Cryptic randomness in Standard of Care Research

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Conflicts of Interest

Dr. Sox is a full-time employee of PCORI. He is not representing PCORI at this forum nor stating PCORI policy.

No conflicts to report.
Definitions

• Cryptic randomness: randomness that the patient does not know about.

• Standard of Care Research:
  – Comparative Effectiveness Research: direct comparison of active, accepted treatments.
Cryptic randomness in Standard of Care Research

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When a patient chooses a doctor, they want to know whether they will get care that reflects the evidence (or a consensus about what’s best).

They also want to know whether they will get the care that is best for them.
Most of the time, they won’t have much advance notice about the doctor’s practice style.

Choosing a doctor has a strong element of chance.

So, now put yourself in the shoes of a patient.
Suppose that you checked your blood pressure at the local drug store. It was 160/110. You are new to the area, so you pick a primary care doctor’s name out of the phone book and make an appointment. Now it’s the day of your appointment, and you walk up to the doctor’s office.
The doctor is in. He uses atenolol for high BP.
The doctor is in.
He uses atenolol for high BP.

That’s nice.
I know what I’m getting in for.
Now suppose that you picked another primary care physician’s name out of the phone book. You approach her office and notice the sign out front.
The doctor is in.
That’s nice. I wonder what treatment she likes to give.

The doctor is in.
From your perspective, the treatment would be **random**.
You would not know what treatment the doctor will choose.
Here’s a third scenario. It’s the same as the others except you pick a third name from the phone book.
The doctor is in.
She practices shared decision making
The doctor is in.  She practices shared decision making.

No problem. I’ll get the treatment that best fits me and my preferences.
What is the message of these scenarios?

• From the patient’s perspective, the care received would seem random if the patient doesn’t know the physician’s routine. The physician might
  – Use any of several treatments depending on non-medical factors such as the weather. Truly random.
  – Use one treatment consistently, regardless of the patient’s special features. Random and bias-prone.
What is the message of these scenarios?

• Care would not seem random if
  – The physician explained his routine.
    • “I always start with atenolol”
  – The physician encouraged shared decision making
How could standard care appear random?

• Several (equivalent) treatments exist.
  – Early stage breast cancer
  – Initial therapy of hypertension

• Two mechanisms
  – The physician literally tosses a coin to determine treatment.
  – The physician has a routine that the patient doesn’t know about.
How could standard care appear random?

• Several equivalent treatments exist.
  – Early stage breast cancer
  – Initial therapy of hypertension

• Two mechanisms
  – The physician literally tosses a coin to determine treatment.
  – The physician has a routine that the patient doesn’t know about.
    • Routines are bias-prone. Do they exist?
What is the evidence that physicians have treatment routines?

- Small area variation
- Instrumental variable analysis
- Physician-specific cohort analysis
Patterns of care by individual physicians:

Small-area variation
Per-capita spending across intensity quintiles

Ratio: High to Low: 1.61  1.58
Small-area variation in care intensity as evidence for that doctors have routines

• Small-area variation means that doctors in one area treat more intensively than doctors in another area.
  – The data are all at the geographic unit level; an average figure within the region.
  – We do not have individual-level data and therefore don’t know the distribution of utilization by doctor within a region.
Distribution of practice intensity: 3 geographic areas compared
Small-area variation in care intensity as evidence that doctors have routines

• We can infer that the distribution of intensity is skewed toward higher utilization in the more intense regions.
  – The practice of some physicians must be skewed toward high intensity
  – We don’t know how consistently high users follow a routine.

• From the patient’s perspective, skewness means the care they will receive, while random, may also be biased toward more/less intense options.
  – They are more likely to get one treatment than another, and they don’t realize it.
Patterns of care by individual physicians:

Instrumental variables
Instrumental Variable Analysis

• An “instrument” is an external cause of the exposure but is not directly related to the outcome.
  – The perfect instrument is randomization. It affects the treatment directly but has no relation to outcome except through the treatment.

• Apart from RCTs, the only approach to ruling out unmeasured confounding is to use instrumental variable (IV) analysis.
Instrumental Variable Analysis

• An instrumental variable represents a “natural” randomization process rather than a physical randomization process.
  – Randomization assigns a subject to a 100% or 0% chance of getting therapy.
  – With IV analysis, two groups have different chances to get the intervention (20% vs. 60%).
Instrumental Variable Analysis

1. Use the IV to divide the population according to the value of the IV.
2. Compare the rates of treatment in the groups.
3. If treatment choice is related to the IV but the outcome is not directly related to the IV, the treatment cannot cause the outcome.
   - The method is best used to rule out a causal relationship.
4. A classic example of an IV analysis.
Why might instrumental variables help us to understand randomness of care?

- An instrumental variable can divide a population randomly → two similar subpopulations.
- When two similar subpopulations get different care, routines may be overriding clinical features.
Validation of an Instrumental Variable

• Index event: prescription of an antipsychotic (APM)
  – Risk factors for bad outcomes are known.
• Physicians are labeled as users or non-users of atypical antipsychotics (APMs) based on their treatment choice for the patient immediately preceding the index event.
• An IV can divide the population randomly, but it must satisfy 3 conditions.

Brookhart MA, et al. Medical Care 2004;45:S116-122
Conditions an IV must meet

• APM preference varies among physicians.
• Physicians’ prior APM preference (the IV) is unrelated to the index patient’s risk factors (independence).
• Physician prior preference (the IV) is related to patient outcome only through the type of APM prescribed (exclusion).
• Because of unobserved variables, independence or exclusion cannot be established empirically.
Result

• The prevalence of risk factors for bad outcomes in index were the same in a-APM prescribers and c-APM prescribers.
  – Physician APM preference (the IV) were not associated with patient characteristics.
  – Physicians appear to stay with their APM preference (conventional or atypical) irrespective of the patient’s characteristics: evidence for prescribing routines
The analysis of care by individual physicians:

physician-specific cohorts
State of the evidence about the strength of prescribing habits

- Small-area variation: suggestive but indirect
- Instrumental variables: suggestive but indirect
- Analysis of physician-specific cohorts: direct

Data sets for tracing prescribing habits
- Medicare Part D
- Prescribing data sets sold to pharmaceutical firms.
### Physician-specific cohort analysis

<table>
<thead>
<tr>
<th>Doctor A</th>
<th>Doctor B</th>
<th>Doctor C</th>
<th>Doctor D</th>
<th>Doctor E</th>
<th>Doctor F</th>
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</table>

New onset hypertension: 1 = atenolol, 2 = ACE inhibitor
Use of physician-specific cohorts

• Data sets for tracing prescribing habits
  – Medicare Part D
  – Prescribing data sets sold to pharmaceutical firms.

• No one that I spoke to knew of published studies that scrutinized these data sets for individual patterns of care.
  – Pharmaceutical companies do analyze the habits of individual physicians to prepare drug detailers for their meetings with individual physicians.
The doctor is in.
The doctor is in.

That’s nice. I wonder what treatment she likes to give.
From your perspective, the treatment would be **random**.
You would not know what treatment the doctor will choose.

The doctor is in.
Conclusions

• From your perspective, the treatment you receive on your first visit to a doctor is random.
  – Exceptions: shared decision making, physician declares her preferences.

• If your new doctor is a creature of habit, your treatment will be biased toward his preferences.
  – Even when you know the care you receive, you will experience the effects of this bias unless you can make an independent assessment.
<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Actual APM Treatment Assignment</th>
<th>Last APM Assigned by Physician (IV)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence Difference (%)</td>
<td>( P^* )</td>
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<tr>
<td>Female patient</td>
<td>5.3</td>
<td>&lt;0.01</td>
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<tr>
<td>Age &gt;80 yr</td>
<td>2.0</td>
<td>&lt;0.01</td>
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<tr>
<td>History of</td>
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<td>Cerebrovascular disease</td>
<td>1.9</td>
<td>0.04</td>
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<tr>
<td>Congestive heart failure</td>
<td>-1.2</td>
<td>0.22</td>
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<tr>
<td>Diabetes</td>
<td>-0.3</td>
<td>0.79</td>
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<tr>
<td>Hypertension</td>
<td>2.6</td>
<td>0.01</td>
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<tr>
<td>Cardiac arrhythmia</td>
<td>0.2</td>
<td>0.43</td>
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<tr>
<td>Myocardial infarction</td>
<td>-0.7</td>
<td>0.07</td>
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<tr>
<td>Other ischemic heart disease</td>
<td>-1.6</td>
<td>0.09</td>
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<tr>
<td>Other cardiovascular disorders</td>
<td>-1.6</td>
<td>0.02</td>
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<tr>
<td>Cancer</td>
<td>-1.9</td>
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<tr>
<td>Psychiatric disorder</td>
<td>14.1</td>
<td>&lt;0.01</td>
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<tr>
<td>Skilled nursing facility stay in previous 180 d</td>
<td>2.4</td>
<td>0.01</td>
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</tbody>
</table>

\(^*\)Computed using a GEE approach that adjusts standard errors for within-physician clustering using a correlation matrix with an exchangeable structure.

\(^*\)Prevalence of risk factor among atypical users minus prevalence of risk factor among conventional users estimated in a linear model adjusting for calendar year.

\(^*\)Prevalence of risk factor among patients of physicians who most recently prescribed an atypical APM minus prevalence among patients of physicians who most recently prescribed a conventional APM estimated in a linear model adjusting for calendar year.

\(^*\)Includes mood disorders, dementia, delirium, and psychotic disorders.