

Cancer Predisposition Syndromes: Investigations and Implications in the Cancer Survivorship Clinic

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I have no conflicts of interest

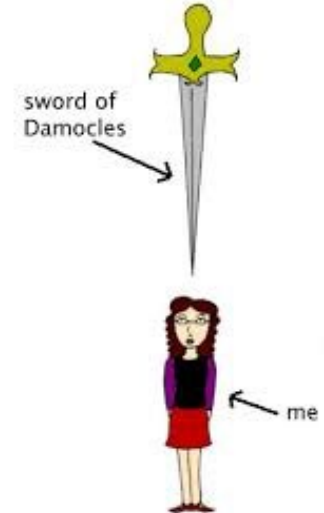


Objectives

- Recognise the features that raise suspicion for a cancer predisposition syndrome during the cancer diagnostic and survivorship journey
- Introduce an eHealth CPS screening tool
- Management considerations for pediatric and adolescent cancer survivors with cancer predisposition syndromes

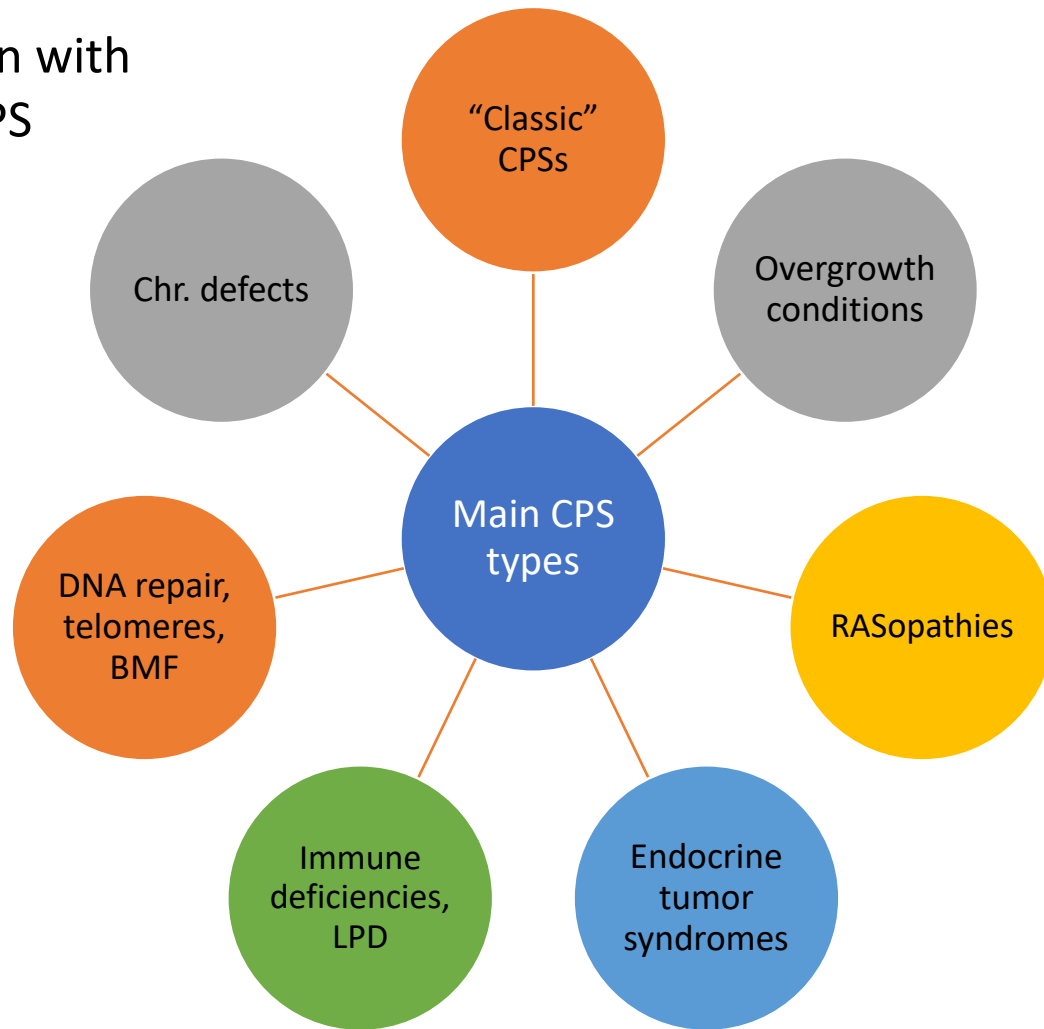
Cancer Predisposition Syndromes - 101

- “Genetic Tumor Syndromes” (WHO)
- > 150 cancer predisposing genes (> 50 CPSs) currently known to be associated with pediatric neoplasms
- **Why do we want to know about a CPS?**
 - Modify immediate cancer management
 - Detect other family members at risk
 - Implement surveillance +/- preventative measures
 - Understand the cause of cancer development
 - Family planning





8-10% of children with cancer have a CPS



Pediatric Oncologists perspective...then



Why this child?

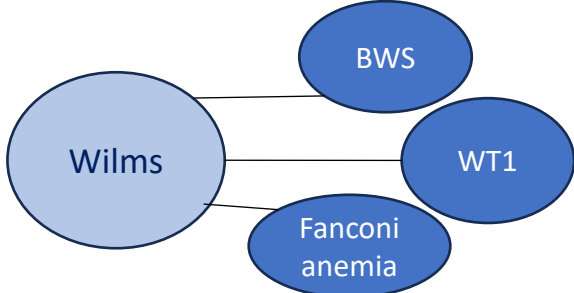
Is anyone else at risk?

Would it matter if a CPS was identified?

What does the child look like?

Should I refer to a genetics service?

Do I refer to genetics urgently?



Now...genetic predisposition to Wilms tumor

BWS **WT1**
Fanconi
anemia

TP53

CDC73

CREBBP

GPC3

BUB1B

NSD1

*PIK3CA**

SETB1

TRIM28

MSH6

MLH1

*DIS3L2**

MSH2

CTR9

DICER1

REST

TRIM37

AMER1

FBXW7

PMS2



Pediatric Oncologists perspective...now



Why this child?

Is anyone else at risk?

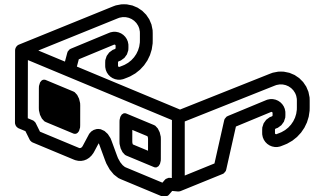
Would it matter if a CPS
was identified?

How should I
investigate?

Research vs clinical vs
both?

**What if I miss
something?**

CPS screening/prediction and diagnostic strategies in pediatric oncology





**60-70% of
patients develop
cancer prior to
CPS recognition**

- Family histories - can be misleading
- Young patients, young families
- Absence of dysmorphic features or non-cancer manifestations
- Non-cancer features not severe enough to seek MD care
- Expanding # cancer genes
- Expanding tumor spectrums in CPS
- CPS definitions are changing
- Variable disease penetrance
- Variable MD expertise
- Communication

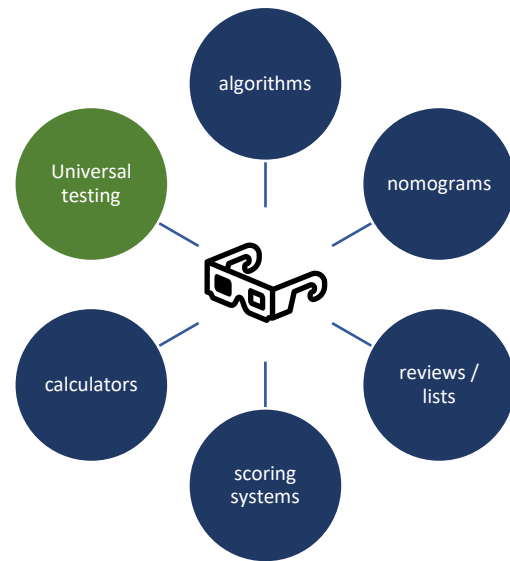
CPS screening strategies

Genotype-driven approach

- **Performing** germline DNA sequencing on **all** children diagnosed with cancer
- **Using** genetic information from the tumor to inform CPS evaluation

Phenotype-driven approach

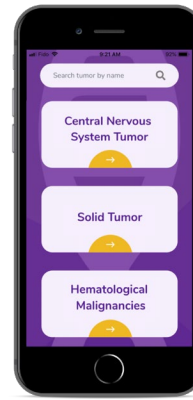
- **Identifying patients who need genetic evaluations:**
 - Malignancy type
 - Congenital anomalies
 - Family history, etc
- **Using** phenotype to **orient** testing strategies or to save time



Studies correlating genotype / phenotype driven approaches in pediatric oncology

	Byrjalsen, 2020 Denmark	Wagener, 2021 Germany	Bakhuizen, 2023 The Netherlands
Population	n=198 <18 y, any cancer	n=160 < 19 y, any cancer	n=824 < 19 y, any cancer
CPS (%)	14.6% 10.6% peds (n=21) 4.5% adult (n=9)	6.9% (n=11)	8.6% (n=71)
Phenotype (P) vs genotype (G)	P: 19/21 and 2/9 G: 2/21 and 6/9	P: 10/11 G: 1/11	P: 68 /71 G: 3/71
Discrepancies	OST/ TP53 ALL/ TP53	HGG/ Lynch	HGG/ TP53 x 2 1 U
Referral rate PPV	35.4% PPV 25.7% (peds)	31.9% PPV 19.6%	22.6% PPV 36.5%

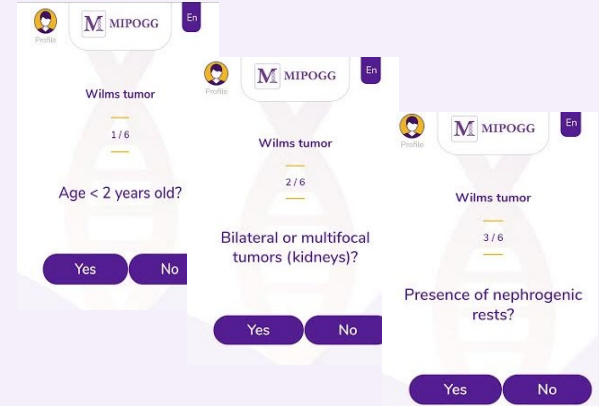
McGill Interactive Pediatric OncoGenetic Guidelines



- Helps clinicians identify **which patients need to be referred to genetics** for the work-up of a CPS
- >140 tumor-specific decisional algorithms based on:
 - Tumor features
 - Personal history and family history features
- Can be run at **any timepoint** in the cancer journey

Step 1. Click on a tumor type

Step 2. Answer Yes/No questions



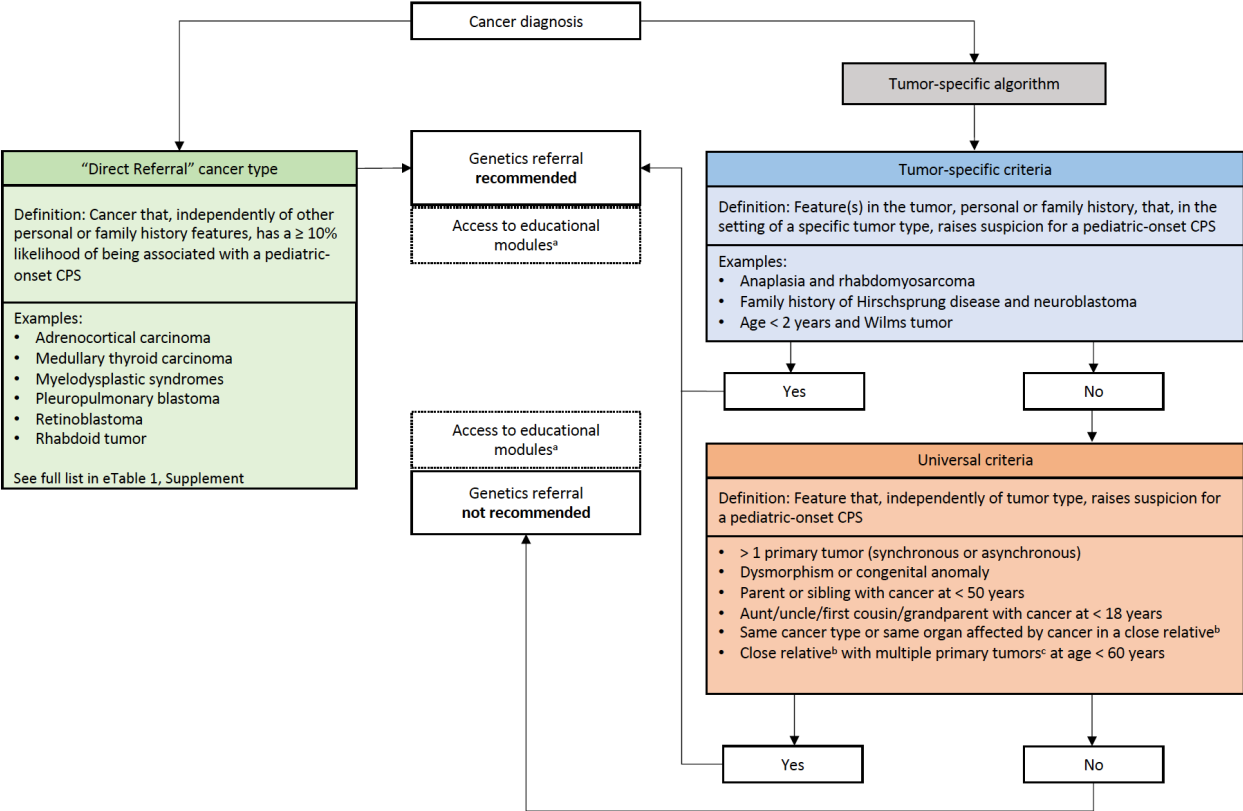
Step 3. App makes recommendation for/against referral for genetic evaluation, based on low/high likelihood of a CPS.

Step 4. Access to educational modules on tumor-CPS associations and relevant literature

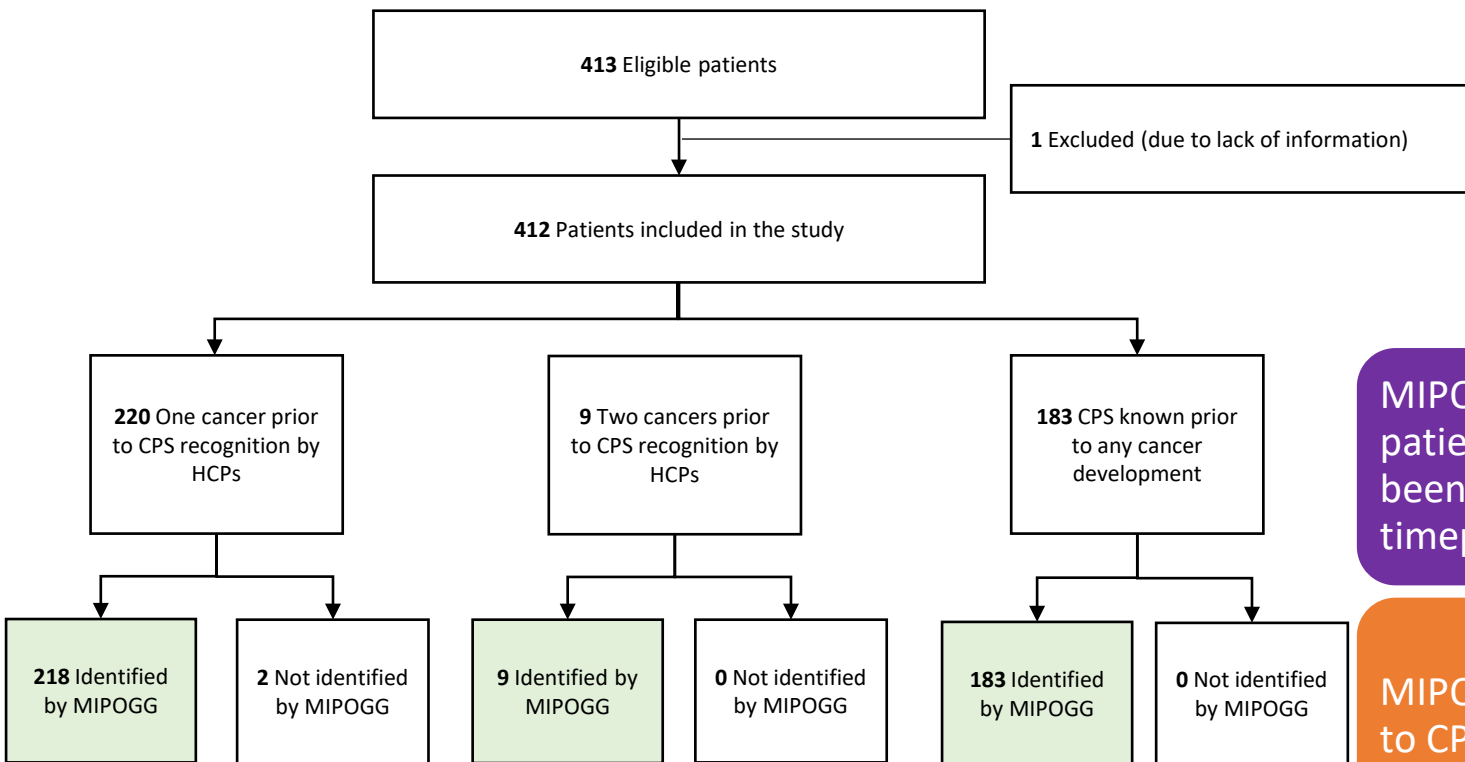


What features are suggestive of CPSs in children with cancer?

- Cancer type
- Cancer presentation
- Pathology / molecular / cytoG features
- Personal history
- Family history



Did MIPOGG perform as well as physicians?



MIPOGG identified >99% of patients with a CPS who had been detected at various timepoints by physicians

MIPOGG can decrease time to CPS recognition

Great! MIPOGG seems to work...

Not good enough...

MDs recognize “clear cut cases”



Retrieved from <https://artsugar.co/products/pheochromocytoma>



Screening accuracy of MIPOGG in children with cancer who underwent extensive germline sequencing?

Research

JAMA Oncology | **Original Investigation**

Performance of the McGill Interactive Pediatric OncoGenetic Guidelines for Identifying Cancer Predisposition Syndromes

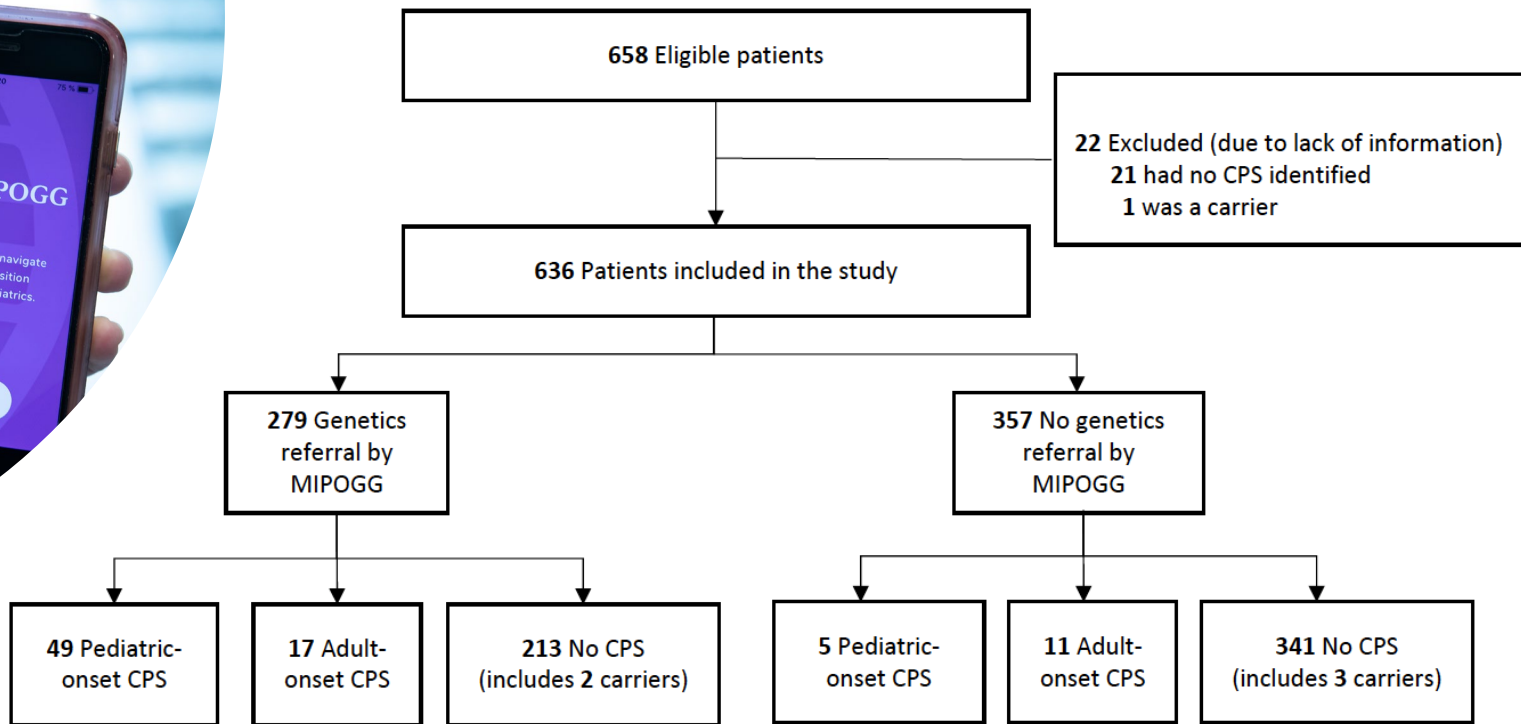


Dana-Farber/Boston Children's Cancer and Blood Disorders Center



Centre intégré universitaire de santé et de services sociaux de l'Estrie – Centre hospitalier universitaire de Sherbrooke





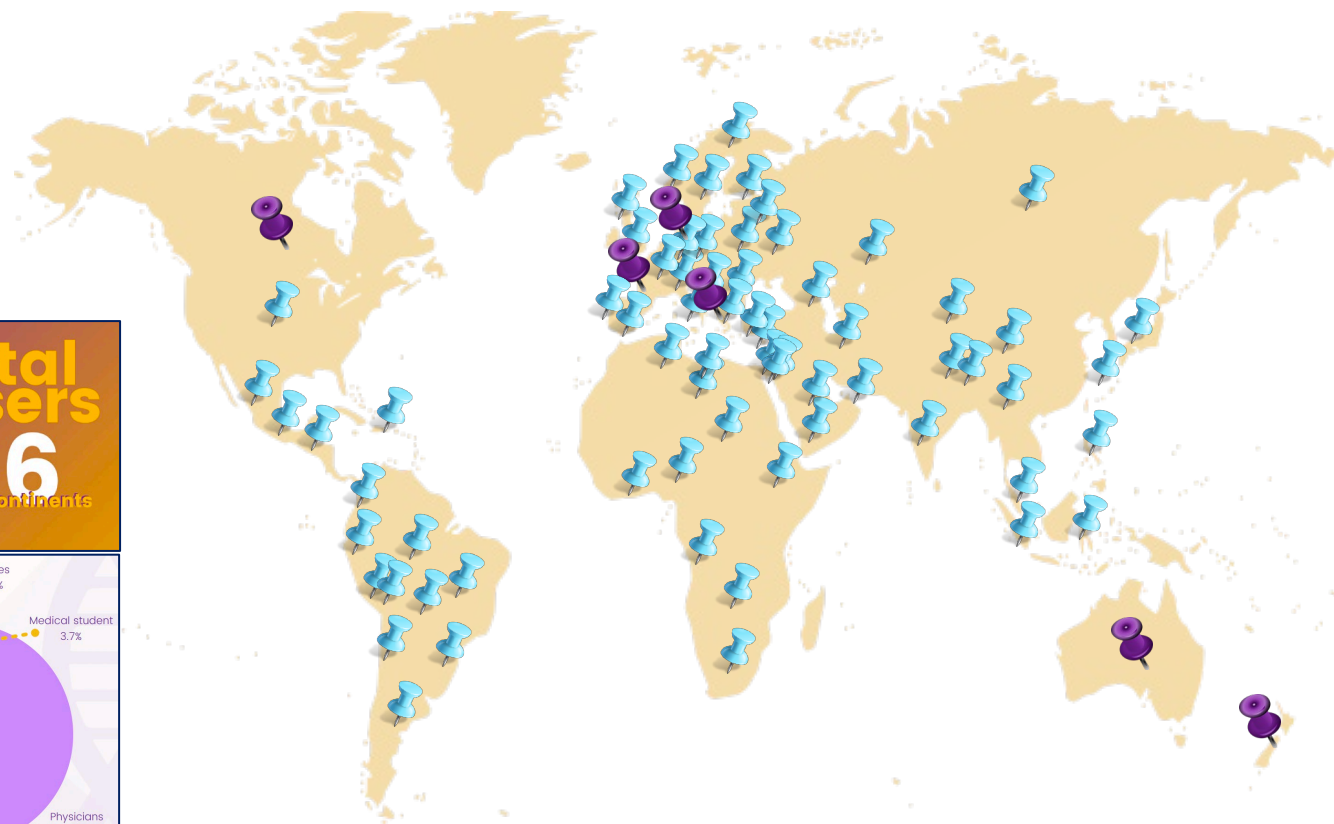
SE 90.7%
SP 60.5%
PPV 17.6%
NPV 98.6%

Utility of a Cancer Predisposition Screening Tool for Predicting Subsequent Malignant Neoplasms in Childhood Cancer Survivors

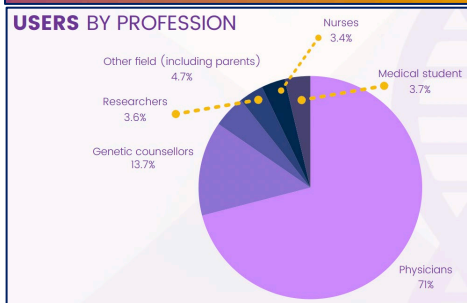
Noelle Cullinan, MD^{1,2}; Ian Schiller, MSc³; Giancarlo Di Giuseppe, MPH^{4,5}; Mohammed Mamun, PhD¹; Lara Reichman, MSc⁶; Chantel Cacciotti, MD^{7,8}; Laura Wheaton, MD⁹; Kimberly Caswell, BSc¹; Bruna Di Monte, BScN⁴; Paul Gibson, MD⁷; Donna L. Johnston, MD¹⁰; Adam Fleming, MD⁷; Jason D. Pole, PhD^{5,11}; David Malkin, MD¹; William D. Foulkes, PhD¹²; Nandini Dendukuri, PhD³; Catherine Goudie, MD^{6,13}; and Paul C. Nathan, MD¹

MIPOGG was predictive of SMN development in childhood cancer survivors, after controlling for therapy exposures

- Nested case-control study using provincial registry data (POGONIS/Ontario Cancer Registry)
 - Childhood cancer survivors (CCS) who developed SMNs (n=317) matched by primary cancer type and year of diagnosis with CCS who did not develop SMNs (n= 1,569 controls)
 - MIPOGG genetic evaluation output (at the time of first cancer diagnosis), chemotherapy and radiation exposures
- MIPOGG output recommending a genetic evaluation was associated with a HR 1.53 (CI 1.06-2.19) of SMN development (multivariable model with cancer type and therapy exposures)
 - Highest value for solid tumors & non-exposure to radiation

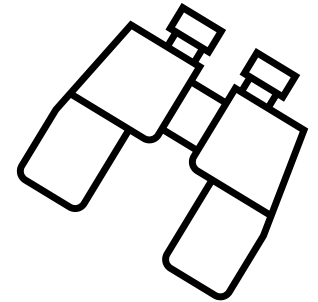


2135 total users
85 & 6 countries & continents



Cancer Survivorship clinics

Investigation and Management of CPSs



Anastasia's story



Time.....

Longitudinal follow-up of the patient and their family

Progress in our knowledge of cancer predisposition syndromes

Advances in sequencing technologies / Expansion of genetic investigation options



CPS – Cancer survivor combo...

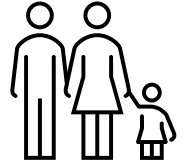


Practical aspects

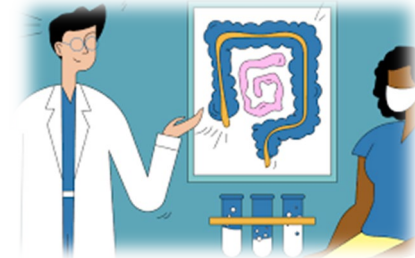
- Appointments, duplication, coordination
- Finding “homes” for these patients (adult care)

Risk assessment and priorities

- Tailored surveillance strategies
- Prevention strategies
- Fertility and family planning



Dealing with uncertainty...



Investigating for CPS in cancer survivors

Time



**Emotional &
Psychosocial &
Familial burden**



**Patient – Doctor
relationship**

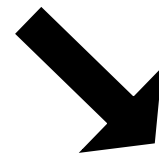
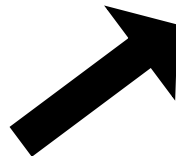


Family history questionnaires

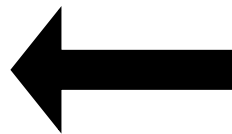
Research initiatives

Genetic counselors

Decision-aids / apps



CPSs extend beyond the
primary “active” cancer
setting



Special Thanks

la fondation
de l'hôpital
de montréal
pour enfants
the montreal
children's
hospital
foundation



POGO
PEDIATRIC ONCOLOGY GROUP OF ONTARIO

Patients & Families



**TD READY
COMMITMENT**

SickKids | Garron Family
Cancer Centre



CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche
en santé du Canada

Leora Witkowski
Lara Reichman
Claire Freycon
Crystal Budd
Claudie Saulnier

William Foulkes
Anita Villani
David Malkin
Paul Nathan
Meredith Irwin
Bartha M Knoppers
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Yvonne Bombard
Noemi-Fuentes Bolanos
Noelle Cullinan
Orli Michaeli
Nicolas Waespe
Kalene van Engelen
Marjolijn Jongmans
Uri Tabori

Nada Jabado
Hallie Coltin
Vincent-Philippe Lavallée
Sonia Cellot
Carol Provost



CF Fondation
Cole
Foundation

 **Fondation
Charles-Bruneau**

**Fonds de recherche
Santé**

Québec



**GREAT
CYCLE
CHALLENGE**



**Cancer
Research Society**

**BITE
SIZE**
ENTERTAINMENT

Centre universitaire
de santé McGill



McGill University
Health Centre

LE FONDS DE
SARAH
DES CÉDRÉS



**SARAH'S
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Kim E Nichols
Junne Kamihara



MIPOGG