Opportunities to Advance Subsequent Neoplasm Ascertainment in Survivors of Childhood Cancer

Pilot use of the Virtual Pooled Registry

Gregory T. Armstrong

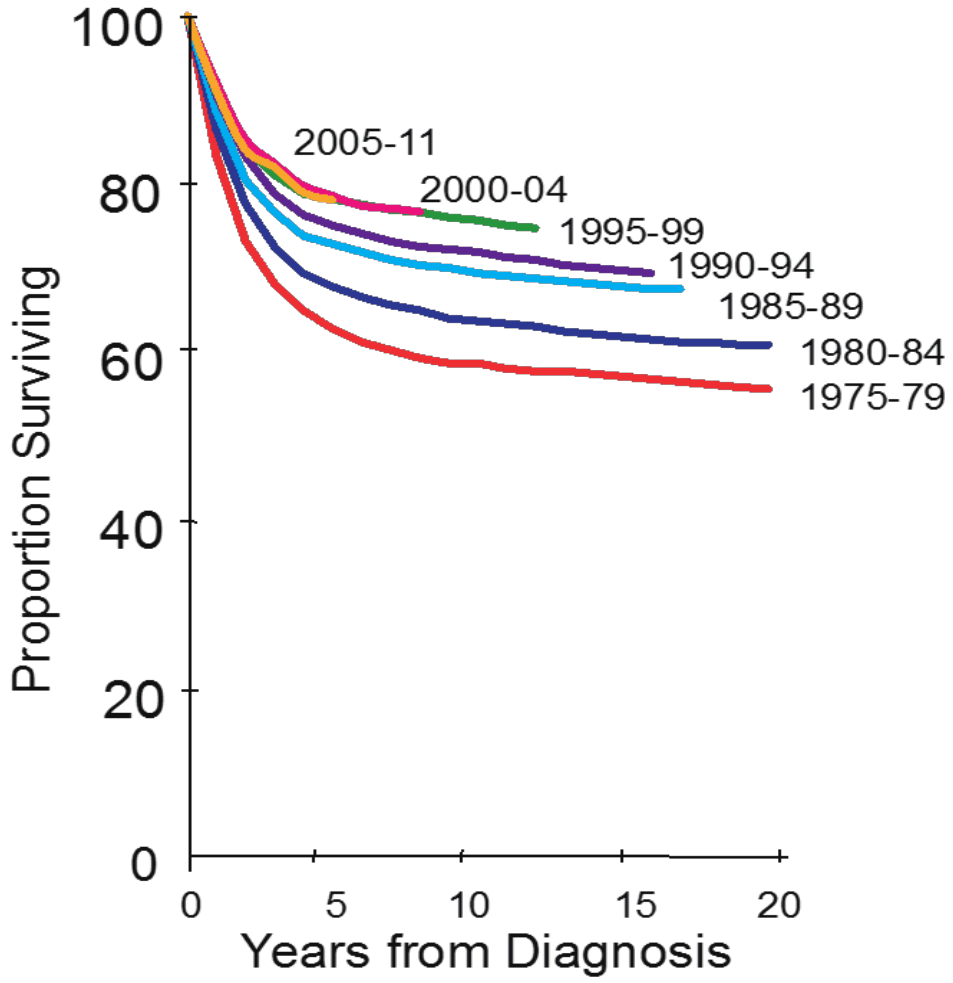
Principal Investigator, CCSS

CCSS
Childhood Cancer Survivor Study

An NCI-funded Resource

Cancer Survival, 0-14 Years of Age

CCSS



Survivorship Statistics

- >83% of children with a malignancy will achieve five-year survival
- In 2013, estimated 420,000 survivors of childhood cancer in the U.S.
- By 2020, estimated 500,000 survivors
- 1 in 750 in US is a childhood cancer survivor

Howlader N, SEER 1975-2012; Phillips et al, *CEBP*, 2015; Robison L. & Hudson MM, *Nature Reviews Cancer* 2014

Childhood Cancer Survivor Study

An NCI-funded resource

Rationale for a Survivor Cohort Study

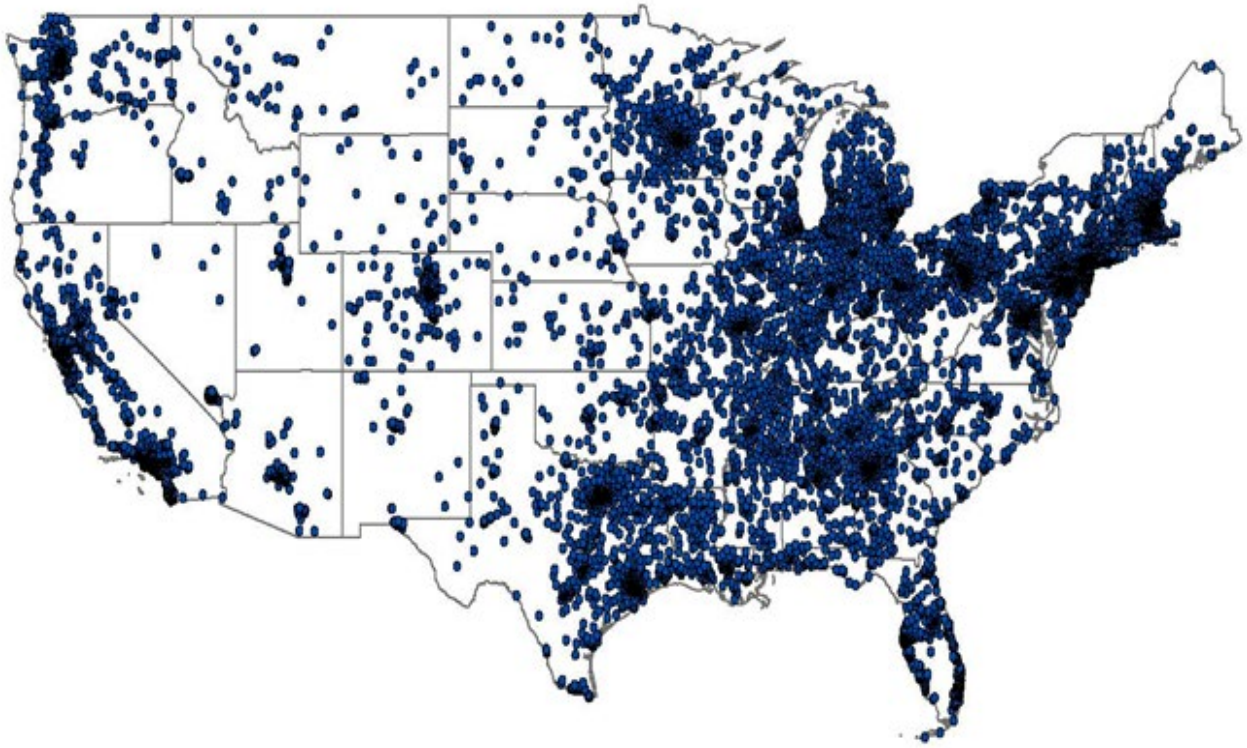
CCSS

- **Limitations of single institution studies**
  - Sample size
  - Heterogeneity of exposure
- **Lack of extended follow-up of childhood cancer survivors**
  - Incomplete and passive follow-up

Childhood Cancer Survivor Study (U24 CA 55727) Study Participants

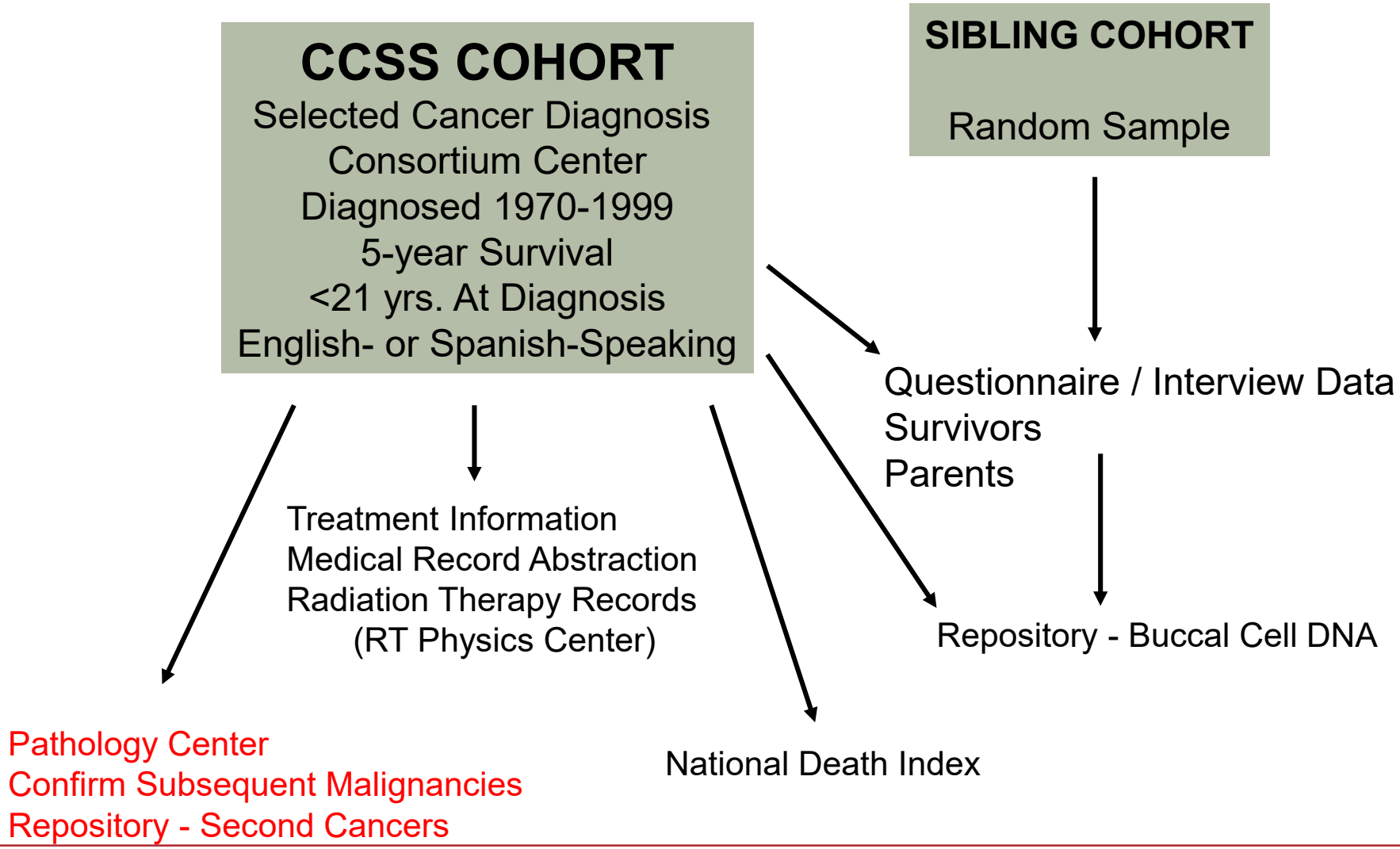
CCSS

- Funded in 1994
- Retrospective cohort, survivors diagnosed 1970-1999
- 31 contributing centers
- 5-year survival
- Leukemia, lymphoma, CNS, bone, Wilms, NBL, soft-tissue and bone sarcoma
- Detailed treatment data
- Wide range of health outcomes
- 37,593 eligible; 25,664 participating



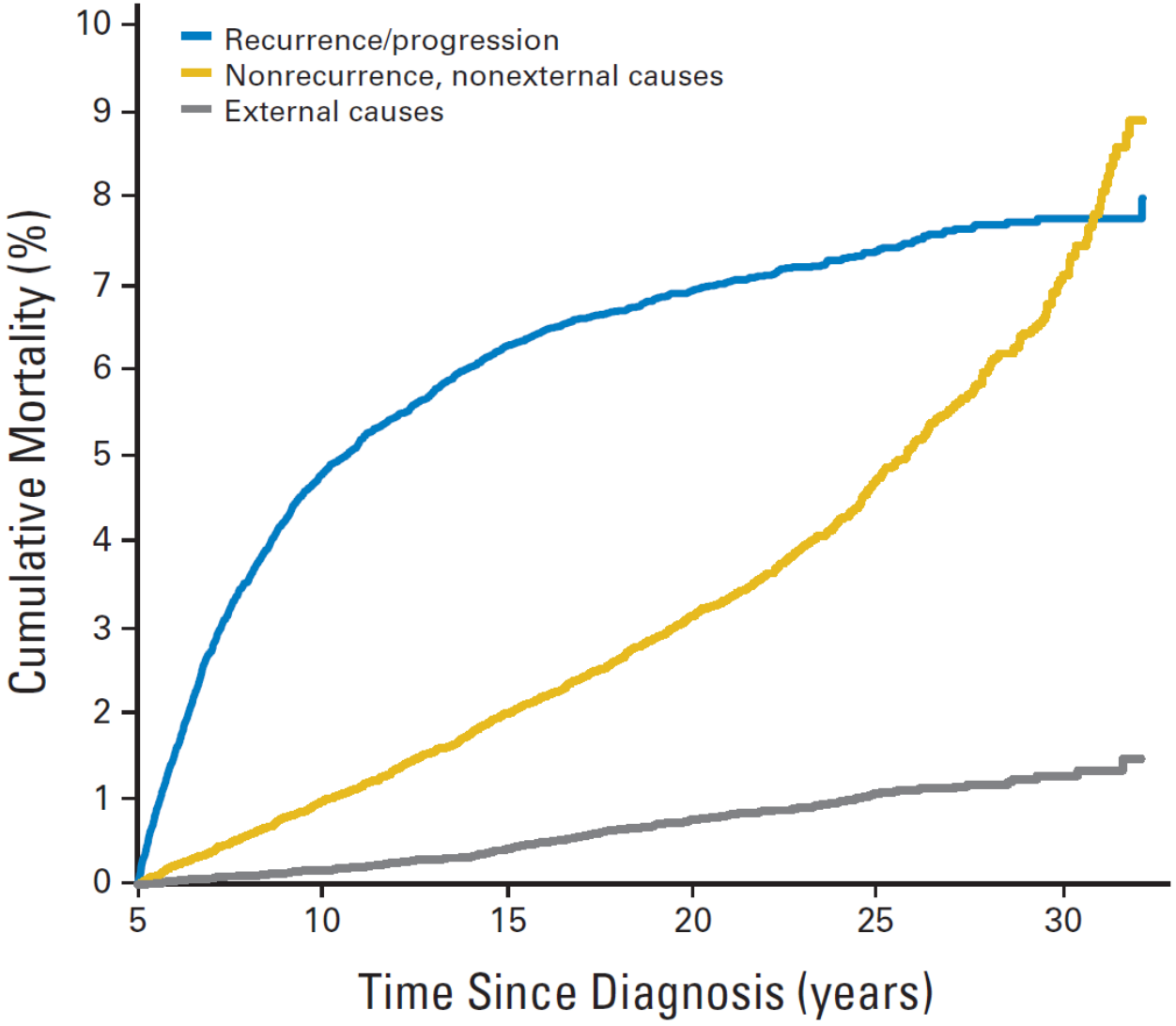
Childhood Cancer Survivor Study (U24 CA 55727) Study Overview

CCSS



Cause-specific Late Mortality Among Aging Survivors

CCSS



Standardized Mortality Ratio

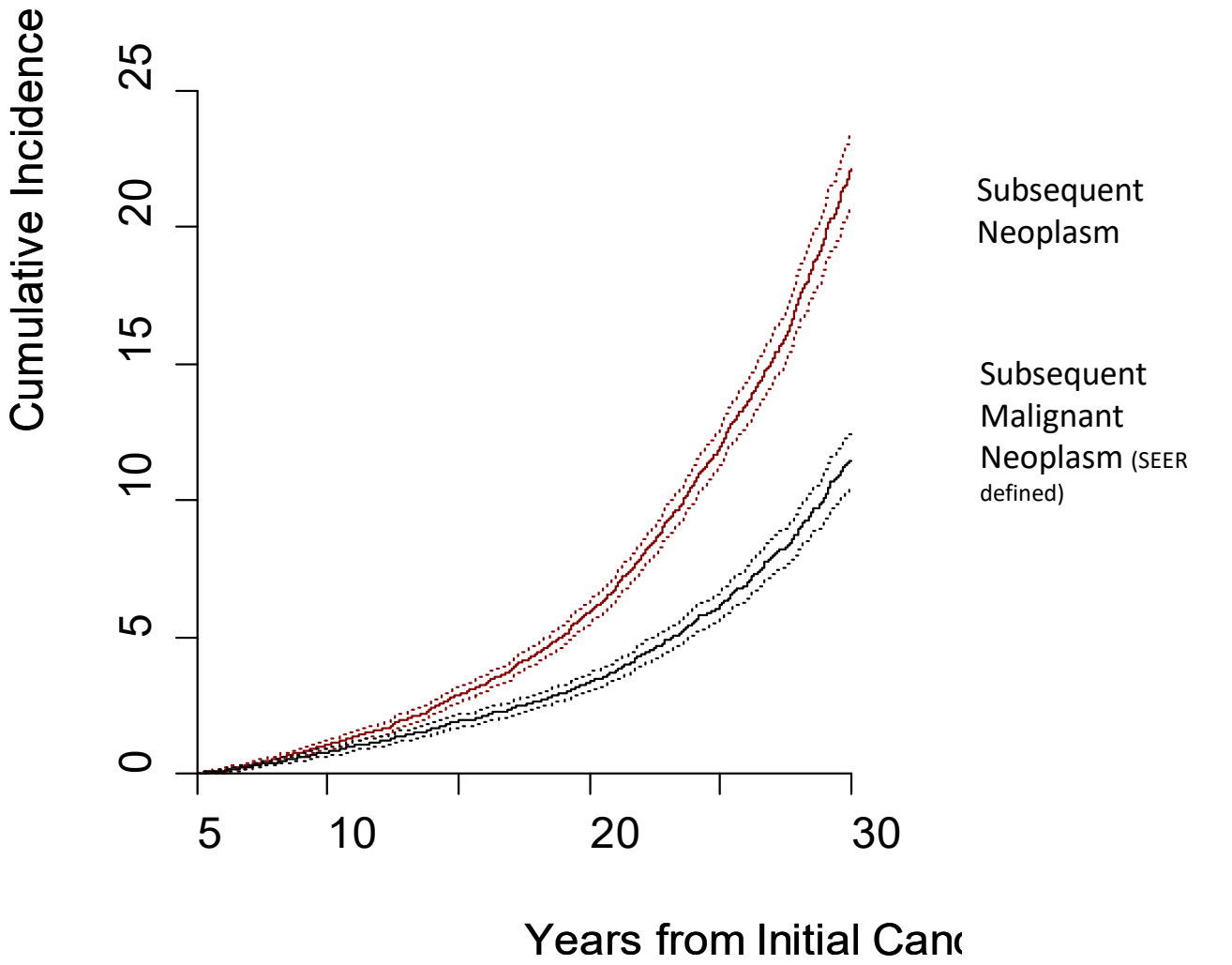
SMN =15.2

Cardiac = 7.0

J Clin Oncol, 2009

Subsequent Neoplasms Among 5+ Year Survivors of Childhood Cancer

CCSS



N= 14,359 five-years survivors of leukemia, lymphoma, neuroblastoma, CNS, bone, soft-tissue and kidney cancer

- Cumulative incidence of subsequent neoplasm at 30 years = 22%
- Cumulative incidence of subsequent malignancy at 30 years = 11%
- Well-established association with radiotherapy

Anthracycline Chemotherapy and Risk for Subsequent Neoplasms

CCSS

- Nested case/control, 271 women with subsequent breast cancer
- Odds ratio for breast cancer increased with cumulative anthracycline dose:
    - OR per 100mg/m^2 = 1.23 (95% CI 1.09-1.3)

Breast RT Dose	Anthracyclines	
	No	Yes
	OR (95% CI)	OR (95% CI)
0 - <1Gy	1.0	1.0
1 - <10Gy	2.1 (0.9-4.8)	3.7 (1.4-10.3)
10+ Gy	**9.6 (4.4-20.7)**	**19.1 (7.6-48.0)**

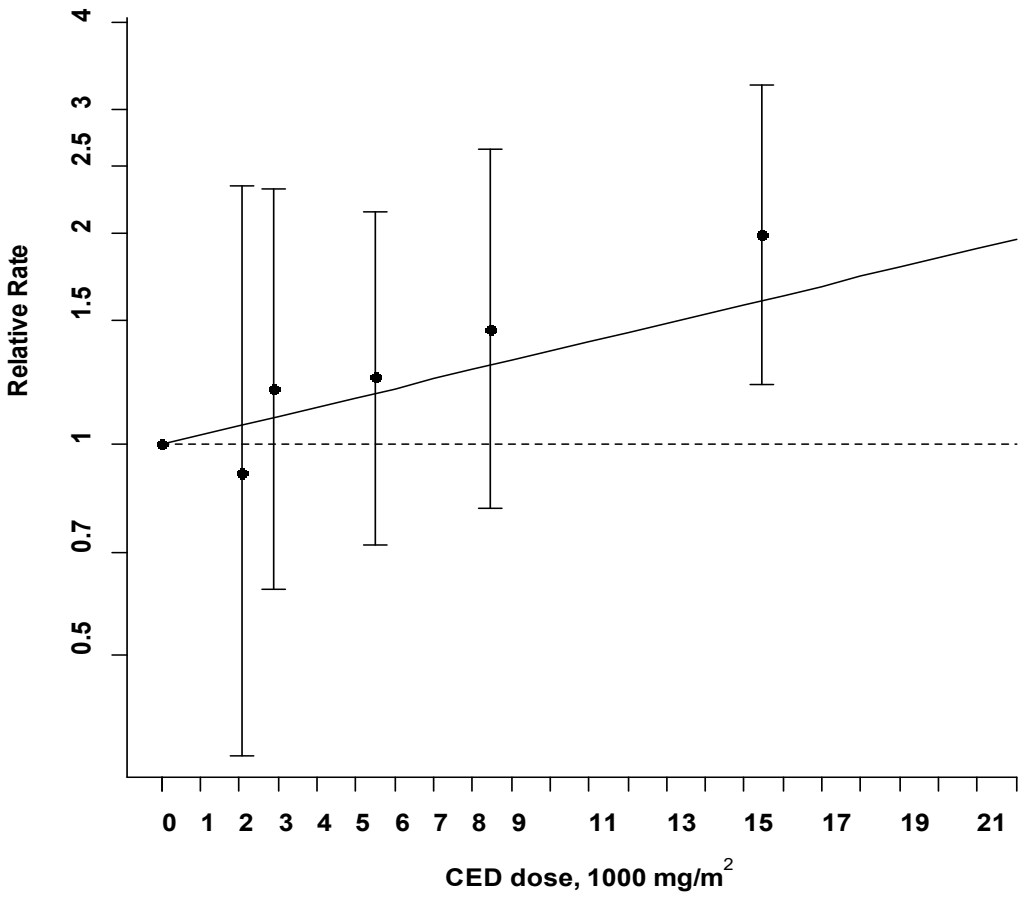
Anthracycline chemotherapy increases risk for breast cancer.

Veiga LH et al, JAMA Pediatr, 2019 in press

Chemotherapy and Risk for Subsequent Neoplasms

ccss

Cumulative Alkylating Dose and SMN



- 7,448 treated with chemo only
- Linear dose response for Alkylators
- SMN risk associated with high dose (>750 mg/m2) cisplatin: RR 2.7, 95% CI 1.1-6.5

There is emerging evidence for novel associations between chemotherapy exposures and SMNs decades later.

Studies across larger populations and multiple cohorts are needed.

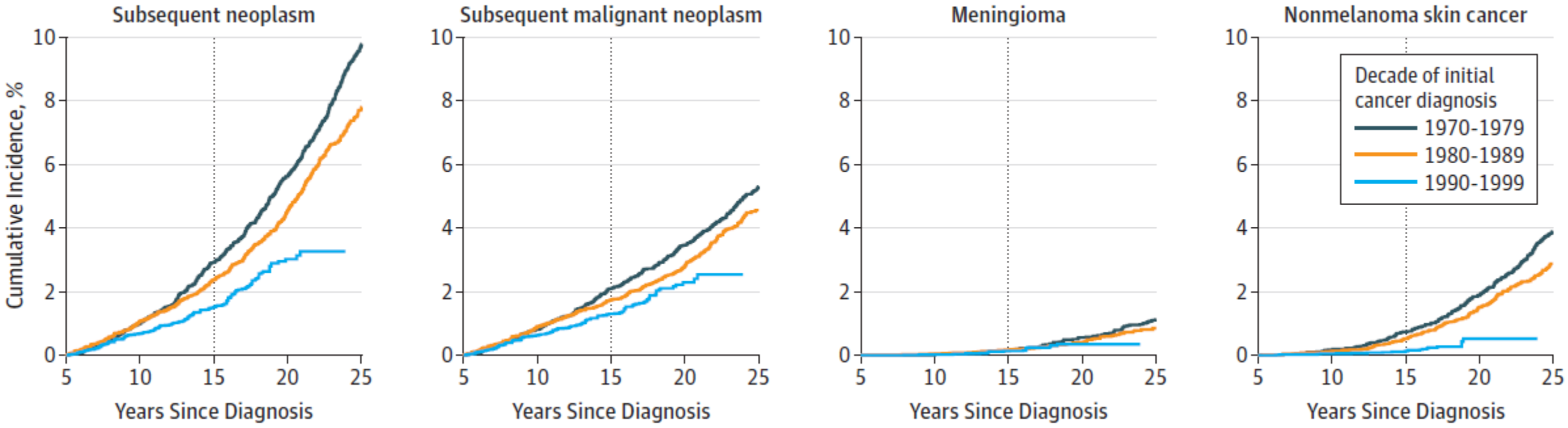
Turcotte LM et al, J Clin Oncol 2019

Childhood Cancer Survival: Subsequent Neoplasms

CCSS

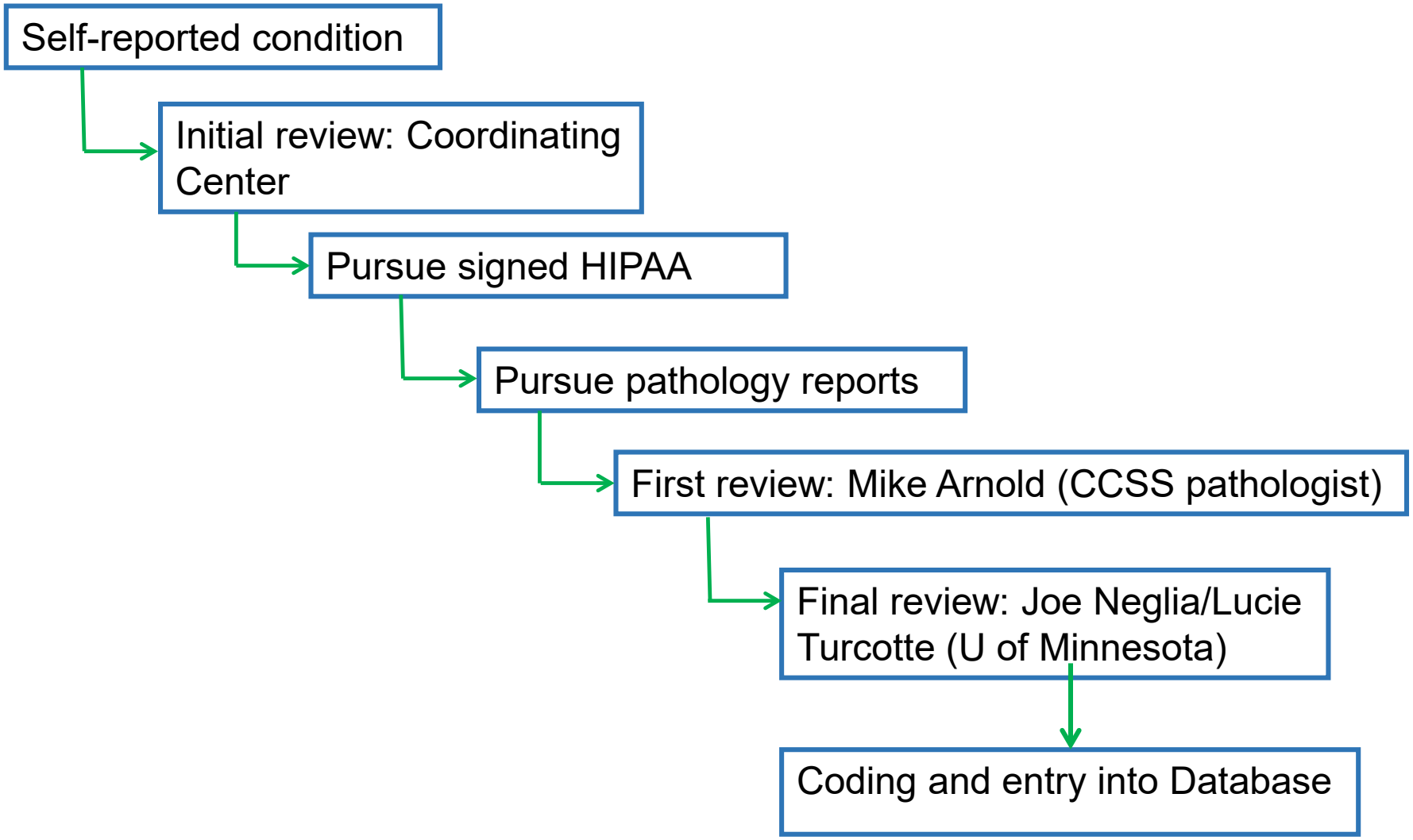
- Reduced risk for SN and SMN for survivors diagnosed in more recent decades

JAMA 2017



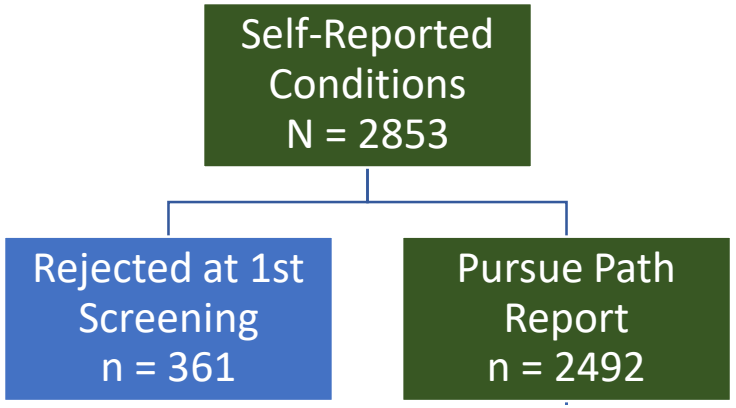
Subsequent Neoplasm Review and Confirmation

ccss



Magnitude of SN Review: Follow-up 6 Survey

ccss



Virtual Pooled Registry

CCSS

Funded by NCI SEER and managed by NAACCR

Designed to facilitate minimal risk linkage studies

- One-stop-shopping for linkage application and secure file exchange
- Standard linkage methodology across registries
- Streamlined process to apply for and track registry/IRB requests for release of individual-level data

Minimize burden and cost to researchers and registries/IRBs

Increase ease of access and timely use of high quality and complete registry data

VPR Cancer Linkage System (VPR-CLS)

ccss

VPR: Phase I

CCSS

Phase I successfully completed:

- Test linkage performed by 34 state registries (74.5% of U.S. population)
- Varying coverage through 2016 (23 registries included data from 1995+)
    - 10,440 total high quality matches (not requiring manual review)
    - 6,541 matched with the primary childhood cancer (2 year window)
    - **3,899** matches classified as a subsequent neoplasm

Phase II Pilot Testing

CCSS

Participating Studies: Childhood Cancer Survivor Study and Transplant Cancer Match Study

Provides requestor with the following:

- Review of Phase I match counts and selection of Phase II registries
- Online completion and submission of Templated IRB/Registry Application (TIRA) to accepting registries
- List of any state-specific forms or additional required documents
- Ability to track the status of application review, approval, DUA completion, and data release
- Information on renewal, publication, and data destruction requirements
- Automated registry and requestor reminders to ensure progress

VPR: Phase II, Ongoing

CCSS

Phase 2: Obtain individual-level data on the matched cases

- Each registry has its own requirements for releasing data
- VPR has developed and obtained registry approvals for:
  - Templated IRB/Registry application (TIRA)
  - Templated Data Use Agreement (planned)

} Avoid need for 50 separate applications

Progress:

- Of 30 selected registries 26 have accepted VPR template, 14 approved study, 10 under review
- CCSS has received data from six registries to date (others in progress)

Coverage: Represents 54% of U.S population, 80% of phase I matches

-adding Texas increases to 62% of U.S. and 89% of match counts

VPR Challenges

CCSS

A variety of documents may be required in addition to TIRA, with varying requirements for each registry:

- Legal agreements: data use, confidentiality, data transfer, and PI assurances
- Study materials: protocol, IRB outcome letter, consent form, grant award verification
- Research team credentials: human subjects research training certificates, CVs

A comprehensive library of registry documents and requirements is needed in the VPR portal.

- Many of the applications and agreements direct the researcher to reference other documents or include a checklist of additional required documents

Terms and agreements for the registries have been non-negotiable with very rare exception.

- Administrative management is required to ensure continued compliance with each registry

Strengths of using VPR to ascertain SNs

CCSS

- Evaluate all survivors for CCSS (37,593) vs. active participants (25,664)
  - Reduce potential participation bias in longitudinal follow-up
- Avoid use of self-report as primary ascertainment methodology
- Reduction in effort/resources
  - No HIPPA authorization, contact of institutions to obtain report
  - Limited case review

Summary: the VPR may provide an opportunity to improve the validity of subsequent neoplasm ascertainment while reducing time and cost