Reliable Real-World Evidence for Equitable Health Care

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Washington University School of Medicine in St Louis

CS531a AI for Health Guest Lecture
Mar 26, 2024
The goal is to integrate causal modeling with machine learning to generate reliable real-world evidence and to build an equitable healthcare system.
Team

Trainees

Yichen Sun
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Washington University

Hsin-Yi “Cindy” Chen
MD/PhD candidate
Columbia University

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Senior data analyst

Recruiting
- PhD students
- Post-docs

Mentors and Collaborators

Adam Wilcox
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Charles Goss
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George Hripcsak
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David Blei
Columbia

Yixin Wang
UMich

Wenyu Song
HMS&MGB

https://linyingzhang.com
Real-world data (RWD) in health care

Electronic Health Records (EHRs)

Medical Images

Genomics

Clinical Notes

Wearables

Demographics  Diagnoses  Drugs  Procedures  Labs

RWD are data generated from their natural setting (i.e., not strictly controlled clinical trials).
BJC HealthCare/WashU EHRs

- 14 hospitals
- 2M patients

From routine care to the most advanced treatments, we are nearby to cover your every health need across 14 hospitals, multiple convenient care locations, virtual care video visits, outpatient centers, and much more.

Explore all BJC locations and care options.
Data -> Evidence -> Practice

**TREATMENT EFFECT ESTIMATION**
- Is a treatment effective?
- Is a treatment safe?

**HEALTH EQUITY**
- Is the healthcare system fair?
- Is the clinical algorithm fair?

**RISK PREDICTION**
- Can we predict mortality?
- What are the risk factors?
Why real-world evidence is needed in healthcare

All health outcomes of interest

Figure: Patrick Ryan
Mission: To improve health by empowering a community to collaboratively generate the evidence that promotes better health decisions and better care

A multi-stakeholder, interdisciplinary, international collaborative with a coordinating center at Columbia University

http://ohdsi.org

George Hripcsak  Patrick Ryan
Experts in informatics, statistics, epidemiology, clinical sciences
Active participation from academia, government, industry, providers
Currently records on about **800 million unique patients** in >300 databases
344 papers, specific influence on EMA and FDA for COVID-19
Core foundations for OHDSI

OMOP Common Data Model

Open-Source Analytics
Lack of standards across EHR databases and analytics

"What's the adherence to my drug in the data assets I own?"

Analytical method: Adherence to Drug

Application to data

Christian Reich
Solution 1: OMOP Common Data Model

"What's the adherence to my drug in the data assets I own?"

Analytical method: Adherence to Drug

Standard vocabulary
Standard data structure

Christian Reich
Solution 2: Open-source Analytics

HADES includes over 20 open-source R packages for large scale analytics, including:

- population characterization
- population-level effect estimation
- patient-level prediction
- other supporting packages

https://github.com/OHDSI

Martijn Schuemie
Verified and Open

**VERIFIED**

- Employ only previously validated methods
- Advanced, systematic methods to control bias
- Extensive diagnostics and large-scale controls
- Test many hypotheses to assess operating characteristics
- Study many databases, locations, practice types

**OPEN**

- Fully pre-specified public protocol
- All software open-source with public parameters
- All diagnostics made public with results initially blinded
- All results made publicly available
- Results paired with detailed attestation and characterization of populations studied

Washington University School of Medicine in St. Louis
Treatment effect estimation

1. **Method**: Large-scale propensity score
2. **Clinical example**: Anti-VEGF and kidney failure
Randomized controlled trials (RCTs) are prospective studies that measure the efficacy and safety of a treatment.

RCT is considered as the gold-standard for establishing cause-and-effect relationships.

Randomization balances participants characteristics and reduces confounding bias.
RCT is not always a viable option

- Cost
- Time
- Ethics
- Generalizability

How can we estimate causal effects with observational data?
Confounding bias

Confounding remains one of the major challenges to causal inference with observational data.
Propensity score is a popular method to adjust for confounding.

\[ p(D = 1 | X = x_i) \]

Propensity score is the probability of a patient receiving the treatment given the patient’s baseline characteristics.
Propensity scores can be estimated from data

\[
\text{logit}(\hat{p}) = \hat{\beta}_0 + \hat{\beta}_1 x_{i1} + \cdots + \hat{\beta}_j x_{ij}
\]

- In practice, propensity score is often estimated with a logistic regression.
- Treatment status is regressed on measured covariates that are believed to be confounders.
How are confounders selected?

- **Domain Knowledge**
- **Literature Review**
- **Empirical association**

Confounders

$X$

domains

$D$

treatment

$Y$

outcome

EHR database

Demographics

Diagnoses

Drugs

Procedures

Labs
How well do observational studies agree on confounders?

Hicks 2018: age, sex, year of cohort entry, body mass index, smoking status, alcohol related disorders (including alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis, and hepatic failure), and history of lung diseases (including pneumonia, tuberculosis, and chronic obstructive pulmonary disease), duration of HTN Rx, statin use, #drugs

Ku 2018: age, sex, race, income status, baseline HF, baseline myocardial infarction, baseline peripheral artery disease, baseline stroke, baseline eGFR, baseline proteinuria, and time-dependent covariates including diabetes mellitus, obesity, systolic blood pressure, statin use, aspirin use, diuretic use, and concurrent use of other antihypertensive agents for the outcome of HF

Magid 2010: age, gender, days on thiazide prior to 2nd agent start, # of visits prior to thiazide, Mean Systolic BP, Mean Diastolic BP, Chronic Obstructive Pulmonary Disease, Hyperlipidemia, Cancer, Dementia, Chronic liver disease, Depression

Hasvold 2014: age, gender, elevated blood glucose, overweight and low socio-economic status are known risk factors for diabetes, High cholesterol and hypertension are additionally known risk factors for CVD

Blue: good agreement. Green: partial agreement. Red: lack of agreement
Unmeasured confounder leads to biased estimates

- **Poor agreement** among manually selected confounders.
  - Confounding structure is rarely known.
- Missing a confounder will lead to **biased effect estimates**.
- Poor agreement on confounders across studies **weakens the reliability** of evidence from real-world data.
Large-Scale Propensity Score (LSPS): A systematic approach to adjust for confounding

\[ p(D = 1 | X = x_i) \]

LSPS includes (nearly) all covariates in the propensity model to adjust for confounding.

All covariates except
- Mediators (pre-treatment only)
- Simple colliders (pre-treatment only)
- “Instruments” (diagnostics, domain knowledge)
- M-structure collider (no bias if its causes are measured and adjusted)
Study Design: Manual PS vs LSPS

X: Selected covariates (~100s) based on domain knowledge and existing literature.
• Manual (X+U)
• Manual (X)

X: All pre-treatment covariates (~60,000)
• LSPS (X+U)
• LSPS (X)

Note: U includes all T2DM diagnoses and anti-glycemic medications (~50).
Manual PS vs LSPS

LSPS is more robust to unmeasured confounding than classical PS with manual covariate selection.
Treatment effect estimation

1. Method: Large-scale propensity score

2. Clinical example: Anti-VEGF and kidney failure
To answer the question: is there a difference in the risk of kidney failure comparing patients who received ranibizumab, afiblercept, and bevacizumab?

### SOS Challenge Weekly Tutorial Schedule

<table>
<thead>
<tr>
<th>Date</th>
<th>Times</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mar. 28</td>
<td>11 am / 7 pm ET</td>
<td>SOS Week 1 Tutorial: Initiating A Network Study</td>
</tr>
<tr>
<td>Apr. 4</td>
<td>11 am / 7 pm ET</td>
<td>SOS Week 2 Tutorial: Data Diagnostics</td>
</tr>
<tr>
<td>Apr. 11</td>
<td>11 am / 7 pm ET</td>
<td>SOS Week 3 Tutorial: Phenotype Development</td>
</tr>
<tr>
<td>Apr. 18</td>
<td>11 am / 7 pm ET</td>
<td>SOS Week 4 Tutorial: Phenotype Evaluation</td>
</tr>
<tr>
<td>Apr. 25</td>
<td>11 am / 7 pm ET</td>
<td>SOS Week 5 Tutorial: Creating Analysis Specifications</td>
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<tr>
<td>May 2</td>
<td>11 am / 7 pm ET</td>
<td>SOS Week 6 Tutorial: Network Execution</td>
</tr>
<tr>
<td>May 9</td>
<td>11 am / 7 pm ET</td>
<td>SOS Week 7 Tutorial: Study Diagnostics</td>
</tr>
<tr>
<td>May 16</td>
<td>11 am / 7 pm ET</td>
<td>SOS Week 8 Tutorial: Evidence Synthesis</td>
</tr>
<tr>
<td>May 23</td>
<td>11 am / 7 pm ET</td>
<td>SOS Week 9 Tutorial: Interpreting The Results</td>
</tr>
</tbody>
</table>

4 network studies in 9 weeks:

- Anti-VEGF and kidney failure
- Fluoroquinolone and aortic aneurysms
- Risankizumab and cerebrovascular events
- Multiple Sclerosis biologics and progressive multifocal leukoencephalopathy
Anti-VEGF and kidney failure

- Anti-vascular endothelial growth factor (anti-VEGF) medications
- Systemic administration of anti-VEGF agents have known adverse kidney side effects
  - Acute kidney injury
  - Proteinuria
  - Hypertension
  - Vascular clotting events
  - Glomerular disease
  - Risk factors for: kidney failure (need for renal replacement therapy with dialysis or kidney transplant, aka end stage kidney disease or end stage renal disease)
Intravitreal Anti-VEGF and Systemic Absorption

<table>
<thead>
<tr>
<th>Drug</th>
<th>Size</th>
<th>Systemic Elimination (half-life)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranibizumab</td>
<td>48 kDa</td>
<td>2 hours</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>115 kDa</td>
<td>5-6 days</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>149 kDa</td>
<td>20 days</td>
</tr>
</tbody>
</table>

Detectable/elevated serum drug levels
Decreased plasma concentrations of free-VEGF

**Bevacizumab > aflibercept >> ranibizumab**

**Hypothesis:** In pairwise comparisons, lower risk of kidney failure in patients with blinding diseases who are exposed to ranibizumab

**Question:** Is there evidence for preferentially choosing ranibizumab to lower the risk of kidney failure?

https://www.randeye.com/intravitreal-injection/
https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125085s0169lbl.pdf
OHDSI Study: Intravitreal anti-VEGF and Kidney Failure

- Estimating the **comparative risk of kidney failure** associated with intravitreal anti-vascular endothelial growth factor exposure in patients with blinding diseases (DR/DME, AMD, VO)
  - Amongst people with blinding diseases, does exposure to **ranibizumab** increase the risk of kidney failure, relative to **aflibercept**?
  - Amongst people with blinding diseases, does exposure to **bevacizumab** increase the risk of kidney failure, relative to **aflibercept**?
  - Amongst people with blinding diseases, does exposure to **bevacizumab** increase the risk of kidney failure, relative to **ranibizumab**?

Hypothesis: in these pairwise comparisons, lower risk of kidney failure in patients with blinding diseases who are exposed to ranibizumab
Data databases/partners

- 12 databases:
  - 6 claims and 6 EHRs
- Total 485 million patients

<table>
<thead>
<tr>
<th>Data Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBM Health MarketScan Medicare Supplemental and Coordination of Benefits Database (MDCR)</td>
</tr>
<tr>
<td>IBM Health MarketScan Commercial Claims and Encounters Database (CCAE)</td>
</tr>
<tr>
<td>IBM Health MarketScan Multi-State Medicaid Database (MDCD)</td>
</tr>
<tr>
<td>Optum(R) de-identified Electronic Health Record Dataset (OptumEHR)</td>
</tr>
<tr>
<td>Optum’s Clinformatics Extended Data Mart - Socio-economic Status (SES)</td>
</tr>
<tr>
<td>Japan Medical Data Center (JMDC)</td>
</tr>
<tr>
<td>Johns Hopkins Medical Enterprise (JHME)</td>
</tr>
<tr>
<td>Department of Veterans Affairs (VA)</td>
</tr>
<tr>
<td>PharMetrics Plus (NEU)</td>
</tr>
<tr>
<td>Columbia University Medical Center (CUMC)</td>
</tr>
<tr>
<td>Stanford (STARR)</td>
</tr>
<tr>
<td>University of Southern California (USC)</td>
</tr>
</tbody>
</table>
Cohort definition

- New users of 3 monthly anti-VEGF medications with blinding diseases
- Study protocol: [https://ohdsi-studies.github.io/AntiVegfKidneyFailure/Protocol.html](https://ohdsi-studies.github.io/AntiVegfKidneyFailure/Protocol.html)
Phenotype Development

• Phenotypes:
  o Binding diseases
  o anti-VEGF medications
  o kidney failure

• Tools:
  o ATLAS WebAPI: https://atlas-demo.ohdsi.org/
  o PHOEBE (concept recommender) https://data.ohdsi.org/PHOEBE/
  o PheValuator (phenotype diagnostic) https://doi.org/10.1016/j.jbi.2019.103258
Population-level effect estimation

• Large-scale propensity score (LSPS) was used to match target/comparator cohorts using 1:1 propensity score matching

• Cox proportional hazards model was used to estimate the risk of kidney failure

• Code repository: https://github.com/ohdsi-studies/AntiVegfKidneyFailure
### Study diagnostics

<table>
<thead>
<tr>
<th>Comparison groups</th>
<th>Database</th>
<th>Maximum standardized mean difference (balance diagnostic)</th>
<th>Equipoise (equipoise diagnostic)</th>
<th>MDRR (MDRR diagnostic)</th>
<th>Attrition Fraction (attrition diagnostic)</th>
<th>EASE (EASE diagnostic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept / Ranibizumab</td>
<td>CCAE</td>
<td>0.065 (pass)</td>
<td>0.607 (pass)</td>
<td>2.049 (pass)</td>
<td>0.536 (pass)</td>
<td>0.054 (pass)</td>
</tr>
<tr>
<td></td>
<td>MDCR</td>
<td>0.056 (pass)</td>
<td>0.729 (pass)</td>
<td>2.736 (pass)</td>
<td>0.498 (pass)</td>
<td>0.050 (pass)</td>
</tr>
<tr>
<td></td>
<td>MDCD§</td>
<td>0.118 (fail)</td>
<td>0.624 (pass)</td>
<td>3.396 (pass)</td>
<td>0.693 (pass)</td>
<td>0.109 (pass)</td>
</tr>
<tr>
<td></td>
<td>OptumEHRA</td>
<td>0.117 (fail)</td>
<td>0.382 (pass)</td>
<td>4.058 (pass)</td>
<td>0.758 (pass)</td>
<td>0.180 (pass)</td>
</tr>
<tr>
<td></td>
<td>SES</td>
<td>0.054 (pass)</td>
<td>0.781 (pass)</td>
<td>1.805 (pass)</td>
<td>0.511 (pass)</td>
<td>0.032 (pass)</td>
</tr>
<tr>
<td></td>
<td>JMDC§</td>
<td>0.260 (fail)</td>
<td>1 (pass)</td>
<td>NA (fail)</td>
<td>0.486 (pass)</td>
<td>0.431 (fail)</td>
</tr>
<tr>
<td></td>
<td>JHME§</td>
<td>0.953 (fail)</td>
<td>0.472 (pass)</td>
<td>NA (fail)</td>
<td>0.981 (pass)</td>
<td>NA (fail)</td>
</tr>
<tr>
<td></td>
<td>NEU</td>
<td>0.064 (pass)</td>
<td>0.900 (pass)</td>
<td>3.217 (pass)</td>
<td>0.583 (pass)</td>
<td>0.085 (pass)</td>
</tr>
<tr>
<td></td>
<td>CUMC§</td>
<td>0.965 (fail)</td>
<td>0.391 (pass)</td>
<td>NA (fail)</td>
<td>0.963 (pass)</td>
<td>NA (fail)</td>
</tr>
<tr>
<td></td>
<td>STARR§</td>
<td>NA (fail)</td>
<td>NA (fail)</td>
<td>NA (fail)</td>
<td>NA (fail)</td>
<td>NA (fail)</td>
</tr>
<tr>
<td></td>
<td>VA</td>
<td>0.080 (pass)</td>
<td>0.357 (pass)</td>
<td>3.746 (pass)</td>
<td>0.847 (pass)</td>
<td>0.092 (pass)</td>
</tr>
<tr>
<td></td>
<td>USC§</td>
<td>NA (fail)</td>
<td>NA (fail)</td>
<td>NA (fail)</td>
<td>NA (fail)</td>
<td>NA (fail)</td>
</tr>
</tbody>
</table>

**EASE** = Expected Absolute Systematic Error, **MDRR** = minimum detectable relative risk
Anti-VEGF OHDSI Study: Results

- 6.1 million patients with blinding diseases
  - 240,247 anti-VEGF
    - 37,189 received ranibizumab
    - 39,447 aflibercept
    - 163,611 bevacizumab
  - 1209 kidney failure outcomes

- Standardized incidence proportion of kidney failure: 680 per 100,000 persons

- In all pairwise comparison, the hazard ratio was around 1.0

For retina colleagues: can choose between any of these 3 anti-VEGF medications for those at risk for kidney failure
Similar risk of kidney failure among patients with blinding diseases who receive ranibizumab, aflibercept, and bevacizumab: an OHDSI Network Study

Cindy X. Cai MD, MS, Akihiko Nishimura PhD, Mary G. Bowring MPH, Erik Westlund PhD, Dep Tran MSc, Jig H. Ng MD, MSCE, Paul Nagy PhD, Michael Cook BS, Jody-Ann McLeggan MPH, Scott L. DuVall PhD, Michael E. Matheny MD, MS, MPH, Asieh Golozor PhD, Anna Ostropalets MD, PhD, Evan Mistry MD MSc, Priya Desai MS, Fan Bu PhD, Brian Toy MD, Michelle Hribar PhD, Thomas Falconer MS, Linying Zheng PhD...Patrick B. Ryan PhD

https://doi.org/10.1016/j.oret.2024.03.004
Anti-VEGF and kidney failure

- Study protocol: [https://ohdsi-studies.github.io/AntiVegfKidneyFailure/Protocol.html](https://ohdsi-studies.github.io/AntiVegfKidneyFailure/Protocol.html)
- Code: [https://github.com/ohdsi-studies/AntiVegfKidneyFailure](https://github.com/ohdsi-studies/AntiVegfKidneyFailure)
- Results explorer:
  - [https://data.ohdsi.org/AntiVegfKidneyFailure/](https://data.ohdsi.org/AntiVegfKidneyFailure/) (main results);
  - [https://data.ohdsi.org/AntiVegfKidneyFailure2/](https://data.ohdsi.org/AntiVegfKidneyFailure2/) (sensitivity analysis)

### RESEARCH PROTOCOL

Estimating the comparative risk of kidney failure associated with intravitreal anti-vascular endothelial growth factor exposure in patients with blinding diseases

#### Version: 0.0.2

1 List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Anti-VEGF</td>
<td>anti-vascular endothelial growth factor</td>
</tr>
<tr>
<td>DR</td>
<td>diabetic retinopathy</td>
</tr>
<tr>
<td>AMD</td>
<td>age-related macular degeneration</td>
</tr>
<tr>
<td>VD</td>
<td>vein occlusion</td>
</tr>
<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>CPT</td>
<td>Current Procedural Terminology</td>
</tr>
<tr>
<td>OHDSI</td>
<td>Observational Health Data Sciences and Informatics</td>
</tr>
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</table>
OHDSI

• Website: https://ohdsi.org/
• Weekly community call: Tuesday 10 am Central Time
  o Recordings: https://ohdsi.org/community-calls/
• Annual Global Symposium: https://www.ohdsi.org/ohdsi2023/
• 32 Workgroups: https://www.ohdsi.org/workgroups/

#JoinTheJourney
Data -> Evidence -> Practice

TREATMENT EFFECT ESTIMATION
- Is a treatment effective?
- Is a treatment safe?

HEALTH EQUITY
- Is the healthcare system fair?
- Is the clinical algorithm fair?

RISK PREDICTION
- Can we predict mortality?
- What are the risk factors?
Explaining Treatment Disparities with Causal Modeling

1. **Method:** Causal fairness model
2. **Application:** Revascularization in cardiology
Advancing Health Equity

“Health equity is attainment of the highest level of health for all people.”

-- Healthy People 2030
Clinical process

Care Access → Testing → Diagnosis → Treatment → Outcome Follow-up
Understanding Treatment Disparities

Care Access → Testing → Diagnosis → Treatment → Outcome Follow-up
In health disparities research, women and racial and ethnic minorities are often found to receive less treatment in various clinical domains.

However, research on health disparities often relies on correlational analysis, which may not reveal the underlying causal mechanisms behind disparities.

Question: How can we explain observed disparities in the data in terms of the unobservable causal mechanisms?
There is racial difference in treatment pattern.
• Possible scenario 1:
  • Race is used *directly* in treatment decision-making.
Causal Mechanisms

- Possible scenario 2.1:
  - Race *indirectly* causes difference in treatment patterns (via social factors)
Possible scenario 2.2:

- Race *indirectly* causes difference in treatment patterns (via clinical factors).
Causal Mechanisms

- Possible scenario 3:
  - Race is associated with other demographics (via complex societal processes).
Causal Mechanisms

race \quad \leftrightarrow \quad \text{treatment}
Standard Fairness Model

Standard Fairness Model

Health disparity decomposition formula:

\[ TV_{x_0,x_1}(y) = DE_{x_0,x_1}(y|x_0) + \left(-IE_{x_0,x_1}(y|x_0)\right) + \left(-CE_{x_0,x_1}(y)\right) \]

Question: What is the difference in getting the treatment between Black and non-Black patients?

\[ TV_{x_0,x_1}(y) = E[Y|X = x_1] - E[Y|X = x_0] \]
Standard Fairness Model

Health disparity decomposition formula:

\[ TV_{x_0,x_1}(y) = DE_{x_0,x_1}(y|x_0) + (−IE_{x_0,x_1}(y|x_0)) + (−CE_{x_0,x_1}(y)) \]

**Question:** What is the direct effect of race on treatment? ⇔ What is the difference in treatment probability that is due to the direct effect of changing race from Black to non-Black?

**Formula:**

\[ DE_{x_0,x_1}(y|x_0) = E[Y_{x_1,w|x_0} | x_0] - E[Y_{x_0} | x_0] \]
Standard Fairness Model

(a) Causal fairness model
(b) Direct effect
(c) Indirect effect via SCDoH
(d) Confounded effect

Health disparity decomposition formula:

\[ TV_{x_0,x_1}(y) = DE_{x_0,x_1}(y|x_0) + (-IE_{x_0,x_1}(y|x_0)) + (-CE_{x_0,x_1}(y)) \]

Question: What is the indirect effect of race on treatment?
⇔ What is the difference in treatment probability that is due to the effect of changing race from Black to non-Black on the mediators (ie, social and clinical determinants of health)?

\[ IE_{x_0,x_1}(y|x_0) = E[Y_{x_1,w_0} | x_0] - E[Y_{x_1} | x_0] \]
Standard Fairness Model

(a) Causal fairness model
(b) Direct effect
(c) Indirect effect via SCDoH
(d) Confounded effect

Health disparity decomposition formula:

$$TV_{x_0,x_1}(y) = DE_{x_0,x_1}(y|x_0) + (−IE_{x_0,x_1}(y|x_0)) + (−CE_{x_0,x_1}(y))$$

Question: What is the confounded effect of race on treatment? ⇔ What is the difference in treatment probability that is due to the effect of changing race from Black to non-Black on the confounders (ie, age, sex, etc)?

$$CE_{x_0,x_1}(y) = E[Y_{x_0} | x_1] - E[Y_{x_0} | x_0]$$
Standard Fairness Model

Health disparity decomposition formula:

\[ TV_{x_0,x_1}(y) = DE_{x_0,x_1}(y|x_0) + (-IE_{x_0,x_1}(y|x_0)) + (-CE_{x_0,x_1}(y)) \]

Question: What is the confounded effect of race on treatment? ⇔ What is the difference in treatment probability that is due to the effect of changing race from Black to non-Black on the confounders (ie, age, sex, etc)?

\[ CE_{x_0,x_1}(y) = E[Y_{x_0} | x_1] - E[Y_{x_0} | x_0] \]
Explaining Treatment Disparities with Causal Modeling
1. Method: Causal fairness model
2. Application: Revascularization in cardiology
Coronary artery disease

- Coronary artery disease is the most common type of heart disease.
- Patients with coronary artery disease are at higher risk of developing AMI.

Phenotype

Outcome

Coronary artery disease (CAD)

Acute myocardial infarction (AMI)
Women, racial and ethnic minorities, patients without health insurance, and those who live in low-income neighborhoods may have inadequate access to revascularization.

**Disparities in CAD Treatments**

- Question: What causes racial disparities in allocating revascularization to CAD patients?
- Question: What causes sex disparities in allocating revascularization to CAD patients?
Data and Cohort

• Data
  o Source: Columbia University Irving Medical Center (CUIMC) electronic health record (EHR)
  o Format: Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) v5.4

• Cohort
  o The coronary artery disease (CAD) cohort: coronary arteriosclerosis diagnosis codes.
  o Treatment group: Patients treated with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).
  o Control group: Patients with CAD but no CABG or PCI.
  o Index date: The index date was the date of the initial treatment in a patient’s EHR. The index date for the control group was the latest clinical visit with a coronary arteriosclerosis diagnosis.
  o Patients with missing race or gender were excluded from the study.
Clinical and Social Determinants of Health

- Demographics (race, sex, age)
  - Age
  - Sex
  - Race

- Clinical factors
  - Medical conditions (200+)

- Social determinants of health (SDoH)
  - Health insurance
  - Area deprivation index (ADI) from census data
Source: geocoding tool developed by OHDSI’s Geographic Information System (GIS) working group that leverages PostGIS Tiger Geocoder functionality.

To link ADI to geocoded data, an analysis package, written in R 4.0, was developed at CUIMC and then run on both CUIMC and TMC data. The package was designed to generate both cancer cohorts and then link each patient’s geocoded address to state-based ADI data. The package is publicly available on our GitHub repository: https://github.com/cukarthik/CancerTreatmentCharacterization.

ADI data used the R package downloaded from Neighborhood Atlas, an open-source website developed by the University of Wisconsin with the aim of making national and state ADI rankings available to researchers. In this study we used state ADI scores instead of national scores because these scores are based on state-level indicators of socioeconomic status—instead of US-wide indicators—and therefore provide a more granular measure of socioeconomic deprivation relative to each state.

The ADI data used in this study was from 2019, which is based on five-year estimates from the 2015-2019 American Community Survey. ADI rankings can be downloaded with one of two possible geographic entity linkages: 12-digit US census block group FIPS codes or 9-digit zip code. Since block groups are the smallest geographic unit in census data that ADI rankings are calculated for, US Census Block Group FIPS codes were used.

ADI rankings were linked to patient addresses using the workflow shown in Figure 1. Geocoded addresses were then joined to FIPS codes, stored in TIGER shapefiles. The process generated an intermediate table containing the mappings between block group FIPS and location id. With the intermediate geocode location table created, state ADI rankings could then be assigned to each patient in a separate output table housing each patient’s location id, FIPS code and ADI ranking.

Figure 1. Linkage of ADI to OMOP location table workflow

The R package also included code to generate visualizations showing the geographic distribution of ADI scores by mapping the number of patients within each cohort to their geographic location and corresponding ADI score. ADI scores were determined for each county by taking the median block group ADI ranking for all patients located within.

Code: https://github.com/cukarthik/CancerTreatmentCharacterization
Method for Causal Estimation

- We estimate the **direct effect**, **indirect effect**, and **confounded effect**.
- We used double machine learning to estimate causal quantities in the forms of $E[Y_{x_1}]$ or $E[Y_{x_1, w_{x_0}}]$.
- The estimator is **doubly-robust**, meaning that the estimator will be **consistent** as long as one model involved in the estimator is consistent, a highly desired property for estimators.
Results

Figure 2. The decomposition of racial and sex disparity on treatment allocation for CAD cohort.
Results

- The final cohort consists of 41,630 patients,
  - Treatment: 8,428 (20.2%) patients; Control: 33,202 (79.8%) patients
  - Black or African American: 6298 patients (15.2%)

Total disparity: Black patients were 5.0% [95%CI: 4.1% to 6.0%] less likely to receive revascularization treatment compared to non-Black patients.
Results

Racial Disparity Decomposition

- **Indirect effect**: If a non-Black patient were Black, their probability of receiving treatment would have decreased by $2.2\%$ [95%CI: 1.0% to 3.5%].

- This indicates the impact of race on treatment allocation that is mediated through clinical conditions and SDoH.
Results

Confounded effect: Other demographic factors contributed 0.0% [95%CI: -1.0% to 1.0%], difference in probability of receiving treatment between Black and non-Black patients.
Results

• Direct effect measures any residual impact of race on treatment allocation that is not accounted by the other demographic factors (confounded), medical conditions, and SDoH (indirect).

• **Direct effect:** 3.0% [95%CI: 4.1% to 1.9%], suggesting that if a non-Black patient were Black, their probability of receiving treatment would have decreased by 3.0%, assuming all other features remain the same.

• Race has a statistically significant direct effect on the treatment allocation.
Summary

In this study, we

• Adapted a causal fairness analysis framework to better understand the causes and their impact on treatment disparities.
  o Coronary artery disease

• Quantified the effect of race on treatment allocation by decomposing the effect of race into
  o Direct effect
  o Indirect effect (via baseline medical conditions and social determinants of health (SDoH))
  o Confounded effect (via age and sex)
References

This work:


Related work:

• Plečko D and Bareinboim E, Causal Fairness Analysis, Foundations and Trends® in Machine Learning. 2024.

Acknowledgments

Xinzhou (Zoey) Jiang, MS  Karthik Natarajan, PhD  George Hripcsak, MD, MS

The goal is to integrate causal modeling with machine learning to generate reliable real-world evidence and to build an equitable healthcare system.

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