

# Chronic Disease Working Group

A Report from the Childhood Cancer Survivor Study

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Kevin C. Oeffinger



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Kevin C"how" Oeffinger



**CCSS**

Childhood Cancer  
Survivor Study

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# Working Group Membership

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## Individual

Kevin Oeffinger  
Eric Chow (co-chair)  
Charles (Chuck) Sklar (Ex-officio)  
Melissa Hudson  
Daniel Green  
Louis (Sandy) Constine  
Todd Gibson  
Christopher Weldon  
Daniel Mulrooney  
Emily Tonorezos  
Sogol (Goli) Mostoufi-Moab  
Elizabeth (Beth) Wells  
Dana Barnea  
Rebecca Howell  
Kayla Stratton  
Wendy Leisenring

## Expertise

Primary care  
Pediatric oncology  
Pediatric endocrinology  
Pediatric oncology  
Pediatric oncology  
Radiation oncology  
CCSS Project Director  
Surgery  
Pediatric oncology  
Primary care  
Pediatric endocrinology / oncology  
Pediatric neuro-oncology  
Primary care  
Radiation dosimetry  
Biostatistician  
Lead biostatistician

Boston Children's / DFCI Surgery Group: Chris Weldon, Brent Weil, Arin Madenci, Bryan Dieffenbach, Andrew Murphy

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# Working Group Progress

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- 15 Published/In Press Manuscripts (since 2017 Investigator Meeting)
- 7 Currently Submitted Manuscripts
- 21 Analysis/Manuscript in Process
- 12 Concepts in development
- >20 New AOs (total, since 2017 Investigator Meeting)

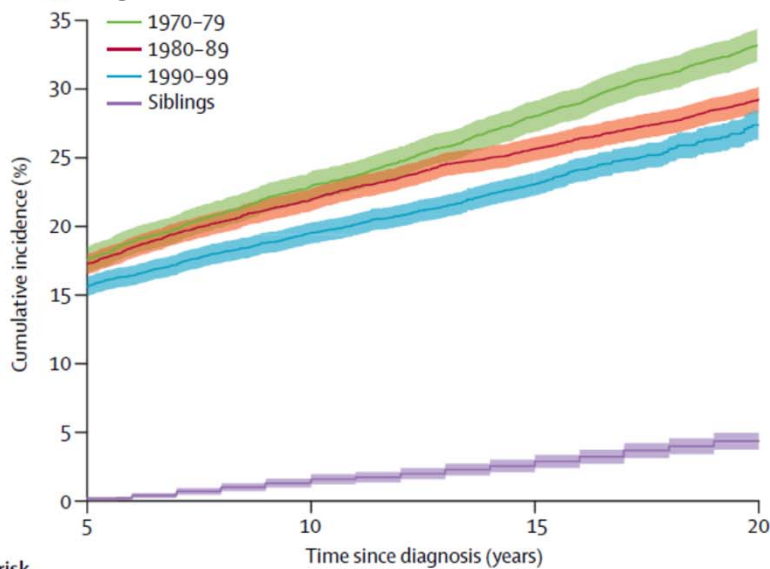
Highlighted Recent Analyses...

# Temporal Patterns in Risk of Chronic Conditions

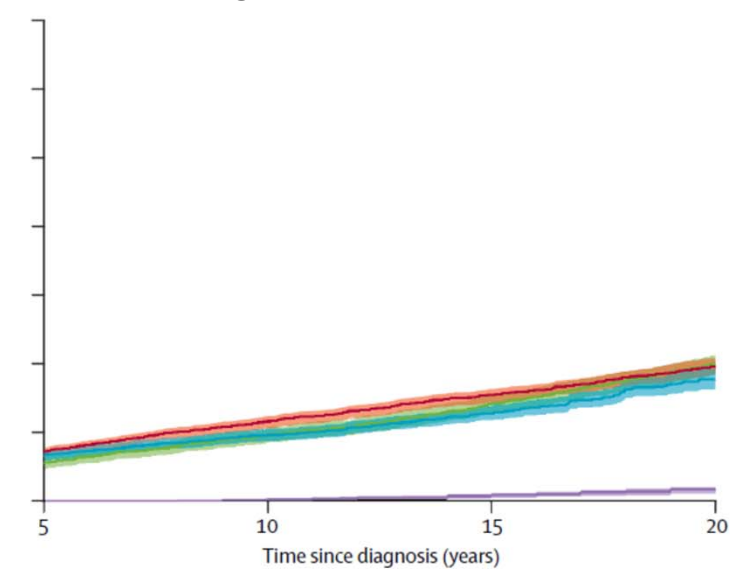
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## Cumulative incidence of grade 3-5 chronic health conditions

First grade 3-5 condition



Two or more grade 3-5



*Harmonized follow-up 5 years, with 10 to prior based CTCAE chronic condition matrix*

Number at risk  
(number censored)

	5	10	15	20	5	10	15	20
1970-79	6197 (0)	4546 (0)	4152 (1)	3611 (211)	6222 (0)	5606 (0)	5328 (4)	4809 (273)
1980-89	9373 (0)	6948 (102)	6009 (663)	4698 (1642)	9420 (0)	8421 (120)	7462 (802)	6036 (1979)
1990-99	7929 (0)	5942 (103)	3471 (2287)	702 (4922)	7956 (0)	7167 (140)	4251 (2859)	872 (6119)
Siblings	4905 (0)	4772 (62)	4355 (420)	3492 (1207)	5046 (0)	4966 (65)	4582 (437)	3734 (1263)

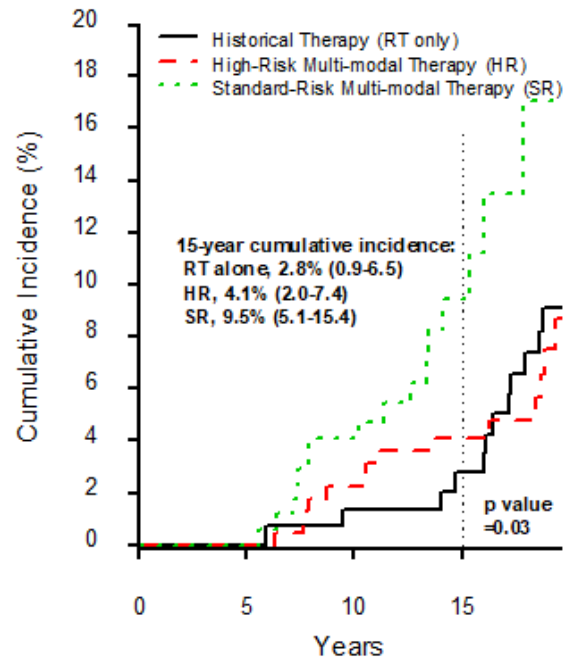
Todd Gibson & Goli Mostoufi-Moab... Kevin Oeffinger, Lancet Oncology 2018

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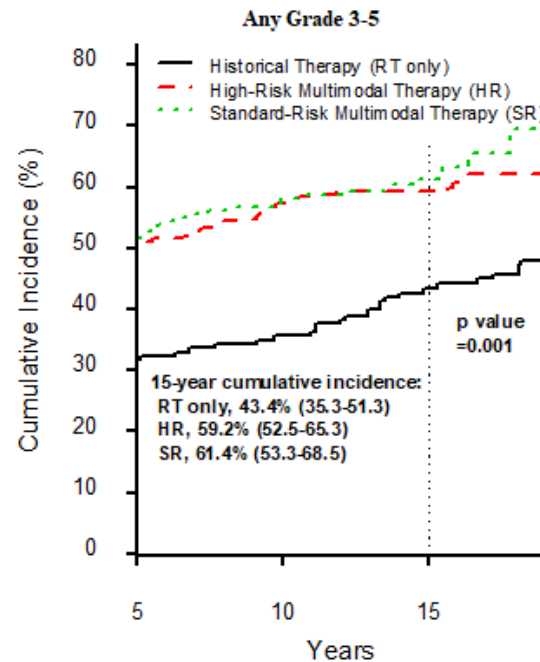
# Medulloblastoma across three decades

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## Late Mortality



## Late Morbidity



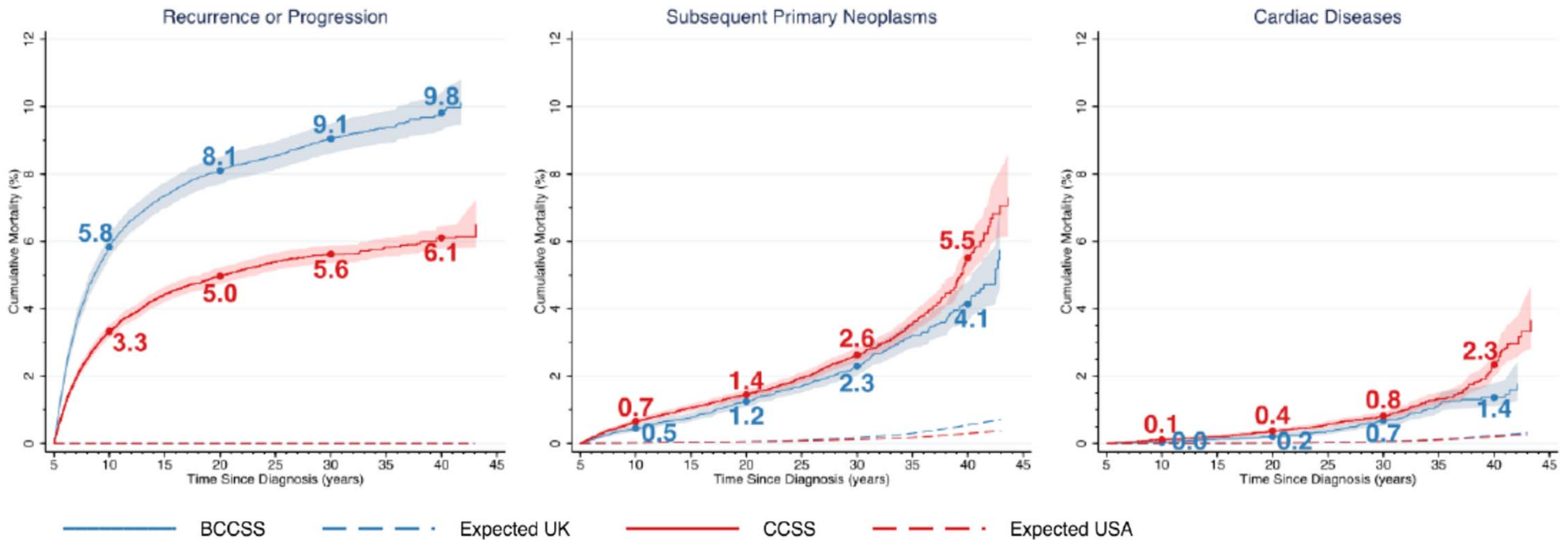
## Other disease-specific analyses in progress:

- ALL – Stephanie Dixon
- AML – Lucie Tucotte
- Astrocytoma – Peter DeBlank
- Hodgkin – Kevin Oeffinger
- NHL – Matt Ehrhardt
- Neuroblastoma – Danielle Friedman
- Osteosarcoma – Kerri Bechtell (CDA)
- Rhabdomyosarcoma – Pooja Hingorani
- Sarcoma (pelvic) – Arin Madenci
- Wilms – Brent Weil

# Late Mortality – CCSS and BCSS

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## Cumulative (comparative) mortality probabilities



Miranda Fidler (2015 CDA Awardee) ... Mike Hawkins, manuscript in preparation

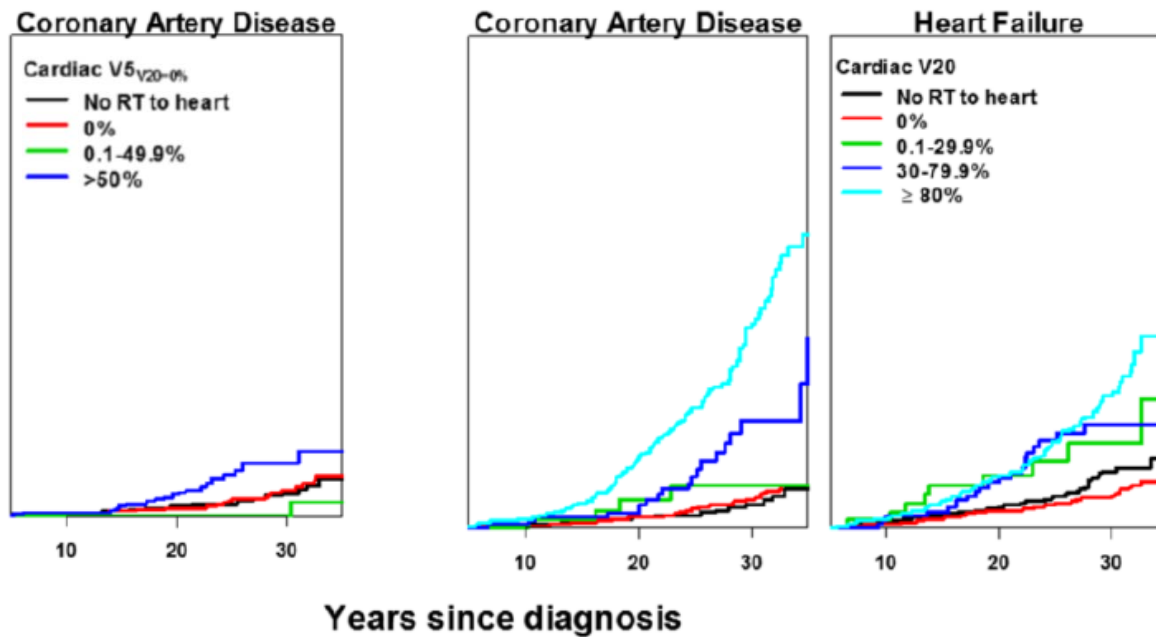
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# Radiation dose and volume to the heart

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Low dose – large volume

High dose – small volume



**Take home, risk factors for heart disease include:**

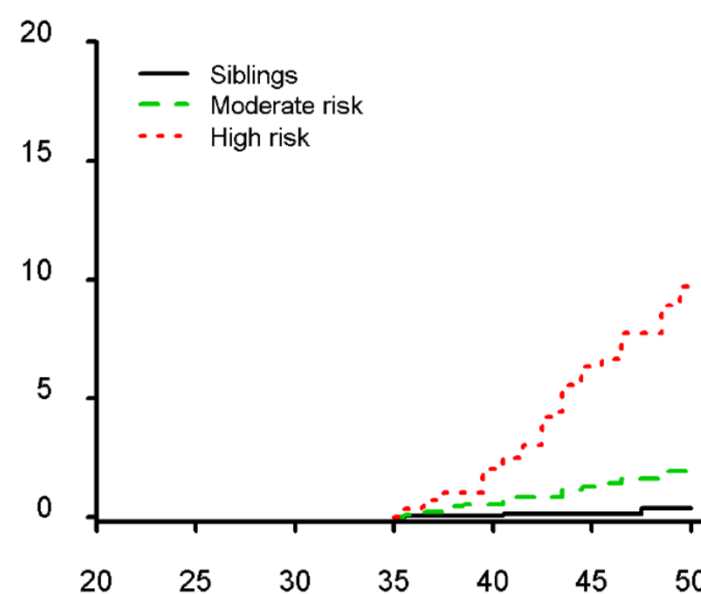
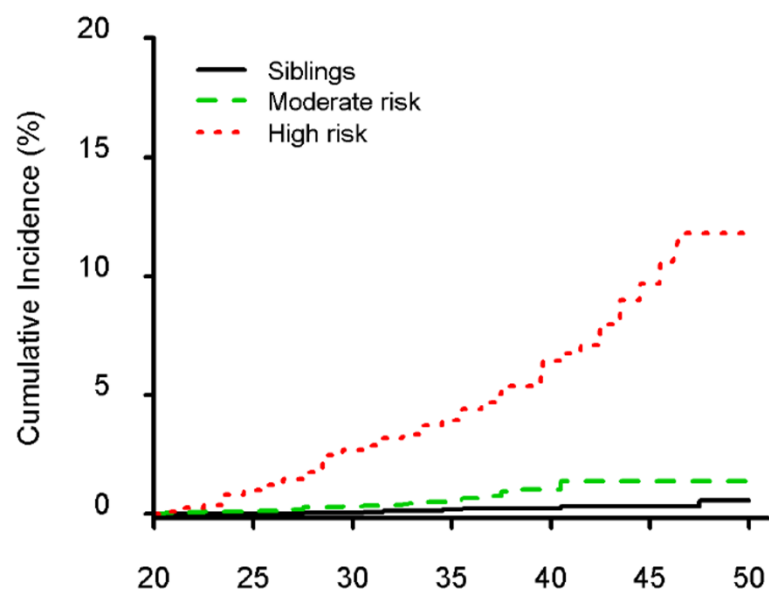
- Low/mod doses <20Gy to large volumes (≥50%)  
OR
- High doses ≥20Gy to small volumes (<30%)



# Cardiovascular Disease Risk Prediction

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## Age-based models for HF, CAD, Stroke including cancer tx & CVRFs



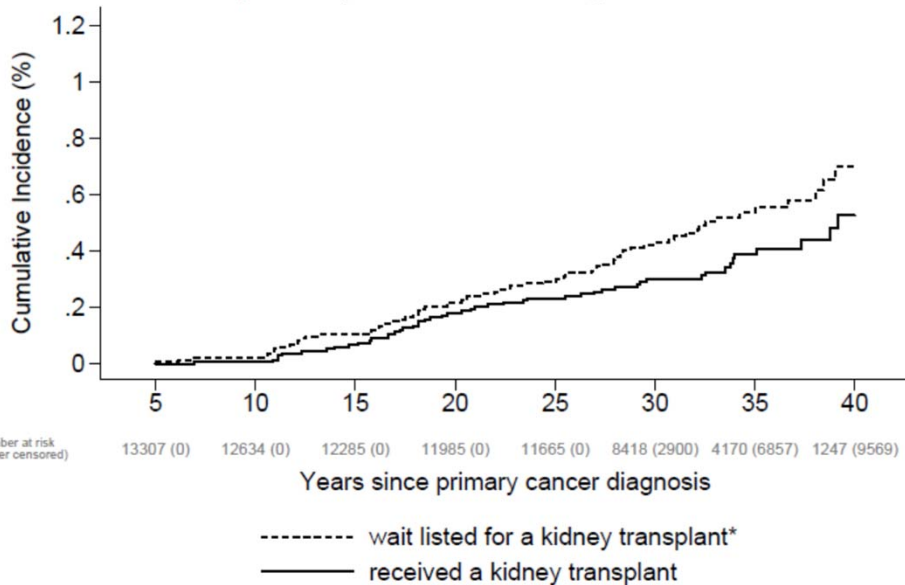
Online calculator being updated:  
[ccss.stjude.org/cvcalc](https://ccss.stjude.org/cvcalc)

**Similar online calculators being developed for other outcomes being studied in CCSS**

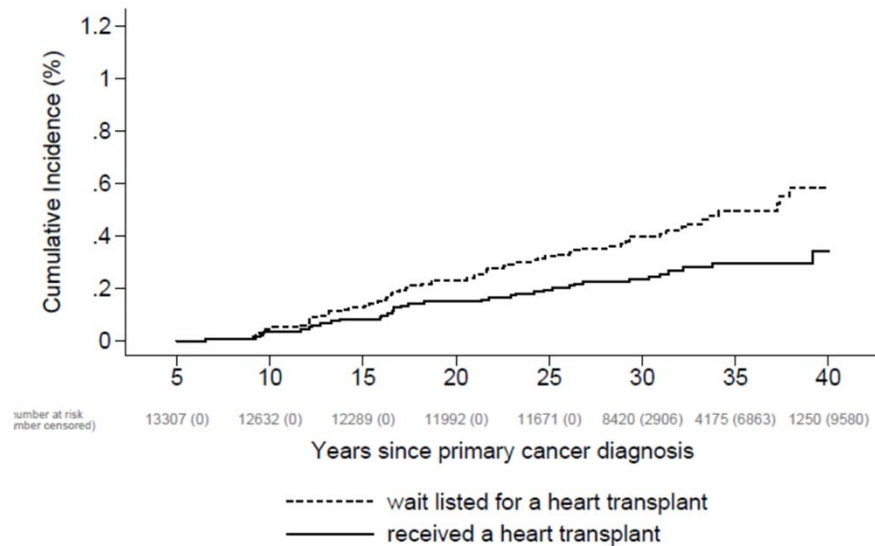
# Solid Organ Transplantation

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Kidney transplantation among CCSS survivors



Heart transplantation among CCSS survivors



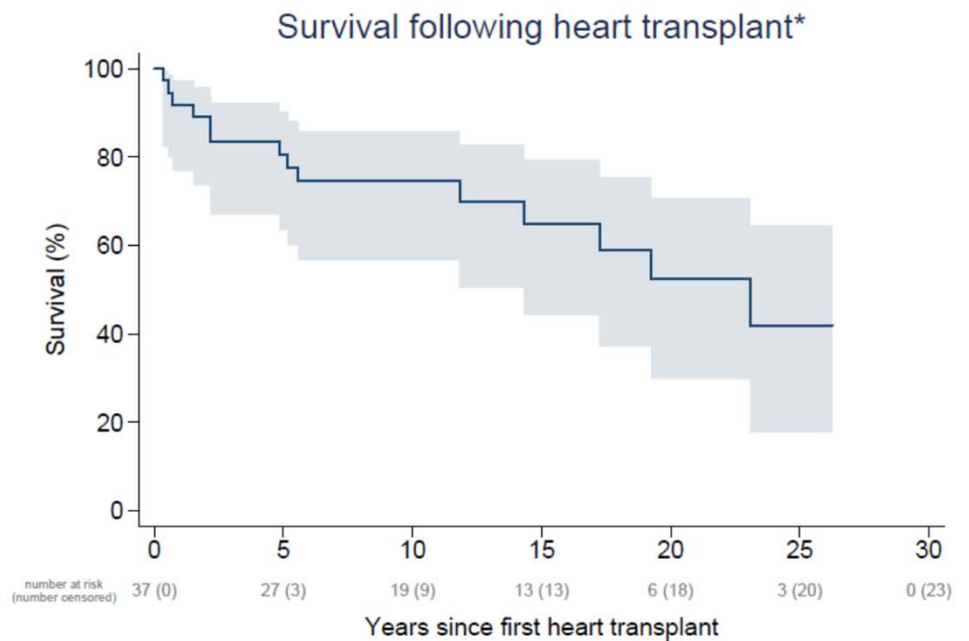
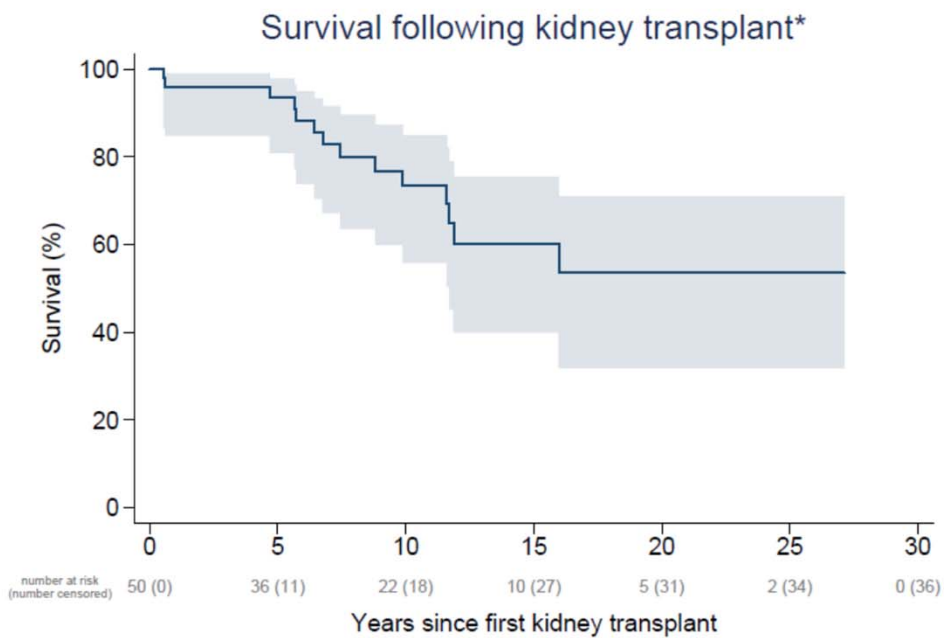
CCSS linkage with US Organ Procurement & Transplantation Network (OPTN) registry data  
 Also examined liver & lung transplant (less common)

Andrew Dietz... Amanda Termuhlen, Lancet Oncol (in press)

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# Solid Organ Transplantation

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Andrew Dietz... Amanda Termuhlen, Lancet Oncol (in press)

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# Approved Concepts – Manuscript Phase

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## In Press

- Solid Organ Transplantation in 5-year Survivors of Childhood Cancer (Dietz/Termuhlen)
- Chronic Health Conditions in Survivors of Non-Hodgkin Lymphoma (Ehrhardt)

## Under Peer Review

- Medical and Psychosocial Outcomes of Survivors of AYA Cancer (Suh/Henderson)
- Diabetes in Survivors Treated with Abdominal Radiation (Friedman/Sklar)
- Cardiac Outcomes in Long-Term Survivors of Childhood Cancer (Mulrooney)
- Incidence of Late Anorectal Complications among Childhood Cancer Survivors (Weldon)

## *Manuscript in Preparation*

- Gallbladder Disease among Childhood Cancer Survivors (Diffenbach/Barnea)
- Genitourinary Complications in Survivors of Childhood Cancer (Shnorhavorian/Weil)
- Using the Cumulative Illness Rating Scale to characterize the burden of chronic conditions among childhood cancer survivors (Esbenshade/Ness)
- Changes in Long-Term Outcomes in Hodgkin Lymphoma Survivors with Contemporary Risk-Adapted Therapy (Oeffinger)
- Comparison of Risks of Long-Term Outcomes with the British CCSS (Fidler/Oeffinger)
- Risk of Increased Morbidity and Mortality in Underweight Survivors (Tonorezos/Meacham)
- Changes in Long-term Outcomes among Survivors of Childhood Acute Lymphoblastic Leukemia (Dixon)

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# Concepts under Active Analysis

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- Esophageal strictures after childhood cancer therapy: Experience from three childhood cancer survivor cohorts (Asdahl)
- Assessment of Hearing Impairment in Long-Term Survivors of Childhood Cancer (Brown)
- Impact of Chronic Health Conditions on Sexual Dysfunction in Female Childhood Cancer Survivors (Bjornard)
- Exercise and Preventive Chronic Health Conditions and Health Care Utilization (Scott / Jones)
- Long-term Outcomes of Pelvic Sarcoma Based on Initial Treatment (Madenci)
- Changes in Long-Term Outcomes in Neuroblastoma Survivors Treated With Contemporary Therapies (Friedman / Sklar)
- Impact of Treatment Era on Long-Term Health Outcomes in Wilms Tumor Survivors (Weil / Armenian)
- Outcomes in Survivors of Astrocytoma and Ependymoma Across Three Decades of Diagnosis and Treatment (DeBlank)
- Comprehensive Comparative Analysis of Chronic Health Conditions, Health Status, Social Outcomes, and Mortality in Patients with Rhabdomyosarcoma by Treatment Era (Hingorani/Ness)
- Patterns in Motor and Sensory Neuropathy and Associated Outcomes in Long Term Survivors of Childhood Cancer (Rodwin / Kadan-Lottick)
- Infertility, Assisted Reproductive Technology Utilization and Pregnancy Outcomes: A CCSS and SART CORS data linkage study (Keefe)
- Long-term Outcomes among Survivors of Childhood Acute Myeloid Leukemia (Turcotte)
- Long-term Follow-up of Survivors of Childhood Osteosarcoma (Becktell)
- Burden of Late Surgery in Survivors of Childhood Cancer (Dieffenbach)

# Ancillary Studies

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- Currently Funded
  - Improving assessment and treatment of cardiovascular risk factors among childhood cancer survivors (Chow / Fred Hutch / R01CA204378)
  - Estimating the burden of disease associated with late-effects among childhood cancer survivors (Yeh / Boston Children's / 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 / R01CA227576)
- Applying for Funding
  - Health-related outcomes after CML (Roth / MD Anderson)
  - Risk of adverse cardiometabolic outcomes after TBI (Friedman / MSKCC)

# Current Priorities

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- Completing disease-specific papers
- 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
  - **PENDING:** CTCAE v4.03 to v5.0 harmonization



Also Dr. Caleb Nannes, Duke

# Current Priorities

CCSS

Master Matrix for Chronic Conditions 20160811.xlsx - Excel

Organ or system	Chronic Condition	Variable number	Grade	Uses ICD codes from text responses or NDI? (see ICD sheet)	Original Base	ICD9	row	grade	Dan	FU5 variable	Kevin Row	Kevin Grade				
	Heart Attack	14	1	YES	DOTHHRT_DOT4(F20); HTATT(IANGINA(F10); CORONH(F6); HRTDRUG(B8.1)	43 Cardiovascular	14	Heart Attack	5	411.: oth ac ischemic hrt dis	411					
	Congestive Heart Failure	15	1	YES	DOTHHRT_DOT4(F20); HTATT(IANGINA(F10); CORONH(F6); HRTDRUG(B8.1)	44 Cardiovas										
2			YES	DOTHHRT_DOT4(F20); HTATT(IANGINA(F10); CORONH(F6); HRTDRUG(B8.1)	45 Cardiovas											
3			YES	DOTHHRT_DOT4(F20); HTATT(IANGINA(F10); CORONH(F6); HRTDRUG(B8.1)	46 Cardiovas											
4			YES	DOTHHRT_DOT4(F20); HTATT(IANGINA(F10); CORONH(F6); HRTDRUG(B8.1)	47 Cardiovas											
5			YES	DOTHHRT_DOT4(F20); HTATT(IANGINA(F10); CORONH(F6); HRTDRUG(B8.1)	48 Cardiovas											
			1	YES	HTATT(F5);HTC:BYPASS(I7)	49 Cardiovas										
			2	YES	HTATT(F5);HTC:BYPASS(I7)	50 Cardiovas										
			3	YES	HTATT(F5);HTC:BYPASS(I7)	51 Cardiovas										
			4	YES	HTATT(F5);HTC:BYPASS(I7)	52 Cardiovas										
			5	YES	HTATT(F5);HTC:BYPASS(I7)	53 Cardiovas										
			1	YES	DOTHHRT_DOT4(F20); CONGHF(F4); DOTHHRT2-4(F5); CONGHF(F4); H8.12); DOTHR DOTHHRT2-4(F5); DOTHHRT_DOT4(F20); HRTTR	54 Cardiovas	198	Z94.1	Heart transplant status	V42.1	15. chfC	4	4	heart or circulatory problem 1	15. chfC	4
			2	YES	DOTHHRT_DOT4(F20); CONGHF(F4); DOTHHRT2-4(F5); CONGHF(F4); H8.12); DOTHR DOTHHRT2-4(F5); DOTHHRT_DOT4(F20); HRTTR	55 Cardiovas	199	Z95.0	Presence of cardiac pacemaker	V45.01	16. arrhyC	3	3	heart or circulatory problem 3	16. arrhyC	3
			3	YES	DOTHHRT_DOT4(F20); CONGHF(F4); DOTHHRT2-4(F5); CONGHF(F4); H8.12); DOTHR DOTHHRT2-4(F5); DOTHHRT_DOT4(F20); HRTTR	56 Cardiovas	200	Z95.1	Presence of aortocoronary bypass graft		4	14.hrtC	heart or circulatory problem 2	hrtC	4	
			4	YES	DOTHHRT_DOT4(F20); CONGHF(F4); DOTHHRT2-4(F5); CONGHF(F4); H8.12); DOTHR DOTHHRT2-4(F5); DOTHHRT_DOT4(F20); HRTTR	57 Cardiovas	201	Z95.2	Presence of prosthetic heart valve	V43.3	18. valvC	4	4	heart or circulatory problem 2	18. valvC	4
			5	YES	DOTHHRT_DOT4(F20); CONGHF(F4); DOTHHRT2-4(F5); CONGHF(F4); H8.12); DOTHR DOTHHRT2-4(F5); DOTHHRT_DOT4(F20); HRTTR	58 Cardiovas	202	Z95.3	Presence of xenogenic heart valve		4	18.valvC	heart or circulatory problem 1	valvC	4	
			6	YES	DOTHHRT_DOT4(F20); CONGHF(F4); DOTHHRT2-4(F5); CONGHF(F4); H8.12); DOTHR DOTHHRT2-4(F5); DOTHHRT_DOT4(F20); HRTTR	59 Cardiovas	203	Z95.5	Presence of coronary angioplasty implant and graft	V45.82	4	14.hrtC	F4 Coronary heart disease details 1	hrtC	4	

fu5 CARDIAC FINAL Chow Mulrooney\_KCO.xlsx - Excel  
Kevin Oeffinger, M.D.



# Current & Future Priorities

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- More detailed radiation dose/volume relationships
- Exploring/analyzing late surgery dataset (whole new dimension of outcomes!)
- Additional risk prediction of other (non-CV) chronic conditions
- Improved phenotyping of self-reported outcomes (and exposures) beyond SMN
  - mHealth methods for data collection?
  - Linkage to other administrative datasets (e.g., NDI, OPTN, SART)?
  - Resurrection of broader home visits data collection effort?
  - Case-control studies of select key outcomes?
- Genetic contribution to chronic conditions
- Begin to study effects of new agents/exposures from the past 20 yrs..

# Questions?

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# Five Year Plan: Progress Update

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- Quantifying risk and risk factors for late health outcomes in adolescent populations – AYA paper under peer review
- Home sample to identify prevalent late effects beyond those self-reported by survivors – casualty of NCI budget cut
  - Subsumed / being done in part via ancillary “CHIIP” R01 for high/moderate CV risk participants (limited to cardiometabolic assessment)
- mHealth UCSF / Eureka collaboration
  - EASE chronic pain pilot (Alberts, 2017 CDA awardee) – Psychology WG
  - EMPOWER II breast cancer screening RCT (Oeffinger, R01) – Cancer Control / SMN WGs
  - SLEEP (Brinkman, pilot for subsequent R01) – Psychology WG
  - CHIIP BP pilot (Chow, R01) – Chronic Dz WG