Pediatric Cancer Predisposition Syndromes

Joshua J. Bies, MD
Assistant Professor
Pediatric Hematology/Oncology
Gwen Reiser, MS, CGC

University of Nebraska Medical Center | Children's NEBRASKA

1

Disclosures

Gwen Reiser has no financial disclosures

Dr. Joshua Bies has no financial disclosures.

2

Objectives

1. Identify clinical features, natural history and inheritance patterns for pediatric hereditary cancer syndromes.

2. Assess evidence-based surveillance guidelines for children and adults with common hereditary pediatric cancers.

3

Pediatric Cancer SEER Statistics

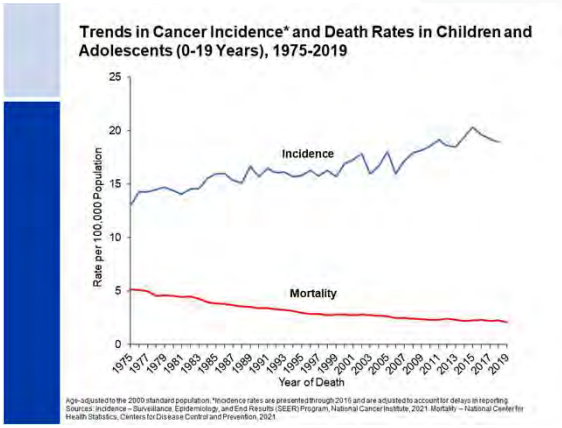
Incidence rate increase 0.8% per year since 1970

- 10,470 new cases in 2022 (*children* 1-14 yo)
- 5,480 new cases in 2022 (*adolescents* 15-19yo)

2nd most common cause of death children
4th most common cause of death in adolescents

Cancer death rates decrease

- 71% (*children* 1-14)
- 61% (*adolescents* 15-19)



https://www.nejm.org/doi/full/10.1056/NEJMoa1508054

4

Pediatric Cancer and Germline Predisposition Studies

Prior large studies: 8-11%
2021 MSKCC Study (largest solid tumor cohort): 13%
Biases exist and are different between centers

Table 1 | Broad germline sequencing studies of pediatric cancer with >100 patients

Study	Hematologic	CNS	Solid tumor (non-CNS)	Percent reported with germline P/LP variants in high/moderate-penetrance cancer predisposition genes
Michigan: Mody et al.[3]	30	8	64	10
St. Jude: Zhang et al.[2]	588	245	287	8
Baylor: Parsons et al.[6]		56	94	10
Columbia: Oberg et al.[5]	36	16	49	10
Australia: Wong et al.[7]	43	92	112	11
MSKCC: present study		139	612	13

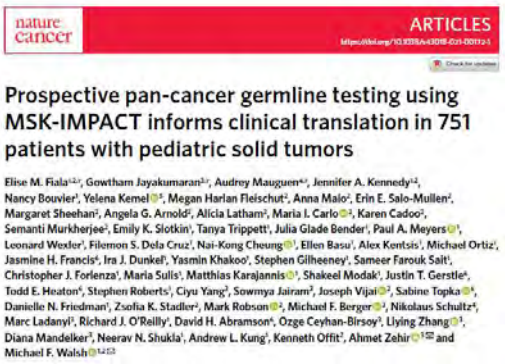
Fiala et al. 2021
Memorial Sloan Kettering Cancer Center

5

Evidence suggests germline testing should be considered for all children with solid tumors

13% patients with positive results
- High and moderate penetrance dominant genes

18% patients with positive results
- High, moderate, low penetrance dominant and AR genes


nature cancer ARTICLES

Prospective pan-cancer germline testing using MSK-IMPACT informs clinical translation in 751 patients with pediatric solid tumors

Elise M. Fiala[1,2,7], Gowtham Jayakumaran[2,7], Audrey Mauguen[4,7], Jennifer A. Kennedy[1,2], Nancy Bouvier[1], Yelena Kemel[1,5], Megan Harlan Fleischut[1], Anna Maio[2], Erin E. Salo-Mullen[2], Margaret Sheehan[2], Angela G. Arnold[2], Alicia Latham[2], Maria I. Carlo[2,3], Karen Cadoo[2], Semanti Murkherjee[2], Emily K. Slotkin[1], Tanya Trippett[1], Julia Glade Bender[1], Paul A. Meyers[1], Leonard Wexler[1], Filemon S. Dela Cruz[1], Nai-Kong Cheung[1], Ellen Basu[1], Alex Kentsis[1], Michael Ortiz[1], Jasmine H. Francis[4], Ira J. Dunkel[1], Yasmin Khakoo[1], Stephen Gilheeney[1], Sameer Farouk Sait[1], Christopher J. Forlenza[1], Maria Sulis[1], Matthias Karajannis[1], Shakeel Modak[1], Justin T. Gerstle[4], Todd E. Heaton[4], Stephen Roberts[1], Ciyu Yang[2], Sowmya Jairam[2], Joseph Vijai[2], Sabine Topka[4], Danielle N. Friedman[1], Zsofia K. Stadler[2], Mark Robson[2], Michael F. Berger[2], Nikolaus Schultz[4], Marc Ladanyi[2], Richard J. O'Reilly[1], David H. Abramson[4], Ozge Ceyhan-Birsoy[3], Liying Zhang[3], Diana Mandelker[3], Neerav N. Shukla[1], Andrew L. Kung[1], Kenneth Offit[2], Ahmet Zehir[1,2] and Michael F. Walsh[1,2,3]

34% high/moderate penetrant variants were unexpected based on pts dx

6

CCR Pediatric Oncology Series

- Produced by the Pediatric Cancer Working Group (PCWG) of the American Association for Cancer Research (AACR)
- Published in *Clinical Cancer Research* ***(CCR)***
- 18 articles focusing on various aspects of cancer predisposition.
- Majority published in 2017 – many in process of updates.
- May be referred to as "AACR Childhood Cancer Predisposition Workshop Articles" or "CCR Pediatric Oncology Series"

https://aacrjournals.org/clincancerres/collection/57/Pediatric-Oncology-Series

7

AACR Childhood Cancer Predisposition Workshop Articles

- **Pediatric Cancer Predisposition and Surveillance: An Overview and Tribute to Alfred G. Knudson**
- The Future of Surveillance
- Genetic Counselor Recommendations
- Imaging: Focus on Whole Body MRI

8

Pediatric Cancer Predisposition

Predisposition Group	Condition	Genes
Li-Fraumeni Syndrome	Li-Fraumeni syndrome	*TP53*
Neurofibromatoses	Neurofibromatosis Type 1 Neurofibromatosis Type 2 Schwannomatosis Meningioma predisposition	*NF1* *NF2* *SMARCB1, LZTR1* *SMARCE1*
Overgrowth Syndromes, Wilms tumor	Beckwith-Wiedemann syndrome Wilms-Aniridia-GU-Retardation Denys-Drash and Frasier syndromes Perlman syndrome Bohring-Opitz syndrome Mulibrey Nanism Simpson-Golabi-Behmel syndrome	11p15.5 *WAGR* *WT1* *DIS3L2* *ASXL1* *TRIM37* *GPC3, GPC4*
Neural Tumor Syndromes	Retinoblastoma Hereditary neuroblastoma Gorlin syndrome Malignant Rhabdoid Tumor syndrome	*RB1* *ALK, PHOX2B* *PTCH1, SUFU* *SMARCB1, SMARCA4*
GI Cancer Syndromes	Familial Adenomatous Polyposis Juvenile polyposis Peutz-Jeghers syndrome Constitutional Mismatch Repair	*APC, MUTYH* *SMAD4, BMPR1A* *STK11, LKB1* *MSH2, MSH6, MLH1, PMS2, EPCAM*
Neuroendocrine Syndromes	Multiple Endocrine Neoplasia Von Hippel Lindau Hereditary Paraganglioma/Pheo Parathyroid cancer syndrome	*MEN1, RET, CDKN1B* *VHL* *SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127, MAX* *CDC73*
Leukemia Predisposition Syndromes	Li-Fraumeni syndrome CMMRD Familial ALL MDS/AML Ataxia-pancytopenia syndrome	*TP53* *MSH2, MSH6, MLH1, PMS2, EPCAM* *PAX5* *GATA2, CEBPA, RUNX1, SMAD9* *SAMD9L*
DNA Instability Syndromes	Ataxia telangiectasia Bloom syndrome Fanconi anemia Xeroderma pigmentosum Nijmegen breakage syndrome Diamond-Blackfan syndrome Dyskeratosis congenita Rothmund-Thompson syndrome	*ATM* *BLM* *FANCA-V, RAD51C* *XPA, XPC, ERCC2, POLH, DDB2* *NBN* *RPS7, RPLS* *DKC1, TINF2,TERC, TERT, NHP2, NOP10, WRAP53* *RECQL4*
Miscellaneous Syndromes	PTEN Hamartoma tumor syndrome Pleuropulmonary Blastoma syndrome Noonan syndrome Costello syndrome Sotos syndrome Weaver syndrome Rubenstein-Taybi syndrome Schinzel-Giedion syndrome NKX2-1 syndrome Hereditary Leiomyomatosis and RCC	*PTEN* *DICER1* *PTPN11, SOS1, RAF1, RIT1, KRAS* *HRAS* *NSD1* *EZH2* *CREBBP, EP300* *SETBP1* *NKX2-1* *FH*

Pediatric Cancer Predisposition and Surveillance: An Overview, and a Tribute to Alfred G. Knudson, Jr

Clin Cancer Res. 2017 Jun 1; 23(11): e1–e5.
doi: 10.1158/1078-0432.CCR-17-0702

9

AACR Childhood Cancer Predisposition Workshop Articles

- **Overgrowth Syndromes** and Predisposition to **Wilms and Hepatoblastoma**
- Inherited **Gastrointestinal Cancer** Syndromes in Childhood
- **Retinoblastoma and Neuroblastoma** Predisposition
- **Multiple Endocrine Neoplasia (MEN) and Hyperparathyroid-Jaw Tumor** Syndromes
- **RASopathies** and Other Rare Genetic Conditions with Increased Cancer Risk
- ***PTEN, DICER1, FH*** (fumarate hydratase), and their Associated Tumor Syndromes
- **Von Hippel Lindau and Hereditary Pheochromocytoma/Paraganglioma** Syndromes
- **Gorlin Syndrome and Rhabdoid Tumor** Predisposition Syndrome
- Pediatric **Neurofibromatosis 2** and Related Disorders
- Pediatric **Neurofibromatosis 1**
- **Li-Fraumeni Syndrome**
- **Leukemia-Predisposing** Conditions
- **DNA Repair** Disorders
- **Inherited Mismatch Repair Deficiency**

10

Major subgroups of pediatric cancer susceptibility disorders reviewed

Predisposition group	Specific disorders reviewed
LFS	**LFS (*TP53*)**
Neurofibromatoses	**Neurofibromatosis type I (*NF1*),** neurofibromatosis type II (*NF2*), Schwannomatosis (*SMARCB1, LZTR1*), meningioma predisposition (*SMARCE1*)
Overgrowth syndromes, Wilms tumor	BWS/hemihypertrophy (11p15.5), Wilms tumor-aniridia-GU anomaly-retardation (WAGR) syndrome, Denys–Drash and Frasier syndromes (*WT1*), Perlman syndrome (*DIS3L2*), Bohring–Opiz syndrome (*ASXL1*), Mulibrey Nanism (*TRIM37*), Simpson–Golabi–Behmel syndrome (*GPC3, GPC4*), non-syndromic hereditary Wilms tumor
Neural tumor syndromes	**Hereditary retinoblastoma (*RB1*),** hereditary neuroblastoma (*ALK, PHOX2B*), Gorlin syndrome (*PTCH1, SUFU*), malignant rhabdoid tumor syndrome (*SMARCB1, SMARCA4*)
GI cancer syndromes	Familial adenomatous polyposis (*APC, MUTYH*), juvenile polyposis syndrome (*SMAD4, BMPR1A*), Peutz–Jeghers syndrome (*STK11*), Lynch syndrome (*MSH2, MSH6, MLH1, PMS2, EPCAM*), CMMRD (see Lynch syndrome genes)
Neuroendocrine syndromes	Multiple endocrine neoplasia (MEN)-1 (*MEN1*), MEN2A (*RET*), MEN2B (*RET*), MEN4 (*CDKN1B*), von Hippel–Lindau (*VHL*), hereditary paraganglioma/pheochromocytoma syndrome (*SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127, MAX*), familial thyroid cancer (*RET, NTRK1*), hyperparathyroidism-jaw tumor syndrome (*CDC73*)
Leukemia predisposition syndromes	LFS, CMMRD, susceptibility to ALL 3 (*PAX5*), *GATA2*-associated predisposition to myelodynsplasia/AML, *CEBPA*-associated predisposition to AML, thrombocytopenia, type 5 (*ETV6*), familial platelet disorder with associated myeloid malignancy (*RUNX1*), ataxia-pancytopenia syndrome (*SAMD9L*), myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy (*SAMD9*)
DNA instability syndromes	Ataxia telangiectasia (*ATM*), Bloom syndrome (*BLM*), Fanconi anemia (*FANCA-V, RAD51C*), xeroderma pigmentosum (*XPA, XPC, ERCC2, POLH, DDB2*), Nijmegen breakage syndrome (*NBN*), Diamond–Blackfan syndrome (*RPS7, -10, -17, -19, -24, -26; RPL5, -11, -19, -35A*), dyskeratosis congenita (*DKC1, TINF2, TERC, TERT, NHP2, NOP10, WRAP53*), Rothmund–Thompson syndrome (*RECQL4*)
Miscellaneous syndromes	PTEN hamartoma tumor syndrome (*PTEN*), **pleuropulmonary blastoma syndrome (*DICER1*),** Noonan syndrome (*PTPN11, SOS1, RAF1, RIT1, KRAS*, others), Costello syndrome (*HRAS*), Sotos syndrome (*NSD1*), Weaver syndrome (*EZH2*), Rubenstein–Taybi syndrome (*CREBBP, EP300*), Schinzel–Giedion syndrome (*SETBP1*), NKX2-1 syndrome (*NKX2-1*), hereditary leiomyomatosis and renal cancer syndrome (*FH*), metabolic disorders (*L2HGA, FAH*)

Brodeur, GM *et al.,* (2017) Pediatric Cancer Predisposition and Surveillance: An Overview, and a Tribute to Alfred G. Knudson Jr. Clin Cancer Res (2017). 23 (11): e1-e5.

11

Children's Oncology Group Guidelines

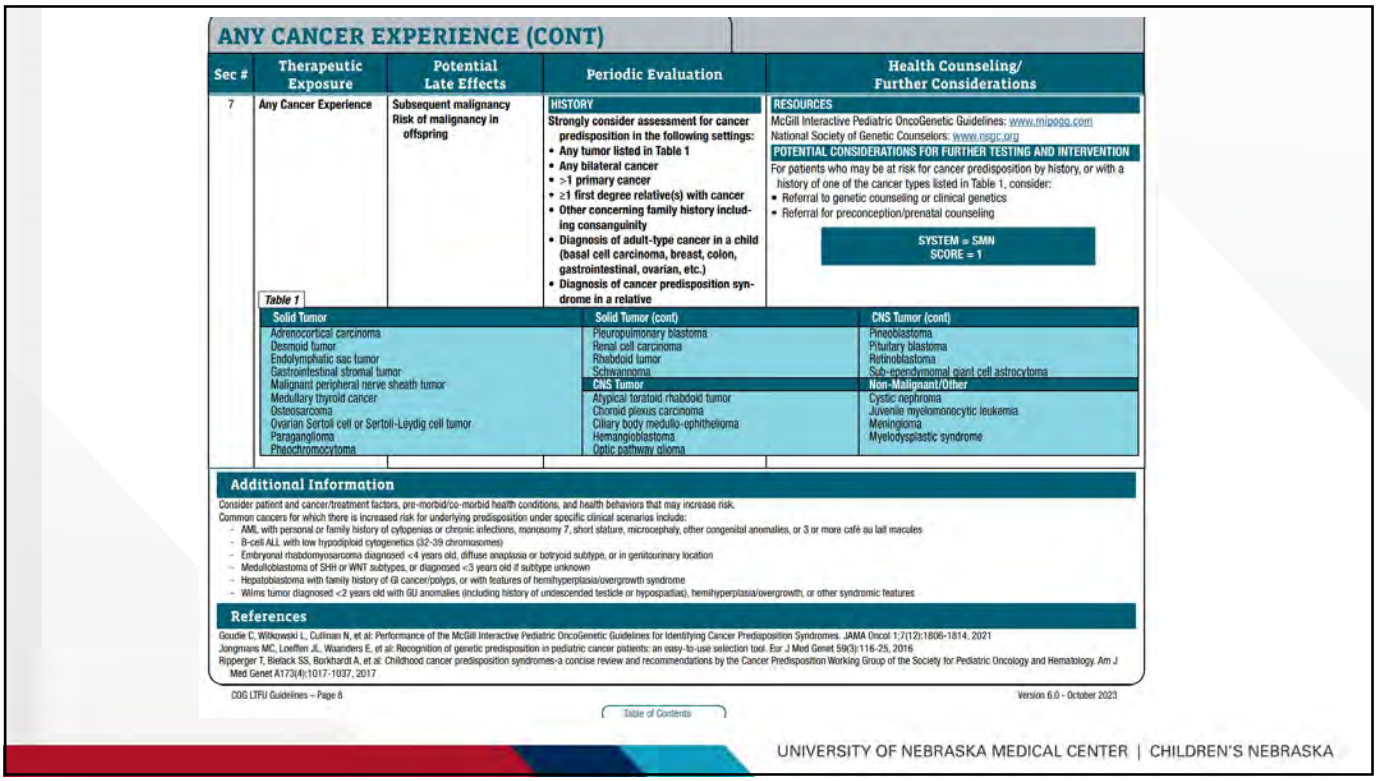
- Children's Oncology Group (COG) Long Term Follow Up Guidelines v6.0 includes new guidance for genetic testing.
- Section #7, Page 8 – "Subsequent malingancy/Risk of malignancy in offspring"
- www.survivorshipguidelines.org

Guidelines: Children's Oncology Group. Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers, Version 6.0. Monrovia, CA: Children's Oncology Group; October 2023; Available on-line: www.survivorshipguidelines.org.

Guidelines Methodology : Landier W, Bhatia S, Eshelman DA, Forte KJ, Sweeney T, Hester AL, Darling J, Armstrong FD, Blatt J, Constine LS, Freeman CR, Friedman DL, Green DM, Marina N, Meadows AT, Neglia JP, Oeffinger KC, Robison LL, Ruccione KS, Sklar CA, Hudson MM. Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group long-term follow-up guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. J Clin Oncol 2004; 22(24):4979-90.

Health Links Background and Application : Eshelman D, Landier W, Sweeney T, Hester AL, Forte K, Darling J & Hudson MM. Facilitating care for childhood cancer survivors: integrating Children's Oncology Group long-term follow-up guidelines and health links in clinical practice. J Pediatr Oncol Nurs 2004; 21(5): 271-280.

12



ANY CANCER EXPERIENCE (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
7	Any Cancer Experience	Subsequent malignancy Risk of malignancy in offspring	**HISTORY** **Strongly consider assessment for cancer predisposition in the following settings:** • **Any tumor listed in Table 1** • **Any bilateral cancer** • **>1 primary cancer** • **≥1 first degree relative(s) with cancer** • **Other concerning family history including consanguinity** • **Diagnosis of adult-type cancer in a child (basal cell carcinoma, breast, colon, gastrointestinal, ovarian, etc.)** • **Diagnosis of cancer predisposition syndrome in a relative**	**RESOURCES** McGill Interactive Pediatric OncoGenetic Guidelines: www.mipogg.com National Society of Genetic Counselors: www.nsgc.org **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** For patients who may be at risk for cancer predisposition by history, or with a history of one of the cancer types listed in Table 1, consider: • Referral to genetic counseling or clinical genetics • Referral for preconception/prenatal counseling **SYSTEM = SMN SCORE = 1**

Table 1

Solid Tumor	Solid Tumor (cont)	CNS Tumor (cont)
Adrenocortical carcinoma	Pleuropulmonary blastoma	Pineoblastoma
Desmoid tumor	Renal cell carcinoma	Pituitary blastoma
Endolymphatic sac tumor	Rhabdoid tumor	Retinoblastoma
Gastrointestinal stromal tumor	Schwannoma	Sub-ependymomal giant cell astrocytoma
Malignant peripheral nerve sheath tumor	**CNS Tumor**	**Non-Malignant/Other**
Medullary thyroid cancer	Atypical teratoid rhabdoid tumor	Cystic nephroma
Osteosarcoma	Choroid plexus carcinoma	Juvenile myelomonocytic leukemia
Ovarian Sertoli cell or Sertoli-Leydig cell tumor	Ciliary body medullo-ephithelioma	Meningioma
Paraganglioma	Hemangioblastoma	Myelodysplastic syndrome
Pheochromocytoma	Optic pathway glioma	

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors that may increase risk.
Common cancers for which there is increased risk for underlying predisposition under specific clinical scenarios include:
- AML with personal or family history of cytopenias or chronic infections, monosomy 7, short stature, microcephaly, other congenital anomalies, or 3 or more café au lait macules
- B-cell ALL with low hypodiploid cytogenetics (32-39 chromosomes)
- Embryonal rhabdomyosarcoma diagnosed <4 years old, diffuse anaplasia or botryoid subtype, or in genitourinary location
- Medulloblastoma of SHH or WNT subtypes, or diagnosed <3 years old if subtype unknown
- Hepatoblastoma with family history of GI cancer/polyps, or with features of hemihyperplasia/overgrowth syndrome
- Wilms tumor diagnosed <2 years old with GU anomalies (including history of undescended testicle or hypospadias), hemihyperplasia/overgrowth, or other syndromic features

References

Goudie C, Witkowski L, Cullinan N, et al: Performance of the McGill Interactive Pediatric OncoGenetic Guidelines for Identifying Cancer Predisposition Syndromes. JAMA Oncol 1;7(12):1806-1814. 2021
Jongmans MC, Loeffen JL, Waanders E, et al: Recognition of genetic predisposition in pediatric cancer patients: an easy-to-use selection tool. Eur J Med Genet 59(3):116-25, 2016
Ripperger T, Bielack SS, Borkhardt A, et al: Childhood cancer predisposition syndromes-a concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. Am J Med Genet A173(4):1017-1037, 2017

13

Tumors to prompt genetic testing

- **Solid Tumors**
  - **Adrenocortical carcinoma**
  - Desmoid tumor
  - Endolymphatic sac tumor
  - GIST
  - Malignant peripheral nerve sheath tumor
  - Medullary thyroid cancer
  - Osteosarcoma
  - **Ovarian Sertoli cell tumor**
  - **Sertoli-Leydig cell tumor**
  - Paraganglioma
  - Pheochromocytoma
  - **Pleuropulmonary blastoma**
  - Renal cell carcinoma
  - Rhabdoid tumor
  - Schwannoma
- **CNS tumors**
  - Atypical teratoid rhabdoid tumor (ATRT)
  - **Choroid plexus carcinoma**
  - Ciliary body medullo-epithelioma
  - Hemangioblastoma
  - Optic pathway glioma
  - Pineoblastoma
  - Pituitary blastoma
  - **Retinoblastoma**
  - Sub-ependymomal giant cell astrocytoma (SEGA)
- **Non-malignant/other**
  - Cystic nephroma
  - Juvenile myelomonocytic leukemia (JMML)
  - Meningioma
  - Myelodysplastic syndrome (MDS)

14

Cancer subtypes with high genetic risk

- **AML** with personal or family history of cytopenias or chronic infections, monosomy 7, short stature, microcephaly, congenital anomalies, >3 café au lait macules
- **B-cell ALL** with *low hypodiploid cytogenetics (32-39* chromosomes)
- **Embryonal (fusion negative) rhabdomyosarcoma** < 4 years old, with *diffuse anaplasia*, botryoid subtype, or in GU location
- **Medulloblastoma** with SHH or WNT subtypes or if <3 years old and subtype unknown
- **Hepatoblastoma** with FH of GI cancer/polyps or hemihyperplasia/overgrowth
- **Wilms tumor** <2 years old with GU anomalies (ie: undescended testicles, hypospadias), hemihyperplasia/overgrowth, or syndromic features.

15

COG Genetic Assessment Recommendations

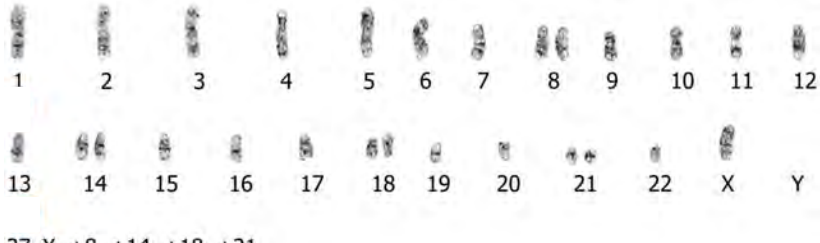
Strongly consider assessment for cancer predisposition in the following settings:

- Any of the previously listed tumors (table 1 in article)
- Any **bilateral** cancer
- >1 primary cancer
- 1 or more first degree relative with cancer
- Concerning family history including consanguinity
- **Diagnosis of adult type cancer in a child (basal cell carcinoma, breast, colon, GI, ovarian, lung, etc.)**
- Diagnosis of cancer predisposition in relative.

16

Case 1

3 y/o female referred to Hereditary Cancer Clinic
Hypodiploid acute lymphoblastic leukemia



27, X, +8, +14, +18, +21

3% ALL, gross aneuploidy, very poor outcome
90% low hypodiploid cases have *TP53* variants
40% have Li-Fraumeni syndrome

 Holmfeldt, Nature Genetics 2013

17

Li-Fraumeni Syndrome (*TP53*)

18

Cancer risk in LFS

- Heterozygous germline mutation of *TP53* tumor suppressor gene encoding the transcription factor p53
- 78% developed at least one cancer in their lifetime
- 4% with cancer by 12 months of age
- 22% with cancer by age 5 years
- **41% by age 18 years**

Kratz, CP *et al.,* (2017) Cancer Screening Recommendation for Individuals with Li-Fraumeni Syndrome. Clin Cancer Res (2017). 23 (11): e38-45

19

LFS Spectrum Tumors

- CNS Tumors
  - Choroid plexus carcinoma
  - Sonic Hedgehog (SHH) subtype medulloblastoma
  - Glioma
- Adrenocortical carcinoma (ACC)
- Soft Tissue Sarcomas (STS)
- Embryonal (Fusion negative) Anaplastic Rhabdomyosarcoma
- Bone Tumors
  - Osteosarcoma
- Hematological Malignancies
- Breast cancer – very early onset (pre-menopause)

Kratz, CP *et al.,* (2017) Cancer Screening Recommendation for Individuals with Li-Fraumeni Syndrome. Clin Cancer Res (2017). 23 (11): e38-45

20

When to test for LFS - "Chompret criteria"

(i) Familial presentation: proband with an LFS spectrum tumor (premenopausal breast cancer, STS, brain tumor, ACC) prior to age 46 years and at least one first- or second-degree relative with an LFS tumor (except breast cancer, if the proband has breast cancer) before the age of 56 years or with multiple tumors;

(ii) Multiple tumors: proband with multiple malignancies (except two breast cancers), of which at least two belong to the LFS spectrum, before the age of 46 years;

(iii) Rare tumors: patients with **ACC, choroid plexus carcinoma, or embryonal anaplastic subtype rhabdomyosarcoma independent of family history;**

(iv) Breast cancer before the age of 31 years

Summary – patient with 1 or more tumors before age 46 +/- family history of LFS tumor before age 56.

- Chompret A, *et al*. Sensitivity and predictive value of criteria for p53 germline mutation screening. *J Med Genet* 2001; 38:43–7
- Bougeard G, et al Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers. *J Clin Oncol* 2015;33:2345–52

21

Incidence of Germline *TP53* Mutations in Pediatric Cancers

Adrenocortical carcinoma: 50-80% Nearly 100% if < 5 yrs old

Osteosarcoma: ~5-10%

Rhabdomyosarcoma: ~10%

Hypodiploid Acute Lymphoblastic Anemia: 40%

SHH Medulloblastoma: 40%

- Importance of de novo risk and screening implications
- Importance of family history in identification

22

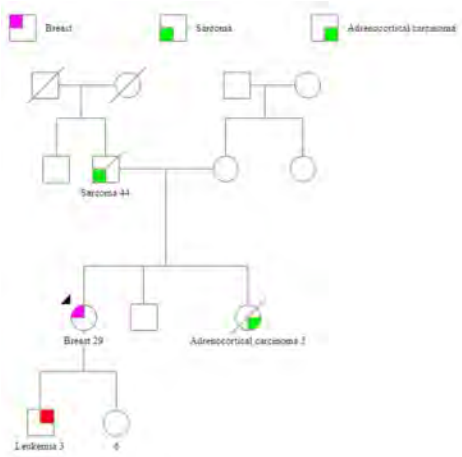
Genetic Testing Results
TP53+

RESULTS	
TP53	**Variant, Likely Pathogenic: p.R181H**

Fibroblast cultured cells confirmed diagnosis of Li-Fraumeni syndrome

23

Family History



24

Tumor type	TORONTO CRITERIA FOR LFS SCREENING
ACC	• **Ab US q 3-4 m: birth–40 y**
	• **Biochemistry (17-OH-progesterone, total testosterone, DHEAS, androstenedione) q 3-4 m: birth–40 y**
	• 24-h urine cortisol, if feasible
Breast cancer	• BSE monthly: from 18 y
	• CBE q 6 m: from 20–25 y or 5–10 y before earliest case of breast cancer in family
	• Annual mammography and breast MRI: from age 20–75 y or 5–10 y before earliest case of breast cancer in family
	• Breast MRI alternates with WBMRI
	• Breast US with mammography as indicated by breast density
	• Consider risk-reducing bilateral mastectomy
Brain tumor	• **Annual brain MRI: from birth**
Sarcoma	• **Annual rapid WBMRI: from birth**
	• AUS q 3-4 m: from 18 y
Hematopoietic	• **CBC, ESR, LDH q3-4m: from birth**
CRC	• Colonoscopy q 2 y: from age 25 or 10 y before earliest onset of CRC in family
Gastric cancer	No screening described
Skin cancer	• Annual dermatologic exam: from 18 y

- Villani A et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study. *Lancet Oncol.* 2011;12:559–67
- Villani A 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

25

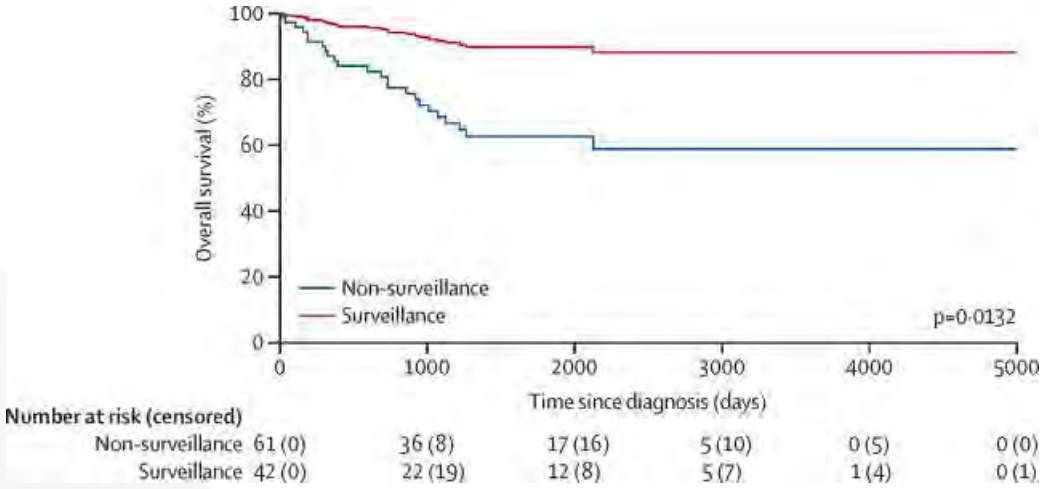
LFS Screening – Pediatric Summary

- **Abdominal US every 3-4 months – focus on adrenals**
- **Labs – Adrenal Cortical Carcinoma biochemistry labs, CBC, ESR, LDH every 3-4 months**
- **Brain MRI and Whole Body MRI every 12 months**
- Colonoscopy every 2 years starting at 10 years prior to earliest colorectal cancer diagnosis in family, or age 25, which occurs sooner.
- Dermatological exams and breast cancer screening start at 18 years.

Kratz, CP *et al.,* (2017) Cancer Screening Recommendation for Individuals with Li-Fraumeni Syndrome. Clin Cancer Res (2017). 23 (11): e38-45

26

Surveillance improves survival in LFS



Lancet Oncol. 2016 Sep;17(9):1295-305. **Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study.** Anita Villani[1], Ari Shore[2], Jonathan D Wasserman[3], Derek Stephens[4], Raymond H Kim[5], Harriet Druker[6], Bailey Gallinger[7], Anne Naumer[8], Wendy Kohlmann[8], Ana Novokmet[9], Uri Tabori[1], Marta Tijerin[10], Mary-Louise C Greer[10], Jonathan L Finlay[11], Joshua D Schiffman[8], David Malkin[12]

27

Screening Considerations

- Not all LFS patients choose to participate in the screening, and some find it too anxiety provoking or burdensome.
- As is the case with the management of patients with any cancer predisposition syndrome, **screening and surveillance strategies impose physical, psychosocial, and financial challenges to patients and families.**
- With the wide adoption of next-generation sequencing (NGS) panels, many individuals with *TP53* mutations lack classic personal or family history of LFS-related cancers.

28

Case 2

6 mo old male recently diagnosed with bilateral retinoblastoma

Family history is negative for retinoblastoma and other cancers

Germline testing identified a *RB1* gene variant

29

Retinoblastoma (*RB1)*

30

Retinoblastoma Overview

- General population risk for retinoblastoma: 0.007%
- Most retinoblastomas occur before age 2. Almost all occur by age 5.

Unilateral
- 60% of all cases
- ~10-15% are hereditary

Bilateral
- 40% of all cases
- Presumed hereditary

Sporadic
- ~60% of cases
- Mean age dx: ~24 mo
- Unilateral
- LOH in 60-70% of tumors

Hereditary
- ~40% of cases
- Mean age dx: ~10 mo
- Most are bilateral and/or multifocal
- 90-95% risk for RB with most variants
- Increased risk for non-ocular tumors
- AD inheritance
- ~80% de novo
- LOH in 70% of tumors

31

Retinoblastoma Clinical Features

RB1 gene on chr 13
Penetrance >90%
May present as
- Unilateral
- Bilateral
- Trilateral (pineoblastoma))

Symptoms:
- Leukocoria (white reflected with flash
- Stabismus (crossed eye)
- Glaucoma
- Painful/red eye
- Poor vision
- Heterochromia

Other Cancer Risks (1% per year; increased with radiation):
- Osteosarcoma
- Soft Tissue Sarcoma
- Melanoma
- Other

32

Retinoblastoma Screening

- **All children** of parents with known Rb mutations and **all siblings** of those with known Rb mutations must be **screened with eye exams at birth and every 4 weeks until genetic testing is completed.**
- **If RB1 testing is POSITIVE –** must continue **dilated eye exams** **every 4 weeks** due to high penetrance of the mutation.

33

Secondary Malignancies

- The **most common cause of death for patients with hereditary retinoblastoma is a secondary malignancy and not the initial retinoblastoma**
  - Cumulative incidence 36% at 50 years
- **Most are radiation induced**
  - RT exposure almost doubles the risk from 20 to 40%
- 60-70% of second malignancies are in the **head and neck area**. There is a clear dose-effect and age-effect, higher risk if <1 year old.
- **Osteosarcoma (25-40%): the most common** **both in and out** **of radiation field**
- **Soft tissue sarcoma (10-15%): more common inside than outside irradiated fiel**d **(leiomyosarcoma > fibrosarcoma** > MFH> STS NOS > *RMS)*
- Melanoma and skin cancer (15-20%)
  - Regular skin checks with PCP/Derm recommended to start by age 18
- Lung cancers and other common adult cancers

34

Cancer Screening in Hereditary Rb

Eye exam for Rb

- Initially q4 weeks
- After treatment completed, will slowly space out timing.
- Eventually - every 4-6 months until age 4-5 years old

MRI Brain for extra-orbital Retinoblastoma, "trilateral" CNS lesions

- Every 6 months until age 4-5 years old

Yearly skin exams for melanoma

- PCP or Dermatology, start at age 18 years at the latest

Whole Body MRI for sarcomas

- Not a consensus recommendation
- Start at age 8-10 years, whenever able to tolerate without anesthesia.
- Risk increased if history of radiation therapy

J Kamihara *et al* (2017) Retinoblastoma and Neuroblastoma Predisposition and Surveillance. Clinical Cancer Research. July 2017, Vol 23, Issue 13.

35

Case 3

5 y/o with spontaneous pneumothorax

Recurred after chest tube removal

Resection of 2 cystic areas

Pathology reported likely regressed Pleuropulmonary Blastoma

DICER1 genetic testing initiated

36

DICER1 Related Disorder

(Pleuropulmonary Blastoma Syndrome)

37

DICER1 Gene

Pleuropulmonary Blastoma Familial Tumor Predisposition Syndrome
DICER1-Related Disorder

Pleuro Pulmonary Blastoma (PPB) and lung cysts (66-70% have *DICER1* variants)

Ovarian tumors (56% have *DICER1* variants)

Cystic nephroma (kidney cyst)

Thyroid gland cysts/tumor

Other rare childhood tumors reported

38

DNA Genetic Test Results

MOLECULAR GENETICS REPORT:
DICER1 Syndrome via the *DICER1* Gene

SUMMARY OF RESULTS: **Indeterminate**

Sequence Variant(s):

Gene, Transcript	Mode of Inheritance, Gene OMIM	DNA Variants, Predicted Effects, Zygosity	ClinVar ID	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
DICER1, NM_030621.4	AD, 606241	c.1753-9A>G, Intronic, Heterozygous	690483	Not Present	Not Applicable	UNCERTAIN

DICER1 gene variant identified, classified as a Variant of Uncertain Significance (VUS)

- Not reported before in literature or population database
- Intronic variant predicted to interfere with splicing
- Recommend further testing to clarify
  - Test other family members
  - Consider RNA analysis

39

DICER1-related disorder

Thoracic embryonal rhabdomyosarcoma
Genitourinary sarcomas
Cervical or ovarian embryonal rhabdomyosarcoma
Genitourinary/gynecologic neuroendocrine tumors
Ciliary body medulloepithelioma
Nasal chondromesen-chymal hamartoma
Pineoblastoma
Pituitary blastoma

Clin Cancer Res. 2018 May 15; 24(10): 2251–2261. doi:10.1158/1078-0432.CCR-17-3089.

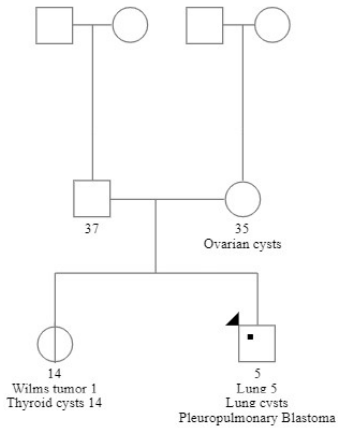
***DICER1* and associated conditions: Identification of at-risk individuals and recommended surveillance strategies**

Kris Ann P. Schultz[1,2,3], **Gretchen M. Williams**[1,2,3], **Junne Kamihara**[4], **Douglas R. Stewart**[5], **Anne K. Harris**[1,2,3], **Andrew J. Bauer**[6], **Joyce Turner**[7], **Rachana Shah**[8], **Katherine Schneider**[9], **Kami Wolfe Schneider**[10], **Ann Garrity Carr**[11], **Laura A. Harney**[11], **Shari Baldinger**[12], **A. Lindsay Frazier**[4], **Daniel Orbach**[13], **Dominik T. Schneider**[14], **David Malkin**[15], **Louis P. Dehner**[16], **Yoav H. Messinger**[1,2,3], and **D. Ashley Hill**[17]

[1]International Pleuropulmonary Blastoma Registry, Children's Minnesota, Minneapolis, MN, USA

40

Family History



41

Follow-up RNA Genetic Test Results

RESULTS

DICER1 **Variant, Likely Pathogenic: c.1753-9A>G**

SUMMARY

POSITIVE: Likely Pathogenic Variant Detected (See RNA Impact below)

INTERPRETATION

- This individual is heterozygous for the **c.1753-9A>G** likely pathogenic variant in the *DICER1* gene.
- This result is consistent with a diagnosis of *DICER1* syndrome.
- **Risk estimate**: increased lifetime risk of pleuropulmonary blastoma, ovarian sex cord stromal tumors, cystic nephroma, thyroid cancer, and other rare tumors.
- RNA Impact:
  - RNA data contributed to a clinically significant variant classification for this individual.

Confirms Hereditary DICER1-Associated Condition
Provides guidance for family surveillance

42

DICER1 Screening

- **Initial chest CT between 3 and 6 months of age**
- If the initial chest CT is normal, a **second chest CT is recommended between 2.5 and 3 years** of age.
- **CXR and Renal Ultrasound (Wilms, cystic nephroma) every-6-month until 8 years of age**
- CXR and Renal Ultrasound annually from age 8 to 12 years.
- **Pelvic US every 6-12 months "throughout early and late childhood and adulthood"**
  - Sertoli Leydig Cell Tumors, gynandroblastoma, embryonal rhabdomyosarcoma
- **Thyroid ultrasound starting at age 8 years, then q 3 years**
  - If normal, repeating every 3 years is justified by the risk for thyroid cancer, which is generally indolent but is curative with surgery alone when found in its earliest form.
  - If nodules are seen, routine follow-up per standard pediatric endocrinology guidelines is recommended

43

Case 4

12 mo M with polydactyly and concern for naso-lacrimal duct obstruction. Mom noticed something “fleshy” blocking a nostril and breathing changes

Head imaging showed a nasal mass

Family History:

Paternal uncle: heart myxoma, pituitary gland tumor, acromegaly, skin lesions (lipomas, moles)

Father: skin lipomas, groin mass removed 10 years prior (“medically interesting”)

Paternal grandfather: “big fingers”

Mother: polydatyly

Twin sister: polydactyly

44

Case 4

Nasal mass removed surgically

"distinctive admixture f bone, vaguely chondroid appearing matrix and myeloid areas containg a cord and chain-like proliferation of bland stromal cells. Loss of PRKAR1A expression."
"Consistent with osteochondromyxoma, a rare bone tumor seen in patients with Carney Complex."

PRKAR1A Gene Sequencing and Del/Dep: positive pathologic heterozygous variant – c.266del, p. (P89Qfs*40), autosomal dominant.

45

Carney Complex

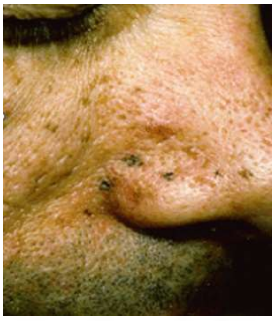
46

PRKAR1A Gene and Carney Complex

NAME syndrome (Nevi, Atrial myxoma, Myxoid neurofibromata, Ephelides)
LAMB syndrome (Lentigenes, Atrial Myxomas, Blue nevi)

Spotty skin pigmentation (lips,eye, vaginal, penile)
Myxoma (cutaneous and mucosal)
Cardiac myxoma 70%
Breast myxomatosis
PPNAD (primary pigmented nodular adrenocortical disease)
Acromegaly (GH-producing adenoma)

Large-cell calcifying Sertoli cell tumor (LCCSCT) 30-75% of males
Thyroid carcinoma or multiple nodules in childhood (nodules in 75%)
Psammomatous melanotic schwannomas (PMS)
Blue nevi, epithelioid blue nevus
Breast ductal adenoma
Osteochondromyxoma (<1%)



47

Carney Complex Screening

- Annual echocardiogram (cardiac myxomas)
- Annual scrotal US for males (large cell calcifying Sertoli tumor)
- Annual thyroid ultrasound after puberty
- Ovarian ultrasound for females, once after puberty
  - Progression of ovarian cysts to carcinoma possible, risk begins at age 40 years.
- Close Endocrinology monitoring of growth and development
- Pituitary and/or adrenal imaging if concerning symptoms (acromegaly, Cushing syndrome, puberty abnormalities)

48

Case 5

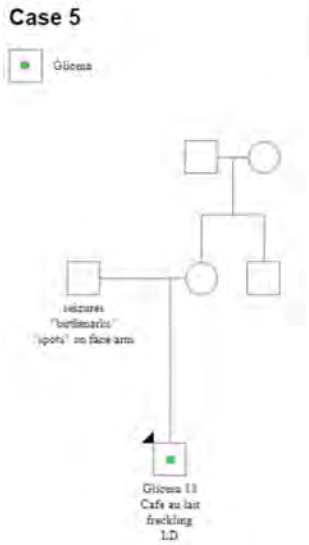
10 yo male with brain stem glioma

Macrocephaly

Learning difficulties

Café-au-lait spots

Axillary freckles



49

Neurofibromatosis Type 1 (NF1)

50

Neurofibromatosis Type 1 (NF1)

NF1, an inhibitor of RAS oncogene
Autosomal Dominant Inheritance
Incidence 1/2500
Multiple Benign Tumors

- Neurofibroma
- Optic glioma
- Glioma
- Pheochromocytoma

Increased risk of leukemia

- JMML
- AML

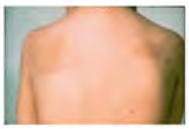


Fig 1. Café au lait spots

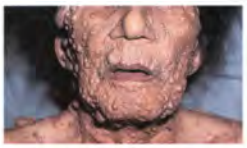


Fig 2. Neurofibromas

Fig 3. Lisch nodules

Fig 1: Courtesy of Dilys Parry, PhD.
Fig 2: Callen JP et al, eds. *Color Atlas of Dermatology*. 2nd ed. New York: WB Saunders; 2000. Reprinted with permission.
Fig 3: White G, Cox N, eds. *Diseases of the Skin: A Color Atlas & Text*. New York: Mosby; 2000. Reprinted with permission.

51

Neurofibromatosis 1 (NF1)

NF1 gene mutation on **Chromosome 17q**

Diagnostic Criteria – must have 2 or more

1. Six or more Café-au-lait macules, the greatest diameter of which is more than 5 mm in prepubertal patients and more than 15 mm in postpubertal patients
2. Two or more neurofibromas of any type, or one plexiform neurofibroma
3. Axillary or inguinal freckling
4. Optic glioma
5. Two or more Lisch nodules
6. A distinctive osseous lesion such as sphenoid dysplasia or pseudarthrosis
7. A first-degree relative with NF1 according to the preceding criteria

52

NF1 Tumors – Summary

Peripheral neurofibromas
Plexiform neurofibromas
Spinal neurofibromas
Optic pathway gliomas (OPG)
Other CNS tumors (including High Grade Gliomas)
Malignant Peripheral Nerve Sheath Tumor (MPNST)
Embryonal Rhabdomyosarcoma
Hamartomas of the iris (Lisch nodules)
Gastrointestinal Stromal Tumors (GIST)
Pheochromocytoma
Duodenal Carcinoid Tumor

53

NF1 Recommendations

	Tumor surveillance
Optic Pathway Glioma	Children with NF1 should have **q6–12 monthly ophthalmic assessments from birth to 8 years.** One baseline assessment of color vision and visual fields should be undertaken when the child is developmentally able.
MPNST	Assess with history and clinical examination annually for typical signs of MPNST: any nondermal neurofibroma with rapid growth, loss of neurologic function, or increasing pain or change in consistency
JMML	Assess for risk of JMML in NF1 in children with juvenile xanthogranulomas
Internal burden	**A baseline whole-body MRI should be considered between ages 16 and 20 years to assess internal tumor burden to determine adult follow-up regimen**
Routine MRI	**MRI surveillance is not currently recommended unless symptomatic or with an already diagnosed tumor**. Specific biochemical or imaging surveillance for tumors with absolute risks in childhood below 1% is not recommended such as for pheochromocytoma, neuroendocrine tumors, MPNST, or non-optic glioma.

54

Children's Nebraska NF1 Clinic

- Multi-disciplinary clinic with Pediatric Hematology/Oncology (Dr. Abromowitch, Dr. Bies), Pediatric Neurology (Dr. Rickard), Behavioral Health, Social Work, Case Management
- 4th Friday of every month

55

Questions?

Thank you!

Thanks!

56

57

References

- Chompret A, *et al.* Sensitivity and predictive value of criteria for p53 germline mutation screening. *J Med Genet* 2001; 38:43–7
- Bougeard G, et al Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers. *J Clin Oncol* 2015;33:2345–52

- Villani A et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study. *Lancet Oncol.* 2011;12:559–67
- Villani A 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

58