The Use of Clinical Trial Data in Combination with External Data Sources to Examine Novel Cancer Research Questions:

A Modified Big Data Approach

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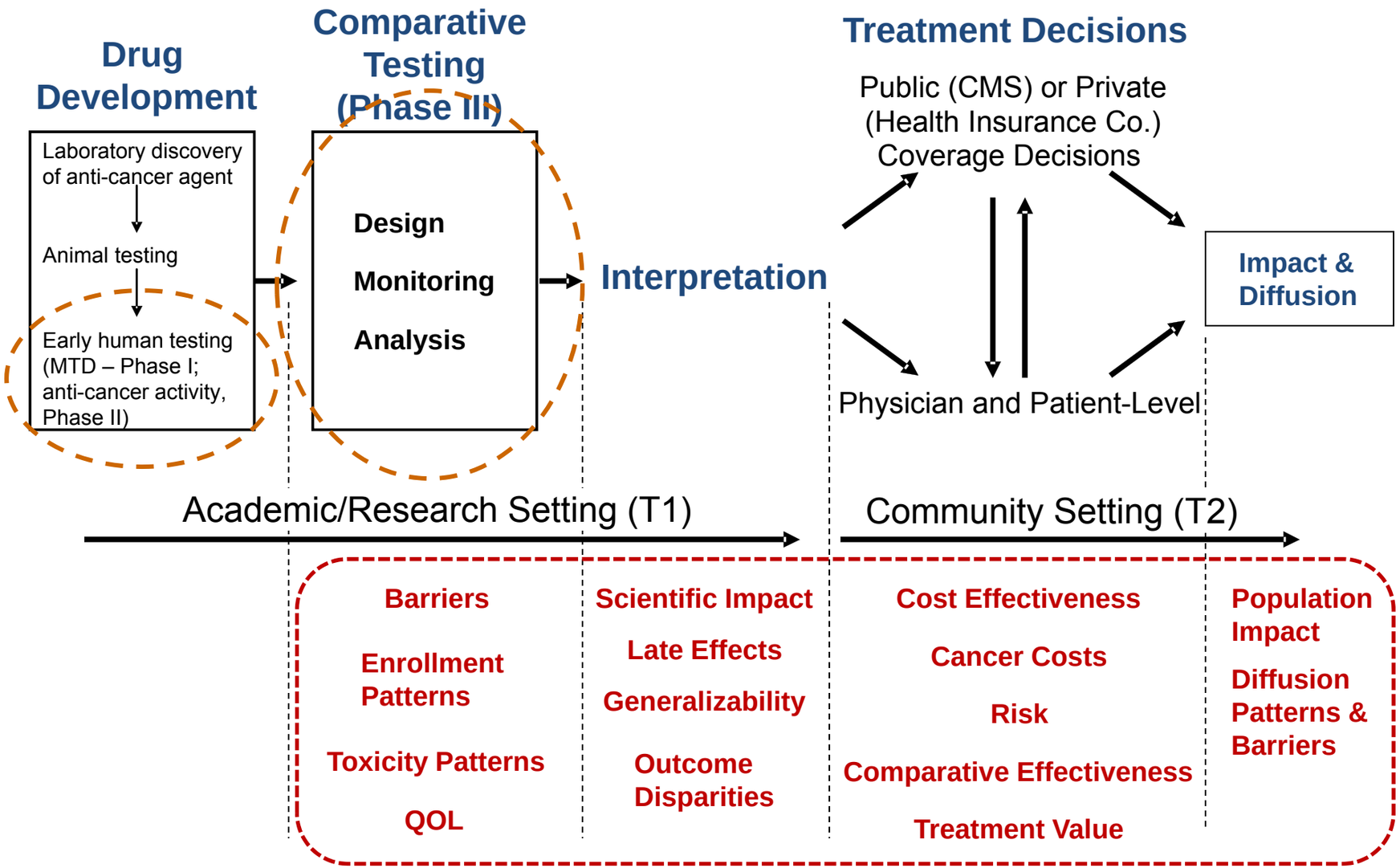
EXIT

Conceptual Model: Study to Diffusion of New Cancer Therapy



OUTLINE

Introduce idea of a modified **big data** approach to examining important issues about…

The Role of clinical trials in cancer (care delivery) research…

Especially as it pertains to studying:

- **Representativeness** of trials
- **Scientific impact** and value
- **Population impact** from cancer clinical trial system
- **Late effects** of treatment

Definition of Big Data

Definition #1:

- OED: “Data of a very large size, typically to the extent that its manipulation and management present significant logistical challenges.”

Definition #2:

- Combining multiple data sources in valid fashion to address meaningful and novel research questions

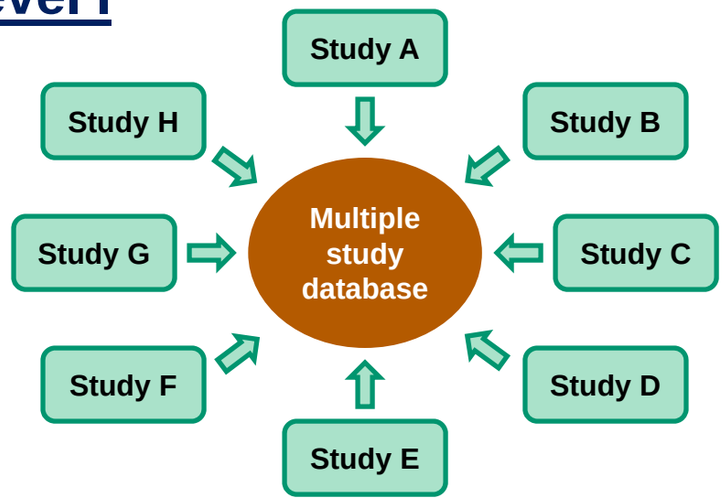
Modified “Big Data” Approach

Using data from a national clinical trials database, in combination with…

- Registry (SEER)
- Life-table
- Census
- Publication Data
- Citation Data
- Medicare claims

Modified “Big Data” Approach

Level I



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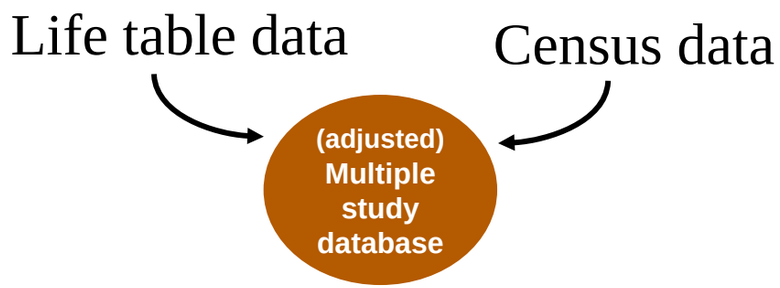

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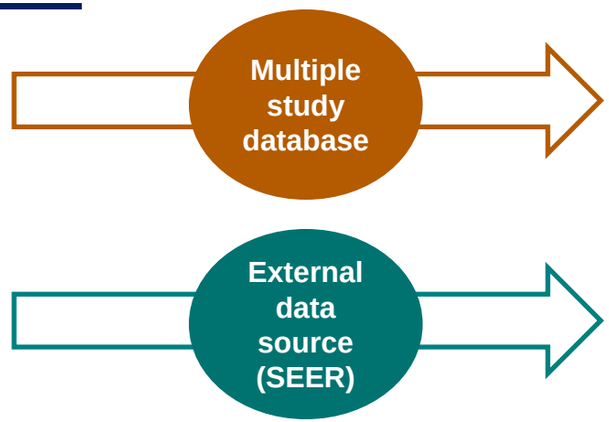

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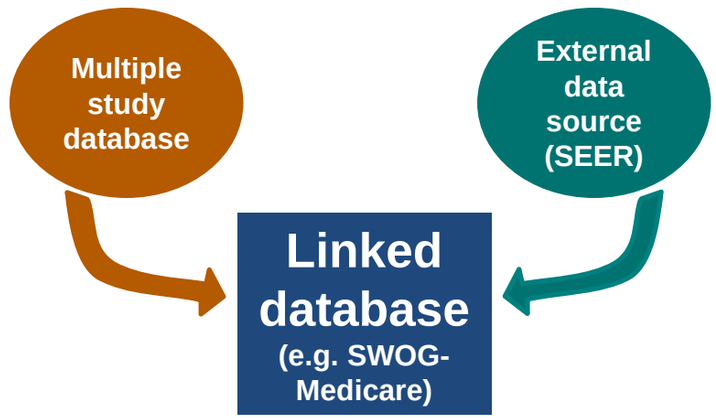
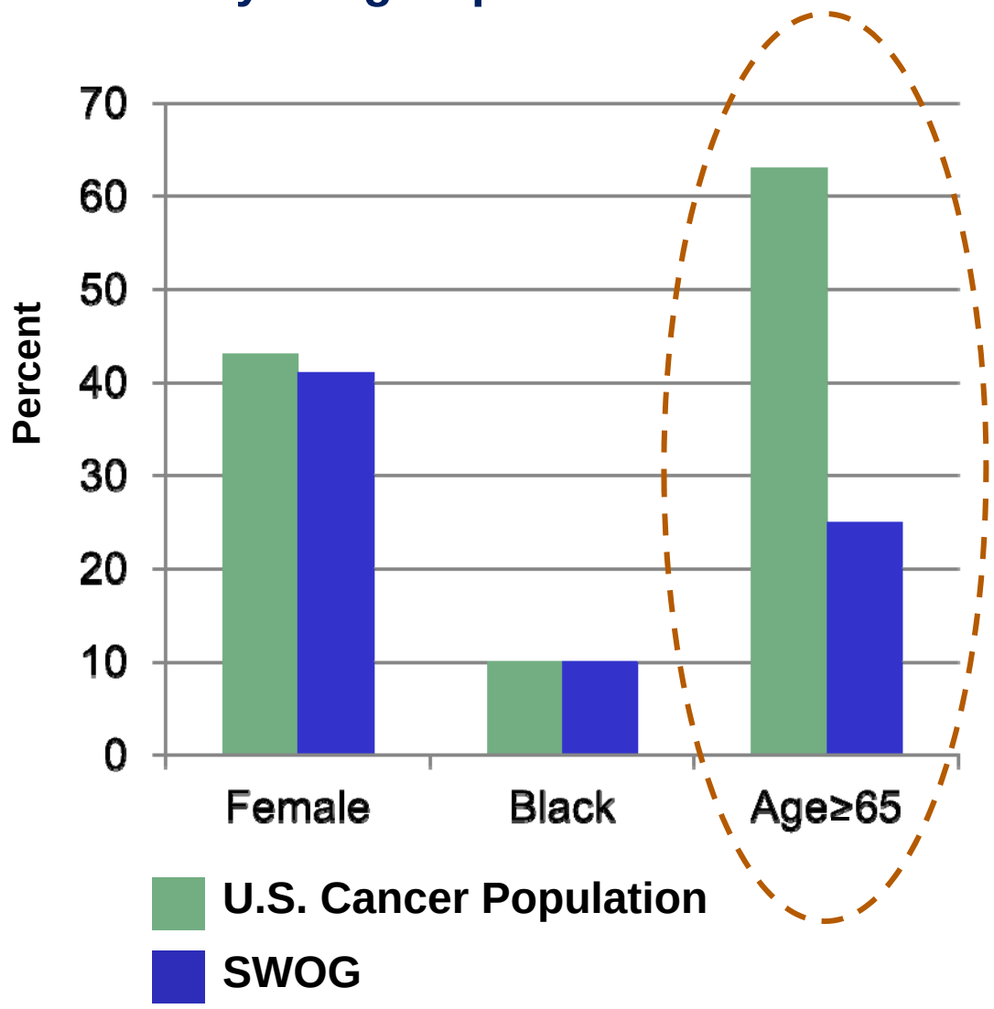


Representativeness

Percent of patients in clinical treatment trials by subgroup



"Underrepresentation of patients 65 years of age or older in cancer-treatment trials"*

- Compared enrollment patterns in SWOG to U.S. cancer population from 1993-1996
- U.S. population estimates derived from SEER and Census data
- Good representation of females and blacks, but dramatic underrepresentation of older patients
- Included in IOM report
- Subsequent policy change by Medicare (in 2000) to cover routine care costs of clinical trials

** Hutchins, Unger, …Albain, NEJM, 1999*

Question: Is the scientific impact of positive trials much greater than negative trials?

Background

Important because…

- NCI-sponsored phase III trial programs are vital national resources and represent substantial investments
- Given the size of the investment, negative trials may be incorrectly regarded as poor investments

Objective

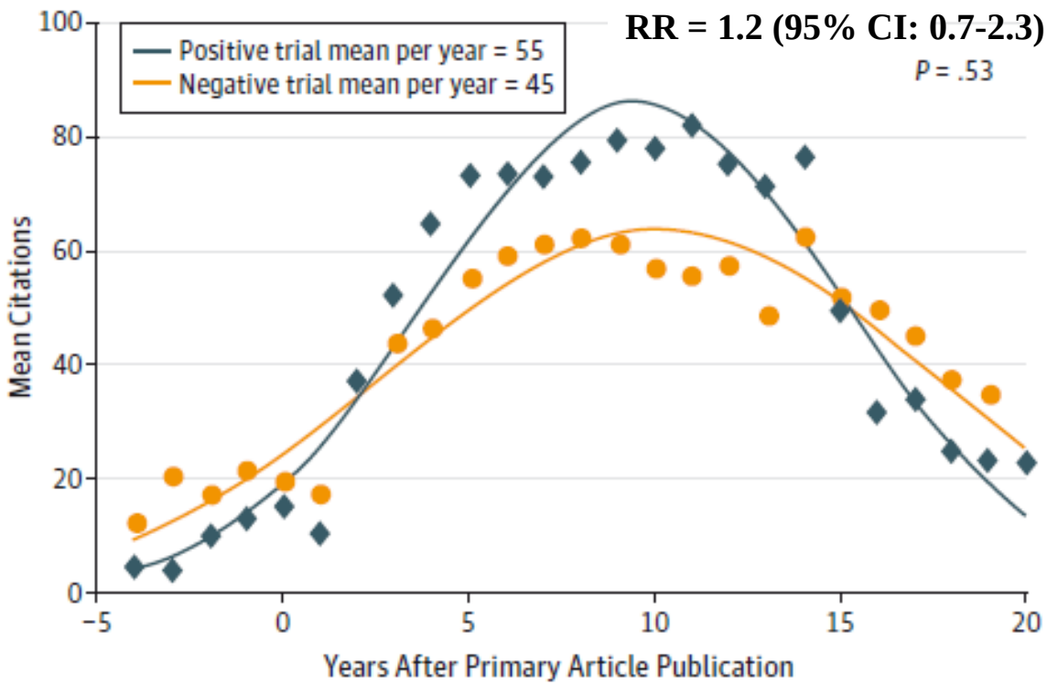
Using multiple data sources including…

- the phase III trial database of SWOG over 30 years (1985-2014), plus
- SWOG's trial publication database, plus
- citation data from Google Scholar

… examine the scientific impact of positive vs. negative phase III cancer treatment trials

Scientific Impact

Mean citations per year, both primary and secondary articles



*"The Scientific Impact of Positive and Negative Phase III Cancer Clinical Trials"**

- Examined 94 trials enrolling 46,424 patients
- 28% of trials were positive
- 42,725 total citations
- For primary articles, positive trials cited twice as often
- When all articles are included (primary and secondary), no differences between positive and negative trials

** Unger et al, JAMA Oncology, 2016*

Implications

Positive trials indicate clinical advances…

But negative trials also have a sizeable scientific impact by:

- Generating important scientific observations
- Generating new hypotheses
- Showing what new treatments should not be used

EDITORIAL

Negative Studies in Cancer Research
Why the Negativity?

Scott F. Huntington, MD, MPH, MSHP; Cary P. Gross, MD

I have not failed 10 000 times. I have successfully found 10 000 ways that will not work.
Thomas Edison describing his efforts to invent the light bulb

Shortly after the US Congress appropriated $5 million to establish the National Cancer Institute (NCI) in 1955, cooperative groups were organized to accelerate the fight against cancer. Their coordinated efforts have been very successful, generating evidence that has influenced the entire spectrum of cancer care. Yet NCI cooperative groups face significant challenges in the current austere research funding

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study accrual but also to ensure that all completed studies are used to their maximal benefit. Knowing that a majority of trials are likely to be negative, it is essential that the data derived from these trials be shared with the scientific community to accelerate learning. That each SWOG data set was used for an average of 4 publications per study suggests that the data are being used by the scientific community, but given the time and expense invested in generating these data, there may be room for improvement. For example, the NCI could consider a platform similar to National Heart, Lung, and Blood Institute's BioLINCC (Biologic Specimen and Data Repository Information Coordinating Center), ensuring patient level trial data are discoverable, accessible, usable, and widely shared.[4]

This work… "supports the notion that cooperative group trials are a sound public investment, and a new wave of publicly funded clinical trials are needed to help define the next phase of high value cancer care."

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

AUGUST 4, 2016

Strengthening Research through Data Sharing

Elizabeth Warren, J.D.

Data sharing has incredible potential to strengthen academic research, the practice of medicine, and the integrity of the clinical trial system. Some benefits are obvious: when researchers have access to complete data, they can answer new questions, explore different lines of analysis, and more efficiently conduct large-scale analyses across trials. Other advantages, such as providing a guardrail against conflicts of interest in a clinical trial system in which external sponsorship of research is common and necessary, are less visible yet just as critical.

I appreciate that there are many policy, privacy, and practical issues that need to be addressed in order to make data sharing practical and useful for the research community, but the stakes are too high to step back in the face of that challenge.

One policy proposal that I am particularly enthusiastic about is making data sharing a condition of publication in major medical journals. In a recent letter to the International Committee of Medical Journal Editors (ICMJE), I applauded the committee's work in developing a framework for data sharing.[1] The ICMJE's proposal would require that, as a condition of having their research manuscripts considered for publication, authors share the deidentified patient data on which their results are based. This requirement would be a significant step forward in improving the transparency of clinical trials for consumers and the academic medical community. Although the privacy of participants must be protected, access to the data underlying trial results can provide an avenue for independent confirmation of results and further analyses of the data set, raising the bar for academic rigor and integrity and speeding the progress of medical research.

As I told the members of the ICMJE, I believe that linking data sharing with publication can also help address the patchwork landscape of current regulations related to the sharing of clinical trial data. Because regulatory agencies have different protocols and requirements for sharing data related to the drugs and devices they approve, access to data about a clinical trial often hinges on which agency handles a regulatory submission rather than on the value of these data to consumers and researchers. By requiring data sharing as a condition of publication, journals can help synchronize and expand existing data-sharing practices.

Senator Elizabeth Warren on:

- Value of data sharing
- Knowledge gained from secondary data analyses

STRENGTHENING RESEARCH THROUGH DATA SHARING

…s J, Baethge C, et al. …data — a proposal …Committee of Medi… …ngl J Med 2016;374:

…vell K, Peterson ED, …Califf RM. Compli… …ing at ClinicalTrials …;372:1031-9.

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4. Miller JE, Korn D, Ross JS. Clinical trial registration, reporting, publication and FDAAA compliance: a cross-sectional analysis and ranking of new drugs approved by the FDA in 2012. BMJ Open 2015;5(11): e009758.

5. Unger JM, Barlow WE, Ramsey SD, LeBlanc M, Blanke CD, Hershman DL. The scientific impact of positive and negative phase 3 cancer clinical trials. JAMA Oncol 2016 March 10 (Epub ahead of print).

DOI: 10.1056/NEJMp1607282

BACKGROUND

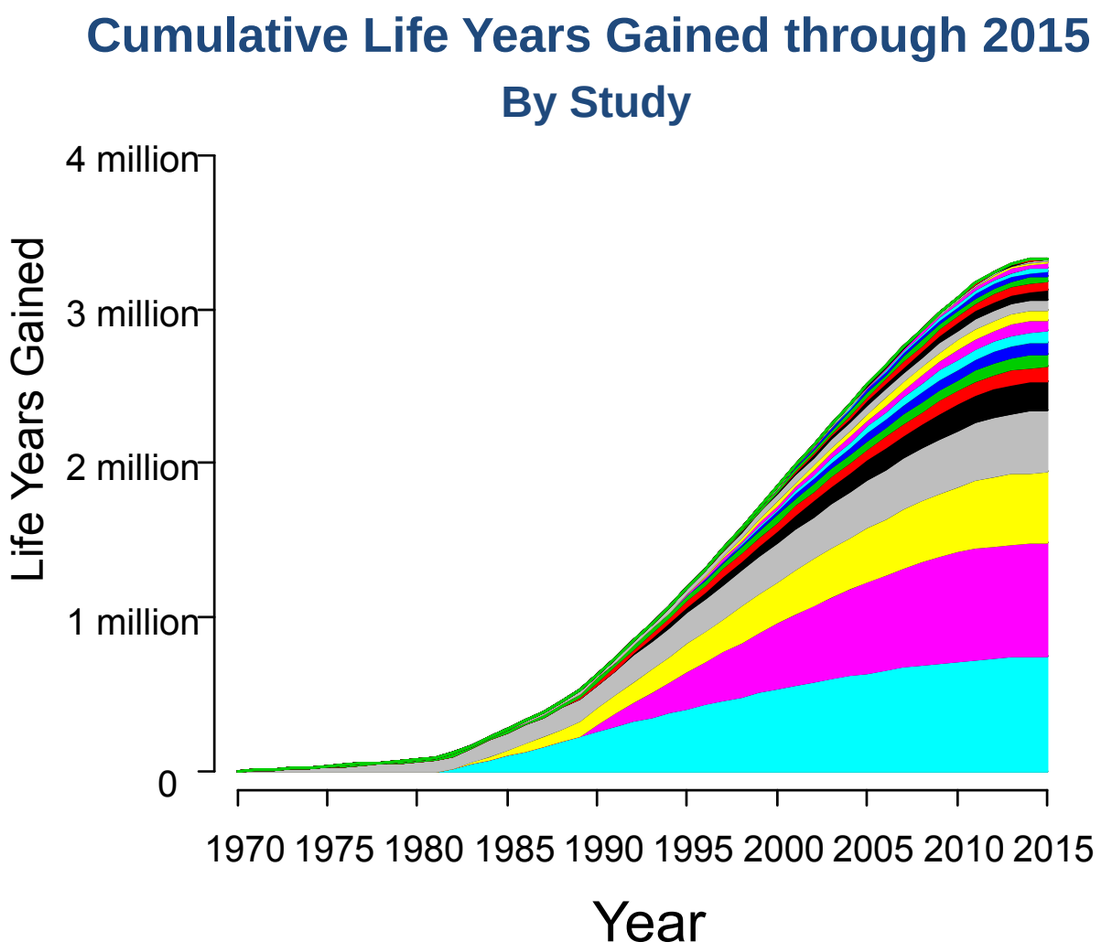
- Recently, tremendous prominence has been given to the investigation of the impact of different research processes as part of the Cancer Moonshot

- ***Aim:*** To examine the extent to which positive NCI-sponsored cancer treatment trials from a large cancer cooperative group have benefited cancer patients in the U.S.

METHODS

- Identified all positive treatment trials for overall survival over SWOG's 60-year history (1956-2016)
- Assumed the new, proven treatments from these trials established new standards for cancer care in the treatment community
- Mapped the impact of the new treatments onto the U.S. cancer population using SEER registry data
- Estimated dollar return on investment:
  - Total investment by the NCI in the SWOG treatment trial program over 60 years divided by the estimate of life-years gained

Population Impact



"The Effect of Positive SWOG Treatment Trials on Survival of Patients with Cancer in the U.S."*

Results:

- Examined 23 positive trials enrolling 12,361 pts
- **3.34** million years of life were gained by 2015
- The dollar return on investment was about **$125** per life year gained.

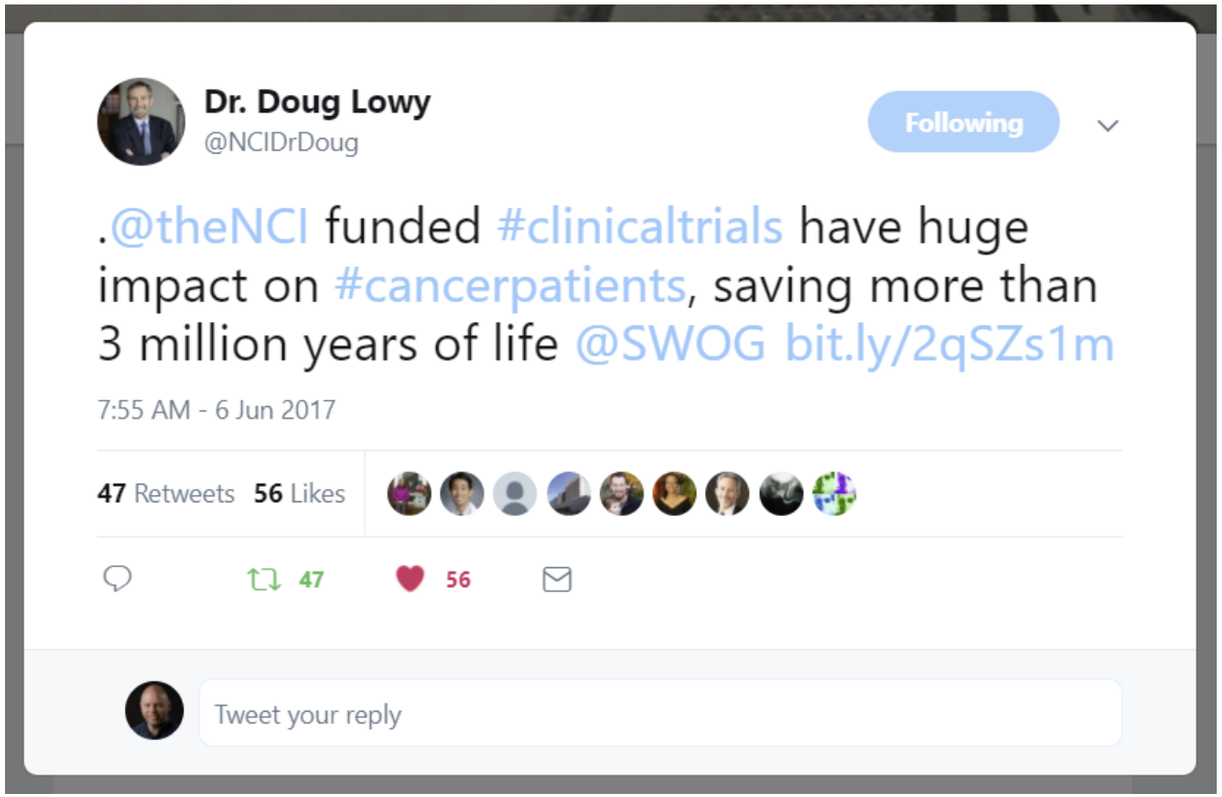
** Unger, LeBlanc, Blanke, JAMA Oncology, 2017*

DISCUSSION

- 3.34 million life years would be sufficient to provide each of the approximately 600,000 individuals expected to die of cancer in 2017 in the U.S. with 5.6 more years of life
- Represents about 1% of the estimated 360 million years of life lost due to cancer since 1969

Implications: The NCI's investment in the network groups has provided exceptional value and benefit to the American public through its cancer research programs

Tweet storm



Covered by Reuters, U.S. News & World Report, Cancer Today, Medscape, UPI, etc.

Limitations of Using Clinical Trial Data for CCDR Analyses

- No adverse events after treatment stops
- Limited long term follow-up
- Limited utilization data (beyond protocol specified therapy)
- No cost data

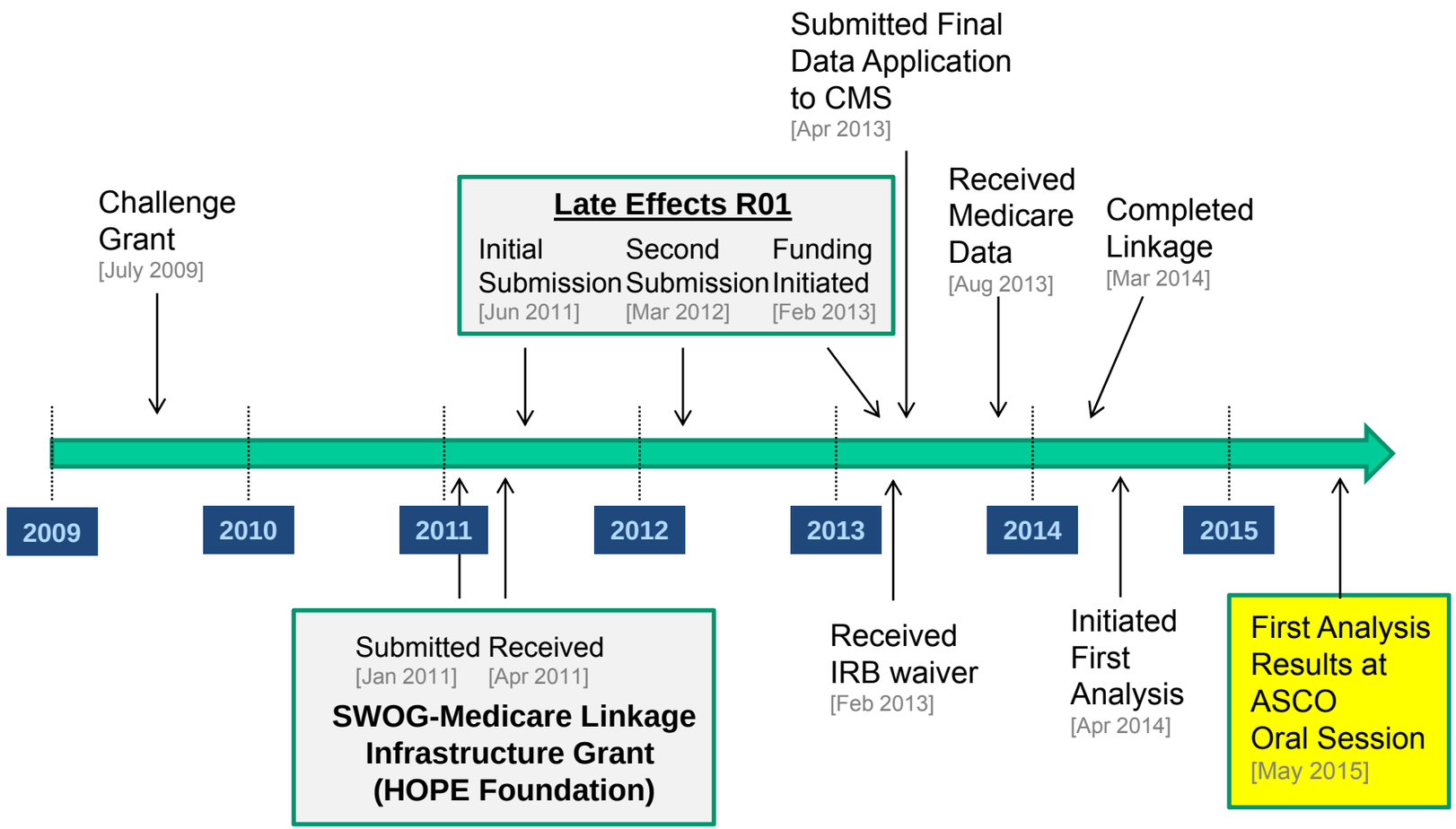
Program Objectives

- To link the SWOG clinical trial records to Medicare claims to leverage the advantages of both databases
- To conduct late effects, treatment utilization, and cost studies in timely fashion at low cost

The Linked SWOG-Medicare Database

- Clinical trials capture demographics; tumor and clinical prognostic factors; treatment and dose; short term toxicities; and recurrence and survival
- Medicare claims data (based on ICD-9, HCPCS, and CPT codes) provides long-term follow-up with underlying illnesses, comorbid conditions, new diagnoses; treatment utilization data; and cost data
- Advantage of random assignment for treatment comparisons from a specific study; limits confounding

Project Timeline

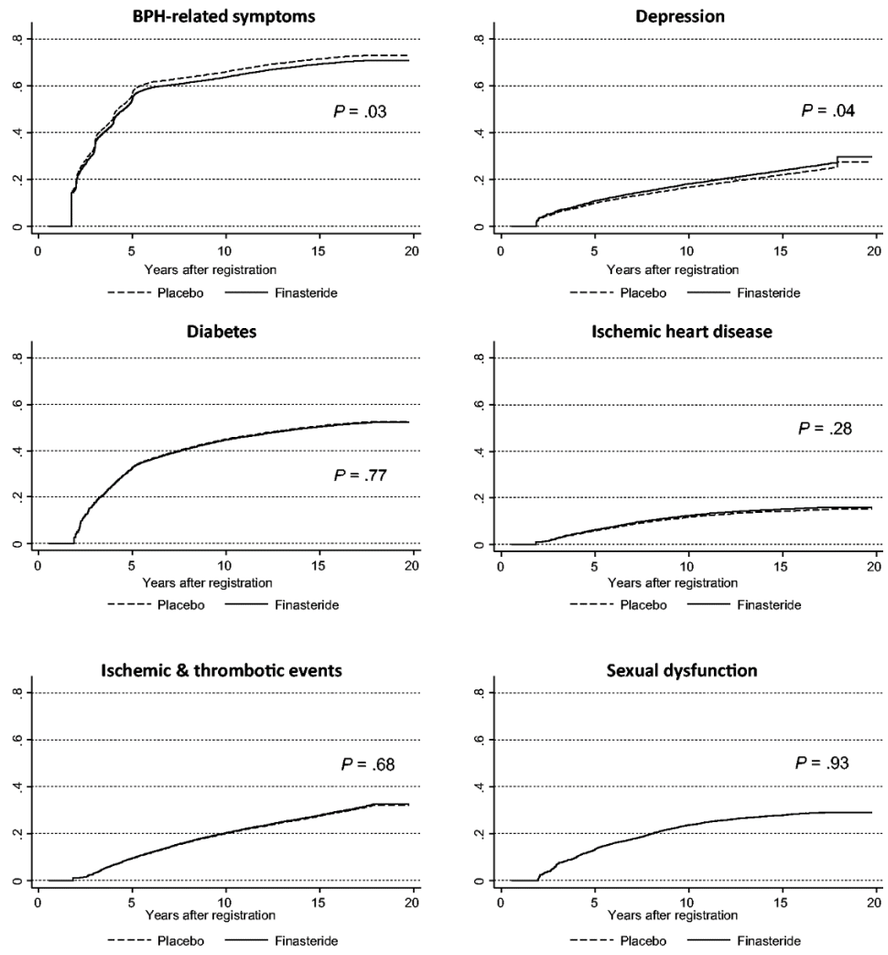


Linkage Statistics

- Submitted 115,623 records for linkage for 13 year period 1999-2011
- Linkage rate among all SWOG patients included in specified hypotheses: **64%**
  - Compared to **16%** from prior prospective study (S9342)

SWOG-Medicare Linkage

Cumulative incidence of selected events by random assignment to finasteride v placebo



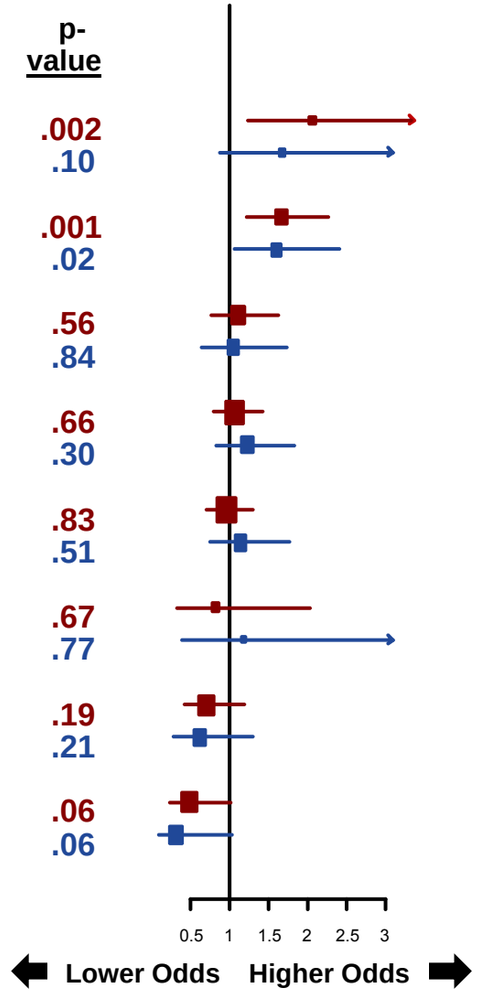
*"Long-term Consequences of Finasteride vs Placebo in the Prostate Cancer Prevention Trial"**

- Median SWOG-Medicare linkage follow-up time of 16 years
- Finasteride participants had 10% higher risk for depression (p=.04) and 6% lower risk for BPH-related events
- No other differences were found
- **Implications:** Overall, there is little need to worry about long-term non-cancer consequences of finasteride use

** Unger et al, JNCI, 2016*

Forest plot of the association of neuropathy grade with each comorbid condition

Disease Predictor	Neuropathy Grade	Odds Ratio	p-value
Diabetes with Chronic Complications	2-4	2.13	.002
	3-4	1.73	.10
Diabetes with or without Chronic Complications	2-4	1.67	.001
	3-4	1.61	.02
Hypothyroid	2-4	1.12	.56
	3-4	1.05	.84
Hypercholesterolemia	2-4	1.07	.66
	3-4	1.23	.30
Hypertension	2-4	0.97	.83
	3-4	1.15	.51
Varicellazoster	2-4	0.82	.67
	3-4	1.18	.77
Peripheral Vascular Disease	2-4	0.71	.19
	3-4	0.62	.21
Autoimmune Disease	2-4	0.49	.06
	3-4	0.32	.06



*"Comorbidities and Risk of CIPN Among Patients ≥65 Years in SWOG Clinical Trials"**

- Neuropathy is a debilitating toxicity associated with various chemotherapy agents
- Examined 1401 patients from 23 studies
- Patients with diabetes complications had >2x the odds of CIPN; patients with autoimmune disease had <0.5x the odds

** Hershman et al, JNCI, 2016*

SWOG-Medicare Studies

Other ongoing studies:

- “Adverse Health Events Following Intermittent and Continuous Androgen Deprivation in Patients With Metastatic Prostate Cancer” – **JAMA Oncology, 2016**
- “History of Diabetes and Survival Outcome Among Participants 65 or Older in SWOG Clinical Trials” – **In press at JCO CCI**
- “Using Medicare Claims to Examine Long Term Prostate Cancer Risk of Finasteride on the Prostate Cancer Prevention Trial” – **Submitted to JNCI**
- “Osteoporosis in Colorectal Cancer Survivors on SWOG Trials” – **Manuscript in preparation**
- “Association Between Cardiovascular Risk Factors and Survival Outcomes Among Breast Cancer Patients Enrolled in SWOG Clinical Trials” – **Manuscript in preparation**

Conclusions

- Many important questions about the role of cancer clinical trials in the pathway from drug development to diffusion of new treatments into the community
- Better understanding these issues is vital for increasing access to trials, interpreting trial results, and understanding their value and impact
- These investigations can influence policy
- Innovative big data type approaches are necessary to address many of these questions
- SWOG has been very productive in this area

Acknowledgements

Collaborators

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- NIH (1R01CA166084-01A1): Using SWOG-Medicare Database To Evaluate Long-Term Toxicities Of Cancer Survivors, 2013-2017 [Hershman; Unger (Co-I)]