Personalized Evidence Based Medicine: Predictive Approaches to Heterogeneous Treatment Effects (HTE)
Limitations of RCTs for Clinical Decision Making
While RCTs can determine the better treatment on average, they “do not answer the practicing doctor's question: what is the most likely outcome when this particular drug is given to a particular patient?”

- Austin Bradford Hill
Evidence Based Medicine

- Hill was wrong.
- RCTs should be used by doctors to determine what’s best for individual patients.
- “Evidence based medicine is the conscientious, explicit, judicious and reasonable use of current best evidence in making decisions about the care of individual patients.”
- EBM proposed to repurpose RCTs from tools to establish causation into tools for prediction in single cases.
Single Case Prediction: Two distinct approaches

- **Inside view:**
  - focuses on the specifics of a case and weighs many characteristics that make it unique.
  - the view of traditional physicians (i.e. pre-EBM) and the view we spontaneously adopt for many decisions in virtually all aspects of life.

- **Outside view:**
  - predicts by explicitly identifying a group of similar cases (i.e. a “reference class”) by ignoring particulars;
  - the reference class provides a statistical basis for prediction.
The practice of EBM relies on making inferences for single cases (individual patients) based on the frequency of outcomes (or treatment effects) in a reference class to which the individual of interest is similar.

But how does one define similarity?
Mathematician John Venn pointed out in 1876 "every single thing or event has an indefinite number of properties or attributes observable in it, and might therefore be considered as belonging to an indefinite number of different classes of things".

Alternative methods of classifying will lead to different inferences for a patient.
The standard EBM approach

- To emphasize the broadest possible reference class, the overall effect in a randomized clinical trial (RCT).
- “if the patient meets all the inclusion criteria, and doesn’t violate any of the exclusion criteria—there is little question that the results are applicable.”

*User’s Guide to the Medical Literature II*
Another approach: Reichenbach

- recommended calibration to 'the narrowest reference class for which reliable statistics can be compiled'.

- The reference class problem is a model selection problem.
Why Risk Based Subgroup Analysis Should be Routine

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Why privilege risk-based HTE analysis?

- Risk is a known mathematical determinant of treatment effect.
### Risk Reduction (RR)

<table>
<thead>
<tr>
<th>Absolute RR</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>EER - CER</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Relative RR</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>1 - (\frac{EER}{CER})</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\frac{EER}{1-EER}) (\frac{CER}{1-CER})</td>
<td></td>
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</tbody>
</table>

\(CER = \text{control event rate}\)

\(EER = \text{experimental event rate}\)
Figure 1: Distribution of Mortality Risk with Thrombolytic Therapy in Patients with Acute Myocardial Infarction

Figure 1: Distribution of Mortality Risk with Thrombolytic Therapy in Patients with Acute Myocardial Infarction

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Predicted risk distributions in RCTs

Relative risk reduction across risk quartiles

Treatment effect heterogeneity on the proportional scale across patients at different baseline risk was rare
Substantial differences in absolute treatment effects were common.

Displaying results across subgroups defined by risk is feasible and can lead to clinically important findings.
Participants: 3060 nondiabetic persons with evidence of impaired glucose metabolism.

Intervention: Intervention groups received metformin or a lifestyle-modification program.

Main Outcome Measure: Development of diabetes

The DPP study was conducted by the DPP Investigators and supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).
DPP Risk Stratified Results

**Lifestyle**

- $p$ value = NS

**Metformin**

- $p$ value = 0.0008

DPP Risk Stratified Results

Digitalis Investigator Group (DIG) Study

- **Participants:** Participants with HF and LVEF less than or equal to 45% (main DIG study, n=6800) or LVEF >45% (ancillary DIG study, n=988).

- **Intervention:** digoxin versus placebo

- **Main Outcome Measure:** Hospitalization due to worsening HF, all cause hospitalization

DIG Risk Stratified Results

Heart failure hospitalization

Odds ratio

Absolute risk reduction (%)

Risk quartile

DIG Risk Stratified Results

Hospitalizations per person year

Risk ratio

Absolute risk reduction (%)

Risk quartile

National Lung Screening (NLST) Trial

- **Participants**: Smokers between the ages of 55 and 74 years with a minimum of 30 pack-years of smoking and no more than 15 years since quitting
- **Intervention**: Low-dose CT screening or chest radiography
- **Main Outcome Measure**: Lung-cancer deaths

NLST Risk Stratified Results

A Lung-Cancer Mortality Ratio, for Low-Dose CT versus Radiography

\[ P=0.80 \text{ for trend} \]

B Lung-Cancer Deaths Prevented by Low-Dose CT

\[ P=0.01 \text{ for trend} \]

Lung-Cancer Death

- 5-yr risk

Lung-Cancer Risk

- Bach 2003
- LLP 2008
- Spitz 2007
- Tammemagi 2011

Risk based analyses can reveal counter-intuitive findings

- Overall effectiveness results may be driven by a relatively small group of influential (typically high risk) patients;
- The typical (median) risk patient is frequently at considerably lower risk than the overall average;
- The average benefit seen in the summary result often over estimates the benefit (on the RD scale) in most patients (and may obscure harm in many).
Risk based subgrouping is often clinically informative and usually feasible.
### Clinical Conditions where Outcome Risk is Major Determinant of Clinically-Relevant HTE

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Intervention</th>
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<tbody>
<tr>
<td>Symptomatic carotid stenosis</td>
<td>Carotid endarterectomy</td>
</tr>
<tr>
<td>Non-valvular atrial fibrillation</td>
<td>Anticoagulation for primary prevention of stroke</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Coronary artery bypass grafting</td>
</tr>
</tbody>
</table>
| Primary prevention of coronary artery disease | Blood pressure lowering  
Aspirin  
Lipid lowering |
| Acute coronary syndromes                   | Early invasive strategy (versus conservative)  
Clopidogrel (versus placebo)  
Enaxparin (versus unfractionated heparin) |
| ST-Elevation acute myocardial infarction   | tPA (versus streptokinase)  
Percutaneous coronary intervention (versus thrombolytic therapy) |
| Severe sepsis                              | Drotrecogin alfa (activated protein C)                                        |
| Pre-diabetes                               | Lifestyle intervention  
Metformin                                                                         |
| Tobacco smoking                            | Lung cancer screening                                                         |

Caveats

- Outcome risk is not the “ideal” subgrouping variable.
- Ideally, we would model outcome risk with *versus* without therapy, incorporating all important treatment effect interactions.
- Risk-based subgrouping can be done “blinded” to treatment assignment and thus avoids the problems of more “data driven” predictive approaches.
Acknowledgements

- James Burke
- Issa Dahabreh
- Rod Hayward
- John Ioannidis
- David van Klaveren
- Jason Nelson
- Jess Paulus
- Peter Rothwell
- Robin Ruthazer
- Harry Selker
- Ewout Steyerberg
- Jeremy Sussman
This conference is funded through two Patient-Centered Outcomes Research Institute (PCORI) Awards: a Patient-Centered Outcomes Research Institute (PCORI) Eugene Washington PCORI Engagement Award (1900-TMC) and the Predictive Analytics Resource Center (SA.Tufts.PARC.OCSCO.2018.01.25).