ANALYSIS CONCEPT PROPOSAL

1. Title: Long-term cost-effectiveness of cancer predisposition syndrome identification strategies in survivors of pediatric leukemia, brain tumors or bone/soft-tissue sarcomas

2. Investigators and Working Groups

2.1 Working groups

Primary: Biostatistics/Epidemiology
Secondary: Secondary Malignancy, Cancer Control and Intervention, Genetics

2.2 Investigators

Name	Email	Affiliation
Catherine Goudie MD	catherine.goudie@mcgill.ca	McGill University Health Centre
Petros Pechlivanoglou PhD	petros.pechlivanoglou@sickkids.ca	The Hospital for Sick Children Research Institute
Lindsay Morton PhD	mortonli@mail.nih.gov	Division of Cancer Epidemiology and Genetics, NCI
Paul Nathan MD, MSc	paul.nathan@sickkids.ca	The Hospital for Sick Children Research Institute
Yutaka Yasui	yutaka.yasui@stjudes.org	Epidemiology and Cancer Control Department, St Jude Children's research Hospital
Juan David Rios MA	david.rios@sickkids.ca	The Hospital for Sick Children Research Institute
Frances Simbulan MSc Candidate	frances.simbulan@sickkids.ca	Health Technology Assessment, University of Toronto
Lara Reichman MSc	lara.reichman@rimuhc.ca	McGill University Health Centre
Kimberly Caswell BSc	kimberly.caswell@sickkids.ca	Research Institute - Hospital for Sick Children
Stephen W. Hartley PhD	stephen.hartley@nih.gov	Division of Cancer Epidemiology and Genetics, NCI
Danielle Karyadi PhD	karyadid@mail.nih.gov	Division of Cancer Epidemiology and Genetics, NCI

Melissa Tachdjian BA	melissa.tachdjian@rimuhc.ca	Research Institute - McGill University Health Centre
Leora Witkowski PhD	leora.witkowski@muhc.mcgill.ca	Human Genetics, Research Institute - McGill University Health Centre
Joe Neglia MD, MPH	jneglia@umn.edu	Division of Pediatric Hematology and Oncology- University of Minnesota
Wendy Leisenring Sc.D	wleisenr@fredhutch.org	Division of Clinical Research – Fred Hutch
Gregory Armstrong MD, MSCE	greg.armstrong@stjude.org	Division of Neuro-Oncology – St-Jude Children's Research Hospital
Smita Bhatia MD, MPH	sbhatia@peds.uab.edu	Department of Pediatrics – The University of Alabama at Birmingham

3 Background and Rationale

Between 8-10% of childhood cancers are attributed to one of over 125 known cancer predisposition syndromes (CPSs).[1–3] A CPS diagnosis carries a risk of developing multiple cancers over a lifetime, a heavy physical and psychological burden for a patient and their family. For example, a retrospective study cohort of patients with Li-Fraumeni syndrome, a common CPS, found that a 50% of patients who developed a primary cancer would go on to develop a second malignant neoplasm (SMN).[4] In other CPS types, such as hereditary retinoblastoma (germline variant in *RB1*), there is a significantly increased risk for SMN development, particularly in the setting of previous chemotherapy and radiation.[5] CPS identification can lead to direct treatment modifications and implementation of tumor surveillance strategies, which can result in earlier subsequent cancer detection and improved outcomes. Currently, genetic evaluation for a CPS in a child diagnosed with cancer is performed at the discretion of their physician. There is no standardized approach for clinicians to decide which children require genetic evaluation for a CPS. This "physician-guided" approach leads to missed opportunities for early CPS recognition and rapid intervention. In contrast, some experts advocate for genetic testing in all children with cancer.[3] This "universal genetic testing" approach requires significant healthcare resources.

To improve physician detection of a CPS, our team developed an eHealth CPS decision-support tool called the *McGill Interactive Pediatric OncoGenetic Guidelines* (*MIPOGG*).[6] MIPOGG consists of 140 tumor-specific decisional algorithms that generate a recommendation for "referral" or "no referral" for genetic evaluation based on a child's likelihood of a CPS. MIPOGG uses clinical, family history and tumor-specific features to streamline genetic referrals and testing. MIPOGG can be applied at the time of primary cancer diagnosis or at any timepoint in the survivorship journey; it is the first evidence-based tool that incorporates all known CPS types for all pediatric cancers. MIPOGG promises to better care for survivors by identifying those people at higher risk of a CPS and granting them access to the option of genetic testing.

There are multiple challenges in quantifying the impact of genetic testing and CPS diagnosis: A variety of actions follow the detection of a CPS in a child with cancer. These actions vary according to timing of CPS detection as well as type of CPS, and include the implementation of tumor surveillance protocols, genetic counseling/testing of at-risk family members, and the possibility of adapting cancer therapy. The use of tumor surveillance protocols was shown to decrease morbidity and mortality in certain CPSs.[7] Nevertheless, quantifying long-term clinical and economic impacts of CPS detection on patients and families is challenging due to the prolonged follow-up needed to observe the benefits of surveillance on outcomes such as SMN occurrence. This is complicated by the heterogeneity of patient populations and CPS subtypes, and limited evidence regarding the effectiveness of many tumor surveillance strategies considering this field's novelty. This lack of information can make it challenging for clinicians and patients to make decisions about genetic testing and CPS identification. It also makes it difficult for healthcare payers (whether governmental or private) to understand the benefit of reimbursing these types of services for survivors.

To inform the public healthcare payer's decisions on the impact of CPS detection strategies that result in efficient health resource utilization, this study will evaluate the cost effectiveness of genetic testing strategies for CPS detection in pediatric patients with cancer. We will develop a discrete-event simulation model assuming a lifetime horizon to estimate the long-term clinical and economic consequences of CPS detection strategies: physician-based (standard of care), MIPOGG-based, and universal genetic testing.

4. Specific aims/objectives/research hypotheses:

4.1 Study aims: To inform a cost-effectiveness model which compares the long-term impact of three CPS detection strategies in pediatric patients diagnosed with pediatric acute lymphoblastic leukemia (ALL), bone/soft-tissue sarcomas (bone/STS) and brain tumors. The three genetic evaluation strategies are: physician-based, MIPOGG-based, and universal genetic testing.

Model parameters will be informed from a combination of existing data from CCSS on the incidence of SMN in cancer survivors and the discovery germline whole exome sequencing data originating from the ongoing collaborative work between National Cancer Institute (NCI) and CCSS. Model parameters may also be complemented by data from Surveillance, Epidemiology, and End Results (SEER), Cancer in Young People in Canada (CYP-C) registry, existing literature and costing data from Canadian sources.

5. Analysis framework

5.1 Cost effectiveness model:

We will build a decision analytic model to estimate the lifetime genetic sequencing and post-sequencing surveillance on healthcare costs and on the length and quality of life for patients diagnosed at a Canadian tertiary hospital with acute lymphoblastic leukemia (ALL), bone/soft-tissue sarcomas (bone/STS) and brain tumors in pediatric age. We will be modelling outcomes from the decision to refer (or not) for CPS genetic testing until death. We are using a lifetime horizon as the intervention effects are expected to span over the duration of the population's lifetime.

The three CPS detection strategies:

- **MIPOGG:** Individuals are referred for CPS evaluation based on MIPOGG recommendations.
- **Physician referred:** Individuals are referred for CPS evaluation based on observed physician practice. (data will be leveraged from preliminary work and existing MIPOGG database at the Hospital for Sick Children to estimate physician referral practices).
- **Universal testing:** All individuals undergo comprehensive germline testing through next-generation sequencing technology for CPS.

Data will be leveraged from preliminary work and existing MIPOGG database at the Hospital for Sick Children to estimate physician and MIPOGG referral practices. The MIPOGG database allows us to estimate the probability of a MIPOGG referral conditional on a set of clinical characteristics that were collected through chart review. Data from CCSS will not be used to inform the MIPOGG decision support tool, or any other strategy referral strategy.

The costs and impacts of the three strategies above will be estimated using a combination of a decision tree and discrete-event-simulation model.[8] Within the decision tree, we will model genetic referrals/counseling/testing, and CPS types detected for each of the three genetic evaluation strategies. Patients exit the decision tree, with one of three CPS statuses: "CPS detected", "no CPS", or "unknown CPS" status. Afterwards, individuals enter a discrete-event simulation which models surveillance, and the diagnosis and management of SMN according to the timing of detection over an individual's lifetime (**Figure 1**).

We will assign costs from the perspective of a Canadian public healthcare payer. These costs include: healthcare costs associated with genetic counseling and testing, SMN surveillance protocols (i.e. hospital visits, imaging, bloodwork) and the diagnosis and management of SMN. We will also source costs from other jurisdictions, such as the United States, to expand the generalizability of the cost-effectiveness model.

The cost-effectiveness analysis health outcomes will include frequency and time to CPS detection, frequency and type of SMN, quality-adjusted life years (QALY- a composite metric of life expectancy and quality of life), and overall survival. Cost outcomes will include cost per additional CPS diagnosis, cost per life-year gained and cost per QALY gained. If appropriate, we will calculate incremental-cost effectiveness ratios and compare them to commonly used thresholds.

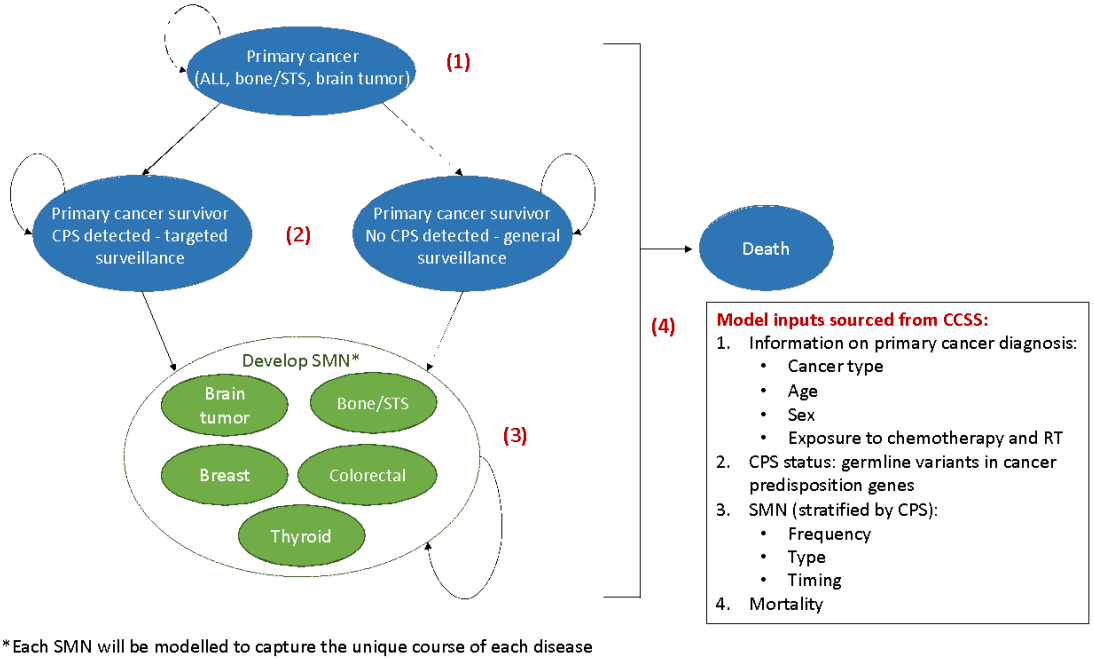

Figure 1. Discrete-event simulation model. All simulated patients start in a primary cancer state that may move through primary cancer remission, progress to SMN-related health states or may remain in their current health state. Patients in cancer remission may either be in CPS-targeted surveillance if CPS is detected or in general surveillance if no CPS is detected. At all health states, simulated patients are susceptible to death from SMN-related cause or all other causes. ALL, acute lymphoblastic leukemia; STS, soft-tissue sarcoma; CPS, cancer predisposition syndrome; SMN, subsequent malignant neoplasm.

5.2 Study population

Our study population used to estimate model parameters will include:

1. Survivors of ALL (N=1501), bone/STS (N=964), and brain tumors(N=119), who have undergone germline whole exome sequencing as part of the collaboration between NCI and CCSS.
2. Survivors of any cancer type who have developed any SMN (N=906), with focused analyses of the following specific types: brain tumor (N=207), breast cancer (N=239), bone/STS (N=90), colorectal cancer (N=35), or thyroid tumor (N=136) and who have undergone germline sequencing as part of the collaboration between NCI and CCSS

5.3 Outcome(s) of interest:

Model inputs to be collected from CCSS (and related publications):

1. Clinical characteristics of the simulated cohort:
    a. Primary cancer type
    b. Age at primary cancer diagnosis
    c. Sex
    d. Whether a patient received treatment with chemotherapy? (Y/N). If yes received the following:
        i. Alkylating agents? (Yes/No)
        ii. Anthracyclines? (Yes/No)
        iii. Platinums? (Yes/No)

iv. Epipodophyllotoxines? (Yes/No)

e. Whether a patient received radiation therapy, as well as radiation field (and radiation dose for the modelling related thyroid malignancies as a SMN).
f. CPS status. Where the presence of a CPS will be defined as having a "pathogenic" or "likely pathogenic" germline variant in one of the cancer predisposition genes listed in **Appendix 1**. We will use the interpretation of pathogenicity currently used by the NCI and collaborate closely with their bioinformatics team for unique queries and updates regarding potential changes in the interpretation of certain variants as time advances. The absence of a CPS will be defined as having no variant identified or having a variant of uncertain significance, a likely benign or benign variant in one of the previously listed cancer predisposition genes.

2. Probability of developing various types of SMN conditional on CPS status, primary cancer diagnosis, and primary cancer treatment (e.g. receiving radiation, anthracyclines, alkylating agents, epipodophyllotoxin).
3. All-cause mortality (time from diagnosis to death or censoring) using data from the National Death Index (NDI.
4. SMN cause-specific mortality (time from primary cancer diagnosis to diagnosis of SMN, death or censoring).

5.4 Analytic plan:

Outcome 1- Clinical characteristics of simulated cohort: Initially, we will estimate descriptive statistics for the population, including CPS status, using medians and interquartile ranges for continuous variables and frequencies (counts and percentages) for categorical outcomes (**Table 1)**. Subsequently and in order to simulate the population of interest in our decision model, we will estimate a series of regression models that describe the association between all the baseline characteristics (i.e., present at the time of primary cancer diagnosis). These regression models, when used jointly, can adequately inform the characteristics of a synthetic (simulated) cohort. This synthetic cohort will look similar to the original data, will maintain the joint relation across the baseline characteristics but without compromising in any way the privacy of the original de-identified data.

Outcome 2 - Probability of developing a SMN: Initially, we will descriptively present the probability of remaining SMN free over time from diagnosis to maximum end of follow up using a Kaplan Meier curve. We will then fit survival distributions on data from the CCSS study cohort where the event of interest is time between primary cancer diagnosis and SMN diagnosis, where death is treated as a competing event. We will use a survival regression approach to incorporate baseline and time dependent covariates which can adjust for temporal (e.g. diagnosis cohort) and individual level differences in the data. We will select the best-fitting survival distribution as judged by Akaike Information Criterion (AIC), Bayesian Information Criteria (BIC) and clinical expertise. We will model independently the probability of developing a SMN stratified by location (brain, thyroid, breast, colon, sarcoma, etc.) stage and CPS status. (**Figure 2**). The best-fitting survival distribution will be used to inform the probability of a simulated individual of having a SMN diagnosis over time conditional on CPS status and other relevant covariates. These methods are commonly used in cost-effectiveness analyses and will allow us to

extrapolate predictions beyond the follow-up available within the CCSS data.[9] We will assess the impact of model fit on cost-effectiveness outcomes as well as the uncertainty generated by extrapolating survival outcomes.

Outcome 3- All-cause mortality: We will estimate all-cause mortality using similar methods as those used for outcome 2. We will fit survival distributions on the data from the CCSS study cohort where the event of interest is all-cause mortality (**Figure 3**). The best fitting distribution will be used to make extrapolations of all-cause mortality outside of the study period.

Outcome 4 - SMN related mortality: We will estimate SMN related mortality using similar methods as those used in outcome 2 and 3. We will fit survival distributions on the data from a subset of the CCSS cohort which were diagnosed with a SMN. The event of interest will be mortality due to a SMN, death from other causes will be treated as censoring. (**Figure 4**).

6 Special consideration:

Potential study limitations: We acknowledge that germline sequencing was performed in cancer survivors (who have survived more than 5 years after their cancer diagnosis) as this is the patient population included in the CCSS. We are currently lacking definitive evidence on whether the frequency of certain CPS types in cancer survivors is lower compared to patients with an initial cancer diagnosis. This may lead to a bias in the study population that informs the modelling. We will need to compare the frequency of germline findings in the CCSS cohort with the frequency of CPSs identified in newcomers with cancer. Recent publications and our collaboration with teams who are comprehensively sequencing children diagnosed with primary cancers will help contextualize CCSS germline findings.

We do not consider a “no testing” strategy in this analysis as this would not be the current standard of care in the majority of centres, especially in North America. However, the model will be designed in a flexible way to allow inclusion of additional strategies (e.g. no testing) with only minor modifications.

DNA collection for the sequenced populations was not collected completely at random due to competing risk of death, lost to follow up, presence of a subsequent neoplasm or location of treatment (St. Jude vs elsewhere). We will test the similarity of sequenced vs non sequenced cohorts of CCSS patients by comparing their baseline demographic and clinical characteristics, as well as their overall survival and SMN outcomes. If evidence of significant difference between the sequenced and non-sequenced cohorts, is found appropriate weighting methods will be used to reweight the sequenced cohort so that it resembles the overall cohort.

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Appendix 1. Proposed cancer predisposition gene list*

Genes	CPS covered	Cancers					
		ALL / AML	Bone / STS	Brain tumors	Breast cancer	Colorectal cancer	Thyroid cancer
APC	Familial adenomatous polyposis			x		x	x
ATM	Ataxia-telangiectasia	x			x		
BLM	Bloom syndrome	x				x	
BMPR1A	Polyposis					x	
BRCA1	Breast cancer predisposition				x		
BRCA2	Breast cancer predisposition				x		
BRIP1	Fanconi anemia	x					
CBL	Leukemia predisposition	x					
CDKN1B	MEN4						
CEBPA	Leukemia predisposition	x					
CHEK2	Breast cancer predisposition				x		
DICER1	DICER1 syndrome			x			x
DKC1	Dyskeratosis congenita	x					
EPCAM	CMMRD	x		x		x	
ETV6	Leukemia predisposition	x					
FANCA	Fanconi anemia	x					
FANCB	Fanconi anemia	x					
FANCC	Fanconi anemia	x					
FANCD2	Fanconi anemia	x					
FANCE	Fanconi anemia	x					
FANCF	Fanconi anemia	x					
FANCG	Fanconi anemia	x					
FANCI	Fanconi anemia	x					
FANCL	Fanconi anemia	x					
FANCM	Fanconi anemia	x					
GATA2	Leukemia predisposition	x					
GREM1	Polyposis					x	
MEN1	MEN1					x	x
MLH1	CMMRD	x		x		x	
MSH2	CMMRD	x		x		x	
MSH6	CMMRD	x		x		x	
MUTYH	Polyposis					x	
NF1	NF1		x	x			
NF2	NF2			x			
PALB2	Fanconi anemia, Breast cancer predisposition	x			x		
PAX5	Leukemia predisposition	x					
PMS2	CMMRD	x		x		x	
POLD1	CMMRD	x		x		x	
POLE	CMMRD	x		x		x	
PRKAR1A	Carney						x
PTCH1	Gorlin syndrome			x			
PTCH2	Gorlin syndrome			x			
PTEN	PTEN-hamartoma tumor syndrome				x	x	x
RAD50	Fanconi anemia	x					
RAD51	Fanconi anemia	x					

RAD51C	Fanconi anemia	x					
RAD51D	Fanconi anemia	x					
RB1	RB		x	x	x		
RECQL4	Rothmund-Thompson		x				
RET	MEN2						x
RTEL1	Dyskeratosis congenita	x					
RUNX1	Leukemia predisposition	x					
SLX4	Polyposis					x	
SMAD4	Polyposis					x	
SMARCA4	Rhabdoid tumor predisposition		x	x			
SMARCB1	Rhabdoid tumor predisposition		x	x			
SMARCE1	Meningioma predisposition			x			
STK11	Polyposis					x	
SUFU	Gorlin syndrome			x			
TERC	Dyskeratosis congenita	x					
TERT	Dyskeratosis congenita	x					
TINF2	Dyskeratosis congenita	x					
TP53	Li-Fraumeni syndrome	x	x	x	x		
TSC1	Tuberous sclerosis			x			
TSC2	Tuberous sclerosis			x			
VHL	von Hippel Lindau			x			
XRCC2	Fanconi anemia	x					
XRCC3	Fanconi anemia	x					

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CMMRD: constitutional mismatch repair deficiency; CPS: cancer predisposition syndrome; NF1: neurofibromatosis type 1; NF2: neurofibromatosis type 2; RB: retinoblastoma; STS: soft-tissue sarcoma

* This list is subject to change depending on the genes investigated via the collaboration between NCI and CCSS.

Appendix II Example tables and Figures:

	All (N =, 100%)	CPS detected (N =, %)	No CPS detected (N =, %)
Age at diagnosis, median (IQR)			
Year of diagnosis, median (IQR)			
Follow up, median (IQR)			
Primary cancer diagnosis, N (%)			
Bone/STS			
ALL			
Brain tumor			
Male, N (%)			
Received chemotherapy, N (%)			
Received radiation therapy, N (%)			

Appendix III

Example of MIPOGG algorithm questions for acute lymphoblastic leukemia

What is the tumor called?	_____
Date of cancer diagnosis	_____
Was the patient at least 1 year old at the time of cancer diagnosis?	◯ Yes ◯ No
What was the age of the patient, in years, at cancer diagnosis?	_____
What was the age of the patient, in months, at cancer diagnosis?	_____
Was this the first malignant tumor in the patient?	◯ Yes ◯ No ◯ Unknown ◯ N/A
If no, please specify	◯ Second ◯ Third ◯ Fourth ◯ >4
What was the first tumor type?	_____
Is this tumor bilateral?	◯ Yes ◯ No ◯ Unknown ◯ N/A
Is the tumor multifocal (i.e. multiple tumors in the same organ)?	◯ Yes ◯ No ◯ Unknown ◯ N/A
Acute lymphoblastic leukemia (ALL) specific questions	
ALL subtype	◯ T-cell ◯ B-cell ◯ Other ◯ Unknown
Please specify	_____
Does the patient have low-hypodiploid ALL (32-39 chromosomes)?	◯ Yes ◯ No ◯ Unknown
Evidence of cafe au lait spots on the patient?	◯ Yes ◯ No ◯ Unknown

How many cafe au lait spots?	◯ 1 ◯ 2-5 ◯ 6-10 ◯ >10 ◯ Unknown
Does the patient exhibit any of the following?	☐ Ataxia ☐ Ocular/skin telangiectasia ☐ Microcephaly (head circumference < 3rd perc) ☐ None ☐ Unknown
Is there a personal or family history of any of the following:	☐ Thrombocytopenia/ITP ☐ Neutropenia ☐ None ☐ Unknown

General information

Is there clear dysmorphism or known congenital anomaly in the patient?	◯ Yes ◯ No ◯ Unknown ◯ N/A
Describe dysmorphism/congenital anomaly	_____

Does the patient have a known syndrome/genetic disorder at the time of cancer diagnosis?	◯ Yes ◯ No ◯ Unknown ◯ N/A
What is the name of the syndrome?	_____
Was the family history taken at cancer diagnosis?	◯ Yes ◯ No ◯ Unknown ◯ N/A
Who took the family history at cancer diagnosis?	◯ Non-geneticist ◯ Geneticist (or genetic counsellor) ◯ Unknown ◯ N/A
Family history at cancer diagnosis	☐ Parent/sibling/half-sibling with cancer < 50 yrs ☐ Aunt/uncle/first cousin/grandparent with cancer < 19 yrs ☐ Same cancer type or same organ affected by cancer in parent, sibling/half-sibling, aunt/uncle, first cousin, grand-parent ☐ Parent, sibling/half-sibling, aunt/uncle, first cousin, grand-parent with multiple primary tumors (excluding non-melanoma skin cancer) before age 60 ☐ Sarcoma/breast cancer/brain tumor/leukemia/ACC/lung cancer in 1st or 2nd degree relative at age < 56 years ☐ Family history of cancer, but not meeting the previous criteria ☐ No family history of cancer ☐ Cancer predisposition syndrome known in the family ☐ Consanguinity ☐ Unknown ☐ N/A
Family history details at cancer diagnosis	_____
Was the patient seen in Genetics?	◯ Yes prior to cancer (for other health issues) ◯ Yes at or after cancer diagnosis ◯ No ◯ Unknown ◯ N/A
Reason for Genetics referral	☐ Cancer type ☐ Multiple primaries ☐ Family history ☐ Cancer predisposition syndrome in family ☐ Congenital anomaly/clinical suspicion of a syndrome ☐ Unknown ☐ Other ☐ N/A

Why was the patient referred to Genetics?	_____
Family history by Genetics	☐ Parent/sibling/half-sibling with cancer < 50 yrs ☐ Aunt/uncle/first cousin/grandparent with cancer < 19 yrs ☐ Same cancer type or same organ affected by cancer in parent, sibling/half-sibling, aunt/uncle, first cousin, grand-parent ☐ Parent, sibling/half-sibling, aunt/uncle, first cousin, grand-parent with multiple primary tumors (excluding non-melanoma skin cancer) before age 60 ☐ Sarcoma/breast cancer/brain tumor/leukemia/ACC/lung cancer in 1st or 2nd degree relative at age < 56 years ☐ Family history of cancer, but not meeting the previous criteria ☐ No family history of cancer ☐ Cancer predisposition syndrome known in the family ☐ Consanguinity ☐ Unknown ☐ N/A
Family history details by Genetics	_____
Name of cancer predisposition syndrome (in family)	_____
Was the patient sent for genetic testing?	◯ Yes ◯ No ◯ Unknown ◯ N/A
Who sent the patient for genetic testing?	◯ Non-geneticist ◯ Geneticist (or genetic counsellor) ◯ Unknown ◯ N/A
Date of first genetics consultation / testing	_____
What type of testing was done in the patient?	☐ Single gene/genes ☐ Panel ☐ WES ☐ Chromosomal testing (Cytogenetics) ☐ Methylation studies ☐ Familial variant ☐ Unknown ☐ Other ☐ N/A
Please describe the testing done	_____

Was a germline mutation found?	◯ Yes ◯ No ◯ Unknown ◯ N/A
What is the name of the syndrome associated with this mutation?	_____
Classification of mutation	◯ Pathogenic ◯ Likely Pathogenic ◯ VUS ◯ Likely Benign ◯ Benign ◯ N/A ◯ Unknown
Zygosity of mutation	◯ Heterozygous ◯ Homozygous ◯ Compound heterozygous ◯ Unknown
What year was genetic testing done?	_____
Gene involved	_____
DNA change (if available)	_____
Protein change (if available)	_____
What came first, the cancer or the cancer predisposition syndrome?	◯ Cancer ◯ Cancer predisposition syndrome ◯ Unknown ◯ N/A
Comments	_____

All algorithms: https://redcapexternal.research.sickkids.ca/surveys/?s=7L4FDJ8DYW

Table 1: Clinical characteristics of CCSS study used to generate the simulated cohort of pediatric patients diagnosed with ALL, bone/STS and brain tumors.

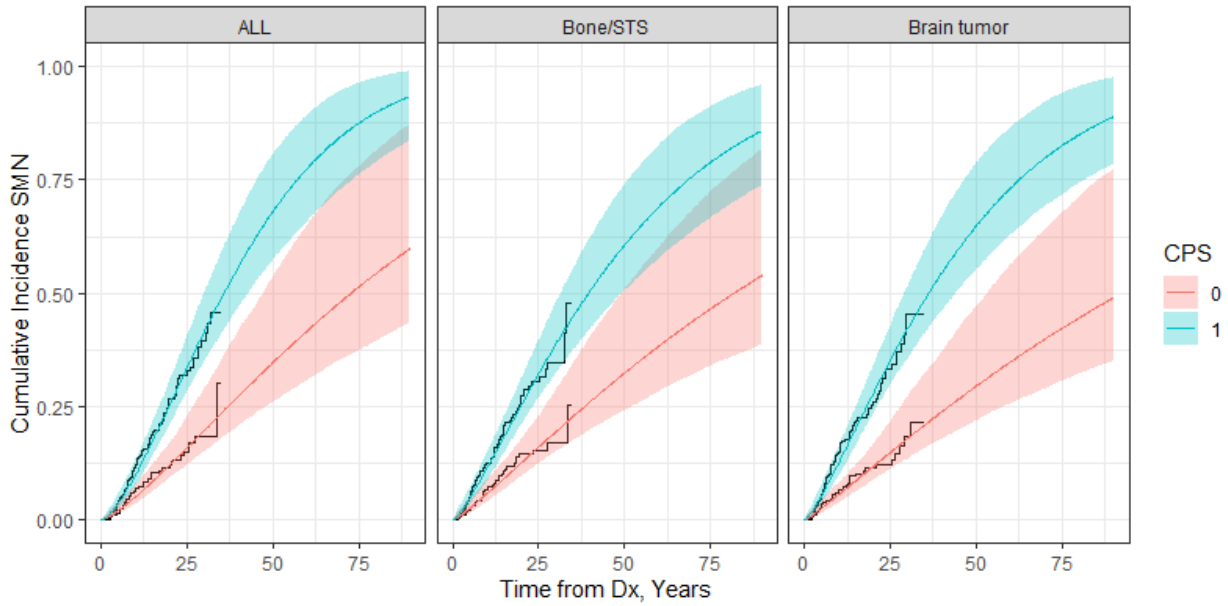

Figure 2: Cumulative incidence of SMN and extrapolated estimates from best fitting curve. Observed cumulative incidence in black. Extrapolated estimates and 95% confidence intervals sourced from the fitting distribution.

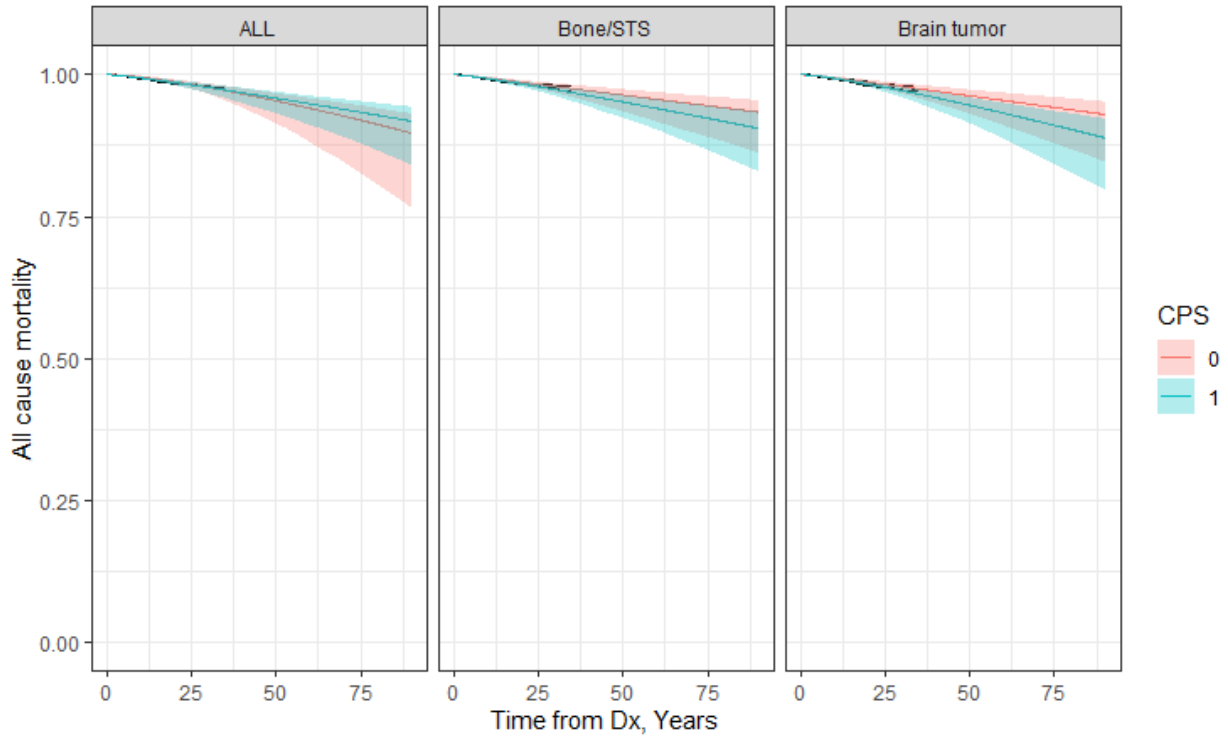

Figure 3: All-cause mortality stratified by CPS status. Kaplan-Meier estimates in black. Extrapolated estimates and 95% confidence intervals sourced from the fitting distribution.

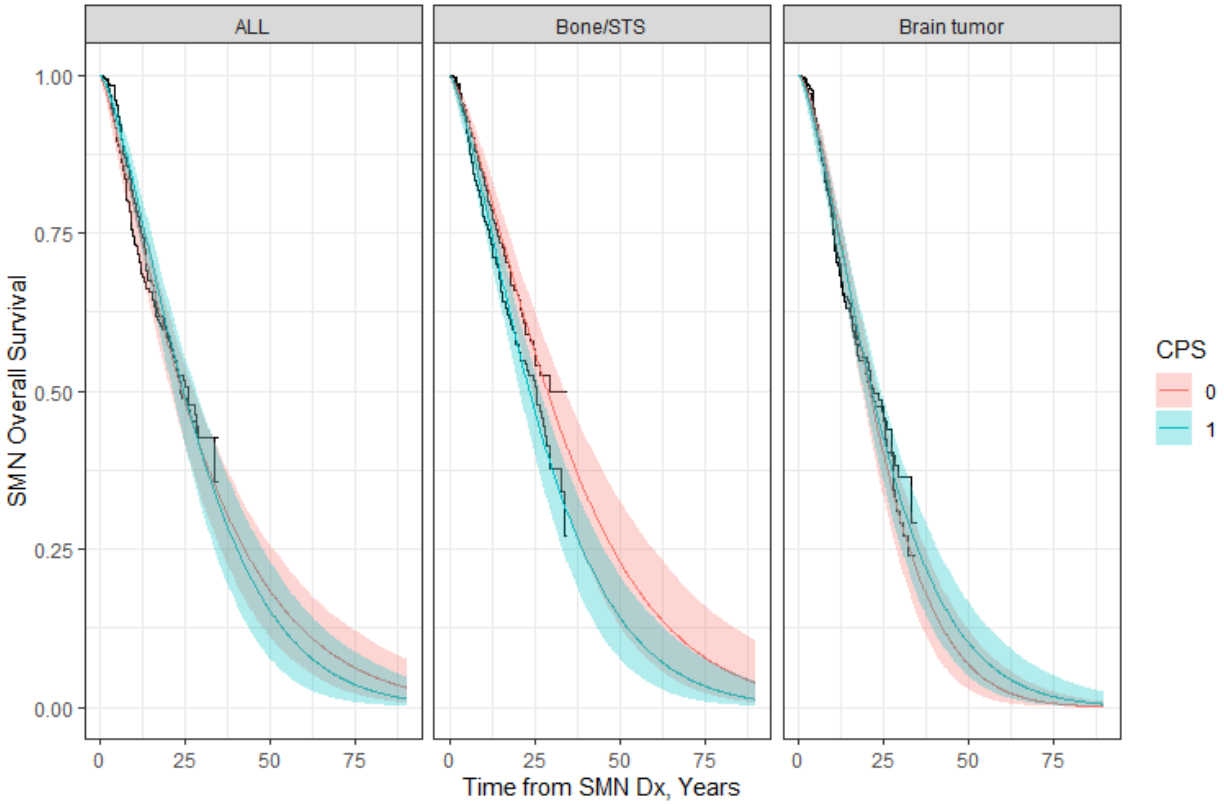

Figure 3: SMN related mortality stratified by CPS status. Kaplan-Meier estimates in black. Extrapolated estimates and 95% confidence intervals sourced from the fitting distribution.