TITLE: Communication of Skin Cancer Risk Profiles to Childhood Cancer Survivors

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SPECIFIC AIMS

Non-melanoma skin cancers (NMSCs), particularly basal cell carcinomas, represent nearly 60% of subsequent neoplasms (SNs) among long-term survivors of childhood cancer. Radiation therapy (RT) and hematopoietic cell transplantation (HCT) exposures are potent risk factors. While NMSCs are highly curable, there is abundant evidence that experiencing a prior NMSC is strongly associated with developing multiple NMSCs. Strikingly, among RT-exposed survivors, experiencing a NMSC as a first SN is also a risk factor for developing an invasive subsequent malignant neoplasm. Therefore, extending a precision medicine approach to NMSC detection and management among survivors is a top priority. Accurately predicting NMSCs would support earlier detection of NMSCs, reducing the probability of receiving more invasive skin cancer treatments that pose considerable physical, psychological, and financial burdens, and also help identify survivors at risk for developing subsequent cancers. However, a sizable gap between recommended skin cancer screening guidelines and practice exists: survivors at risk for NMSCs do not practice strategies that promote early NMSC detection, with only ~13% reporting full adherence to national evidence-based recommendations.

We hypothesize that a provider-based educational intervention to communicate a personalized assessment of NMSC risk will enhance uptake of skin cancer screening strategies among long-term childhood cancer survivors. Risk calculators that incorporate cancer treatment history and primary cancer diagnosis information have been successfully developed to estimate personalized absolute risks for specific late effects among childhood cancer survivors, including subsequent breast and thyroid cancer, cardiovascular late effects (heart failure, ischemic heart disease, stroke), and acute ovarian failure. Although including information about genetic susceptibility could further explain some of the inter-individual variability in risks for late effects among survivors, none of these published late effects risk calculators incorporate genetic risk factors. Externally validated skin cancer polygenic risk scores, which compile results from published large-scale genome-wide association study meta-analyses (N>100,000), are now available. These risk calculators have also not been formally connected to interventions to reduce the burden of corresponding late effects. Notably, interventions directed at survivors and primary care providers to promote early NMSC detection are currently under investigation (Advancing Survivors' Knowledge [ASK] About Skin Cancer Study), but have not been linked to a reliable NMSC risk stratification tool. Additional resources to support providers with the interpretation of NMSC risks and the delivery of effective survivor NMSC risk communication and education are needed.

In this project, our objectives are to: (1) create an online risk calculator to communicate individual absolute risks for subsequent NMSCs among survivors using data from the Childhood Cancer Survivor Study (CCSS) and St. Jude Lifetime Cohort Study (SJLIFE); and (2) utilizing a Delphi panel, establish consensus as to how to best interpret, communicate, and manage care based on NMSC risk prediction profiles, thereby improving the process to identify appropriate patients for screening and follow-up. Our specific aims are as follows:

Aim 1: Create and validate an online risk calculator combining clinical, genetic, and lifestyle risk factors to communicate absolute individual risks for developing subsequent NMSCs to childhood cancer survivors. NMSC risk prediction models that pragmatically accommodate varying risk factor information availability and risk assessment timing will be developed and independently validated.

Aim 2: Assess whether the NMSC risk calculator can also improve identification of survivors at high risk for adverse NMSC-related outcomes. Newly developed NMSC risk prediction models may also help identify

those at risk for related adverse outcomes, including experiencing a NMSC at a younger age (<30 years), multiple/recurrent NMSCs, multiple SNs, or invasive subsequent malignant neoplasms.

Aim 3: Using the input of healthcare providers and a consensus-based approach, determine how personalized estimates of NMSC risk will facilitate appropriate skin cancer clinical care management. Our multidisciplinary team, with expertise in pediatric oncology, cancer survivorship, pediatric dermatology, and implementation science, will conduct a Delphi panel study to obtain expert consensus-based interpretation of NMSC risk prediction estimates. Panel input will inform the development of a provider-focused NMSC risk education program to be carried out in the future.

The proposed project is significant as it will provide a unique path forward to connect NMSC risk prediction to a provider education intervention to mitigate the burden of skin cancer among survivors. The expected outcome is to enhance provider-based communication and education of individualized risks for NMSCs and possibly other adverse outcomes including invasive subsequent malignant neoplasms, ultimately improving the uptake of skin cancer detection practices among survivors. These results will have a significant impact on the long-term health of childhood cancer survivors, informing both survivorship care guidelines and secondary interventions differentially for those at high risk versus those at low or no risk for NMSCs.

A. SIGNIFICANCE

A.1. Burden of non-melanoma skin cancers and risk factors among childhood cancer survivors. Advances in treatments have dramatically improved long-term survival after childhood cancer to >85%.[1,2] With this success, the number of long-term survivors of childhood cancer in the United States currently exceeds 500,000. However, curative treatments for childhood cancer have significant consequences: survivors face greater risks for chronic health conditions compared to the general population,[3-6] including risks for subsequent neoplasms (SNs).[7,8] Non-melanoma skin cancers (NMSCs), primarily basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs), are the most common, accounting for ~59% of SNs.[9,10] The cumulative incidence for subsequent NMSCs at 30 years after primary cancer diagnosis range from ~5-9%.[10,11] While NMSCs are highly curable, they contribute to more disability-adjusted life years than melanoma in the US and pose a substantial economic burden on the US healthcare system.[12,13]

Previous studies in long-term childhood cancer survivors have investigated associations between risks for developing subsequent BCCs or SCCs with risk factors reported in the general population, including age, sex, race/ethnicity, and markers of sun sensitivity (e.g., freckling; hair and eye color), and survivor-specific clinical features such as primary cancer diagnosis, age at primary cancer diagnosis, hematopoietic cell transplantation (HCT), and exposures to radiation therapy (RT) and specific chemotherapies (alkylating agents, anthracyclines, epipodophyllotoxins, vinca alkaloids, and platinums).[9,10,14] These studies have consistently shown that ionizing radiation is an important risk factor for developing subsequent NMSCs, and for BCCs in particular (**Figure 1**). Receipt of any RT alone is strongly associated with BCC risk (odds ratio [OR] up to 4.3, relative to surgery-only survivors), with increased risk in the treatment field (OR up to 39.8 for doses ≥35 Gy versus surgery only).[10,14] A radiation dose-response relationship with BCC risk has been documented, including by surface area of skin exposed.[9,10,14] Although BCC/SCC risk associations with specific chemotherapies are inconsistent across studies, a recent analysis in 5,843 European long-term childhood cancer survivors indicates chemotherapeutic agents are likely useful predictors, given the estimated standardized incidence ratio (SIR) for survivors exposed to both RT and chemotherapy (SIR=59.3, 95% CI: 51.5-68.0) was 3-fold greater than those exposed to RT only (SIR=20.0, 95% CI: 13.7-28.2).[10]

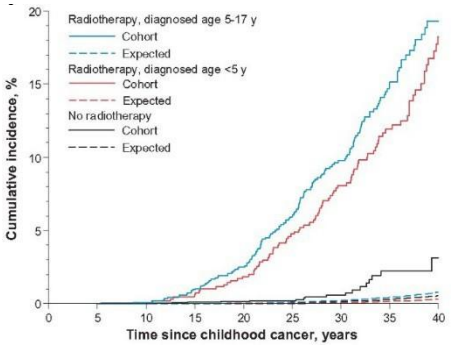

Figure 1: BCC cumulative incidence among 5-year childhood cancer survivors (red/blue) versus the general population (black) (Teepen *et al*., 2019).

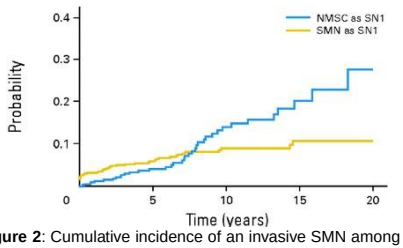

Figure 2: Cumulative incidence of an invasive SMN among RT-exposed survivors after experiencing a NMSC (blue) or an invasive SMN (yellow) as the first subsequent neoplasm (SN1) (Armstrong *et al*., 2011).

Several general population studies have shown that a prior history of NMSC is a strong predictor for experiencing multiple NMSCs[15-20], and may also be a risk factor other cancers[21,22]. Among childhood cancer survivors, the estimated 10-year cumulative incidence of developing a subsequent NMSC after a first NMSC was 49.0% (95% CI: 43.5-54.5%).[23] Strikingly, survivors exposed to RT who went on to develop a NMSC as a first SN experienced a 20.3% (95% CI: 13.0-27.6%) 15-year cumulative incidence of developing an invasive SMN

(non-NMSC) compared to 10.7% (95% CI: 7.2-14.2%) whose first SN was an invasive neoplasm (**Figure 2**).[23] These results indicate that a tool that reliably predicts NMSC risks among survivors may also identify other high-risk subgroups of survivors, including survivors at risk for multiple NMSCs and invasive SMNs.

Table 1: QSkin Study model to predict 3-year risk for developing any BCC/SCC

Predictors	Risk categories	AUC (95% CI)
Age group (years)	40-49 (reference); 50-59; 60-69; 70+	Derivation data (N=25,842): 0.79 (0.78-0.80)
Sex	Female (reference); male	
Ethnicity	Non-White (reference); White	Validation data (N=12,884): 0.80 (0.79-0.81)
Skin color	Dark (reference); medium; fair	
Tanning ability	Deeply tan (reference); moderately tan; lightly tan, not tan	
Freckling tendency	None (reference); a few; some; many	Among those no history of skin cancer*: Validation data (N=16,021): 0.72 (0.70-0.75)
# sunburns <10 years	Never (reference); 1-5; 6-10; 11-20; 21-50; >50	
# skin cancers excised	None (reference); 1; 2-10; 11-20; >20	*Excluded skin cancers excised and smoking; included melanoma family history
# skin lesions destroyed	None (reference); 1-5; 6-10; 11-20; 21-50; >50	
Smoking status	Never (reference); former; current	

A.2. Skin cancer screening practices among childhood cancer survivors. Current guidelines issued by the Children's Oncology Group ("Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers") recommend monthly skin self-examinations and yearly whole-body dermatological exams by a physician for early skin cancer detection, along with adherence to health promotion behaviors to avoid excessive UV exposure.[24] Even with clear evidence identifying cancer treatment risk factors, previous studies have reported poor adherence to recommended early skin cancer detection guidelines,[25,26] with the most recent study observing only 13.1% adherence among RT-treated survivors.[26] The Advancing Survivors' Knowledge (ASK) About Skin Cancer Study, a clinical trial for interventions to improve early skin cancer detection practices among childhood cancer survivors, is ongoing[27] and focuses on "activating" survivors' participation in the management of their care by asking physicians to provide a full skin cancer examination or utilizing teledermoscopy. However, the ASK Study intervention: (1) has not been connected to a reliable tool for NMSC risk stratification; (2) does not communicate the potential association between NMSCs and development of additional SMNs; and (3) does not fully leverage the role of healthcare providers to promote early skin cancer detection and risk evaluation.

A.3. Advantages and limitations of existing risk prediction models. Delayed detection of NMSCs has been linked to larger-diameter carcinomas, more invasive treatments, and worse treatment outcomes.[13,28,29] Therefore, the availability of tools to reliably identify at-risk survivors is key to reducing morbidity. Validated prediction tools for NMSCs in the general population exist, including the a risk calculator to estimate 3-year future risk of developing BCCs or SCCs,[20] using data from the Australian QSkin prospective skin cancer cohort study[30] (N=38,726). This QSkin risk calculator includes up to ten risk predictors (**Table 1**) and shows very good discriminatory power when considering previous skin cancer history (area under the receiver operating characteristic curve or AUC=0.80, 95% CI: 0.79-0.81) and good discriminatory power among individuals with no previous history of skin cancer (AUC=0.72, 95% CI: 0.70-0.75). More recently, global disease risk scores for BCC, SCC, and melanoma that include skin cancer polygenic risk scores (PRSs), along with 31 other non-genetic risk factors, have been validated (training N=103,008)[31]. These risk scores have very good discriminatory power among individuals with no previous history of skin cancer (validation N=88,924; AUCs ranging from 0.78-0.80). Unfortunately, only the combined prediction performance of the non-genetic and genetic risk score components are available and it is unknown whether a 31-item survey combined with genetic screening is clinically operable. Neither of these NMSC risk calculators/scores have been linked to care management options.

In the context of childhood cancer survivorship, the most notable limitation of existing NMSC risk calculators/scores is that they do not consider clinical features relevant to survivors. While sun sensitivity markers show associations with BCC risk among survivors, these risk factors do not attenuate risks posed by cancer treatments.[14] Published risk prediction models for other late effects have consistently demonstrated that incorporating information related to survivors' primary cancer diagnosis and cancer treatments is crucial for effective late effects risk stratification: survivor-specific web-based risk calculators with good risk prediction performance are currently available for subsequent breast[32] and thyroid cancer[33], various cardiovascular late effects (heart failure, ischemic heart disease, stroke)[34,35], and acute ovarian failure[36]. Yet many childhood cancer survivors exposed to RT do not develop NMSCs, suggesting genetic risk factors may also contribute. Our recent study of pulmonary late effects in childhood cancer survivors demonstrated that including genetic information within late effects risk prediction models can significantly improve discriminatory power (**Figure 3**): we found the inclusion of polygenic risk scores (PRSs), particularly a PRS with genetic variants that potentially modify the risk effects of RT and chemotherapies, significantly improved discriminatory performance relative to a model with

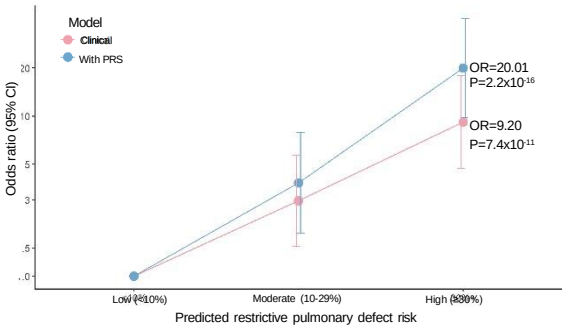

Figure 3: Odds of restrictive ventilatory defects among survivors at high vs. low predicted risk, using models with clinical predictors only (pink) vs. including genetic predictors (blue) (Im *et al.*, 2022).

only clinical (non-genetic) risk factors.[37] For NMSCs, we can now leverage results from large-scale (N>100,000) meta-analyses of genome-wide association studies (GWASs) for BCC[38] and SCC[39] risk. PRSs based on these meta-analyses have shown strong associations with corresponding NMSC risks and reasonable discriminatory performance in independent validation data.[40] A novel locus for BCC risk identified in irradiated childhood cancer survivors[41] further supports the need to also consider genetic predictors for NMSCs derived from analyses of survivor data. Using data from ~23,000 childhood cancer survivors in the Childhood Cancer Survivor Study (CCSS) and ~5,500 survivors in the St. Jude Lifetime Cohort Study (SJLIFE), we propose to develop and validate prediction models that can reliably stratify childhood cancer survivors by their predicted risk for NMSCs considering relevant clinical, genetic, and lifestyle risk factors.

A.4. Increasing the clinical utility of risk prediction models in survivorship care. Risk prediction models that are built with the consideration of who the end user will be and how they will be implemented are more likely to be clinically useful.[42] Although available late effects risk calculators show robust personalized risk assessment performance, these tools are not optimized with respect to their presentation of the degree of risk (e.g., communicating the difference between "high" versus "moderate" risk) or linked to specific interventions. Given that a lack of awareness, familiarity, and agreement with clinical decision tools affects their utility,[43,44] we propose to employ the Delphi technique to conduct a consensus-building panel study, bringing together healthcare providers with cancer survivorship expertise to determine how to interpret, communicate, and manage the NMSC and other SMN risks identified with the newly developed survivor-specific NMSC risk calculator.

B. INNOVATION

Novel NMSC risk prediction models for childhood cancer survivors. To date, prediction models that estimate patient-specific NMSC risks adapted to childhood cancer survivors do not exist. We propose to develop a new tool to estimate individual absolute risks for NMSCs in childhood cancer survivors (Aim 1). Innovative aspects include developing and validating multiple statistical prediction models considering when NMSC risks will be communicated and what types of clinical, genetic, and lifestyle risk factor information are available. Specifically, we will develop models that estimate 5-year NMSC risks: (a) immediately after treatment for primary cancer concludes; (b) at follow-up, including survivors who have already experienced at least one NMSC; and (c) based on availability, relevant clinical factors (e.g., attained age, sex, cancer treatment exposures, sun sensitivity markers), genetic predictors (e.g., published PRSs), and modifiable risk factors (e.g., smoking).

Improved NMSC risk stratification and personalized risk communication. The proposed research is significant in its potential to help identify childhood cancer survivors at differential risk for NMSCs, allowing clinicians to communicate a personalized assessment of future NMSC risk instead of relying solely on general long-term survivorship clinical follow-up guidelines. We also propose to further evaluate the newly developed NMSC risk calculator for its potential to also identify survivors at risk for earlier-onset NMSCs, multiple NMSCs, multiple SNs, and additional invasive SMNs (Aim 2). These results would support healthcare providers' efforts to educate survivors of their risk for adverse NMSC-related outcomes, including additional invasive SMNs.

Translation of late effects risk prediction modeling to inform a provider-based educational intervention. To support the implementation of the childhood cancer survivor NMSC risk calculator, we plan to employ the Delphi panel study approach. In healthcare settings, the Delphi method involves a structured iterative process of information-gathering and evaluation to build consensus for clinical decisions when scientific evidence is limited.[45] Delphi panel studies have previously been used to evaluate screening and management recommendations for childhood cancer survivors at risk for cardiomyopathy.[46,47] Here, a panel of healthcare providers with survivorship expertise will build a consensus to determine how the NMSC risk calculator findings will be interpreted by providers (i.e., connected to care management options), communicated to survivors, and implemented into screening practices. Ultimately, this information can be used to inform a future provider-based educational intervention.

Table 2: CCSS/SJLIFE childhood cancer survivor characteristics

	CCSS (N=23,219)		SJLIFE (N=5,531)	
Characteristics	N	%	N	%
Sex				
Female	10,774	46.4%	2,656	48.0%
Male	12,445	53.6%	2,875	52.0%
Race/ethnicity (self-reported)				
Black (Non-Hispanic)	1,212	5.5%	880	15.9%
Hispanic/Latinx	1,969	9.0%	205	3.7%
White (Non-Hispanic)	17,523	79.9%	4,303	77.8%
Other	1,221	5.6%	143	2.6%
Number of NMSCs				
None	21,969	94.6%	5,265	95.2%
1 to 4	989	4.3%	209	3.8%
5 or more	261	1.1%	57	1.0%
Number of BCCs				
None	22,049	95.0%	5,275	95.4%
1 to 4	917	3.9%	199	3.6%
5 or more	253	1.1%	57	1.0%
Any radiation therapy	11,819	55.5%	2,817	50.9%
Total body irradiation	547	2.6%	149	2.8%
Any alkylating agents	11,411	53.9%	3,214	58.1%
Any anthracyclines	9,890	46.6%	3,097	56.0%
Any epipodophyllotoxins	3,396	16.0%	1,925	34.8%
Any platinums	2,497	11.7%	959	17.3%
Any vinca alkaloids	13,666	68.3%	3,758	67.9%
Genotype data available	7,632	32.9%	4,481	81.0%
Age characteristics	Median	IQR	Median	IQR
Age at primary cancer diagnosis	7.0	3.1-13.2	6.6	2.8-12.8
Attained age	33.5	25.8-41.5	32.5	23.7-41.7
Age at first NMSC	37.1	31.2-43.1	37.2	30.9-44.2

Table 3: Adjusted RT and HCT relative rates (RRs) for any and multiple NMSCs

	Any NMSC		Multiple NMSCs (>3)	
	RR (95% CI)	P	RR (95% CI)	P
RT				
No RT	Reference		Reference	
Cranial RT	5.55 (4.24-7.26)	<.001	12.22 (6.65-22.46)	<.001
Total body irradiation	4.52 (2.50-8.17)	<.001	16.58 (4.86-56.61)	<.001
Other RT	4.76 (3.66-6.20)	<.001	10.84 (6.06-19.42)	<.001
HCT				
No HCT	Reference		Reference	
Allogeneic	3.83 (2.20-6.65)	<.001	4.02 (1.33-12.20)	0.01
Autologous	2.52 (1.34-4.73)	0.004	1.89 (0.72-4.98)	0.20

C. APPROACH

C.1. Preliminary data. In **Table 2**, we summarize sociodemographic and clinical characteristics of non-overlapping childhood cancer survivors participating in the CCSS and SJLIFE cohort studies that would be included in our prediction modeling analyses (unpublished data). Approximately 5.4% (N=1,250) of the 23,219 CCSS participants and 4.8% (N=266) of the 5,531 SJLIFE participants experienced at least one subsequent NMSC. Among survivors in SJLIFE and CCSS, the median age at which the first subsequent NMSC occurred was ~37 years; one-quarter of NMSCs occurred before 26 years of age in CCSS and 24 years of age in SJLIFE. Co-I Dr. Boull is currently leading the largest and most up-to-date epidemiologic analysis of late NMSCs in CCSS, with the first in-depth analysis of multiple subsequent NMSCs among survivors. Preliminary multivariable regression model results from this analysis (**Table 3**, unpublished) show strong adjusted associations between any RT and HCT receipt and NMSC rates relative to those who did not receive these treatments, even after adjusting for attained age, sex, race/ethnicity, a proxy for sun exposure (geographic treatment region), smoking, treatment era, and cumulative dosages of specific chemotherapy categories (anthracyclines, epipodophyllotoxins, alkylating agents) among other covariates. Notably, RT-related relative rates for multiple NMSCs are substantially greater than those considering first NMSC events only. **Figure 4** shows preliminary results (unpublished) from an evaluation of a published 32-SNP PRS for BCC risk in CCSS and SJLIFE. This BCC PRS was independently validated in the Michigan Genomics Initiative (N=30,702; OR_{SD}=1.62, 95% CI: 1.53-1.71, P=2.8x10^{-60}). While slightly attenuated, a strong association between subsequent NMSC risk and the 32-SNP BCC PRS was observed across all survivor cohorts after adjusting for clinical risk factors (combined HR_{SD}=1.32, 95% CI: 1.23-1.43, P=7.8x10^{-14}), indicating genetic risk factors should also be considered.

A

BCC PRS (Chahal *et a* ., 2016) association with subsequent BCC risk				
Cohort	N	# BCCs	HR per PRS SD (95% CI)	P
Combined	8962	717	1.32 (1.23-1.43)	7.8x10^{-14}
SJLIFE	3216	202	1.42 (1.23-1.63)	1.2x10^{-6}
CCSS (original)	3769	455	1.24 (1.14-1.36)	2.2x10^{-6}
CCSS (expansion)	1977	60	1.71 (1.30-2.26)	1.3x10^{-4}

B

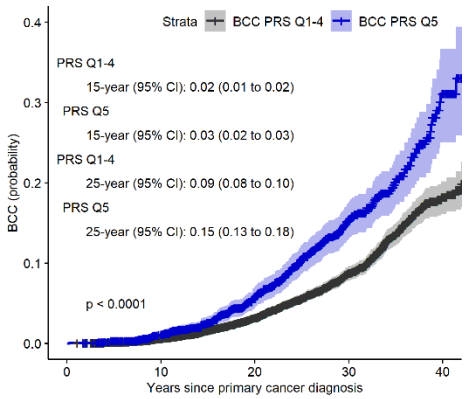

Figure 4: Published BCC PRS and subsequent BCC risk among childhood cancer survivors. Treatment-adjusted BCC PRS associations with subsequent BCC risk shown in Panel A. Subsequent BCC cumulative incidence for the combined CCSS and SJLIFE cohorts (European genetic ancestry, N=8,962) by PRS quintile groupings are shown in Panel B (top PRS quintile in blue; all other quintiles in grey).

C.2. Multidisciplinary research team. Our multidisciplinary team at the University of Minnesota (UMN) has a proven track record in childhood cancer survivorship research and is uniquely qualified to lead the proposed research. The PI (**Cindy Im, PhD**) has expertise in statistical prediction modeling and genetic epidemiology, with relevant first-author publications (e.g., *Cancer Research*, *American Journal of Human Genetics*); she currently leads a NCI-funded methodologically-oriented project to develop PRSs that account for gene-treatment interaction associations (NCI R21CA261833; MPIs C. Im/Y. Yuan). The Co-I team features three clinician-scientists: **Lucie Turcotte, MD**, a pediatric oncologist with an exceptional subsequent neoplasm epidemiology publication track record (e.g., *JAMA*, *Journal of Clinical Oncology*) and the current Chair of the CCSS Second Malignancies Working Group; **Christina Boull, MD**, a pediatric dermatologist currently leading a project in CCSS that will provide the most current overview of NMSC epidemiology to date among survivors; and **Karim Sadak, MD**, Director of the UMN Cancer Survivor Program, with extensive experience in health services research focused on longitudinal health care delivery to survivors. To lead implementation science aspects, our team includes: **Deborah Pestka, PharmD**, a health system researcher with expertise in the evaluation of evidence-based practices; and **Helen Parsons, PhD**, a survivorship mixed-methods researcher with expertise in health intervention implementation. Collectively, this team has the expertise needed to optimally use SJLIFE/CCSS study resources; develop and validate risk prediction models; and design and execute the Delphi panel study that produces clinically relevant expert consensus-based conclusions.

C.3. Materials/Databases

St. Jude Lifetime Cohort Study (SJLIFE). The proposed project will use existing data from SJLIFE[48] (NCI U01CA195547, MPIs: M.M. Hudson and K.K. Ness), a retrospective cohort study with prospective follow-up of 5-year childhood cancer survivors treated at St. Jude Children's Research Hospital. All participants undergo comprehensive and uniform clinical/laboratory/functional evaluations during study visits, which are repeated longitudinally. Detailed medical record abstraction is used to characterize treatment exposures (cumulative doses of specific chemotherapies, radiation fields and doses, surgical interventions) and ascertain clinical events (e.g., primary cancer recurrence; subsequent neoplasms). Other data, including sociodemographic and lifestyle factors, are gathered using clinician interviews and self-reported surveys. Whole-genome sequencing for 4,481 samples has been completed by the HudsonAlpha Institute for Biotechnology Genomic Services Laboratory (Huntsville, AL) using the Illumina HiSeq X10 platform (average coverage per sample of ≥30X).

Childhood Cancer Survivor Study (CCSS). We will also use existing data from CCSS[49] (NCI U24CA055727, PI: G.T. Armstrong), a 31-institution retrospective cohort study of 5-year childhood cancer survivors with prospective follow-up. A total of 25,658 survivors diagnosed/treated in 1970-1999 are participating in CCSS. This resource includes comprehensive treatment exposure data abstracted from medical records, along with longitudinal data for self-reported health conditions with the exception of SMNs (including NMSCs), which are confirmed by pathology report. Sequenced/genotyped data for 8,739 CCSS survivors are available (primarily coordinated by NCI Cancer Genomics Research Laboratory; Bethesda, MD).

C.4. Methodology

C.4.1. Aim 1: Develop and validate a NMSC risk calculator for childhood cancer survivors.

The objective of this aim is to create and validate a unified NMSC risk calculator that reliably estimates 5-year risks for BCCs and NMSCs overall (separate risk prediction models for SCCs will not be pursued given the relatively small number of SCCs in CCSS and SJLIFE, **Table 2**). This risk calculator will incorporate a series of BCC and overall NMSC risk prediction models accommodating: (a) risk factor information availability (e.g., cumulative treatment dosages; sun sensitivity markers; genotype data); and (b) the survivor's life stage at assessment (e.g., immediately after treatment concludes vs. early adulthood or after experiencing a NMSC).

Methods and data analysis.

NMSC risk prediction model framework: Two separate childhood cancer survivor datasets will be pre-specified: (1) a training dataset, for risk prediction model selection; and (2) an external validation dataset, to obtain an unbiased evaluation of the prediction performance of selected models. Our primary strategy is to use CCSS for model training (N~23,000, excluding participants also enrolled in SJLIFE) and SJLIFE (N~5,500) for independent model validation (**Table 2**). A set of key biological variables will be identified *a priori* based on the literature[9,10,14] and results from Co-I Dr. Boull's ongoing analysis of NMSC risk factors in CCSS. Minimally, these include sex, race/ethnicity, attained age, primary cancer diagnosis, age at primary cancer diagnosis, and cancer treatment exposures (HCT [allogeneic or autologous], RT field/dose [particularly TBI, head/neck, trunk], chemotherapy dose [alkylating agents, anthracyclines, epipodophyllotoxins, vinca alkaloids, platinums]). General population risk factors for NMSCs identified in the literature[19,20,31] will be considered and adapted based on data collected in CCSS/SJLIFE, including markers of sun sensitivity (e.g., eye and hair color, freckling tendency), known predisposing genetic syndromes (e.g., Gorlin's syndrome), and childhood/adult sun exposure (primary cancer treatment location; geocoded follow-up location; prior history of peeling sunburns or tanning bed exposures). We will also identify relevant time-dependent risk factors, or risk factors that become more pertinent as survivors age (e.g., history of NMSCs; smoking). Lastly, we will compile a set of genetic risk factors, including validated PRSs[38-40] and as appropriate, gene-treatment interactions from ongoing analyses (NCI R21CA261833, MPIs Im/Yuan). Since the availability/relevance of risk factor information depends on the timing of the risk assessment, we will develop a series of models that consider different sets of risk factor information to maximize clinical operability. Therefore, we plan to construct BCC and overall NMSC risk scores with a ***base risk score*** accounting for key biological variables relevant to childhood cancer survivors, and 3 modular risk scores that may be incorporated additively: (1) the *general population risk score*, or risk factors included in general population NMSC risk calculators, e.g., sun sensitivity markers; (2) the *time-dependent risk score*, e.g., including prior NMSC history and modifiable risk factors; and (3) the *genetic risk score*, including pre-specified genetic predictors.

Prediction model selection in training data: As described in previous work[34-36], we will build risk scores in the training data in a manner that prioritizes clinically interpretability. We plan to leverage clinical input (clinician Co-Is) and use generalized linear models[50] (GLMs) for prevalence-binary (logistic regression) or time-to-event data (piecewise-exponential regression, approximating semi-parametric Cox proportional hazards regression) and backward selection to identify influential predictors[51]. Interactions between key biological variables (e.g., RT and specific chemotherapies) will be investigated using a regularization approach such as Lasso[52] or Elastic Net[53] with 10-fold cross-validation to estimate tuning parameters. The final series of risk prediction models will include the 8 possible combinations of base and modular risk scores per skin cancer phenotype, where modular risk scores will be built with base risk scores entering as an offset and then combined as simple weighted sums. All risk score weights will be estimated in the full training dataset. Before external validation, the study team will develop a risk score categorization scheme using predicted risk bins (e.g., very low, low, moderate, high, very high risk) considering training data prediction performance metrics (see below).

Evaluation in independent validation data: SJLIFE data will be used for prediction model validation. We will examine a range of established prediction performance metrics, including simple association statistics (e.g., odds/hazard ratio), BCC/NMSC prevalence or cumulative incidence per risk score quantile bins, and various

discrimination and calibration metrics[54] such as the time-dependent area under the (receiver operating characteristic or ROC) curve[55] (AUC) and Brier score.

C.4.2. Aim 2: **Evaluate whether the survivor NMSC risk calculator can also identify additional subgroups of survivors at high risk for correlated adverse outcomes.**

Given that prior NMSCs are risk factors for multiple NMSCs, multiple SNs, and invasive SMNs among childhood cancer survivors[23], the objective of this aim is to assess whether predicted risks for NMSCs may also be predictive of other related adverse outcomes. Specifically, we will investigate whether the newly developed NMSC risk scores are also significantly associated with experiencing: (a) early-onset NMSCs; (b) multiple NMSCs; (c) multiple SNs; and (d) invasive SMNs, using methods described in C.4.1. Ultimately, these results have the potential to further enhance personalized risk communication efforts and improve uptake of early skin cancer detection strategies among at-risk survivors.

C.4.3. Aim 3: To support implementation and assure the survivor NMSC risk calculator is clinically useful, conduct a Delphi panel study to systematically incorporate healthcare provider input.

The objective of this aim is to leverage healthcare provider input to maximize adoption of the survivor NMSC risk calculator. Recommendations that achieve consensus will be connected to the NMSC risk calculator outputs. These results can be used to inform the future development of a provider-based educational intervention.

Methods and data analysis.

Overview of Delphi panel study components: The following proposed study procedures are modeled from previous Delphi studies in childhood cancer survivorship care[46,47]. We will use a purposeful sampling strategy to assemble a panel of 20-25 physician and advanced practice providers with childhood cancer survivorship expertise. To gain diverse perspectives, we will recruit 30 panelists from different specialties, including primary care, pediatric oncology, adult or pediatric dermatology, or adult dermato-oncology. All panelists will be recruited from 5 regional health systems with pediatric oncology programs (UMN Masonic Children's Hospital; Children's Hospital and Clinics of Minnesota, Essentia Health-St. Mary's Medical Center [Duluth], Mayo Clinic, Sanford Health). The Delphi study process will include up to 3 rounds of anonymous surveys and evaluation, with the goal of achieving a ≥90% response rate in each round. For each round of questioning, we will perform mixed-methods analysis to obtain modal responses for questions with categorical responses and coded themes from a semi-structured content analysis of written responses; these results will be summarized and shared during the subsequent rounds to support consensus-building among panelists. The primary outcome of interest is whether consensus is reached on risk interpretation, care management, and survivor risk communication recommendations for each clinical risk vignette. *A priori* definitions of consensus, moderate agreement, and disagreement will be as follows: ≥90%, 70-89%, and <70%, respectively. Specifically, the objectives of each round are as follows: during the first round, the panel will identify all factors that contribute to the proposed risk categorizations for each clinical vignette and each set of corresponding follow-up options; during the second round, the panel will refine these factors and follow-up options into shared interpretations of risk; during the final round, the panelists will focus on gaining consensus.

Questionnaire content and development: To provide background information that is consistent to all panelists, we will present a user-friendly summary of the features of the newly developed online survivor NMSC risk calculator and a summary of the available literature that describes any established or proposed methods to screen/manage skin cancers among survivors, including an overview of the educational materials designed by the ASK About Skin Cancer Study[27]. For the first-round questionnaire, the study team will present a limited set of clinical vignettes (e.g., asymptomatic adolescent pediatric cancer patient who received low-dose cranial radiation within the last year; asymptomatic 35-year old survivor of acute lymphoblastic leukemia treated with HCT) and a range of possible predicted risk estimate scenarios. Using these vignettes and predicted risk scenarios, we will ask open-ended questions about: (a) risk interpretation and care management, and (b) survivor risk communication. Subsequent questionnaires will present mixed-methods analysis results of previous questionnaires. All questionnaires will be tested for content and cognitive validity before use.

C.4.4. Power considerations. The proposed study requires detecting associations necessary for good prediction performance. Assuming a NMSC cumulative incidence of 5% in the CCSS training data (N=23,219), we calculated power under different minimum prevalences for a given predictor (5%, 10%, 15%) for a range of effect sizes (**Figure 5**), using a power calculation approach for time-to-event analysis[56] assuming a type I error probability of 0.05. For NMSC risk prediction model development, we have sufficient power (80%) to detect risk associations with HRs as low as 1.45 when the prevalence of a predictor is 5%. Given the anticipated effect sizes of useful predictors (e.g., HR>2), NMSC risk prediction model development will be sufficiently powered.

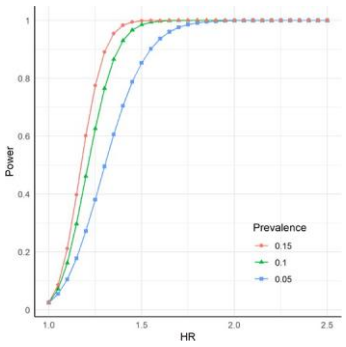

Figure 5: Power calculations in CCSS training data.

C.5. Potential problems and alternative approaches

False positives and over-fitting. Inclusion of false-positive risk factors and overfitting of prediction models are serious concerns. To minimize these threats, we intend to use independent datasets. Cross-validation strategies[57] will also be adopted during development/tuning to reduce prediction performance "optimism". Another possible solution is to seek additional external validation datasets (e.g., DCOG-LATER[8]).

Limitations on NMSC risk calculator translation. Because of the non-random sampling process, the Delphi panel study results may not be generalizable, particularly for community healthcare providers. It is also unlikely that the designed questionnaires will present all possible clinical scenarios, including scenarios that would affect the panelists' final recommendations for the NMSC risk calculator's clinical interpretation and use. We anticipate refining these recommendations in future studies.

C.6. Timeline

Tasks	Year 1, Months 1 6	Year 1, Months 7 12	Year 2, Months 1 6	Year 2, Months 7 12
Task 1: NMSC risk prediction model development (Aim 1)				
Task 2: NMSC risk calculator validation (Aim 1) and ancillary analyses (Aim 2)				
Task 3: Delphi panel study to support NMSC risk calculator implementation (Aim 3)				

Shading intensity corresponds with intensity of research activity for each task.

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