Chronic Disease Working Group

CCSS Investigator Meeting – June 2025

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CCSS
Childhood Cancer Survivor Study

St. Jude Children's Research Hospital

An NCI-funded Resource

Scope of Research

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- Epidemiology of chronic health conditions (i.e., vital organ dysfunction)
  - Adapted NCI-CTCAE v5 grading of conditions (grades 1-5)
  - Focus on “accelerated aging”
  - Inform guidelines of late effects surveillance

Grade	Definition
1	Mild
2	Moderate (meds)
3	Severe/disabling
4	Life-threatening
5	Fatal

- Prediction models for select outcomes
  - Collaboration with Epidemiology, Genetics, Psychology Working Groups

Gibson & Mostoufi-Moab, Lancet Oncol 2018
Oeffinger, NEJM 2006

- Ancillary studies designed to improve ascertainment & mitigate development of serious health conditions
  - Collaboration with Cancer Control Working Group

Working Group Membership

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Kevin Oeffinger (co-chair)	*Primary care*
Eric Chow (co-chair)	Pediatric oncology
Saro Armenian	Pediatric oncology
James Bates	*Radiation oncology*
Rusha Bhandari	Pediatric oncology
Louis (Sandy) Constine	*Radiation oncology*
Stephanie Dixon	Pediatric oncology
Danielle Friedman	*General pediatrics*
Rebecca Howell	*Radiation dosimetry*
Melissa Hudson	Pediatric oncology
Nina Kadan-Lottick	Pediatric oncology
Wendy Leisenring	*Biostatistics*
Sogol (Goli) Mostoufi-Moab	*Pediatric endocrinology / oncology*
Daniel Mulrooney	Pediatric oncology
Tim Ohlsen	Pediatric oncology
Kayla Stratton	*Biostatistics*
Emily Tonorezos	*Internal medicine / NIH*
Brent Weil	*Surgery*
Christopher Weldon	*Surgery*
Vikki Nolan*	*CCSS Data Coordinating Ctr*

Calls q1-2mo to review concepts / analyses, discuss priorities

1st Tuesdays of the month @ 11am PT

Surgery working group
Danielle Cameron – Gen Surg
Erik Geiger - Ortho
Andrew Murphy – Gen Surg
Duncan Ramsey – Ortho
Brent Weil – Gen Surg
Chris Weldon – Gen Surg

Working Group Progress

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12 Published/In Press Manuscripts (since 1/1/2024)
4 Manuscripts under Review
15 Analyses/Manuscripts in Process
12 Concepts in development
9 New AOIs (since 1/1/2024)

Ancillary Studies

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- Estimating the burden of disease associated with late-effects among childhood cancer survivors (Yeh / ACS Research Scholar Grant)
- Genetic testing to guide pediatric cancer care and follow up: using anthracycline-associated cardiac toxicity as a model for the future (Yeh / R01)
- CHIIP Study: Improving assessment & treatment of CV risk factors (Chow / R01)
- SALSA – Study of Active LifeStyle Activation to improve diet & activity (Chow / R01 / "CHIIP2")
- Risk of adverse cardiometabolic outcomes after TBI (Friedman / ACS Clinician Scientist Award; CIBMTR linkage/support)
- Improving prediction of late cardiac disease associated with radiotherapy (Howell / Mulrooney / Yasui / R01)
- Examining the immune phenotype of long-term survivors vs controls (Dhodapkar / institutional funds)
- Decreasing cardiometabolic risk via time-restricted eating – randomized clinical trial (Friedman / R01)

Featured Study: Health Outcomes in Older Survivors

Rusha Bhandari – 2022 CDA awardee

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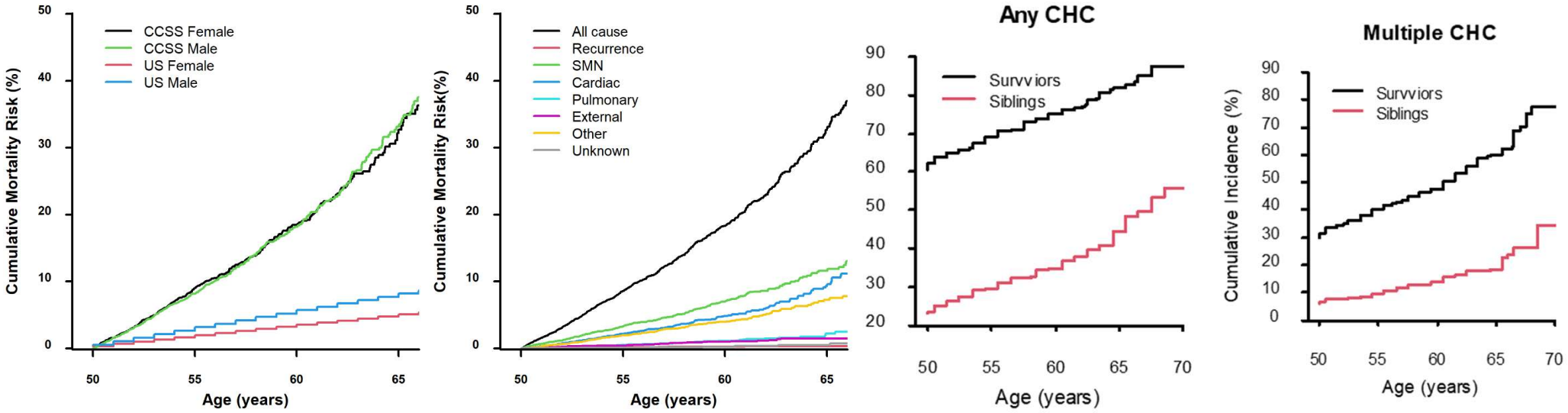
- Focused on outcomes condition on surviving to age 50 (n=7490)
  - Mortality, SMNs, CHCs, frailty, health status



SMR ~5 for new cancers, driven by RT exposure; 40% population attributable fraction for new cancers

Risk for CHCs incr'd vs siblings, but only in RT-exposed group

Bhandari et al., Under Review

Childhood Cancer Survivor Study

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Featured Study: Modeling Accelerated Aging

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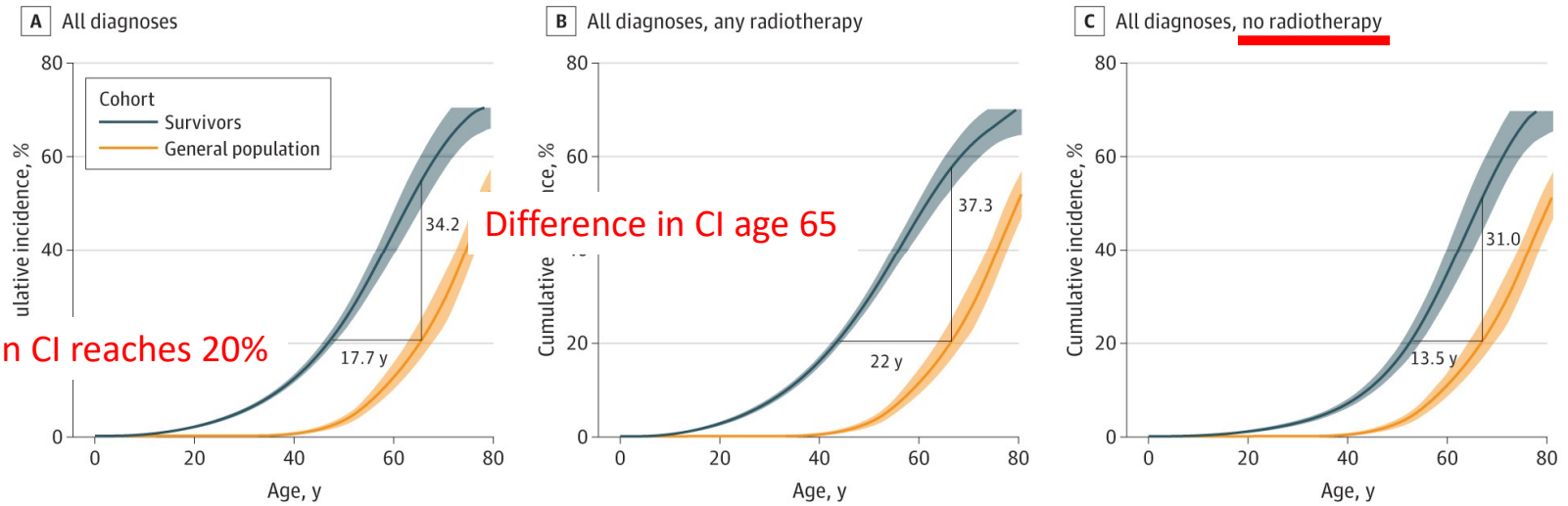
- Estimate lifetime risks of 8 key late effects among CCS vs Gen Pop



- No differences between sexes
- 1990s had greater excess deaths from these conditions vs 1970s (due to decr'd late recurrence)

Yeh et al., JAMA Oncol 2025

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Featured Study: Exposure-based Risk Stratification of Future Conditions & Mortality

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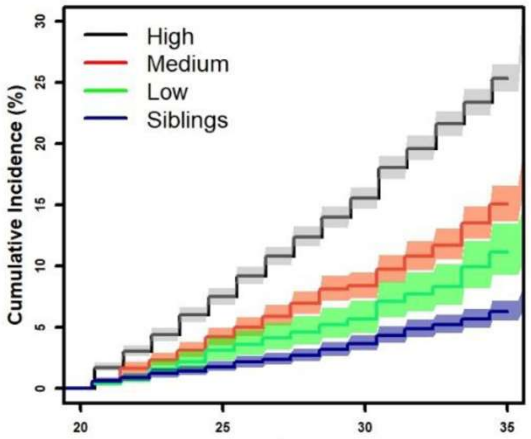
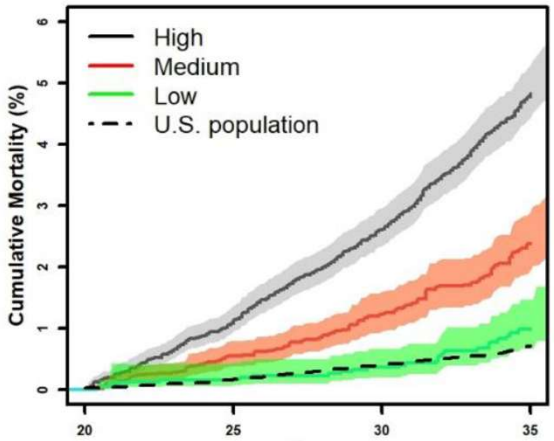
- Test UK-based exposure-based risk stratification model *(Frobisher et al., BJC 2017)* & development of future chronic conditions and mortality

Risk	Dx	Original UK	*CCSS adapted*
Low	ALL	No RT	Limit DED ≤100 mg/m^2
	Wilms	Surgery only	No RT, no anthracycline
	Non-CNS	Surgery only	Same
Medium	CNS	No RT	Same
	Others	All NHL	Anyone not low/high risk
High	Any	ALL with transplant or CRT ≥24 Gy	Same but any dx with those exposures
		Any RT or chemo (except NHL)	Any RT to neck, chest, abdomen, pelvis CED ≥10 gm/m^2; CDDP >400 mg/m^2; DED ≥250 mg/m^2





The UK model was able to stratify CCSS into distinct groups & may form the basis for future strategies that refine long-term follow-up

Dinan et al., Under Review

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Featured Study: Many More at ISLCCC

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- Oral
  - Bottinor et al., CV risk factor severity & subsequent adverse CV events
  - Friedman et al., CV risk factors among BMT survivors: CCSS-CIBMTR linkage
- Posters
  - Ohlsen et al., Treatment and lifestyle profiles of healthy aging survivors
  - Petrykey et al., Risk prediction of dyslipidemia: SJLIFE & CCSS
  - Ramsey et al., Long-term outcomes among Ewing sarcoma survivors
  - Ramsey et al., Local control procedures & outcomes in lower extremity sarcoma survivors

Plan to Utilize FU7 Newly Frozen Data

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Expands number of serious CHCs, facilitating prediction models

- Review/revise CVD prediction models – some discrepancies with subsequent guidelines & develop as possible EHR-embedded tool (Noyd/Chow)

- Explore other potential serious outcomes for prediction?
  - Infectious death (Chebab/Fisher)
  - Pulmonary outcomes? Obstructive / restrictive disease
- Inverse of current models – predictors of <u>healthy</u> lifespan?
  - Concept focused on healthy survivors (Ohlsen/Chow)
- Other analyses of conditional outcomes after an event
  - Concept to examine CHCs after growth hormone deficiency (Yoshida/Delaney/Close/Meacham)
  - AOI/concept to examine CV outcomes with early menopause (Ketterl/Levine)
  - Select surgical outcomes? CABG, cataract, joint replacement, valve replacement (Surgical WG)

Plan for Concept Development Using FU8 Survey Data Focused on Aging

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- Older survivor analyses under review *(Bhandari/Armenian)*
- Blood banking of participants with grade 3-4 CHCs (n~1500 and ongoing) & matched controls (n~1900)
  - Study of CHIP? *(Bolton/Friedman)*
- Functional outcomes? Other rare outcomes?
  - GHD safety & late effects *(Yoshida/Delaney/Close/Meacham)*
- Case-control of frail vs non-frail? Healthy vs accelerated aging?
  - Study of “healthy” aging already ongoing *(Ohlsen/Chow)*

Opportunities for Collaboration with Other Working Groups

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- Incorporation of genetic predictors to demographic and clinical predictors
  - Interesting, but hard to say when would become clinically impactful
  - CHIP more likely to become clinical biomarker than PRS? (Friedman / Bolton)

- Clinical trials to mitigate serious CHCs
  - Health services and lifestyle focused; many leverage behavioral modification strategies
  - Primary focus has been cardiovascular/metabolic -> can we propose a more holistic PCP facing intervention addressing multiple serious CHCs, which include SMNs? (Henderson – Lurie Children's)
  - Challenge of drug-based intervention? Metformin proposal with decentralized clinical trial structure (Bramante – UMN)

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

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- Greater involvement of survivor scientists / advocates within CCSS leadership

- Bi-directional engagement with Participant Advisory Committee to further inform research projects, future scientific direction

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

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1. New therapies, including radiation and surgical approaches
2. More diverse population than those from 1970s-90s
3. Expanding outcomes assessments beyond PROs? EHR-based outcomes?
4. Possibility of comparing outcomes with COG clinical trial participants (randomized)
5. Renew cohort numbers given attrition

Special Considerations for a Cohort Expansion Specific to Your Working Group

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- Are existing PROs sensitive enough to detect new toxicities? Many new treatments are immune-based; immune/infectious outcomes are only crudely captured; auto-immune phenomena not at all
  - More sensitive neuropathy PROs
  - Better assessment of late infections
  - Better assessment of auto-immune/rheumatologic conditions
- Interest in younger generation in filling out long PROs?
- Explore outcomes assessments via other methods (claims data, registries, EHRs)
- mHealth tools deployed more broadly? Physical activity, sleep, arrhythmia, spirometry?
- Cohort expansion an opportunity for CCSS to reposition itself as a truly unique cohort as ability to enrich survivors with novel cancer exposures leverages COG's reach with clean comparators

Five Year Plan: Progress Update

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Areas of focus specified in the U24 renewal:

- Evaluating risk based on organ system & cancer type, by temporal changes in therapy

Disease	Status
ALL	JCO 2020
AML	Blood 2023
CNS-MB CNS-Glioma	JCO 2019 Nat Cancer 2024
HL	JCO 2021
NHL	JCO 2019
NB	JCO 2023; JNCI 2024
OS	PBC 2024
Ewing	Manuscript drafted
RMS	Analysis underway
Wilms	JCO 2023

Five Year Plan: Progress Update

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Areas of focus specified in the U24 renewal:

- Evaluating risk based on organ system & cancer type, by temporal changes in therapy
- Improve phenotyping of outcomes & exposures, including surgical outcomes (Dieffenbach, Lancet Oncol 2023; several other detailed surgical papers in process)
- Effects of aging, accelerated aging? (Esbenshade, JCO 2023; Bottinor, JACC 2024; Yeh, JAMA Onc 2025; Bhandari, under review)
- Risk prediction, adding in genetic predictors (Bhatia/Sapkota, CV genetics; Wu, kidney; Im/Yuan, ovarian; Dinan/Oeffinger, overall)
- Develop interventions to mitigate chronic health outcomes, leverage genetics to enhance precision survivorship (CHIIP, SALSA, STRENGTH, ECHOS2)
- Linkages with other datasets to enhance the resource (CARDIA, CIMBTR, Medicaid, Medicare?, OPTN, SART, STS?)
- Refine radiation dosimetry (Bates/Constine/Howell, cardiac substructure, JCO 2023)