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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Conceptual Model: Study to Diffusion of New Cancer Therapy

Drug Development
Laboratory discovery of anti-cancer agent
Animal testing
Pre-clinical testing

Comparative Testing (Phase I&II)
Drug Development

Design Monitoring Analysis
Impact & Diffusion

Treatment Decisions
Public (CMS) or Private (Health Insurance Co.)
Coverage Decisions

Barriers
Enrollment Patterns
Toxicity Patterns QOL

Scientific Impact
Late Effects
Generalizability
Disparities
Impact & Diffusion

Cost Effectiveness
Cancer Costs Risk
Comparative Effectiveness Treatment Value

Population Impact Diffusion Patterns & Barriers

QOL

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
- Study A
- Study B
- Study C
- Study D
- Study E
- Study F
- Study G
- Study H

Level II
- Life table data
- Census data

Level III
- Multiple study database
- External data source

Level IV
- Linked database

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

Scientific Impact

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

**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 48,424 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
Generating important scientific observations
Generating new hypotheses
Showing what new treatments should not be used

Scientific Impact

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

Senator Elizabeth Warren on:

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

**BACKGROUND**

- 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

**METHODS**

- 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*
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

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## DISCUSSION

- 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

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>2009</td>
<td>Received Challenge Grant</td>
</tr>
<tr>
<td>2011</td>
<td>Submitted Final Data Application to CMS</td>
</tr>
<tr>
<td>2012</td>
<td>Submitted Challenge Grant</td>
</tr>
<tr>
<td>2013</td>
<td>Received Medicare Data</td>
</tr>
<tr>
<td>2014</td>
<td>Completed Linkage</td>
</tr>
<tr>
<td>2015</td>
<td>First Analysis Results at ASCO Oral Session</td>
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</tbody>
</table>
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)
**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=0.04) 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

**Cumulative incidence of selected events by random assignment to finasteride vs placebo**

**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

<table>
<thead>
<tr>
<th>Disease Predictor</th>
<th>Odds Ratio</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Diabetes with Chronic Complications</td>
<td>2.13</td>
<td>.002</td>
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<tr>
<td>Diabetes with or without Chronic Complications</td>
<td>1.67</td>
<td>.001</td>
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<tr>
<td>Hypothyroid</td>
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<td>.56</td>
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<tr>
<td>Hypercholesterolemia</td>
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<td>Hypertension</td>
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<td>Varicellazoster Disease</td>
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<td>.77</td>
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<tr>
<td>Peripheral Vascular Disease</td>
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<td>.99</td>
</tr>
<tr>
<td>Autoimmune Disease</td>
<td>0.49</td>
<td>.96</td>
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</tbody>
</table>

* Hershman et al, JNCI, 2016

**Odds of Neuropathy for Patients with Specified Condition**

<table>
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<th>Grade</th>
<th>Odds Ratio</th>
<th>p-value</th>
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<tbody>
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<tr>
<td>5-6</td>
<td>1.07</td>
<td>.66</td>
</tr>
</tbody>
</table>

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

**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

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- NIH (1R01CA168084-01A1): Using SWOG-Medicare Database To Evaluate Long-Term Toxicities Of Cancer Survivors, 2013-2017 [Hershman; Unger (Co-I)]