Cancer Predisposing Syndromes nei bambini con tumore solido

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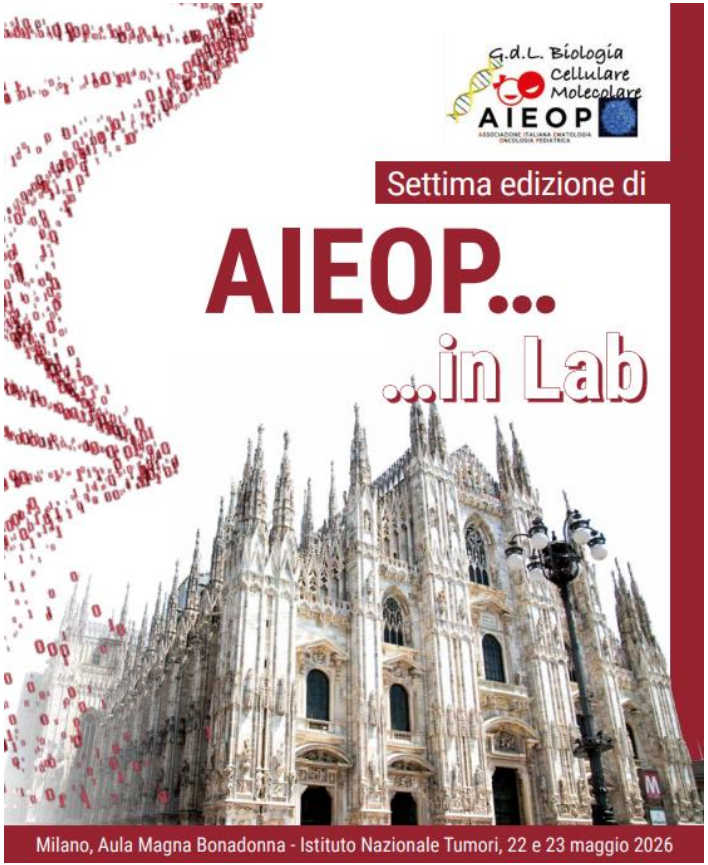
22 maggio 2026



How Common Are CPS in Children with Cancer?

8–18%

Carry a CPS

Children with cancer harboring an identifiable germline predisposition syndrome

>150

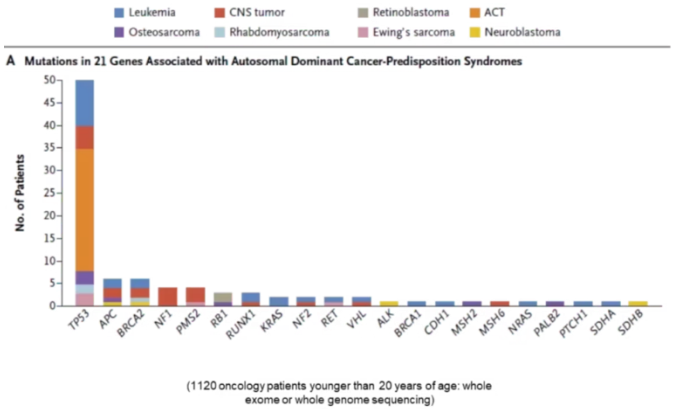
Predisposing Genes

Germline genes involved in pediatric cancer predisposition syndromes

>50

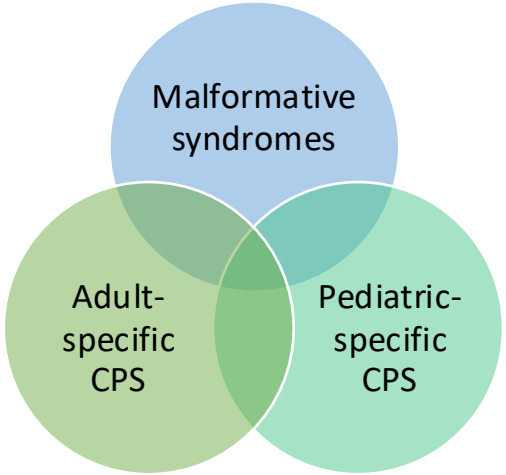
Known CPS

Internationally classified cancer predisposition syndromes in children



(1120 oncology patients younger than 20 years of age: whole exome or whole genome sequencing)

Zhang, J. et. al., 2015, NEJM, 373: 2336-46.



When Should We Suspect a CPS?

Three independent diagnostic pathways should each trigger a genetic evaluation — even in isolation.

Pediatric Cancer Diagnosis

Any malignancy at a young age, especially with unusual histology or bilateral/multifocal presentation, warrants germline testing.

Known Genetic Disorder

Pre-existing conditions such as NF1, Gorlin, or constitutional mismatch repair deficiency that intrinsically confer elevated cancer risk.

Atypical or Suspicious Tumor

Unusual tumor type, early age at onset, multiple primary tumors, or strong family history — all flags for underlying predisposition.

⚠ Each pathway, independently, is sufficient to initiate genetic counseling and germline evaluation. Do not wait for all three criteria to be met.

De Voer et Valle L., 2026, EJHG

The Role of the Pediatric Pathologist in CPS Detection

Germline genetic alterations account for approximately **8–18%** of pediatric cancers. Histopathology is the cornerstone for classifying pediatric malignancies and identifying patients at high risk of an underlying CPS. Pathologists must recognize tumor types and be aware of underlying genetic aberrations — specific morphological patterns may be the **first clue** to a CPS.

Histopathologic Analysis

Morphologic patterns flag CPS probability and guide further molecular workup.

Molecular Integration

DNA and RNA testing produce integrated diagnostic reports combining somatic and germline data.

Clinical Detection

Non-tumoral findings and clinical features prompt targeted genetics referral.

Multidisciplinary Board

Integrate pathology, molecular data, and genetics expertise in tumor board settings.

Schurink B. et al., 2025, Virchows Archiv

Why Recognizing a CPS Is Clinically Critical

Diagnosis & Risk Stratification

Early identification enables tailored surveillance programs and early detection of subsequent malignancies, improving long-term outcomes.

Personalized & Safe Treatment

CPS may contraindicate specific therapies (e.g., radiotherapy in Gorlin syndrome) or guide targeted drug selection based on molecular vulnerability.

Family Cascade Testing

A germline diagnosis extends beyond the proband — cascade testing identifies at-risk relatives and enables preventive interventions.

Research & Clinical Trial Access

Patients with confirmed CPS may be eligible for genotype-specific clinical trials, accessing novel therapies and contributing to evidence generation.

Caeser et al., 2024, Familial Cancer

CHAPTER 02 — CLASSIC CPS

Li-Fraumeni Syndrome

One of the most severe cancer predisposition syndromes, caused by germline alterations of the *TP53* tumor suppressor gene. Hallmarked by near-complete penetrance, a broad tumor spectrum, and early onset across pediatric and adult life.

1:5K

Prevalence

Estimated 1:5,000–1:20,000 individuals worldwide

80%

Lifetime Cancer Risk

Extremely high penetrance; multiple tumors across a lifetime are common

>350K

Germline TP53 Carriers

Estimated globally. Most frequent cause of autosomal dominant CPS in children

Classic, updated Chompret, and Birch criteria define indications for *TP53* germline screening. Meeting **any single criterion** justifies genetic testing. Missense variants account for 73%, frameshift 9%, and nonsense 8% of pathogenic alterations.

Zhang, J. et al., 2015, NEJM

LFS: Prognostic and Therapeutic Implications

Radiotherapy Caution

Ionizing radiation should be minimized or avoided whenever possible. LFS patients face significantly elevated risk of radiation-induced secondary malignancies; treatment planning must carefully balance curative intent against long-term secondary cancer burden.

WEE1 Inhibition — SHH Medulloblastoma

WEE1 represents a promising therapeutic target in LFS-associated SHH medulloblastoma. Combined inhibition with vincristine demonstrates preclinical efficacy, providing a compelling rationale for dedicated clinical trial investigation in this population.
SHH p53 altered MB: high risk protocols.

Immune Checkpoint Inhibitors

In a 3-year-old with metastatic choroidal melanoma and constitutional *TP53* variant, **nivolumab + ipilimumab** achieved complete remission at 24 months. High PD-L1 expression in LFS tumors may predict ICI response and guide patient selection.

Choroid Plexus Carcinoma

A significant proportion of CPCs carry *TP53* alterations. Mosaicism must be considered in apparently sporadic cases. Routine germline sequencing is recommended for all CPC diagnoses to ensure appropriate surveillance and family counseling.

SHH MB p53 altered

Mandatory genetic test for Li Fraumeni syndrome. High risk patients.

Chen K. et al. 2024; Tuller P. et al., 2025; Kolodziejczak A. et al., 2026

GUIDELINE SUMMARY: SURVEILLANCE PROTOCOL IN CARRIERS OF GERMLINE DISEASE-CAUSING *TP53* VARIANTS

Exam	Periodicity	Age to start	Age to end	Condition	Evidence*
Clinical examination with, in children, specific attention to signs of virilisation or early puberty and measurement of blood pressure and, in patients who received radiotherapy, to occurrence of basal cell carcinomas within the radiotherapy field	Every 6 months	Birth	17 years		Moderate
	Annual	18 years	-		Moderate
Whole-Body MRI without gadolinium enhancement	Annual	Birth	-	High cancer risk *TP53* variant** or patient previously treated by chemotherapy or radiotherapy	Moderate
		18 years	-		Strong
Breast MRI	Annual	20 years	65 years		Strong
Brain MRI***	Annual	Birth	18 years	High cancer risk *TP53* variant	Moderate
		18 years	50 years		Moderate
Abdominal ultrasound	Every 6 months	Birth	18 years		Strong
Urine steroids	Every 6 months	Birth	18 years	When abdominal ultrasound does not allow a proper imaging of the adrenal glands	Weak
Colonoscopy***	Every 5 years	18 years	-	Only if the carrier received abdominal radiotherapy for the treatment of a previous cancer or if there is a familial history of colorectal tumours suggestive of an increased genetic risk	Weak

European Reference Networks

European Reference Network for rare or low prevalence complex diseases — Network Genetic Tumour Risk Syndromes (ERN GENTURIS)

www.genturis.eu

GUIDELINES FOR THE LI-FRAUMENI AND HERITABLE *TP53*-RELATED CANCER SYNDROMES

Guidelines for the identification of individuals who should be tested for germline disease-causing *TP53* variants and for their subsequent clinical management

Publication date 26 May 2020

Authors: Prof. Thierry Frebourg, France; Ass. Prof. Svetlana Bajalica Lagercrantz, Sweden; Prof. Carla Oliveira, Portugal and Rita Magenheim, Germany / Hungary; Prof. D. Gareth Evans, U.K

CHAPTER 02 — CLASSIC CPS

Neurofibromatosis Type 1

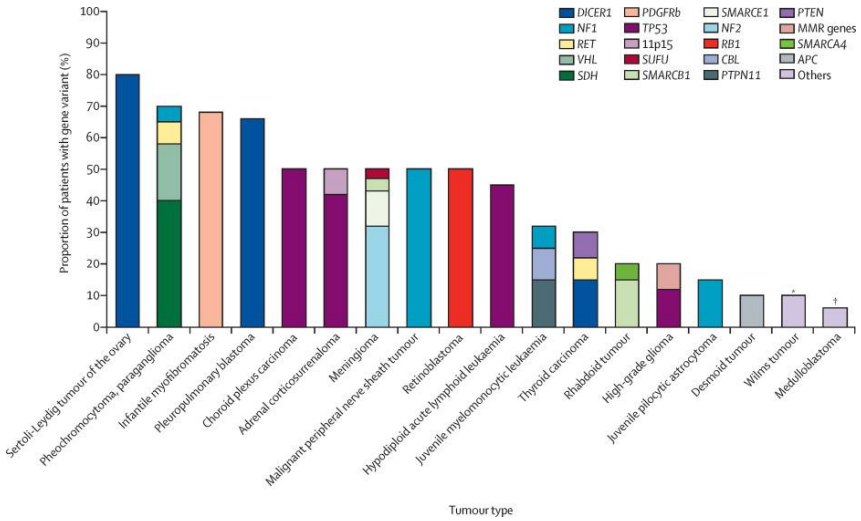
NF1 is one of the most common autosomal dominant genetic disorders in humans. Complete penetrance with extremely variable expressivity makes it a clinically heterogeneous and therapeutically challenging cancer predisposition syndrome.

1:2,500	100%	50%
Prevalence	*Penetrance*	*De Novo Variants*
Among the most common monogenic diseases worldwide	All carriers develop clinical signs, though expressivity varies widely	Half of cases have no family history

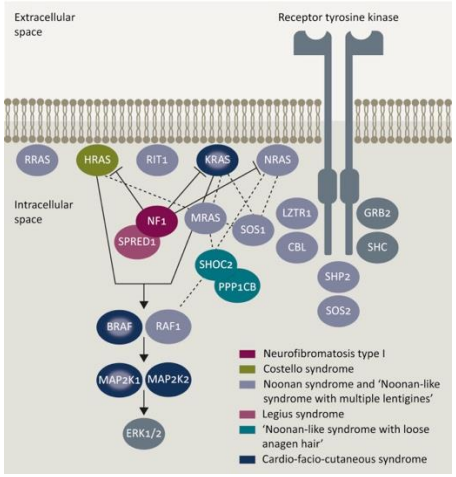
Genotype-Phenotype Highlights: 90–95% of causative variants are intragenic. Less than 10% are whole-gene deletions — associated with more severe phenotype, higher neurofibroma burden, and cognitive impairment. Diagnosis is primarily clinical; expressivity varies significantly even within the same family.

Peduto et al. 2023, Cancers

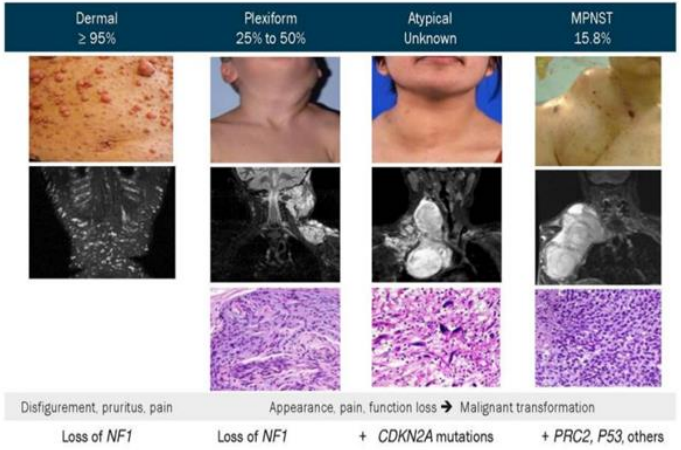
Neurofibromatosis Type 1



Selected cancer predisposition genes by biological function
The Lancet Child & Adolescent Health 2021 5142-154DOI: (10.1016/S2352-4642(20)30275-3)



Germline and sporadic cancers driven by the RAS pathway: parallels and contrasts.
Ann Oncol. 2020;31(7):873-883.



Kim A, et al. *Sarcoma*. 2017;2017:7429697.

Child's Nervous System (2021) 37:1909–1915
https://doi.org/10.1007/s00381-021-05127-6

ORIGINAL ARTICLE

Trametinib for orbital plexiform neurofibromas in young children with neurofibromatosis type 1

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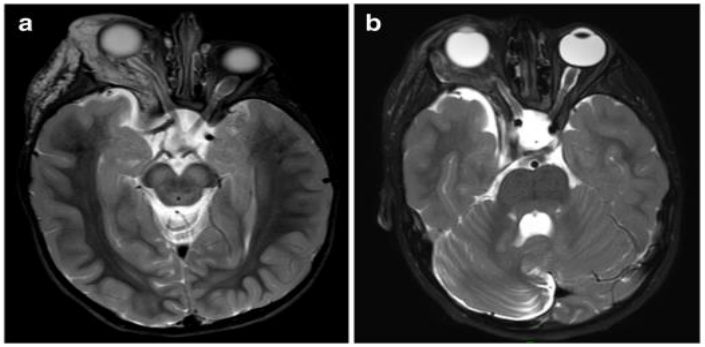
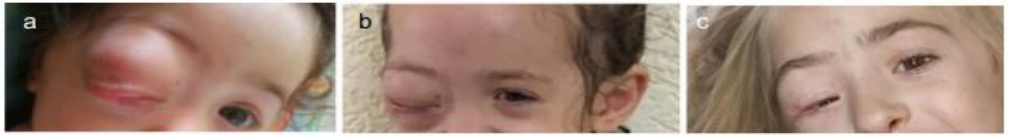




Before

After 36 months

Current Oncology Reports (2021) 23: 45
https://doi.org/10.1007/s11912-021-01032-y

EVOLVING THERAPIES (RM BUKOWSKI, SECTION EDITOR)

Neurofibromatosis in the Era of Precision Medicine: Development of MEK Inhibitors and Recent Successes with Selumetinib

Robert Galvin[1] · Adrienne L. Watson[2] · David A. Largaespada[3] · Nancy Ratner[4] · Sara Osum[3] · Christopher L. Moertel[5,6]

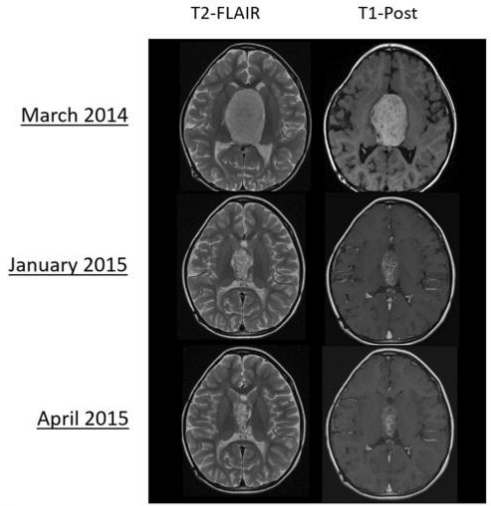
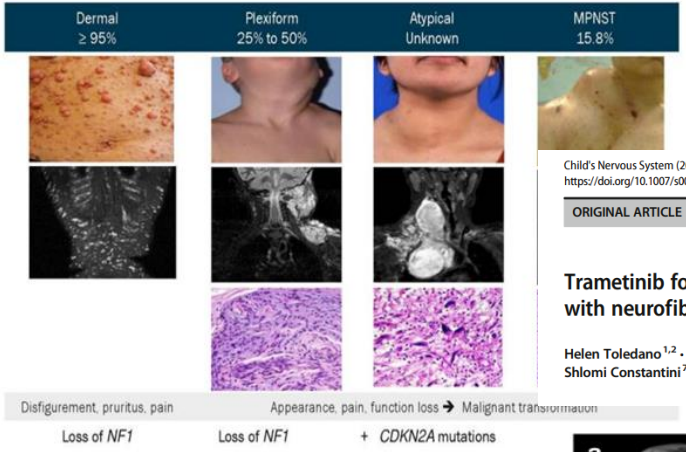


Fig. 1 PBTC-029 phase 2, stratum 3 (recurrent NF1-associated low-grade glioma): Example of radiographic response with selumetinib monotherapy. Reproduced with permission by Dr. Jason Fangusaro and the Pediatric Brain Tumor Consortium



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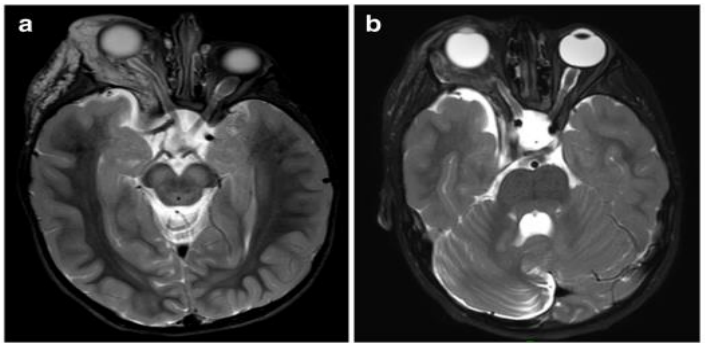
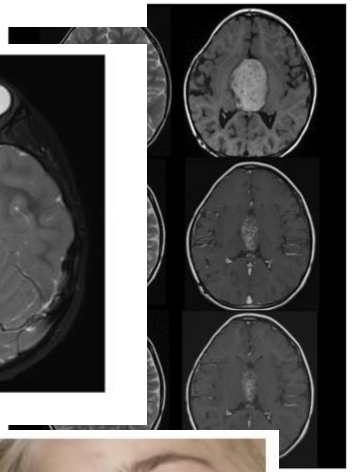
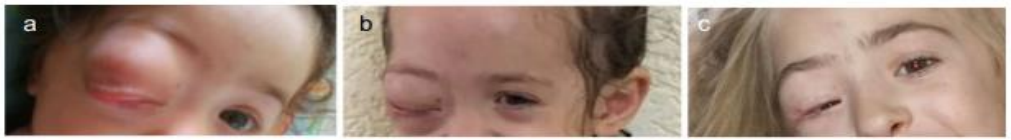
Medicine: Development th Selumetinib

[3] · Nancy Ratner[4] · Sara Osum[3] ·

T1-Post







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CHAPTER 02 — CLASSIC CPS

Constitutional Mismatch Repair Deficiency (CMMRD)

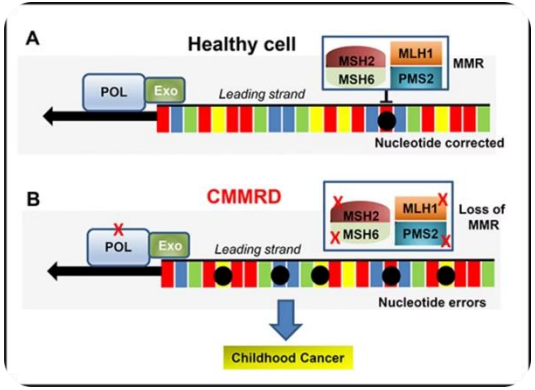
CMMRD is a rare, recessively inherited childhood cancer predisposition syndrome caused by **biallelic germline mutations** in any of the four mismatch repair genes (*MLH1, MSH2, MSH6*, or *PMS2*). Estimated prevalence: **1 in 1 million** live births.

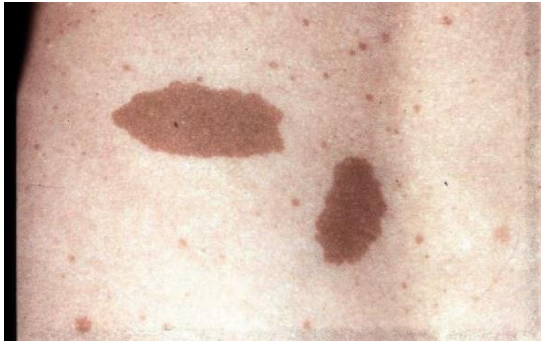
Tumor Spectrum

- **Hematological:** T-cell lymphoblastic lymphoma
- **CNS:** High-grade glioma, medulloblastoma
- **Gastrointestinal:** Colorectal cancer

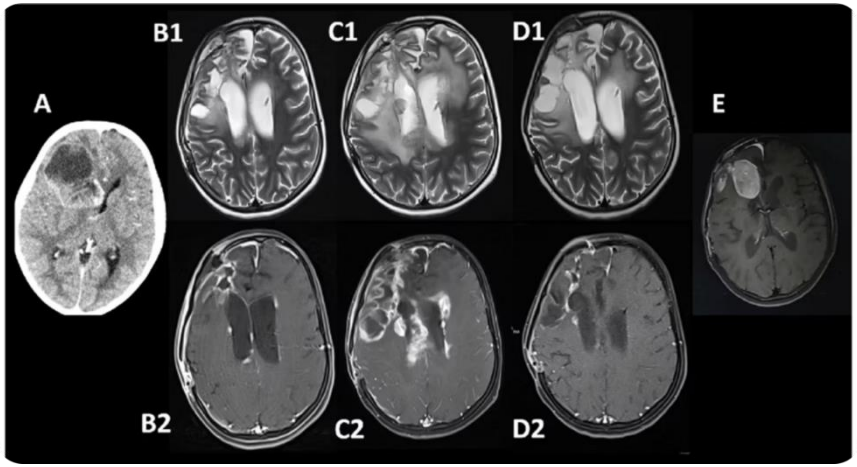
Primary MMRD is a pan-cancer mechanism. Alterations in MSH2, MSH6, MLH1, or PMS2 cause dysfunctional protein, leading to errors during DNA replication. Gliomas are a major cause of cancer-related death in individuals aged 0–40 years.

Malak Abedalthagafi 2018, Oncotarget; Logine Negm et al. 2025, The Lancet Oncol.





Radiological Response to Nivolumab in CMMRD



High tumor mutational burden secondary to MMRD creates robust immunogenicity, explaining the dramatic and durable response to immune checkpoint blockade in this patient population.

Alphones S. et al. 2021, Child's Nervous System

ICIs in Pediatric CNS Tumors: A Systematic Review

Gulsuna et al. | Published November 2025

309 Patients

12 studies · Mean age 10.35 yrs · 64% HGG

ORR 4.1%

3 CR + 9 PR · SD in 30.7% · PD predominant

CMMRD Benefit

Hypermutated HGG ORR **10%** vs. 4.5% overall

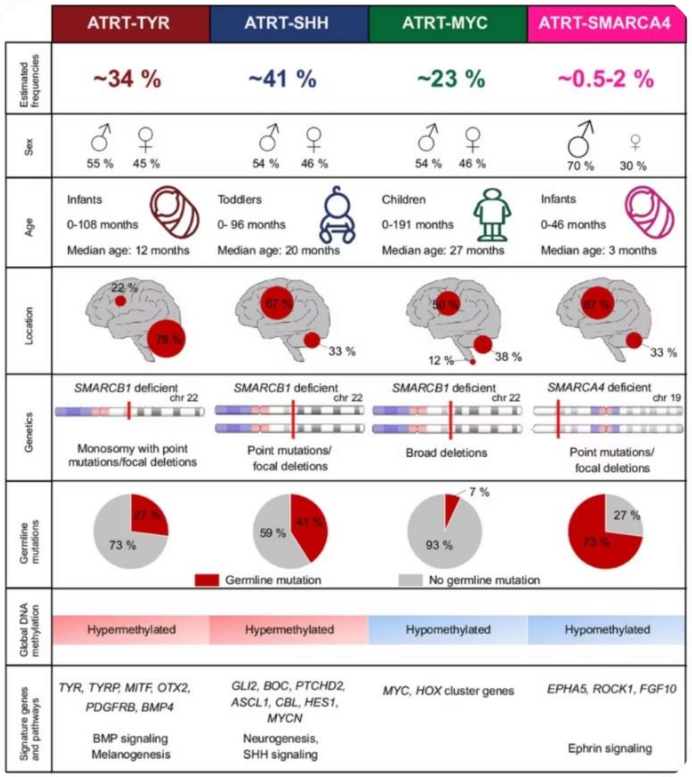
Safety

Grade ≥3 irAEs up to 50% with dual/combo therapy · No treatment-related deaths

Conclusion

Limited benefit outside molecularly defined subgroups · Biomarker-driven selection essential

Atypical Teratoid Rhabdoid Tumour (ATRT)



Common Characteristics

- Autosomal dominant
- More than 70% of individuals with RTPS present before age 12 months with synchronous tumors
- Potentially have a worse prognosis than those with a sporadic rhabdoid tumor, although long-term survival has been reported in some individuals
- 2/3 de novo

SMARCB1 (RTPS1)

- The vast majority of individuals with *SMARCB1*-related RTPS have a *de novo* disease-causing *SMARCB1* germline variant
- Proportion of RTPS Attributed to Disease-Causing Variants in Gene: 85%-95%
- Penetrance of *SMARCB1*-related RTPS may be extremely high (>90% by age 5 years)
- The risk of germline mutations is reported to be between 26% and 41% in *SMARCB1*-deficient tumours

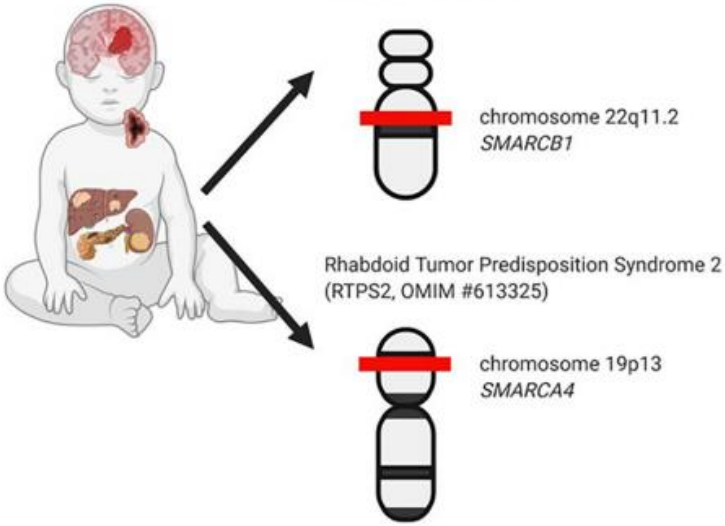
SMARCA4 (RTPS2)

- Most reported individuals diagnosed with *SMARCA4*-related RTPS inherited a disease-causing variant from a parent without a history of a rhabdoid tumor or SCCOHT
- Proportion of RTPS Attributed to Disease-Causing Variants in Gene: 5%-15%
- Less is know. The penetrance of *SMARCA4*-related RTPS appears to be incomplete
- May be substantially higher in *SMARCA4*-deficient tumours

Del Baldo et al, Front. Oncol. 11:586288 (2021)

The diagnosis of **RTPS** should be considered in patients with:
1) **rhabdoid tumors**;
2) especially if they have **multiple primary tumors**;
3) and/or in individuals with a **family history**

Other features suggesting RTPS: SCCOHT or other malignant entities such as cribriform neuroepithelial tumor, malignant peripheral nerve sheath tumor, and non-malignant schwannoma or meningioma



Warning

Unaffected adult carriers and gonadal mosaicism have been reported: if the *SMARCB1* or *SMARCA4* disease-causing variant identified in the proband cannot be detected in the constitutional DNA of either parent, **the recurrence risk to sibs is still greater** than that of the general population because of the possibility of parental germline mosaicism. Germline mosaicism may account for up to half of the families with sibs affected by RTPS.

Pay attention to p53 somatic mutation according to variant allele frequency

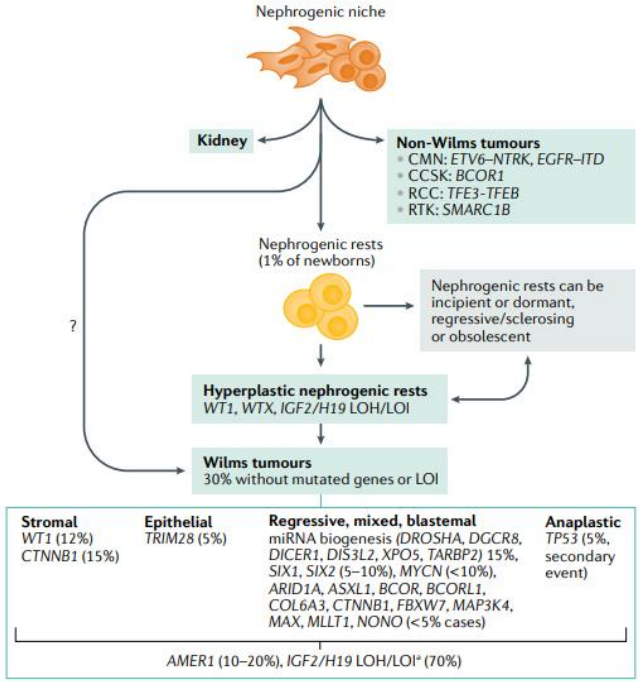
TABLE 1. Patient Characteristics

Case No.	Sex	Age (y)	Tumor Location	SMARCB1	SMARCA4	TP53 Mutation	VAF (Tumor)
1	Male	17	Temporo-occipital	Loss/retained	Retained	TP53:NM_000546.6: c.586C > T (p.Arg196*)	0.87
2	Male	5	Parietotemporal	Loss	Retained	TP53:NM_000546.6:c.783-2A > G	0.98
3	Male	19	Frontotemporal	Retained	Loss	TP53:NM_000546.6:c.1024C > T (p.Arg342*)	0.97

Wilms tumour

Filippo Spreafico[1]✉, Conrad V. Fernandez[2], Jesper Brok[3], Kayo Nakata[4], Gordan Vujanic[5], James I. Geller[6], Manfred Gessler[7], Mariana Maschietto[8], Sam Behjati[9,10,11], Angela Polanco[12], Vivian Paintsil[13], Sandra Luna-Fineman[14] and Kathy Pritchard-Jones[15]

NATURE REVIEWS | DISEASE PRIMERS | Article citation ID: (2021) 7:75



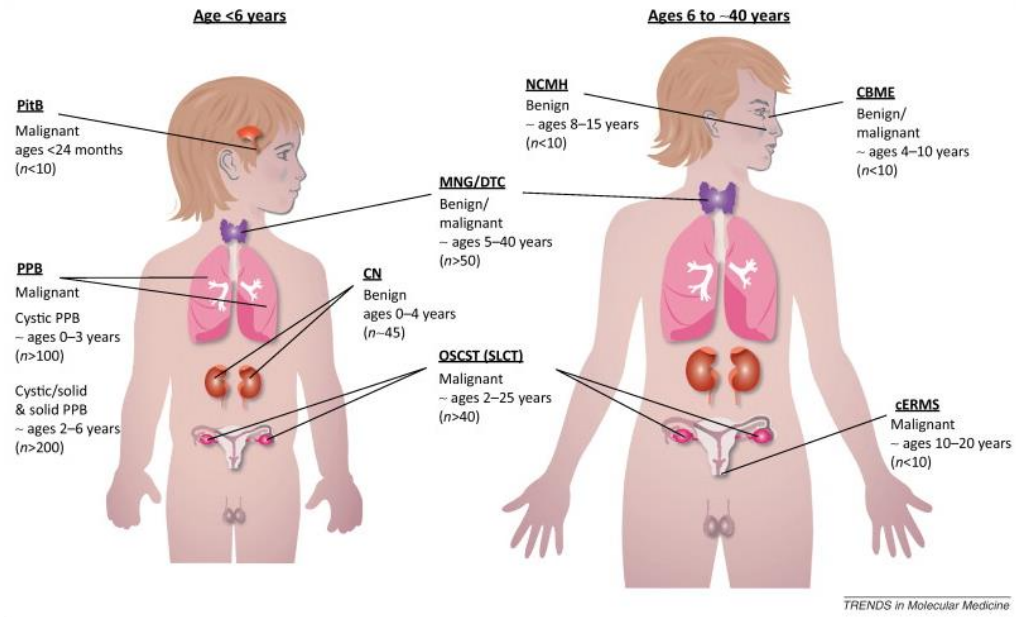
Genetic Predisposition to Wilms Tumour

Table 1 | **Heritable syndromes associated with an increased risk of Wilms tumour**

Syndrome	Locus	Genetic lesion	Phenotype	Estimated risk of WT (%)	Refs
WAGR	11p13	11p13 deletion encompassing *WT1*	Aniridia, genitourinary anomalies, delayed-onset renal failure	~50	209
Denys–Drash	11p13	Point mutation zinc-finger region of *WT1*	Early-onset nephrotic syndrome (diffuse mesangial sclerosis), ambiguous genitalia	~75	210
Frasier	11p13	Point mutation in *WT1* intron 9 donor splice site	Ambiguous genitalia, streak gonads, focal segmental glomerulosclerosis, diffuse mesangial sclerosis	Case reports	72
Beckwith–Wiedemann	11p15	Dysregulation of imprinted genes including *IGF2* and *H19*	Overgrowth syndrome. Organomegaly, large birthweight, macroglossia, omphalocele, hemihypertrophy, ear pits and creases, neonatal hypoglycaemia	0.2–24	28,211
Simpson–Golabi–Behmel	Xq26.2	*GPC3* mutations/deletions	Overgrowth syndrome. Prenatal and postnatal overgrowth, visceral and skeletal abnormalities (course facies), congenital heart defects, a variable degree of psychomotor impairment	~3	211
Li–Fraumeni	17p13	Heterozygous *TP53* mutations. Genome instability disease	Familial predisposition to cancer	Low, but several cases reported	212
Mosaic variegated aneuploidy	15q15	Biallelic *BUB1B* or *TRIP13* mutations. Genome instability disease	Microcephaly, intellectual disabilities, cataracts, heart defects	>70	213,214
Fanconi anaemia D1	13q12	Biallelic *BRCA2/FANCD1* mutations. Genome instability disease	Short stature, radial ray defects, bone marrow failure, but heterogeneous clinical presentation (one-third of individuals with Fanconi anaemia have a normal appearance)	20–40	215,216
Hyperparathyroid-jaw tumour	1q25–q31	Heterozygous *HRPT2* mutations	Fibro-osseous lesions of jaw, parathyroid tumours	Low, but several cases reported	217,218
Bloom	15q26	Biallelic *BLM* mutations. Genome instability disease	Short stature, photosensitivity, microcephaly, insulin resistance, immunodeficiency	3	219
Perlman	2q37	Biallelic inactivating variants in *DIS3L2*	Prenatal overgrowth, facial dysmorphism, developmental delay, cryptorchidism, renal dysplasia	~64	220
Trisomy 18 (Edward)	18q11.2–q23	Complete trisomy 18 (95%); mosaic trisomy 18 (5%)	Congenital cardiac anomalies; dysmorphic facial features, clenched hands, and rocker-bottom feet	Case reports	221
Mulibrey nanism	17q22–q23	Biallelic *TRIM37* mutations	Growth deficiencies, cardiomyopathies, characteristic facies, a predisposition towards developing metabolic disorders (type II diabetes mellitus) (Finnish population)	~6–8	222,223

WT, Wilms tumour.

DICER 1 spectrum



Abbreviations: CMBE, ciliary-body medulloepithelioma; cERMS, cervical embryonal rhabdomyosarcoma; CN, cystic nephroma; DTC, differentiated thyroid carcinoma; MNG, multinodular goiter; NCMH, nasal chondromesenchymal hamartoma; OSCST, ovarian sex cord-stromal tumor; PitB, pituitary blastoma or pineobastoma; SLCT, Sertoli–Leydig cell tumor.

Choong CS et al. Trends Mol Med. 2012 Sep;18(9):503-5.

European Reference Networks | Genetic Tumour Risk Syndromes (ERN GENTURIS)

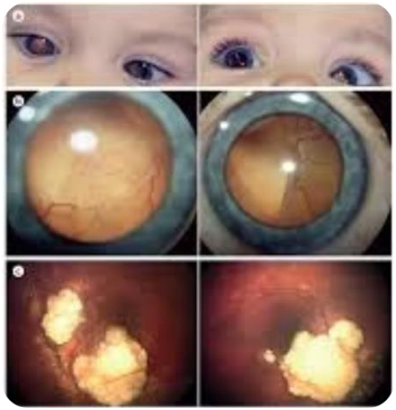
DICER1 tumour predisposition syndrome

Last update: August 2025

CHAPTER 02 — CLASSIC CPS

Retinoblastoma & the RB1 Gene

Retinoblastoma is very common in people with heritable *RB1* alterations, occurring in **9 of 10 individuals** with a pathogenic *RB1* germline variant. Frequent eye examinations for early detection — when tumors are most treatable — are strongly recommended for all carriers.



Tumors Associated with Hereditary Retinoblastoma

- **Osteosarcoma** — most common secondary malignancy
- Soft tissue sarcomas
- Melanoma
- **Brain/pineal tumors** (trilateral retinoblastoma)
- **Epithelial cancers** in adult survivors: lung, breast, bladder

⚠ Risk of secondary malignancies is further increased after radiotherapy and persists lifelong. Surveillance must continue into adulthood.

Dimaras H. et al. 2015, Nature Reviews Disease Primers; ES Knudsen, 2020, Comm. Biology

Lynch Syndrome?

Hereditary Cancer Syndrome

Autosomal dominant; germline variants in *MLH1, MSH2, MSH6, PMS2*, or *EPCAM*

Prevalence

~1 in 279 people; most common hereditary colorectal cancer syndrome

Traditionally Adult-Onset

Colorectal, endometrial, ovarian, gastric, brain cancers — childhood risk less established

Pediatric Enrichment

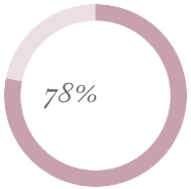
LS found in 0.5–0.9% of pediatric cancer cohorts vs. 0.3% population frequency

55 Cases: Key Findings

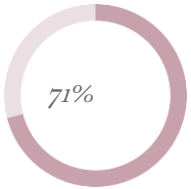
55
Total Cases
8 institutional + 47 literature

12.7
Avg. Age (yrs)
Range: 1–24 years

64%
Male
Sex distribution

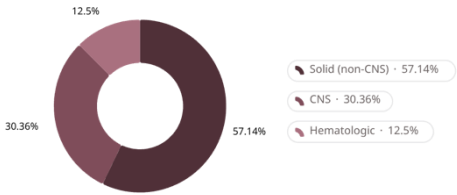


LOH Present
Loss of heterozygosity confirmed (21/27 tested)



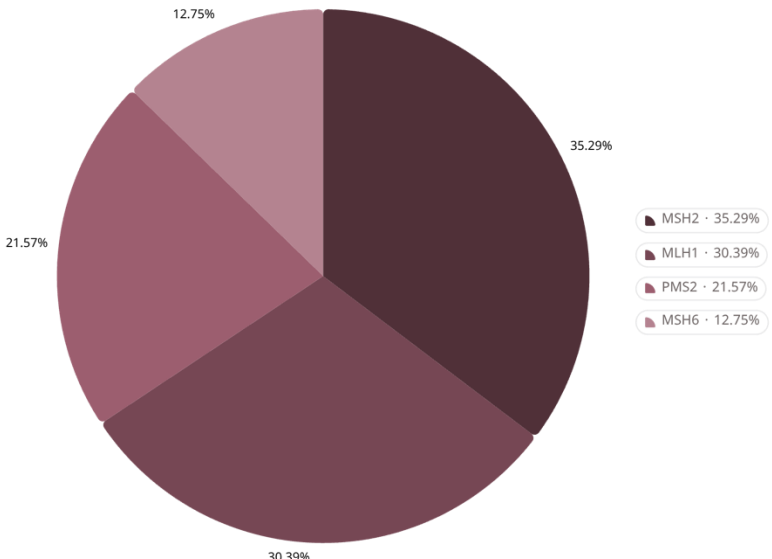
MSI-High
Microsatellite instability high (17/24 tested)

Tumor Categories



40% of all cases were **colorectal cancer**. CNS tumors included 7 high-grade gliomas. Hematologic malignancies are atypical for LS — more commonly seen in CMMRD.

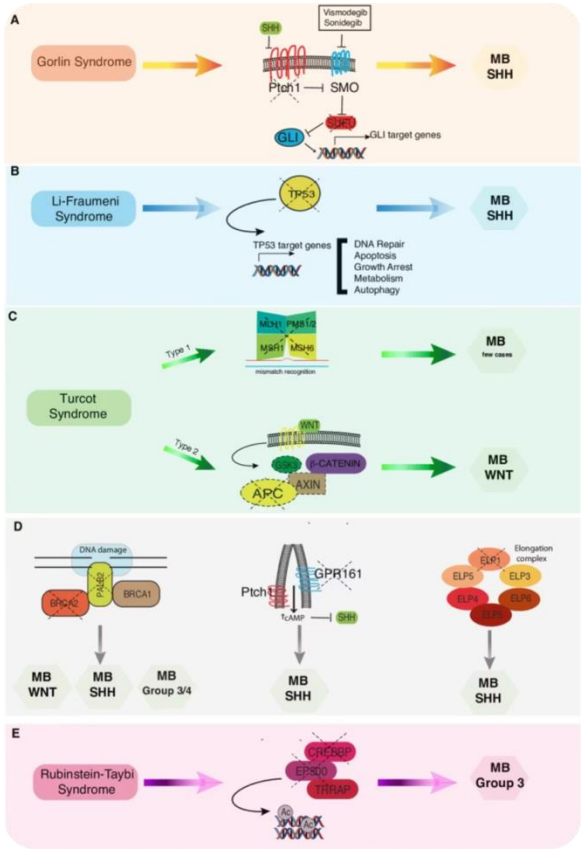
Gene Distribution



Current Guidelines

Childhood LS screening not recommended; genetic testing not advised before age 18. Retrospective data do not yet warrant guideline change.

CPS & Medulloblastoma Subtypes



Correlations between cancer predisposition syndromes and medulloblastoma molecular subtypes. (A) Gorlin syndrome (PTCH1/SUFU) → MB-SHH. (B) Li-Fraumeni syndrome (TP53) → MB-SHH. (C) Turcot type 1 (MMR) → MB-WNT; Turcot type 2 (APC) → MB-WNT. (D) BRCA2, PALB2, GPR161, ELP genes → various subtypes. (E) Rubinstein-Taybi syndrome (CREBBP/EP300) → MB Group 3.

Carta et al. 2020, Front. Oncol.

CHAPTER 05 — EMERGING GENES

New Cancer Predisposition Genes: The DDR Pathway Frontier

Next-generation sequencing is uncovering novel germline predisposition genes, fundamentally expanding the CPS landscape beyond c lassical syndromes. Analysis of **DNA Damage Response (DDR)** pathway perturbations has led to four validated new gene:cancer associations.

SMC5 → Medulloblastoma

Germline loss-of-function variants in **SMC5** (structural maintenance of chromosomes) predispose to medulloblastoma. Validated in three replication cohorts with evidence of biallelic tumor inactivation — a hallmark of tumor suppressor behavior.

BRCA1 → Ependymoma & HGG

Germline **BRCA1** variants — classically linked to breast/ovarian cancer in adults — have been associated with pediatric ependymoma and high-grade glioma, expanding the phenotypic scope of this well-known gene. *(Pre-print: needs validation)*

SPIDR → High-Grade Glioma

SPIDR (scaffolding protein involved in DNA repair) alterations associate with pediatric high-grade glioma — a tumor type already enriched for CPS. This represents a new DDR-related predisposition entry point.

SMARCAL1 → Osteosarcoma

SMARCAL1 (SWI/SNF-related chromatin remodeling) germline variants predispose to osteosarcoma. Biallelic inactivation confirmed in tumor tissue, establishing causality and potential for therapeutic exploitation via HRD vulnerability.

Ninad Oak et al. 2025, Biology of Neoplasia

MYCN Microduplications & New Diagnostic Imperatives

Germline duplication of *MYCN* predisposes to childhood embryonal tumours

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eBioMedicine
2026;124: 106132

BACKGROUND

Neuroblastoma & Wilms tumour (WT) are common childhood embryonal malignancies linked to germline 2p24 duplications involving **MYCN** and **DDX1**.

METHODS

WGS analysis of **113,431 genomes** — structural/CNV workflow, 2 kb–20 Mb duplications at 2p24 loci, Fisher's exact test & Bayesian penetrance estimation.

Key Finding

6 participants with MYCN-inclusive microduplication — **2 WT, 1 neuroblastoma**

Significance

3/197 cases vs 3/113,234 controls **($p < 0.0001$)**

Penetrance

Estimated at **~13%** by Bayesian calculation

DDX1 Alone

12 carriers — **no** childhood embryonal tumours observed

MYCN-inclusive 2p24.3 microduplications should be **routinely assessed** in WT/neuroblastoma predisposition workups.

Why New Genes Change Clinical Practice

Expand Diagnostic Panels Now

Panel multigene testing with ≥50 genes, WES, or WGS should include newly validated genes. Patients tested with older panels may need re-evaluation.

Biallelic Inactivation as Therapeutic Target

Biallelic inactivation of DDR genes (SMARCAL1, SMC5) creates homologous recombination deficiency — a potential vulnerability to PARP inhibitors and platinum-based chemotherapy.

Inform Clinical Trial Eligibility

Patients with newly identified germline DDR gene alterations may qualify for genomically stratified or basket trials targeting DNA repair deficiency.

CHAPTER 06 — THERAPEUTIC IMPLICATIONS

CPS & Treatment: A Syndrome-by-Syndrome Quick Reference

The identification of a cancer predisposition syndrome is not the end of the diagnostic workup — it is the **beginning of a personalized therapeutic roadmap**.

Syndrome	Gene(s)	Treatment Caution / Contraindication	Targeted / Emerging Therapy
Li-Fraumeni	TP53	Minimize radiotherapy — high secondary tumor risk	WEE1 inhibitor + vincristine (SHH-MB); ICI (nivolumab/ipilimumab) in PD-L1-high
Gorlin (PTCH1)	PTCH1	Radiotherapy absolutely contraindicated	Vismodegib (Hedgehog inhibitor); PI3K/CDK4/6 inhibitors (preclinical)
Gorlin (SUFU)	SUFU	Radiotherapy contraindicated; 20× higher MB risk	Itraconazole; combination inhibitors (AKT, FGFR)
NF1	NF1	Avoid unnecessary surgical debulking in OPG	Selumetinib / trametinib (OPG, plexiform NF); CAR-T, oHSV (emerging)
CMMRD / Lynch	MLH1/MSH2/MSH6 /PMS2	Alkylating agents may be less effective	Anti-PD-1 immunotherapy (pembrolizumab) — high MSI drives response
ATRT	SMARCB1, SMARCA4	No specific contraindication established	EZH2 inhibitors; AURKA inhibitors; immunotherapy under evaluation
New DDR genes	SMARCAL1, SMC5	None firmly established yet	PARP inhibitors, platinum sensitivity (HRD vulnerability — preclinical)

Take Home Messages

CPS Are Not Rare — Actively Seek Them

8–18% of pediatric cancers have a germline origin. Predisposition syndromes must be **actively investigated** in every patient, not merely considered as a possibility.

The Syndrome Determines the Treatment

CPS can radically change treatment decisions — radiotherapy is contraindicated in Gorlin, targeted therapies are indicated in NF1 and LFS. Knowing the syndrome saves lives and prevents harm.

Use Extended Sequencing — Include New Genes

Multigene panels with ≥50 genes (or WES/WGS) are the current standard. SMC5, SPIDR, SMARCAL1, and BRCA1 (ependymoma) must be included. Older negative panels may require re-testing.

Don't Miss Mosaicism

Standard germline testing misses low-VAF mosaic variants. Ultra-sensitive NGS is essential in clinically suggestive cases, particularly ATRT, CPC, and GS with atypical presentation.

Think Beyond the Patient — Think Family

A germline diagnosis implies a family diagnosis. Cascade testing, genetic counseling, and reproductive options must be offered to all first-degree relatives as an integral part of care.

Thank You for Your attention