CCSS
Childhood Cancer Survivor Study

Epidemiology/Biostatistics Working Group

Yutaka Yasui

St. Jude Children's Research Hospital

An NCI-funded Resource

Working Group Progress

CCSS

7 Published/In Press Manuscripts (10+ as Secondary WG)

1 Currently Submitted Manuscripts

4 Analysis/Manuscript in Process

8 Concepts in development

11 New AOIs

Highlights of Recently Completed Research

CCSS

Cost-Effective Cardiomyopathy Surveillance Strategies

Matt Ehrhardt, MD, MS
St. Jude Children's Res. Hospital

Jennifer M. Yeh, PhD
Boston Children's Hospital

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Highlights of Recently Completed Research

CCSS

Objective: Evaluate cost-effectiveness of cardiomyopathy screening of the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG)

Approach: Microsimulation model of the clinical course of congestive heart failure (CHF) among 5-year survivors of childhood cancer

Highlights of Recently Completed Research

CCSS

	Anthracycline dose	Chest RT dose	Anthracycline + chest RT
High Risk	**≥ 250 mg/m²**	**≥ 35 Gy**	**≥ 100 mg/m² + ≥ 15 Gy**

Cost-effectiveness of Cardiomyopathy Screening, Ehrhardt & Yeh

Highlights of Recently Completed Research

CCSS

Screening strategy	Heart Failure Risk	
	Age 40 yrs %	Lifetime %
No screening	**9.9**	**36.7**
Every 10-year	9.3	35.4
Every 5-year	8.9	34.6
Every **2-year**	**8.2**	**33.6**
Every 1-year	7.9	33.0

Cost-effectiveness of Cardiomyopathy Screening, Ehrhardt & Yeh

Highlights of Recently Completed Research

CCSS

Screening strategy	Heart Failure Risk		Required Cost / Quality-Adjusted Life Years Gained
	Age 40 yrs %	Lifetime %	
No screening	**9.9**	**36.7**	–
Every 10-year	9.3	35.4	$34,604 / year
Every 5-year	8.9	34.6	$37,703 / year
Every **2-year**	**8.2**	**33.6**	**$77,877** / year
Every 1-year	7.9	33.0	$223,168 / year
	17.1% reduction	**8.4% reduction**	

Cost-effectiveness of Cardiomyopathy Screening, Ehrhardt & Yeh

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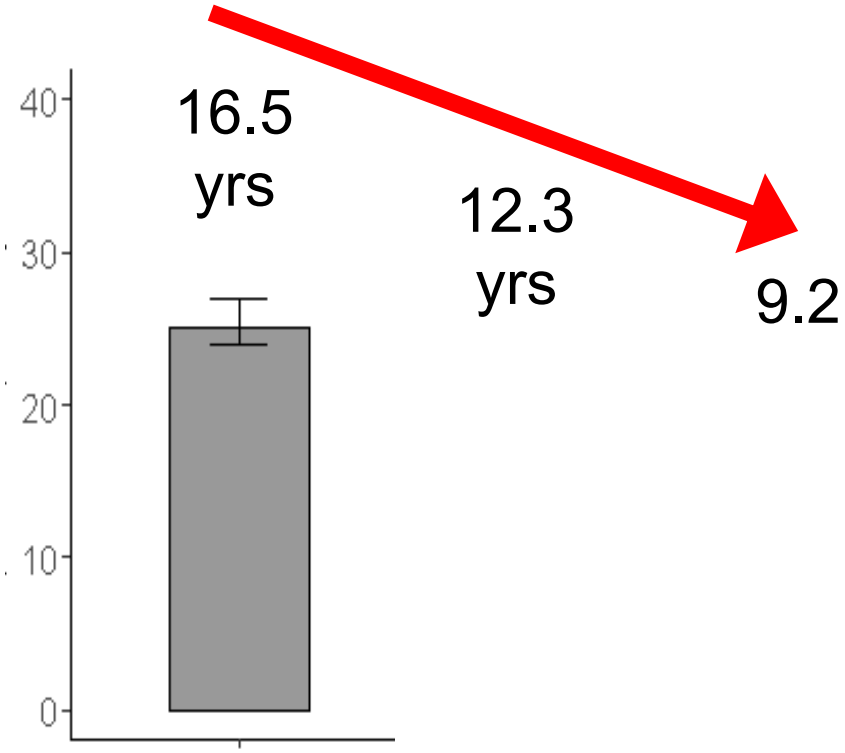
Highlights of Recently Completed Research

CCSS

Projections in Trends in Life Expectancy

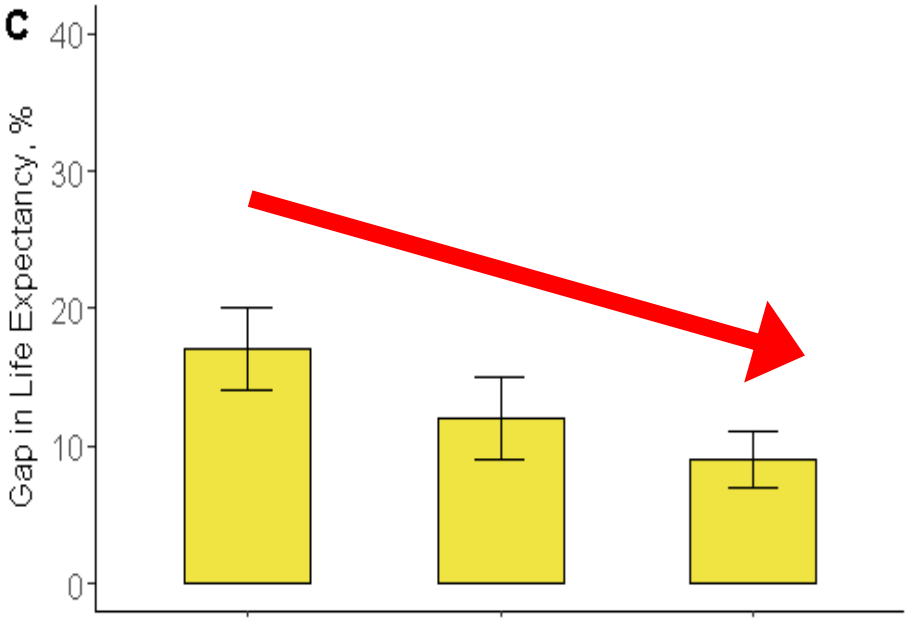


Jennifer M. Yeh, PhD.
Boston Children's Hospital

Highlights of Recently Completed Research

CCSS

Chemo-only group



	70s	80s	90s
None	0.3	0.2	0.5
Surgery only	5.3	7.0	10.0
Chemo only	18.8	36.7	53.3
RT only	14.8	9.4	3.4
Chemo + RT	60.8	46.6	32.9

Mortality Trends, Yeh

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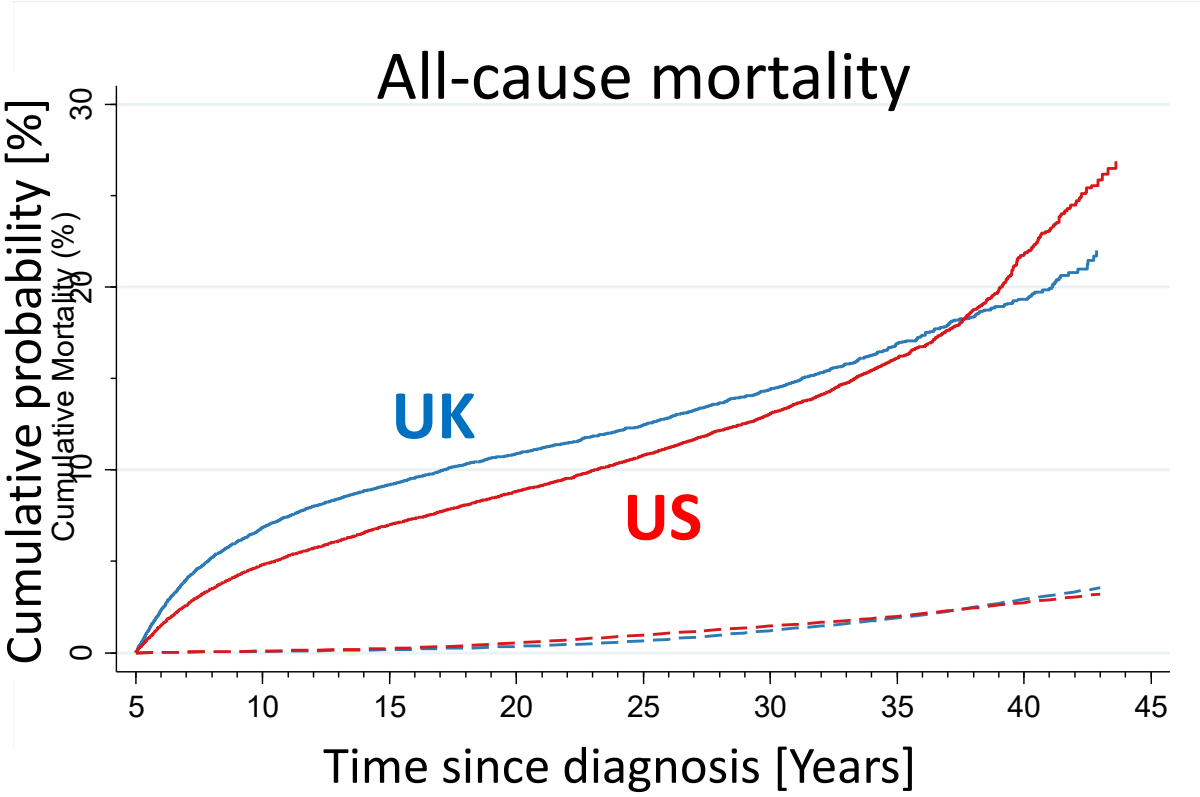
Highlights of Recently Completed Research

CCSS

Mortality Comparison

UK vs. US CCSS

Miranda M Fidler, PhD
Alberta Health Services
(CDA winner)



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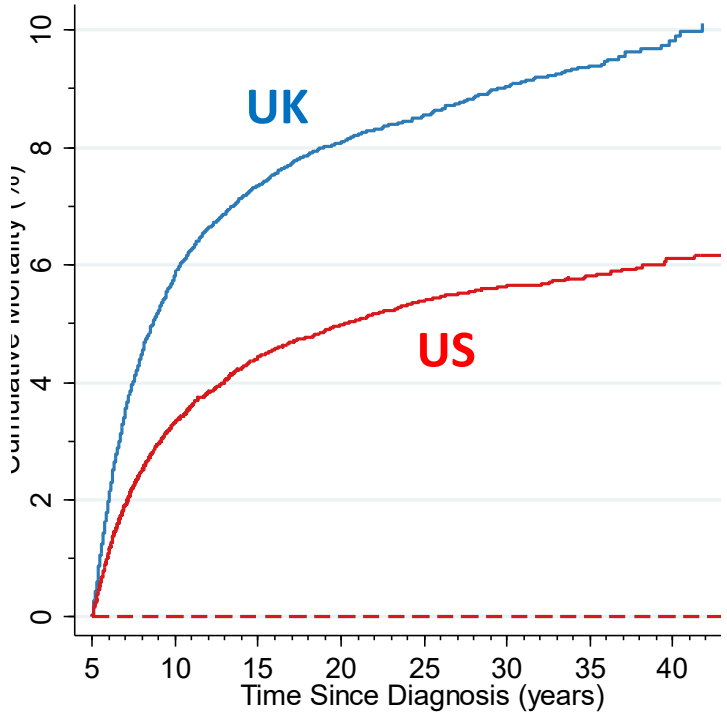
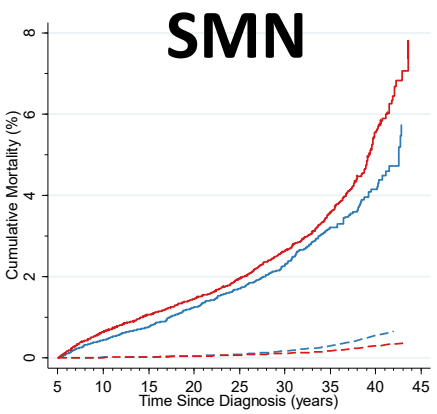
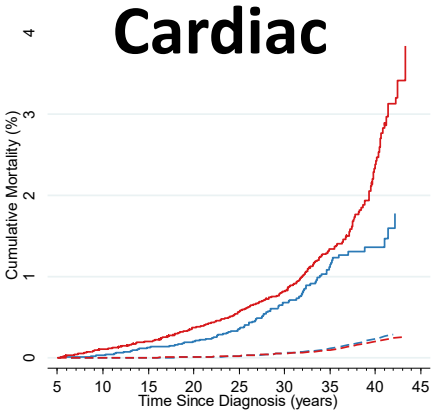
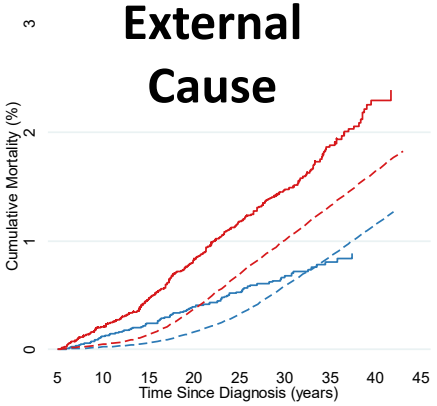
Highlights of Recently Completed Research

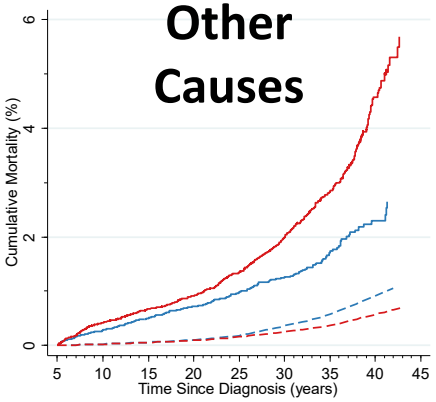
CCSS











Mortality
UK vs. US
Fidler

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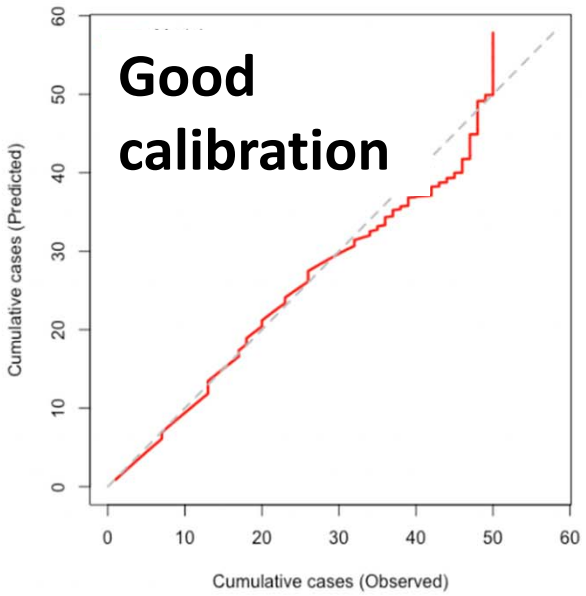
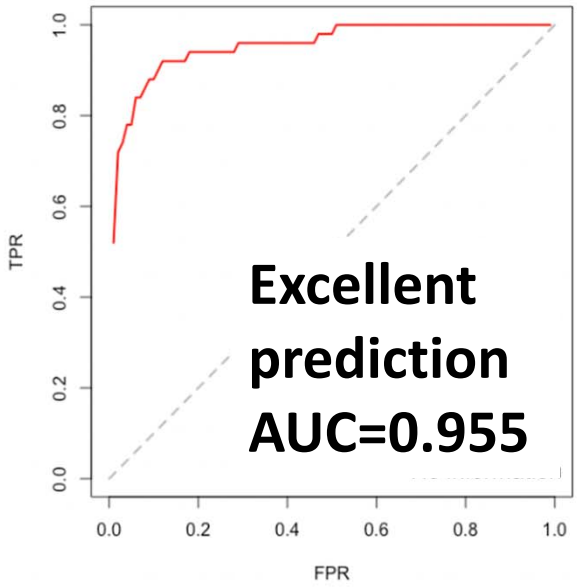
Highlights of Recently Completed Research

CCSS

Prediction Modeling Acute Ovarian Failure





Yan Yuan, PhD
Univ. of Alberta

Predictors: Ovarian radiation dose, TBI, Age at dx, Cyclophosphamide Eq. Dose

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Highlights of Recently Completed Research

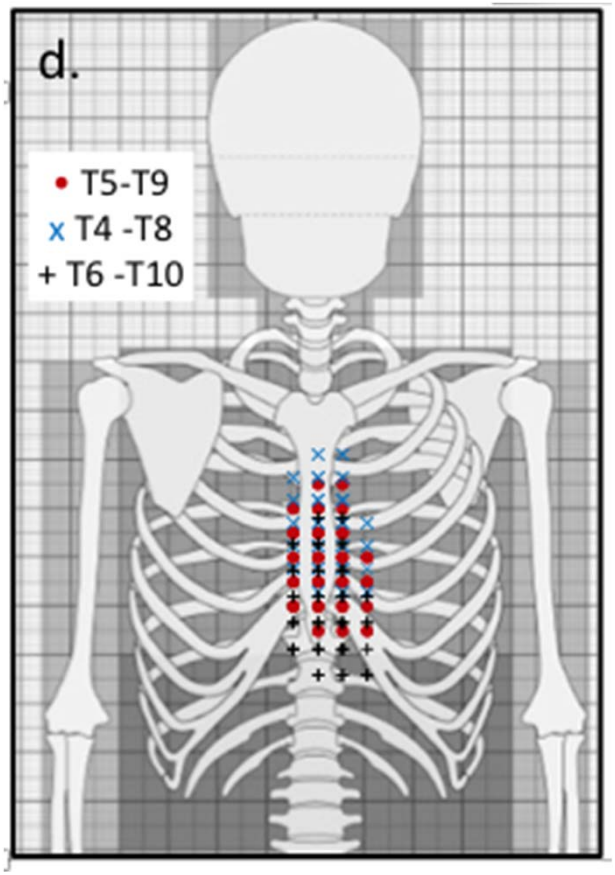
CCSS

Uncertainty in RT dosimetry

Rebecca Howell, PhD
MD Anderson Cancer Center
(CDA Winner)

Highlights of Recently Completed Research

CCSS



- Mean heart doses in CCSS
  A single heart model located between thoracic vertebral bodies T5 and T9 (base heart)

- Assess the effect of age-specific interpatient heart anatomy on the dose-response relationship of heart RT and cardiac disease risks

Dosimetry uncertainty, Howell

Highlights of Recently Completed Research

CCSS

Mean Heart Dose (Gy)	Heart Failure Rate Ratio (95% CI)	
	Base Heart	**Age-based**
None	Ref	**Ref**
0.1 – 9.9	0.7 (0.5, 0.9)	**0.7 (0.5, 0.9)**
10 – 19.9	1.6 (1.0, 2.4)	**1.8 (1.2, 2.6)**
20 – 29.9	2.9 (1.9, 4.4)	**3.3 (2.2, 5.0)**
≥ 30	6.5 (4.4, 9.6)	**6.8 (4.5, 10.3)**

Dosimetry uncertainty, Howell

Highlights of Recently Completed Research

CCSS

Mean Heart Dose (Gy)	Heart Failure Rate Ratio (95% CI)		Coronary Artery Disease Rate Ratio (95% CI)	
	Base Heart	**Age-based**	Base Heart	**Age-based**
None	Ref	**Ref**	Ref	**Ref**
0.1 – 9.9	0.7 (0.5, 0.9)	**0.7 (0.5, 0.9)**	1.0 (0.6,1.5)	**1.0 (0.6, 1.5)**
10 – 19.9	1.6 (1.0, 2.4)	**1.8 (1.2, 2.6)**	2.8 (1.7, 4.5)	**3.2 (2.1, 5.0)**
20 – 29.9	2.9 (1.9, 4.4)	**3.3 (2.2, 5.0)**	3.3 (2.0, 5.5)	**3.3 (2.0, 5.5)**
≥ 30	6.5 (4.4, 9.6)	**6.8 (4.5, 10.3)**	7.2 (4.8, 10.9)	**7.3 (4.8, 11.1)**

Dosimetry uncertainty, Howell

Ancillary Studies

CCSS

Principal Investigator: Liang Zhu (University of Texas MD Anderson)
Title: Statistical Analysis for Mixed Outcome Measures in Recurrent Event Studies
Dates of Funding: 8/17 - 7/19
Funding Source: National Cancer Institute (R03)
Award: $89,412
Study Aims: Develop a likelihood-based semiparametric estimation method for regression analysis of mixed panel-binary and panel-count data.

Principal Investigator: Lennie Wong (City of Hope)
Title: Cost effectiveness of breast cancer screening guidelines for female survivors of pediatric cancers
Dates of Funding: 7/17 - 6/20
Funding Source: American Cancer Society
Award: $527,000
Study Aims: 1) Examine the cost-effectiveness of 1) annual clinical breast examination, 2) annual breast tomosynthesis vs. MRI as adjunct to mammography.

Ancillary Studies

CCSS

Principal Investigator: Yan Yuan (University of Alberta)
Title: Risk Prediction Model of Premature Menopause in Childhood Cancer Survivors
Dates of Funding: 7/16 - 12/18
Funding Source: Canadian Institutes of Health Research
Award: $179,858
Study Aims: To develop a prediction model for early menopause.

Principal Investigator: Yutaka Yasui, Jinghui Zhang (St. Jude Children's Research Hospital)
Title: Late Effects Prediction using Clinical Phenotypes and Whole Genome Sequencing
Dates of Funding: 4/17 - 3/22
Funding Source: National Institutes of Health (RO1)
Award: $3,457,455
Study Aims: 1) Build individual risk prediction models with the SJLIFE cohort for 11 outcomes including meningioma, basal cell carcinoma, and multiple subsequent neoplasms, 2) Validate the risk prediction models in a larger cohort study with higher SN counts (CCSS).

Five Year Plan: Progress Update

CCSS

1) Close collaboration with CCSS Genetics Working Group and the NCI's DCEG in analyses of GWAS and exome sequence data (imputation, ancestry adj., leading multiple GWAS analyses/papers)
2) Methodological research for the analysis of temporally dense, "big data" from mHealth devices
3) Continue to develop methodologies for prediction modeling and evaluation of prediction performance, in keeping with the increasing number of proposals targeting individual risk prediction (2 ancillary studies and 2 manuscripts)
4) Continue to develop innovative population-science methodologies relevant to CCSS, including a study-design that specifically targets efficient assessment of long-term outcomes in a relatively short study/grant length

Five Year Plan: Progress Update

CCSS

1) Close collaboration with CCSS Genetics Working Group and the NCI's DCEG in analyses of GWAS and exome sequence data (imputation, ancestry adj., leading multiple GWAS analyses/papers)
2) Methodological research for the analysis of temporally dense, "big data" from mHealth devices (Machine Learning analysis of I-Chan Huan's survey symptom data)
3) Continue to develop methodologies for prediction modeling and evaluation of prediction performance, in keeping with the increasing number of proposals targeting individual risk prediction (2 ancillary studies and 2 manuscripts)
4) Continue to develop innovative population-science methodologies relevant to CCSS, including a study-design that specifically targets efficient assessment of long-term outcomes in a relatively short study/grant length (Eric Chow's tiled design work)

Top Priorities/Opportunities

CCSS

Association (Does the risk of the late effects of interest differ by X? If so, how much?)

Risk Prediction/Quantification (How well can we predict/quantify the risk of future late effects?)

Top Priorities/Opportunities

CCSS

Association (Does the risk of the late effects of interest differ by X? If so, how much?)

- Linkage to external databases
  - Census
  - Environmental data (built or physical environment)
  - Outcomes/Healthcare data (e.g., Medicaid, Optum)

Top Priorities/Opportunities

CCSS

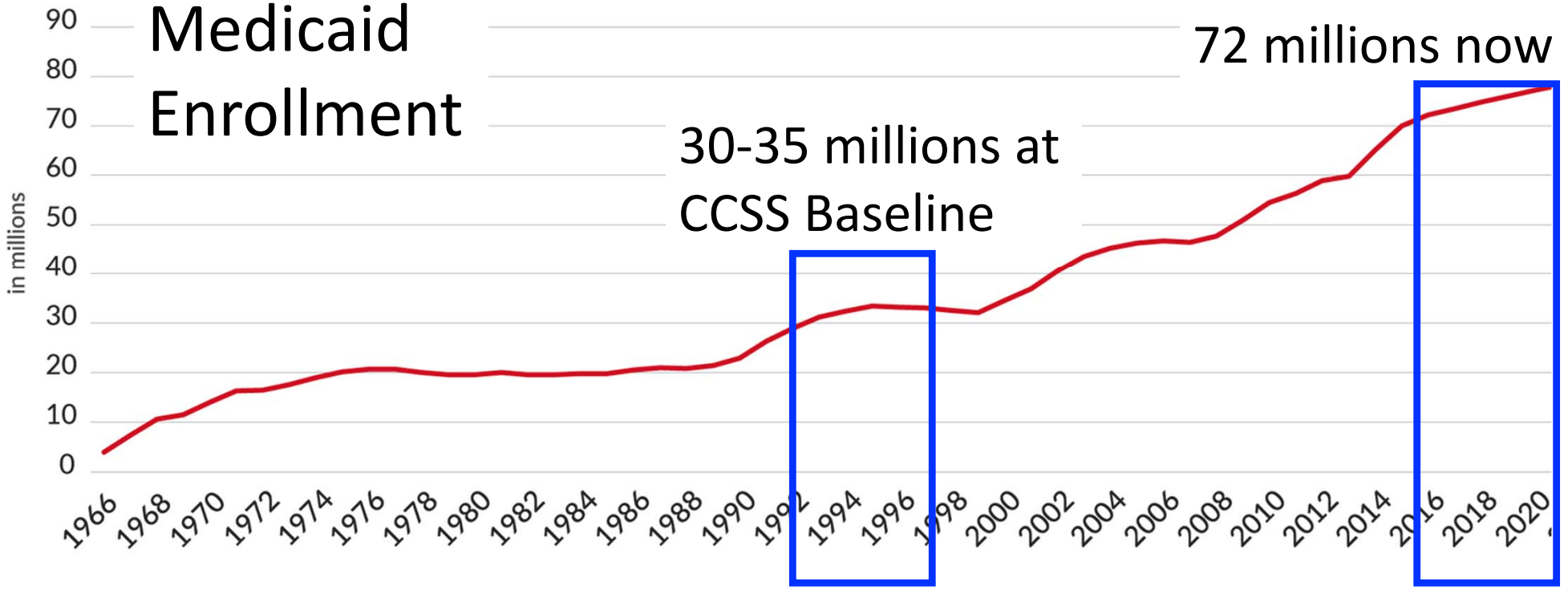
Association via census/built environment databases

04.29.19	Neighborhood Effect and Chronic Conditions in the CCSS Cohort	Howell/SJCRH
04.29.19	Socioeconomic and Rural/Urban Differences in Adverse Outcomes among Childhood Cancer Survivors	Winestone/UCSF

GIS (Latitude, Longitude) coordinates of CCSS participants' addresses => Utilization in future studies

Top Priorities/Opportunities

CCSS



Childhood Cancer Survivor Study

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Top Priorities/Opportunities

CCSS

Original Article | Free Access

Impact of insurance type on survivor-focused and general preventive health care utilization in adult survivors of childhood cancer

The Childhood Cancer Survivor Study (CCSS)

Jacqueline Casillas MD, MSHS ✉, Sharon M. Castellino MD, MSHS, Melissa M. Hudson MD, Ann C. Mertens PhD, Isac S. F. Lima BS, Qi Liu MS, Lonnie K. Zeltzer MD, Yutaka Yasui PhD, Leslie L. Robison PhD, Kevin C. Oeffinger MD

Childhood Cancer Survivor Study

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Top Priorities/Opportunities

CCSS

Association via Medicaid Outcomes/Healthcare data

- Disadvantaged population studies
- Uniformly verified (non self-report) late effects outcomes
- Cost studies
- Ancillary Study grant opportunity

Top Priorities/Opportunities

CCSS

Association methodological research for self-report data

- Application of Mean Score Method (Pepe et al., J. of Statistical Planning and Inference 1994)
- Self-report outcomes available for the cohort
- Verified outcomes available for a subgroup only
- Home sampling or data linkage for verified outcomes

Top Priorities/Opportunities

CCSS

Association methodological research for genetics data

- Effective rare-variant analysis methodology
- Extensive bioinformatics databases to link and/or place prior knowledge over rare and common variants
- Modern statistical/machine learning methodologies

Top Priorities/Opportunities

CCSS

Risk Prediction/Quantification (How well can we predict/quantify the risk of future late effects?)

- Clinical utility
- Decomposition of contributions from various risk factors (clinical/tx, demographic, and genetic)
- Machine learning applications

Discussion: Opportunities and Threats

CCSS

Major Strength/Opportunity

- Discover, support junior investigators w/ methodology interest
- Focus on methodological issues of high impact
- Seek additional methodological collaborators
- Method webinar or workshop to expand the use of CCSS data and disseminate accumulated methodological knowledge

Discussion: Opportunities and Threats

CCSS

Major Threat/Challenges

- Abundant demands on method applications to projects
- Supervision of many MS-level analysts by PhD-level epidemiologists and biostatisticians
- Lack of emphasis by methodologists on methodological work
- Small numbers of methodologists

Working Group Membership

CCSS

- Yutaka Yasui (Chair), St. Jude Children's Research Hospital
- Wendy Leisenring, Fred Hutchinson Cancer Research Center
- Chaya Moskowitz, Memorial Sloan Kettering Cancer Center
- Kiri Ness, St. Jude Children's Research Hospital
- Jennifer Yeh, Boston Children's Hospital
- Yan Yuan, University of Alberta
- Liang Zhu, University of Texas Health Science Center at Houston
- Todd Gibson, St. Jude Children's Research Hospital
- Eric Chow, Fred Hutchinson Cancer Research Center
- Arin Madenchi, Boston Children's Hospital
- Ann Mertens, Emory University

Epi/Biostat Working Group

CCSS

Working Group => Your entry to CCSS

PLEASE CONTACT ME IF YOU HAVE ANY INTEREST OR IDEA ON POTENTIAL EPI/BIOSTAT PROJECTS

Yutaka.Yasui@stjude.org