Genetics Working Group

Monica Gramatges

Yadav Sapkota

CCSS
Childhood Cancer Survivor Study

St. Jude Children's Research Hospital

An NCI-funded Resource

Thank you!

CCSS

- Thank you, Smita, for your valuable contributions and support of CCSS as Chair of the Genetics Working Group!

Scope of Research

CCSS

The Genetics Working Group, in collaboration with the Second Neoplasm, Chronic Disease, Psychology, and Epidemiology/ Biostatistics Working Groups, is charged with understanding the role of genetic susceptibility in understanding the pathogenesis of treatment-related adverse events and explaining the inter-individual variability in the association between treatment and adverse events.

Working Group Membership

CCSS

Adam Green
Lindsay Morton
Seth Rotz
Cindy Im
Lisa Mirabello
Zhaoming Wang
Eileen Dolan
Yadav Sapkota
Monica Gramatges

Working Group Progress

CCSS

14 Published/In Press Manuscripts (since 1/1/2023)
6 Currently Submitted Manuscripts
9 Analysis/Manuscript in Process
8 Ancillary Studies (with active NIH funding)
7 Concepts in development
14 New AOIs (total, since 1/1/2023)

Published/In Press Manuscripts (n=14)

CCSS

Year	Concept #	Title	Investigator
2023	21-09	Polygenic risk and chemotherapy-related subsequent malignancies in childhood cancer survivors: A Childhood Cancer Survivor Study and St. Jude Lifetime Cohort Study report (JCO)	Im/University of Minnesota
2024	21-09	Trans-ancestral genetic risk factors for treatment-related type 2 diabetes mellitus in survivors of childhood cancer (JCO)	Im/University of Minnesota
2023	20-24	Development and validation of age-specific risk prediction models for primary ovarian insufficiency in long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study and St. Jude Lifetime Cohort (Lancet Oncology)	Yuan/University of Alberta
2025	22-09	Contributions of cancer treatment and genetic predisposition to risk of subsequent neoplasms in long-term survivors of childhood cancer: a report from the St. Jude Lifetime Cohort and the Childhood Cancer Survivor Study (Lancet Oncology)	Sapkota/SJCRH
2025	18-02	DNA damage response and repair genes and anthracycline-induced cardiomyopathy in childhood cancer survivors: a report from the Children's Oncology Group and the Childhood Cancer Survivor Study (Circulation: Genomic and Precision Medicine)	Bhatia/UAB

Published/In Press Manuscripts (n=14)

CCSS

Year	Concept #	Title	Investigator
2025	18-02	Gene-level analysis of anthracycline-induced cardiomyopathy in cancer survivors: a report from COG-ALTE03N1, BMTSS and CCSS (JACC: CardioOncology)	Bhatia/UAB
2025	Ancillary study	The role of TTN and BAG3 in cancer therapy-related cardiomyopathy among long-term survivors of childhood cancer (JAMA Network Open)	Sapkota/SJCRH
2025	Ancillary study	Predicting the 10-year risk of cardiomyopathy in long-term survivors of childhood cancer (Annals of Oncology)	Sapkota/SJCRH
2024	17-20	Comparison of GWAS results between de novo tinnitus and cancer treatment-related tinnitus suggests distinctive roles for genetic risk factors (Scientific Reports)	Dolan/University of Chicago
2024	Ancillary study	The ENGAGE study: a 3-arm randomized hybrid type 1 effectiveness and implementation study of an in-home, collaborative PCP model of remote telegenetic services to increase update of cancer genetic services in childhood cancer survivors (BMC Health Services Res)	Henderson/University of Chicago

Published/In Press Manuscripts (n=14)

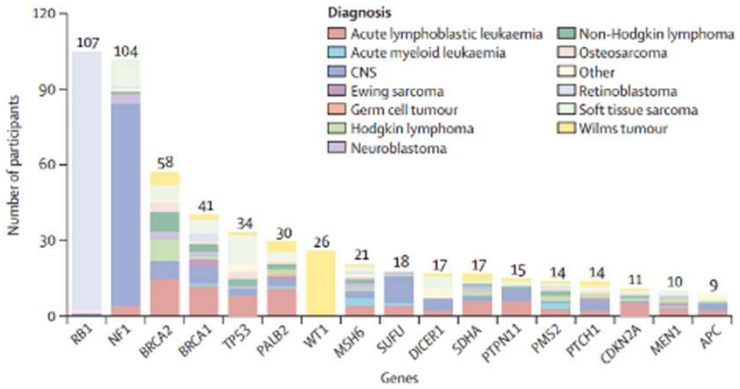
CCSS

Year	Concept #	Title	Investigator
2023	15-06	Targeted long-read sequencing of the Ewing sarcoma 6q25.1 susceptibility locus identified germline-somatic interactions with EWSR1-FL1 binding (AJHG)	Morton/NCI
2024	15-06	Frequency of pathogenic germline variants in pediatric medulloblastoma survivors (Frontiers in Oncology)	Morton/NCI
2024	No concept/used public data	Polygenic risk scores, radiation treatment exposures and subsequent cancer risk in childhood cancer survivors (Nature Medicine)	Gibson/NCI
2023	No concept/used public data	Cancer germline predisposing variants and late mortality from subsequent malignant neoplasms among long-term childhood cancer survivors: a report from the St. Jude Lifetime Cohort and the Childhood Cancer Survivor Study (Lancet Oncology)	Wang/SJCRH

Highlights of Recently Completed Research

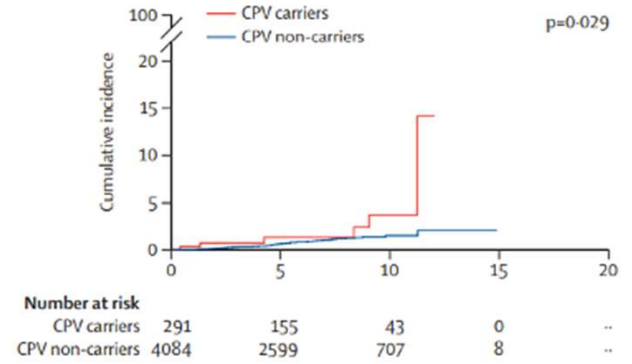
CCSS

Chen et al. (Wang) Cancer Germline Predisposing Variants & Late Mortality from SMN (*Lancet Oncology*, 2023)



Cohort	SMN-related mortality		
	subHR	95% CI	P-value
SJLIFE (4,402)	3.40	1.37-8.43	0.0082
CCSS (8,067)	3.58	2.27-5.63	<.0001
Combined (12,469)	3.54	2.36-5.32	<.0001

SJLIFE

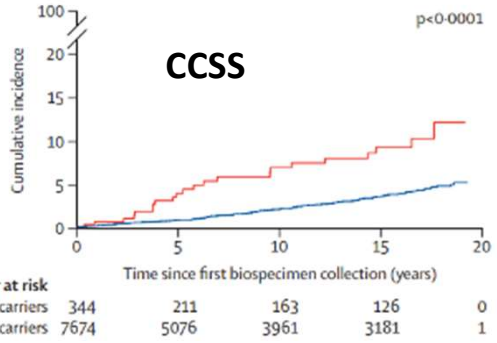


10-yrs

3.7%

1.5%

CCSS



10-yrs

6.9%

2.1%

Childhood Cancer Survivor Study

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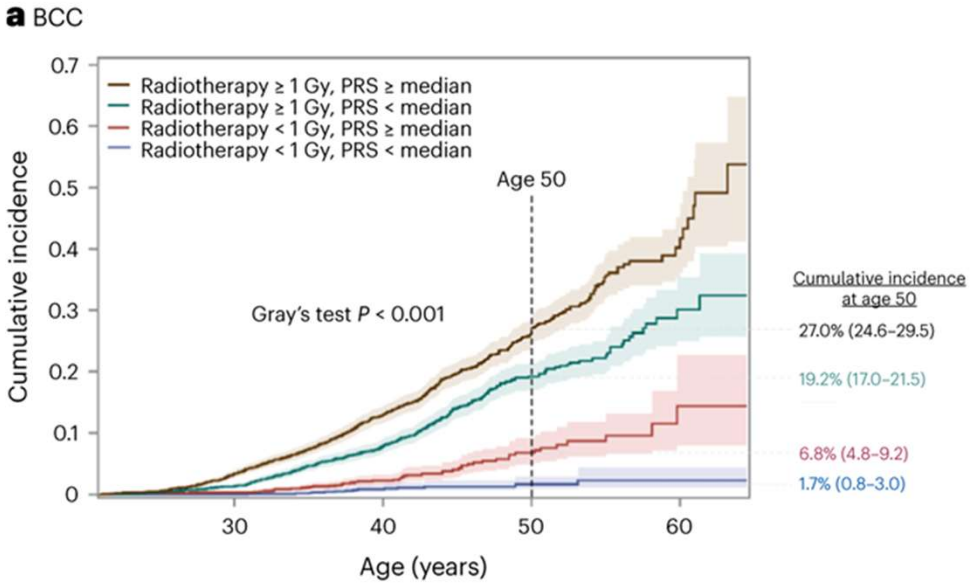
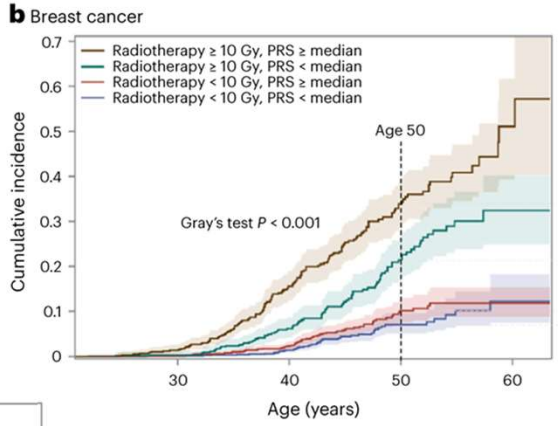
Highlights of Recently Completed Research

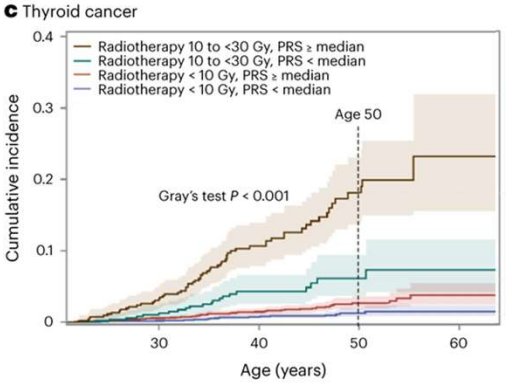
CCSS

<u>Gibson et al. (Morton)</u> Polygenic risk scores, radiation treatment exposures and subsequent cancer risk in survivors (*Nature Medicine*, 2024)



In joint effects analysis, the combination of high PRS and radiation exposure resulted in more-than-additive increased risk for BCC, breast cancer and thyroid cancer





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Highlights of Recently Completed Research

CCSS

Matt et al. (Zhou) St. Jude Survivorship Portal: Sharing and Analyzing Large Clinical and Genomic Datasets from Pediatric Cancer Survivors (*Cancer Discovery*, 2024)

Data content

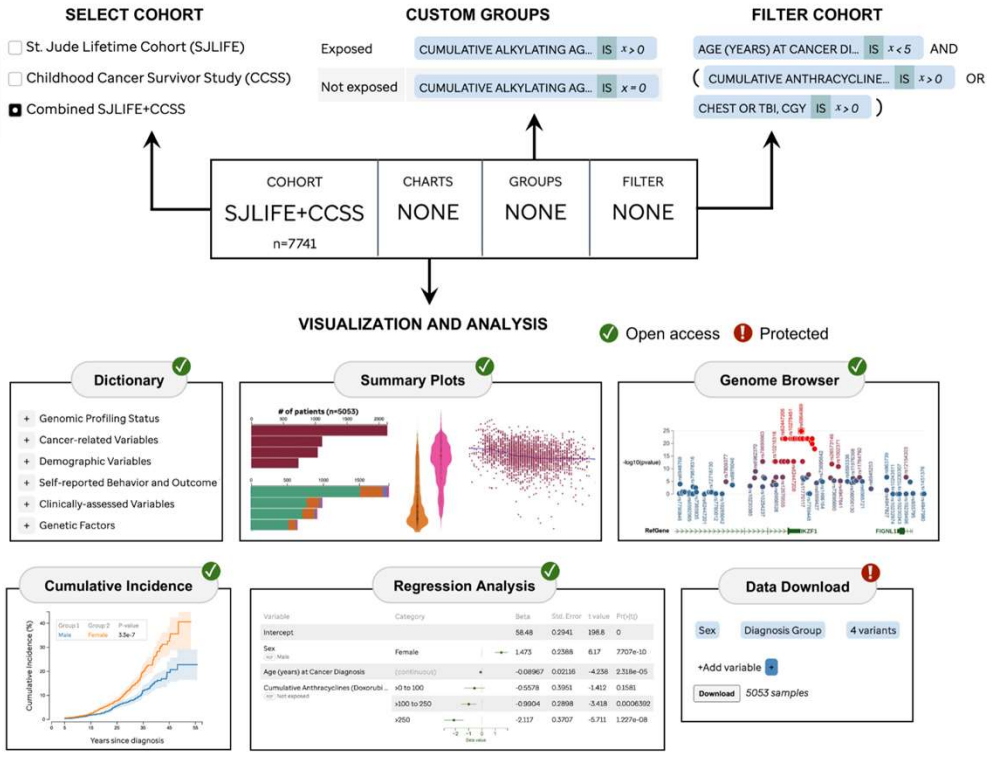
COHORTS
St. Jude Lifetime Study (SJLIFE), n = 5,053
Childhood Cancer Survivor Study (CCSS), n = 25,735

PHENOTYPIC DATA
Demographics, 36 variables
Cancer diagnosis and treatment, 99 variables
Clinical assessments, 350 variables
Chronic health conditions, 400 variables
Self-reported and questionnaire, 776 variables
Over 8.6M data points

GENETIC DATA
Whole-genome sequencing
>400M genotyped variants
>81M polygenic risk scores for >500 traits
Genetically defined ancestries
Ancestry-specific PCs and LD
~1.5TB genotype data

In collaboration with Zhou lab

Features



Childhood Cancer Survivor Study

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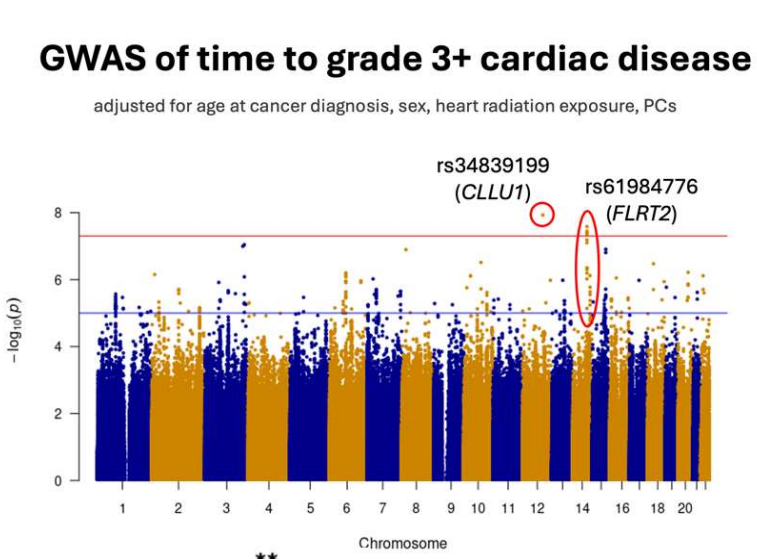
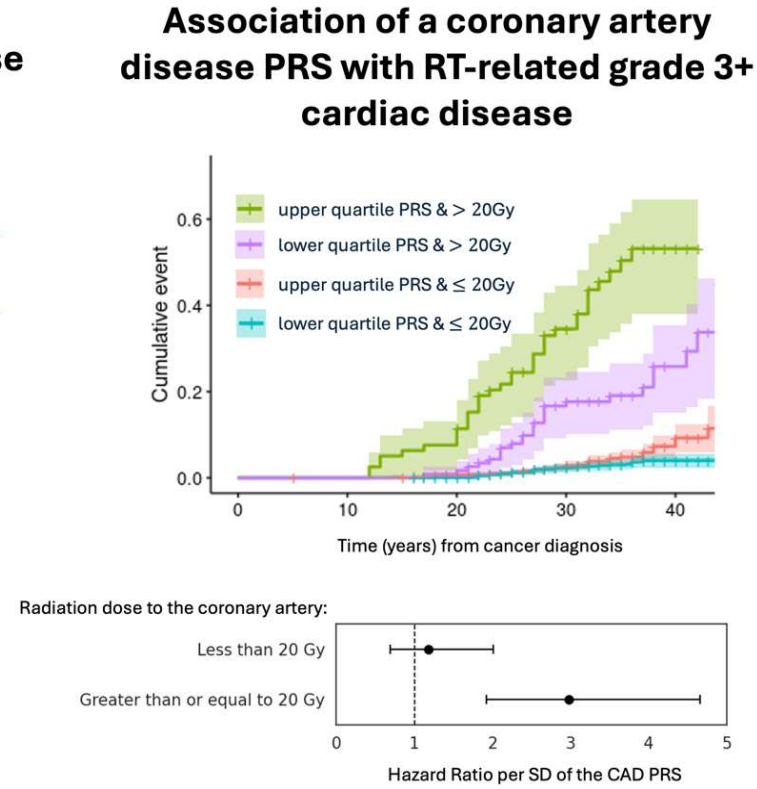
Highlights of Recently Completed Research

CCSS

Kerns et al. GWAS of radiation-associated cardiac disease (abstract, presented at RPS, 2024)



FLRT2 mRNA is elevated in rat heart @ 10wks post-RT vs sham treated



Childhood Cancer Survivor Study

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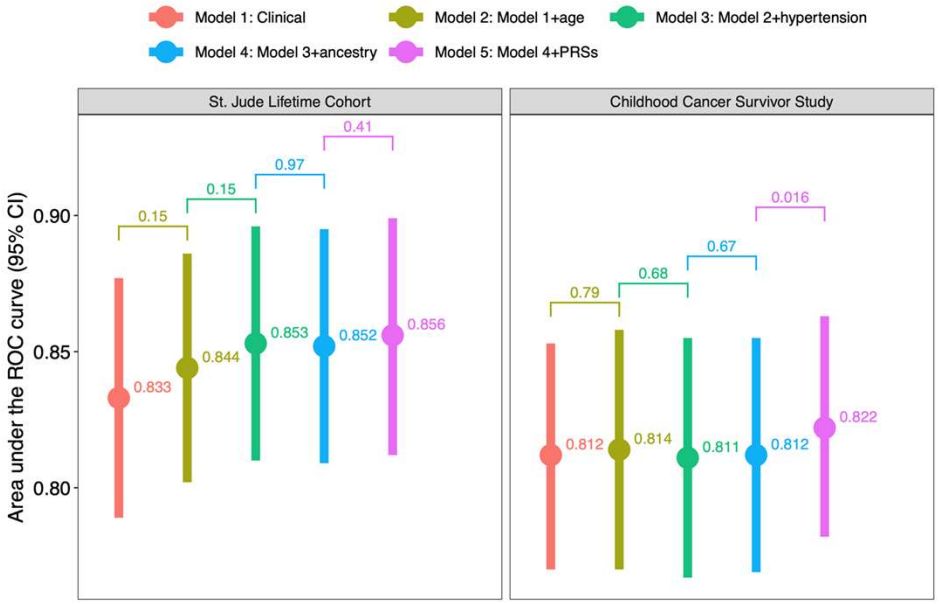
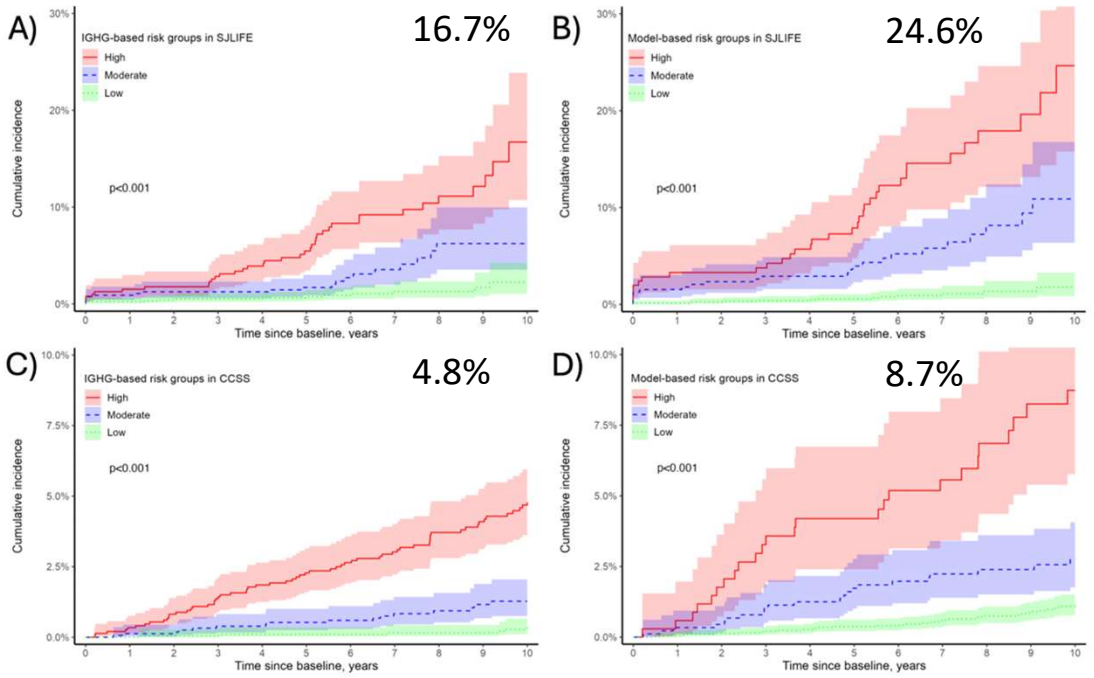
Highlights of Recently Completed Research

CCSS

<u>Petrykey et al. (Sapkota)</u> Predicting the 10-year risk of cardiomyopathy in long-term survivors of childhood cancer (*Annals of Oncology*, 2025, In Press)



Developed/validated models with highest-to-date performance for estimating 10yr risk of cardiomyopathy in survivors



IGHG-based Model-based

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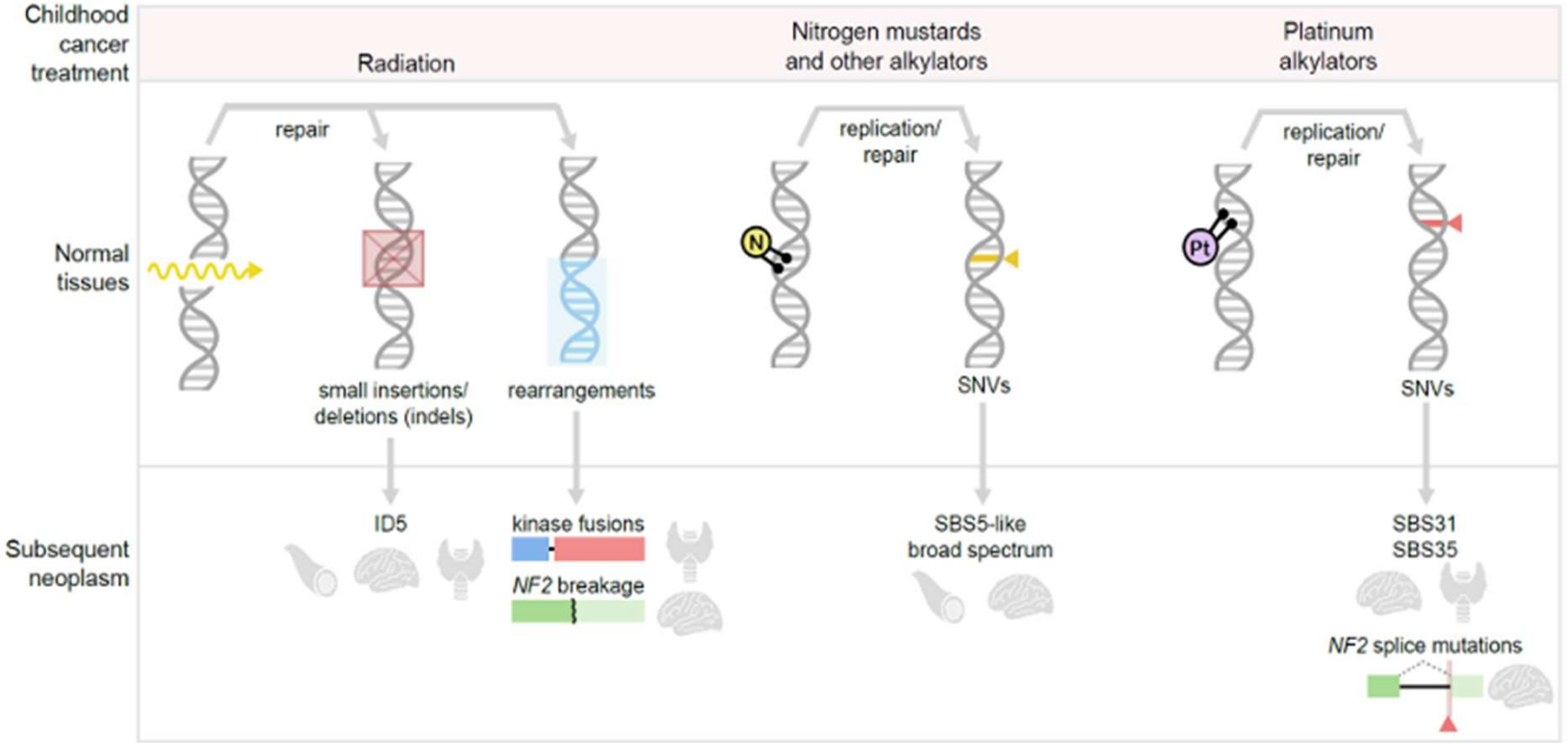
Highlights of Recently Completed Research

CCSS

<u>Brady et al. (Armstrong)</u> Impact of therapy-induced mutational signatures of SNs (manuscript in revision)



Currently Submitted Manuscripts (n=6)

CCSS

Year	Concept #	Title	Investigator
2025	Ancillary study	Genetic Risk for Pediatric ALL: Harnessing Data from SJLIFE and CCSS for Discovery of Etiology	Wang/SJCRH, Im
2022	23-15	Communication of Skin Cancer Risk Profiles to Childhood Cancer Survivors	Im/University of Minnesota
2021	21-20	The Genomic Landscape of Second Malignant Neoplasms from the Childhood Cancer Survivor Study	Brady/SJCRH*
2020	20-05	Genetic Contribution to Treatment-Related Dyslipidemia in Adult Survivors of Childhood Cancer: Findings from the CCSS, SJLIFE, and DCCSS-LATER Cohorts	Pluimakers/Princess Maxima
2020	Ancillary study	Improving delivery of genetic services to high-risk childhood cancer survivors (ENGAGE study)	Henderson/Univ of Chilcago
2018	18-02	Genetic Susceptibility to Anthracycline-Related Congestive Heart Failure	Bhatia/UAB

Analysis/Manuscript in Process (n=9)

CCSS

Concept #	Title	Investigator	Status
24-05	Rare and common variation associated with primary ovarian insufficiency risk in survivors of childhood cancer	Im/University of Minnesota, SAPKOTA	In progress: analysis underway
24-04	Actionable genetic variants and their associations with late effects risks and mortality among long-term survivors of childhood cancer	Im/University of Minnesota, SAPKOTA	In progress: analysis underway
22-11	Whole-genome sequencing of the youngest osteosarcoma cases using our current dataset plus in-house CCSS cases.	Mirabello/NCI	In progress: structural variant calling and analyses
22-08	Genetic Modification of Chemotherapy-Associated Subsequent Malignant Neoplasms	Watt/MSK	In progress: expansion analysis with SJLIFE
20-08	Genetic Association Study of Cardiac Toxicity Following Chest Radiotherapy	Kerns/MCW	In progress: SJLIFE validation underway
20-17	Long-Term Cost-Effectiveness of the Identification of Cancer Predisposition Syndromes in Survivors of Pediatric Leukemia, Brain Tumors and Bone/Soft-Tissue Sarcomas	Goudie/McGill University	In progress: PI notes issues with data access/analysis
19-17	A Genome-Wide Association Study for Frailty in Adult Survivors of Childhood Cancer	Gramatges/BCM	In progress: working with Dutch cohort
19-05	Genetic Susceptibility to Neurocognitive Impairment Secondary to Childhood Cancer Treatment	Scheurer/BCM	In progress: manuscript in draft
18-19	iPSC-Cardiomyocyte and RNAseq Identified Genes and Cardiomyopathy (via GWAS RFP Process)	Reyes/Hildebrandt/MD Anderson	In progress: revisiting the analysis and updating manuscript

Ancillary Studies with active funding

CCSS

Cardiomyopathy/Cardiovascular Outcomes

- Wang: Epigenetic Approach in Understanding the Risk of Cardiometabolic Conditions
  - R01CA290112*
- Im/Sapkota, Leveraging clinical, genetic, and social determinants of health-related risk information to predict cardiomyopathy risk in African American survivors
  - R01HL173881*
- Yeh, Cardiomyopathy Simulation Model Utilizing GWAS Data
  - R01CA227576

* **Awarded since 01/01/2023**

Ancillary Studies with active funding

CCSS

Novel Approaches and Uses of Genetic Data

- Wang/Im: Genetic pleiotropy across pediatric cancers, and cancer-related outcomes
  - R01CA283333*
- Wang: Trajectories of Epigenetic Aging & Health Outcomes in Survivors
  - R01CA279520*
- Im: Treatment-specific genetic risk scores for late effects prediction in survivors
  - R21CA261833

Understanding and Communicating Genetic Risk

- Green: Investigation of Germline Predisposition to Pediatric Treatment-Induced HG Glioma
  - R01NS133339*
- Henderson/Kim: Improving delivery of genetic services to high-risk survivors
  - R01CA255269

* **Awarded since 01/01/2023**

Concepts in development (n=7)

CCSS

Outcomes

Cardiovascular disease/cardiomyopathy (1)

Radiation-related late effects (1)

Mortality (2)

Colorectal SMN (1)

Approaches

Pharmacogenomics (1)

X chromosome PheWAS (1)

Career Development Award

CCSS

Han-Wei Wu, MD
Memorial Sloan Kettering Cancer Center

Mentor: Chaya Moskowitz, PhD

Aim 1: To characterize and compare the prevalence and distribution of P/LP variants in survivors with subsequent colorectal cancer, compare it with those in the general population, and explore if results differ by treatments

Aim 2: To estimate the associations of P/LP variants with subsequent colorectal cancer risk and explore how results differ by treatment exposures

Plan to Utilize FU7 Newly Frozen Data

CCSS

- Assess if FU7 the number of survivors affected by health outcomes increased, if necessary to revisit previously conducted genetic analyses
  - e.g., mortality and number of death events
- New genetic analyses on outcomes previously not feasible due to limited sample size
  - e.g., aging-related outcomes, subsequent neoplasms

Plan for Concept Development Using FU8 Survey Data Focused on Aging

CCSS

- Genetic associations with aging outcomes
- Utilize DNA methylation and clonal hematopoiesis data ~2,300 CCSS survivors (NCI supplemental funding, data availability pending)

Opportunities for Collaboration with Other Working Groups

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- Chronic disease (aging-related outcomes)
- SMN (as sample size increases)
- Funding opportunities that connect those with clinical and genomic expertise (e.g., an RFA that supports/requires clinical and basic/statistical collaboration)

As CCSS Engages with Participants This Year What Would You Like to Learn From Them?

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- New SMNs, aging-related conditions
- Return of results: do participants wish to know their genetic risk?
  - What if results are clinically actionable?
  - Would survivors be interested in a lay language CCSS portal describing results (access to general results available, but not personal results)?

Value Added to Your Working Group by a 2000-2025 Cohort Expansion (Top 5)

CCSS

- Genetic contributions to late effects associated with more contemporary approaches to treatment
- Novel therapeutics data
- Larger sample size
- Sample heterogeneity (with respect to background)
- Geographic representation
- Added late effects granularity from automated disease and treatment data extraction

Special Considerations for a Cohort Expansion Specific to Your Working Group

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- Focus on recruiting heterogeneous survivors, representative of the US general population

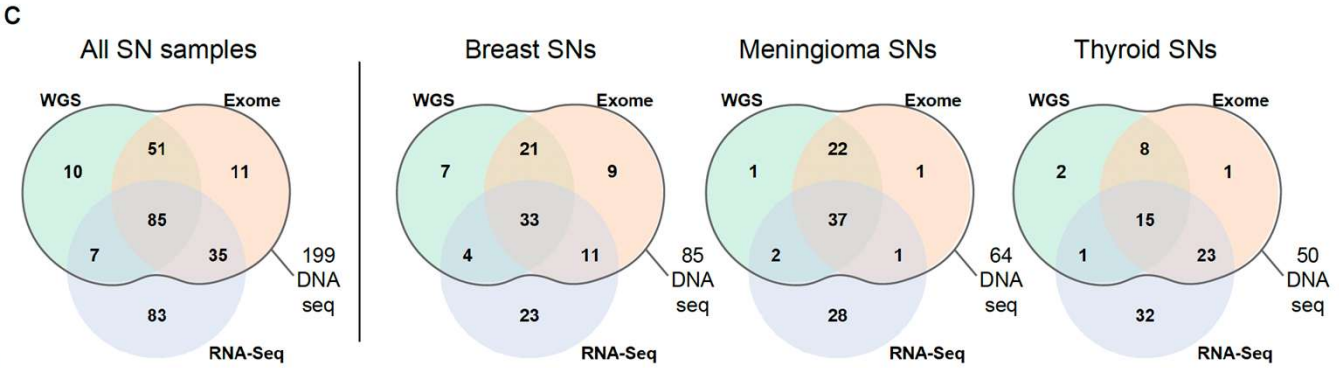
- Prioritize collecting blood samples for biomarkers studies
  - Consider obtaining longitudinal samples
  - Explore novel approaches to collect biospecimens

- Extraction of family history and disease-based genetics data

Five Year Plan: Progress Update

CCSS

- Conduct hypothesis-driven research *(prior stated goal)*
  - Understand mechanistic pathways for treatment-related complications, develop integrated risk-prediction models for precision prevention & identify druggable targets
- Enhance resources (*prior stated goal*)
  - WGS/WES/RNAseq of 199 SNs (breast, meningioma, thyroid) from 159 CCS + germline
  - DNA, RNA, plasma from 1,350 survivors with Grade 3+ CHCs (ongoing)
  - DNA methylation & clonal hematopoiesis data (underway)



Childhood Cancer Survivor Study

An NCI-funded resource

Current Top Priorities: One-Year Deliverables

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- Develop guidance for when/under what circumstances an AOI, or concept is needed
- Develop criteria for inclusion of risk calculators developed using CCSS data as a tool on the CCSS website
- Consider publishing GWAS summary statistics on the CCSS website (in addition to required data deposition)
- Continue to investigate genetic/molecular associations with late effects as well as novel approaches to using the genomic data

Discussion: Opportunities and Threats

CCSS

Threats:

- Limited dissemination of risk scores/tools developed using genetic data
- Lack of available information to guide investigators regarding benefits/pitfalls to access/use of the public data vs. use of the CCSS concept submission pathway
  - Need for transparency regarding data strengths and limitations

Opportunities:

- Develop strategies to augment clinical utility and dissemination of risk scores/tools
- Develop resources to guide investigators seeking genomic data for survivor research
  - Encourage investigators to reach out to team that collected the data to understand data elements
- Collaboration with other survivor cohorts – need for an international consortium?
  - Augment representation of heterogenous populations and include sites that represent new geographic areas/rural regions of the country (and their biospecimens)
  - Harmonize phenotype and molecular data