Chronic Disease Working Group

A Report from the Childhood Cancer Survivor Study

Investigator Meeting – June 2023

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CCSS

Childhood Cancer
Survivor Study

Childhood Cancer
Survivor Study

Scope of Research

- Epidemiology of chronic health conditions (i.e., vital organ dysfunction)
  - Adapted NCI-CTCAE 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

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

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

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

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Working Group Membership

Kevin Oeffinger (co-chair)	*Primary care*
Eric Chow (co-chair)	Pediatric oncology
Saro Armenian	Pediatric oncology
James Bates	*Radiation 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*
Aaron McDonald*	*Epidemiology/CCSS Data Coordinating Ctr*
Sogol (Goli) Mostoufi-Moab	*Pediatric endocrinology / oncology*
Daniel Mulrooney	Pediatric oncology
Kayla Stratton	*Biostatistics*
Emily Tonorezos	*Internal medicine / NIH*
Brent Weil	*Surgery*
Christopher Weldon	*Surgery*

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

1st Tuesdays of the month @ 11am PT

Contact Eric Chow
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Working Group Progress

14 New AOIs (since 2020; but only 3 since 2022)

6 Concepts in development (not yet approved)

22 Analyses/manuscripts in process

10 Published/in press (since 2022)

Concepts in Development

- Outcomes after spinal tumor cancers (Geiger)
- CHCs and lifestyle in twins (ancillary study-Haydon)
- Infant cancer outcomes (Goldsby)
- BMI at cancer diagnosis and risk of future CHCs (Turcotte)
- Early menopause and CHC risk (Ketterl)
- Upper extremity sarcoma outcomes (Becktell)

Published since 2022

- Bates/Constine/Howell – Cardiac substructures & XRT, JCO 2023
- Chow/Yasui – CVRF underdiagnosis & undertreatment, JAHA 2022
- Esbenshade/Ness – Cumulative Illness Rating Scale, JCO 2023
- Friedman/Henderson – Infant neuroblastoma, JCO 2023
- Geiger/Srivastava/Wustrack – 2ndary amputation / limb salvage, CORR 2022
- Dieffenbach/Murphy/Weil/Weldon – Late surgeries, Lancet Oncol 2023
- Noyd/Oeffinger – CV disparities, JACC Card Onc 2023
- Turcotte/Leisenring/Chow – AML outcomes, Blood 2022
- Weil/Armenian – Wilms tumor, JCO 2023
- Wu/Yasui/Chow – Kidney failure prediction, JCO 2023

Analyses under peer review or final draft

- Becktell/Schwartz – Osteosarcoma outcomes
- Bottinor/Chow – Conditional CV outcomes
- Keefe/Leisenring/Ginsburg – Society for assisted reproductive technologies linkage
- Lange/deBlank/Bowers/Okcu – Astrocytoma & ependymoma outcomes
- Murphy/Weil – Pelvic sarcoma
- Wilson/Ness – ALL & NHL physical function

Approved Concepts – Current Status

Active analyses

Focused outcomes

- Bhandari/Armenian – Older survivors
- Bottinor/Chow – Update on CVRF development
- Brown – Hearing Impairment
- Cohen-Levy/Weil – Total joint arthroplasty
- Hoover/Oeffinger/Scott – Activity changes & trajectory of CVRF
- Ronsley/Chow/Mostoufi-Moab – CNS tumor endocrine outcomes

Disease-based analyses

- DeBlank – Astrocytoma & ependymoma
- Demedis/Chow/Ness –Rhabdomyosarcoma
- Friedman/Phelan/Leisenring/Chow – CIBMTR-TBI
- Murphy – Pelvic sarcoma
- Ramsey/Shulman/DuBois – Ewing sarcoma

Ancillary Studies

- Yeh/Leisenring – Microsimulation modeling of health outcomes
- Chow/Oeffinger/Yasui – CHIIP Study (CVRF control)
- Chow/Oeffinger – SALSA Study (lifestyle)
- Dhodapkar/Bhatia – Immune phenotypes of survivors

Manuscripts in preparation

- Dinan/Oeffinger/Leisenring – Chronic conditions prediction
- Friedman/Oeffinger/Henderson – Neuroblastoma outcomes by sub-group
- Janitz/Lupo – Congenital conditions & impact on chronic health
- Bjornard/Ness – Female sexual dysfxn & chronic health

Active Ancillary Studies

- <u>Estimating the burden of disease</u> associated with late-effects among childhood cancer survivors (Yeh / ACS Research Scholar Grant)

- <u>Genetic testing</u> 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 and treatment of <u>CV risk factors</u> among childhood cancer survivors (Chow / R01)

- SALSA – Study of Active LifeStyle Activation to improve <u>diet & activity</u> (Chow / R01 / "CHIIP2")

- Risk of adverse <u>cardiometabolic outcomes</u> after TBI (Friedman / ACS Clinician Scientist Award; CIBMTR linkage/support)

- Examining the <u>immune phenotype</u> of long-term survivors vs controls (Dhodapkar / institutional funds)

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- Central review of all late major surgeries (requiring gen'l anesthesia; <u>n>30k</u>), mapped to ICD-9 CM codes

- Survivors vs siblings: RR 1.8 (1.7–1.9)
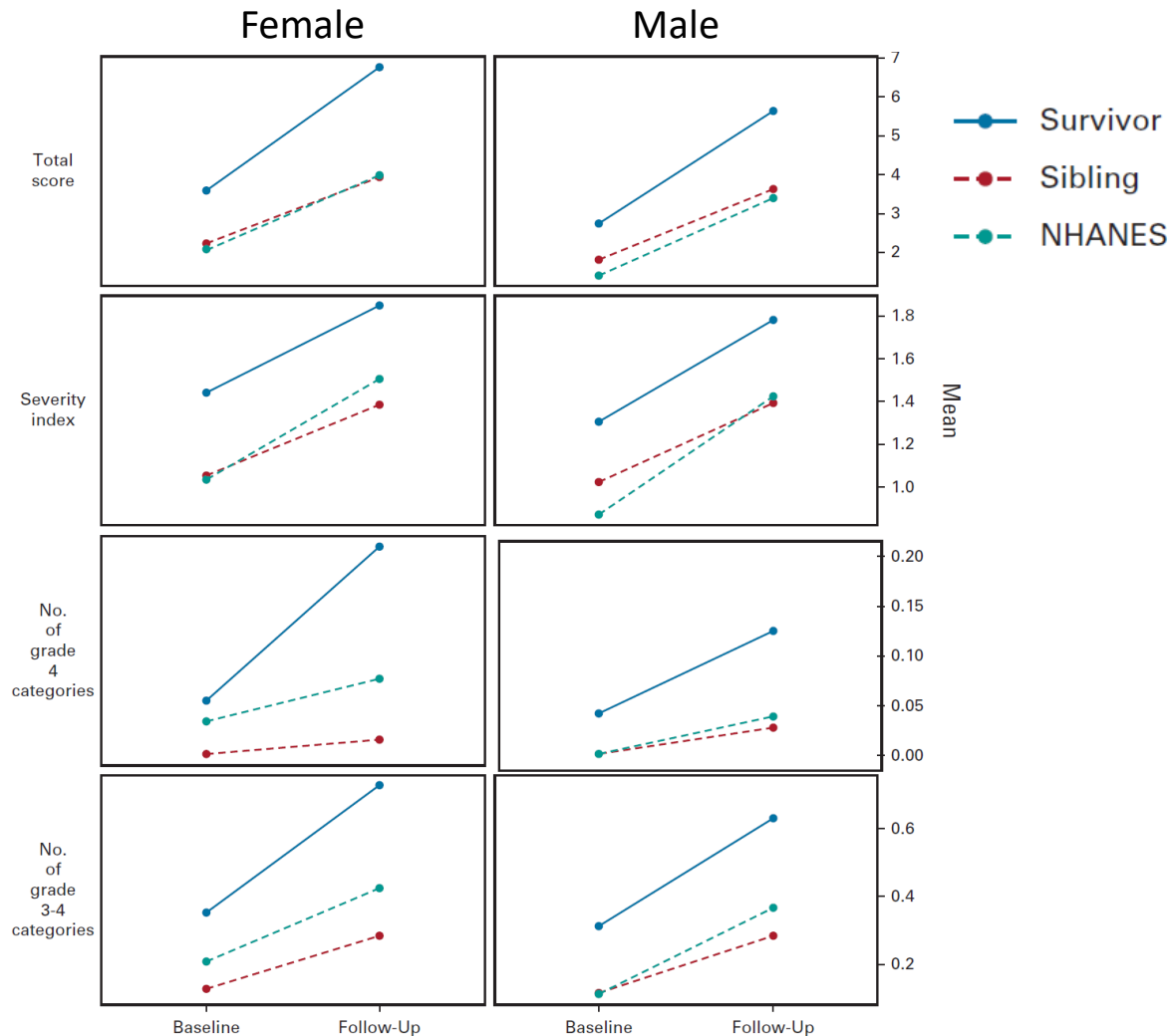
- 1990s vs 70s: RR 1.4 (1·3–1·5)
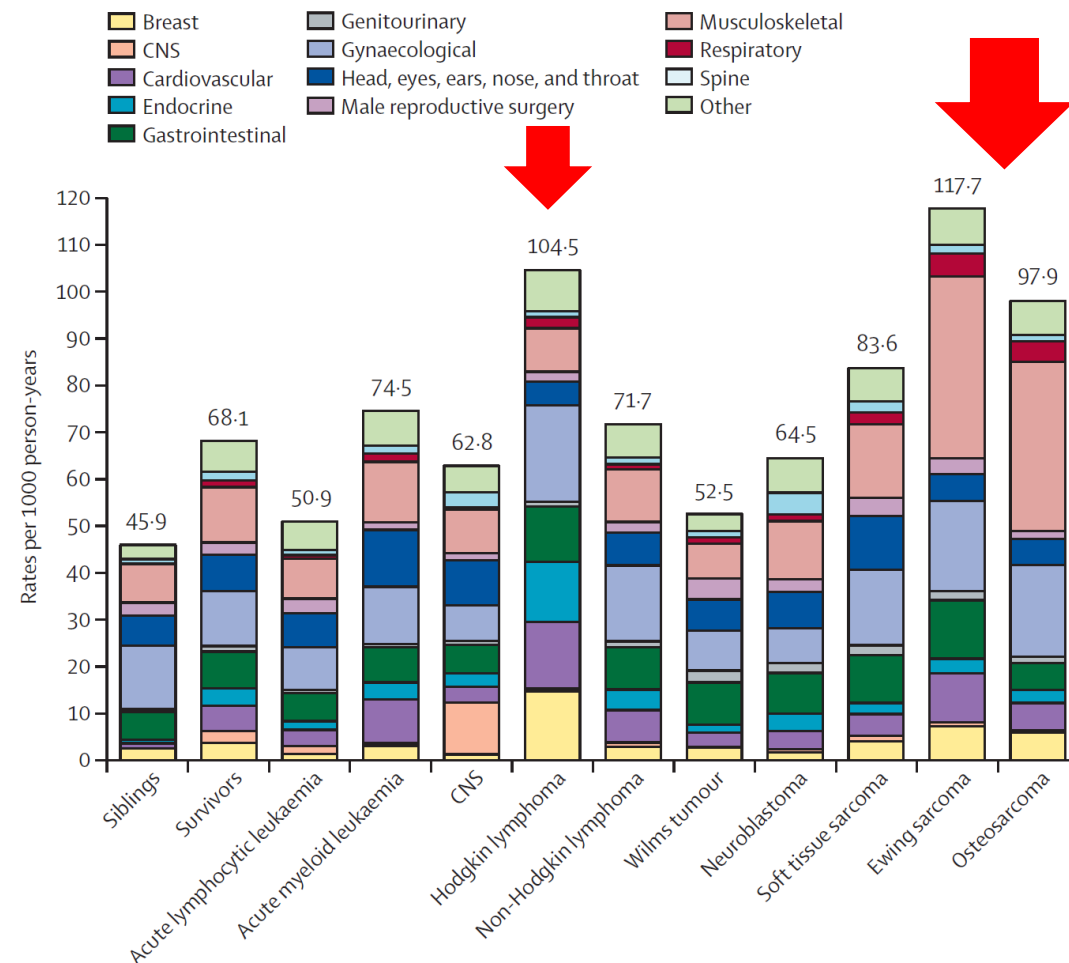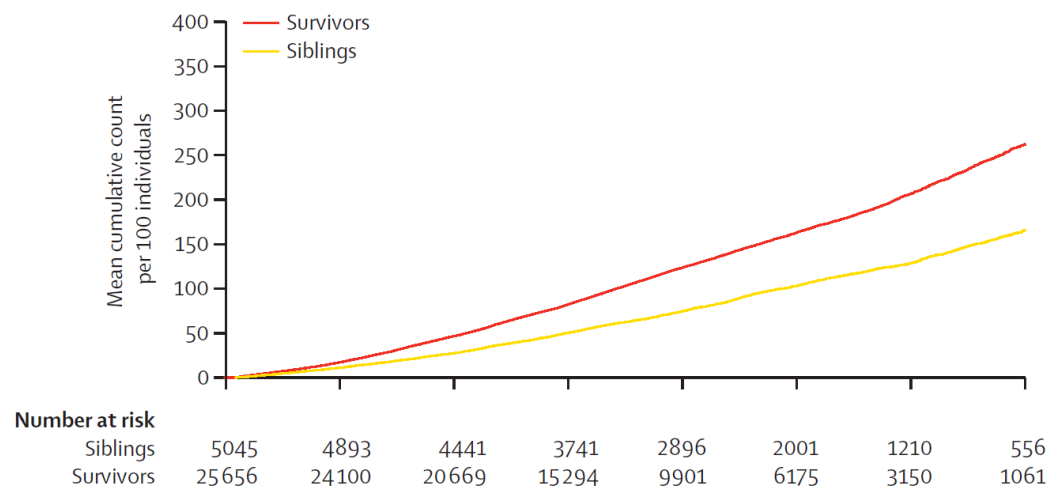
- Hodgkin, Ewing, Osteosarcoma: ~3 major surgeries/survivor on average over 35 year period

Whole new domain of outcomes to explore in detail

Dieffenbach/Murphy, Lancet Oncol 2023

Featured Study: Accelerated Aging

- Applied Cumulative Illness Rating Scale for Geriatrics (CIRS-G) to survivors, siblings, and NHANES to describe the accumulation of comorbidities over time

- Survivors - median age 24y (IQR, 18-30); siblings - median age 26y (IQR, 19-33)

- Mean increase in CIRS-G total score over time significantly steeper in survivors vs siblings (sibs were similar to NHANES)

- *Every point increase in baseline total score increased hazard for death by 9% (95% CI 8-10%) among survivors*

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Esbenshade A, et al., JCO 2023

- Use CCSS to develop prediction models for kidney failure (ie, dialysis, kidney transplantation, or kidney-related death) by age 40 years; *validation datasets: SJLIFE, NWTS*

- CCSS (204 events) AUC 0.65-0.67; SJLIFE (8 events) AUC 0.88; NWTS (91 events) AUC 0.67

- Low, moderate, and high-risk groups: <1%, 1 to <5%, and >5% risk, respectively, by age 40 (sibs 0.2% risk)
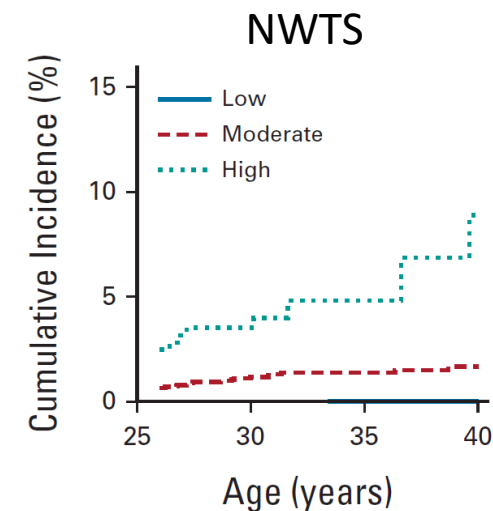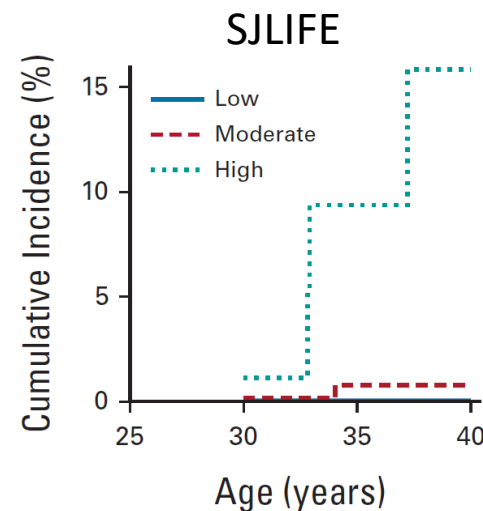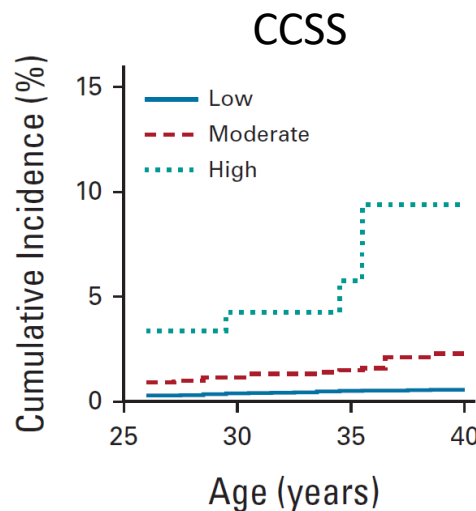
- *Most influential predictors:* early onset hypertension (within 5yrs of cancer diagnosis), any nephrectomy, high dose ifosfamde (60+gm/m2), kidney radiation (12+ Gy), any GU anomaly

Wu N, et al., JCO 2023

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Featured Study: CHIIP

Communicating
Health
Information &
Improving Coordination with
Primary Care

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- RCT testing <u>NP/PA remote counseling</u> per chronic disease self-management model to improve control of hypertension, dyslipidemia, and diabetes in childhood cancer survivors
  - 643 home visits across 9 cities; mean age 38y, 29y since cancer dx
  - Home visit results (labs, anthropometry) given to participants & primary care providers
  - Intervention: survivorship care plan with individualized CV risk, booster session with NP/PA

Risk factors (adjusted ORs)	UnderDX	UnderTX	Potential actions
Male vs Female	1.8	1.9	More intense follow-up for males, high BMI, chest XRT
Overwgt/Obese vs. normal BMI	2.3	1.7-2.9	
Chest XRT	-	2.0	
≥2 adverse lifestyle factors	-	2.2	Target smoking, inactivity, poor diet
Health-related self-efficacy	-	0.5	Target of CHIIP counseling intervention
Internal locus of control	-	0.7	

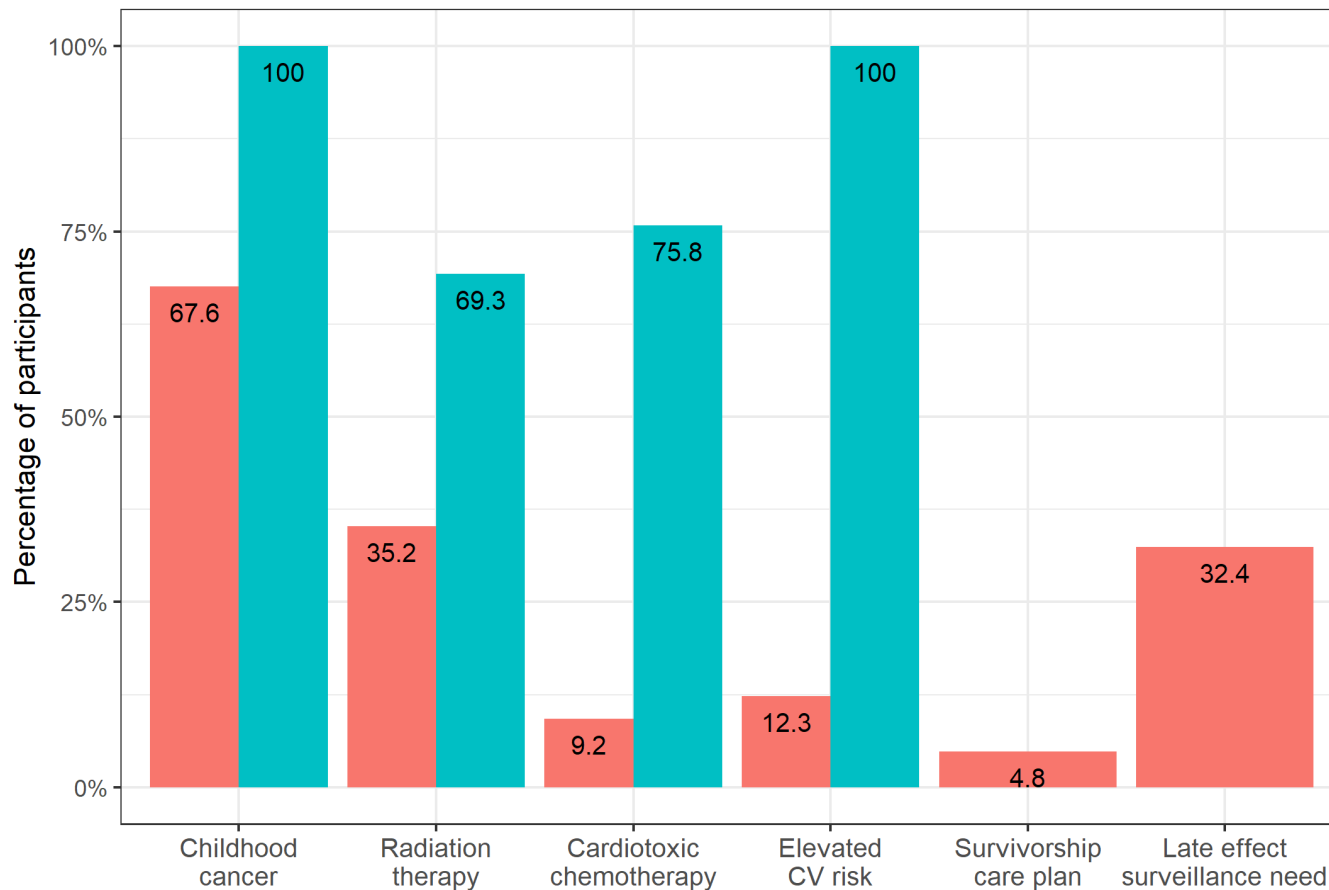*Childhood cancer survivors <u>2x</u> undertreated for hypertension, dyslipidemia, diabetes vs. NHANES*

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Featured Study: CHIIP

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- Primary care medical records reviewed (n=293)

- 81% primary care visit past 2y (median 3 visits)

- Major gaps in documentation

- **Only 29% had any cardiac testing done/planned (22% echo); predictors of CV testing:**
  - *Documentation of incr'd CV risk*
  - *Late effect surveillance need*
  - *Existing CV condition (hypertension, dyslipidemia, diabetes)*

**NEXT STEPS:** Examine RCT primary outcomes to see if BP, lipid profile, glucose tolerance improved after 1 year (n=347)

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NCT05075759
CCSS Ancillary Study

salsa Study of Active LifeStyle Activation

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- Builds upon CHIIP intervention to focus on improving diet (HEI-2015) and physical activity (sedentary time) across a set of intervention strategies

- SMART adaptive study design: poor initial responders re-randomized after 3 months

Five Year Plan: Progress Update

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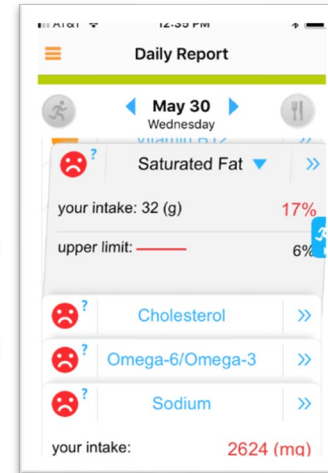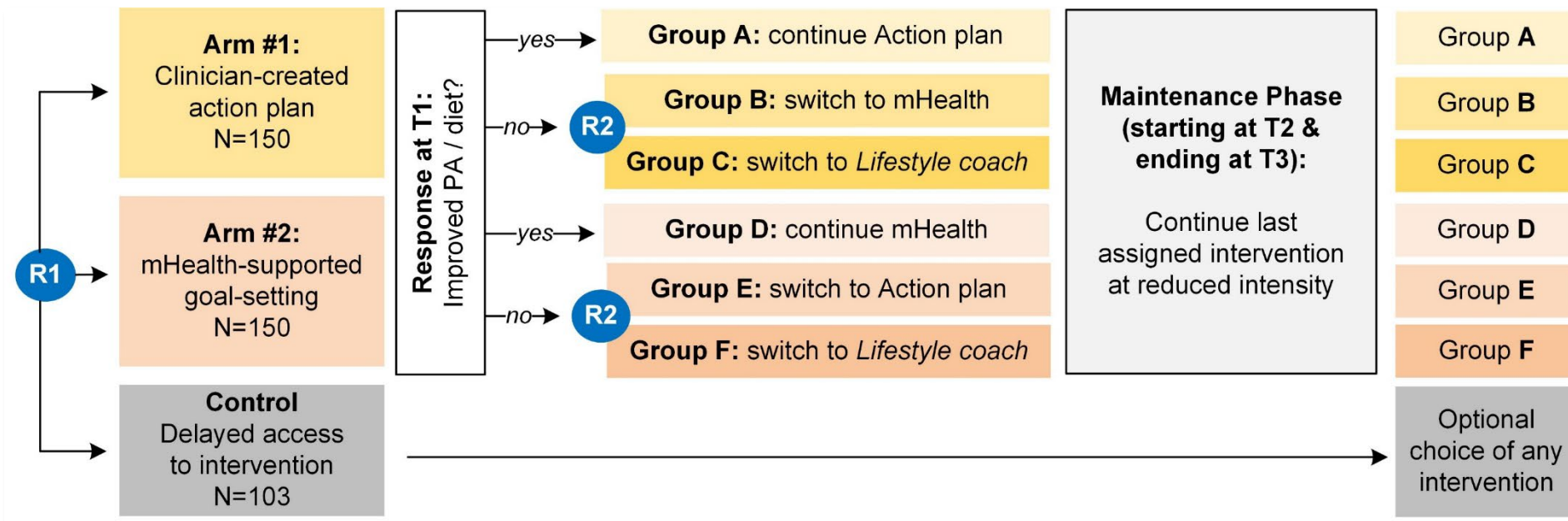
Areas of focus specified in the U24 renewal:

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

- Improve phenotyping of outcomes & exposures, including surgical outcomes

- Effects of aging, accelerated aging?

- Risk prediction, adding in <u>genetic</u> predictors

- Develop interventions to mitigate chronic health outcomes, leverage genetics to enhance precision survivorship

- Linkages with other datasets to enhance the resource

- Refine radiation dosimetry (e.g., Bates et al., cardiac substructure – JCO 2023)

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Progress Update

- Complete disease-specific papers

- CTCAE updated (FU5, ICD10, v4.03 to v5.0)
  - <u>2202</u> items reviewed, categorized, graded
    - ICD9 – numeric
    - ICD10 – alpha numeric
    - 5X more diagnoses in ICD10 vs ICD9

- Late surgery dataset finalized; initial paper published

- New frozen CHC dataset from FU7 this Summer

Disease	Status
ALL	JCO 2020
AML	Blood 2022
CNS-MB CNS-Astro	JCO 2019 ASCO 2022 oral; paper drafted
HL	JCO 2021
NHL	JCO 2019
NB	JCO 2023; 2nd analysis near final
OS	Manuscript drafted
Ewing	Analysis underway
RMS	Analysis underway
Wilms	JCO 2023

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Progress Update & Priorities

- Risk Prediction
  - AOF (Clark, 2020); *ongoing work to incorporate genetics (Im/Yuan)*
  - *Breast cancer (Moskowitz, 2021)*
  - CV outcomes (Chow…); *ongoing work to incorporate genetics (Bhatia)*
  - Kidney failure (Wu, 2023)

- Dataset linkages
  - NDI / OPTN-UNOS – Armstrong, NEJM 2016; Dietz, Lancet Oncol 2019
  - SART (Keefe-Smith) – In press…
  - CIBMTR (Friedman) –linkage w/ ~1000 CCSS survivors; used linked data for AML analysis (Turcotte); develop joint process with CIBMTR to vet future proposals
  - Medicaid (Ji) – R03 funded 2022 (ASCO 2023 oral presentation)

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- Effects of aging?
  - Older survivor concept (Bhandari/Armenian)
  - Blood banking of participants with grade 3-4 CHCs (n~1300; 30% response [still expanding]) & matched controls (n~300) – *study of CHIP?*
  - *Functional outcomes? Other rare outcomes (e.g., adult GH deficiency)?*
  - *Case-control of frail vs non-frail? Healthy vs accelerated aging? (Follow-up 8?)*

- Interventions
  - CHIIP & SALSA Studies
  - *Use of EHR nudges to improve outcomes?*
  - *Pharmacologic therapy or other interventions to improve cardiometabolic parameters?*

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Challenges & Opportunities

Challenges:

- Reliance on self-reported chronic health conditions only; have successfully conducted joint projects with other cohorts like SJLIFE, Dutch LATER that feature in-person / clinical assessments

- Easy to repeat prior analyses with "new" data, but risk being derivative; seek projects that take a new perspective

Opportunities:

- More novel exposure / outcomes assessments
  - mHealth, EHR (Care Everywhere?), other administrative linkages (other insurers besides Medicaid?)

- More collaborative efforts with other working groups to design more complex, innovative analyses, ancillary studies

- Incorporate growing **biomarker data** beyond genetics into concepts, analyses
  - New RFA process to solicit and prioritize proposals using limited samples?

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Thank you!

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If I have seen further, it is by standing on the shoulders of giants.
- Isaac Newton