CCSS
Childhood Cancer Survivor Study

Second Neoplasm Working Group Report

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An NCI-funded Resource

Working Group Membership

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Lucie Turcotte, University of Minnesota
Michael Arnold, University of Colorado
Miriam Conces, Nationwide Children's Hospital
Tara Henderson, University of Chicago
Chaya Moskowitz, Memorial Sloan Kettering
Rebecca Howell, M.D. Anderson
Sandy Constine, University of Rochester
James Bates, Emory University
Greg Armstrong, St. Jude Children's Research Hospital

Scope of Research

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- 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

Current Available SNs for Cohort Study

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Characteristics of Subsequent Neoplasms in CCSS

Subsequent Neoplasm	Total Cases Ascertained		Initial Cohort		Expansion Cohort		Ascertained during Current Grant Period	
	N	%	N	%	N	%	N	%
All Subsequent Neoplasms	9317	100.0	7252	100.0	2065	100.0	5647	100.0

- 61% of SNs ascertained during the most recent grant period

Current Available SNs for Cohort Study

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Subsequent Neoplasm	Total Cases Ascertained		Initial Cohort		Expansion Cohort		Ascertained during Current Grant Period	
	N	%	N	%	N	%	N	%
All Subsequent Neoplasms	**9317**	**100.0**	**7252**	**100.0**	**2065**	**100.0**	**5647**	**100.0**
Leukemia	**86**	**0.9**	**60**	**0.8**	**26**	**1.3**	**22**	**0.4**
Lymphoma	**87**	**0.9**	**64**	**0.9**	**23**	**1.1**	**38**	**0.7**
CNS	**919**	**9.9**	**723**	**10.0**	**196**	**9.5**	**541**	**9.6**
Meningioma	730	7.8	603	8.3	127	6.2	477	8.4
Solid Organ	**1818**	**19.5**	**1369**	**18.9**	**449**	**21.7**	**816**	**14.5**
Breast	668	7.2	547	7.5	121	5.9	284	5.0
Bone	66	0.7	50	0.7	16	0.8	12	0.2
Soft tissue sarcoma	220	2.4	159	2.2	61	3.0	78	1.4
Thyroid	389	4.2	247	3.4	142	6.9	184	3.3
Other solid organ	475	5.1	366	5.0	109	5.3	258	4.6

Current Available SNs for Cohort Study

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Subsequent Neoplasm	Total Cases Ascertained		Initial Cohort		Expansion Cohort		Ascertained during Current Grant Period	
	N	%	N	%	N	%	N	%
All Subsequent Neoplasms	**9317**	**100.0**	**7252**	**100.0**	**2065**	**100.0**	**5647**	**100.0**
Skin	**6003**	**64.4**	**4733**	**65.3**	**1270**	**61.5**	**3951**	**70.0**
Melanoma	163	1.7	119	1.6	44	2.1	95	1.7
Non-melanoma Skin Cancer	5840	62.7	4614	63.6	1226	59.4	3856	68.3

- NMSCs make up 63% of SNs in the cohort
- NMSCs make up 68% of SNs ascertained in current grant period

Working Group Progress

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3 Published/In Press Manuscripts (since 1/1/2021)

- Ghosh T et al. Lung Cancer as a Subsequent Malignant Neoplasm in Survivors of Childhood Cancer. Cancer Epidemiology, Biomarkers & Prevention 2021; 30: 2235-2243.
- Henderson TO et al. Subsequent Malignant Neoplasms in the Childhood Cancer Survivor Study: Occurrence of Cancer Types where Human Papillomavirus is an Established Etiologic Risk Factor. Cancer 2022; 128: 373-382.
- Moskowitz CS et al. Development and validation of a Personalized breast cancer risk prediction model for childhood cancer survivors treated with chest radiation: A report from the Childhood Cancer Survivor Study and the Dutch Hodgkin Late Effects and LATER cohorts. Journal of Clinical Oncology 2021; 39: 3012-3021.

1 Currently Submitted Manuscripts

- Henderson TO et al. Impact of Changes in Cancer Therapy Over Three Decades on Risk of Subsequent Breast Cancer Among Female Childhood Cancer Survivors: A Report from the Childhood Cancer Survivor Study (CCSS).

Highlights of Recently Completed Research

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original reports

Development and Validation of a Breast Cancer Risk Prediction Model for Childhood Cancer Survivors Treated With Chest Radiation: A Report From the Childhood Cancer Survivor Study and the Dutch Hodgkin Late Effects and LATER Cohorts

Moskowitz CS et al. Journal of Clinical Oncology 2021; 39: 3012-3021.

Highlights of Recently Completed Research

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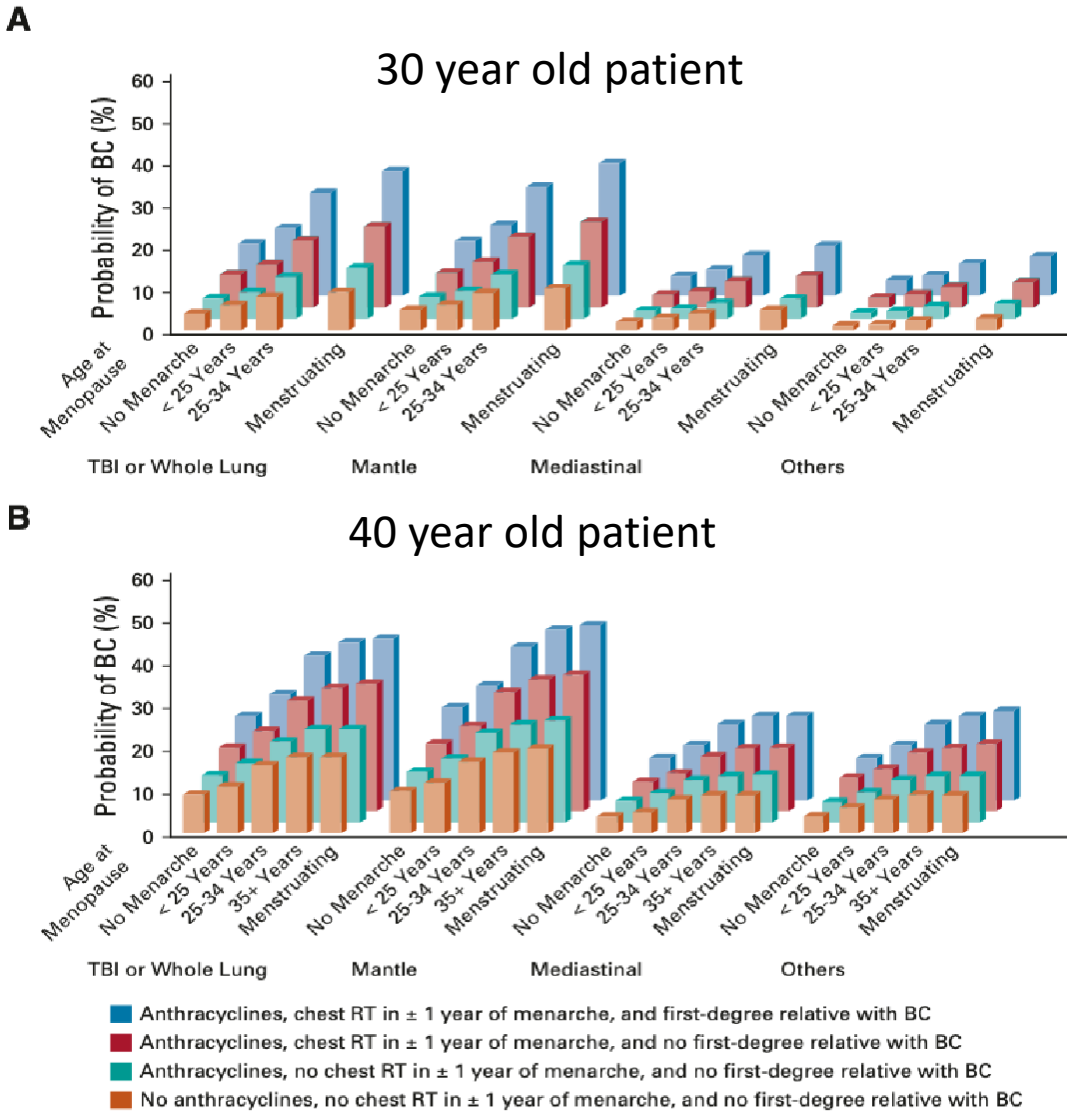
- 1,120 female CCSS (1970-86) participants
  - 242 with breast cancer
- 1,027 female CCSS (1987-1999), Dutch LATER cohort, Dutch Hodgkin Late Effects cohort participants
  - 105 with breast cancer
- Risk factors considered: primary cancer and treatment, hormonal-related risk factors, and other risk factors (FH, obesity, race/ethnicity, breast biopsies)



Moskowitz CS et al. Journal of Clinical Oncology 2021; 39: 3012-3021.

Highlights of Recently Completed Research

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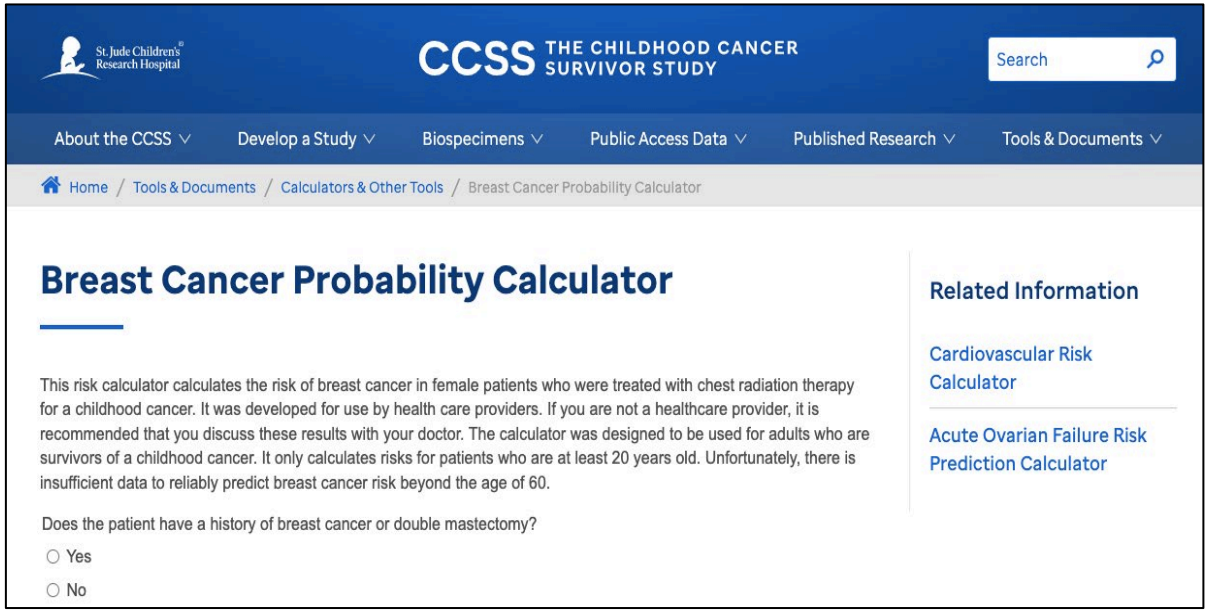
- Risk strongly dependent on age
- Highest for women treated with mantle XRT within 1 year of menarche, still menstruating, and who had a 1st degree relative with breast cancer
- Probability calculator available on CCSS website



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Highlights of Recently Completed Research

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Impact of Changes in Cancer Therapy Over Three Decades on Risk of Subsequent Breast Cancer Among Female Childhood Cancer Survivors: A Report from the Childhood Cancer Survivor Study

- Among 11,550 female survivors, 489 developed 583 breast cancers
  - 427 invasive
  - 156 DCIS

Henderson TO et al. *Under review.*

Highlights of Recently Completed Research

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	Adjusted Treatment variables	Invasive BC	
		RR (95% CI)	P
Entire cohort	All adjusted	0.85 (0.76 - 0.95)	0.003
	All adjusted but chest RT dose	0.82 (0.73 - 0.91)	<.001
	All adjusted but anthracycline dose and pelvic RT	0.89 (0.81 - 0.99)	0.029

Henderson TO et al. *Under review at JAMA Oncology.*

Highlights of Recently Completed Research

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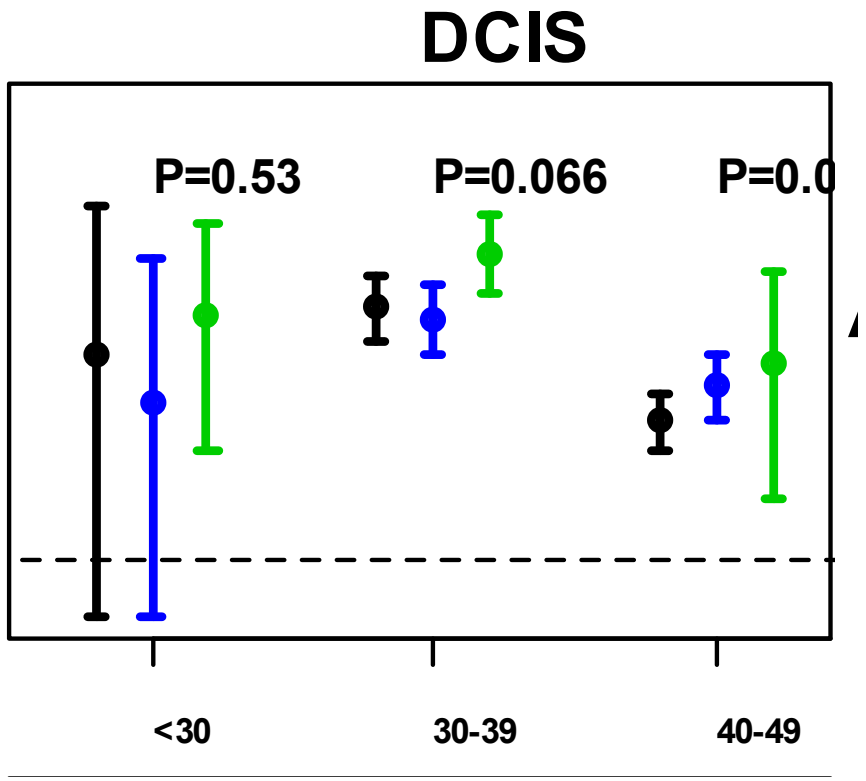

Interestingly, SIRs of DCIS appeared to be increasing over time, but a significant difference in incidence was not detected

Working Group Progress: Analysis/Manuscript in Process (Approved Concepts)

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Concept	Author / Institution	Approval Year
Late subsequent leukemia after childhood cancer	Turcotte / Minnesota	2020
Body Mass Index and Risk of Subsequent Neoplasms	Joffe / Columbia	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 / DFCI	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

New AOIs – Concepts in Development

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Concept	Author/Institution	AOI Submitted
Socioeconomic status as a predictor of subsequent malignant neoplasms among survivors of childhood cancer	Turcotte / Minnesota	April 2022
Radiotherapy- and Chemotherapy-Related Risks of Thyroid Cancer	Morton / NCI	March 2021

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)
- Gramatges/Dhodapkar/Bhatia (proposed, pending funding), Immune Deficits in Survivors of Childhood Cancer

Ideas/Priorities for New Studies

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- Comprehensive analysis of subsequent malignancies among aging survivors of childhood cancer
- Quality of life and perceived morbidity following subsequent malignancy diagnosis
- Interventions for to promote subsequent neoplasm screening (consider NMSC screening as a target)

Priorities from the Competitive Renewal

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1. Evaluate non-treatment exposures, including obesity, as risk factors for SNs [Lenat Joffee]

2. Identify genetic susceptibility for specific SNs that modifies risk conferred by therapeutic exposure [multiple]

3. Evaluate populations at high risk for SNs among aging survivors [included in Rush Bhandari concept in Chronic Disease group]

4. Describe treatment of SNs and associated toxicities and outcomes [examining breast cancer in ancillary study, Lucie Turcotte]

Five Year Plan: Additional Research Priorities

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- Expand working group membership to include greater depth/breadth of research interests to sustain work long term
- Develop projects that use the subsequent neoplasm tissue biorepository
- Enhance cross-cohort collaborations to allow for investigation of rare exposures and rare outcomes
- Focus on aging survivors and changing patterns of SMNs, impact of multiple SMNs, and long-term morbidity and mortality after SMNs

Discussion: Challenges and Opportunities

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Current Challenges

- Small number of engaged junior faculty members
  - Goal: Expand our core group of SMN researchers by providing close mentorship and support to new investigators

- Burden of SN reviews: aging survivor population means rapidly increasing number of SNs requiring review, particularly NMSCs
  - Goal: Engage new individuals in review/validation process

Need for Surveillance Innovation: Subsequent Neoplasm Review and Confirmation

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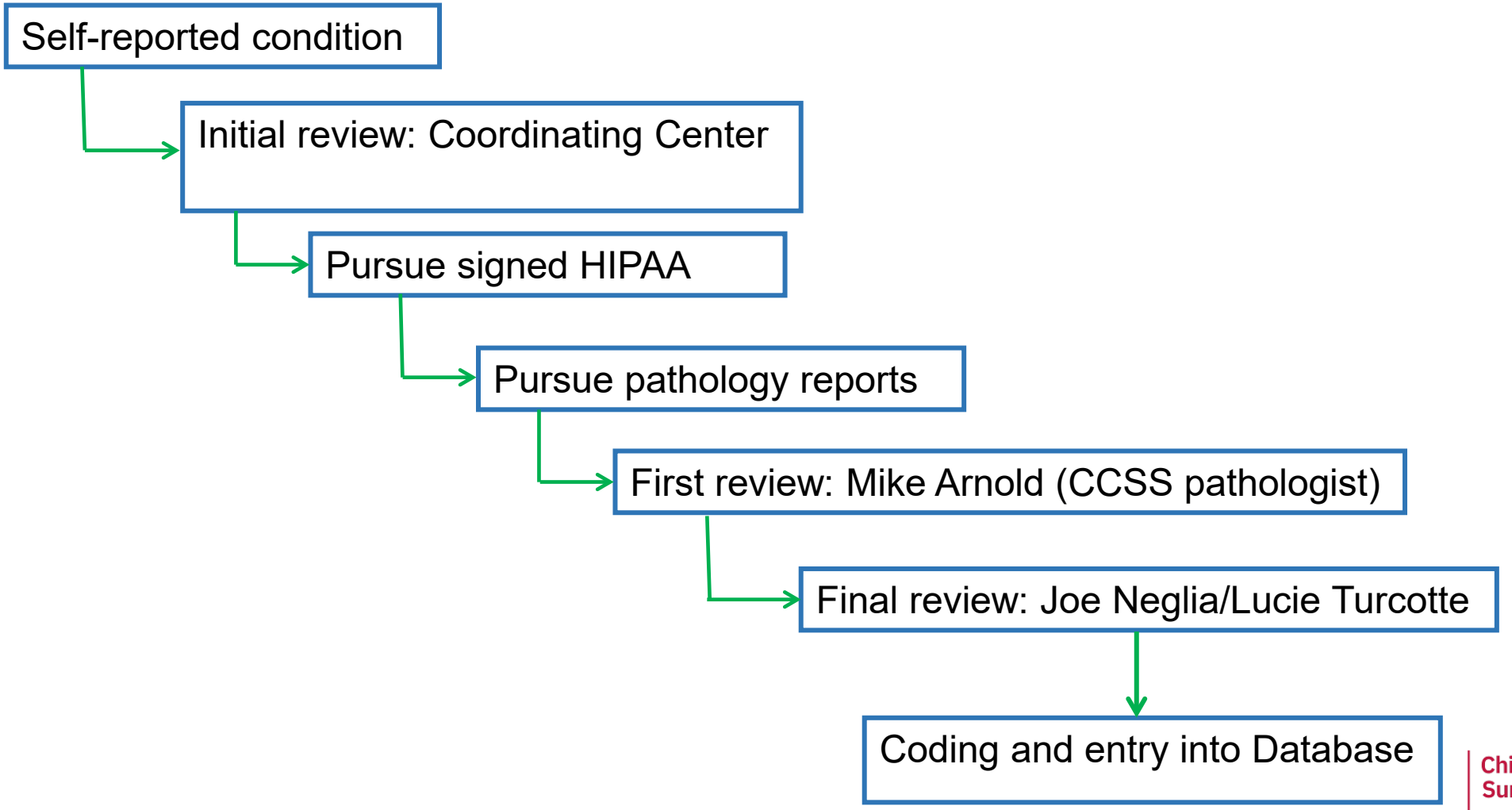

Magnitude of SN Review: Follow-up 7 Survey

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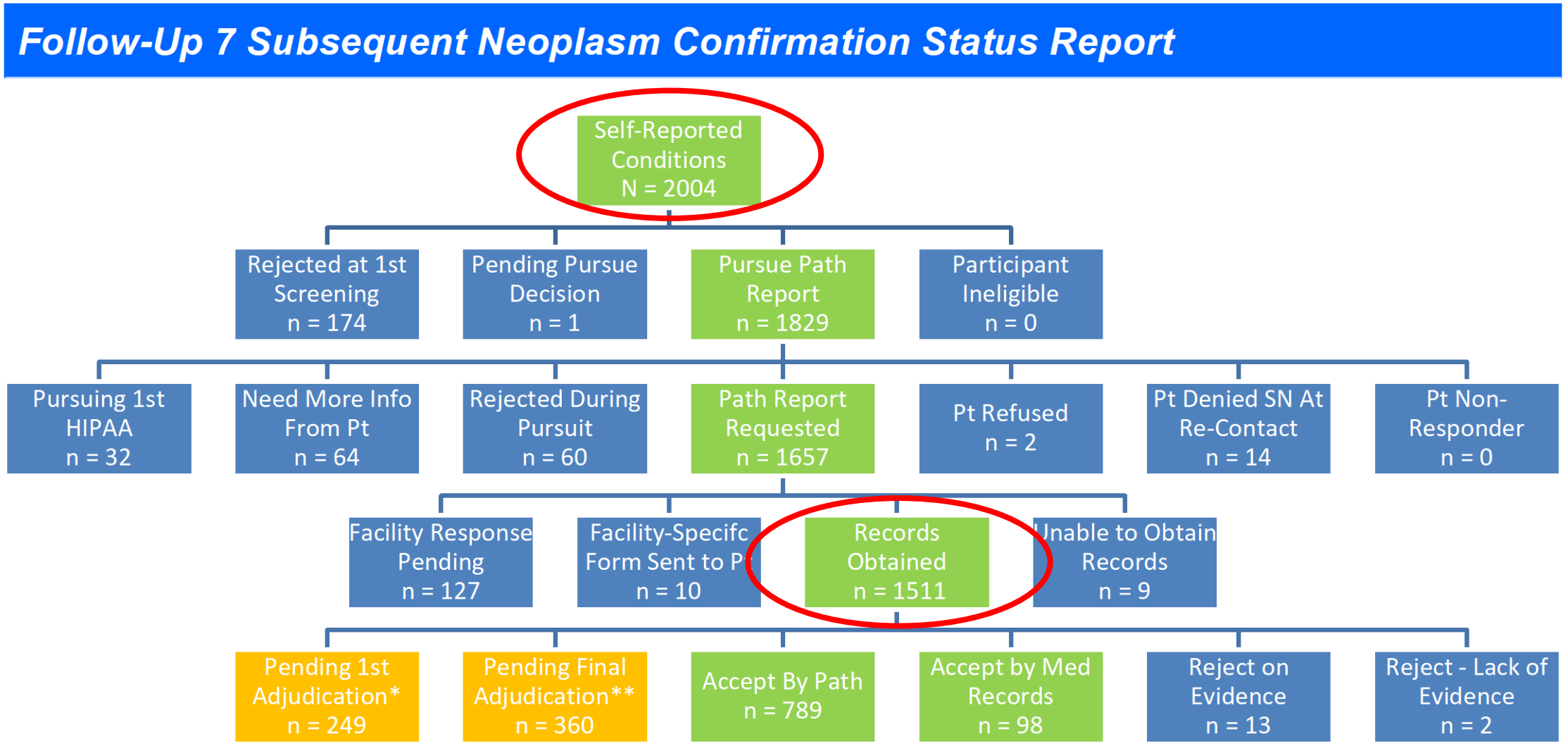

Virtual Pooled Registry (VPR)

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- Managed by the North American Association of Central Cancer Registries (NAACCR)
- Designed to facilitate streamlined linkages to multiple cancer registries using standard methodology
- CCSS one of two studies selected to pilot test VPR linkage – received data from 26 registries
  - Allows evaluation of all CCSS vs active participants only
  - Among potential SMNs identified by VPR, a reasonable match identified in CCSS for ~80% (i.e. may allow for identification of 20% more SMNs)
  - Strong concordance between site and diagnosis between CCSS and VPR
  - Limitations: different requirements for data release across registries (fixes in process), not all registries participating (increasing) , does not include non-malignant neoplasms (meningiomas)

Discussion: Challenges and Opportunities

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Current Opportunities

- 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
- VPR may provide a more efficient means of confirming SMNs

Questions? Interested in getting involved?

Contact Lucie Turcotte (turc0023@umn.edu) or
Joe Neglia (jneglia@umn.edu)

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St. Jude Children's Research Hospital