Assessing and Reporting Heterogeneity of Treatment Effect in Clinical Trials

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November 1, 2017
Background

• Person-level heterogeneity of treatment effects (HTE) is ubiquitous.

• Group-level HTE is rarely reliably identifiable in clinical trials.
Problems with conventional subgroup analysis

- Patients have too many attributes
- Low power
Why privilege risk-based HTE analysis?

- Risk is a known mathematical determinant of treatment effect.
Common measures of treatment effect

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

CER = control event rate  
EER = experimental event rate
Why privilege risk-based HTE analysis?

• Risk is a known mathematical determinant of treatment effect.

• When baseline risk heterogeneity is present (and the treatment effect is non-zero), there is always HTE.

• Risk provides a summary measure that takes into account multiple variables that are relevant and provides “patient-centered” evidence.
Figure 1: Distribution of Mortality Risk with Thrombolytic Therapy in Patients with Acute Myocardial Infarction

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DANAMI-2

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.
Absolute risk reduction across risk quartiles

- Substantial differences in absolute treatment effects were common.
- Displaying results across subgroups defined by risk is feasible and can lead to clinically important findings.
Diabetes Prevention Program (DPP) Randomized Controlled Trial

- **Participants**: 3060 non-diabetic 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: Hazard Ratios

- **Lifestyle**
  - Hazard Ratio vs Risk Quartile
  - p-value = not statistically significant

- **Metformin**
  - Hazard Ratio vs Risk Quartile
  - p-value = 0.0008
DPP Risk Stratified Results: Absolute Risk
Improving Diabetes Prevention with Benefit-Based Tailored Treatment

• Making the risk model available at the point of care
  - Stakeholder partners:
    - AMGA (formerly American Medical Group Association)
  - Project teams:
    - Mercy (St. Louis) – 3,000 providers
    - Premier Medical Associates (Pittsburgh) – 100 providers

• Incorporating EHR-compatible model
  - Epic (Mercy)
  - Allscripts (Premier)
Redevelopment of DPP risk model in EHR

- Model developed and geographically validated in OptumLabs
- Risk factors: age, gender, race, ethnicity, height, BMI, smoking status, hypertension, A1c, FPG, triglycerides, HDL, SBP

development
\[ n = 1,076,983 \]
\[ c\text{-statistic} = 0.735 \]
\[ E = 0.92\% \]
\[ E90 = 2.25\% \]

validation
\[ n = 1,075,833 \]
\[ c\text{-statistic} = 0.763 \]
\[ E = 1.48\% \]
\[ E90 = 1.73\% \]
**HIGH RISK PATIENT**

Predicted Risk of Type 2 Diabetes at 3 Years
- 50.0% Usual Care
- 40.0% Metformin, NNT = 10.0
- **21.0% DPP-Lifestyle, NNT = 3.4**

*NNT = Number Needed to Treat*
Questions?
Thank You!

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