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ORIGINAL ARTICLE

Whole body magnetic resonance imaging (WB-MRI) and brain MRI baseline surveillance in *TP53* germline mutation carriers: experience from the Li-Fraumeni Syndrome Education and Early Detection (LEAD) clinic

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Abstract Individuals with Li-Fraumeni syndrome (LFS) have a significantly increased lifetime cancer risk affecting multiple organ sites. Therefore, novel comprehensive screening approaches are necessary to improve cancer detection and survival in this population. The objective of this study was to determine the diagnostic performance of whole body MRI (WB-MRI) and dedicated brain MRI screening as part of a comprehensive screening clinic called Li-Fraumeni Education and Early Detection (LEAD) at MD Anderson Cancer Center. Adult (≥21 year old) and pediatric (<21 year old) patients were referred to the LEAD clinic by healthcare providers or self-referred and screened at 6 month intervals. During the study period, 63 LFS individuals were seen in the LEAD clinic including 49 adults (11 male, 38 female) and 14 children (7 male, 7 female). Fifty-three of 63 potentially eligible individuals underwent baseline WB-MRI (41 adults and 12 children) with primary tumors detected in six patients, tumor recurrence in one patient and cancer metastases in one patient. Thirty-five of 63 patients (24 adults and 11 children) underwent baseline brain MRI with primary brain tumors detected in three individuals, also noted on subsequent WB-MRI scans. Three additional tumors were diagnosed that in retrospect review were missed on the initial scan (false negatives) and one tumor noted, but not followed up clinically, was prospectively found to be malignant. The high incidence of asymptomatic tumors identified in this initial screening (13%), supports the inclusion of WB-MRI and brain MRI in the clinical management of individuals with LFS.

Keywords Whole body MRI · Cancer screening · Li-Fraumeni syndrome · TP53 · LEAD clinic

Introduction

Li-Fraumeni syndrome (LFS) is a devastating hereditary cancer syndrome originally described by Li and Fraumeni in 1969 [1]. It is characterized by a high risk of early onset cancers, primarily breast cancer, sarcoma (bone and soft tissue), adrenal cancer, leukemia and brain, as well as other later onset common adult cancers. Multiple primary cancers are common [2–4]. It was originally described clinically as an unusual familial aggregation of young onset cancers, and later shown to be attributable to germline mutation in the *TP53* tumor suppressor gene [5]. Early attempts at cancer screening were able to identify asymptomatic cancers, but at advanced stages, which may not provide survival benefit [6, 7].

Cancer surveillance for LFS is complicated; screening must be conducted at regular intervals over a lifetime, and should not utilize modalities that use ionizing radiation

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which may increase cancer risk in this uniquely sensitive population [8–10]. The only effective surveillance shown to offer survival benefit for LFS involves multi-modal screening using novel whole body rapid sequence MRI (WB-MRI) among other modalities [11]. The dramatic survival benefit achieved with that protocol led us to initiate a comprehensive screening and education program incorporating WB-MRI and brain MRI for both adult (see Supplementary Table 1 in Supplementary Information) and pediatric LFS individuals (see Supplementary Table 2 in Supplementary Information) called Li-Fraumeni Education and Early Detection (LEAD). Here we report the results of the baseline WB-MRI and brain MRI screening for our first 63 LFS individuals over the initial three and half year period.

Methods

Study design and setting

Our cohort was comprised of 49 adults and 14 children with LFS (confirmed as carrying a germline pathogenic *TP53* variant by genetic testing), who underwent at least one LEAD screening between April 1, 2013 and October 1, 2016 at MD Anderson Cancer Center. The LEAD clinic surveillance protocol is an adaptation of the previously published protocol [11], modified to suit our patient population and available expertise. LEAD eligibility included LFS individuals with no personal history of cancer, cancer survivors who were at least 1 year past completion of active treatment (such as chemotherapy and/or radiation) or cancer survivors who were at least 6 months past completion of surgery (if that was the only cancer treatment). LEAD exclusion criteria included people who do not have confirmed genetic diagnosis of LFS, patients who were in current active cancer treatment or patients with identified metastatic cancer. Individuals were referred to LEAD by healthcare providers or were self-referred. Patients age 0–21 years were seen in the pediatric LEAD clinic, whereas patients age ≥ 21 were seen in the adult LEAD clinic within the Cancer Prevention Center.

Screening exams

WB-MRI was completed either at the initial screening or at the subsequent visit 6 months later. Adult patients alternated WB-MRI and brain MRI at 6 month intervals, whereas pediatric patients had both WB-MRI and brain MRI in same visit to minimize exposure to anesthesia and associated side effects. WB-MRI was performed on Siemens Aera 1.5T with and without contrast with coverage from the skull vertex (including the brain) to the feet. Brain MRI was performed on GE Signa HD 1.5T and Siemens Aera 1.5T, with and without contrast, coverage including the full head region. (More details can be found in Supplementary Table 3 in Supplementary Information). Concerning lesions identified by these exams were followed with dedicated imaging or biopsy. Results of follow up investigations were documented in medical records and further reviewed in a multidisciplinary meeting. New cancer diagnoses were confirmed by pathology review or dedicated imaging reports, with patients referred to the appropriate specialty oncology center for tumor management.

Reporting of variables

For this report we retrospectively reviewed patient demographics, previous cancer history, screening exam reports and follow up investigations on patients who had completed at least one LEAD clinic screening exam. For this type of study, formal consent is not required. WB-MRI and brain MRI reports were reviewed by primary author (J.B) and investigable lesions further confirmed by diagnostic radiologist (B.A). Results were grouped into three categories (i) no findings, (ii) benign findings, no further follow up (e.g. cysts, hemangioma etc.), (iii) possible malignant findings—further follow up. We defined false negative as any tumor that was either missed or reported as a benign lesion on the imaging report, but subsequently confirmed malignant. False positive was defined as a suspected tumor leading to biopsy that was then proven by pathology to be benign. Follow up time was calculated in months from the time of the first WB-MRI or brain MRI (whichever came first) until the conclusion of the study period.

Results

Patient characteristics

Between April 1, 2013 and October 1, 2016, we evaluated 63 individuals from 48 families for LEAD screening. Fourteen (22%) of these were seen in the pediatric LEAD clinic (<21 year old), the other 49 (78%) patients in the adult LEAD clinic (≥21 year old). The majority of patients were female (71%), Caucasian (79%) and had previous cancer history (68%) (Table 1).

WB-MRI

Of 63 potentially eligible individuals, 53 underwent baseline WB-MRI screening exam. The other ten individuals did not due to insurance issues (n = 3), declined exam (n = 1), will have exam on next visit (n = 4), pregnancy (n = 1), failure to return for exam (n = 1) (Fig. 1a). No findings were reported in 19 individuals (category 1), and 22 benign findings that

Table 1 Description of patient population

Characteristic	N (%)
Gender	
Male	18 (29%)
Female	45 (71%)
Age (years)	
0–20	14 (22%)
21–40	26 (41%)
41–60	16 (26%)
60+	7 (11%)
Ethnicity	
Caucasian	50 (79%)
Hispanic	6 (10%)
African American	3 (5%)
Arabic	3 (5%)
Caucasian/Asian	1 (1%)
Previous cancer history	43 (68%)
Follow up time (median months, inter quartile range)	16 (5.5–24.5)

did not require further follow up (category 2) were identified in 14 individuals. Possible malignant findings requiring follow-up (category 3) were observed in 29 individuals. In 16/24 individuals undergoing follow up the category 3 lesions were deemed clinically not significant after dedicated imaging (MRI, CT or PET scan). Six individuals had follow up with dedicated imaging and/or biopsy to confirm the nature of the lesion. Of note, some individuals had more than one lesion, so both benign and possible malignant lesions could be reported in the same individual. At the time of analysis, two individuals are undergoing further imaging to clarify the pathogenicity of their identified lesions. Furthermore, three individuals did not return for their follow up appointment.

Brain MRI

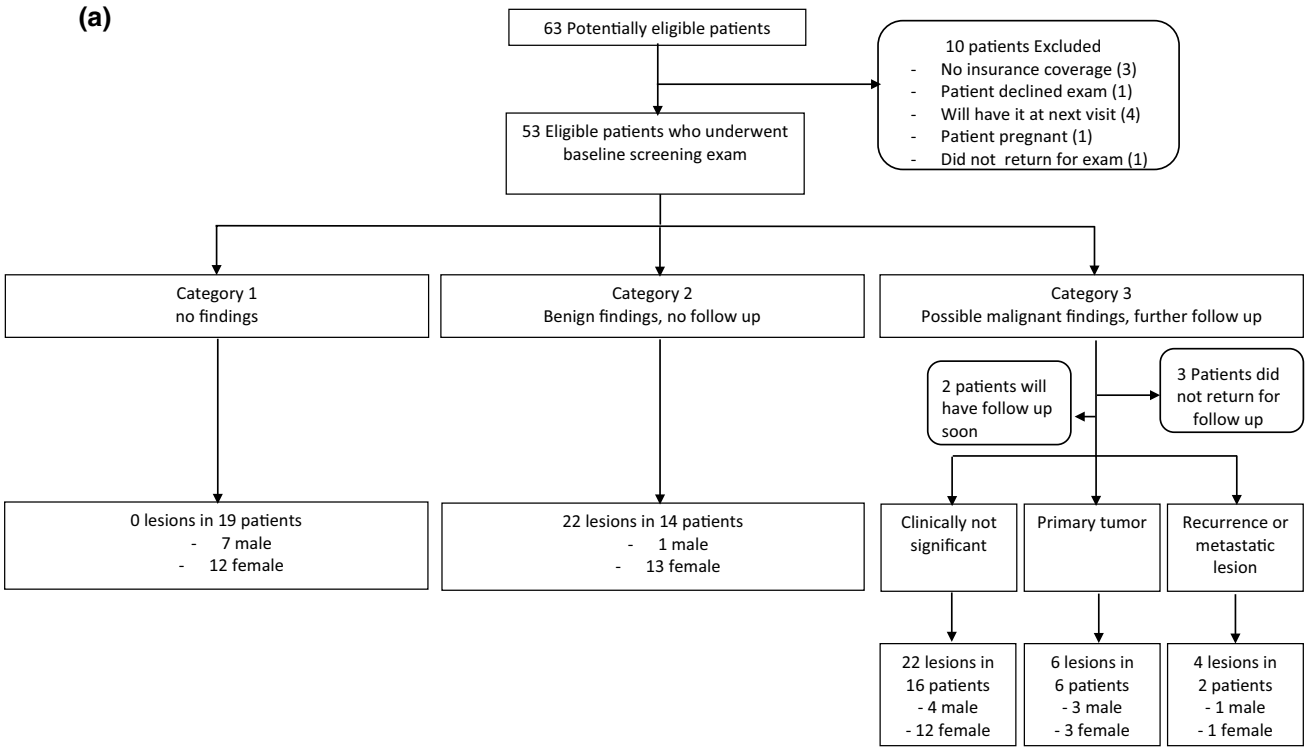
Of the 63 potentially eligible individuals, 35 underwent baseline brain MRI exam. The other 28 patients did not due to new cancer diagnosis (n = 2), no insurance coverage (n = 4), will have it at next visit (n = 15), pregnancy (n = 1), failure to return for exam (n = 5), had scan at outside institution (n = 1) (Fig. 1b). No findings were reported in 25 individuals (category 1) and three benign findings (vascular enhancements, venous lake) were identified in two individuals, not requiring further follow up (category 2). Possible malignant findings (category 3) were identified in eight individuals. Further dedicated imaging (MRI, CT) confirmed five of those lesions as not clinically significant and three constituted low grade tumors in one male and two females. Notably, the primary low-grade tumors identified in the three individuals were also visualized on their baseline WB-MRI. There were no recurrent or metastatic lesions identified on baseline brain MRI.

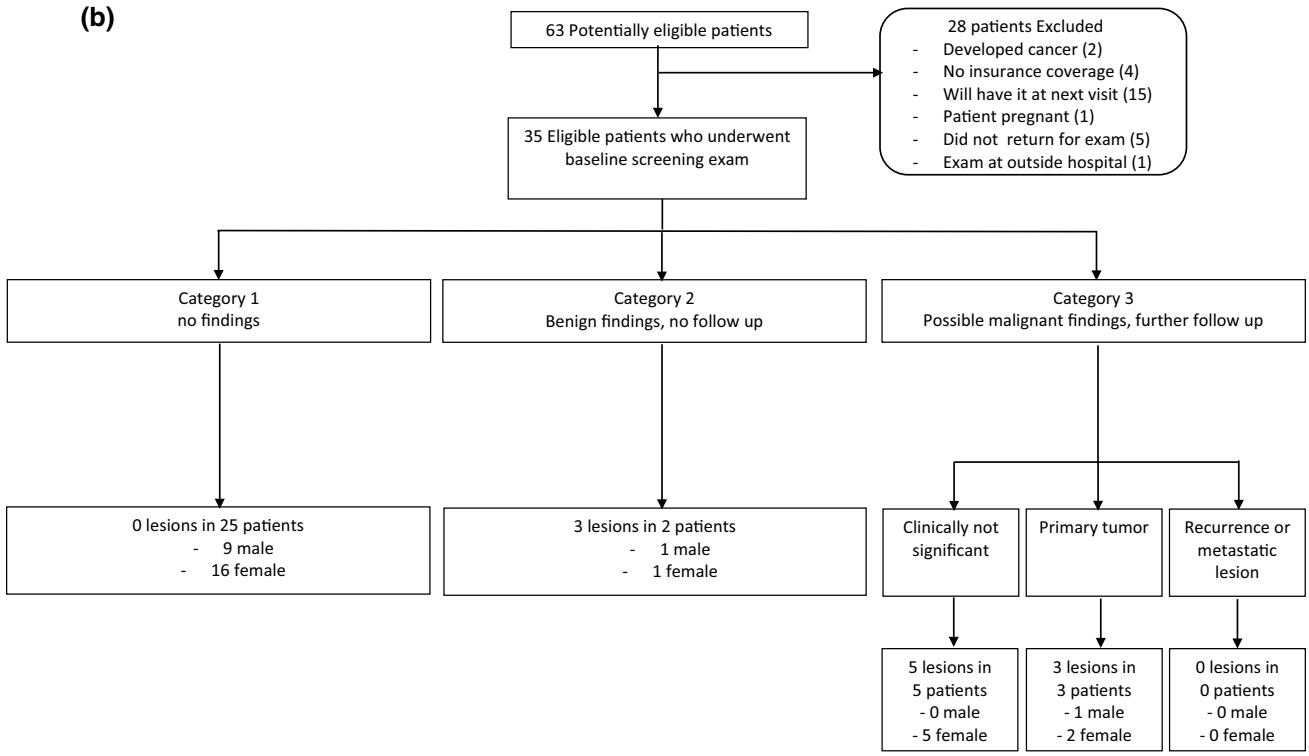
Clinically significant findings

Over a median period of 16 months (IQR 5.5–24.5), the baseline WB-MRI and brain MRI exams identified 12 clinically significant lesions (benign and malignant) in ten asymptomatic patients (Table 2). Patient #1 was found to have a recurrent soft tissue sarcoma and a new primary abdominal soft tissue sarcoma. Patient #2 was found to have sarcoma metastases and is currently undergoing chemotherapy. Patient #3 had thyroid nodules concerning for malignancy, which on biopsy revealed a papillary thyroid cancer. She had surgical resection and is doing well. The next three pediatric patients (#4, 5, 6) were all noted to have brain lesions most consistent with low-grade gliomas, detected on both brain MRI and WB-MRI baseline scans. All are undergoing short interval MRI surveillance and continue to be asymptomatic. Patient #7 was found to have a benign peripheral nerve sheath tumor on baseline WB-MRI, confirmed by subsequent dedicated scan and biopsy. The same patient had no findings noted on his baseline brain MRI, however upon further review of the images a small brain low-grade glioma was noted (false negative). Patient #8 had no lesions noted on her baseline WB-MRI, however a screening esophagogastroduodenoscopy (EGD) performed a few weeks later revealed a stomach cancer. This mass was retrospectively identified on the baseline WB-MRI (false negative). Patient #9 was noted to have bilateral thyroid cysts considered not clinically significant on baseline WB-MRI scan, however she was later diagnosed with bilateral thyroid cancer (false negative). Patient #10 had a lesion noted on her shoulder recommended for further detailed imaging, however clinical exam suggested a lipoma and no further imaging was performed. The patient had the lesion excised before her next scan due to pain and discomfort, and the pathology revealed a small well differentiated liposarcoma/atypical lipomatous tumor, which was surgically excised and has required no further treatment. Each of the 12 lesions have either been treated with curative intent or are being followed by short interval MRI as shown in Table 2. Overall, the detection of six asymptomatic tumors/cancers, one recurrent cancer and metastases in one patient shows an unexpectedly high detection rate of 13%. All patients participating in the screening program were alive at the conclusion of the study period.

Discussion

In this retrospective clinical review of *TP53* germline mutation carriers undergoing WB-MRI and brain MRI as part





of the LEAD comprehensive cancer screening program, we demonstrate high baseline detection of localized benign and malignant tumors, a recurrent lesion and a metastatic lesion (13%). These findings are consistent with a previous study where cancer was detected in 9.1% (4/44) LFS individuals by baseline WB-MRI, with no cancers identified in the

◂**Fig. 1** Results from **a** WB-MRI baseline exams and **b** brain MRI for eligible adult and pediatric patients screened through the LEAD clinic at MD Anderson Cancer Center. Patients were categorized into groups based on reports from exams. Category (1) no findings = there were no lesions noted on exam. Category (2) Benign findings, no follow up = small benign lesions (e.g. cysts, hemangiomas etc.) noted on exam without any recommended follow up. Category (3) possible malignant findings, further follow up = lesions noted on scan that warrant further investigation with imaging or biopsy. Note: some patients were found to have more than one lesion; and both benign and possible malignant lesions could be reported in the same individual. Number of lesions in category 2 and category 3 ranged from 1 to 4 per person

healthy control group [12]. This underscores the importance of WB-MRI and brain MRI inclusion in the clinical management of LFS individuals.

Individuals with LFS are at an increased lifetime risk for cancer in many organ sites, presenting a significant challenge for cancer risk management. Earlier studies have investigated F18-Fluorodeoxyglucose-PET combined with CT (FDG-PET/CT) as a possible strategy to survey the whole body. Using this modality, three asymptomatic cancers were identified in 15 adults (20%) [7], whereas another study detected three asymptomatic lesions in 30 adult patients (10%) [6]. While this modality showed some promise, most of the tumors were detected at advanced stages with low survival benefit. In addition, this modality uses ionizing radiation, which would not be advisable for repeated exams over a lifetime in this unique, radiation sensitive population [8–10].

As an alternative, WB-MRI avoids ionizing radiation exposure and therefore presents a more ideal whole body screening option for the LFS population. Use of WB-MRI for tumor screening is a relatively new option, as it has been used primarily in the past to stage disease and assess the extent of distant disease from solid tumors [13, 14].

The seminal study by Villani et al. [11] demonstrated the feasibility and clinical benefit of comprehensive screening program (incorporating WB-MRI and brain MRI) for LFS patients by demonstrating a remarkable 100% overall 3-year survival for patients in the surveillance group, compared to 21% in the non-surveillance group. Those findings inspired our group to develop the LEAD program (Supplementary Tables 1, 2 in Supplementary Information). Our comprehensive screening program has many benefits, including a centralized approach to patient management, exams performed at the same institution, using same technique and same machines enabling more consistent comparison of findings between and across interval exams in patients. Additionally, our multidisciplinary team reviews all findings and patient issues to develop follow up recommendations.

Over 3.5 years (42 months) we identified eight clinically significant lesions (benign, low-grade, malignant, recurrent malignant and metastatic) in seven asymptomatic individuals (see Table 2). Three additional lesions were missed on the baseline scan but subsequently diagnosed (false negative). One lesion was noted on the baseline scan but deemed to be benign by clinical exam, however subsequently was shown to be a well-differentiated liposarcoma.

The LEAD clinic evaluated 49 adults (11 males and 38 females) ranging in age from 21 to 63 years. Of these, patient (#1) was found to have primary abdominal soft tissue sarcoma, as well as a recurrent lesion from a previous soft tissue sarcoma in the lower extremity. Patient #2 was found to have metastatic lesion in her rib and vertebrae from a previous groin sarcoma. While the purpose of our surveillance program was to detect new primary cancers, as opposed to detecting recurrent or metastatic lesions, both these asymptomatic patients were deemed free of disease before screening and their sarcoma diagnoses had occurred more than 5 years previously. Given that the majority of our LFS population (68%) had a previous cancer history, we may expect to encounter other such lesions in our screenings. These findings also suggest that perhaps clinical follow-up of LFS patients after a cancer diagnosis should be prolonged relative to other patients, as the underlying tumor biology may be more aggressive and less predictable.

In our pediatric clinic, we evaluated 14 children (seven male and seven female) ranging in age from 1 to 20 years. We detected one malignancy (papillary right thyroid cancer) in a 17 year old female (patient #3), which was successfully treated with surgical resection. Other lesions included a benign peripheral nerve sheath tumor (BPNST) in a 9 year old male (patient #7) and low-grade gliomas in three other children (patient #4, #5, #6). Interestingly, Villani et al. reported detection of low-grade gliomas in six LFS individuals (predominantly children) undergoing cancer screening [15]. Therefore, the association of low-grade gliomas in the pediatric LFS population may be more significant than previously appreciated, and may need further investigation in a larger cohort of LFS children to determine the frequency of the lesions and the biologic behavior.

Three lesions were missed on the initial baseline exams (false negatives), but were detected at a later time. One lesion in patient #8 was a gastric adenocarcinoma detected by EGD screening exam. On further review, this lesion could be seen on the baseline WB-MRI, but due to respiratory motion from the diaphragm was not clearly visible. Patient #9 was found to have thyroid cysts on the baseline scan which were deemed benign findings, but she developed an interval thyroid cancer between screening exams. Thyroid cysts are fairly common on imaging, and the development of thyroid cancer in this patient may suggest that incidental thyroid nodules guidelines developed for the general population may not be applicable to LFS. Lastly, pediatric patient #7 was found to have low-grade glioma on his second brain MRI, which upon review had been present at baseline brain MRI. Interestingly, the baseline WB-MRI on patient #10

Table 2 Clinically significant benign and malignant findings detected by baseline exams

Patient	Age at exam	Gender	Previous cancer history	Tumor	Mode of detection	Clinical follow up
#1	63	Male	LK, LLE STS, RLE STS, ESO ACA	Abdominal STS	WB-MRI	Surgical resection
#1	63	Male	LK, LLE STS, RLE STS, ESO ACA	LLE STS recurrence	WB-MRI	Short interval MRI w possible resection
#2	44	Female	R BR DCIS, L BR DCIS, RLE FXA, L GRN STS, R THY CA	STS mets (rib, vertebrae)	WB-MRI	Chemotherapy
#3	17	Female	None	R THY CAN	WB-MRI	Surgical resection
#4	13	Female	None	LGG	Brain MRI and WB-MRI	Short interval brain MRI
#5	15	Male	None	LGG	Brain MRI and WB-MRI	Short interval brain MRI
#6	6	Female	None	LGG	Brain MRI and WB-MRI	Short interval brain MRI
#7	9	Male	None	BPNST	WB-MRI	Short interval MRI
#7	9	Male	None	LGG	Brain MRI[a] and WB-MRI	Short interval brain MRI
#8	41	Female	L BR IDC, R BR DCIS	ST CA	EGD (false negative by WBMRI)[a]	Surgical resection and chemotherapy
#9	35	Female	None	Follicular THY CA	None (false negative by WBMRI)[a]	Surgical resection
#10	50	Female	RLE STS, UT STS, R ACA, PA CA, RUE MEL, LUE MEL IS	STS (shoulder)	WB-MRI[b]	Surgical resection

Multiple tumours detected in the same patient are listed in separate rows

RLE STS right lower extremity soft tissue sarcoma, *UT STS* uterine soft tissue sarcoma, *R ACA* right adrenal cortical adenoma, *PA CAN* pancreatic cancer, *RUE MEL* right upper extremity melanoma, *LUE MEL IS* left upper extremity melanoma in situ, *STS* soft tissue sarcoma, *THY CA* thyroid cancer, *L BR IDC* left breast invasive ductal carcinoma, *R BR DCIS* right breast ductal carcinoma in situ, *RLE FXA* right lower extremity fibroxanthoma, *L GRN STS* left groin soft tissue sarcoma, *LK* leukaemia, *LLE STS* left lower extremity soft tissue sarcoma, *RLE STS* right lower extremity soft tissue sarcoma, *ESO ACA* esophageal adenocarcinoma, *BPNST* Benign peripheral nerve sheath tumor, *LGG* low-grade glioma

[a]Lesion not reported on baseline WB-MRI report, but upon further review of images lesion was identified on the baseline scan (false negative)

[b]Lesion detected on WB-MRI but clinician discounted it based on clinical exam. It was excised in-between exams and found to be STS

noted a small shoulder lesion, judged on clinical exam to be a lipoma. However, it was excised later due to pain and discomfort and shown to be a well differentiated liposarcoma by pathology. These findings underscore some of the challenges and limitations of these screening exams and the importance of practicing a high index of suspicion for lesions identified on screening. As noted by Villani et al. [15], management of small lesions with indeterminate characteristics is challenging, as false positive findings for which aggressive intervention is pursued can cause more harm than good. Of note, we have not had any false positive findings (as defined by Villani et al. [15]) in our LEAD cohort to date.

We documented all lesions noted on the baseline WB-MRI and brain MRI reports (see Fig. 1a, b). Most of the incidental lesions occurred on WB-MRI exams, the majority being benign cysts, hemangiomas, enchondromas etc. (see Fig. 1a). High numbers of incidental findings from WB-MRI exams have been reported previously [16, 17]. Importantly, our findings are in agreement with the SIGNIFY LFS screening study in the UK where 15 LFS carriers and seven healthy controls underwent 43 further investigations following their baseline WB-MRI, which did not result in cancer diagnosis [12]. In addition, similar observations were reported when 50 WB-MRI examinations in 24 children with hereditary predisposition syndromes (ten of which had LFS) were reviewed and 55 incidental findings were found in 23 of 24 patients [18]. We concur with that study's recommendations that clinicians should always discuss the potential of identifying incidental benign findings as part of the informed consent with patients, and that interpretation of exams should be performed by radiologists familiar with WB-MRI and LFS, so they can appropriately stratify lesions and minimize unnecessary intervention [18]. It is important to note that while there may be significant medical benefits to such detailed and intense screening, many patients may experience significant anxiety and stress induced by incidental findings, as well as testing fatigue and emotional strain, as suggested by one case report [19]. Although LFS patients have expressed some of these concerns, overall patients undergoing WB-MRI screening seem to have positive psychological outcomes from participating in such screening, with significantly reduced anxiety scores 2 weeks post WB-MRI scan [20]. Indeed, LFS individuals undergoing screening through our LEAD clinic remarked that the perceived

benefit of screening (early detection, peace of mind, centralized screening, the power of knowledge, screening making LFS more livable) outweighed the drawbacks (negative emotions, logistical issues, navigation and draining nature of the program), and for this reason 100% of patients plan to continue with the screening in the future [21].

Major strength of the LEAD program is that it is offered to LFS adults as well as children. Given the high cancer burden in children with LFS [22], it is important to offer genetic testing and cancer screening to this young population. Many of the children that participate in our screening clinic have either a parent or sibling that is also being screened through the LEAD program, which may decrease the anxiety associated with the scans and help 'normalize' all the clinic visits that these families have to attend. Further strength is that our protocol does include screening by other modalities in addition to WB-MRI and brain MRI (Supplemental Tables 1, 2 in Supplementary Information). As noted previously, WB-MRI is an excellent screening modality, however on its own it is an insufficient to detect all cancers and therefore LFS individuals need multimodal screening to optimize effective asymptomatic tumor detection [15].

We acknowledge that our study has certain limitations. This was a single arm study that did not include patients who were not screened by the LEAD program. In general, patients who were offered the option for referral to the screening clinic accepted and were seen by the LEAD providers. It will be important to assess the clinical utility of this type of screening for LFS patients across different clinics and/or studies and see how it may compare to a single center experience such as the LEAD clinic presented here. This effort is currently underway with cohorts from the Li-Fraumeni Exploration Research Consortium [23] and the results from that study have recently been published [24]. Another limitation was that compliance for the screening exams was variable among patients as noted in Fig. 1a, b. Given that most patients had to travel out of state, pay for lodging/travel and the clinical service (as opposed to a research study), we were pleased with the attendance rate of 84% completing baseline WB-MRI and 56% completing baseline brain MRI exam. The biggest barrier to participation in our experience was the lack of reliable insurance coverage. We hope the growing availability of the screening and the associated survival benefits demonstrated to date [15] along with the results from large international meta-analysis study [24], will lead to wide acceptance of this type of screening as the standard of care for LFS individuals supported by adequate health insurance coverage.

Conclusions

The baseline WB-MRI and Brain MRI scans in our LFS population identified six asymptomatic primary cancers, one recurrent lesion and one individual with metastatic lesions. In addition, three tumors that were missed on the baseline scan were diagnosed subsequently. The high incidence of identified localized asymptomatic tumors in this initial cohort (13%), supports the inclusion of WB-MRI and brain MRI as standard of care in the management individuals with LFS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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