

# Chronic Disease Working Group

A Report from the Childhood Cancer Survivor Study

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CCSS Investigator Meeting – June 2021

# Scope of Research

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- Epidemiology of chronic health conditions (i.e., vital organ dysfunction)
  - Adapted CTCAE grading of conditions (grades 1-5)
  - Focus on “accelerated aging”
  - Inform guidelines of late effects surveillance
- Prediction models for select outcomes
  - Collaboration with Epi, Genetics, Psychology WG’s
- Ancillary studies designed to improve ascertainment & mitigate development of serious health conditions
  - Collaboration with Cancer Control & Intervention WG

# Working Group Membership

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## Individual

Kevin Oeffinger (co-chair)  
Eric Chow (co-chair)  
Charles (Chuck) Sklar (Ex-officio)  
Saro Armenian  
James Bates  
Louis (Sandy) Constine  
Danielle Friedman  
Rebecca Howell  
Melissa Hudson  
Wendy Leisenring  
Aaron McDonald  
Sogol (Goli) Mostoufi-Moab  
Daniel Mulrooney  
Kayla Stratton  
Emily Tonorezos  
Elizabeth (Beth) Wells  
Brent Weil  
Christopher Weldon

## Expertise

Primary care  
Pediatric oncology  
Pediatric endocrinology  
Pediatric oncology  
Radiation oncology  
Radiation oncology  
General pediatrics  
Radiation dosimetry  
Pediatric oncology  
Biostatistician  
CCSS Project Director  
Pediatric endocrinology / oncology  
Pediatric oncology  
Biostatistician  
Internal medicine  
Pediatric neurology  
Surgery  
Surgery

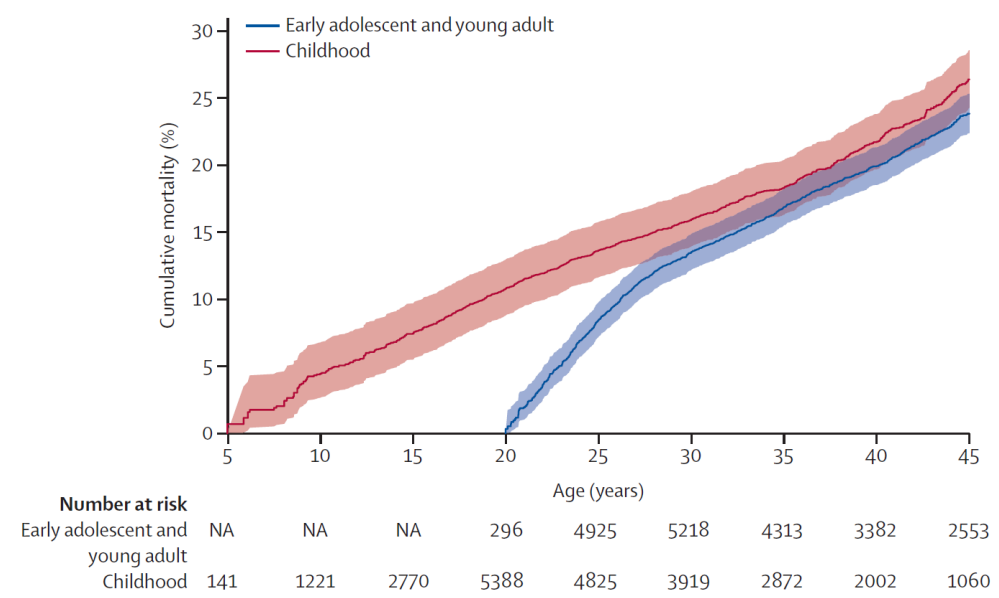
*Monthly calls to review  
concepts / analyses,  
discuss priorities*

# Working Group Progress

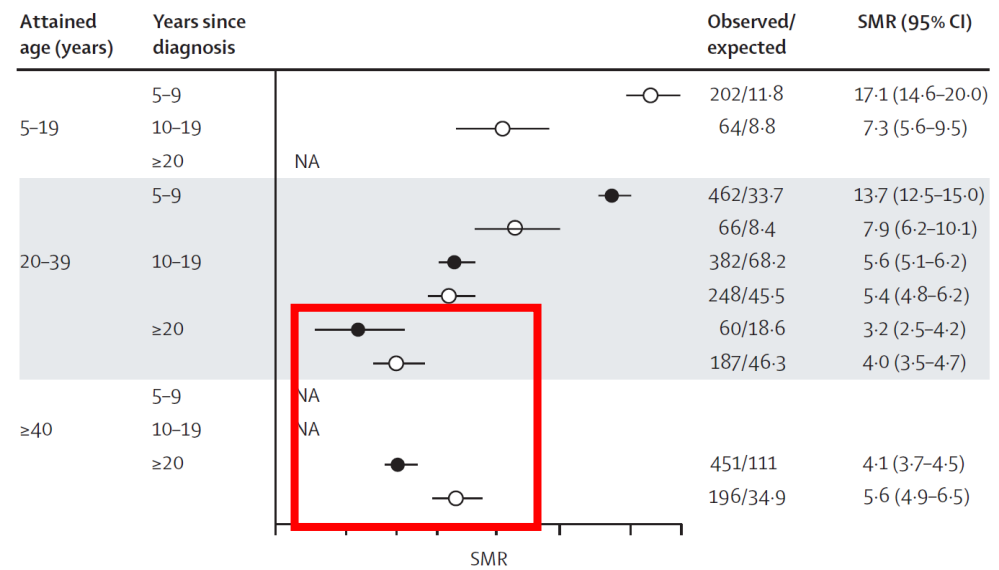
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- 14 New AOIs (since 6/2019 investigator meeting)
- 10 Concepts in development (not yet approved)
- 26 Analyses/manuscripts in process
- 13 Published/in press (since 6/2019)

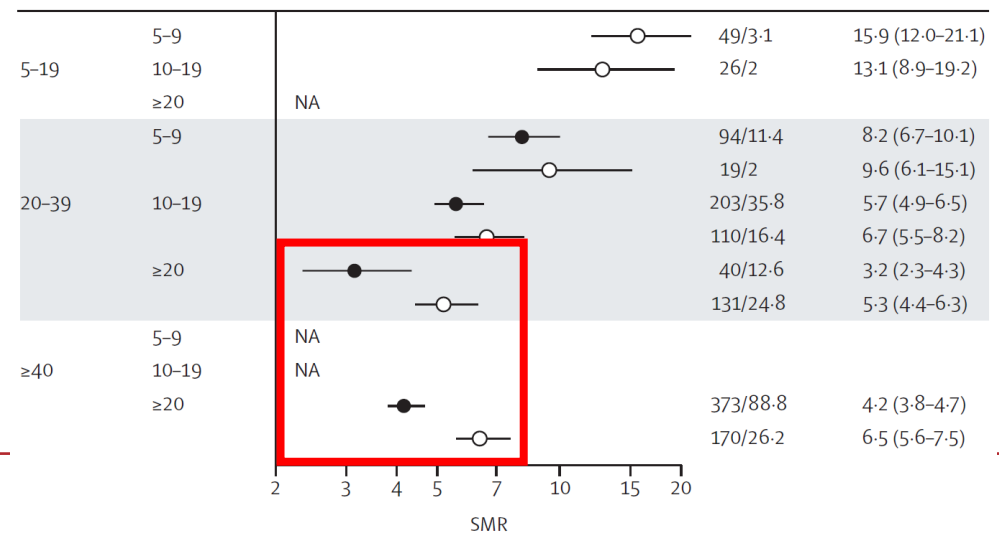
# Featured Study: AYA Outcomes



**A All-cause mortality**



**B Non-recurrent, health-related causes**

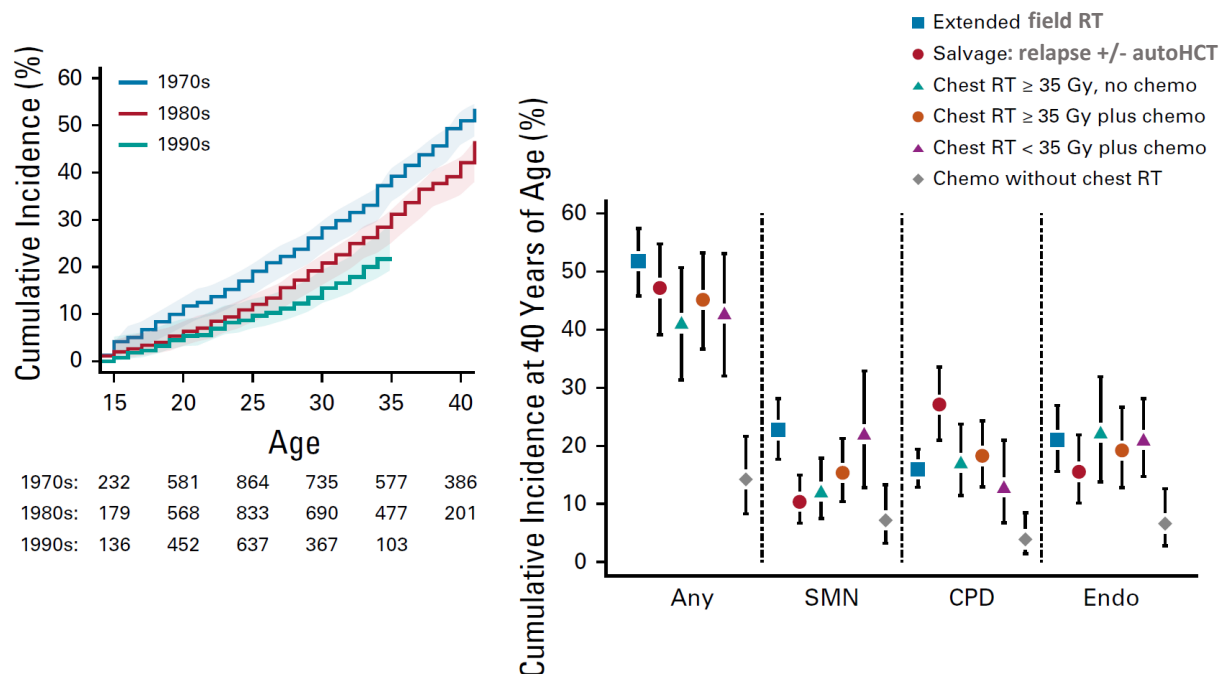


Black Circle: AYA  
Open Circle: Childhood

Relative to childhood cancer survivors (<15yo), AYA survivors (15-20yo) appeared to have decreased risks of mortality and chronic conditions over time (esp. 20+yrs after cancer)

# Featured Study: Hodgkin outcomes 1970-99

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Cumulative Incidence by 30yrs of age

Tx group	Any grade 3-5	SMN	CV/Pulm	Endo
Contemporary tx* (AHOD0431 / AHOD0031)	15%	5%	8%	7%
Chemo w/o chest RT	8%	5%	3%	3%
Salvage tx	29%	5%	12%	12%
Chest RT 35+Gy	25%	6%	7%	13%

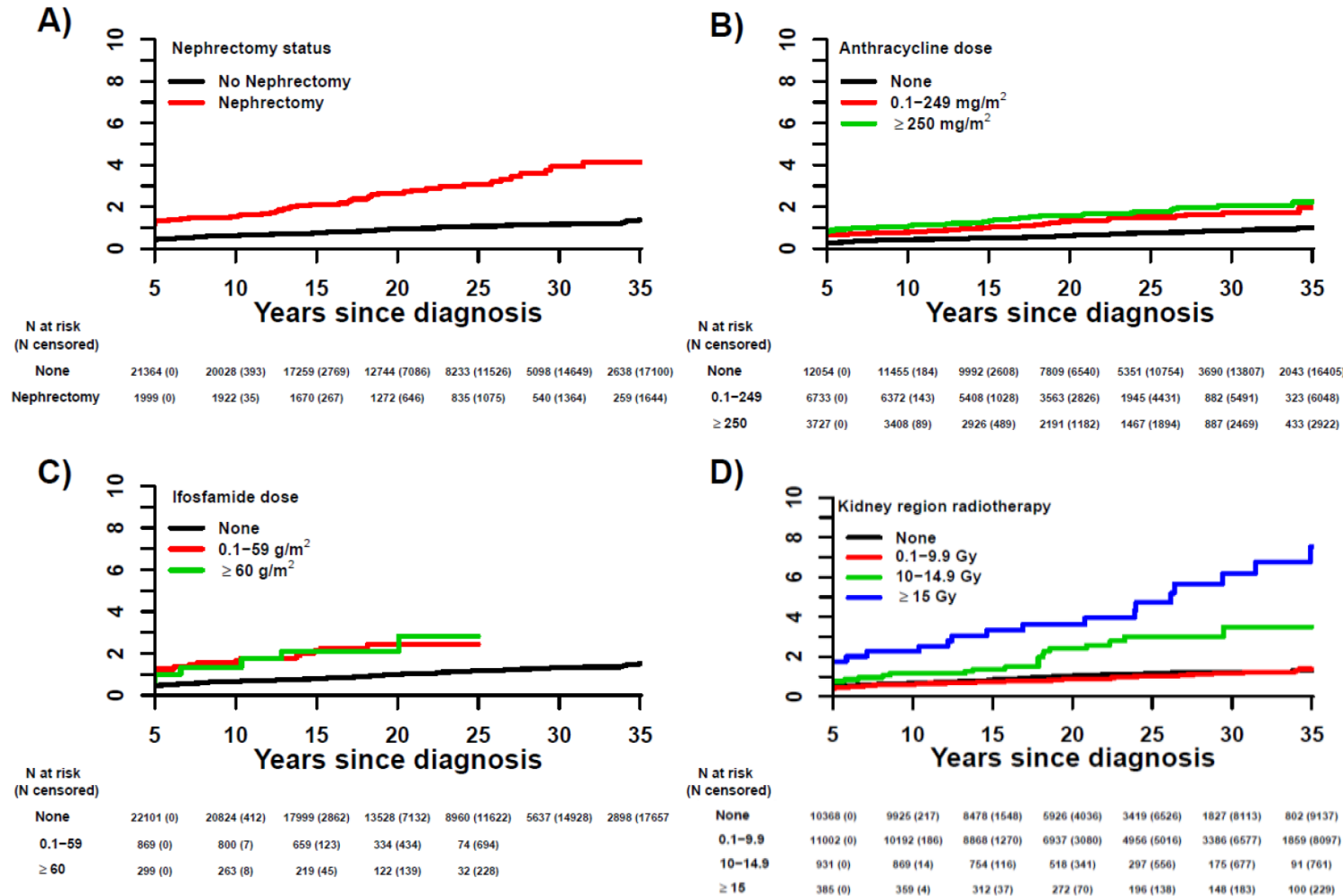
\* Dox <250 mg/m<sup>2</sup>, Cytosan 2-3.9 gm/m<sup>2</sup>, Vcr, Pred, RT ≤26Gy

20% reduction in decade-specific risk of grade 3-5 chronic condition

Contemporary regimens for low/intermediate risk HL associated with 40% reduction vs chest RT 35+ Gy (with Dox/CPM)

# Featured Study: Late Kidney Failure

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Expanded cohort enables study of rare but serious outcomes:

- 35yr cumulative incidence of late-onset kidney failure 1.7% (95% CI 1.4–1.9), n=206 (siblings, n=10)
- Data now also being adapted for risk prediction model
- Preliminary risk scores with AUC/C-statistics of 0.65/0.68 (CCSS)
- Validation risk scores 0.83/0.86 (SJLIFE) and 0.61/0.63 (NWTs) – Natalie Wu (ASCO 2021 abstract; 2020 CCSS trainee award)

# Approved Concepts – Current Status

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## *Published since 6/2019*

- Bates/Howell/Constine – CV & RT dose volume, JCO 2020
- Chen/Chow/Yasui – CV risk prediction, JNCI 2019
- Dieffenbach/Barnea – Gallbladder disease, Eur J Cancer 2019
- Dietz/Termuhlen – Solid organ transplantation, Lancet Oncol 2019
- Dixon/Nathan – ALL outcomes, JCO 2020
- Ehrhardt/Mulrooney – NHL outcomes, JCO 2019
- Fidler/Oeffinger/Hawkins – BCCSS vs CCSS comparisons, JNCI 2020
- Friedman/Sklar - Diabetes & abdominal radiation, JNCI 2019
- Madenci/Weldon – Anorectal complications, Cancer 2019
- Mulrooney/Armstrong - Cardiac outcomes update, BMJ 2020
- Oeffinger/Robison – Hodgkin outcomes, JCO 2021
- Rodwin/Kadan-Lottick – Neuropathy, CEBP 2021
- Suh/Henderson – AYA survivor outcomes, Lancet Oncol 2020

## *Analyses under peer review or final draft*

- Dieffenbach/Weil – Renal outcomes
- Chow/Yasui – CVRF underdiagnosis & undertreatment
- Geiger/Srivastava/Wustrack – Secondary amputation / limb salvage
- Keefe/Leisenring/Ginsburg – Society for assisted reproductive technologies linkage

# Approved Concepts – Current Status

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## *Manuscript in preparation*

- Esbenshade/Ness – Cumulative Illness Rating Scale (CIRS)
- Friedman/Oeffinger – Neuroblastoma outcomes
- Turcotte/Leisenring/Chow – AML outcomes
- Weil/Armenian – Wilms tumor outcomes
- Wu/Chow – Kidney failure prediction

## *Active analyses*

### *Focused outcomes*

- Asdahl – Esophageal strictures
- Brown – Hearing Impairment
- Bjornard – Female sexual dysfunction & chronic health condition
- Dieffenbach/Murphy/Weil/Weldon – Late surgery burden
- Noyd/Oeffinger – CV health outcomes disparities
- Bates/Howell/Constine – CV substructures and radiation outcomes

### *Disease-based analyses*

- Beckett/Phelan/Schwartz – Osteosarcoma outcomes
- DeBlank – Astrocytoma & ependymoma outcomes
- Friedman/Phelan/Chow – BMT outcomes [CIBMTR linkage]
- Hingorani/Ness – Rhabdomyosarcoma outcomes
- Murphy – Pelvic sarcoma outcomes
- Yeh/Leisenring – Microsimulation modeling of chronic health outcomes

- Currently Funded
  - CHIP Study: Improving assessment and treatment of **cardiovascular risk factors** among childhood cancer survivors (Chow / R01 CA204378)
  - **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 CA227576)
  - Risk of adverse **cardiometabolic outcomes** after TBI (Friedman / ACS Clinician Scientist Award; CIBMTR linkage/support)
  - EMPOWER: **Predicting chronic health conditions** among female survivors (Oeffinger / R01 CA134722)
- Applying for Funding
  - SALSA – Study of Active **Lifestyle** Activation (Chow / R01 / “CHIP2”)

# Current Priorities

- Complete disease-specific papers

Disease	Status
ALL	JCO 2020
AML	Manuscript drafted
Astrocytoma	Data analyses
Medulloblastoma	JCO 2019
Hodgkin	JCO 2021
Non-Hodgkin	JCO 2019
Neuroblastoma	Final analyses (ASCO 2021)
Osteosarcoma	Final analyses
Ewing	Concept being finalized
Rhabdomyosarcoma	Final analyses
Wilms	Manuscript drafted

- CTCAE update (FU5, ICD10, v4.03 to v5.0)
  - 2202 items to review, categorize, and grade
  - ICD9 – numeric
  - ICD10 – alpha numeric
  - 5-times as many diagnoses included in ICD10 than in ICD9

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# Fiver Year Plan: Research Priorities

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- Improved understanding of accelerated aging
  - Case-control study of frail vs. non-frail? Healthy vs. “accelerated” aging?
- More detailed radiation organ-specific dose/volume relationships
- Exploring/analyzing late surgery dataset (whole new dimension of outcomes!)
- Risk prediction of chronic conditions, adding in genetics
  - For example, bone density (Im, 2021), CV (Bhatia, under review)
- Improved phenotyping of self-reported outcomes (and exposures)
  - mHealth methods for data collection? SALSA study (diet, physical activity, BP, wgt)
  - Linkage to other administrative datasets (e.g., SART, CIBMTR)?
  - EHR-based strategies to improve coordination with primary care? Nudges?
  - Use of biomarker/physiologic data on those with selected chronic illness?
  - Case-control studies of select key outcomes?

# Discussion: Threats & Opportunities

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## Major Threats or Challenges:

- Reliance on self-reported chronic health conditions only
- Volume of AOs and Concepts in working group (assigning concepts to core WG members to assist)

## Major Opportunities:

- More novel exposure / outcomes assessments
  - mHealth, EHR (Care Everywhere?), administrative linkages
  - Case-control study of select serious chronic condition
- More collaborative efforts with other working groups to design more complex, innovative analyses, ancillary studies
- Incorporate growing biomarker data beyond genetics into concepts, analyses