill criteria over time. Additionally, to investigate any potential contributions to sensitivity, families not meeting any criteria at time of initial cancer diagnosis of the index patient were analyzed to determine whether they would have been detected by the Birch and/or Eeles diagnostic criteria, two additional schema originally designed prior to the advent of the Chompret testing criteria to identify “LFS-life” families not fitting the stringent Classic LFS criteria (Birch et al., 1994; Eeles 1995). The aforementioned analyses were performed twice; once to allow any individual in the family to fill the role of ‘proband’ as defined by the testing criteria, and again to restrict the role of ‘proband’ to only the index patient.

Data Analysis

Sensitivity and specificity estimates were derived using the fraction of positive and negative families that met or did not meet Classic LFS, revised Chompret, and NCCN criteria.

Positive families that met, evolved, or were missed by criteria were categorized by mode of inheritance, mutation type, and individual and family cancer histories. Breast cancer and melanoma in mutation carriers were also characterized by prevalence and age at first diagnosis. Sarcoma was characterized by average age at first sarcoma diagnosis, and the potential effect of testing for early-onset sarcoma on overall testing criteria efficacy was considered.

RESULTS:

In total, 124 mutation positive family histories and 456 mutation negative family histories were available for review. The 124 mutation-positive families represented 22 from the OST cohort, 18 from the STS cohort, 4 from the ACC cohort, 1 from the BTX cohort, 35 from the SMN cohort, and 44 from the MGC cohort. 2 of the 124 mutation-positive families (both from the MGC cohort), were excluded on the basis of absence of cancer in the index patient. As specified in the methods section, 240 mutation-negative families were selected for review.

The results and discussion presented in this paper reflect the analysis in which any individual in the family is allowed to fill the role of ‘proband.’ The results of the second analysis, in which the role of ‘proband’ is restricted to the index patient, show decreased sensitivity and increased specificity of criteria and are available for review in the appendix.

Efficacy of cumulative NCCN testing criteria

At the time of the index patient’s first cancer diagnosis, the cumulative sensitivity of the NCCN guidelines for *TP53* genetic testing was 78% with a specificity of 65%. Over a median follow-up period of 10 years (range 2-45 years), sensitivity increased to 95% and specificity decreased to 45% as additional cancers accumulated in the index patients’ personal and family histories. The component and cumulative performance of the NCCN criteria are described in Table 2.

Table 2. Performance of Classic LFS, revised Chompret, and cumulative NCCN guidelines for *TP53* genetic testing when any individual in the family is allowed to fill the role of ‘proband’

Criteria	Families meeting criteria with <i>TP53</i> mutations			Sensitivity ³ (%)	Specificity ⁴ (%)	LR+ ⁵	LR- ⁶
	No. of families	No.	%				
<i>At initial presentation¹</i>							
Classic LFS	42	36	86	30	98	11.80	0.72
Chompret	150	85	57	70	73	2.57	0.42
NCCN	179	95	53	78	65	2.22	0.34
Families not detected by any criteria	183	27	15	--	--	--	--
<i>At last contact²</i>							
Classic LFS	68	53	78	43	94	6.95	0.60
Chompret	227	112	49	92	52	1.92	0.16
NCCN	248	116	47	95	45	1.73	0.11
Families not detected by any criteria	114	6	5	--	--	--	--

Abbreviations: LFS, Li-Fraumeni syndrome; LR+, likelihood ratio positive; LR-, likelihood ratio negative

¹Based on personal and family history at the time of the proband's first cancer diagnosis.

²Based on personal and family history at the time of last contact with the family.

³Sensitivity: Number of positive families meeting criteria/122 total positive families (x100)

⁴Specificity: Number of negative families excluded by criteria/240 total negative families (x100)

⁵LR+: sensitivity/(1-specificity)

⁶LR-: (1-sensitivity)/specificity

The majority (85 of 95; 89%) of families fulfilling NCCN *TP53* testing guidelines at the time of the index patient's first cancer diagnosis would have been detected by the Chompret criteria alone (component sensitivity of 70%). Nine of the 95 families detected by NCCN criteria at the time of the index patient's initial diagnosis were identified only on the basis of breast cancer ≤ 35 years and did not meet either Classic LFS or Chompret criteria. Three of 9 met this criterion based on an individual with a diagnosis of breast cancer between the ages of 31 and 35 and would have therefore been missed by the NCCN's previous criterion of breast cancer diagnosed ≤ 30 years. Six of 9 also evolved over time to meet Chompret criteria subsequent to additional cancer diagnoses in the index patients or their family members over a median period of 5 years (range 2-19). Five evolved at the diagnosis of a second primary cancer in the index patient, and 1 at the diagnosis of an LFS-spectrum tumor in the index patient's 2-year-old son.

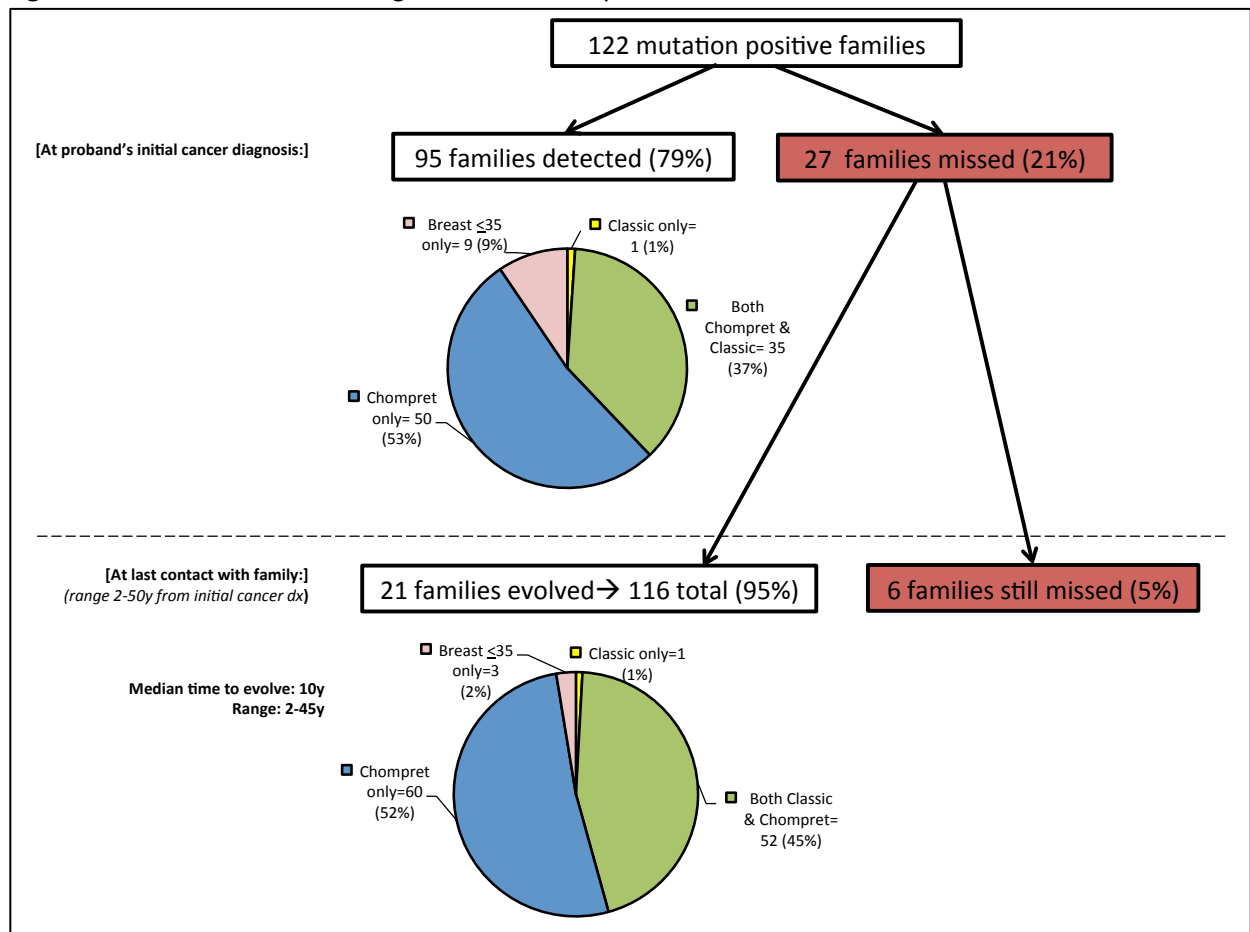
Overall, the Classic LFS criteria identified 2 families that were not also identified by the Chompret criteria or on the basis of early-onset breast cancer; one at the time of the index patient's initial cancer diagnosis, and one at time at last contact. In one case, the Classic LFS criteria detected a family characterized by one early-onset sarcoma and several additional early-onset tumors (<45 years) outside of the NCCN's accepted LFS spectrum (2 ovarian cancers, one colon cancer, and 1 melanoma). Eight years after the index patient's initial diagnosis, sarcomas were diagnosed in his son and brother, fulfilling Chompret criteria at that point in time. In the second case, a family with no cancer history in first or second-degree relatives at the time of the index patient's initial diagnosis of osteosarcoma at 10 years, evolved to meet Classic LFS criteria 15 years later following the diagnoses of pancreatic cancer at 37 in the patient's father and thyroid cancer at 30 in his sister. However, because the tumors in the patient's relatives did not fit the typical LFS spectrum, the family did not fulfill Chompret criteria and would have continued to go undetected if not for the inclusion of Classic LFS criteria in NCCN testing guidelines.

Of note, the Birch criteria detected no additional families. The Eeles criteria detected an additional seven families at the index patient's first diagnosis (84% initial cumulative sensitivity) and an additional 3 families over time, leaving only 2 families undetected at last contact (98% cumulative sensitivity). Of note, 4 of the 7 newly detected individuals met criteria on the basis of prostate cancer ≥ 55 years or breast cancer ≥ 58 years in inferred wild-type individuals (index patient's mutation either known *de novo*, or known to be inherited from the opposite lineage).

Evolution of families to meet criteria

Of the 27 families missed by NCCN guidelines at the time of the index patient's initial diagnosis, 21 met criteria with additional years of observation (Median time to evolve: 10 years; Range: 2-45 years) (Figure 1).

Figure 1. Performance of NCCN guidelines at two points in time



Thirteen met criteria due to a new diagnosis in the index patient and 8 due to new diagnoses in the family (Table 3).

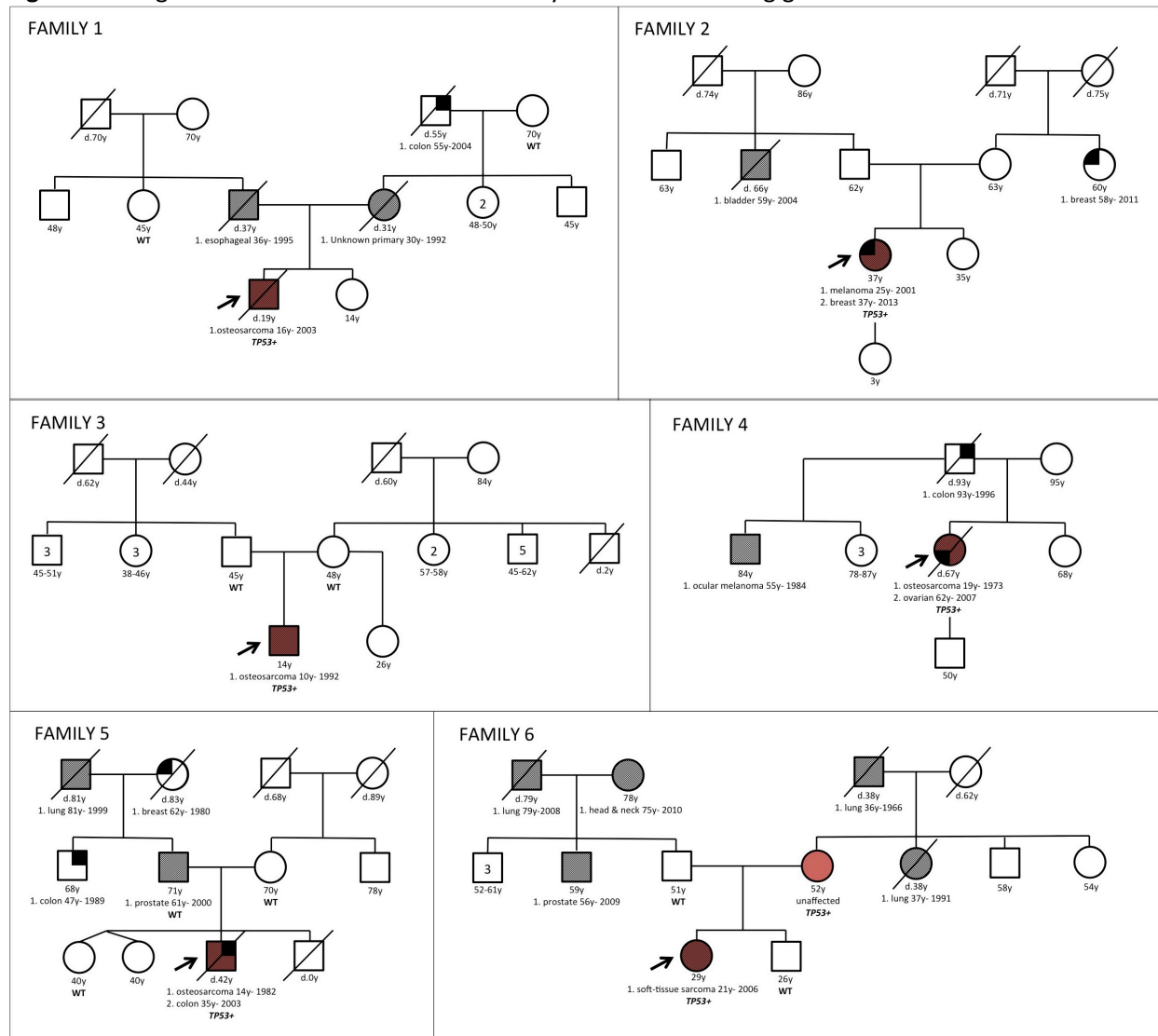
Table 3. Characteristics of 21 mutation-positive families and individuals that met NCCN testing guidelines with additional years of observation following the index patient's initial diagnosis

#	Initial diagnosis of index patient (IP)	Family cancer history at initial diagnosis of IP	Years to evolve	Criteria met	Basis on which criteria was met	New cancer diagnoses during interim period	Inheritance	Gender (IP)
1	OST 12y	Father: esophageal 42y; PGF: brain 59y	3	Classic & Chompret	Diagnosis in family	Sib: STS 13y	Paternal	F
2	OST 14y	None	12	Chompret	2nd Primary (IP)	IP: breast 26y	De novo	F
3	OST 10y	None	15	Classic	Diagnosis in family	Father: pancreatic 37y; Sib: thyroid 30y	Paternal	F
4	OST 19y	MU: Lung 37y	14	Classic & Chompret	Diagnosis in family	Sib: breast 34y	Paternal	M
5	brain 3y	PGM: colon 54y	17	Chompret	Diagnosis in family	PGM: breast 82y (2nd primary)	Maternal	F
6	OST 17y	MGM: breast 65y	3	Chompret	3rd Primary (IP)	IP: colon 17y, OST 20y	De novo	M
7	OST 25y	PGF: colon 70y	2	Chompret	3rd Primary (IP)	IP: melanoma 27y IP: lung adenocarcinoma * 27y	De novo	F
8	brain 4y	None	9	Chompret	2nd Primary (IP)	IP: OST 13y	Paternal	F
9	OST 13y	None	16	Chompret	2nd Primary (IP)	IP: breast 29y	Unknown	F
10	STS 2y	None	12	Chompret	2nd Primary (IP)	IP: OST 14y	Maternal	F
11	STS 22y	PGF: prostate 68y; MA: gallbladder 44y	9	Chompret	2nd Primary (IP)	IP: brain 31y; MA: uterine 52y	De novo	F
12	OST 13y	None	21	Chompret	2nd Primary (IP)	IP: OST 35y	Unknown	M
13	STS 1y	None	3	Chompret	2nd Primary (IP)	IP: OST 4y	De novo	M
14	STS 2y	None	8	Chompret	2nd Primary (IP)	IP: OST 10y	Paternal	M
15	BAC 43y	Mother: thyroid 60y	13	Chompret	2nd Primary (IP)	IP: breast 56y	Unknown	F
16	STS 3y	None	3	Classic & Chompret	Diagnosis in family	Sib: STS 3y	Paternal	F
17	breast 37y	MGM: squamous cell 64y	10	Chompret	Diagnosis in family	Father: colon, 81y; Father: lymphoma, 81y (multiple primaries)	Unknown	F
18	STS 1y	PGF: pancreatic 64y	23	Chompret	Diagnosis in family	MGM: breast & kidney, 78y (multiple primaries)	Unknown	F
19	STS 2y	None	6	Chompret	Diagnosis in family	Sib: STS, 0y	Paternal	F
20	STS 1y	MU: prostate 55y	6	Classic & Chompret	Diagnosis in family	Sib: STS 1y; PGF: lung 61y	Paternal	M
21	STS 5y	PGF: melanoma 54y	16	Chompret	2nd Primary (IP)	IP: OST 20y; Father: melanoma 45y; PGM: uterine 66y	Paternal	M

Abbreviations: OST, osteosarcoma; STS, soft tissue sarcoma; BAC, broncho alveolar carcinoma; PGF, paternal grandfather; MU, maternal uncle; PGM, paternal grandmother; MGM, maternal grandmother; MA, maternal aunt
*medical record available, pathology suggestive of BAC

In 4/21 families (19%), six individuals died after being diagnosed with a new cancer during the period between the index patient's first cancer diagnosis and the time the family met NCCN testing criteria. All six were either known mutation-positive or were probable mutation-carriers based on family structure and diagnosed with an LFS-spectrum tumor before the age of 56. Of the 27 families that would have been missed by NCCN criteria at the time of the index patient's initial diagnosis, 6 families had still not evolved to meet criteria at time of last contact with each family. The pedigrees of the 6 families still missed by cumulative NCCN testing criteria at time of last contact with each family are provided in Figure 2.

Figure 2. Pedigrees of the 6 families still missed by NCCN *TP53* testing guidelines at time of last contact



Breast cancer in LFS

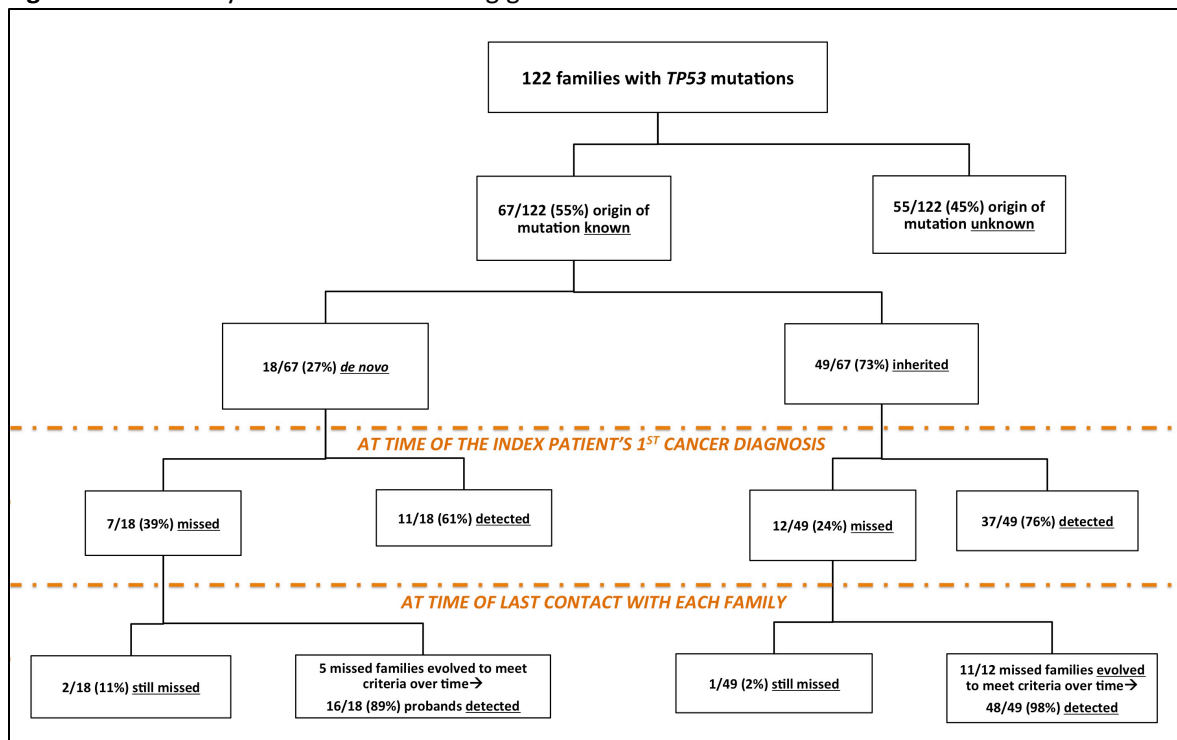
In our sample of 122 index patients and their first and second-degree relatives, 105/151 (70%) mutation-positive females ≥ 18 years old had a personal history of at least one diagnosis of breast cancer. The average age at first breast cancer diagnosis among these women was 33 years (median 33 years, range 18-56 years). Among the 75 mutation-positive women who had breast cancer as their first cancer diagnosis, the average age at first breast cancer diagnosis was 32.7 years (median 33 years, range 19-49 years).

Among deceased, adult, mutation-positive females in our sample (age of death 18-67 years), 56/70 (80%) had a diagnosis of breast cancer during her lifetime.

Effect of *de novo* and paternally inherited mutations on criteria fulfillment by family history

Inheritance was known for 67/122 (55%) mutation-positive families. Of those families, 18/67 (27%) of mutation-positive index patients were confirmed *de novo* cases. At the time of the initial diagnosis of the index patient, 7/18 (39%) *de novo* mutations and 12/49 (24%) confirmed inherited mutations were missed by NCCN testing guidelines (Figure 3).

Figure 3. Sensitivity of NCCN *TP53* testing guidelines for inherited vs. *de novo* mutations



Of the 11 '*de novo*' individuals identified, 2 were identified on the basis of breast cancer ≤ 35 and did not meet Classic LFS or Chompret criteria, 4 were identified by Chompret criteria on the basis of adrenocortical carcinoma with no contributory family history, and 3 were identified by Chompret criteria, because the index patient had a child that had previously been diagnosed with an LFS spectrum tumor. At the time of last contact with each family, (2/18) 11% of '*de novo*' mutations and 1/49 (2%) of inherited mutations were still not detected by NCCN guidelines.

Of the 27 families missed by NCCN testing guidelines at the time of the initial diagnosis of the index patient, 19 had sufficient information available to determine inheritance. 7/19 (37%) of missed mutations were '*de novo*,' and 12/19 (63%) of missed mutations were inherited. 9/12 (75%) of missed, inherited mutations were paternally inherited, and 3/12 (25%) were maternally inherited. In all but one case (father diagnosed with esophageal cancer at 42), the transmitting parent was unaffected at the time of the index patient's initial diagnosis.

Of the 9 families detected only on the basis of breast cancer diagnosed ≤ 35 , 2 represented '*de novo*' mutations in the index patient, 3 represented mutations inherited paternally from unaffected fathers, 1 was inherited from a father diagnosed with an unknown primary at 51, 2 were of unknown inheritance with no family history of LFS-spectrum tumors, and 1 was of unknown inheritance with a strong family history of breast cancer, but no other LFS-spectrum tumors.

Melanoma in patients with germline TP53 mutations

There were a total of 317 mutation-positive individuals in our population (all 122 index patients and their mutation-positive first- and second-degree relatives). Because the strength of association between melanoma and LFS has been contended, we sought to characterize it in our study population. 12/317 (3.8%) mutation-positive individuals in our population had a diagnosis of melanoma at some point in time. For 6/12 (50%) mutation-positive individuals with melanoma, melanoma was their first cancer diagnosis at a median age of 33 years (range 21-48 years).

DISCUSSION:

The predisposition to a wide range of cancers, significant *de novo* mutation rate, and variable penetrance of *TP53* mutations make the timely identification of individuals with LFS exceptionally challenging. As the availability of comprehensive cancer screening and risk management protocols increases, so does the need for prompt identification of *TP53* mutation carriers. Further, identification of germline *TP53* mutations may provide added benefit in guiding treatment decisions and/or facilitating reproductive decision-making for affected individuals.

Currently, NCCN guidelines recommend that *TP53* genetic testing be offered to all patients diagnosed with adrenocortical carcinoma, choroid plexus tumor, or early-onset breast cancer (≤ 35 years), regardless of personal or family cancer history. However, for individuals presenting with other types of cancer, guidelines require the presence of multiple cancers in patients and/or their relatives before recommending genetic testing. Prior studies on the efficacy of clinical testing guidelines have examined individual and family histories at the time of test requisition. This study is, to our knowledge, the first to evaluate the sensitivity of LFS testing criteria at the time of the initial diagnosis of the index patient. Additionally, we concurrently evaluate the individual (Classic LFS, revised Chompret) and cumulative sensitivities of the NCCN guidelines for *TP53* genetic testing. Our analysis shows that 22% of index patients with germline *TP53* mutations would not have been detected at the time of their first cancer diagnosis by medical professionals adhering to NCCN testing guidelines for LFS.

Individuals with *de novo* mutations lack a significant family history of cancer, and therefore are most likely to be missed by current NCCN guidelines at initial diagnosis. In our sample, '*de novo*' mutations accounted for 15% (18/122) of total cases and 27% (18/67) of cases for which there was sufficient information available to determine inheritance. These findings support prior studies suggesting that '*de novo*' mutations are not uncommon in LFS (Gonzalez et al., 2009a). Individuals with paternally inherited *TP53* mutations were also more likely to be missed by testing criteria when compared to individuals with maternally inherited mutations, presumably due in part to the older age

of onset in males. Each of these scenarios highlights the need for additional criteria capable of identifying mutation-positive individuals in the absence of significant family history.

The utility of universal *TP53* genetic testing in individuals with early-onset breast cancer has been debated (Ginsburg et al., 2009; Lee et al., 2012; McCuaig et al., 2012; Mouchawar et al., 2010; Tinat et al., 2009). In our study population, 9 mutation-positive families were initially identified only on the basis of breast cancer ≤ 35 years and would not have been detected by combined Chompret and Classic LFS criteria alone. This increased the overall sensitivity at initial diagnosis of the index patient from 70 to 78%, demonstrating the added benefit of including this guideline in the cumulative NCCN criteria. Of note, with that increase in sensitivity came a decrease in specificity from 73 to 65%.

If criteria were expanded to allow for genetic testing of *TP53* in any individual diagnosed with sarcoma ≤ 25 years, 22 of the 27 mutation-positive families initially missed in our population would have been identified, increasing cumulative sensitivity at the time of the index patient's initial diagnosis from 78 to 95%. As expected, this increase in sensitivity was accompanied by a decrease in specificity from 72 to 40% in the index patient and 65 to 36% on the family level. Among sarcoma cases unselected for age, personal, or family history, the *TP53* mutation detection rate has been estimated at 3.6%-4.1% (Mitchell et al., 2013; Toguchida et al., 1992). Among families selected on the basis of a child with sarcoma before age 16, mutation detection rate has been estimated at 6.5% (Hwang et al., 2003). Among children diagnosed with rhabdomyosarcoma before 18 years and without suggestive personal or family history, mutation detection rate is 9% (Diller et al., 1995). Sarcomas account for approximately 15% of childhood cancer with an average annual incidence of 19.7 per million for children and adolescents younger than 20 years of age, resulting in an estimated 1,700 cases of childhood sarcoma per year in the US (Ries et al., 1999).

It should be noted that clinical application of these retrospective estimates, for which we allowed any family member to fulfill the role of 'proband', requires careful attention to the selection of individuals for genetic testing, as the index patient may not always be the most appropriate first

individual in whom to pursue germline analysis. Conversely, a negative result in the index patient may not rule out LFS elsewhere in the family, particularly if the family met criteria from the viewpoint of an untested relative.

Due to the substantial '*de novo*' rate and demonstrated incomplete penetrance of *TP53* mutations, it must be emphasized that absence of family history does not indicate absence of LFS. It is not unreasonable to consider *TP53* genetic testing in any individual with an early-onset, high-risk tumor, such as childhood sarcoma, regardless of family history.

APPENDIX

Supplementary Table 1. Component and cumulative performance of NCCN guidelines for *TP53* genetic testing when the role of ‘proband’ is restricted to the index patient

Criteria	Families meeting criteria with <i>TP53</i> mutations			Sensitivity ³ (%)	Specificity ⁴ (%)	LR+ ⁵	LR- ⁶
	No. of families	No.	%				
<i>At initial presentation¹</i>							
Classic LFS	21	16	76	13	98	6.30	0.89
Chompret	123	73	59	60	79	2.87	0.51
NCCN	151	83	55	68	72	2.40	0.45
Families not detected by any criteria	211	39	18	--	--	--	--
<i>At last contact²</i>							
Classic LFS	44	31	70	25	95	4.69	0.79
Chompret	193	102	53	84	62	2.21	0.26
NCCN	215	108	50	89	55	1.99	0.21
Families not detected by any criteria	147	14	10	--	--	--	--

Abbreviations: LFS, Li-Fraumeni syndrome; LR+, likelihood ratio positive; LR-, likelihood ratio negative

¹Based on personal and family history at the time of the proband's first cancer diagnosis.

²Based on personal and family history at the time of last contact with the family.

³Sensitivity: Number of positive families meeting criteria/122 total positive families (x100)

⁴Specificity: Number of negative families excluded by criteria/240 total negative families (x100)

⁵LR+: sensitivity/(1-specificity)

⁶LR-: (1-sensitivity)/specificity

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