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Childhood Cancer Survivor Study

Principal Investigator: Greg Armstrong, MD, MSCE

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Cancer Therapy Evaluation Program, NCI
March, 2015

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Topics to Address

- Background
- Key accomplishments
- Incorporation of genomic studies into CCSS research program
- Approach to verification of patient reported outcomes
- Intervention Research
- Relationship of scientific research programs of COG and CCSS and interactions
- Relationship between CCSS and St. Jude Life Cohort

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Childhood Cancer Survivor Study (CCSS) Background

- Retrospectively ascertained cohorts of survivors of pediatric cancer diagnosed between 1970-1999:
  - First cohort initiated with first CCSS award in 1994; Second 2007
  - 14,370 long-term (five-year or more) survivors of childhood cancer diagnosed between 1970 and 1986
  - 10,102 long term survivors of childhood cancer diagnosed between 1987-1999
  - Total: 24,466 survivors
  - 3,737 sibling controls recruited for comparison purposes
- Data collected:
  - Clinical data on malignancy and treatment abstracted from medical records
  - Self-reported data on risk factors (e.g., family history), and health and psychosocial outcomes data collected via baseline and follow-up questionnaires
- Biospecimens, public use dataset

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CCSS Impact on Late Effect Guidelines

Exposure Type	Number of COG Late Effect Guidelines Informed by CCSS Publications	Number of CCSS References
Chemotherapy	6/18 (33%)	8
Radiation	30/54 (55%)	47
Surgery	3/27 (11%)	3
Any Cancer Experience	5/6 (83%)	18
Blood/Serum Products	1/3 (33%)	1
Cancer Screening Guidelines	3/9 (33%)	5
TOTAL	48/117 (41%)	82

- 82 total references to CCSS publications
- 41% of **COG Guidelines** are informed by CCSS publications
  - Radiation and Cancer Experience late effects most impacted
- **International Late Effects of Childhood Cancer Guideline Harmonization Group** (first one published)
  - Recommendations for breast cancer surveillance for female survivors of childhood, adolescent and young adult cancer given chest XRT(Lancet Oncology, 2013)
- **Scottish Intercollegiate Guidelines Network (SIGN)**: Long term follow-up of survivors of childhood cancer (2013)
  - 8 of 9 total late effect categories informed by 21 CCSS articles

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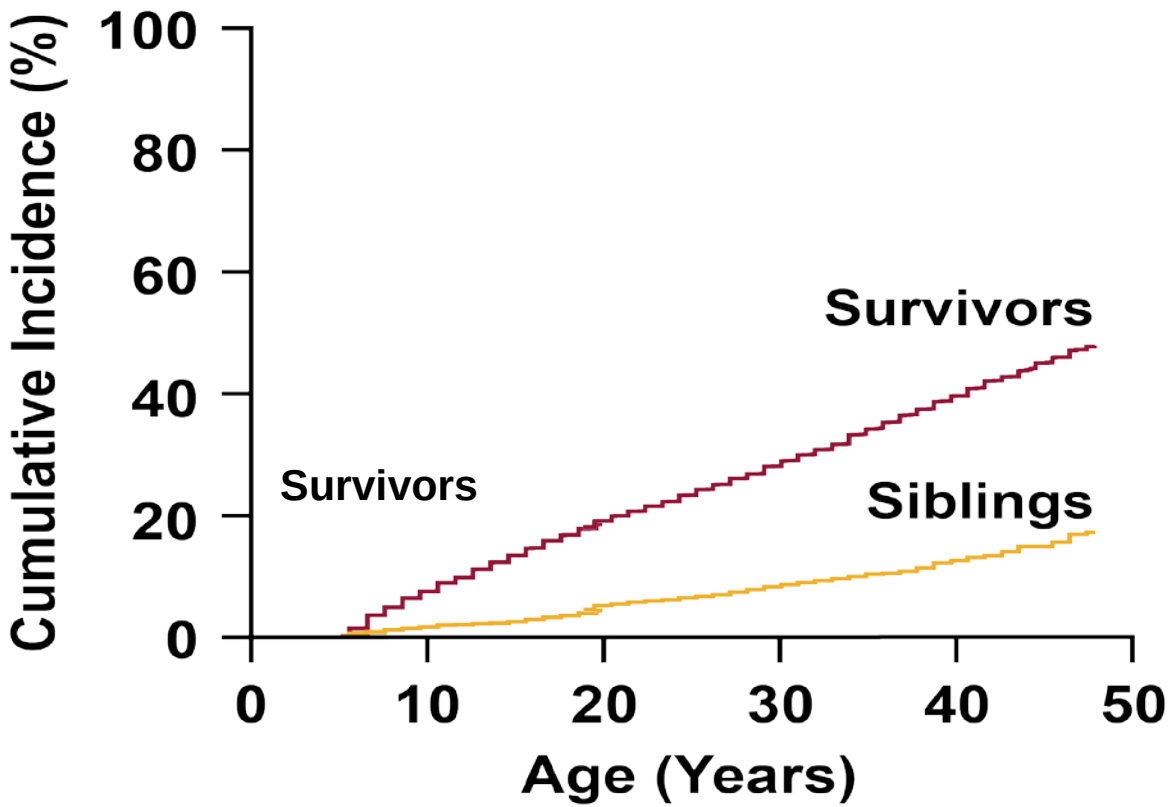
Morbidity and Mortality Risks in Childhood Cancer Survivors



<u>Conclusion</u>: By 50 years of age, 51% of survivors have experienced a severe or life-threatening health condition compared to only 19% of siblings. The "health gap" between survivors and the general population continues to widen with age.

Armstrong GT et al. Aging and Risk of Severe, Disabling, Life-Threatening, and Fatal Events in the Childhood Cancer Survivor Study. *J Clin Oncol,* 2014; 32(12): 1218-27.

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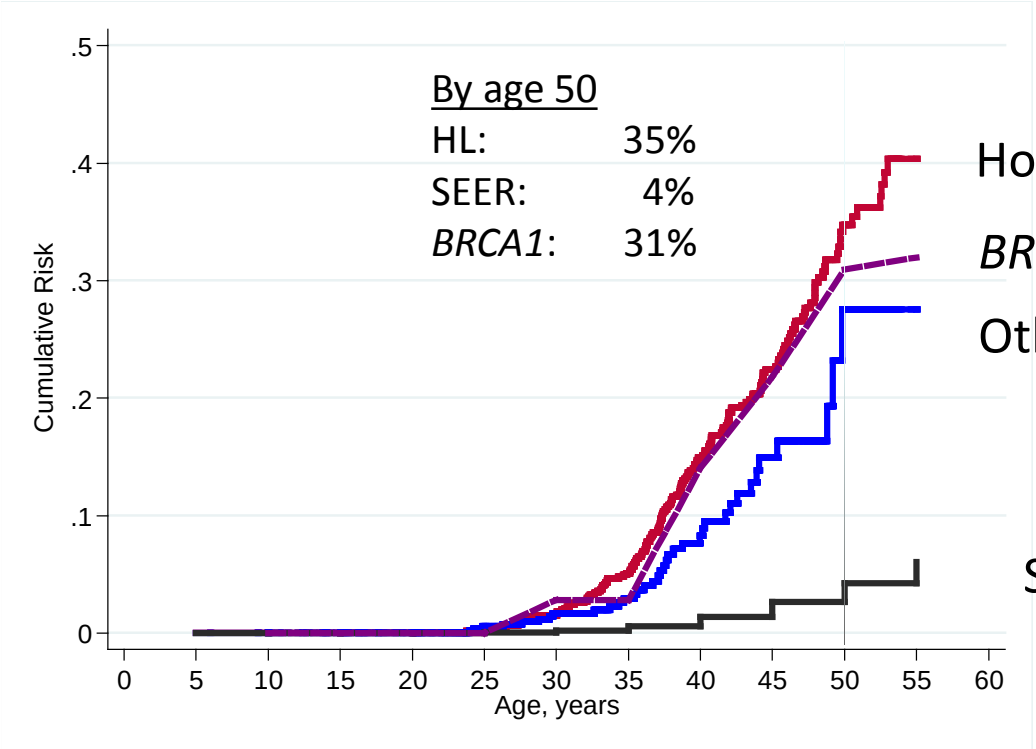
Breast Cancer Risk After Chest Radiation



Moskowitz CS, Chou JF, Wolden SL, Bernstein JL, Malhotra J, Novetsky, Friedman D, Mubdi NZ, Leisenring WM, Stovall M, Hammond S, Smith SA, Henderson TO, Boice JD, Hudson MM, Diller LR, Bhatia S, Kenney LB, Neglia JP, Begg CB, Robison LL, Oeffinger KC. Breast Cancer After Chest Radiation Therapy for Childhood Cancer. *J Clin Oncol*, 2014; 32(21): 2217-23.

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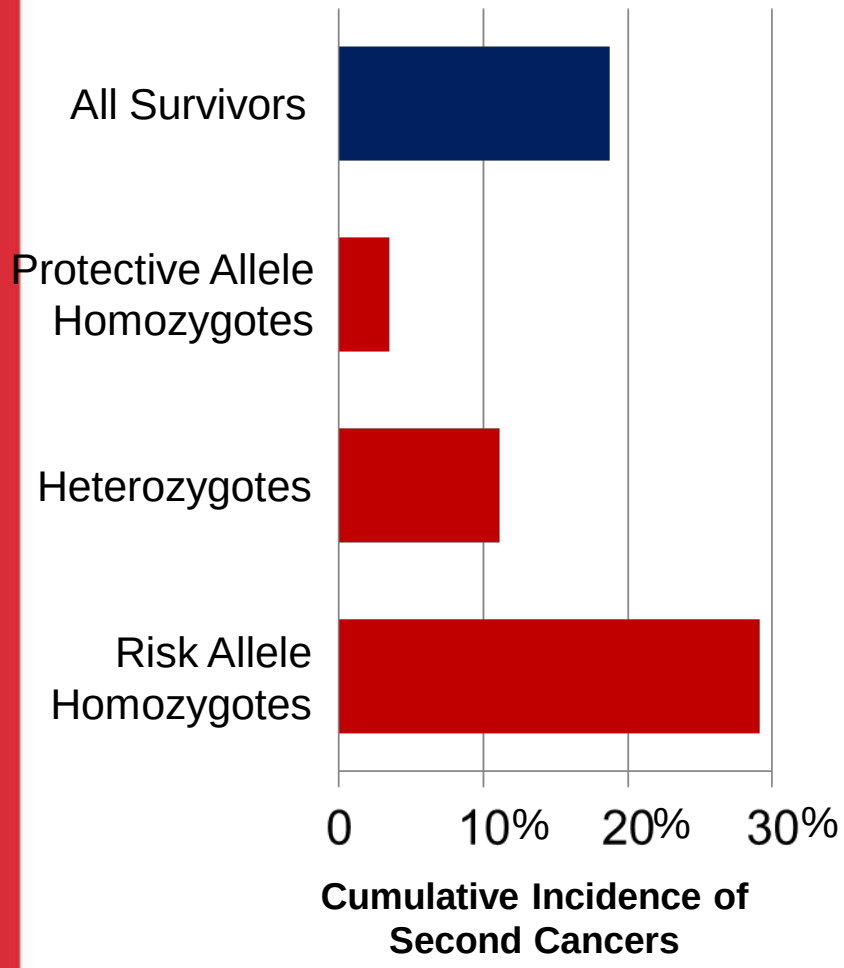
Genomics Projects

Study Title	PI/ Institution	Funding	Status
Published Studies			
Genetic variation in the leptin receptor gene and obesity in survivors of childhood acute lymphoblastic leukemia	Ross/Univ. of Minnesota		*Ross JA et al. J Clin Oncol,* 2004; 22(17): 3558-62
Genetic polymorphisms in the carbonyl reductase 3 gene CBR3 and the NAD(P)H: quinone oxidoreductase 1 gene NQO1 in patients who developed anthracycline-related congestive heart failure after childhood cancer	Blanco/Univ of Buffalo		*Blanco JG,* ***Cancer****,* 2008; 112(12): 2789-95
GWAS of SMNs after Hodgkin lymphoma	Onel/University of Chicago	NIH R21	*Best T et al,* ***Nat Med*** *2011;17:941-3*
Evaluation of SNPs in the EWS Breakpoint Region in People with and without Ewing Sarcoma	DuBois/UCSF	Institutional training grant	*Dubois S et al.* ***Pediatr Blood Cancer****, 2012;59:52-6*
Genome-wide Meta-analysis of Nodular Sclerosing Hodgkin Lymphoma Identifies Risk Loci at 6p21.32	Cozen/Univ. of Southern California		*Cozen W et al.* ***Blood*** *2012; 119(2): 469-75*
Telomere Length and Risk for Second Malignancy in Pediatric Cancer Survivors	Gramatges/Baylor	Institutional training grant	Gramatges et al. ***Clin Cancer Res****,* 2014 Feb 15;20(4):904-11
Genomic Alterations in Radiation-Related Breast Cancer Using ArrayCGH (Comparative Genomic Hybridization)	Yang/NCI	NIH – intramural funds	***PLoS One*** (in press)
Approved Concepts – under analysis			
Genetic Polymorphisms and Metabolic Outcomes in Childhood Leukemia Survivors	Kamdar/Texas Children's Hospital	LLS	Genotyping complete/ statistical analysis underway
Genetic Alterations in Second Malignant Neoplasms	Nakamura/UCSF	St. Baldrick's Foundation	Samples released/ targeted exome sequencing and genotyping underway
Genetic Epidemiology of Basal Cell Carcinoma in Childhood Cancer Survivor	Davies/ Cincinnati Kids	NIH (U01)	Genotyping done/ Statistical analysis complete/ manuscript under preparation
Susceptibility genes for radiation-induced breast cancer after Hodgkin lymphoma	van Leeuwen/ Netherlands		Genotyping complete/ Statistical analysis underway
Epigenomic Profiling of Metabolic Outcomes in Childhood Leukemia Survivors	Lupo/Baylor	CCSS CDA	Samples released (9/14) – methylation studies over next 2-3 mo./ statistical analysis by March, 2015

Childhood Cancer Survivor Study (U24 CA55727)

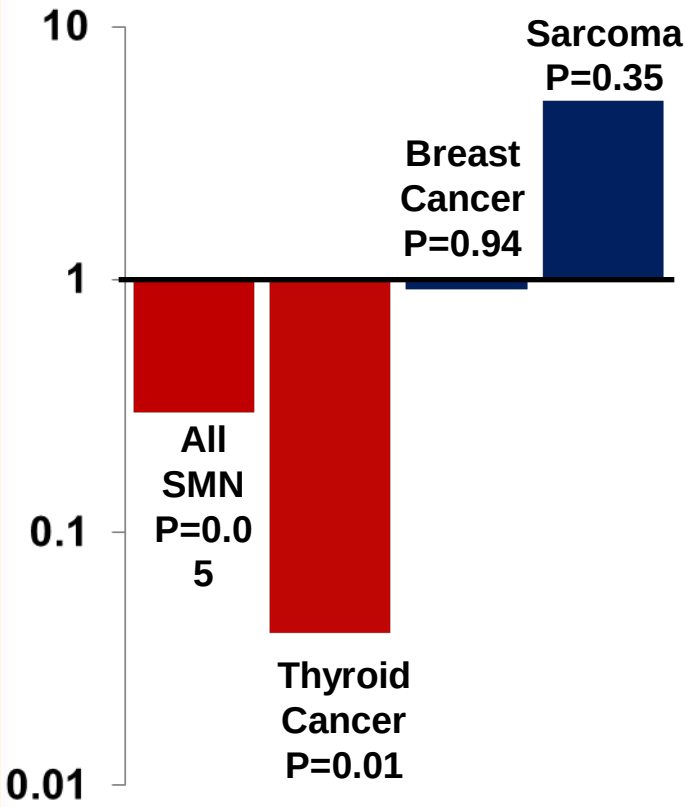
Genetic Risks of Treatment-related Second Cancer



- Survivors of childhood cancer, particularly survivors of Hodgkin lymphoma, are at increased risk for developing a treatment-related second cancer.
- Most common second cancers are skin, breast, thyroid, CNS, and soft-tissue sarcoma.
- Using a genome-wide approach, *PRDM1* was found to be significantly associated with radiation-associated second cancers.
- Homozygosity for the risk allele was associated with a 29% incidence of second cancer compared to only 3.5% in those without the risk allele.

Best et al. Nat Med 2011;17:941-3

Genetic Risks of Treatment-related Second Cancer



* Risk per unit change to single-copy gene ratio, adjusted for sex, race, family history, smoking status, age at primary cancer

- Shorter telomere length has been associated with increased cancer incidence.
- Intensive cancer chemotherapy and radiation has been observed to shorten telomeres.
- A statistically significant inverse relationship was found between telomere content and occurrence of second malignant neoplasms among survivors of childhood cancer.
- The association was most apparent for risk of secondary thyroid cancer.

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Genomic Factors in Risk and Survival

- GWAS resource for genetic investigation (n=5,739)
  - Collaboration with Division of Cancer Epidemiology and Genetics
  - Identify genetic variants that modify the effect of RT and chemotherapy on risk of subsequent neoplasms, and of risk independent of treatment exposure
  - Request For Proposals (RFP):
    - unparalleled resource for investigation of associations between genetic variants and risk of other chronic health conditions
    - To be issued in 2015
    - GWAS data available on dbGaP
    - Full annotation with exposure and outcome data pending completion and approval through the application process
  - Whole exome sequencing to discover genetic variants predisposing childhood cancer survivors to SN

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Genomic Projects

AOI approved – pending concept approval			
Evaluation of the intrinsic molecular profiles of radiation-preceded breast cancer	Barcellos-Hoff/NYU		Pending approval by Publications Committee
Genetic Susceptibilities to Second Cancers	Onel/University of Chicago		Concept being finalized/ Request awaiting completion of primary analysis of NCI/CCSS GWAS
PRDM1 and Somatic Mutations in SMNs after Hodgkin Lymphoma	Onel/University of Chicago		Concept is being finalized
Multiple SMNs & Genomic Instability/DNA Repair	Bhatia/City of Hope	NIH (R01)	Samples to be released post NCI GWAS effort
Genetic susceptibility to anthracycline-related CHF	Bhatia/City of Hope	LLS	Cases and controls identified for validation Samples to be released post NCI GWAS effort
Identification of susceptibility loci in radiation-induced breast cancer by exome and CNV analysis	Hodgson/Princess Margaret Hospital		Pending procurement of funding
Radiation-related thyroid cancer	Nikiforov, U of Pittsburgh	NIH (R01)	Cases and controls identified Samples to be released post NCI GWAS effort

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Verification of Patient Reported Outcomes

- Addition of direct assessment of survivors to historical survey-based outcomes
  - CCSS Home Sample

Key Outcomes To Be Ascertained by Direct Assessment in the CCSS Home Sample	
Primary Outcome	Direct Measure
Obesity	Height, Weight, BMI
Hypertension	Blood Pressure
Adiposity	Waist circumference
Diabetes	Insulin, Hgb A1c, Fasting Blood Glucose
Dyslipidemia	LDL, HDL, Triglycerides,Cholesterol
Renal Function/Failure	Creatinine, electrolytes, GFR
Hepatic Function/Failure	Liver function test panel
Future genetic and/or biomarkers	Bank whole blood

  - Use of mobile health technology
    - Sensor-based direct outcome measures including: blood pressure, activity, EKG, diet etc.
- Electronic engagement

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Intervention Studies

- Previous studies: smoking cessation (Emmons, Klesge); use of virtual information center to improve screening (Oeffinger)

Title	Principal Investigator(s)	Institution	NIH Funding Source
Evaluation of Cardiovascular Outcomes Among Childhood Cancer Survivors (ECHOS)	Melissa Hudson Cheryl Cox	St. Jude Children's Research Hospital	RO1
Encourage Mammography and Prevention Opportunities for Women Exposed to Radiation (EMPOWER)	Kevin Oeffinger	Memorial Sloan Kettering Cancer Center	RO1
Advancing Survivors Knowledge (ASK) about Skin Cancer	Alan Geller	Harvard School of Public Health	RO1
Exercise and Quality Diet after Leukemia Study (EQUAL)	Emily Tonorezos	Memorial Sloan Kettering Cancer Center	RO1

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The Relationship Between the Children's Oncology Group (COG) and CCSS (1)

- Survivors in CCSS are not restricted to those enrolled on COG trials.
  - Not all children between 1-15 years old are treated on COG protocols and hence these survivors would be missed;
- Increased heterogeneity of treatment regimens/exposures by including patients treated on local protocols such as St. Jude, Dana-Farber, MSKCC, Stanford, etc.
- CCSS directly abstracts treatment (e.g., chemotherapy doses and radiation doses/fields) from medical records.
  - COG classifies patients according to protocol specified treatment (inferred exposure vs actual exposure)

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The Relationship Between the Children's Oncology Group (COG) and CCSS (2)

- COG focuses on therapeutic research in which patients are followed closely for 5-10 years
  - Member institutions are pediatric hospital-based
  - Geographic mobility of young adults today
- CCSS focuses on survivor research involving research subjects who are generally 10 or more years from diagnosis
  - Local institutions typically do not maintain a relationship with these survivors into adulthood
  - Long-term follow-up infrastructure needed for tracking survivors and maintaining contact
- CCSS/COG liaison committee between CCSS leadership and COG late-effects leaders; meets at COG meetings

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Comparison of the Childhood Cancer Survivor Study and St. Jude Life

Characteristics	CCSS	SJLIFE
Cohort size	35,937	3951 as of 12/15/2014
Years of diagnosis	1970-1999	1962-2009
Entry criteria (years from diagnosis)	**≥ 5 years**	≥10 years
Age at diagnosis	<21 years	<25 years
Cancer diagnoses	Leukemia, CNS tumors, HL, NHL, Wilms tumor, neuroblastoma, soft tissue sarcoma, bone tumors	All diagnoses – children treated at St. Jude Children's Research Hospital
Method of data collection	Periodic surveys; longitudinal follow-up; investigator initiated ancillary studies	Clinic visits; self-reported outcomes; longitudinal follow-up; investigator initiated ancillary studies
Study design	Hospital-based (31 centers)	Hospital-based (single center)
Comparison population	Siblings, general population	Frequency-matched community controls, general population
Therapeutic exposure data	Yes: >95%	100%
Ascertainment of vital status	Linkage with death registries	Linkage with death registries
Ascertainment of non-malignant adverse outcomes	Patient/parent-reported outcomes	Medical assessments; patient-reported outcomes
Ascertainment of malignant adverse outcomes	Self/parent-report (pathology verified)	Self-report (pathology verified) and medical assessments (screening)
Second tumor samples	Specimens for 205 second cancers	No
Collection of germline DNA	8,835 survivors (as of 01/01/2015)	98% of survivors
Open resource	Yes	No

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Plan for Continuation of CCSS

- Request approval to reissue a letter RFA for 5 years. Proposed funding: $4.31 M/year for a total $21.1 M
- Co-sponsorship from DCCPS, DCEG, DCP
- Additional Evaluation criteria to include:
  - Utilization of expanded cohort data (1970-99)
    - Identify how risk stratification of therapy has changed patterns of late effects
  - Explore the AYA population
  - Novel approaches for validation of certain late effects
  - Electronic engagement of the cohort
  - Maintenance of the merged cohort
  - Increase in conduct of intervention studies
  - Expansion of scientific disciplines within the leadership
  - Development and conduct of hypothesis-testing molecular genetic studies
  - Additional collaboration with other childhood cancer survivor groups internationally
  - Successful training/mentorship
  - Continued accessibility of the cohort to new researchers

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CCSS Budget

- Request same budget approved for current grant cycle starting with $4.31 in Y 23 (FY 2017)

Year	NOA Budget	Actual Award
18	$4,314,800	$4,314,800
19	$4,233,958	$3,978,213
20	$4,197,131	$4,071,218
21	$4,180,297	$3,762,268
22	$4,172,225*	

* Budget reflected in Y 22 NOA

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Key Changes in Therapeutic Exposures Between Cohorts

- 44% received RT 1987-99, compared to 68% in the original cohort (1970-86)
- 33% with leukemia received cranial RT 1987-99, compared to 69% in the original cohort
- 78% with HL received RT, compared to 94% in the original cohort
  - 22% received >30 Gy, compared to 68% in the original cohort
- Increased use of Cisplatin (739 original cohort + 1,353 in expansion = 2,092 overall)
- Increased use of Ifosfamide (190 original cohort + 978 in expansion = 1,168 overall)
- Almost 12,000 survivors exposed to anthracyclines overall
- Over 10,000 exposed to cyclophosphamide overall

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Intervention Studies

- Previous studies: smoking cessation (Emmons, Klesge); use of virtual information center to improve screening (Oeffinger)

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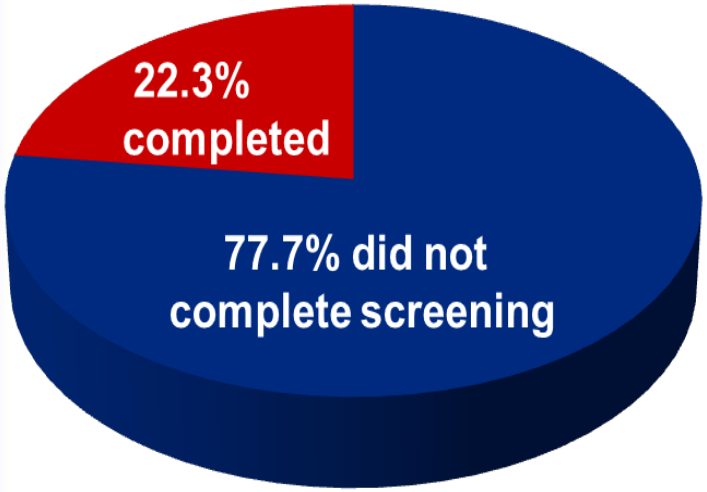
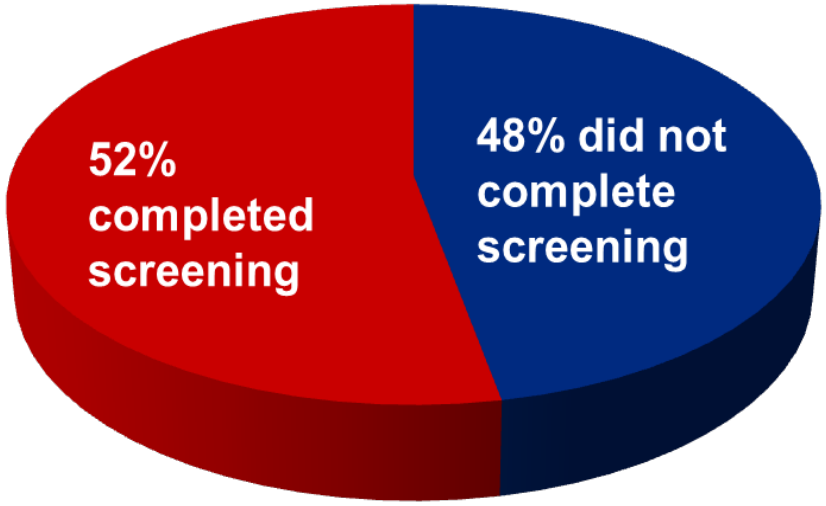
ECHOS: Screening Outcomes



SCP Only Control (n=206)



SCP + APN Intervention (n=205)

SCP + APN > 2x more likely than SCP alone to complete screening (RR 2.31; 95% CI: 1.74-3.07).

Hudson MM, Leisenring W, Stratton K et al. Increasing cardiomyopathy screening in at-risk adult survivors of pediatric malignancies: a randomized controlled trial. J Clin Oncol, 2014

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2011 CCSS Aims

- Maintain CCSS has a strong and productive resource and primary source for exposure based screening and health surveillance recommendations for childhood cancer survivors
- Enhance the CCSS resource- by facilitating the collection of additional biospecimens to facilitate understanding of the molecular underpinnings of treatment-related adverse outcomes
- Promote and facilitate the continued use of CCSS as a resource

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Minority Recruitment Plan Summary

- Serious consideration given to recruitment of a minority cohort: Determined Not Feasible
  - Sufficient numbers of Blacks and Hispanics (diagnosed 1987-99, treated at all COG institutions) do not exist to allow diagnosis-specific, and treatment-specific assessment of late effects.
  - Approach to address minority-related concerns
    - New Minority Task Force (Armstrong/Signorello): Guide minority recruitment
      - Revised recruitment materials: personal appeal from minority participants, altruistic, simplified language)
      - Use new materials for recruitment of four minority-enriched institutions (January 2015)
    - Comprehensive analysis of race-ethnicity across all CCSS outcomes (Yasui)
      - 1,806 Hispanic, 1,581 Black (diagnosed 1970-99), largest analysis of minority survivors to date
    - Position paper on minority research (Bhatia)
      - Provide definitive resource for what is known about minority childhood cancer survivors and major gaps in knowledge, barriers to research

New Recruitment Brochure

New recruitment brochure

- Simplified, universal language
- Altruistic
- Personal appeal from current participants

Cover letter from CCSS Institutional PI

Notes incentive after completion of baseline survey

Simplified HIPAA authorization form

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New Recruitment Brochure

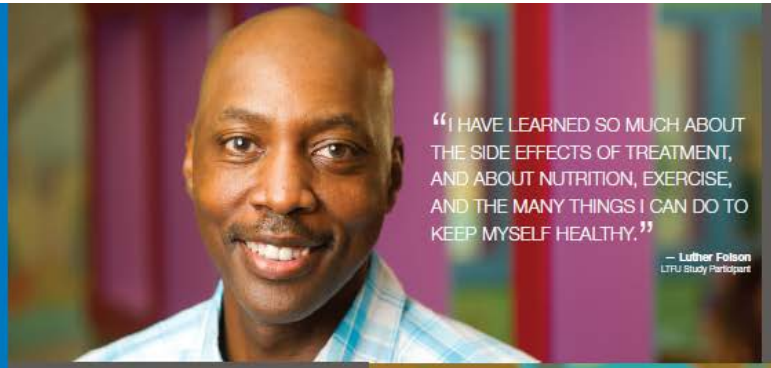
OUR HISTORY

Thankfully more children than ever before are surviving serious illnesses like cancer. For the past 20 years, the Long-Term Follow-Up (LTFU) study has collected information from thousands of survivors to find out about the long-term effects of treatments they received. We've been able to answer many questions, but there is still a lot to learn. We hope you will help us.

WHAT WE'VE LEARNED SO FAR

The LTFU study has helped people understand health problems that may happen many years after their illness. The things we've learned also helped improve the care for children who are now ill.

Each participant has a personal reason for participating in the **LTFU** Study. **Here are two of them ▶**



LUTHER'S REASON:
An opportunity to give back

For Luther Folson, participating in the LTFU Study is a way to contribute to the well-being of other survivors like himself. Luther was diagnosed with Hodgkin lymphoma when he was 11 years old. Now age 44, the police officer and former Army paratrooper has participated in the LTFU Study for more than 10 years and his commitment to the study is for life. "It's an opportunity to give back by helping somebody else, even after I'm gone," he says. "I will do anything I can to help."

He has also benefitted in a practical way from participating in the study. He finds the study newsletters and research updates to be a big help in staying on top of his own health.

TAYDE'S REASON:
Helping survivors lead healthy lives

Tayde Cruz believes in the power of research. She was 7 years old when she was diagnosed with acute lymphoblastic leukemia. She spent many years in treatment but is now cancer-free and married at age 34. "It was a big part of my life and I wanted to give a little bit back," she says. Because of this she's chosen to work for the fundraising organization that supports the hospital where she was treated.

While she is healthy today, Tayde has had some side effects from her cancer treatment. She participates in the LTFU Study because she understands that the information she shares will help to reduce the risk of health problems for future patients.

Special credit to: Melissa Hudson, Catherine Moen, Aaron McDonald and CCSS Education Committee

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Expansion Recruitment: Minority Participation

Main Characteristics of the Initial and Expanded Cohorts (as of 9/2014)

Characteristic	Initial Cohort*		Expanded Cohort		
	Eligible	Recruited	Eligible	Completed Baseline	% of Eligible Completing Baseline
Total			14,347	9,636	
Sex					
Male	N (%)	N (53.7%)	8,055 (56.1%)	5,129 (53.2%)	63.7
Female		46.3%	6,292 (43.9%)	4,510 (46.8%)	71.7
Race/ethnicity					
White non-Hispanic	-	83.2%	10,954 (76.3%)	7,680 (79.7%)	70.1
Black non-Hispanic	-	4.7%	1,510 (10.5%)	897 (9.3%)	59.4
American Indian/Alaska Nat.	-	0.6%	64 (0.4%)	38 (0.4%)	59.4
Asian or Pacific Islander	-	1.2%	300 (2.1%)	177 (1.8%)	59.0
Hispanic	-	2.8%	1,153 (8.0%)	635 (6.6%)	55.1
Other	-	7.3%	72 (0.5%)	42 (0.4%)	58.3
Unknown	-	0.3%	294 (2.1%)	170 (1.7%)	57.8

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Minority Task Force

- Hispanic focused task force meeting, USC 1/2013
- African-American focused task force meeting, Vanderbilt 4/2014

- <u>CCSS Minority Task Force</u>
  - Co-Chairs: Lisa Signorello (NCI) and Greg Armstrong

Lourdes Baezconde-Garbanati PhD
-Assoc. Professor, Preventive Medicine, USC
-PI, Tobacco Education and Material Lab (TEAM Lab)

Donna Spruijt-Metz, PhD
-Assoc. Professor, Health Promotion/Disease Prevention, USC

Pam Hull, PhD
-Asst. Professor Epidemiology, Vanderbilt

Elizabeth Williams, PhD
-Asst. Professor, Public Health, Tennessee State University

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Overview of Strategies to Increase

1. Expand CCSS to include a minority cohort

2. Improve participation rates among currently eligible
   -Minority Task Force

3. Increase total number of minorities eligible
   -Addition of four probationary institutions

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Working Group Recommendations

Utilize four new institutions to pilot revised recruitment documents

-Simplification of recruitment documents

- Lower reading level
- Better art with more images that appeal to hopeful message of survivorship
- HIPAA “too legal” and should be modified: content (if possible) and structure (conversational tone)

– Tailoring or targeting of recruitment documents, not recommended

- Brochure in Spanish
- Privacy is very important and must be communicated to the target group
- Stronger appeal to altruism

– Consider an incentive

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Significant Findings from CCSS

- Conducted first study in late effects in long term survivors of standard risk ALL. They found that the incidence was low. This enables oncologists to not only reassure patients/families about the outcome from ALL but also about the l quality of life after cure.. Essig S et al. Lancet Oncology, 2014
- Using GWAS, *PRDM1* was found to significantly associated with radiation-associated second cancers. Homozygosity for the risk allele was associated with 29% incidence of second cancer compared to 3.5% in those without the risk allele. (Best et al Nat Med 2011)
- Shorter telomere length has been associated with increased cancer incidence. Using CCSS, a statistically significant inverse relationship was found between telomere content and occurrence of second malignant neoplasms, most apparent in thyroid cancer.(Gramatges et al Clin Cancer Res, 2013)
- Using 13,000 CCSS survivors, a heart failure prediction model was developed using gender, patient's age at diagnosis and patient's anthracycline and/or chest/heart radiation doses; validated in 3 external cohorts (Chow et al, J Clin Oncol 2014)

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Significant Findings from CCSS

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Evaluators

- Paul Jacobsen, PhD- Associate Center Director, Division of Population Sciences, Moffit Cancer Center; JCO Associate Editor
- Jorgen Olsen, MD, DMSc, Director of Danish Cancer Society Research Center, Copenhagen
- Michael Link, MD-Professor, Pediatrics-Hematology & Oncology, Stanford, former ASCO president
- Mary McCabe, RN, MN, Director, Cancer Survivorship Initiative, MSKCC
- Saro Armenian, DO, MPH, former Young Investigator; Medical Director, Pediatric Survivorship Clinic, Childhood Cancer Survivorship Program, City of Hope
- Martha Linet, MD, MPH, Chief, Radiation Epidemiology Branch- NCI

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Evaluation Findings - Strengths

- Interviewees noted that the CCSS was the **first** cohort of pediatric cancer survivors ever assembled at this scale, and it remains the **largest** cohort of its type in the world.
- The CCSS cohort itself is perhaps the most important product of the study and has advanced research effort on childhood cancer survivorship worldwide; Major source of data concerning survivors of childhood cancer
- Impressive leadership team which has pioneered the majority of survivorship investigations; Expertise from all relevant specialties are represented; Acknowledged experts in the methodology employed
- Utilizes current and widely used methodology for health outcomes and health services
- Provides critical information about late effects and quality of life for survivors of childhood cancer; No other study is able to combine all these qualities(detailed case history including treatment delivered, and sibling comparison)
- Worldwide impact on clinical follow up for childhood cancer survivors
- Addition of studies to interrogate the genome of cancer survivors looking for markers of susceptibility to specific toxicities
- Comprehensive infrastructure, oversight and governance- functional without being bureaucratic
- Transparent and efficient mechanism for initiating projects within CCSS
- Participant education

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Evaluation-Weaknesses

- Self reporting by survey and lack of confirmation of outcome data from medical sources except for second malignancies
- Expand scientific disciplines represented among leadership
- Focus on clinical apparent disease
- Reliance on older treatment era
- Increase intervention studies and expand intervention strategies to ensure at risk patients receive screening tests
- Minority representation

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Standard Risk ALL: Specific Chronic Health Conditions

Specific Health Disorders	Odds Ratio (95% CI)	P-value
Subsequent Malignant Neoplasm	2.2 (0.8-6.2)	0.13
CHF or Cardiomyopathy	1.5 (0.2-11.8)	0.68
Stroke or Cerebrovascular Disease	3.3 (0.5-22.8)	0.73
Osteoporosis	5.5 (1.5-19.5)	0.0089
Hypothyroidism	1.4 (0.7-2.4)	0.36
Obesity	1.1 (0.9-1.4)	0.40
Short Stature	3.9 (2.0-7.7)	<0.0001

Conclusion: The prevalence of adverse long-term outcomes in children treated for standard risk ALL is low.

Essig S, Li Q, Chen Y, Hitzler J, Leisenring W, Greenberg M, Sklar C, Hudson MM, Armstrong GT, Krull KR, Neglia JP, Oeffinger KC, Robison LL, Kuehni CE, Yasui Y, Nathan PC. Risk of Late Effects of Treatment in Children Newly Diagnosed with Standard-Risk Acute Lymphoblastic Leukaemia: A Report from the Childhood Cancer Survivor Study Cohort. *Lancet Oncol*, 2014; 15(8): 841-51.

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Career Development Award

Category	Awardee	Project Title
2013: 15 Applicants		
Junior Faculty	Sogol Mostoufi-Moab Children's Hospital of Philadelphia	Overall risk of Chronic Endocrine Disorders in Adult Survivors of Childhood Cancer
2014: 10 Applicants		
Junior Faculty	Philip Lupo, PhD Baylor College of Medicine	Epigenomic profiling of metabolic outcomes in childhood leukemia survivors
Junior Faculty	Rebecca Howell, PhD UT MD Anderson Cancer Center	Radiation dose reconstruction methods for intensity modulated radiation therapy
Trainee	Giselle Perez, PhD Massachusetts General Hospital	Mental healthcare service availability and utilization among childhood cancer survivors
Trainee	Melissa Schapiro, MD St. Louis Children's Hospital	Cognitive and academic difficulties in survivors of head/neck rhabodomyosarcoma

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Accomplishments

- Merger of the two cohorts
- Completion of 3 randomized interventions studies (Klesges, Hudson, Oeffinger);
- 2 new randomized interventions studies
  - ASK about skin cancer (Geller, Harvard RO1)
  - EQUAL(Tonorezos, MSKCC R01)
- Collaboration with international investigators
- Utilization of biospecimens
  - GWAS of second malignancies (with DCEG); RFP
  - Genetic susceptibility to obesity(Kamdar, LLS)
  - Neurofibromin and genotoxins (Nakamura, St. Baldricks)

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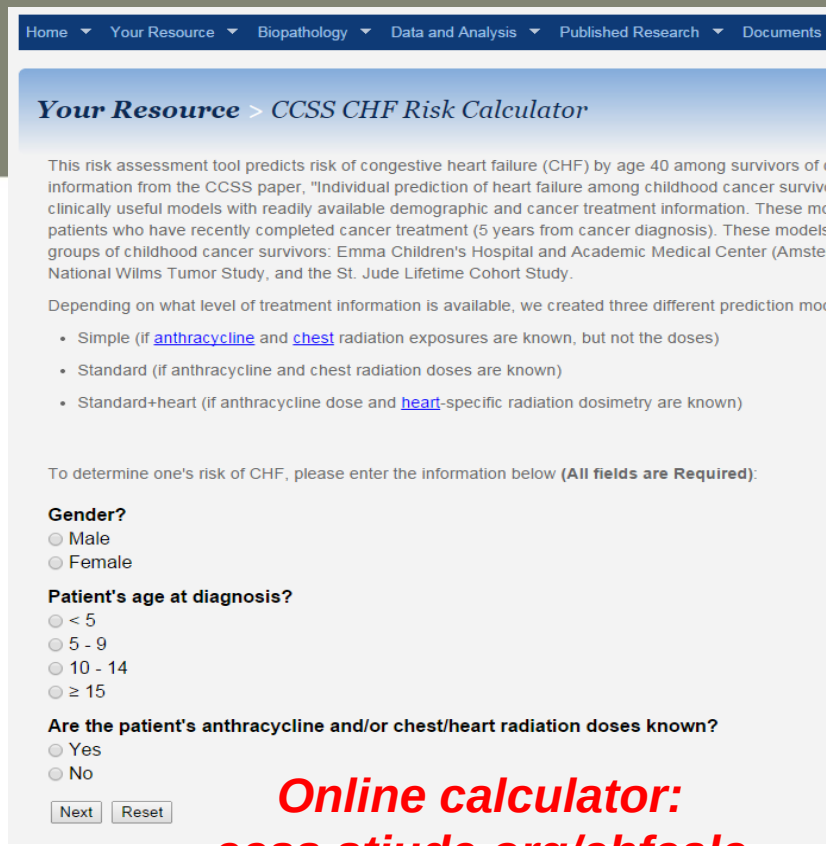
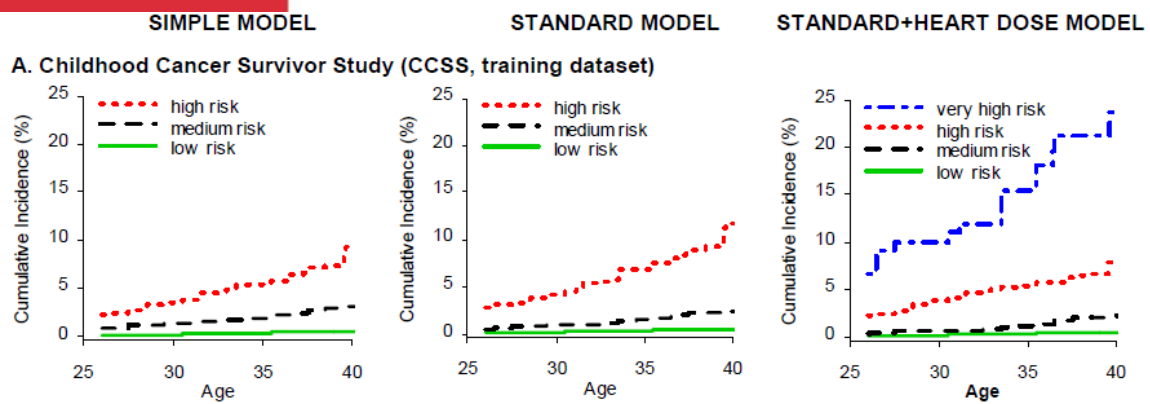
Heart Failure Risk Prediction

- Cardiovascular disease is one of the leading causes of morbidity/mortality among childhood cancer survivors
- Cardiovascular risk predictors exist for the general population, but are inadequate for childhood cancer survivors
- Use 13,000 CCSS survivors (285 CHF cases) to develop heart failure prediction model
- Validate with 3 external cohorts (Nat'l Wilms Tumor Study, St. Jude, Dutch; 93 CHF cases)



Online calculator: ccss.stjude.org/chfcalc



- AUC/C-statistics ~0.75; able to segregate low, moderate, and high-risk groups
- Chow et al, J Clin Oncol 2014

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New Opportunities

- Exploit for outcomes of survivors of adolescent and young adult cancers
- Ongoing resource for intervention studies
- Using international collaborations, validate GWAS studies and risk prediction models and address novel questions pertaining to access to care, screening and transition across diverse health care models
- Use of this cohort to address questions of the impact of ethnic/racial diversity on survivor outcome

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Activities and Outputs: Working Group Studies, Ancillary Studies and Late Effect Guidelines; Training

- 316 Working Group Studies identified through 2014
- Analysis complete for 265 (84% of 316); ongoing for 50 (16%).
  - 236 (75% of 316) have resulted in at least one publication
- 40 approved ancillary studies, 21 funded through NIH awards(14 RO1, 4 R21, 2 K07, 1 UO1);19 additional non-NIH awards
- 41% COG Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers reference CCSS publications; 55% of radiation related guidelines
- 54 investigators have participated in the CCSS while undergoing medical, graduate, or postdoctoral training
- 40 trainees are or will be first author on CCSS publication as part of their postgraduate training
- Of the 236 CCSS publications, 79 (33%) had a CCSS trainee as first author; One or more of the CCSS trainees has appeared as an author on 133 (56%) distinct publications

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Approach

- Fall 2014: Roll out new recruitment materials + Incentive to four minority-enriched institutions
- Fall 2015: initial response rates for competitive renewal available
- Fall 2015: Go back to expansion cohort non-responders utilizing new materials

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Summary

- Not feasible nor wise to construct a minority cohort
  - Over time, over budget, logistical barriers

- Approach to address minority-related concerns
  - Expert Minority Task Force to guide ongoing minority recruitment (Armstrong)
  - Comprehensive analysis of race-ethnicity across outcomes (Yasui)
  - Position paper on minority research (Bhatia)