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RASTREIO DE CANCRO EM CRIANÇAS COM SÍNDROMES PREDISPONENTES

19º CONGRESSO NACIONAL DE PEDIATRIA
SOCIEDADE PORTUGUESA DE PEDIATRIA
SESSÃO MR11: HEMATO-ONCOLOGIA PEDIÁTRICA

Overview



Introduction

Classification of pediatric cancer predisposing syndromes

Cancer surveillance in children with predisposing syndromes

- MEN1 and MEN2
- Li-Fraumeni syndrome
- *DICER1* syndrome
- Constitutional mismatch repair-deficiency syndrome (CMMRD)

Hereditary tumors in children

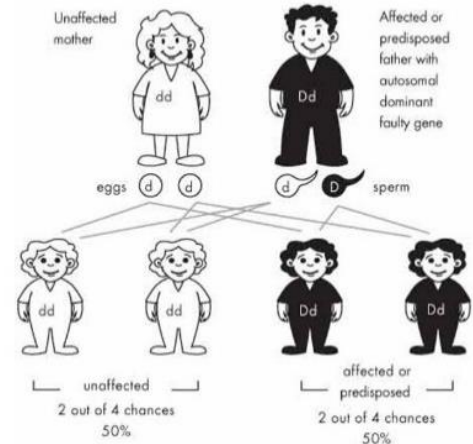
- “A saúde dos Portugueses. Perspectiva 2015” DGS (data 2009-2013)
 - ▣ Leading cause of death in children aged 5 to 14 years
 - ▣ Second leading cause of death after accidents between 1-4 years
- >25% of patients may have criteria for referral to a cancer genetics clinic, based on family history, tumor type or physical findings (Knapke 2012)
- at least 10% of pediatric cancer patients harbor a pathogenic germline mutation in a known cancer predisposition gene (Zhang 2015; Mody 2015; Parsons 2016)
 - ▣ Some have +FH suggestive of a cancer predisposing syndrome
 - ▣ Many others (up to 60%) do not have FH (Zhang 2015)
- > 100 CPSs were discovered during the past decades
- Next generation sequencing (NGS) techniques
 - ▣ unravelling the somatic tumor mutations
 - ▣ disclose underlying cancer predisposition syndrome

Type of tumor	Fraction of hereditary tumors	Genes
Retinoblastoma	40-50%	<i>RB1</i>
Adrenocortical carcinoma	40-60%	<i>TP53</i>
Rhabdomyosarcoma of embryonal anaplastic subtype	73%	<i>TP53</i>
Choroid plexos tumor	42-100%	<i>TP53</i>

Hereditary tumors in children

- Majority Autosomal dominant
- Many do not follow Mendelian genetics:
 - ▣ incomplete or reduced penetrance; age-dependent
 - ▣ penetrance may vary according to the mutation
 - ▣ inter and intrafamilial variable expressivity
- ▣ *de novo* mutations (20-25% in FAP; 14% in Li-Fraumeni)
 - post-zygotic (mosaics) *de novo* mutations (20% of the total of *de novo* mutations in Li-Fraumeni syndrome)
- ▣ parental gonadal mosaicism (e.g. *SMARCB1*, *APC*, *DICER1* etc.)
- Autosomal recessive
 - ▣ most types of Fanconi anemia, many immunodeficiency syndromes
- X-linked
 - ▣ Dyskeratosis congenital caused by mutation of *DKC1*

Autosomal Dominance Inheritance



When to suspect of a hereditary tumor?

- **Family history of the same cancer or of related cancers**
 - same tumors or known tumor combinations (e.g. adrenocortical carcinoma and breast cancer)
- **Earlier age of onset**
 - compared to sporadic tumors of the same type
- **Bilateral, multifocal, or multiple tumors**
- **Specific tumor types that frequently occur in the context of genetic predisposition**
 - e.g. choroid plexus tumor; adrenocortical carcinoma; pleuropulmonary blastoma
- **Suggestive physical findings/non malignant manifestations**
 - e.g. congenital hypertrophy of the retina; specific skin lesions; macroglossia; macrocephaly; developmental delay or congenital defects

When should genetic testing be considered?

- **Personal and/or family history (including ethnicity) is suspicious for genetic predisposition cancer**
- **Genetic test available and sufficient sensitivity and specificity to be interpreted**
- **The test result will impact:**
 - Individual's diagnosis
 - Cancer treatment
 - Cancer surveillance
 - Cancer risk clarification in family members

Childhood cancer predisposition syndromes—A concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology

If at least one criterion is fulfilled, the patient may benefit from pediatric cancer referral/genetic counseling

Adapted from Ripperger, Am J Med Genet A. 2017 Apr;173(4):1017-1037

2. One of the following Neoplasms was diagnosed:

- ☐ Adrenocortical carcinoma / adenoma
- ☐ ALL (low hypodiploid)
- ☐ ALL (ring chromosome 21)
- ☐ ALL (Robertsonian translocation 15;21)
- ☐ ALL relapse (*TP53* mutated)
- ☐ AML (Monosomy 7)
- ☐ Basal cell carcinoma
- ☐ Botryoid rhabdomyosarcoma of the urogenital tract (fusion-negative)
- ☐ Chondromesenchymal hamartoma
- ☐ Choroid plexus carcinoma / tumor
- ☐ Colorectal carcinoma
- ☐ Cystic nephroma
- ☐ Endolymphatic sack tumor
- ☐ Fetal rhabdomyoma
- ☐ Gastrointestinal stromal tumor
- ☐ Glioma of the optic pathway (with signs of NF1)
- ☐ Gonadoblastoma
- ☐ Hemangioblastoma
- ☐ Hepatoblastoma (*CTNNB1* wildtype)
- ☐ Hepatocellular carcinoma
- ☐ Infantile myofibromatosis
- ☐ Juvenile myelomonocytic leukemia
- ☐ Keratocystic odontogenic tumor
- ☐ Large cell calcifying Sertoli-cell-tumor
- ☐ Malignant peripheral nerve sheath tumor
- ☐ Medullary thyroid carcinoma
- ☐ Medulloblastoma (SHH activated)
- ☐ Medulloblastoma (WNT activated, *CTNNB1* wildtype)
- ☐ Medullary renal cell carcinoma
- ☐ Medulloepithelioma
- ☐ Melanoma
- ☐ Meningioma
- ☐ Myelodysplastic syndrome
- ☐ Myeloproliferative neoplasms (except CML)
- ☐ Myxoma
- ☐ Neuroendocrine tumor
- ☐ Paraganglioma / pheochromocytoma
- ☐ Parathyroid carcinoma / adenoma
- ☐ Pineoblastoma
- ☐ Pituitary adenoma / tumor
- ☐ Pituitary blastoma
- ☐ Pleuropulmonary blastoma
- ☐ Renal cell carcinoma
- ☐ Retinoblastoma
- ☐ Rhabdoid tumor
- ☐ Rhabdomyosarcoma with diffuse anaplasia
- ☐ Schwannoma
- ☐ Schwannomatosis
- ☐ Sertoli-Leydig cell tumor
- ☐ Sex cord stromal tumor with annular tubules
- ☐ Small cell carcin. of the ovary hypercalcemic type
- ☐ Squamous cell carcinoma
- ☐ Subependymal giant cell astrocytoma
- ☐ Thyroid carcinoma (non-medullary)
- ☐ Transient myeloproliferative disease
- ☐ Other rare cancers or cancers that typically occur in adults, unusually early manifestation age

If at least one criterion is fulfilled, the patient may benefit from pediatric cancer referral/genetic counseling

Childhood cancer predisposition syndromes—A concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology

1. Family history (3 generation pedigree)

- ≥2 malignancies occurred in family members before age 18 years, including index patient
- Parent or sibling with current or history of cancer before age 45 years
- ≥2 first or second degree relatives in the same parental lineage with cancer before age 45 years
- The parents of the child with cancer are consanguineous

3. Genetic tumor analysis reveals defect suggesting a germline predisposition

4. A patient with ≥2 malignancies (e.g. secondary, bilateral, multifocal, metachronous)

5. A child with cancer and congenital or other anomalies

<i>Sign</i>	<i>Think of</i>
☐ Congenital anomalies	Abnormal organs, skeletal anomalies, oral clefting, abnormal teeth, urogenital anomalies, abnormal hearing or vision, etc.
☐ Facial dysmorphism	
☐ Mental impairment, developmental delay	Abnormal behavior, learning difficulties
☐ Abnormal growth	Height, head circumference, birth weight, hemihyperplasia, growth chart
☐ Skin anomalies	Abnormal pigmentation such as ≥2 café-au-lait spots, vascular lesions, hypersensitivity to sun, benign tumors, etc.
☐ Hematological abnormalities (not explained by current cancer)	Pancytopenia, anemia, thrombocytopenia, neutropenia, leukopenia, macrocytic erythrocytes
☐ Immune deficiency	Frequency of infections, lymphopenia
☐ Endocrine anomalies	Primary hyperparathyroidism, precocious puberty, gigantism/acromegaly, Cushing syndrome

6. The patient suffers from excessive toxicity of cancer therapy

Genetic diagnostic testing

- **Timing of the genetic testing**
 - Should be made at the time of diagnosis
 - Lowered lymphocyte counts following chemotherapy
 - Difficult of obtaining a germline sample after donor bone marrow transplant
 - If the child has a poor prognosis, DNA banking should be considered
- **Pretest genetic counseling and informed consent**
 - Children and parents should meet genetic counselor or other qualified professional prior to undergoing germline cancer genetic testing
 - Appropriate language for age and understanding
 - Incidental findings

Genetic diagnostic testing

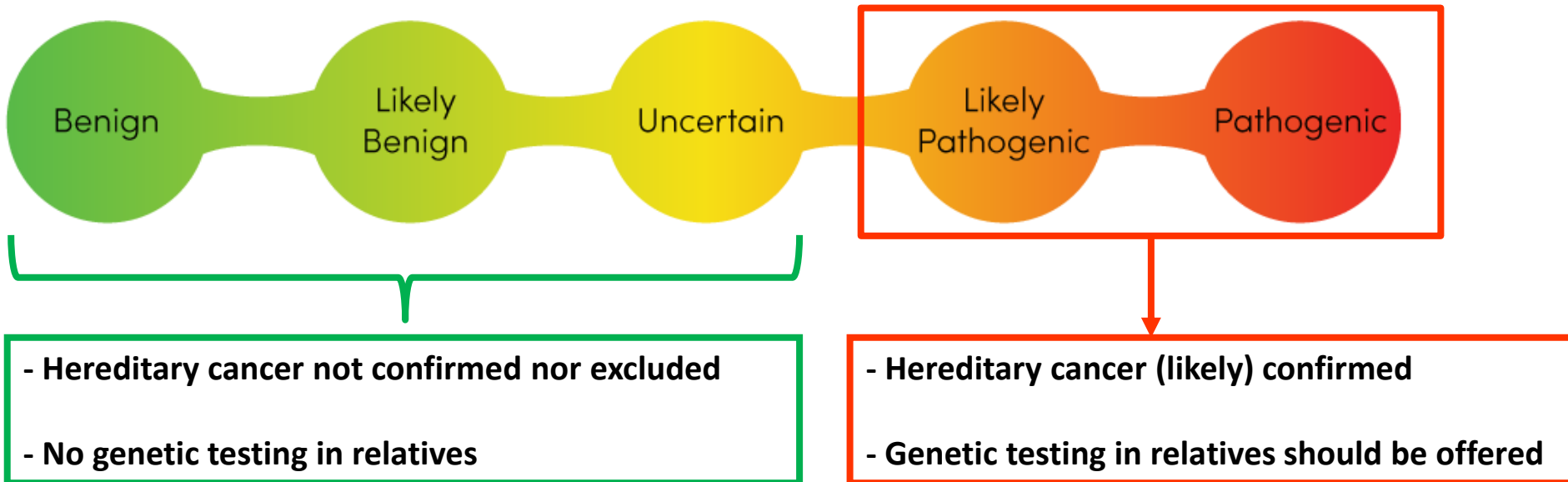
- **Posttest genetic counseling**
 - ▣ Reinforce information
 - ▣ Address age-specific risks and management
 - ▣ Evaluate needs for additional psychologic support
 - ▣ Revisit genetic counseling in the mid- to late teenage years and again at times of family planning

- **Psychosocial issues related to surveillance**
 - ▣ “Scanxiety” – anticipation of the surveillance test and wait to receive results
 - Reporting as quickly as possible is strongly recommended

Classification of genetic variants

Richards, S. *et al.* "Standards and Guidelines for Interpretation of Sequence Variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and Association for Molecular Pathology." *Genetics in Medicine*. 2015 17: 405-423.

<https://www.ashg.org/education/csertoolkit/intro.html>



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Classification of pediatric cancer predisposing syndromes

Cancer surveillance in children with predisposing syndromes

- MEN1 and MEN2
- Li-Fraumeni syndrome
- *DICER1* syndrome
- Constitutional mismatch repair-deficiency syndrome (CMMRD)

Classification of pediatric cancer predisposing syndromes

Table 1. Major subgroups of pediatric cancer susceptibility disorders reviewed

Predisposition group	Specific disorders reviewed
LFS	LFS (<i>TP53</i>)
Neurofibromatoses	Neurofibromatosis type I (<i>NF1</i>), neurofibromatosis type II (<i>NF2</i>), Schwannomatosis (<i>SMARCB1</i> , <i>LZTR1</i>), meningioma predisposition (<i>SMARCE1</i>)
Overgrowth syndromes, Wilms tumor	BWS/hemihypertrophy (11p15.5), Wilms tumor-aniridia-GU anomaly-retardation (WAGR) syndrome, Denys-Drash and Frasier syndromes (<i>WT1</i>), Perlman syndrome (<i>DIS3L2</i>), Bohring-Opiz syndrome (<i>ASXL1</i>), Mulibrey Nanism (<i>TRIM37</i>), Simpson-Golabi-Behmel syndrome (<i>GPC3</i> , <i>GPC4</i>), non-syndromic hereditary Wilms tumor
Neural tumor syndromes	Hereditary retinoblastoma (<i>RBI</i>), hereditary neuroblastoma (<i>ALK</i> , <i>PHOX2B</i>), Gorlin syndrome (<i>PTCH1</i> , <i>SUFU</i>), malignant rhabdoid tumor syndrome (<i>SMARCB1</i> , <i>SMARCA4</i>)
GI cancer syndromes	Familial adenomatous polyposis (<i>APC</i> , <i>MUTYH</i>), juvenile polyposis syndrome (<i>SMAD4</i> , <i>BMPRI1A</i>), Peutz-Jeghers syndrome (<i>STK11</i>), Lynch syndrome (<i>MSH2</i> , <i>MSH6</i> , <i>MLH1</i> , <i>PMS2</i> , <i>EPCAM</i>), CMMRD (see Lynch syndrome genes)
Neuroendocrine syndromes	Multiple endocrine neoplasia (MEN)-1 (<i>MEN1</i>), MEN2A (<i>RET</i>), MEN2B (<i>RET</i>), MEN4 (<i>CDKN1B</i>), von Hippel-Lindau (<i>VHL</i>), hereditary paraganglioma/pheochromocytoma syndrome (<i>SDHA</i> , <i>SDHB</i> , <i>SDHC</i> , <i>SDHD</i> , <i>SDHAF2</i> , <i>TMEM127</i> , <i>MAX</i>), familial thyroid cancer (<i>RET</i> , <i>NTRK1</i>), hyperparathyroidism-jaw tumor syndrome (<i>CDC73</i>)
Leukemia predisposition syndromes	LFS, CMMRD, susceptibility to ALL 3 (<i>PAX5</i>), <i>GATA2</i> -associated predisposition to myelodysplasia/AML, <i>CEBPA</i> -associated predisposition to AML, thrombocytopenia, type 5 (<i>ETV6</i>), familial platelet disorder with associated myeloid malignancy (<i>RUNX1</i>), ataxia-pancytopenia syndrome (<i>SAMD9L</i>), myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy (<i>SAMD9</i>)
DNA instability syndromes	Ataxia telangiectasia (<i>ATM</i>), Bloom syndrome (<i>BLM</i>), Fanconi anemia (<i>FANCA-V</i> , <i>RAD51C</i>), xeroderma pigmentosum (<i>XPA</i> , <i>XPC</i> , <i>ERCC2</i> , <i>POLH</i> , <i>DDDB2</i>), Nijmegen breakage syndrome (<i>NBN</i>), Diamond-Blackfan syndrome (<i>RPS7</i> , <i>-10</i> , <i>-17</i> , <i>-19</i> , <i>-24</i> , <i>-26</i> ; <i>RPL5</i> , <i>-11</i> , <i>-19</i> , <i>-35A</i>), dyskeratosis congenita (<i>DKC1</i> , <i>TINF2</i> , <i>TERC</i> , <i>TERT</i> , <i>NHP2</i> , <i>NOP10</i> , <i>WRAP53</i>), Rothmund-Thompson syndrome (<i>RECQL4</i>)
Miscellaneous syndromes	PTEN hamartoma tumor syndrome (<i>PTEN</i>), pleuropulmonary blastoma syndrome (<i>DICER1</i>), Noonan syndrome (<i>PTPN11</i> , <i>SOS1</i> , <i>RAF1</i> , <i>RIT1</i> , <i>KRAS</i> , others), Costello syndrome (<i>HRAS</i>), Sotos syndrome (<i>NSD1</i>), Weaver syndrome (<i>EZH2</i>), Rubenstein-Taybi syndrome (<i>CREBBP</i> , <i>EP300</i>), Schinzel-Giedion syndrome (<i>SETBP1</i>), NKX2-1 syndrome (<i>NKX2-1</i>), hereditary leiomyomatosis and renal cancer syndrome (<i>FH</i>), metabolic disorders (<i>L2HGA</i> , <i>FAH</i>)

Abbreviations: AML, acute myeloid leukemia; GI, gastrointestinal; CMMRD, congenital mismatch repair syndrome.

Predisposing groups	CCR Ped Oncol series	Specific disorders	Gene
Li-Fraumeni syndrome	Li-Fraumeni syndrome	Li-Fraumeni syndrome	<i>TP53</i>
Neurofibromatoses	Neurofibromatosis 1	Neurofibromatosis type 1	<i>NF1</i>
	Neurofibromatosis 2 and related disorders	Neurofibromatosis type 2	<i>NF2</i>
		Schwannomatosis	<i>SMARCB1, LZTR1</i>
		Meningioma predisposition	<i>SMARCE1</i>
Overgrowth syndromes, Wilms tumors	Overgrowth syndromes and predisposition to Wilms tumors and hepatoblastoma	BWS/hemihypertrophy	1p15.5 locus
		WAGR syndrome	
		Denys–Drash and Frasier syndromes	<i>WT1</i>
		Perlman syndrome	<i>DIS3L2</i>
		Bohring–Opiz syndrome	<i>ASXL1</i>
		Mulibrey Nanism	<i>TRIM37</i>
		Simpson–Golabi–Behmel syndrome	<i>GPC3, GPC4</i>
		Non-syndromic hereditary Wilms tumor	
Neural tumor syndromes	Retinoblastoma and neuroblastoma	Hereditary retinoblastoma	<i>RB1</i>
		Hereditary neuroblastoma	<i>ALK, PHOX2B</i>
	Gorlin syndrome and rhabdoid tumor predisposition syndrome	Gorlin syndrome	<i>PTCH1, SUFU</i>
		Malignant rhabdoid tumor syndrome	<i>SMARCB1, SMARCA4</i>

Table: Major groups of pediatric cancer predisposition disorders.

[adapted from Brodeur *et al*, Clin Cancer Res. 2017 Jun 1;23(11):e1-e5.]

Predisposing groups	CCR Ped Oncol series	Specific disorders	Gene
GI cancer syndromes	Inherited GI cancer syndromes in childhood	Familial adenomatous polyposis	<i>APC</i>
		<i>MUTYH</i> -associated polyposis	<i>MUTYH</i>
		Juvenile polyposis syndrome	<i>SMAD4, BMPR1A</i>
		Peutz–Jeghers syndrome	<i>STK11</i>
		Lynch syndrome	<i>MSH2, MSH6, MLH1, PMS2, EPCAM</i>
	CMMRD	Constitutional mismatch repair-deficiency syndrome (CMMRD)	<i>MSH2, MSH6, MLH1, PMS2</i>
Neuroendocrine syndromes	MEN and Hyperparathyroid-Jaw Tumor Syndromes	Multiple endocrine neoplasia type 1	<i>MEN</i>
		Multiple endocrine neoplasia type 2	<i>RET</i>
		Hyperparathyroid-jaw tumor syndrome	<i>CDC73</i>
	von Hippel–Lindau and hereditary pheochromocytoma-paranglioma syndromes	von Hippel–Lindau syndrome	<i>VHL</i>
		Hereditary paraganglioma/pheochromocytoma syndrome	<i>SDHA, SDHB, SDHC, SDHD, SDHAF2</i>

Table: Major groups of pediatric cancer predisposition disorders (cont.)

[adapted from Brodeur *et al*, Clin Cancer Res. 2017 Jun 1;23(11):e1-e5.]

Predisposing groups	CCR Ped Oncol series	Specific disorders	Gene
Leukemia-predisposing syndromes	Leukemia-predisposing conditions	LFS	<i>TP53</i>
		CMMRD	
		Susceptibility to ALL3	<i>PAX5</i>
		<i>GATA2</i> -associated predisposition to myelodysplasia/AML	<i>GATA</i>
		<i>CEBPA</i> -associated predisposition to AML	<i>CEBPA</i>
		Thrombocytopenia, type 5	<i>ETV6</i>
		Familial platelet disorder with associated myeloid malignancy	<i>RUNX1</i>
		Ataxia-pancytopenia syndrome	<i>SAMD9L</i>
		Myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy	<i>SAMD9</i>
DNA instability syndromes	DNA repair disorders	Ataxia telangiectasia	<i>ATM</i>
		Bloom syndrome	<i>BLM</i>
		Fanconi anemia	<i>FANCA-V, RAD51C</i>
		Xeroderma pigmentosum	<i>XPA, XPC, ERCC2, POLH, DDB2</i>
		Nijmegen breakage syndrome	<i>NBN</i>
		Diamond–Blackfan syndrome	<i>RPS7, RPS10, -RPS17, RPS19, RPS24, RPS26, RPL5, RPL11, RPL19, RPL35A</i>
		Dyskeratosis congenita	<i>DKC1, TINF2, TERC, TERT, NHP2</i> , others
		Rothmund–Thompson syndrome	<i>RECQL4</i>

Table: Major groups of pediatric cancer predisposition disorders (cont.)

[adapted from Brodeur *et al*, Clin Cancer Res. 2017 Jun 1;23(11):e1-e5.]

Predisposing groups	CCR Ped Oncol series	Specific disorders	Gene
Miscellaneous syndromes	<i>PTEN</i>-, <i>DICER1</i>-, <i>FH</i>-associated tumor susceptibility syndromes	<i>PTEN</i> hamartoma tumor syndrome	<i>PTEN</i>
		<i>DICER1</i> syndrome	<i>DICER1</i>
		Hereditary leiomyomatosis and renal cancer syndrome	<i>FH</i>
	RASopaties and other rare genetic conditions with increased cancer risk	Noonan syndrome	<i>PTPN11, SOS1, RAF1, RIT1, KRAS, others</i>
		Costello syndrome	<i>HRAS</i>
		Sotos syndrome	<i>NSD1</i>
		Weaver syndrome	<i>EZH2</i>
		Rubenstein–Taybi syndrome	<i>CREBBP, EP300</i>
		Schinzel–Giedion syndrome	<i>SETBP1</i>
		NKX2-1 syndrome	<i>NKX2-1</i>
		metabolic disorders	<i>L2HGA, FAH, others</i>

Table: Major groups of pediatric cancer predisposition disorders (cont.)

[adapted from Brodeur *et al*, Clin Cancer Res. 2017 Jun 1;23(11):e1-e5.]

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

- An AACR-sponsored workshop was held in October 2016 in Boston, Massachusetts, USA
 - 11 countries
 - 65 professionals including 51 physician directors or codirectors of cancer predisposition programs (pediatric oncologists or medical geneticists), 7 genetic counselors, 3 radiologists, 3 directors of adult cancer predisposition programs, and 1 pediatric endocrinologist
- Review of existing guidelines from professional organizations, prior publications, cancer risk estimates, and assessment of the potential side effects associated with screening, balanced against the potential morbidity and mortality of clinically detected tumors of more advanced stage
- The main goal:
 - to establish international consensus recommendations for cancer surveillance of children and adolescents for the most common cancer predisposition syndromes
- These syndromes were organized into 9 groups based on specific themes
 - Attendees were organized into these groups based on prior experience and expertise

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

- A $\geq 5\%$ chance of developing a childhood cancer was considered to be a reasonable threshold to recommend screening
- Conditions for which the cancer risk was between 1% to 5% were addressed individually
- For some newly described or rare disorders, no prior guidelines existed, so the committees endeavored to develop consensus recommendations as to whether surveillance was indicated, and what tests and schedule would be a good starting point for surveillance recommendations
 - Unanimous agreement that providing surveillance recommendations where none existed would provide a foundation on which to make rational decisions for the management of children with cancer predisposition going forward.
- Consistent approaches worldwide will facilitate future revisions of the proposed recommendations and evolution of surveillance protocols.
- These recommendations are likely to change over time, as more experience and information become available.
- New syndromes, as well as more specific information about genotype-phenotype associations and gene-gene or gene-environment interactions, will allow screening recommendations to be further customized.

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Multiple endocrine neoplasia type 1

Wasserman et al. Clin Cancer Res. 2017 Jul 1;23(13):e123-e132

Table 1. Surveillance for *MEN1* mutation carriers

MEN1 manifestation	Screen starting at age	Clinical screening	Annual biochemical tests	Imaging
Insulinoma	5 yrs	Syncope, light-headedness, documented hypoglycemia	Fasting glucose and insulin	None
PitNET	5 yrs ^a	Headaches, visual changes, galactorrhea, ↑growth	Prolactin, IGF-1	Brain MRI (q 3 yrs)
Parathyroid adenoma/ 1° HyperPTH	8 yrs	Back pain, bone pain, weakness, fatigue, psychiatric changes, kidney stones, nausea, vomiting, constipation. Multiple or pathologic fractures.	Calcium ^b	None
Pancreatic NET	10 yrs	Generally not identified symptomatically. VIPoma can cause profuse diarrhea. Glucagonoma associated with hyperglycemia, nausea, polyuria, thirst.	(Chromogranin A, glucagon, proinsulin, pancreatic polypeptide, VIP) ^c	Abdominal MRI (annually)
Adrenal adenoma	10 yrs	None	None	MRI (contemporaneous with pancreatic imaging)
Gastrointestinal, bronchial, and thymic NETs	20 yrs	Frequently asymptomatic, but h/o flushing, diarrhea, wheezing, edema or abdominal pain should arouse suspicion		CT/MRI chest and abdomen (q 1-2 yrs)
Gastrinoma (duodenal and pancreatic)	20 yrs	Abdominal pain, gastric ulcers. Proton-pump inhibitor usage.	Fasting gastrin	None

NOTE: Data from Thakker et al.; ref. 5).

Abbreviations: h/o, history of; HyperPTH, hyperparathyroidism; NET, neuroendocrine tumor; q, every; VIP, vasoactive intestinal polypeptide; yrs, years.

^aMRI surveillance is to begin once patient is able to tolerate a nonsedated MRI. In the authors' experience, this is generally at about the age of 5 years but may be deferred on an individualized basis.

^bHypercalcemia on screening should prompt assessment with contemporaneous serum calcium and intact parathyroid hormone (iPTH) to establish a diagnosis of PHPT.

^cPancreatic tumors may be nonsecretory, therefore, the added sensitivity contributed by biochemical screening has not been demonstrated.

Multiple endocrine neoplasia type 2

Wasserman et al. Clin Cancer Res. 2017 Jul 1;23(13):e123-e132

Familial medullary thyroid carcinoma is now widely considered to be a variant of MEN2A with decreased penetrance of pheochromocytoma and primary hyperparathyroidism

American Thyroid Association risk categories for aggressive MTC:

- ATA-HST, highest risk
- ATA-H, high risk
- ATA-MOD, moderate risk.

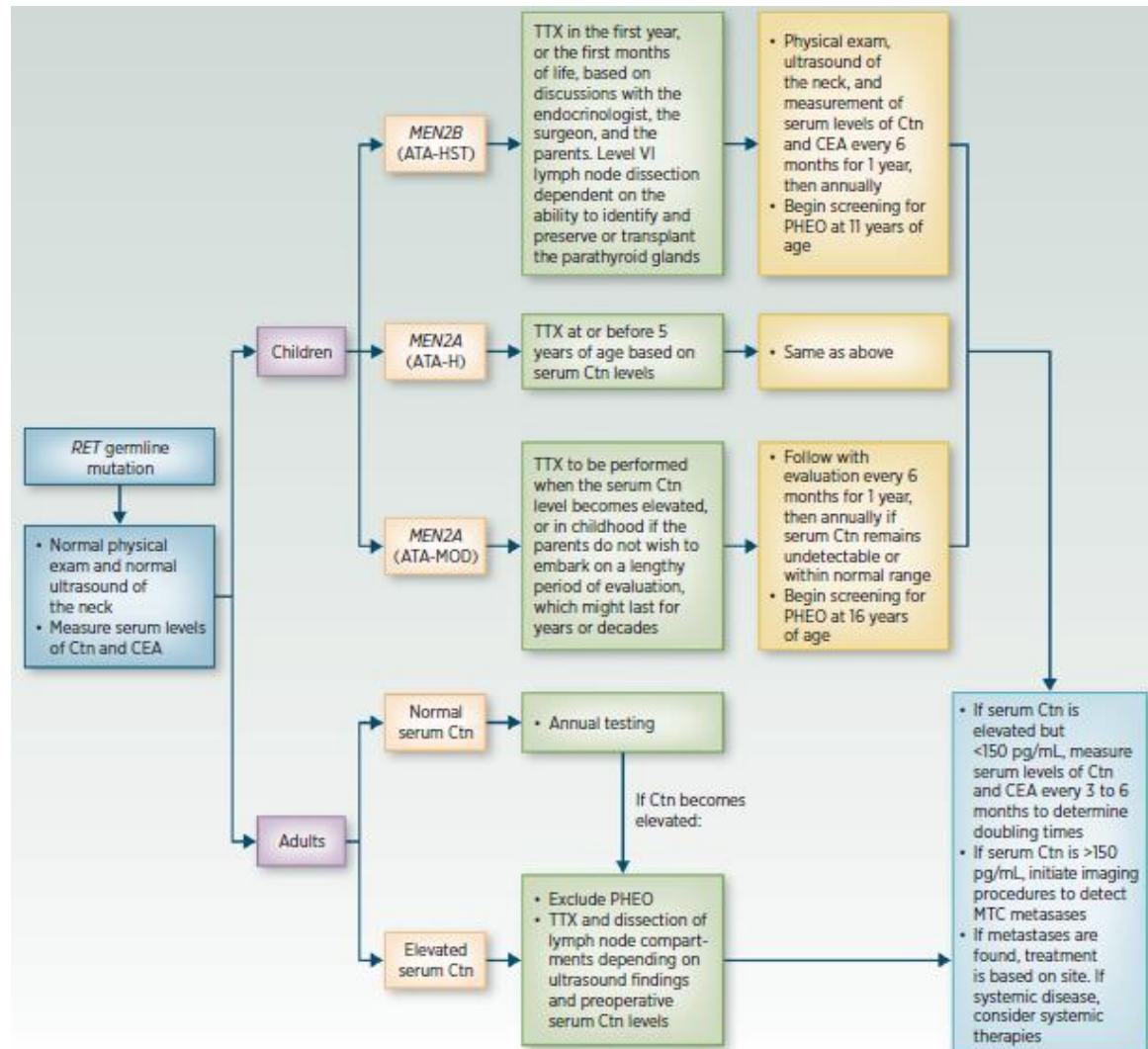
CEA - carcinoembryonic antigen;

Ctn - calcitonin;

HPTH - hyperparathyroidism;

RET - REarranged during Transfection;

TTX - total thyroidectomy.



Li-Fraumeni syndrome

Bougeard *et al.* J Clin Oncol. 2015 Jul 20;33(21):2345-52

Table 3. 2015 Version of Chompret Criteria

Familial presentation	Proband with tumor belonging to LFS tumor spectrum (eg, premenopausal breast cancer, soft tissue sarcoma, osteosarcoma, CNS tumor, adrenocortical carcinoma) before age 46 yr, AND at least one first- or second-degree relative with LFS tumor (except breast cancer if proband has breast cancer) before age 56 yr or with multiple tumors
Multiple primitive tumors	Proband with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum and first of which occurred before age 46 yr
Rare tumors	Patient with adrenocortical carcinoma, choroid plexus tumor, or rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of family history
Early-onset breast cancer	Breast cancer before age 31 yr

Table 1. Distribution of Tumors in Affected Germline *TP53* Mutation Carriers

	No. of			Mean/Median Age at Tumor
	In Children (n = 132; 70†, 62‡)			
Osteosarcoma	40 (20†; 20‡)	39 (19†; 20‡)	30	14/14 (8-18†; 5-18‡)
Adrenocortical carcinoma	37 (25†; 12‡)	36 (24†; 12‡)	27	2/1 (0.5-11†; 0.7-17‡)
CNS tumor	34 (19†; 15‡)	34 (19†; 15‡)	26	8/9 (0.3-18†; 1-18‡)
Soft tissue sarcoma	33 (13†; 21‡)	31 (12†; 19‡)	23	5/2 (0.5-17†; 0.5-16‡)
Leukemia	13 (7†; 6‡)	12 (6†; 6‡)	9	11/12 (6-17†; 2-16‡)
Lymphoma	4 (2†; 2‡)	4 (2†; 2‡)	3	9/10 (11-13†; 2-9‡)
Nephroblastoma	3 (0†; 3‡)	3 (0†; 3‡)	2	3/2 (1-6‡)
Testis choriocarcinoma	1 (1‡)	1 (1‡)	2‡	17/17 (17‡)
Neuroblastoma	1 (1†; 0‡)	1 (1†; 0‡)	0.8	0.5/0.5 (0.5†)
Lung cancer	1 (1†; 0‡)	1 (1†; 0‡)	0.8	14/14 (14†)
Stomach carcinoma	1 (0†; 1‡)	1 (0†; 1‡)	0.8	17/17 (17‡)

Li-Fraumeni syndrome

Bougeard *et al.* J Clin Oncol. 2015 Jul 20;33(21):2345-52

- 4% had developed a tumor during the first year of life
- 22% had developed a tumor by age 5
- 41% had developed a tumor by age 18

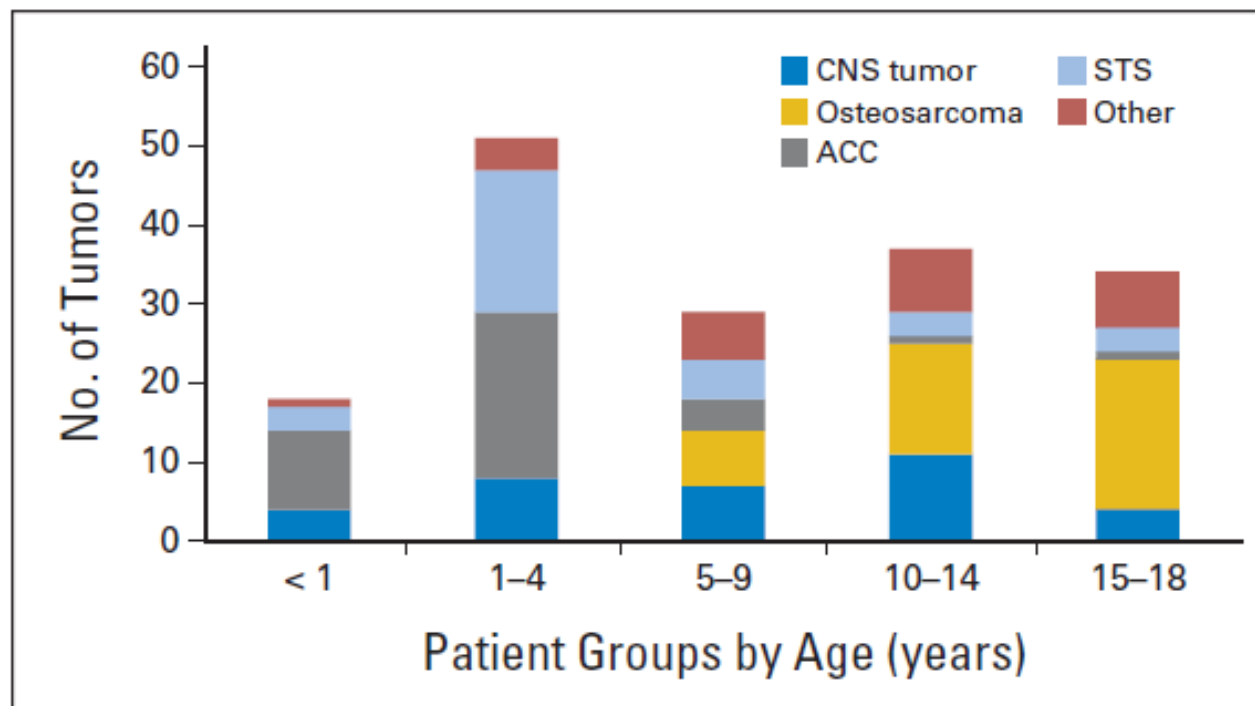


Fig A1. Distribution of the childhood tumors according to age group. ACC, adrenocortical carcinoma; STS, soft tissue sarcoma.

Biochemical and imaging surveillance in germline *TP53* mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study

Anita Villani, Ari Shore, Jonathan D Wasserman, Derek Stephens, Raymond H Kim, Harriet Druker, Bailey Gallinger, Anne Naumer, Wendy Kohlmann, Ana Novokmet, Uri Tabori, Marta Tijerin, Mary-Louise C Greer, Jonathan L Finlay, Joshua D Schiffman, David Malkin

89 carriers in 39 unrelated families

- 49 (55%) initially declined surveillance
 - 61 symptomatic tumors were diagnosed in 88% (43/49) patients
 - 21% (19) patients crossed over from the non-surveillance to the surveillance group
- 66% (59/89) individuals underwent surveillance for a median of 32 months (IQR 12–87)
 - 40 asymptomatic tumors detected in 32% (19/59) patients
 - 2 additional cancers were diagnosed between surveillance assessments (false negatives)
 - 2 biopsied lesions were non-neoplastic entities on pathological review (false positives)

49% (21/43)
of the individuals initially not on surveillance
who developed cancer were alive after a
median follow-up of 46 months (IQR 22–72)

84% (16/19) of the individuals
undergoing surveillance who developed
cancer ($p=0.012$) after a median follow-
up of 38 months (12–86)

5 year overall survival

- 88.8% (95% CI 78.7–100) in the surveillance group
- 59.6% (47.2–75.2) in the non-surveillance group ($p=0.0132$)
- long-term compliance with a comprehensive surveillance protocol is feasible
- early tumor detection through surveillance is associated with improved long-term survival

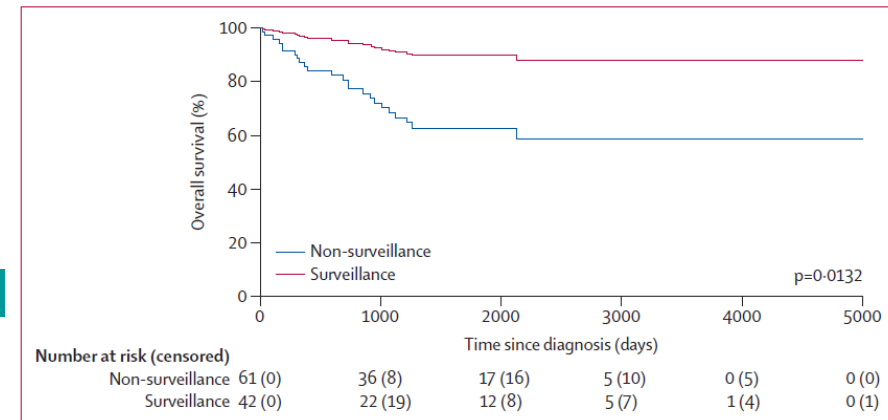


Figure 1: Overall survival in the surveillance and non-surveillance groups
Number at risk refers to the number of tumours, not individuals.

Li-Fraumeni syndrome

Kratz *et al.* Clin Cancer Res. 2017 Jun 1;23(11):e38-e45

Table 2. Recommended LFS screening protocol [based on the Toronto Protocol (55, 56)]

Children (birth to age 18 years)

General assessment

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

ACC

- **US of abdomen and pelvis every 3–4 months**
- In case of unsatisfactory US, blood tests^{a,b} may be performed every 3–4 months: total testosterone, dehydroepiandrosterone sulfate, and androstenedione

Brain tumor

- **Annual brain MRI** (first MRI with contrast; thereafter without contrast if previous MRI normal and no new abnormality)

Soft tissue and bone sarcoma

- **Annual WBMRI**

Family history of

- **Breast cancer at or around 20**

- awareness and screening can be considered to begin 5 to 10 years before the earliest age of onset.
- risk-reducing bilateral mastectomy should be considered and discussed with female patients;

- **Gastrointestinal cancer:**

- upper endoscopy and colonoscopies every 2 to 5 years starting at age 25 years or 5 years before the earliest age of onset in the family

Li-Fraumeni syndrome

Bougeard *et al.* J Clin Oncol. 2015 Jul 20;33(21):2345-52

Table A3. Distribution of the Germline Alterations in Patients With Childhood Tumors

Type of Mutation	ACC		RMS		Osteosarcomas		CNS	
	n	%	n	%	n	%	n	%
All types	34	100	22	100	20	100	29	100
Dominant-negative missense mutations	8	24	8	36	8	40	18	62
Non-dominant-negative missense mutations*	16	47	5	23	4	20	6	21
Splicing mutations	5	15	7	32	1	5	3	10
Frameshift deletions/insertions	2	6	2	9	2	10	1	3
Nonsense mutations	1	3	0	0	2	10	1	3
In frame deletions/insertions	0	0	0	0	2	10	0	0
Genomic rearrangements	2	6	0	0	1	5	0	0

NOTE. n indicates number of patients with this tumor as first malignancy. Bold font indicates, for each tumor type, the most frequent types of mutation. Abbreviations: ACC, adrenocortical carcinoma; RMS, rhabdomyosarcoma.

*Note that, among these mutations, some may correspond to bona fide dominant-negative mutations because not all mutations have been tested.

Table 2. Comparison of Age of Tumor Onset in LFS According to Type of Germline *TP53* Alteration (N = 322 affected mutation carriers)

Type of Alteration*	P, Mann-Whitney test
Missense mutations (n = 208): 23.8 ± 17.7 yr	
Other alterations (n = 114): 26.9 ± 17.8 yr	.1248
Loss of function mutations† (n = 72): 28.5 ± 16.4 yr	.0354
Genomic rearrangements (n = 19): 35.8 ± 18.3	.0042
Dominant-negative missense mutations (n = 120): 21.3 ± 14.8 yr	
Other alterations‡ (n = 202): 27.0 ± 19.1 yr	.0121
Loss of function mutations† (n = 72): 28.5 ± 16.4 yr	.0042
Genomic rearrangements (n = 19): 35.8 ± 18.3	.0008
Missense mutations within p53 DBD (n = 189): 23.0 ± 17.5 yr	
Missense mutations outside p53 DBD (n = 19): 31.3 ± 19.1 yr	.0561

NOTE. Boldface indicates $P < .05$.

Abbreviation: DBD, DNA binding domain; LFS, Li-Fraumeni syndrome; SD, standard deviation.

*For each type of alteration, the number of patients and mean age ± SD at tumor onset are indicated.

†Frameshift or in frame deletions/insertions, nonsense mutations, and genomic rearrangements.

‡Note that, among these mutations, some may correspond to bona fide dominant-negative mutations because not all mutations have been tested.

DICER1 syndrome

Schultz et al. Clin Cancer Res. 2018 May 15;24(10):2251-2261

Table 1. Indications for *DICER1* testing

Major:	Minor:
- Individuals with PPB (all types) (Pleuropulmonary blastoma) - Lung cyst(s) in childhood, especially if multi-septated, multiple or bilateral - Thoracic ERMS^a - Cystic nephroma - Genitourinary sarcomas including undifferentiated sarcoma^a - Ovarian SLCT (Sertoli-Leydig cell tumor) - Gynandroblastoma - Uterine cervical or ovarian ERMS^a - Genitourinary/gynecologic neuroendocrine tumors - Multinodular goiter or thyroid cancer in two or more first-degree relatives or in an index patient with a family history consistent with <i>DICER1</i> syndrome^a - Childhood-onset multinodular goiter^a or differentiated thyroid cancer^a - CBME - NCMH - Pineoblastoma - Pituitary blastoma	- Lung cyst(s) in adults - Renal cyst(s)^a - Wilms tumor - Multinodular goiter or differentiated thyroid cancer - ERMS other than thoracic or gynecologic^a - Poorly differentiated neuroendocrine tumor - Undifferentiated sarcoma^a - Macrocephaly^a - Consider testing for any childhood cancer in constellation with any other minor criteria

NOTE: Consider germline *DICER1* genetic testing in an individual with one major or two minor indications.

^aMultinodular goiter, differentiated thyroid cancer (papillary or follicular carcinomas), sarcomas, Wilms tumor, neuroendocrine tumors, renal cysts, and macrocephaly may also be associated with other genetic predisposition syndromes. Consider testing for additional hereditary cancer predispositions and/or a next-generation sequencing panel that includes deletion/duplication of *DICER1* and/or other genes indicated by clinical and family history.

Table 2. Suggested signs and symptoms and imaging surveillance by system for individuals with *DICER1* pathogenic variants

System	Signs/symptoms to consider	Condition of interest	Screening: clinical and radiographic
Lung	Tachypnea, cough, fever, and pain; pneumothorax	- PPB - Lung cysts - Pulmonary blastoma	CXR at birth and every 4–6 months until 8 years of age, every 12 months 8–12 years of age; consider a CT of chest at 3–6 months of age.^a Toddlers: if initial CT normal: repeat between 2.5 and 3 years of age.^a If mutation detected at >12 years of age, consider baseline CXR or chest CT.
Thyroid	Visible or palpable thyroid nodule(s) Persistent cervical lymphadenopathy Hoarseness Dysphagia Neck pain Cough	- Multinodular goiter - Differentiated thyroid cancer	Baseline thyroid US by 8 years of age, then every 3 years or with symptoms/findings on physical exam. With anticipated chemotherapy or radiotherapy: baseline US and then annually for 5 years, decreasing to every 2–3 years if no nodules are detected.
Female reproductive tract	Hirsutism Virilization Abdominal distension, pain, or mass	- SLCT - Gynandroblastoma - Cervical ERMS	For females beginning at 8–10 years of age: pelvic and abdominal US every 6–12 months at least until age 40. End of interval is undetermined, but current oldest patient with <i>DICER1</i>-associated SLCT was 61 years of age. Education regarding symptoms strongly recommended.
Renal	Abdominal or flank mass and/or pain, hematuria	- Wilms tumor - Renal sarcoma - Cystic nephroma	Abdominal US every 6 months until 8 years of age, then every 12 months until 12 years of age. If mutation detected at >12 years of age, consider baseline abdominal US. Education regarding symptoms recommended.
Gastrointestinal	Signs of intestinal obstruction	Small intestine polyps	Physical exam. Annual routine dilated ophthalmologic exam (generally unседated) with visual acuity screening from 3 years of age through at least 10 years of age. Further testing if clinically indicated. Recommend urgent MRI for any symptoms of intracranial pathology.
Central nervous system and head and neck (excluding thyroid)	Headache, emesis, diplopia, decreased ability for upward gaze, altered gait (pineoblastoma); precocious puberty; Cushing syndrome (pituitary blastoma); decreased visual acuity and leukocoria (CBME); nasal obstruction (NCMH)	- Macrocephaly - Pineoblastoma - Pituitary blastoma - CBME - NCMH	

Abbreviation: MRI, magnetic resonance imaging.

^aWhen CT is performed, techniques to minimize radiation exposure should be employed. As novel MRI techniques are developed that will eventually allow detection of small cystic lesions, transition to nonradiation containing cross-sectional imaging should be considered.

Constitutional mismatch repair-deficiency syndrome (CMMRD)

Wimmer *et al.* J Med Genet. 2014 Jun;51(6):355-65

Table 5 Indication criteria for CMMRD testing in cancer patients

Indication for CMMRD testing in a cancer patient	≥3 points
Malignancies/premalignancies: one is mandatory; if more than one is present in the patient, add the points	
Carcinoma from the LS spectrum* at age <25 years	3 points
Multiple bowel adenomas at age <25 years and absence of APC/MUTYH mutation(s) or a single high-grade dysplasia adenoma at age <25 years	3 points
WHO grade III or IV glioma at age <25 years	2 points
NHL of T-cell lineage or sPNET at age <18 years	2 points
Any malignancy at age <18 years	1 point
Additional features: optional; if more than one of the following is present, add the points	
Clinical sign of NF1 and/or ≥2 hyperpigmented and/or hypopigmented skin alterations Ø>1 cm in the patient	2 points
Diagnosis of LS in a first-degree or second-degree relative	2 points
Carcinoma from LS spectrum* before the age of 60 in first-degree, second-degree, and third-degree relative	1 point
A sibling with carcinoma from the LS spectrum*, high-grade glioma, sPNET or NHL	2 points
A sibling with any type of childhood malignancy	1 point
Multiple pilomatricomas in the patient	2 points
One pilomatricoma in the patient	1 point
Agnesis of the corpus callosum or non-therapy-induced cavernoma in the patient	1 point
Consanguineous parents	1 point
Deficiency/reduced levels of IgG2/4 and/or IgA	1 point

*Colorectal, endometrial, small bowel, ureter, renal pelvis, biliary tract, stomach, bladder carcinoma.

CMMRD, constitutional mismatch repair deficiency; LS, Lynch syndrome; NHL, non-Hodgkin's lymphomas; sPNET, supratentorial primitive neuroectodermal tumours.

Table 2 Malignancies in 146 CMMRD patients

Malignancies	Number of tumours	Median age at diagnosis in years	Age range at diagnosis in years
Haematological malignancies			
Non-Hodgkin's lymphoma	31	5	0.4-17
Lymphoid leukaemia	9	6	2-21
Acute myeloid leukaemia	5	9.5	6-17
Malignant lymphoma	1	15	
Atypical chronic myeloid leukaemia	1	1	
Acute leukaemia	1	2	
Total	48	6	0.4-21
Malignant brain and central nervous system tumours			
High-grade gliomas	58	9.5	2-40
sPNET	8	8	4-17
Medulloblastoma	7	7	4-12
Infiltrating cerebral angiosarcoma	1	2	
Cerebral anaplastic ganglioma	1	9	
Papillary ganglioneural tumour	1	11	
Not specified brain tumour	5	8	4-24
Total	81	9	2-40
LS-associated carcinomas			
Colon/rectum*	59	16	8-48
Duodenum/jejunum/ileum	18	28	11-42
Endometrium	6	28	23-44
Bladder/ureter (papillary transitional cells)	2	20	19 & 21
Ureter/renal pelvis (unspecified)	2	19	15 & 22
Ovaries	1	17	
Total	88	17	8-48
Others			
Neuroblastoma	1	13	
Nephroblastoma (Wilms tumour)	1	4	
Ovarian neuroectodermal tumour	1	21	
Infantile myofibromatosis	1	1	
Rhabdomyosarcoma	1	4	
Basal cell carcinoma	1	n.r.	
Muco-epidermoid ca. of parotis	1	11	
Osteosarcoma	1	24	
Total	8		

*Multiple synchronous bowel carcinomas were counted as one malignancy.

CMMRD, constitutional mismatch repair deficiency; LS, Lynch syndrome; sPNET, supratentorial primitive neuroectodermal tumours.

Constitutional mismatch repair-deficiency syndrome (CMMRD)

Wimmer *et al.* J Med Genet. 2014 Jun;51(6):355-65

Table 2. Surveillance protocol for patients with CMMRD

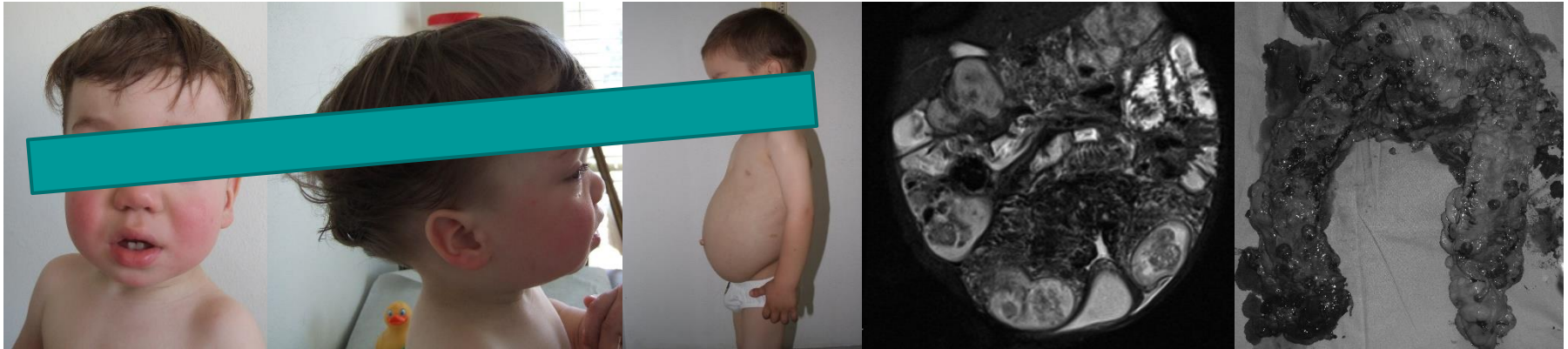
Examination	Start age	Frequency	Tumors	Comment
MRI brain	At diagnosis	Q 6 months	Brain tumors	Should not be replaced with WBMRI
WBMRI	6 years	Once a year	All tumors	Should not replace dedicated CNS imaging
CBC	1 year	Q 6 months	Leukemia	May be considered
Abdominal U/S	1 year	Q 6 months	Lymphoma	May be considered
Upper gastrointestinal endoscopy; VCE, ileocolonoscopy	4 to 6 years	Once a year	Gastrointestinal tumors	Can be alternated with WBMRI Upper and lower endoscopy, to increase once polyps are found
GYN exam, transvaginal U/S, pipelle curettage, urine cytology, dipstick	20 years	Once a year	Genitourinary cancers	As per LS guidelines

Abbreviations: GYN, gynecologic; Q, every; U/S, ultrasound; VCE, visual capsule endoscopy.

Chromosomal abnormalities

Juvenile polyposis of infancy in a child with deletion of *BMPR1A* and *PTEN* genes: Surgical approach

Patrícia Horta Oliveira^{a,*}, Catarina Cunha^a, Susana Almeida^b, Ricardo Ferreira^b, Sofia Maia^c, Jorge Manuel Saraiva^{c,d}, Maria Francelina Lopes^{a,d}



Referred because of developmental delay and dysmorphisms
significant abdominal distension (which was painful most of the time), umbilical hernia, rectal prolapse, anemia and ASD, 2 café-au-lait spots

macrocephaly

- At age 2y: 54cm > P99 (+3.8 SD)
- At age 11y: 60cm > P99 (+4.7 SD)

10q23.1q23.31 (3.34 Mb) *de novo* deletion, which encompasses, among others, the *PTEN* and *BMPR1A* genes

The MR enterography identified large and small bowel polyps

The resected colon

- subtotal colectomy and resection of the larger ileal polyps by intraoperative enteroendoscopy and colonoscopic polypectomy in the rectal stump
- **110 colonic polyps greater than 1 cm** (the biggest ones with 4.5 and 3.5 cm of height) and of the **21 endoscopically resected polyps, revealed juvenile polyposis, without features of dysplasia.**

Chromosomal abnormalities



Online Submissions: <http://www.wjgnet.com/esps/wjg@wjgnet.com>
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CASE REPORT

Aggressive juvenile polyposis in children with chromosome 10q23 deletion

The Contribution of Whole Gene Deletions and Large Rearrangements to the Mutation Spectrum in Inherited Tumor Predisposing Syndromes



Miriam J. Smith,¹ Jill E. Urquhart,¹ Elaine F. Harkness,² Emma K. Miles,¹ Naomi L. Bowers,¹ Helen J. Byers,¹ Michael Bulman,¹ Carolyn Gokhale,¹ Andrew J. Wallace,¹ William G. Newman,¹ and D. Gareth Evans^{1*}

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www.nature.com/ejhg



ARTICLE

Genotype–phenotype correlations in patients with retinoblastoma and interstitial 13q deletions

Diana Mitter^{*1}, Reinhard Ullmann², Artur Muradyan², Ludger Klein-Hitpaß³, Deniz Kanber¹, Katrin Öunap⁴, Marc Kaulisch⁵ and Dietmar Lohmann¹

Human Mutation

Variation, Informatics, and Disease



Research Article

Large deletions of the APC gene in 15% of mutation-negative patients with classical polyposis (FAP): A Belgian study*

Geneviève Michils, Sabine Tejpar, Reinhilde Thoelen, Eric van Cutsem, Joris Robert Vermeesch, Jean-Pierre Fryns, Eric Legius, Gert Matthijs

First published: 10 January 2005 | <https://doi.org/10.1002/humu.20122> | Cited by: 70

Human Mutation

Variation, Informatics, and Disease



Research Article

Molecular studies in 20 submicroscopic neurofibromatosis type 1 gene deletions

Catalina López Correa, Hilde Brems, Conxi Lázaro, Xavier Estivill, Maurizio Clementi, Silvia Mason, J. Lynn Rutkowski, Peter Marynen, Eric Legius



RESEARCH ARTICLE

Multiple DICER1-related tumors in a child with a large interstitial 14q32 deletion

Leanne de Kock, Dominique Geoffrion, Barbara Rivera, Rabea Wagener, Nelly Sabbaghian, Susanne Bens, Benjamin Ellezam, Dorothee Bouron-Dal Soglio, ... See all authors

First published: 09 January 2018 | <https://doi.org/10.1002/gcc.22523>

Whole-body MRI in cancer surveillance in children with predisposing syndromes

Table 1. WBMRI surveillance coverage in childhood CPS

Syndrome	WBMRI	Brain MR	Spine MR	NCAP WB	CAP WB + Neck MR
LFS	Q 12 mo from Dx	Q 12 mo from Dx (alternating Q 6 mo with WBMRI unless under GA)			
NF1	Baseline scan between 16 and 20 years				
NF2 and schwannomatosis	Based on Sx and location	Add IAM Q 6–24 mo Q 6 mo if positive	Q 24–36 mo Q 6 mo if positive		
RB	Q 12 mo from 8 y	Q 6 mo to 5 y			
CMMRD (+/– LS)	Q 12 mo from 6–8 y (no anesthesia)	Q 6 mo from Dx			
DICER 1 syndrome	Consider	Q 6 mo from Dx			
RTS	Consider	Urgent if Sx			
HPP syndrome				Q 24 mo from 6–8 y	Q 24 mo from 6–8 y *option
NOT INDICATED	Adenomatous polyposis syndromes (APC, MUTYH), juvenile polyposis coli (BMPRIA, SMAD4, PTEN), Peutz–Jeghers syndrome (STK11/LKB1), RASopathies, NS, NSLAH, NSML, CFCS, CS, LeS, CBLS, Sotos, Weaver, Rubinstein–Taybi, Schinzel–Giedion, and NKX2-1 syndromes; metabolic disorders linked to childhood cancers; rare DNA repair disorders: ataxia telangiectasia, Bloom syndrome, Fanconi anemia, dyskeratosis congenita, Nijmegen breakage syndrome, xeroderma pigmentosum, PHTS, HLRCC syndrome, Gorlin syndrome; leukemia/lymphoma syndromes <i>unless</i> part of other syndrome, e.g., LFS, CMMRD; overgrowth disorders and kidney tumors, e.g., BWS, BOS, DDS, FS, HB, IHH, SGBS, PROS, PS, WT; NB; MEN syndromes: MEN1, MEN2A and B, MEN4, HPT–JT; vHL disease				

Abbreviations: BOS, Bohring–Opitz syndrome; BWS, Beckwith–Wiedemann syndrome; CBLS, CBL syndrome; CFCS, cardiofaciocutaneous syndrome; CMMRD, constitutional mismatch repair deficiency syndrome; CS, Costello syndrome; DDS, Denys–Drash syndrome; Dx, diagnosis; FS, Frasier syndrome; GA, general anesthesia; HLRCC, hereditary leiomyomatosis and renal cell cancer syndrome; HPP, hereditary paraganglioma and pheochromocytoma syndrome; HPT–JT, hyperparathyroid–jaw tumor; IAM, internal auditory meati; IHH, isolated hemihypertrophy; LeS, Legius syndrome; LS, Lynch syndrome; MEN, multiple endocrine neoplasia; NB, hereditary neuroblastoma; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2; NS, Noonan syndrome; NSLAH, NS like with loose anagen hair; NSML, NS with multiple lentigines; PHTS, PTEN hamartoma tumor syndrome; PROS, PIK3CA-related overgrowth spectrum; PS, Perlman syndrome; RB, hereditary retinoblastoma; RTS, Rothmund–Thomson syndrome; SGBS, Simpson–Golabi–Behmel syndrome; Sx, symptoms; WT, Wilms tumor; vHL, Von Hippel–Lindau; Q, every; mo, months; y, years.

Who should be responsible for coordinating the surveillance?

- General pediatrician?
- Pediatric oncologists/hematologists?
- Pediatric cancer genetics clinic?
 - Organized multidisciplinary team focused on hereditary cancer



let it
be me.
❤️

Inherited Gastrointestinal cancer syndromes

Achatz *et al.* Clin Cancer Res;23(13); e107–e14

Table 1. Cancer surveillance recommendations in the pediatric age range

Syndrome	Gene	Inheritance pattern	Tumor risk	Pediatric surveillance	Frequency
FAP	APC	Autosomal dominant	Colorectum	Flexible sigmoidoscopy or colonoscopy	Starting at age 10–15; annually until surgery.
			Thyroid	Cervical palpation	Starting at age 15–19; annually.
			Liver (hepatoblastoma)	Abdominal ultrasonography and serum AFP (see discussion)	Starting early infancy; every 4–6 months until age 7.
			Desmoid	Annual physical examination Abdominopelvic MRI (for individuals with positive family history of desmoids)	Following colectomy or other surgery; 1–3 years, then lengthen time frame to 5–10 years.
			Medulloblastoma	Annual physical examination	Starting at childhood; annually.
Attenuated FAP			Colorectum	Colonoscopy	Starting at age 15–19; every 3 years until adenomas arise, then yearly.
MUTYH-associated polyposis	MUTYH	Autosomal recessive	Colorectum	Colonoscopy	No childhood surveillance recommended
			Gastric/duodenum	Upper gastroduodenal endoscopy	Starting at age 18; every 2 years.
Peutz–Jeghers syndrome	STK11 (LKB1)	Autosomal dominant	Gastric/duodenum	Upper gastroduodenal endoscopy	Starting at age 25–30; every 1–5 years.
			Gastric/duodenum	Upper gastroduodenal endoscopy	Starting at age 8, baseline; every 3 years if polyps are found. In absence, repeat at age 18.
			Stomach	Gastroduodenal endoscopy	Starting at age 8; every 2–3 years.
			Small bowel	Capsule endoscopy	Starting at age 8; every 2–3 years.
Juvenile polyposis	BMPRIA and SMAD4	Autosomal dominant	Ovary and cervix	Annual physical examination	Starting at childhood; annually.
			Testes	Annual physical examination	Starting at childhood; annually.
			Colorectum	Colonoscopy	Starting at age 12–15; every year until no polyps are found, then lengthen interval to every 3 years.
			Colorectum	Colonoscopy	Starting at age 12–15; every year until no polyps are found, then lengthen interval to every 3 years.
			Stomach	Gastroduodenal endoscopy	Starting at age 15; every 1–2 years.
			Small bowel	Capsule endoscopy	Starting at age 15; every 1–2 years.

Abbreviation: AFP, alpha-fetoprotein.

RA Sopathies and Other Rare Genetic Conditions

Villani et al. Clin Cancer Res; 23(12); e83–e90

Table 1. Summary of cancer surveillance recommendations

Syndrome	Childhood cancer risk	Surveillance guidelines
I. Surveillance warranted		
Costello syndrome	15% by 20 yrs: ERMS, NBL, bladder cancer	0 to 8–10 yrs: physical exam and AP US ± CXR q 3–4 mths From 10 yrs: annual urinalysis
<u>NS—specific <i>PTPN11</i> or <i>KRAS</i> mutations</u>	High risk of myeloproliferative disorder/JMML	0 to 5 yrs: physical exam (with assessment of spleen) and CBC with differential q 3–6 mths
CBL syndrome	High but not precisely defined JMML risk; more rarely other neoplasms	0 to 5 yrs: Physical exam (with assessment of spleen) and CBC with differential q 3–6 mths
SGS—mild	Unknown but may approximate 10–15%: SC-GCT and PNET, HBL	Attention for congenital tumors on baseline imaging for SGS Consider periodic AP US, AFP/βHCG
II. Baseline only		
SGS—severe	Unknown but may approximate 10–15%: SC-GCT and PNET, HBL	Attention for congenital tumors on baseline imaging for SGS Consider addition of AFP/βHCG to baseline bloodwork for SGS
III. No surveillance		
For all of the following:	<5% or unknown but low likelihood	No routine surveillance Increased awareness and low threshold for investigating new potential tumor-related symptoms
<u>NS (non-high risk mutations)</u>	Dysembryoplastic neuroepithelial tumors, ALL, NBL, RMS, others	
NSLAH	e.g., NBL, myelofibrosis	
NSML	e.g., acute leukemias	
CFCS	e.g., ALL, NHL	
Legius syndrome	Few cancers reported to date	
Sotos syndrome	e.g., NBL, ALL, AML, HBL, SCT, etc.	
Weaver syndrome	e.g., NBL, hematologic malignancies	
Rubinstein–Taybi syndrome	e.g., HBL, NBL, RMS, CNS tumors, carcinomas, etc.	
NKX2-1 syndrome	No evidence for cancer predisposition	

Abbreviations: AFP, alpha-fetoprotein; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; AP US, abdominopelvic ultrasound; βHCG, beta human chorionic gonadotrophin; CBC, complete blood count; CFCS, cardiofaciocutaneous syndrome; CNS, central nervous system; CXR, chest x-ray; ERMS, embryonal rhabdomyosarcoma; HBL, hepatoblastoma; JMML, juvenile myelomonocytic leukemia; mths, months; NBL, neuroblastoma; NHL, non-Hodgkin lymphoma; NS, Noonan syndrome; NSLAH, Noonan syndrome-like with loose anagen hair; NSML, Noonan syndrome with multiple lentigines; PNET, primitive neuroectodermal tumor; q, every; RMS, rhabdomyosarcoma; SC-GCT, sacrococcygeal germ cell tumor; SCT, sacrococcygeal teratoma; SGS, Schinzel–Giedion syndrome; yrs, years.

Tumors highly correlated with specific syndromes

Type of tumor	Syndrome
Adrenocortical carcinoma	Li Fraumeni syndrome, BWS, MEN1, FAP
Atypical teratoid malignant rhabdoid tumor	Rhabdoid Predisposition syndrome
Cerebellar gangliocytoma	<i>PTEN</i> hamartoma tumor syndrome
Choroid Plexus Carcinoma	Li Fraumeni syndrome
Endolymphatic sac tumors	Von Hippel-Lindau syndrome
Hemangioblastoma	Von Hippel-Lindau syndrome
Hepatoblastoma	FAP, BWS
Juvenile myelomonocytic leukemia	Neurofibromatosis type 1, Noonan syndrome, <i>CBL</i> germline syndrome, Constitutional Mosaic Trisomy 8
Low hypodiploid acute lymphoblastic leukemia	Li Fraumeni syndrome
Malignant peripheral nerve sheath tumor	Neurofibromatosis type 1
(Malignant) Schwannoma	Neurofibromatosis type 1 and type 2, Schwannomatosis, Carney complex
Medullary thyroid carcinoma	MEN2
Medulloblastoma (in particular age < 3y)	FAP, Gorlin syndrome, <i>SUFU</i> germline mutations
Optic pathway glioma	Neurofibromatosis type 1
Ovarian Sertoli-Leydig cell tumor	<i>DICER1</i> syndrome
Pleuropulmonary blastoma	<i>DICER1</i> syndrome
Pineoblastoma	<i>DICER1</i> syndrome, Retinoblastoma predisposition syndrome
Pituitary blastoma	<i>DICER1</i> syndrome
Retinoblastoma	Retinoblastoma predisposition syndrome