GENERATING EVIDENCE FOR COMPARATIVE EFFECTIVENESS RESEARCH

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OUTLINE

- **Introduction**
  - Three examples

- **Methodology**
  - Assumptions and causal parameters
  - Example

- **High-dimensional data** considerations

- **Remarks**

- **References**

*Thanks:* Lauren Kunz (NHLBI), Jacob Spertus and Sherri Rose (both from HMS Department of Health Care Policy).
Radial artery access permits easier access and easier closure.

Large number of patients undergoing both procedures.

Not particularly well studied and of growing importance in the US.

Marked heterogeneity in predisposition to bleeding.

Significant treatment selection (healthier patients undergo transradial procedures).

Does radial artery access cause fewer complications compared to femoral artery access?

MASSACHUSETTS

Does radial artery access cause fewer complications compared to femoral artery access?

40,000 PCIs in MA adults

Kunz, Rose, et al., 2017
DRUG ELUTING (DES) VERSUS BARE METAL (BMS) CORONARY STENTS

- DES (approved 2003) and BMS (approved in 1990s) frequently implanted keep treated arteries clear and supported after cleaning blocked arteries to heart
- DES improves target-vessel revascularization (TVR) more than BMS
- DES associated with late stent thrombosis (death)
- Have 9000 patients and 500 confounders

Does DES cause fewer revascularizations compared to BMS?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stent Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes, %</strong></td>
<td>BMS</td>
</tr>
<tr>
<td>1 Year Mortality</td>
<td>10.2</td>
</tr>
<tr>
<td>1 Year TVR</td>
<td>9.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Confounders</th>
<th>BMS</th>
<th>DES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>66.4</td>
<td>63.7</td>
</tr>
<tr>
<td>STEMI, %</td>
<td>35.7</td>
<td>18.2</td>
</tr>
<tr>
<td>Cardiomyopathy or LVSD, %</td>
<td>11.1</td>
<td>8.4</td>
</tr>
<tr>
<td>Emergent, %</td>
<td>38.3</td>
<td>20.3</td>
</tr>
<tr>
<td>Shock, %</td>
<td>3.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>

STEMI = ST-elevated myocardial infarction; LVSD = left ventricular systolic dysfunction

Spertus and Normand, 2017 (under review)
SPECIFIC DRUG ELUTING CORONARY STENTS

- Rapid proliferation of DES
- US has 2nd highest number of overall stent insertions per capita
- Multiple competing versions supported by a few manufacturers
- Differences include polymer coating, specific drug, platform type, and delivery system
- Study 21,000+ adults, 10 model-specific DES, 3 manufacturers

Do particular model-specific DES cause fewer MACE compared to other model-specific DES?

MASSECHUSETTS

Histogram displays percent of manufacturer DES of all DES implanted, by hospital.

MACE = Major Adverse Cardiac Events (15.8%)

Rose and Normand, 2017 (under review)
DATA, PARAMETERS, NOTATION

- $T$ denotes treatment
- $Y$ observed outcome
- $Y_t$ potential outcomes under $T = t$
- $X$ is a set of (baseline) covariates
- Data: $(T_i, Y_i, X_i), i = 1, \cdots, N$
- Mean marginal outcome under treatment $t$:
  \[ \mu_t = E_X (E(Y | T = t, X)) \]
- Interested in the marginal effect of $T$ on $Y$
  \[ \Delta = \mu_t - \mu_{t'} \text{ (Difference)} \text{ or } \Delta = \frac{\mu_t}{\mu_{t'}} \text{ (Ratio)} \]
DATA, PARAMETERS, NOTATION

- **Joint Distribution**

\[
P(Y, T, X) = P(Y \mid T, X) \times P(T \mid X) \times P(X) = Q_Y \times \Pi_T \times Q_X
\]  

(1)

- \(\Pi_T\) is the **propensity score** (nuisance)

\[
\Pi_t = P(T = t \mid X)
\]

- Average treatment effect depends **only** on \(Q_Y\) and \(Q_X\)

\[
E_X (E(Y \mid T = t, X)) - E_X (E(Y \mid T = t', X))
\]

(2)

Expected outcome change if units randomly assigned to the two treatments
CONSIDERATIONS: CAUSALITY

Potential Outcomes: assumed to exist (fundamental)

1. Stable Unit Treatment Value Assumption
2. Ignorability of Treatment Assignment
3. Positivity
4. Constant Treatment Effect

If (1) & (2) are violated, then causal parameters can be estimated statistically but cannot be interpreted causally.

X High-Dimensional: more uncertainty in treatment model, outcome model, and subpopulations experiencing heterogeneous effects; parametric assumptions vulnerable

- Need dimension reduction strategy
ASSUMPTIONS

\( (T \text{ Treatment, } Y \text{ Outcomes, } X \text{ Covariates}) \)

**Stable Unit Treatment Value Assumption** no interference and no variation in treatment.

1. Potential outcomes for a unit do not depend on the treatment assignment of other units (no spillover effects)

\[
Y_i(T_1, T_2, \cdots, T_N) = Y_i(T_i) = Y_{it}
\]  

- **Radial artery access:** violated if as physician increases skill in radial artery access, the less likely complications arise, and the more likely the physician is to use radial access on subsequent subject.

2. Treatments are well-defined and the same for all units  

- **Radial artery access:** violated if physicians accessing radial artery use different methods of applying pressure after removing catheter.
ASSUMPTIONS

\((T \text{ Treatment, } Y \text{ Outcomes, } X \text{ Covariates})\)

**Ignorability of Treatment Assignment** unconfoundedness of treatment assignment

1. Within subpopulations defined by \(X\), random treatment assignment

\[ (Y_t, Y_t') \perp T \mid X \] (4)

\[ P(T = t \mid Y_t, Y_t', X) = P(T = t \mid X) \] (5)

- Untestable assumption (sensitivity analysis, multiple comparison groups, falsification outcomes)

- **Radial artery access**: violated if a covariate associated with probability of undergoing radial artery access as well associated with a complication is omitted
ASSUMPTIONS

\((T \text{ Treatment}, Y \text{ Outcomes}, X \text{ Covariates})\)

**Positivity**

1. Requires units at every combination of observed covariates so that probability bounded away from zero

\[ 1 > P(T = 1 \mid X) > 0 \quad (6) \]

- **Structural** violations when units associated with specific covariate values cannot possibly get the treatment
- **Practical** violations due to finite sample size
- Statistically testable
- **Radial artery access:** examine covariate balance and covariate overlap
ASSUMPTIONS

\((T \text{ Treatment, } Y \text{ Outcomes, } X \text{ Covariates})\)

Constant Treatment Effect

1. Observable treatment effect for any two units having the same values of \(X\) should be similar

\[ \Delta_i \mid X = \Delta_j \mid X, \ i \neq j \quad (7) \]

- If not violated, the ATE may be interpreted both marginally and conditionally
- If violated, exploratory & confirmatory approaches to estimation of heterogeneous effects should be utilized (Varadhan et al., 2012 PCORI Report).

Radial Artery Access: women may have a bigger benefit than men

Source: American Journal of Cardiology, 2007, 99(9):1216-1221
### SUMMARY OF APPROACHES

Three approaches by modeling: (1) only the treatment assignment mechanism via regression; (2) only the outcome via regression; (3) both the treatment assignment mechanism and outcome.

<table>
<thead>
<tr>
<th>Approach</th>
<th>Strengths</th>
<th>Weaknesses</th>
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</thead>
<tbody>
<tr>
<td>IPTW</td>
<td>Simple</td>
<td>Large variance estimates</td>
</tr>
<tr>
<td></td>
<td>Non-parametric</td>
<td>Weight trimming bias</td>
</tr>
<tr>
<td>Regression</td>
<td>Parametric</td>
<td>Extrapolation</td>
</tr>
<tr>
<td></td>
<td>Simple</td>
<td>if violate positivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Functional form</td>
</tr>
<tr>
<td>G-Comp</td>
<td>Parametric</td>
<td>Extrapolation</td>
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<tr>
<td></td>
<td>Simple</td>
<td>if violate positivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Functional form</td>
</tr>
<tr>
<td>A-IPTW</td>
<td>Double robust</td>
<td>Finite sample inefficient</td>
</tr>
<tr>
<td></td>
<td>Asymptotic efficiency</td>
<td></td>
</tr>
<tr>
<td>TMLE</td>
<td>Double robust</td>
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<tr>
<td></td>
<td>Asymptotic efficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Finite sample efficiency</td>
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</tr>
</tbody>
</table>
- **Registry** with data on **40,126 patients** PCI patient, 12.9% undergo PCI via radial artery (versus femoral artery)
- **Outcome:** in-hospital bleeding or vascular complications
- **Difference** (Radial - Femoral): $-2.30 \text{ to } -2.04\%$ -- $1.80$

###Radial vs Femoral Artery Access (Kunz, Rose, et al. 2017)

<table>
<thead>
<tr>
<th>All Subjects</th>
<th>Intervention</th>
<th>Radial</th>
<th>Femoral</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Procedures</td>
<td>5192</td>
<td>35022</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>25.3</td>
<td>26.8</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>89.6</td>
<td>89.4</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>3.3</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>4.3</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1.8</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Native American</td>
<td>0.02</td>
<td>0.07</td>
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</tr>
<tr>
<td>Other</td>
<td>1.0</td>
<td>2.2</td>
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<tr>
<td>Health Insurance</td>
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<tr>
<td>Government</td>
<td>46.0</td>
<td>56.3</td>
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<tr>
<td>Commercial</td>
<td>4.8</td>
<td>13.4</td>
<td></td>
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<tr>
<td>Other</td>
<td>49.2</td>
<td>36.3</td>
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<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Diabetes</td>
<td>33.1</td>
<td>32.7</td>
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<tr>
<td>Prior CHF</td>
<td>9.4</td>
<td>12.7</td>
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</tr>
<tr>
<td>Prior PCI</td>
<td>32.0</td>
<td>34.3</td>
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<tr>
<td>Prior myocardial infarction (MI)</td>
<td>28.7</td>
<td>30.1</td>
<td></td>
</tr>
<tr>
<td>Prior bypass surgery</td>
<td>8.4</td>
<td>15.7</td>
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<tr>
<td>Hypertension</td>
<td>79.6</td>
<td>80.7</td>
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</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>12.1</td>
<td>12.8</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>24.8</td>
<td>23.1</td>
<td></td>
</tr>
<tr>
<td>Lung disease</td>
<td>13.7</td>
<td>14.4</td>
<td></td>
</tr>
</tbody>
</table>

###Registry with data on **40,126 patients** PCI patient, 12.9% undergo PCI via radial artery (versus femoral artery)

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<tbody>
<tr>
<td>No. of Procedures</td>
<td>5192</td>
<td>35022</td>
<td></td>
</tr>
<tr>
<td>Cardiac Presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-vessel Disease</td>
<td>10.3</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td>Number of Vessels &gt; 70% stenosis</td>
<td>1.49</td>
<td>1.58</td>
<td></td>
</tr>
<tr>
<td>Left main Disease</td>
<td>3.7</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td>ST-elevated MI</td>
<td>36.9</td>
<td>42.6</td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>0.44</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Drugs Prior to Procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin (unfractionated)</td>
<td>87.3</td>
<td>61.7</td>
<td></td>
</tr>
<tr>
<td>Heparin (low weight molecular)</td>
<td>3.83</td>
<td>4.27</td>
<td></td>
</tr>
<tr>
<td>Thrombin</td>
<td>25.5</td>
<td>54.9</td>
<td></td>
</tr>
<tr>
<td>GP2B3A inhibitors</td>
<td>26.7</td>
<td>26.8</td>
<td></td>
</tr>
<tr>
<td>Platelet Aggregate inhibitors</td>
<td>85.8</td>
<td>86.6</td>
<td></td>
</tr>
<tr>
<td>Intra-Aortic Balloon Pump</td>
<td>0.10</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>In-Hospital Complication, %</td>
<td>0.69</td>
<td>2.73</td>
<td></td>
</tr>
</tbody>
</table>
| Mean Difference, % (95% CI) | $-2.04 \text{ to } -2.30\%$ -- $1.80$}
RADIAL VS FEMORAL ARTERY ACCESS

ASSESSING VALIDITY OF ASSUMPTIONS

Mean(Radial) - Mean(Femoral)
Filled circles = Matched
Comparative Summary

Favors Radial Artery Access

- S−IPTW
- HT−IPTW
- A−IPTW
- TMLE
- Multiple regression
- G−Computation
- Matching
- Stratification
- S−IPTW

Complication Risk Difference (%)

SUTVA: practice makes perfect (physician random effect)

Ignorability: Omitted confounder: odds of radial \( \geq 2.5 \times \) femoral to change findings

Non-constant effect

- Women: -2.67% (se = 0.43%)
- Men: -1.00% (se = 0.58%)

\[ \text{NNT} = 46.49 \]
DIMENSION REDUCTION (HIGH-DIMENSIONAL SETTING)

- High-dimensional propensity score (Schneeweiss et al., 2009)
  - Binary treatment, binary outcome, binary confounders
  - Rank confounders for inclusion
- Generalized boosting approaches (Ridgeway et al., 2014)
  - Toolkit for Weighting and Analysis of Non Equivalent Groups TWANG package in R
- Target maximum likelihood (TMLE package in R)
  - No need to maximize entire likelihood (van der Laan, Rose, 2011)
  - Semi-parametric
- Bayesian model average + adjustment for confounding
  - Binary treatment & outcomes (Zigler and Dominici, 2014)
  - Parametric assumptions for outcome equation
- Bayesian regularization:
  - Discrete mixtures or shrinkage priors
BOLSTERING REPRODUCIBILITY

- Provide justification for all assumptions made
- Demonstrate sensitivity of findings to unmeasured confounding
- Include a falsification test
  - DES vs BMS: should be no mortality difference
  - Model-specific DES: manufacturer bought a device from another manufacturer & sold it in a different package
- Make few parametric assumptions
- High-dimensional settings
  - DES vs BMS: used horseshoe prior
  - Model-specific DES: used TMLE

THANK YOU
REFERENCES


- Ridsgeway G, McCaffrey D, Morral A, Burgette L, Griffin BA. Toolkit for weighting and analysis of nonequivalent groups: A tutorial for the twang package. 2014, R Vignette, RAND.

- Schneeweis S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology, 2009; 20, 512.

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Under Review


- Spertus J, Normand S-LT. Bayesian computation and propensity scores for high-dimensional causal inference: a comparison of drug-eluting to bare-metal coronary stents