Subsequent Neoplasm Working Group Report

Lucie Turcotte, MD, MPH, MS

June 15, 2023

CCSS
Childhood Cancer Survivor Study

St. Jude Children's Research Hospital

An NCI-funded Resource

Scope of Research

CCSS

- Oversee the complete and accurate ascertainment of subsequent neoplasms in the CCSS survivor cohort
- Establish the incidence, therapeutic and clinical risk factors, and temporal changes in subsequent neoplasms
- Identify novel associations, in collaborations with other working groups, with subsequent neoplasm risk and outcomes

Working Group Membership

CCSS

- Lucie Turcotte, University of Minnesota
- Joseph Neglia, University of Minnesota
- Cindy Im, University of Minnesota
- Anne Blaes, University of Minnesota
- Michael Arnold, University of Colorado
- Miriam Conces, Nationwide Children's Hospital
- Tara Henderson, University of Chicago
- Chaya Moskowitz, Memorial Sloan Kettering
- Jennifer Yeh, Harvard Medical School
- Dana Barnea, Tel Aviv Sourasky Medical Center
- Lenat Joffee, Northwell Health
- Taumoha Ghosh, University of Utah
- Rebecca Howell, M.D. Anderson
- Sandy Constine, University of Rochester
- Greg Armstrong, St. Jude Children's Research Hospital

Working Group Progress

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3 **Published/In Press Manuscripts** (since 1/1/2022)

2 **Currently Submitted Manuscripts** —as primary or secondary

9 **Analyses/Manuscripts in Process** —as primary or secondary

8 **Concepts in development**—as primary or secondary

11 **New AOIs** (total, since 1/1/2022)—as primary or secondary

Available SNs for Study

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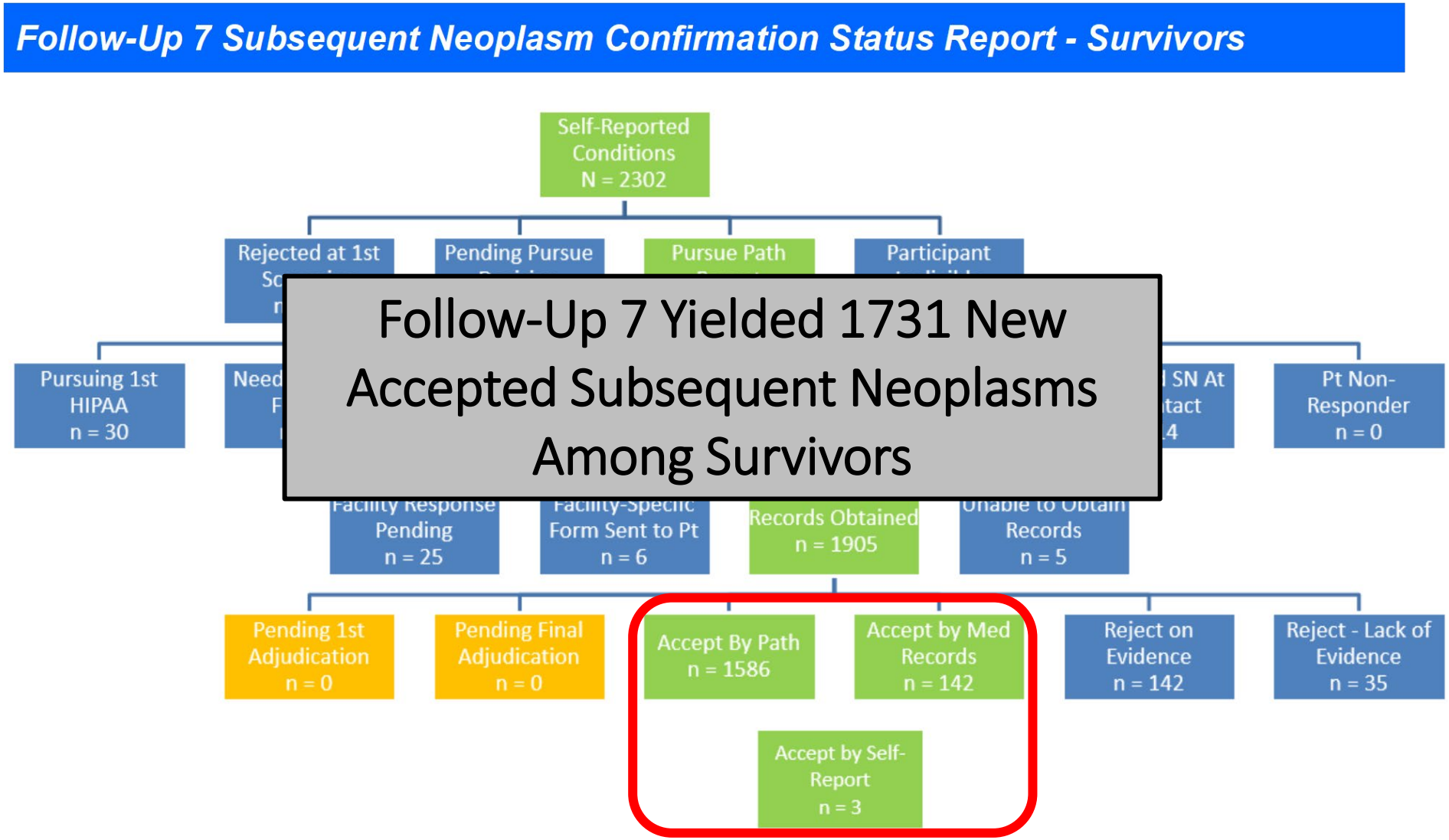

Follow-Up 7 Yielded 1731 New Accepted Subsequent Neoplasms Among Survivors

Available SNs for Study

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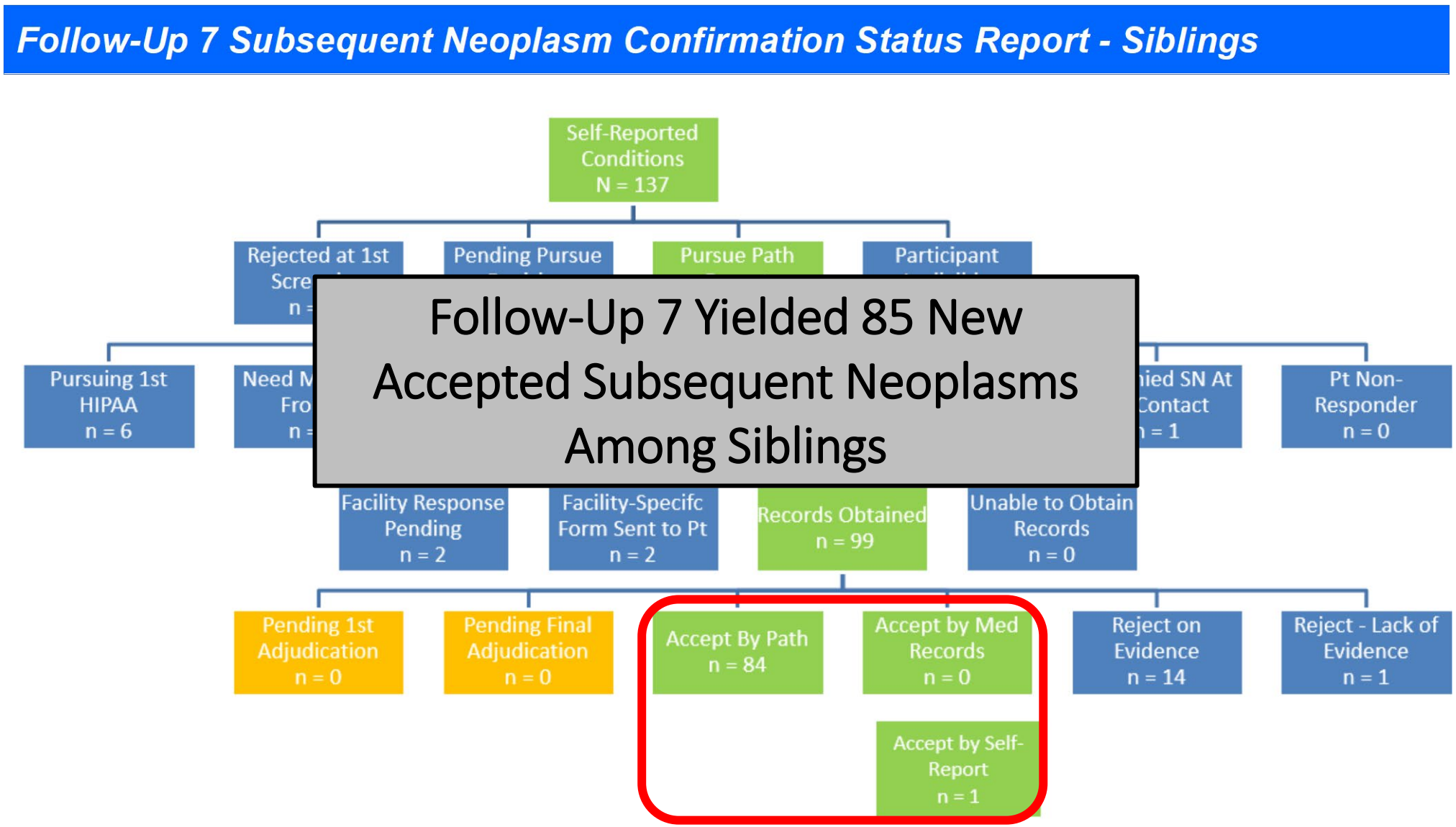

Available SNs for Study

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Subsequent Neoplasm	Total Cases Ascertained		Initial Cohort		Expansion Cohort		Ascertained since June 2020	
	N	%	N	%	N	%	N	%
All Subsequent Neoplasms	**11328**	**100.0**	**8652**	**100.0**	**2676**	**100.0**	**1997**	**100.0**
Solid Organ	**2075**	**18.3**	**1524**	**17.6**	**551**	**20.6**	**251**	**12.6**
Breast	766	6.8	604	7.0	162	6.1	97	4.9
Bone	68	0.6	52	0.6	16	0.6	2	0.1
Soft tissue sarcoma	244	2.2	172	2.0	72	2.7	23	1.2
Thyroid	427	3.8	263	3.0	164	6.1	35	1.8
Other solid organ	570	5.0	433	5.0	137	5.1	94	4.7
Non-melanoma Skin Cancer	7217	63.7	5591	64.6	1626	60.8	1371	68.7

Available SNs for Study

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Characteristics of Biologic Material Available for Subsequent Malignant Neoplasm and Meningioma Cases								
SMN	# with germline tissue		Germline Tissue (any kind) and Treatment Data	Total with SMN Tissue	Number of Cases with SMN Tissue by Type			
	Saliva Oragene	Blood			H&E Slides	Unstained Slides	Scrolls	Blocks
Breast	445	388	539	253	250	141	44	51
Meningioma	679	467	726	130	130	81	16	23
Other CNS	59	33	75	39	38	25	6	7
Thyroid	264	236	301	131	130	99	40	23
Sarcoma	72	52	93	40	39	33	15	9
Leukemia	32	22	36	12	12	10	3	2
Bone	18	17	26	12	12	10	1	3
Melanoma	74	56	83	31	31	18	1	10
Lymphoma	49	40	58	15	14	10	5	4
Renal Cell	55	35	56	22	22	17	6	7
Other Carcinoma	271	193	295	138	138	73	24	66
All Other	52	33	78	89	56	36	40	22
TOTALS	**2,070**	**1,572**	**2,366**	**912**	**872**	**553**	**201**	**227**

Highlights of Recently Completed Research

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Association of Changes in Cancer Therapy Over 3 Decades With Risk of Subsequent Breast Cancer Among Female Childhood Cancer Survivors
A Report From the Childhood Cancer Survivor Study (CCSS)

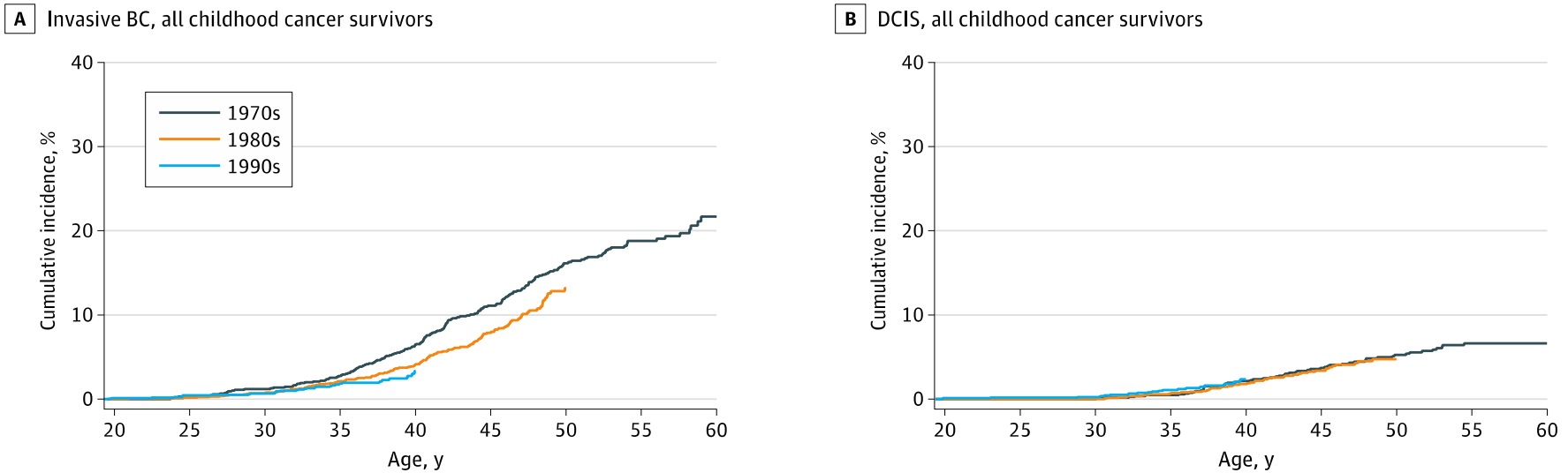
Tara O. Henderson, MD, MPH; Qi Liu, MS; Lucie M. Turcotte, MD, MPH; Joseph P. Neglia, MD, MPH; Wendy Leisenring, ScD; David Hodgson, MD, MPH; Lisa Diller, MD; Lisa Kenney, MD; Lindsay Morton, PhD; Amy Berrington de Gonzalez, DPhil; Michael Arnold, MD; Smita Bhatia, MD, MPH; Rebecca M. Howell, PhD; Susan A. Smith, MPH; Leslie L. Robison, PhD; Gregory T. Armstrong, MD; Kevin C. Oeffinger, MD; Yutaka Yasui, PhD; Chaya S. Moskowitz, PhD

- Study objective was to quantify the association between temporal chemotherapy and radiation dose changes and subsequent breast cancer
- Among 11,550 female survivors, 489 developed 583 breast cancers (427 invasive, 156 in-situ)
- From the 1970s to 1990s, chest (34% → 17%) and pelvic (26% → 13%) radiotherapy decreased, and anthracycline exposure increased (30% → 64%)

Highlights of Recently Completed Research

CCSS

- The invasive breast cancer **rate decreased 18% every 5 years** of primary cancer diagnosis era
  - Findings most pronounced in survivors < 30 years
  - Largely due to reduced use of chest radiotherapy
  - Tempered by concurrent increases in anthracycline exposure



Henderson et al. JAMA Oncol 2022.

Highlights of Recently Completed Research

CCSS

Polygenic Risk and Chemotherapy-Related Subsequent Malignancies in Childhood Cancer Survivors: A Childhood Cancer Survivor Study and St Jude Lifetime Cohort Study Report

Cindy Im, PhD[1]; Noha Sharafeldin, PhD[2,3]; Yan Yuan, PhD[4]; Zhaoming Wang, PhD[5,6]; Yadav Sapkota, PhD[5]; Zhanni Lu, DrPH[1]; Logan G. Spector, PhD[1]; Rebecca M. Howell, PhD[7]; Michael A. Arnold, MD[8]; Melissa M. Hudson, MD[5,9]; Kirsten K. Ness, PhD[5]; Leslie L. Robison, PhD[5]; Smita Bhatia, MD[3]; Gregory T. Armstrong, MD[5,9]; Joseph P. Neglia, MD[1]; Yutaka Yasui, PhD[4,5]; and Lucie M. Turcotte, MD[1]

- Study objective was to quantify the role of genetic susceptibility in chemotherapy-associated SMN risk among survivors of European and African genetic ancestry from the CCSS and SJLIFE
- An externally validated 179-variant polygenic risk score (PRS) associated with pleiotropic adult cancer risk from the UK Biobank Study was computed for each survivor
- Included 9,895 survivors of EUR and 718 of AFR genetic ancestry

Highlights of Recently Completed Research

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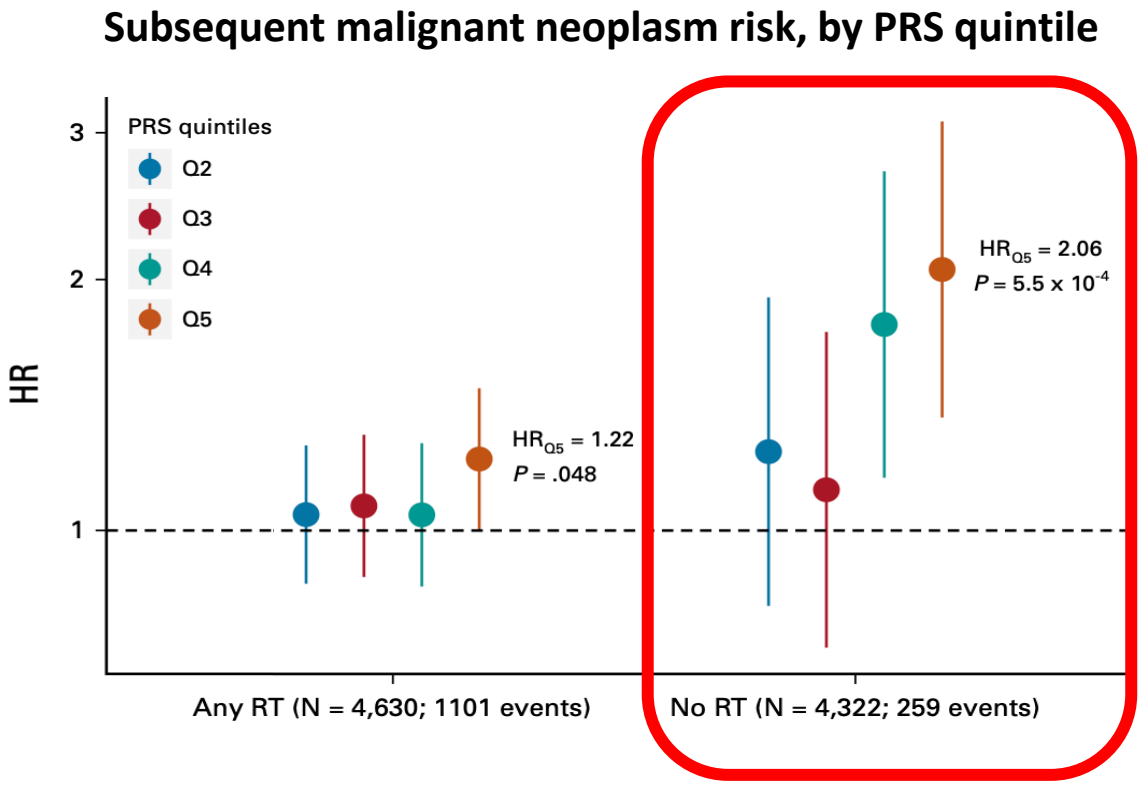
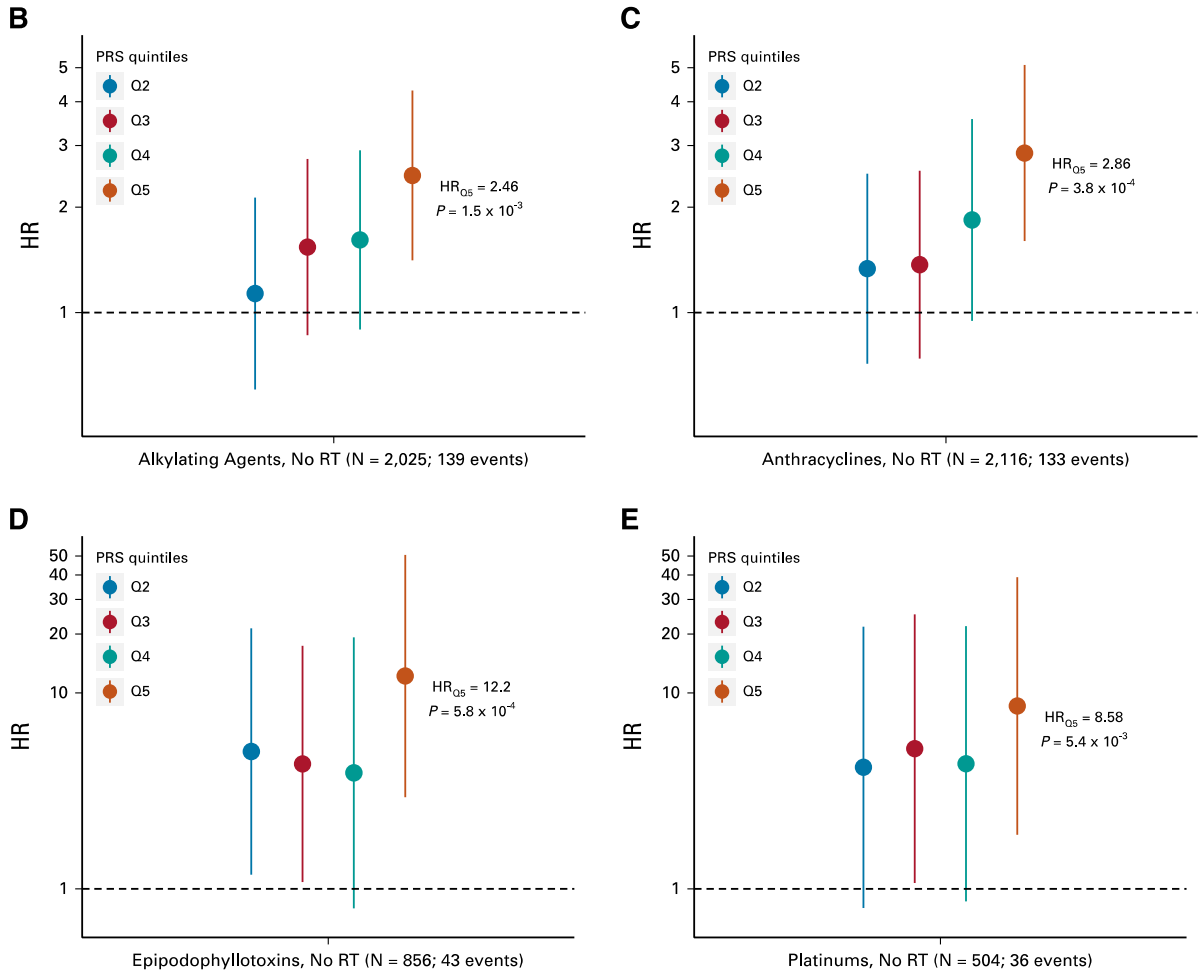


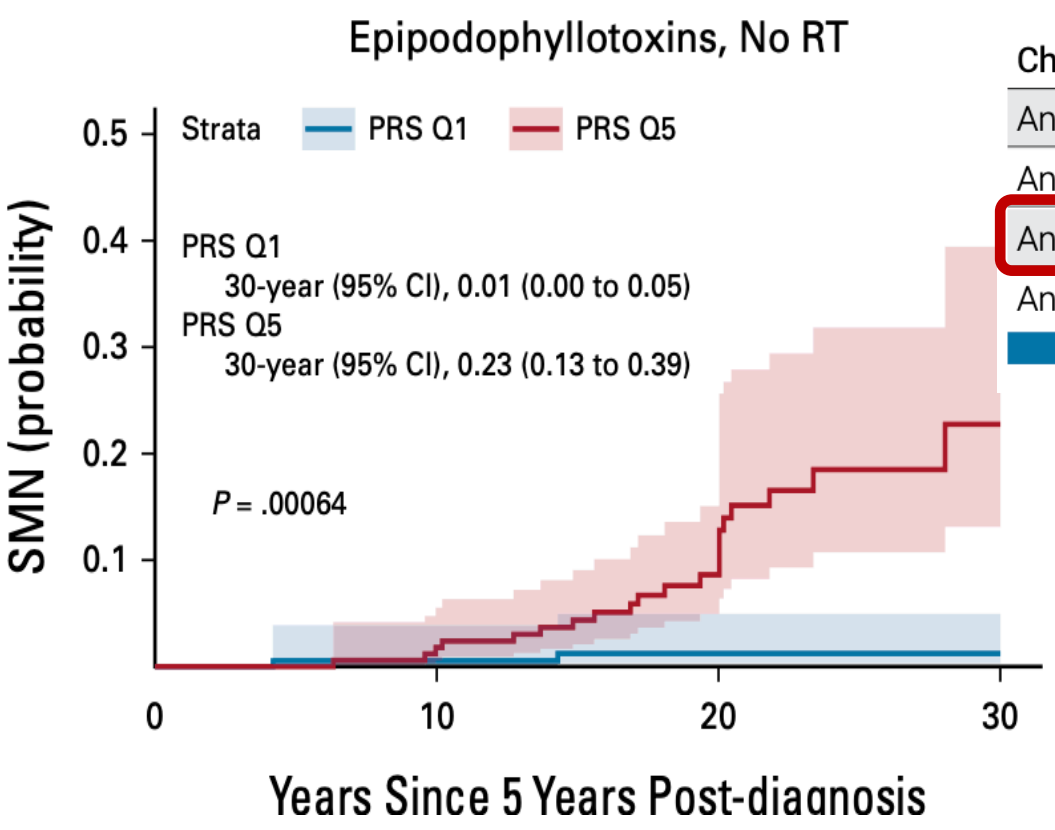
Strong association between PRS and SMN risk in non-irradiated EUR survivors (high vs. low PRS quintiles).



Im et al. JCO, 2023 (in press).

Highlights of Recently Completed Research

CCSS



Pleiotropic cancer PRS and SMN prediction in chemotherapy subgroups

Chemotherapy Subgroup	No.	Clinical Predictors Only AUC[b] (95% CI)	Pleiotropic Cancer PRS Included AUC[b] (95% CI)	P
Any alkylating agents	2,025	0.58 (0.55 to 0.62)	0.62 (0.58 to 0.67)	.069
Any anthracyclines	2,116	0.60 (0.56 to 0.63)	0.64 (0.60 to 0.68)	.076
Any epipodophyllotoxins	856	0.63 (0.54 to 0.70)	0.71 (0.64 to 0.78)	.049
Any platinums	504	0.58 (0.51 to 0.66)	0.68 (0.59 to 0.76)	.052

Trans-ancestral SMN risks: PRS-epipodophyllotoxin interaction

	Different Model Types[d]	HR (95% CI)	P
European ancestry	No PRS: any epipodophyllotoxins	1.39 (0.94 to 2.04)	.10
	PRS-TX interaction (SD)	1.72 (1.29 to 2.28)	1.9×10^{-4}
African ancestry	No PRS: any epipodophyllotoxins	0.90 (0.18 to 4.57)	.90
	PRS-TX interaction (SD)	2.68 (1.34 to 5.39)	5.5×10^{-3}

Im et al. JCO, 2023 (in press).

Highlights of Recently Completed Research

CCSS

UNIVERSITY OF MINNESOTA
Driven to Discover℠
Crookston Duluth Morris Rochester Twin Cities

Treatment and treatment-related toxicity *following* subsequent breast cancer: a report from the Childhood Cancer Survivor Study (CCSS)

Cindy Im,[1] Yutaka Yasui,[2] Emily Stene,[1] Sarah Monick,[3] Ryan Rader,[4] Jori Sheade,[5] Heather Wolfe,[6] Zhanni Lu,[1] Logan G. Spector,[1] Aaron J. McDonald,[2] Leslie L. Robison,[2] Gregory T. Armstrong,[2] Rita Nanda,[3] Kevin C. Oeffinger,[4] Joseph P. Neglia,[1] Anne Blaes,[1] Lucie M. Turcotte[1]

[1]University of Minnesota, Minneapolis, USA, [2]St. Jude Children's Research Hospital, Memphis, USA, [3]University of Chicago, Chicago, USA, [4]Duke University, Durham, USA, [5]Northwestern Medicine Lake Forest Hospital, Lake Forest, USA, [6]UT Southwestern Medical Center, Dallas, USA

CCSS
Childhood Cancer Survivor Study

Study Aims:

1. Describe how breast cancer treated in survivors vs. controls
2. Characterize treatment-related toxicity in survivors vs. controls
3. Compare mortality in survivors vs. controls

Female CCSS survivors who developed BC ≥5 years after primary cancer (N=437)

Excluded:
- Benign/non-carcinoma tumors (e.g., sarcoma)
- No consent or no medical record data

Abstracted detailed **BC clinical, treatment, toxicity data** (N=431)

Matched case-control (sporadic BCs, general pop)

1:1 matching on age at BC dx, BC tx decade, race/ethnicity, BC histology and hormone receptor status

(N=688 or 344 pairs)

Controls: Multi-institutional sampling

UMN, Duke, UChicago. Abstracted medical records for sporadic BCs using the same procedures as cases. Unable to match 87 cases.

Highlights of Recently Completed Research

CCSS

- Study included 431 female survivors with 533 breast cancers
  - 92 (21%) experienced synchronous or metachronous breast cancers
  - 69% received chest RT and 42% received anthracycline for childhood cancer
- In close collaboration with the CCSS Coordinating Center, successfully obtained/abstracted treatment and toxicity data for **>90% of cases and controls**
- We identified **significant differences between cases and controls** in:
  - Breast cancer treatment
  - Treatment-related toxicities
  - Mortality
- Come hear more details Friday, 9:55am at the ISLCCC meeting!

Approved Concept Proposals

CCSS

Concept	Author / Institution	Approval Year
Cause-specific Mortality Among Survivors with Thyroid SMN	Barnea / Tel Aviv Sourasky Med Cntr	2015
Late subsequent leukemia after childhood cancer	Ghosh / Utah	2020
Body Mass Index and Risk of Subsequent Neoplasms	Joffe / Northwell	2020
Risk and Risk Factors for Colorectal Cancers in Childhood Cancer Survivors	Owens / MD Anderson	2020
Updated epidemiology of secondary CNS malignancy following radiotherapy exposure in childhood cancer survivors	Galvin / Minnesota	2021
Evaluation of subsequent meningiomas in childhood cancer survivors	Cooney / Day One Bio	2021
Mortality after Colorectal Cancer Among Survivors of Childhood Cancer	Major / Chicago	2021
Nonmelanoma skin cancer in survivors of childhood and adolescent cancer: An update from the Childhood Cancer Survivor Study	Boull / Minnesota	2021
Melanoma among Adult Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study	Rotz / Cleveland Clinic	2022
Assessing the Contribution of Clinical, Lifestyle, and Genetic factors in Risk of Subsequent Neoplasms	Sapkota / SJCRH	2022

Active Ancillary Studies

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Turcotte (NCI, K08), Treatment Modifications and Provider Decision Making in the Management of Subsequent Breast Cancers Among Survivors

Ronckers/van Leeuwen/Kremer (Children Cancer-Free Foundation), International Pooled Analysis of Breast Cancer Risk after Treatment for Childhood and Young Adult Cancer

Im (NCI, R21), Treatment-specific genetic risk scores for late effects prediction in childhood, adolescent and young adult cancer survivors

Moskowitz/Henderson (NCI, R01), International Study of Subsequent Colorectal Cancer Among Survivors of Childhood, Adolescent, and Young Adult Cancers (I-SCRY)

Active Ancillary Studies—IPD Cohort

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Consortium Core Group	
Dutch KiKa grant	**Study Group Representatives**
Principal investigators **Cecile Ronckers** **Leontien Kremer** **Flora van Leeuwen**	North American Childhood Cancer Survivor Study
	St. Jude Lifetime Cohort
	US National Wilms' Tumor Study
Post doc **Jop Teepen**	Dutch Childhood Oncology Group LATER
	French Childhood Cancer Survivor Study
PhD student **Yuehan Wang**	Swiss Childhood Cancer Survivor Study
	ALiCCS collaborative study (Nordic Countries; Danish part)
	Dutch Hodgkin Late Effects cohort

1. To address 3 clinically relevant research questions on treatment-related subsequent breast cancer risk

- Chest Radiotherapy: prescribed chest-radiotherapy doses <20Gy
- Chemotherapy: role of specific anthracyclines
- Attained Age: to examine whether excess risks remain increased across the lifespan, especially after age 50 yrs

2. To establish a harmonized database of international cohorts

Active Ancillary Studies– I-SCRY

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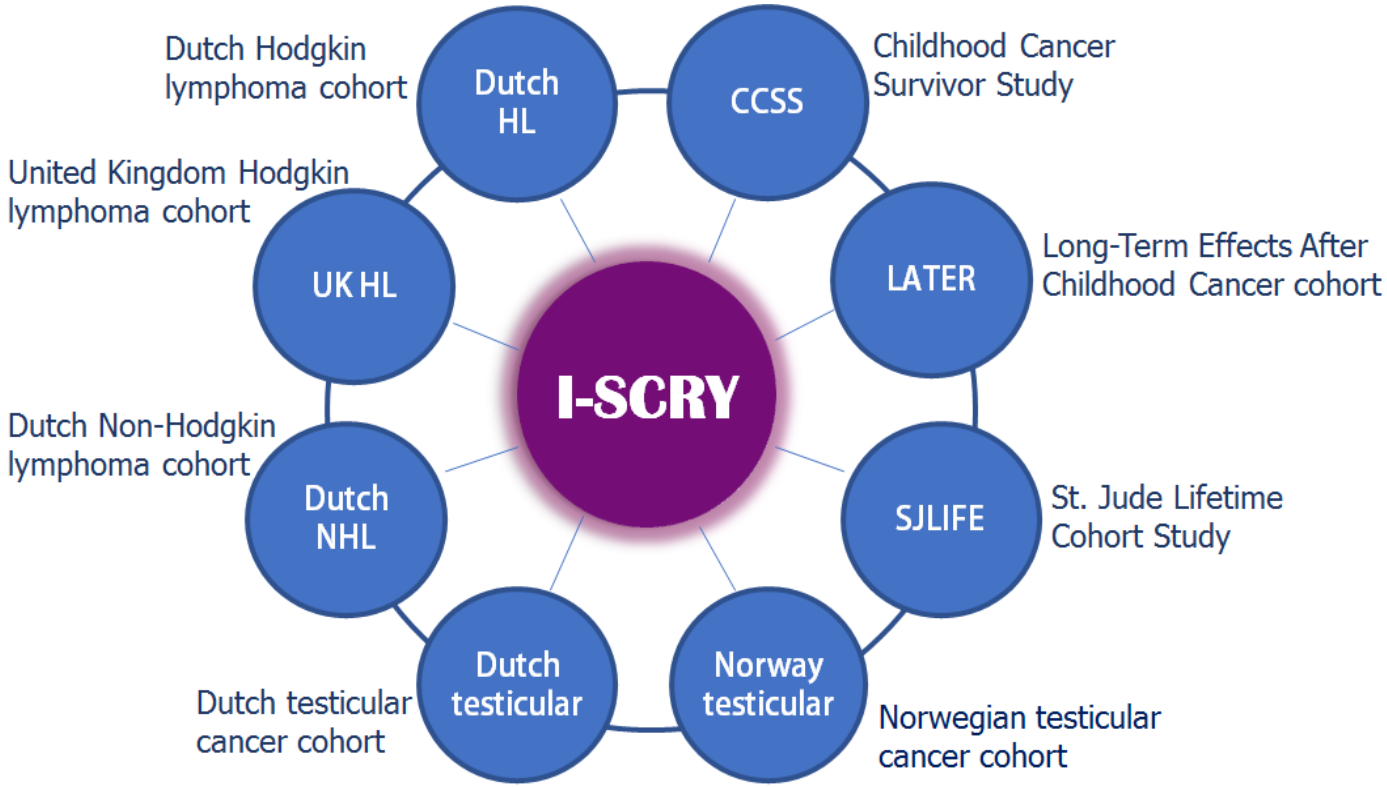
Phase I. Data assembly and harmonization

- 8 multi-national survivorship cohorts
- > 51,000 childhood and AYA cancer survivors
- > 298 with subsequent CRC

Phase II. Analysis and reporting

Primary aim: Evaluate association of childhood and AYA cancer therapy with subsequent CRC

Second aim: Assess burden of CRC in childhood and AYA cancer survivors



AT THE FOREFRONT OF KIDS' MEDICINE
UChicago Medicine
Comer Children's

1884
Memorial Sloan Kettering Cancer Center

Current Working Group Priorities

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- Develop projects that leverage existing biospecimen data
  - *Goal:* Within one year, develop ≥ 2 second neoplasm working group projects that use existing clinical and biospecimen data
- Expand cross-working group collaborations to enhance opportunities for studies on etiology or interventions
  - *Goal:* Identify at least 3 new partnerships within other working groups (Genetics, Cancer Control, Psychology, etc.) that lead to new Concepts in the next year
- Engage young/early-stage investigators in working group
  - *Goal:* Support at least one CCSS Career Development Award application for 2024 cycle (due October 2, 2023!)

Five Year Plan: Research Priorities

CCSS

- Expand working group membership to include greater depth/breadth of research interests to sustain work long term
- Enhance **cross-cohort** collaborations to allow for investigation of rare exposures and rare outcomes
- Increase the number of Ancillary Studies with a focus on subsequent neoplasms
- Focus on subsequent cancer genetics, outcomes, patient-reported outcomes, and decision-making

Discussion: Challenges and Opportunities

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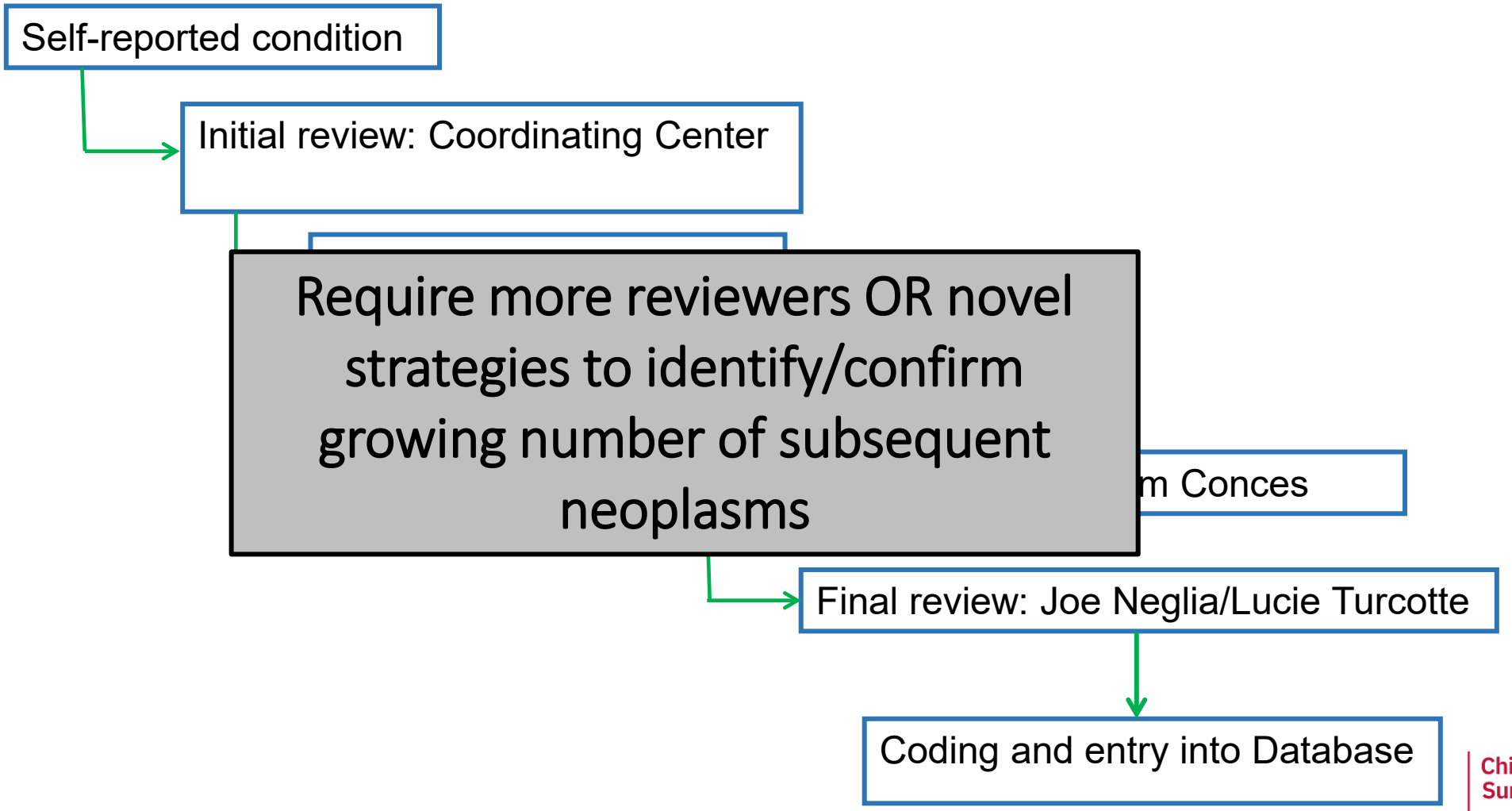
Challenges:

- Burden of SN reviews: aging survivor population means rapidly increasing number of SNs requiring review and validation, particularly NMSCs

Opportunities:

Challenge: Growing Number of SNs

ccss



Discussion: Challenges and Opportunities

CCSS

Challenges:

- Burden of SN reviews: aging survivor population means rapidly increasing number of SNs requiring review, particularly NMSCs

Opportunities:

- Virtual Pooled Registry (VPR) may provide a more efficient means of confirming SMNs

Virtual Pooled Registry

CCSS

- Managed by the North American Association of Central Cancer Registries (NAACCR)
- Designed to facilitate streamlined linkages to multiple cancer registries using standard methodology
- CCSS participated in a pilot study linking the entire cohort to select state registries (N=26)
  - Subsequent malignant neoplasms identified through the data linkage were compared against those identified via CCSS participant self-report process
  - Identified that ~25% more SMNs could be identified using VPR compared to self-report
  - VPR confirmed SMNs identified by death certificates
  - Supplemented CCSS questionnaire data when medical records could not be obtained
- Now ~47 registries (>96% population) available to enhance coverage of CCSS population

Discussion: Challenges and Opportunities

CCSS

Challenges:

- Burden of SN reviews: aging survivor population means rapidly increasing number of SNs requiring review, particularly NMSCs

Opportunities:

- Virtual Pooled Registry (VPR) may provide a more efficient means of confirming SMNs
- Expanded biorepository, including SMN tissue and blood, presents new opportunities for subsequent malignancy investigation
- Growing number of SNs and aging population allows our group to address new/previously unaddressed questions
- International collaborations provide additional avenues to address associations between rare exposures and rare outcomes

Questions? Interested in getting involved?

Contact Lucie Turcotte (turc0023@umn.edu)

Join our Second Cancer Working Group Meetings! Second Mondays of the month, 10:00am CST, via Zoom.

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