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Li-Fraumeni Syndrome in Pediatrics

Nurses Can Make a Difference in Quality of Life and Long-Term Survival Through Screening and Education

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Disclosures

- We have no actual or potential conflict of interest in relation to this presentation.

Objectives

- 1 UNDERSTAND HISTORY AND GENETICS OF LI-FRAUMENI SYNDROME
- 2 REVIEW THE DIAGNOSTIC CRITERIA
- 3 REVIEW THE DISEASE TYPES AND PREVALENCE ASSOCIATED WITH LI-FRAUMENI SYNDROME, STRATIFIED BY AGE GROUP
- 4 REVIEW CURRENT SCREENING GUIDELINES AND MODALITIES FOR PATIENTS
- 5 DISCUSS EXAMPLES FROM CLINICAL PRACTICE

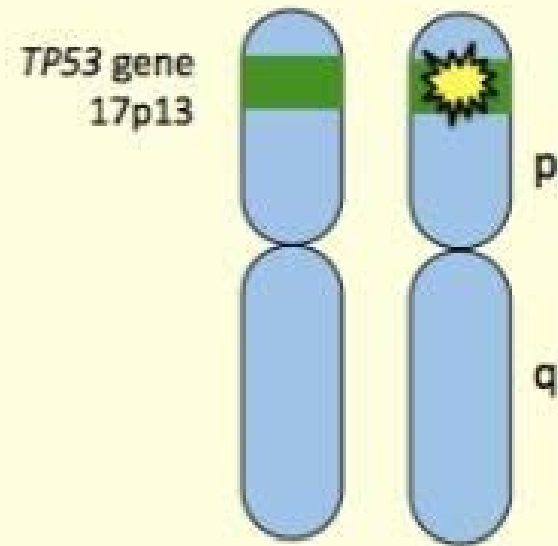
Li and Fraumeni

- Frederick Li and Joseph Fraumeni, Jr. are two American physicians who worked together at the National Cancer Institute.
- In 1969, while studying patients with rhabdomyosarcoma, they discovered families with multiple early onset cancers that were diagnosed in children and young adults.
- This syndrome, named “Li-Fraumeni Syndrome”, was first published about in 1982.
- In 1990, it was found that an inherited mutation in TP53 was likely the cause of this syndrome.

Li-Fraumeni Syndrome

- TP53 (17p13) is the most frequently mutated gene in sporadic cancers
- LFS = any germline mutation in the TP53 tumor suppressor gene that gets passed down in an autosomal dominant pattern
- In response to stress signals, the tumor suppressor gene controls a wide range of processes including apoptosis, DNA replication and repair, and regulatory control over the cell cycle
- There are many different potentially pathogenic variants of TP53, with the most frequent mutation being p.R337H
- 7-20% of families have a de novo mutation of TP53
- Patients are very sensitive to radiation, and should avoid exposure

Li Fraumeni syndrome



Criteria for LFS

- **Classical criteria:**

- Combination of an individual diagnosed age <45y with a sarcoma AND
- A first-degree relative diagnosed age <45y with cancer AND
- An additional first or second degree relative in the same lineage with cancer diagnosed at age <45y or a sarcoma at any age

- **Chompret criteria:**

- Individual with a tumor from the LFS tumor spectrum before 46y, AND at least one first or second degree relative with any of the LFS cancers before the age of 56y or with multiple primaries at any age OR
- Individual with multiple tumors (except multiple breast tumors), two of which belong to the LFS tumor spectrum with the initial cancer occurring before the age of 46y OR
- Individual with ACC, choroid plexus carcinoma, or rhabdomyosarcoma (embryonal anaplastic subtype) at any age of onset OR
- Breast cancer before age 31y

Li-Fraumeni Syndrome

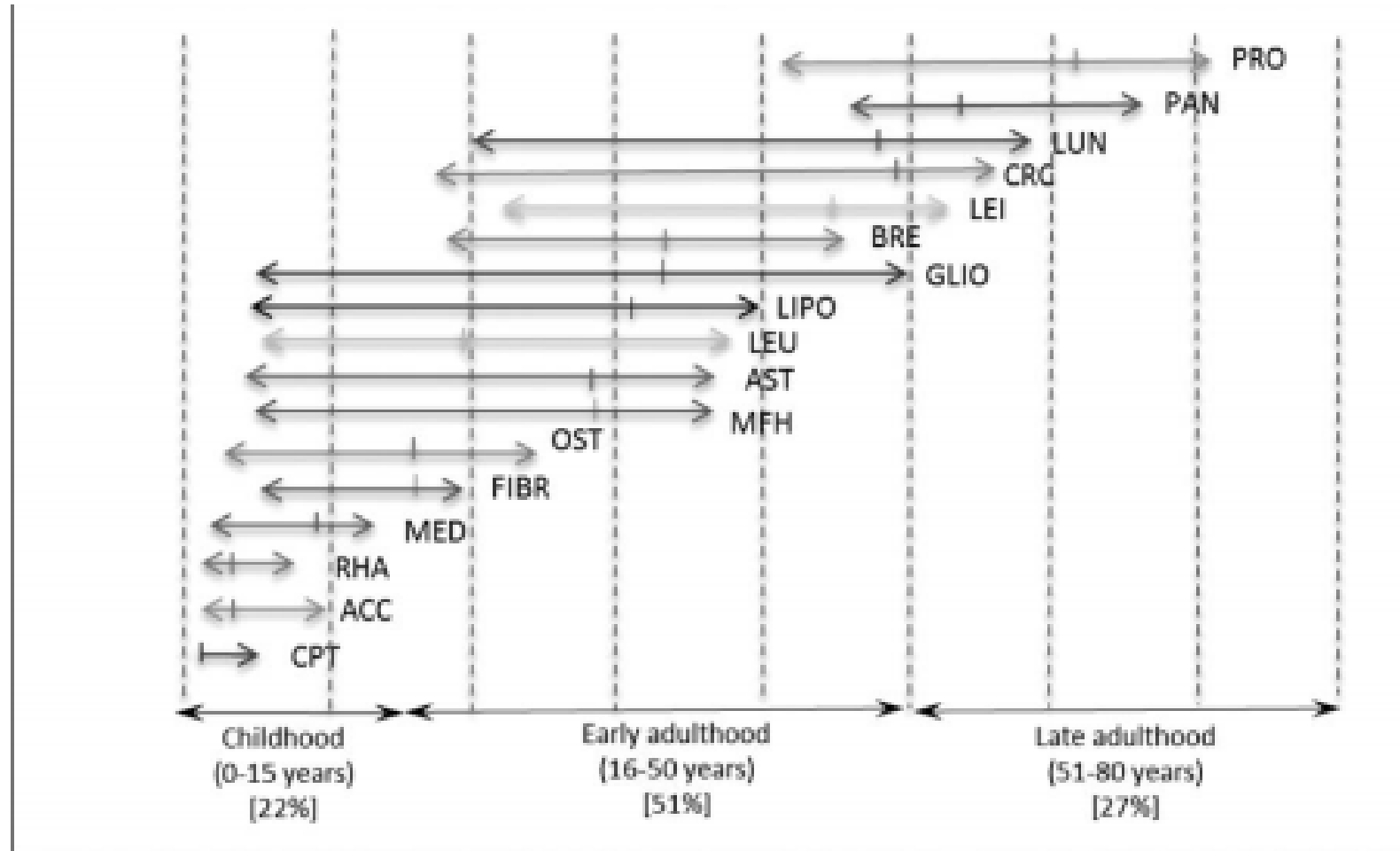
- If the family meets guidelines for Classic LFS, but test negative, they are assumed to have “Li-Fraumeni Like” (LFL) Syndrome, and they could still discuss regular screening with their providers
- LFL means no known mutation of TP53, but still at very high risk of developing cancer
- Most pediatric patients with either a sarcoma or choroid plexus carcinoma diagnosis are being tested to determine if they have a germline mutation
 - Except patients with Ewing’s Sarcoma, as it is a known somatic mutation as opposed to a germline mutation
- Initially the penetrance of TP53 mutations was thought to be close to 100%, however, this estimated penetrance has decreased over time
 - More people with TP53 mutations are being identified that don’t fit the classic presentation
 - Numerous people with LFS have never developed a tumor related to the syndrome

LFS spectrum disease types

- Soft tissue sarcoma
 - Osteosarcoma
 - CNS tumors
 - Choroid plexus carcinoma
 - Early onset breast cancer
 - Adrenocortical carcinoma
 - Leukemia
-
- As more families with TP53 mutations are identified, the spectrum has expanded to include melanoma, GI tract, thyroid, and ovarian cancers
 - Prevalence by tumor type varies greatly based on age

Prevalence

- Among patients with LFS who are <18 years old, soft tissue sarcoma is the most common diagnosis, followed by osteosarcoma, brain tumors, and adrenocortical carcinoma (ACC).
- There are three temporal phases of the disease, each characterized by a specific pattern of cancers:
 - Childhood (0-15 years): 22% of all cancers, mainly ACC, CPC, rhabdomyosarcoma and medulloblastoma
 - Early adulthood (16-50 years): 51% of all cancers, mainly breast cancer, osteosarcoma, leukemia, astrocytoma/glioblastoma, colon cancer, and sarcomas
 - Late adulthood (51+ years): 27% of all cancers, pancreatic and prostate cancer
- Overall penetrance is higher in males than in females during childhood and adolescence (32 vs 20%), mainly due to the higher prevalence of brain tumors and sarcomas.
- In contrast, ACC, a signature diagnosis in LFS, is 2.7 times more common in females than males.



ACC, adrenal cortical carcinoma; AST, astrocytoma; BRE, breast cancer; CPT, choroid plexus carcinoma; CRC, colorectal cancer; FIBR, fibrosarcoma; GLIO, glioblastoma; LEI, leiomyosarcoma; LEU, leukemia; LIPO, liposarcoma; LUN, lung cancer; MED, medulloblastoma; MFH, malignant fibrous histiocytoma; OST, osteosarcoma; PAN, pancreas cancer; PRO, prostate cancer; RHA, rhabdomyosarcoma.

Amadou, A., et al. Revisiting tumor patterns and penetrance in germline TP53 mutation carriers: temporal phases of Li-Fraumeni Syndrome. *Curr Opin Oncol*. 2018.

Prevalence

- In childhood phase, LFS causes the development of cancers that are otherwise exceedingly rare.
- In early adult life, the spectrum shifts to individuals with LFS having more common, rather than rare, cancer types.
- In late adult life, some researchers suggest that a protecting mechanism may suppress the effect of the mutation.
- Age at tumor onset is remarkably constant among all populations.
- There is evidence accumulating that some patients may carry a potentially deleterious germline variant without having an increased risk of early cancer.

TABLE 1. Number and Type of First Cancer by Age Group at the Time of Diagnosis

	Aged Birth to 17 Years	Aged 18 to 29 Years	Aged 30 to 44 Years	Aged \geq 45 Years	Total (Females/Males)
ACC	5	0	0	0	5 (3/2)
Brain	10	8	2	3	23 (9/14)
Breast	0	26	42	8	76 (76/0)
Colorectal	0	2	3	4	9 (5/4)
Leukemia	3	2	0	0	5 (4/1)
Lung	0	0	0	4	4 (2/2)
OS	11	6	1	0	18 (9/9)
Prostate	0	0	0	2	2 (-/2)
STS	12	10	10	9	41 (25/16)
Other ^a	2	8	7	11	28 (14/14)
Total	43	59	63	38	211 (147/64)
Individuals with first cancer diagnosis ^b	41	57	59	33	193 (132/61)
Individuals at risk	286	207	128	42	286 (186/100)
Person-years	4390	2053	1236	383	8062 (5114/2948)

Mai, P., Best, A., & Peters, J. et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni Syndrome cohort. *Cancer*. 2016; 122: 3673-81.

Cumulative Risk

- Cumulative cancer risk associated with LFS has been estimated to be approximately 50% by age 40 years and up to 90% by age 60 years.
- The cumulative cancer incidence was 50% by age 31 years among TP53+ females, and 50% by age 46 in TP53+ males. In both genders, the incidence approached 100% by age 70.
- Individuals with LFS are also at increased risk of developing multiple primary tumors.
 - Rate of second malignancies: ~57%,
 - Rate of third malignancies: ~38%
 - Survivors of childhood cancers were found to have the highest risks for developing additional malignancies
 - *The subsequent malignancies are not all clearly related to the treatment of the previous neoplasms.

Cumulative Risk

- TP53+ males had a higher risk of a first cancer diagnosis before age 25 years and after age 50 years. In contrast, the risk of a first cancer diagnosis among TP53+ females was highest from age 20 to age 50 years.
- Among females, the median time to a second cancer diagnosis was 15 years for those with an age at the time of first diagnosis is <18 years.
- Among males, those with a first cancer diagnosis of <18 years had a longer median time to a second cancer diagnosis.

Screening Guidelines

- Cancer surveillance for LFS is complicated, as screening must be completed at regular intervals over a lifetime, and it should not utilize modalities that involve any kind of ionizing radiation, as it may increase the cancer risk in this sensitive population.
- The only effective surveillance shown to offer benefit for LFS involves multi-modal screening using whole body rapid sequence MRI, in addition to regular MRIs of the brain, abdominal ultrasounds, lab work, and physical examinations.
- Overall, the detection rate of localized, asymptomatic tumors of whole body MRIs is approximately 13%, with very low rates of false positives.
- Earlier studies used PETCT as a screening modality for patients with LFS, but not only does it utilize ionizing radiation, it also mostly detected tumors at advanced stages with low survival benefit.
- MRI whole body imaging has also detected new sites of metastatic disease, which suggests that perhaps clinical follow up after a cancer diagnosis should be prolonged in LFS patients relative to other patients.

Toronto protocol

- It was the first comprehensive surveillance protocol for individuals with LFS that studied their outcomes over 5 years, with patients either selecting to undergo regular surveillance or choose not to.
- Asymptomatic tumors were detected in 32% of patients who underwent surveillance. In patients who declined surveillance, symptomatic tumors were detected in 88%.
- 5 year overall survival was 88% in the surveillance group and 60% in the non surveillance group.
- Shows that long term compliance with a surveillance protocol for early detection in patients with LFS is not only feasible, but it is also associated with improved long term survival.
- There were a very small number of false positives noted in the study.

Children (birth to age 18 years)

Adrenocortical carcinoma

- Ultrasound of abdomen and pelvis every 3–4 months
- Blood tests every 3–4 months:* 17-OH-progesterone, total testosterone, dehydroepiandrosterone sulfate, and androstenedione
- 24 h urine cortisol, if feasible

Brain tumour

- Annual brain MRI

Soft tissue and bone sarcoma

- Annual rapid whole-body MRI

Leukaemia or lymphoma

- Blood tests every 3–4 months: complete blood count, erythrocyte sedimentation rate, lactate dehydrogenase

General assessment

- Complete physical examination every 3–4 months, including anthropometric measurements plotted on a growth curve (with particular attention to rapid acceleration in weight or height), signs of virilisation (pubic hair, axillary moisture, adult body odour, androgenic hair loss, clitoromegaly, or penile growth), and full neurological assessment
- Prompt assessment with primary care physician for any medical concerns

Adults

Adrenocortical carcinoma (age 18–40 years)

- Ultrasound of abdomen and pelvis every 3–4 months
- Blood tests every 3–4 months:* 17-OH-progesterone, total testosterone, dehydroepiandrosterone sulfate, and androstenedione
- 24 h urine cortisol, if feasible

Breast cancer

- Monthly breast self-examination (age 18 years onwards)
- Clinical breast examination twice a year (age 20–25 years onwards, or 5–10 years before earliest known breast cancer in the family [whichever comes first])
- Annual mammography† and breast MRI screening‡ (age 20–75 years, or 5–10 years before earliest known breast cancer in the family [whichever comes first])
- Consider risk-reducing bilateral mastectomy

Brain tumour (age 18 years onwards)

- Annual brain MRI

Soft tissue and bone sarcoma (age 18 years onwards)

- Annual rapid whole-body MRI‡
- Ultrasound of abdomen and pelvis every 3–4 months

Colorectal cancer

- Colonoscopies every 2 years (start at age 25 years, or 10 years before earliest known colon cancer in the family [whichever comes first])

Melanoma (age 18 years onwards)

- Annual dermatological examination

Leukaemia or lymphoma (age 18 years onwards)

- Blood tests every 3–4 months: complete blood count, erythrocyte sedimentation rate, lactate dehydrogenase

General assessment

- Complete physical examination every 3–4 months
- Prompt assessment with primary care physician for any medical concerns

*Serial specimens obtained at the same time of day and processed in the same laboratory.

†Breast ultrasound with mammography as indicated by breast density, but not instead of breast MRI or mammography. ‡Breast MRI to alternate with annual rapid whole-body MRI (one scan every 6 months).

Villani, A., Shore, A., & Wasserman, J. et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. *Lancet Oncol* 2016; 17: 1295-305.

LEAD

- MD Anderson Li Fraumeni Early Assessment and Detection (LEAD) clinic guidelines:



Li-Fraumeni Syndrome Screening - Pediatric

Disclaimer: This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson's specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care.

Li-Fraumeni Syndrome Education and Early Detection (LEAD) – Pediatric Screening Guidelines

Cancer	Age			Frequency
	0-1 Year	1-10 Years	10-20 Years	
General	Physical exam/targeted review of systems • Neurological exam	Physical exam/targeted review of systems • Neurological exam	Physical exam/targeted review of systems • Neurological exam • Thyroid • Skin	Every 6 months
Adrenocortical Tumor (ACT) and Others	• Education of signs and symptoms (virilization, Cushing's syndrome, hypertension) • Testosterone, DHEAS, HCG, AFP, ACTH, urinalysis	• Education of signs and symptoms (virilization, Cushing's syndrome, hypertension) • Testosterone, DHEAS, HCG, AFP, ACTH, urinalysis	• Education of signs and symptoms (virilization, Cushing's syndrome, hypertension) • Testosterone, DHEAS, HCG, AFP, ACTH, urinalysis	• Every 6 months (until 10 years old) • Annually (10 – 20 years old)
	Ultrasound of abdomen and pelvis	Ultrasound of abdomen and pelvis	Whole body MRI ¹	• Every 6 months for ultrasound • Annually for whole body MRI ¹
Brain	• Education of signs and symptoms (vomiting, headaches, vision changes) • Brain MRI ^{1,2}	• Education of signs and symptoms (vomiting, headaches, vision changes) • Brain MRI ^{1,2}	• Education of signs and symptoms (vomiting, headaches, vision changes) • Brain MRI ^{1,2}	Annually
Sarcoma (begin at 2-3 years – based on family history/clinical judgement)	N/A	Whole body MRI ¹	Whole body MRI ¹	Annually
Leukemia/ Lymphoma	• Education of signs and symptoms (anemia, pallor, fatigue, bruising, petechiae) • CBC, erythrocyte sedimentation rate, lactate dehydrogenase	• Education of signs and symptoms (anemia, pallor, fatigue, bruising, petechiae) • CBC, erythrocyte sedimentation rate, lactate dehydrogenase	• Education of signs and symptoms (anemia, pallor, fatigue, bruising, petechiae) • CBC, erythrocyte sedimentation rate, lactate dehydrogenase	• Every six months (until 10 years) • Annually (10 – 20 years old)
Melanoma	N/A	N/A	Refer to Dermatology service as necessary	Annually

¹BUN and creatinine prior to any MRI

²First MRI with contrast; thereafter without contrast if previous MRI normal and no new abnormality

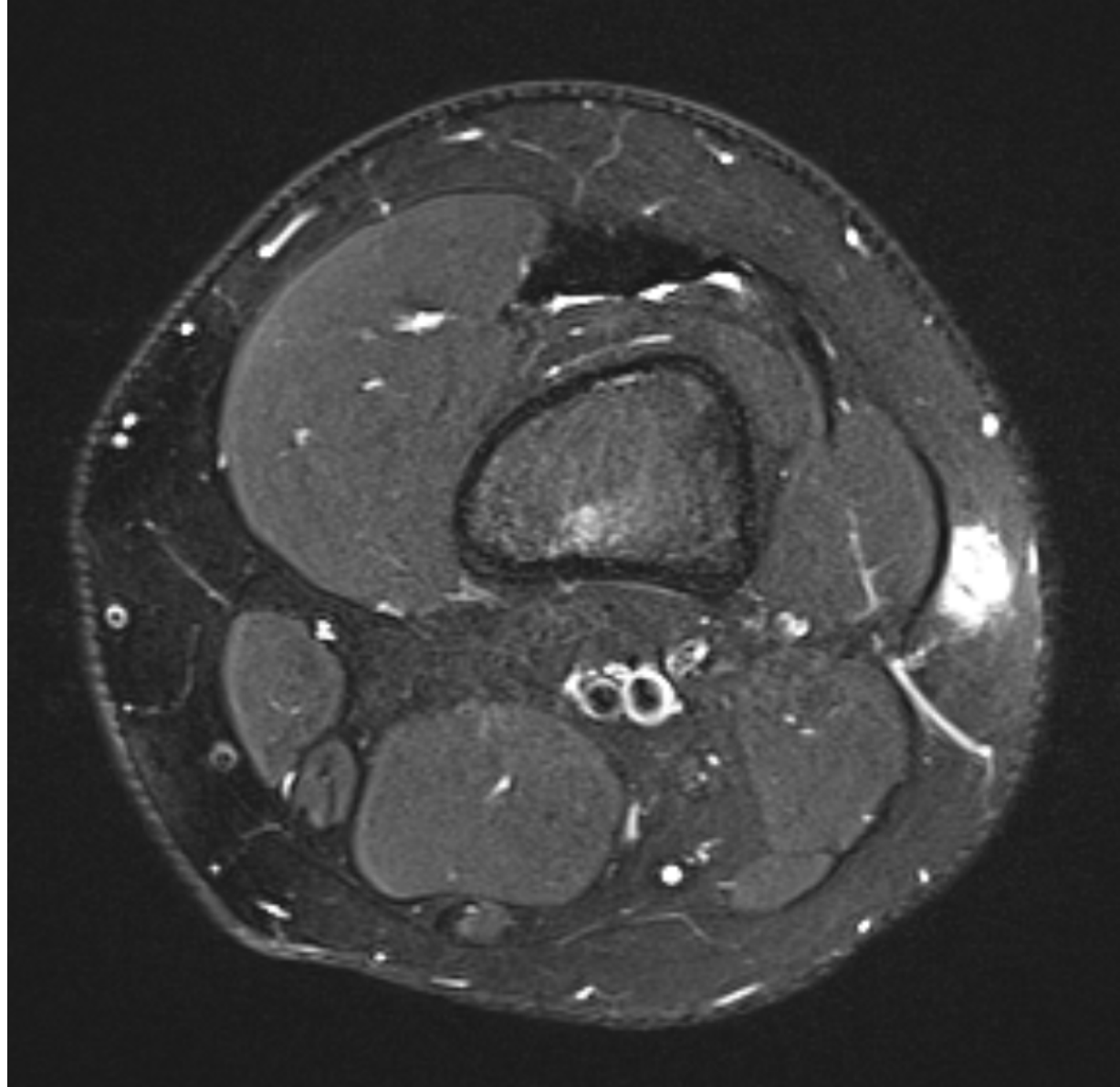
Difficulties/Hesitancies

- AACR recently recommended adoption of screening in children with a pathogenic LFS variant or clinical diagnosis of LFS, but screening recommendations may vary greatly between countries.
- A key tenet of genetic testing is informed consent. Parents may have a hard time achieving fully informed consent if they do not comprehend the long term impact on children. A child's involvement should also vary based on age.
- Potential groups at increased psychological risk may include children who test positive for a mutation, their parents who may experience "transmission guilt", and their siblings who test negative may experience "survivor guilt".
- Perceived advantages of testing children: decrease the anxiety of not knowing, could invoke healthy lifestyle changes if positive, and could begin screening right away, which provided some sense of control.
- Perceived disadvantages: INSURABILITY, loss of autonomy, and negative emotional impact
- Overall, parents seem to have a positive attitude and be eager to have their children undergo genetic testing early, rather than wait until they turn 18. 20

Patient Example

- Patient was diagnosed with adrenocortical carcinoma at 2 years of age after presenting with premature adrenarche with elevated testosterone. Ultrasound showed a small mass in her right adrenal gland. She underwent right adrenalectomy and required no further chemotherapy.
- At age 9, she tested positive for LFS and began screening, and was found to have an asymptomatic brain tumor on her first MRI. Resection of the tumor showed pleomorphic xanthoastrocytoma, with negative margins. She required no further treatment.
- At age 12, a repeat screening MRI brain showed a recurrent brain tumor in the same area of prior resection. She underwent repeat resection, and pathology again showed recurrent PXA. She required no further treatment.
- At age 14, MRI whole body revealed a discrete enhancing nodule in her left distal thigh. Excisional biopsy showed extraskeletal osteosarcoma. She underwent complete resection, followed by chemotherapy as per AOST0331 with MAP. Her end of therapy scans showed no evidence of disease.
- Just a couple of weeks later, she noted a strange mole that seemed to appear quickly on her thigh, near her scar. It was removed, and it showed metastatic osteosarcoma of the dermis. We have been following her closely with scans, and she has had no further recurrences.
- Current status: doing well, ECOG 0, most recent visit showed no questionable lesions.

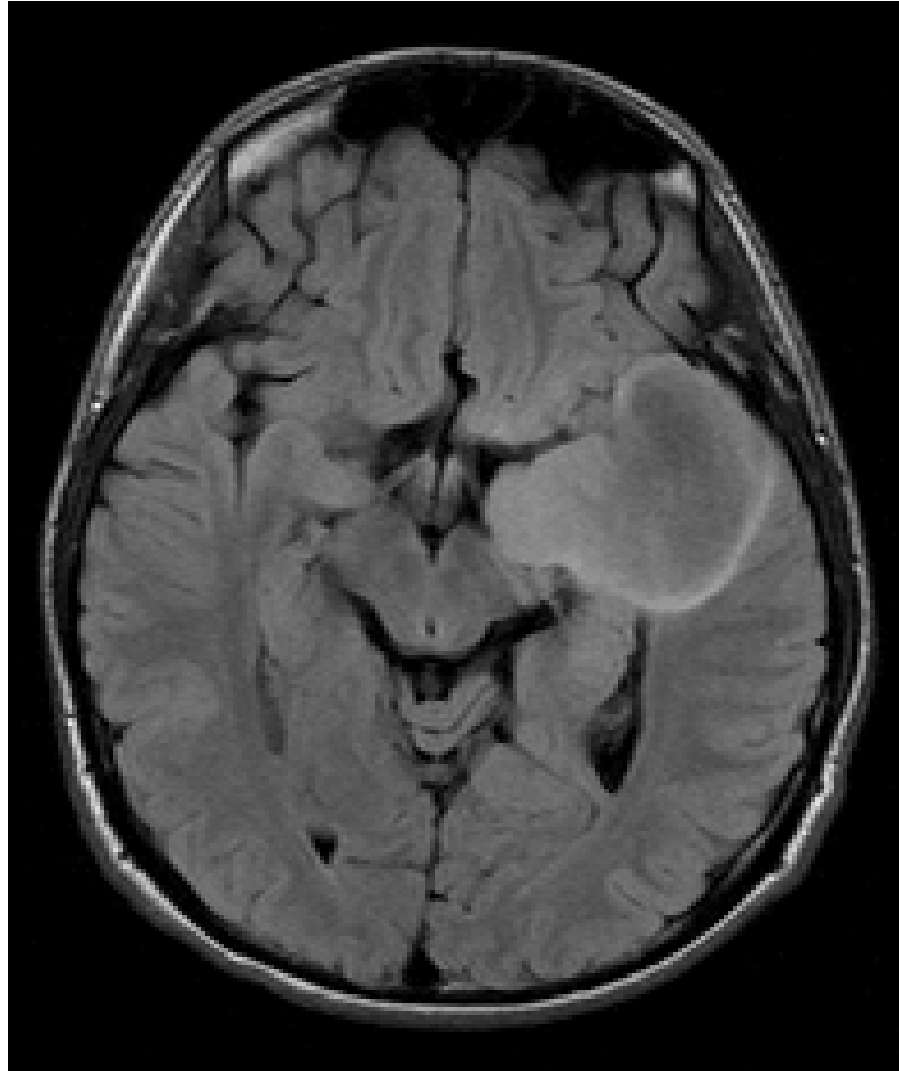
Imaging



Patient Example

- Patient was diagnosed with colorectal cancer after persistent unremitting diarrhea in 1995 at the age of 18 years. He underwent tumor resection in February 1995. He required no additional treatment.
- During work-up, a bony lesion was identified in the pelvis/right hip, which was confirmed an osteosarcoma by biopsy. He received chemotherapy as per AOST0331 with MAP. In July 1995, he underwent partial resection of the pelvis, and his chemotherapy response was poor with 15% tumor necrosis. He received further chemotherapy with ICE starting in July 1995. In October 1997, he experienced a relapse of the osteosarcoma in his right heel. He underwent a right lower leg amputation. In February 1998, he had a second relapse of the osteosarcoma in the left mandible. He received radiation, followed by Samarium in October 1998.
- In 2003, he was diagnosed with a basal cell carcinoma of the left cheek. This was excised and required no additional treatment.
- In April 2006, he developed seizures, initially thought to represent panic attacks. MRI in November 2006 showed a large left temporal hypointense tumor. Biopsy in December 2006 revealed infiltrating astrocytoma.
- Given his personal history of multiple primary cancers, he had genetic testing in December 2006 which consisted of full gene sequencing of the TP53 gene. Testing revealed a TP53 gene mutation. Based upon pedigree analysis, he developed LFS as the result of a de novo mutation.
- January 2007 he presented to MD Anderson for a second opinion. On Feb 14, 2007 brain tumor resection showed Anaplastic Astrocytoma Grade III. He received proton beam radiation from March to April 2007. In September 2009, clinically he had increased seizures, and radiographically, the MRI developed contrast enhancement. In November 2009, a stereotactic biopsy showed pathology had transformed to Glioblastoma. In November 2009, he started chemotherapy with Avastin and Temozolomide. In November 2010, his MRI showed radiographical progression that correlated with clinical progression, with increased slurred speech, aphasia, ataxia, short term memory loss.
- He unfortunately passed away in March 2011.

Imaging



Summary

- LFS = any pathogenic germline mutation in the TP53 tumor suppressor gene that gets passed down in an autosomal dominant pattern
- Both classical and Chompret criteria are widely accepted for genetic testing
- There are three temporal phases of the disease, each characterized by a specific pattern of cancers: childhood, early adulthood, and late adulthood
- Cumulative cancer risk associated with LFS has been estimated to be approximately 50% by age 40 years and up to 90% by age 60 years
- Survivors of childhood cancers were found to have the highest risks for developing additional malignancies
- The only effective surveillance shown to offer benefit for LFS involves multi-modal screening using whole body rapid sequence MRI, in addition to regular MRIs of the brain, abdominal ultrasounds, lab work, and physical examinations.

In the future...

- We will hopefully continue to further define the genetics of Li-Fraumeni to better interpret results of genetic testing.
- Insurance companies will realize the importance of whole body MRI as a good screening tool for those with Li-Fraumeni Syndrome.
- Early detection will continue to increase overall survival in patients with LFS.

Sources

1. Amadou, A., Waddington Achatz, M., Hainaut, P. Revisiting tumor patterns and penetrance in germline TP53 mutation carriers: temporal phases of Li-Fraumeni Syndrome. *Curr Opin Oncol*, 2018; 30: 23-29.
2. Bojadzieva, J., et al. 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. *Familial Cancer* (2018), 17: 287-294. doi: 10.1007/s10689-017-0034-6.
3. Mai, P., Best, A., & Peters, J. et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni Syndrome cohort. *Cancer*. 2016; 122: 3673-81.
4. National Comprehensive Cancer Network. Li-Fraumeni Syndrome (Version 3.2019). http://www.nccn.org/professionals/physician_gls/pdf/lifraumeni.pdf. Accessed October 1, 2019.
5. Villani, A., Shore, A., & Wasserman, J. et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. *Lancet Oncol* 2016; 17: 1295-305.
6. Warby, M., Wakefield, C., Vetsch, J., & Tucker, K. Families' and health care professionals' attitudes towards Li-Fraumeni syndrome testing in children: A systematic review. *Clinical Genetics*, 2019; 95: 140-150.

Contact Information

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Acknowledgements

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