COMPARATIVE EFFECTIVENESS RESEARCH IN GYNECOLOGY: OPPORTUNITIES AND CHALLENGES IN USING BIG DATA

Jason D. Wright, M.D.
Columbia University College of Physicians and Surgeons
Disclosures

• I have no relevant financial disclosures
Overview

• Overview of health services research and use of "big data"
• Tips for using big data and career development
The Practice of Medicine

- 1990's
- 2000's
- 2010's
- 2020's+

- Personalized Medicine
- Patient Centered Outcomes Research
- Comparative Effectiveness Research
- Evidence-Based Medicine
- Eminence Based Medicine

Evidence-Based Medicine

Comparative Effectiveness Research

Patient Centered Outcomes Research

Personalized Medicine

The Practice of Medicine
Comparative Effectiveness Research

• What works when?
• For whom?
• Under what circumstances?

• Delivery of the right care
• To the right patient
• At the right time
• By the right provider
• In the most appropriate setting
Principles of CER

- Re-examination of methodology
  - Recognition that RCTs are increasingly impractical for questions facing clinicians and policy makers
  - Focus on alternate ways to gather evidence
- Emphasis on “real world” populations and the knowledge that “best” treatment varies among populations
- Incorporation of cost, quality of life, and value in medicine
Can Big Data Tell Us What Clinical Trials Don’t?

OCT. 3, 2014
Observational Data

Limitations:
- Selection bias
- Confounding

Developing a Career in Health Services and Outcomes Research
1. Determine What You Want to Do and How You Will Get There.
What Are Your Interests?

- Be honest with yourself
- Do what you enjoy
- Its hard to do everything well
What is Your Career Path?

- Research tracks:
  - Collaborate with others
  - Hybrid clinician-scientist
  - Primary researcher

- Make a plan to move forward
  - Different pathways for each track
2. Find a Mentor/Mentorship Team.
The Value of Mentors

• Guidance on practical aspects of HSR is invaluable
  • Data is complex
  • Infrastructure is difficult to build from scratch

• Roles
  • Project development and conduct
  • Manuscripts and presentations
  • Networking
  • Career development

• May be inside or outside of your department
The Value of a Team

• Joining or building a team is of great value
• Multidisciplinary
  • Clinicians
  • Statisticians
  • Economists
  • Epidemiologists
• Share resources
3. Learn the Tools of Trade.
## Tools of the Trade: Data

<table>
<thead>
<tr>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical data-needed primarily for providing clinical care</strong></td>
<td></td>
</tr>
<tr>
<td>Medical record</td>
<td>Collected by providers</td>
</tr>
<tr>
<td>Patient</td>
<td>Provided by patients</td>
</tr>
<tr>
<td>Administrative</td>
<td>Required to provide care, but not part of the record</td>
</tr>
<tr>
<td><strong>Ancillary data-needed primarily for non-clinical purposes</strong></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>Collected directly from a provider, patient or administrator</td>
</tr>
<tr>
<td>Secondary</td>
<td>Extracted or abstracted for contractual, legal or regulatory need</td>
</tr>
</tbody>
</table>
Robotic-Assisted Hysterectomy for Benign Gynecologic Disease (circa 2012)

- Cochrane review
  - 2 prospective trials, 158 patients
  - Robotic surgery not associated with improved effectiveness or safety

- Meta-analysis of observational data
  - 6 studies
  - Outcomes equivalent to laparoscopy
  - Operative times and cost higher for robotic

Robotic-Assisted Hysterectomy

- Robotic-assisted surgery use increasing rapidly
- No billing codes available to capture robotic-assisted surgery
Robotic-Assisted Hysterectomy

- **Datasource:** Premier (Perspective, Inc)
  - Proprietary database to measure quality
  - Captures 100% of patients at participating hospitals
  - Captures all testing, drugs, and devices utilized during a patient’s hospitalization
    - Uniquely capture use of any robotic equipment
  - **2007-2010**
  - **264,758 patients**
  - **Stratified by type of hysterectomy:**
    - Abdominal
    - Vaginal
    - Laparoscopic
    - Robotic

Robotic-Assisted Hysterectomy

[Line graph showing procedure rates for abdominal, vaginal, laparoscopic, and robotic hysterectomies from Q1 2007 to Q1 2009.]

Robotic-Assisted Hysterectomy

Robotic-Assisted Hysterectomy

<table>
<thead>
<tr>
<th></th>
<th>Laparoscopic</th>
<th>Robotic</th>
<th>( P)-value</th>
<th>Multivariate RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any complication</td>
<td>5.3%</td>
<td>5.5%</td>
<td>NS</td>
<td>1.03 (0.86-1.24)</td>
</tr>
<tr>
<td>Intraoperative complication</td>
<td>2.4%</td>
<td>2.5%</td>
<td>NS</td>
<td>1.05 (0.75-1.47)</td>
</tr>
<tr>
<td>Surgical site complication</td>
<td>2.0%</td>
<td>1.7%</td>
<td>NS</td>
<td>0.85 (0.64-1.13)</td>
</tr>
<tr>
<td>Medical complication</td>
<td>1.2%</td>
<td>1.6%</td>
<td>NS</td>
<td>1.35 (0.97-1.88)</td>
</tr>
<tr>
<td>Transfusion</td>
<td>1.8%</td>
<td>1.4%</td>
<td>NS</td>
<td>0.80 (0.55-1.16)</td>
</tr>
<tr>
<td>LOS &gt;2 days</td>
<td>24.9%</td>
<td>19.6%</td>
<td>&lt;0.001</td>
<td>0.78 (0.67-0.92)</td>
</tr>
<tr>
<td>Non-routine discharge</td>
<td>0.3%</td>
<td>0.2%</td>
<td>NS</td>
<td>0.79 (0.35-1.76)</td>
</tr>
</tbody>
</table>

Robotic-Assisted Hysterectomy

- Median cost
  - Abdominal: $6651
  - Laparoscopic: $6679
  - Robotic: $8868

- Adjusted cost
  - Robotic vs. abdominal +$2317 (95% CI, $2168-2465)
  - Robotic vs. laparoscopic +$2189 (95% CI, $2073-2377)

4. Choose a Question That Matters and That You Care About.
Components of Health Services Research

- Data Source
- Analytic Methodology
- Clinically Meaningful Question
Electric Power Morcellation

- October, 2013 morcellation of leiomyosarcoma at time of hysterectomy for presumed fibroids
- Public awareness campaign began in December, 2013 with publication in WSJ
- Review of available literature suggested scant data evaluating safety of power morcellation or risk of occult cancer in women who underwent the procedure
Electric Power Morcellation

- Datasource: Premier (Perspective, Inc)
  - Capture device codes for commercially available morcellators
- Selected women who underwent MIS hysterectomy
  - 232,882 women
  - 498 hospitals
- Stratified by use of power morcellation

Wright JD, Tergas AI, Burke WM, Cui RR, Ananth CV, Chen L, Hershman DL. JAMA 2014;312(12):1253-5.
Electric Power Morcellation

Utilization of electric power morcellation

Year of diagnosis

Percentage

0 5 10 15 20 25

2006 2007 2008 2009 2010 2011 2012

13.7 16.8 19.6 16 14.9 15.2 14.7

Wright JD, Tergas AI, Burke WM, Cui RR, Ananth CV, Chen L, Hershman DL. JAMA 2014;312(12):1253-5.
Electric Power Morcellation

Wright JD, Tergas AI, Burke WM, Cui RR, Ananth CV, Chen L, Hershman DL. JAMA 2014;312(12):1253-5.
### Electric Power Morcellation

#### Predictors of abnormal pathology.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cancer</th>
<th>Indeterminate smooth muscle neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>0.06%</td>
<td>0.02%</td>
</tr>
<tr>
<td>40-49 years</td>
<td>0.13%</td>
<td>0.12%</td>
</tr>
<tr>
<td>50-59 years</td>
<td>0.60%</td>
<td>0.20%</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>2.45%</td>
<td>0.08%</td>
</tr>
</tbody>
</table>

Wright JD, Tergas AI, Burke WM, Cui RR, Ananth CV, Chen L, Hershman DL. *JAMA* 2014;312(12):1253-5.
5. Address Some “Big” and Some “Small” Questions.
Common Research Themes in HSR

- Efficacy of treatments
- Quality of treatment
- Rare conditions
- Understudied populations

- Uptake of new technologies and treatments
- Long-term complications
- Cost and resource utilization
Outcomes of Uterine Adenosarcoma

- SEER database
- 544 women with adenosarcoma vs. 4952 with carcinosarcoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Adenosarcoma</th>
<th>Carcinosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>84% (n=192)</td>
<td>62% (n=372)</td>
</tr>
<tr>
<td></td>
<td>(77-89%)</td>
<td>(57-68%)</td>
</tr>
<tr>
<td>IB</td>
<td>69% (n=114)</td>
<td>55% (n=934)</td>
</tr>
<tr>
<td></td>
<td>(57-77%)</td>
<td>(52-59%)</td>
</tr>
<tr>
<td>IC</td>
<td>63% (n=21)</td>
<td>39% (n=431)</td>
</tr>
<tr>
<td></td>
<td>(36-80%)</td>
<td>(33-44%)</td>
</tr>
<tr>
<td>II</td>
<td>69% (n=42)</td>
<td>33% (n=480)</td>
</tr>
<tr>
<td></td>
<td>(49-83%)</td>
<td>(29-38%)</td>
</tr>
<tr>
<td>III</td>
<td>48% (n=32)</td>
<td>24% (n=1041)</td>
</tr>
<tr>
<td></td>
<td>(29-65%)</td>
<td>(21-27%)</td>
</tr>
<tr>
<td>IV</td>
<td>15% (n=25)</td>
<td>9% (n=1218)</td>
</tr>
<tr>
<td></td>
<td>(4-33%)</td>
<td>(7-11%)</td>
</tr>
</tbody>
</table>
6. Learn the Tricks of The Trade.
“There are lies, damn lies, and statistics”
Statistics

• Basic understanding of statistics and methodology is essential

• Statistics courses
  • Degree programs (MPH, MS)
  • Take classes of interest (regression, categorical data analysis, decision analysis, etc)

• Read the literature
Statistical Methodology

• How do you overcome confounding and selection bias?
• Natural experimentation
  • Difference-in-differences
  • Regression discontinuity
• Analytic methodology
  • Propensity score
  • Instrumental variable analysis
Effectiveness of Upfront Treatment Strategies for Ovarian Cancer

• Neoadjuvant chemotherapy vs. primary surgery for ovarian cancer
  • EORTC RCT
  • 29 months OS for primary surgery
  • 30 months OS for neoadjuvant chemotherapy

• Comparison of outcomes between primary debulking surgery and neoadjuvant chemotherapy

• SEER-Medicare
  • 1991-2007
  • Stage II-IV epithelial ovarian cancer
  • N=9587

Predictors of primary chemotherapy: older age, more recent year of diagnosis, serous histology, urban residence, increased comorbidity and advanced stage

<table>
<thead>
<tr>
<th></th>
<th>Death from ovarian cancer</th>
<th>All cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Observational</td>
<td>1.26 (1.17-1.35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>1.27 (1.19-1.35)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Two-year survival (95% CI)</th>
<th>Median survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary surgery</td>
<td>Primary chemotherapy</td>
</tr>
<tr>
<td>Observational</td>
<td>0.56 (0.55-0.75)</td>
<td>0.36 (0.34-0.38)</td>
</tr>
</tbody>
</table>

Methodology to Limit Confounding

Regression Analysis

Control Group → Intervention Group → Measured Confounders → Outcome

Propensity Score Analysis

Cohort → Intervention → Propensity Score → Control Group → Intervention Group → Measured Confounders → Outcome
### Death from ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Death from ovarian cancer</th>
<th>All cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observational</td>
<td>1.26 (1.17-1.35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PS reweighted (matched)</td>
<td>1.25 (1.15-1.36)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PS reweighted (IPTW)</td>
<td>1.31 (1.26-1.37)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Two-year survival (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Two-year survival (95% CI)</th>
<th>Median survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary surgery</td>
<td>Primary chemotherapy</td>
</tr>
<tr>
<td><strong>All Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observational</td>
<td>0.56 (0.55-0.75)</td>
<td>0.36 (0.34-0.38)</td>
</tr>
<tr>
<td>PS reweighted (matched)</td>
<td>0.49 (0.46-0.51)</td>
<td>0.40 (0.38-0.43)</td>
</tr>
<tr>
<td>PS reweighted (IPTW)</td>
<td>0.54 (0.53-0.55)</td>
<td>0.45 (0.44-0.47)</td>
</tr>
</tbody>
</table>

### Residual imbalance in covariates

- **Matching**: year of diagnosis
- **IPTW**: year of diagnosis, area of residence, registry, grade, stage

Instrumental Variable (IVA)

- Adjusts for measured and *unmeasured* confounders
- **Instrument**: characteristic associated with treatment but not outcome
  - Geographic variation is most commonly used instrument
- Functions as a quasi randomization
<table>
<thead>
<tr>
<th>All patients</th>
<th>Death from ovarian cancer</th>
<th>All cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Observational</td>
<td>1.26 (1.17-1.35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PS reweighted (matched)</td>
<td>1.25 (1.15-1.36)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PS reweighted (IPTW)</td>
<td>1.31 (1.26-1.37)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Instrumental variable</td>
<td>0.94 (0.58-1.52)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>All Patients</th>
<th>Two-year survival (95% CI)</th>
<th>Median survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary surgery</td>
<td>Primary chemotherapy</td>
</tr>
<tr>
<td>Observational</td>
<td>0.56 (0.55-0.75)</td>
<td>0.36 (0.34-0.38)</td>
</tr>
<tr>
<td>PS reweighted (matched)</td>
<td>0.49 (0.46-0.51)</td>
<td>0.40 (0.38-0.43)</td>
</tr>
<tr>
<td>PS reweighted (IPTW)</td>
<td>0.54 (0.53-0.55)</td>
<td>0.45 (0.44-0.47)</td>
</tr>
<tr>
<td>Instrumental variable</td>
<td>0.49 (0.48-0.51)</td>
<td>23.8 (22.8-24.8)</td>
</tr>
<tr>
<td>&lt;Median value of IV</td>
<td>0.49 (0.48-0.51)</td>
<td></td>
</tr>
<tr>
<td>&gt;Median value of IV</td>
<td>0.50 (0.48-0.52)</td>
<td></td>
</tr>
</tbody>
</table>

Effectiveness of Upfront Treatments for Ovarian Cancer

• A large number of patients did not complete the entire sequence of treatment regardless of initial therapy

• Population-based estimates of survival are dismal compared to clinical trials
  • GOG 172: 50 months IV, 66 months IP chemo
  • EORTC: 30 months chemo, 29 months surgery
  • Current data: 24 months chemo, 24 months surgery

7. Recognize When the “Tools” and “Tricks” Just Don’t Work.
NO, REALLY.
You can stop now.
Intermediate Risk Early Stage: Adjuvant Therapy

**GOG 92**

<table>
<thead>
<tr>
<th>LVI</th>
<th>Stromal invasion</th>
<th>Tumor size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Deep 1/3</td>
<td>Any</td>
</tr>
<tr>
<td>Positive</td>
<td>Middle 1/3</td>
<td>≥ 2 cm</td>
</tr>
<tr>
<td>Positive</td>
<td>Superficial 1/3</td>
<td>≥ 5 cm</td>
</tr>
<tr>
<td>Negative</td>
<td>Deep or middle 1/3</td>
<td>≥ 4 cm</td>
</tr>
</tbody>
</table>

- Recurrence HR 0.54 (0.35-0.81)
- PFS HR 0.58 (0.4-0.85)
- OS HR 0.74 (0.49-1.12)

Intermediate Risk Early Stage: Adjuvant Therapy

- Challenges
  - Inability to capture complete pathologic data
  - Significant confounding (measured and unmeasured)
  - Difficulty measuring outcomes and interventions

- Approaches
  - Multiple datasets (NCDB, SEER)
  - Addressing missing data (imputation)
  - In depth statistical analysis (PS, attempted IVA)

- Conclusion
  - Unable to overcome limitations of the available data
8. Take a 360 Degree Approach to The Problem.
Traditional Health Services Research

- Examines short term outcomes
  - Other outcomes (cost, patient reported outcomes, long term outcomes)
  - Individualized care (decision analysis)
  - Utilization of data (interventional studies)
Readmissions and Length of Stay After Hysterectomy

- Readmissions common after hysterectomy (3.4-6.1%)
  - NSQIP data
  - Associated with complications
- Length of stay highly variable
  - NSQIP
  - Strongly associated with non-modifiable patient factors
- Institutional data
  - Social factors highly associated with prolonged LOS
- Interventional studies
  - Preoperative counseling
  - Novel interventions
In Cancer: Cancer Care Delivery Research (CCDR)

• “Cancer Care Delivery Research (CCDR) is a multidisciplinary science that examines how patient and clinician behavior, organizational structures, health technologies, and financing approaches influence the availability, quality, cost, and outcomes of cancer care. CCDR generates evidence that can be used to improve clinical practice patterns as well as develop and test promising interventions within the health care delivery system”
Inspiration

• Take time to strategize and develop ideas
• Read the literature from other fields
  • Clinical questions
  • New datasources or linkages
  • Methodology
10. Map Your Path Forward.
How Do You Move Your Research Forward

• Traditional pathway
  • Resources from mentor
  • Departmental/institutional resources
  • Career development award (K)
  • Independent funding

• Additional considerations
  • Foundation grants
  • Industry
  • Philanthropy
Where Do You Want to Be in 5 or 10 Years?

• Balancing clinical work and research
  • Do you also want to be “the expert clinician”?

• National recognition
  • If you want to be the expert in something, write about it
  • Papers, meetings, presentations

• Administrative roles
  • Fellowship director
  • Division chief

• Promotion
Pitfalls

- Work-life balance
- Learn to say “no”
- Prioritize and multi-task
- Remember rule #1:

Determine What You Want to Do and How You Will Get There
Conclusions

• There is great interest in health services research and using big data nationally
• HSR can address many questions that otherwise would be impossible to answer
• Careful planning will increase your chances of success