OHDSI in action:
Real-world evidence for clinical characterization

George Hripcsak, MD, MS
Research Goal

• Generate evidence
  – Randomized trial is the gold standard
  – Observational research seen as supporting
Observational Data & Clinical Trials

• Sample size calculations
  – Do we have enough patients to carry out a trial?
• Recruitment
  – Find patients or their clinicians from EHRs
• Pragmatic trials: recruitment and data collection
  – ADAPTABLE aspirin trial
  ...

• Complementary causal evidence (future)
  – New methods to handle confounding and ascertain causes from retrospective observational databases
Characterization

• Today we carry out RCTs without clear knowledge of actual practice
  – Compare treatments within a medical center or several medical centers without knowing what is used in the centers or outside of them
Characterization

• There will be no RCTs without an observational precursor
  – It will be required to characterize a population using large-scale observational data before designing an RCT
  – Disease burden
  – Actual treatment practice
  – Time on therapy
  – Course and complication rate
  – Done now somewhat through literature and pilot studies

• How do the proposed centers differ from the rest of the world?
Research on generalizability

- Set of all RCTs (ClinTrial.gov) as a distribution

(Weng ACI 2014)
Causation

Similar leaps:

• Observational associations -> Causes
• RCT-based causes -> Individual treatment

  1. Study population -> Local population
     • Characterization
  2. Local population -> Individual
     • Precision medicine
     – Are the same causes operative, confounders, etc.
     – That is, if deriving causes from observational data is futuristic, then so is using RCT results

(Fuller 2015)
Characterization

• What do we need to study?
  – Disease burden, current practice, complication rate
• Interactive design (cost of adding exclusions)
  – Fine details in designing my study (age 62 or 65)
• Effect size and variance
  – How many study subjects do we need?
• Will the result generalize
  – Do patients here look like patients at study site?
  – Do observational results on the study population match observational results on the local population
Treatment Pathways

• In literature
  – Recommended sequence of treatments
• How are patients actually treated?
  – Sequence of medications each patient took
Treatment Pathways

• **Stakeholders**
  - Clinician
  - Patient
  - Family
  - Public
  - Consultants
  - Field
  - Industry
  - Regulator

• **Evidence**
  - Randomized trials
  - Observational studies
  - Experience

• **Conduits**
  - Literature
  - Lay press
  - Social media
  - Formulary
  - Guidelines
  - Drug product label
  - Advertising
  - Electronic health record
  - Direct interaction

• **Decision inputs**
  - Clinical course
  - Feasibility of administration
  - Cost
  - Preference
Treatment Pathways

Global stakeholders
- Public
- Academics
- Industry
- Regulator

Evidence
- RCT, Obs

Conduits
- Social media
- Lay press
- Literature
- Guidelines
- Advertising
- Formulary
- Labels

Inputs
- Indication
- Feasibility
- Cost
- Preference

Local stakeholders
- Family
- Patient
- Clinician
- Consultant

Conduits:
- Evidence
- Social media
- Lay press
- Literature
- Guidelines
- Advertising
- Formulary
- Labels

Inputs:
- Indication
- Feasibility
- Cost
- Preference
Treatment Pathways

• Defining a pathway
  – What the clinician orders
  – What prescriptions the patient fills
  – What the patient takes
Network-based Research

• International network of researchers
  – Data holders
  – Standards developers
  – Methods developers
  – Clinical researchers

• Large-scale collaborative research
  – Larger sample sizes
  – More diverse population
  – Greater expertise
Open-source process

1. Join the collaborative
2. Propose a study to the open collaborative
3. Write protocol
4. Code it, run it locally, debug it (minimize others’ work)
5. Publish it: [https://github.com/ohdsi](https://github.com/ohdsi)
6. Each node voluntarily executes on their CDM
7. Centrally share results
8. Collaboratively explore results and jointly publish findings
OHDSI in action: Chronic disease treatment pathways

- Conceived at AMIA: 15Nov2014
- Protocol written, code written and tested at 2 sites: 30Nov2014
- Analysis submitted to OHDSI network: 2Dec2014
- Results submitted for 7 databases: 5Dec2014
## Condition definitions

<table>
<thead>
<tr>
<th>Disease</th>
<th>Medication classes</th>
<th>Diagnosis</th>
<th>Exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (“HTN”)</td>
<td>antihypertensives, diuretics, peripheral vasodilators, beta blocking agents, calcium channel blockers, agents acting on the renin-angiotensin system (all ATC)</td>
<td>hyperpiesis (SNOMED)</td>
<td>pregnancy observations (SNOMED)</td>
</tr>
<tr>
<td>Diabetes mellitus, Type 2 (“Diabetes”)</td>
<td>drugs used in diabetes (ATC), diabetic therapy (FDB)</td>
<td>diabetes mellitus (SNOMED)</td>
<td>pregnancy observations (SNOMED), type 1 diabetes mellitus (MedDRA)</td>
</tr>
<tr>
<td>Depression</td>
<td>antidepressants (ATC), antidepressants (FDB)</td>
<td>depressive disorder (SNOMED)</td>
<td>pregnancy observations (SNOMED), bipolar I disorder (SNOMED), schizophrenia (SNOMED)</td>
</tr>
</tbody>
</table>
# The American College of Physicians Guideline on Oral Medications for Type 2 Diabetes

<table>
<thead>
<tr>
<th>Disease or condition</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target audience</td>
<td>Internists, family physicians, other clinicians</td>
</tr>
<tr>
<td>Target patient population</td>
<td>Adults with type 2 diabetes</td>
</tr>
<tr>
<td>Interventions</td>
<td>Oral pharmacologic treatment for hyperglycemia in type 2 diabetes</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Hemoglobin A₁c levels</td>
</tr>
<tr>
<td>Cardiovascular morbidity and mortality</td>
<td>Weight</td>
</tr>
<tr>
<td>Cerebrovascular morbidity</td>
<td>Plasma lipid levels</td>
</tr>
<tr>
<td>Neuropathy, nephropathy, retinopathy</td>
<td>Adverse effects</td>
</tr>
<tr>
<td>Recommendations</td>
<td></td>
</tr>
<tr>
<td>Recommendation 1: ACP recommends that clinicians add oral pharmacologic therapy in patients diagnosed with type 2 diabetes when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia (Grade: strong recommendation; high-quality evidence).</td>
<td></td>
</tr>
<tr>
<td>Recommendation 2: ACP recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy to treat most patients with type 2 diabetes (Grade: strong recommendation; high-quality evidence).</td>
<td></td>
</tr>
<tr>
<td>Recommendation 3: ACP recommends that clinicians add a second agent to metformin to treat patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia (Grade: strong recommendation; high-quality evidence).</td>
<td></td>
</tr>
<tr>
<td>Clinical Considerations</td>
<td></td>
</tr>
<tr>
<td>Good management of type 2 diabetes with pharmacologic and nonpharmacologic therapies is important and includes patient education, evaluation, and self-management, for microvascular and macrovascular complications, treatment of hyperglycemia, and minimization of cardiovascular and other long-term risk factors.</td>
<td></td>
</tr>
<tr>
<td>Nonpharmacologic therapy includes dietary modifications, regular exercise, lifestyle modifications, and weight loss.</td>
<td></td>
</tr>
<tr>
<td>Initiation of pharmacologic therapy is an important approach for the effective management of type 2 diabetes when weight loss and/or lifestyle modification fails.</td>
<td></td>
</tr>
<tr>
<td>Metformin monotherapy was more effective in decreasing glycemic levels than other monotherapies, as well as in combination therapy with a second agent. In addition, metformin has the advantage of reducing body weight and improving plasma lipid profiles (in most cases).</td>
<td></td>
</tr>
<tr>
<td>Although combination therapy more effectively reduces hemoglobin A₁c levels, it is also associated with more adverse events.</td>
<td></td>
</tr>
</tbody>
</table>

1. Metformin
2. Second agent
Treatment pathway event flow

INDEX: First exposure

- >365 day of prior observation
- ≤ 0 exposures 365d before index

≥1 exposure 121d-240d after index
≥1 exposure 241d-360d after index
≥1 exposure 361d-480d after index
≥1 exposure 481d-600d after index
≥1 exposure 601d-720d after index
≥1 exposure 721d-840d after index
≥1 exposure 841d-960d after index
≥1 exposure 961d-1080d after index

>1095 days of observation post-exposure

≥1 condition occurrence of disease of interest between all time prior to index and all time after index

≤ 0 condition occurrence of any excluded diseases between all time prior to index and all time after index
Treatment Pathways in Chronic Disease

Objective: The objective of this study is to characterize the predictors of different treatment pathways for these chronic diseases: Hypertension, Type 2 Diabetes, and Depression. We will systematically examine the treatment pathways chosen by patients who have at least 3 years of continuous enrollment and presented treatment following admission. We will use the results from this study to evaluate temporal trends, and will further modify by data source to determine if treatment pathways vary by population, geography, and data capture process.

Adverse Events: While surveillance treatment guidelines exist for disease conditions, there is a paucity of data on the real-world treatment pathways that patients experience in practice. Understanding these pathways is essential for establishing context specific guidelines of drug initiation, effectiveness, and adherence.

Project Leads: [Names]

Coordinating Institution: [Institution Name]

Additional Participants:

Initial Proposal Date: [Date]

Launch Date: [Date]

Studv Change Date: [Date]

Final Study Date: [Date]

Requirements

- [List of requirements]

Code

- [List of code]

Discussion

Databases Run

- [List of databases]

References

- [List of references]
## OHDSI participating data partners

<table>
<thead>
<tr>
<th>Code</th>
<th>Name</th>
<th>Description</th>
<th>Size (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUSOM</td>
<td>Ajou University School of Medicine</td>
<td>South Korea; inpatient hospital EHR</td>
<td>2</td>
</tr>
<tr>
<td>CCAE</td>
<td>MarketScan Commercial Claims and Encounters</td>
<td>US private-payer claims</td>
<td>119</td>
</tr>
<tr>
<td>CPRD</td>
<td>UK Clinical Practice Research Datalink</td>
<td>UK; EHR from general practice</td>
<td>11</td>
</tr>
<tr>
<td>CUMC</td>
<td>Columbia University Medical Center</td>
<td>US; inpatient EHR</td>
<td>4</td>
</tr>
<tr>
<td>GE</td>
<td>GE Centricity</td>
<td>US; outpatient EHR</td>
<td>33</td>
</tr>
<tr>
<td>INPC</td>
<td>Regenstrief Institute, Indiana Network for Patient Care</td>
<td>US; integrated health exchange</td>
<td>15</td>
</tr>
<tr>
<td>JMDC</td>
<td>Japan Medical Data Center</td>
<td>Japan; private-payer claims</td>
<td>3</td>
</tr>
<tr>
<td>MDCD</td>
<td>MarketScan Medicaid Multi-State</td>
<td>US; public-payer claims</td>
<td>17</td>
</tr>
<tr>
<td>MDCR</td>
<td>MarketScan Medicare Supplemental and Coordination of Benefits</td>
<td>US; private and public-payer claims</td>
<td>9</td>
</tr>
<tr>
<td>OPTUM</td>
<td>Optum ClinFormatics</td>
<td>US; private-payer claims</td>
<td>40</td>
</tr>
<tr>
<td>STRIDE</td>
<td>Stanford Translational Research Integrated Database Environment</td>
<td>US; inpatient EHR</td>
<td>2</td>
</tr>
<tr>
<td>HKU</td>
<td>Hong Kong University</td>
<td>Hong Kong; EHR</td>
<td>1</td>
</tr>
</tbody>
</table>
Strict criteria

- 250,000,000+ patient records to start
- 4 years continuous observation
- (first treatment for disease)
- 3 years continuous treatment
- 327,110 type 2 diabetes mellitus
- 1,182,792 hypertension
- 264,841 depression

- Sequential and simultaneous are mixed
Publication in revision

• Submitted for publication
  – Policy of open sharing pre-publication
  – Will share more details on publication
Comments

• Will see a day when funding an RCT requires an extensive observational study
  – Characterization

• Future work
  – Causal assessment
  – Foundation for interpreting trials
<table>
<thead>
<tr>
<th>Collaborators</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>George Hripcsak</td>
<td>Columbia University Medical Center, New York, NY, USA</td>
</tr>
<tr>
<td>Patrick B Ryan</td>
<td>Janssen Research &amp; Development, LLC, Titusville, NJ, USA</td>
</tr>
<tr>
<td>Jon D Duke</td>
<td>Regenstrief Institute, Indianapolis, IN, USA</td>
</tr>
<tr>
<td>Nigam H Shah</td>
<td>Stanford University, CA, USA</td>
</tr>
<tr>
<td>Rae Woong Park</td>
<td>Ajou University School of Medicine, Suwon, Republic of Korea</td>
</tr>
<tr>
<td>Vojtech Huser</td>
<td>NIH Clinical Center, Bethesda, MD, USA</td>
</tr>
<tr>
<td>Marc A Suchard</td>
<td>David Geffen School of Medicine, Uni. of California, Los Angeles, CA, USA</td>
</tr>
<tr>
<td>Martijn J Schuemie</td>
<td>University of Hong Kong, Hong Kong; Janssen Research &amp; Development, LLC, Titusville, NJ, USA</td>
</tr>
<tr>
<td>Frank DeFalco</td>
<td>Janssen Research &amp; Development, LLC, Titusville, NJ, USA</td>
</tr>
<tr>
<td>Adler Perotte</td>
<td>Columbia University Medical Center, New York, NY, USA</td>
</tr>
<tr>
<td>Juan Banda</td>
<td>Stanford University, CA, USA</td>
</tr>
<tr>
<td>Christian G Reich</td>
<td>AstraZeneca PLC, Waltham, MA, USA</td>
</tr>
<tr>
<td>Lisa Schilling</td>
<td>University of Colorado School of Medicine, Aurora, CO, USA</td>
</tr>
<tr>
<td>Michael Matheny</td>
<td>Tennessee Valley Healthcare System VA, Nashville, TN, USA</td>
</tr>
<tr>
<td>Daniella Meeker</td>
<td>University of Southern California, Los Angeles, CA</td>
</tr>
<tr>
<td>Nicole Pratt</td>
<td>University of South Australia, Australia</td>
</tr>
<tr>
<td>David Madigan</td>
<td>Columbia University, New York, NY, USA</td>
</tr>
</tbody>
</table>