Transporting DPP model to EHR environment

June 12, 2019
Transporting DPP model to EHR

- Define population cohort
- Develop risk model using EHR compatible variables
- Re-estimate risk predications using DPP placebo arm
- Correct for over-optimism
- Estimate risk-specific DPP treatment effects
  - Lifestyle
  - Metformin
Eligibility Criteria

- Index office visit between 1/1/2012 and 12/31/2016
- Age 25-75
- Pre-diabetes (within 12 months)
  - A1C: 5.7-6.4%
  - Fasting glucose (or glucose measured on same day as lipid panel): 100-125 mg/dL
- No prior evidence of diabetes (outcome criteria)
- Exclude women pregnant within 24 months of index visit

Outcome criteria

- Diabetes:
  - Diagnosis: ICD-09 250.* / ICD-10 E10.* or E11.*
  - Diabetes related pharmacotherapy or procedure (ie HEDIS criteria)
  - A1C: greater than 6.4
  - Fasting glucose (or glucose measured on same day as lipid panel): greater than 125 mg/dL
  - Random glucose >=200 mg/dL on 2 occasions (within 3 months of each other)
  - 2 hour glucose > 199 mg/dL
  - Labs require confirmation by HEDIS criteria or additional lab
Figure 2. Cumulative Incidence of Diabetes According to Study Group.

3-year outcome rate ~ 8%
## A priori model risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OptumLabs EHR (12 month assessment period)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>difference between year of birth and year of index office visit</td>
</tr>
<tr>
<td>Gender</td>
<td>female, male</td>
</tr>
<tr>
<td>Race</td>
<td>AA, Caucasian, Asian, other/unknown</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Hispanic, not Hispanic, unknown</td>
</tr>
<tr>
<td>Smoking status</td>
<td>current, never, previously, other, unknown</td>
</tr>
<tr>
<td>Height</td>
<td>inches, cm</td>
</tr>
<tr>
<td>BMI</td>
<td>structured field and calculate from height and weight</td>
</tr>
<tr>
<td>Hypertension</td>
<td>diagnosis</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>mm HG</td>
</tr>
<tr>
<td>HDL</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>mg/dL (use random if done same day as lipid panel)</td>
</tr>
<tr>
<td>A1c</td>
<td>%</td>
</tr>
<tr>
<td>Physical activity (met-hours per week)</td>
<td>no structured data available</td>
</tr>
<tr>
<td>Waist</td>
<td>no structured data available</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>no structured data available</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>no structured data available</td>
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### Risk model development

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age, 10 years</td>
<td>1.08</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>1.21</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>AA vs White</td>
<td>2.73</td>
<td>0.0069</td>
</tr>
<tr>
<td>Asian vs White</td>
<td>0.01</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Race(missing) vs White</td>
<td>0.16</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Current smoker vs ever</td>
<td>1.22</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Former smoker vs never</td>
<td>1.11</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Smoking(missing) vs never</td>
<td>1.08</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HTN</td>
<td>1.23</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>A1c, 0.1%</td>
<td>1.24</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>A1c(missing)</td>
<td>0.75</td>
<td>&lt; 0.0001</td>
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<tr>
<td>FPG, 10 mg/dL</td>
<td>1.29</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>FPG(missing)</td>
<td>1.03</td>
<td>0.2058</td>
</tr>
<tr>
<td>Triglycerides, 10 mg/dL</td>
<td>1.01</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Triglycerides(missing)</td>
<td>1.08</td>
<td>0.0010</td>
</tr>
<tr>
<td>BMI, 5 units</td>
<td>1.24</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>BMI(missing)</td>
<td>1.22</td>
<td>&lt; 0.0001</td>
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<tr>
<td>SBP, 10 mmHg</td>
<td>1.03</td>
<td>&lt; 0.0001</td>
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<td>SBP(missing)</td>
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<td>&lt; 0.0001</td>
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<td>HDL, 10 mg/dL</td>
<td>0.85</td>
<td>&lt; 0.0001</td>
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<tr>
<td>HDL(missing)</td>
<td>1.23</td>
<td>&lt; 0.0001</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Interaction effects for BMI, 5 unit</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1.24</td>
</tr>
<tr>
<td>Black</td>
<td>1.15</td>
</tr>
<tr>
<td>Asian</td>
<td>1.25</td>
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</table>

<table>
<thead>
<tr>
<th>Interaction effects for A1c, 0.1%</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1.24</td>
</tr>
<tr>
<td>Black</td>
<td>1.23</td>
</tr>
<tr>
<td>Asian</td>
<td>1.34</td>
</tr>
</tbody>
</table>

Development c-statistic = 0.73
Validation c-statistic (DPP placebo) = 0.69
Risk-specific treatment effect estimation

- Assess HTE applying Optum model to DPP
- Risk-by-treatment interaction
  - Lifestyle interaction p-value = 0.69
  - Metformin interaction p-value = 0.07

- Refit Optum model using DPP placebo arm
  - c-statistic = 0.75
  - Optimism corrected c-statistic = 0.74
  - Uniform shrinkage factor = 0.897
Risk stratified treatment effects

<table>
<thead>
<tr>
<th></th>
<th>Metformin</th>
<th>HR</th>
<th>L95</th>
<th>U95</th>
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<tbody>
<tr>
<td>Q1</td>
<td>1.00</td>
<td>0.55</td>
<td>1.84</td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>0.99</td>
<td>0.64</td>
<td>1.53</td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td>0.92</td>
<td>0.63</td>
<td>1.34</td>
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</tr>
<tr>
<td>Q4</td>
<td>0.42</td>
<td>0.32</td>
<td>0.55</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Lifestyle</th>
<th>HR</th>
<th>L95</th>
<th>U95</th>
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</thead>
<tbody>
<tr>
<td>Q1</td>
<td>0.46</td>
<td>0.22</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>0.50</td>
<td>0.30</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td>0.53</td>
<td>0.34</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td>0.33</td>
<td>0.25</td>
<td>0.45</td>
<td></td>
</tr>
</tbody>
</table>

Truncated effect at 60% relative risk reduction
Heterogeneity of treatment effect

- Not every participant in a clinical trial gains the same benefit
- Yet we tend to ascribe the *average* treatment effect to everyone who would have qualified for the trial
- Risk-based analysis → prioritize intervention

Translation initiative in progress

- Re-analysis of the Diabetes Prevention Program Study allows us to identify those most likely to benefit from the interventions studied
- Currently implementing this risk model in the EHRs of two large ambulatory practices
Rationale for Risk-Based Analysis

- Conventional subgroup analysis seldom yields insights useful in clinical practice
  - Patients have many attributes—breaking down the study population, one-variable-at-a-time, doesn’t describe any individual patient
  - Low statistical power

- Risk-based analysis provides a summary measure that takes into account multiple relevant variables and provides “patient-centered” evidence
Distribution of Mortality Risk with Thrombolytic Therapy in Patients with Acute Myocardial Infarction

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

Average Mortality Risk

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

DANAMI-2

Predicted risk distributions in RCTs

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 an intensive lifestyle-modification program
- Main outcome measure: Development of diabetes over 3 years
- The DPP study was conducted by 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 Reduction

All four quartiles achieve some benefit from the DPP intensive lifestyle intervention
Making the risk model available at the point of care

- 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)
Redevelop DPP Risk Model using Typical EHR Data: OLDW

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

development
\[ n = 1,076,983 \]
\[ c \text{-statistic} = 0.735 \]
\[ E = 0.92\% \]
\[ E_{90} = 2.25\% \]

validation
\[ n = 1,075,833 \]
\[ c \text{-statistic} = 0.763 \]
\[ E = 1.48\% \]
\[ E_{90} = 1.73\% \]
Need for Risk Stratification

- Together 2 Goal® – AMGA Foundation campaign to improve care for 1 million people with type 2 diabetes
  - 150 AMGA member organizations
  - Results after 1 year: 600,000 people

- Practice-based screening is a key campaign “plank”
  - 1 out of 4 people with type 2 diabetes doesn’t know they have it
  - 75% of adults are eligible for screening (ADA)
  - Most provider organizations are screening barely half of those eligible
    - Best performance is screening 75% of those eligible
  - One-third of T2G participants are not focusing on improving screening
    - Already “overwhelmed” by number of people with pre-diabetes
Patients with pre-diabetes want a number

- Ages when family members developed type 2 diabetes
- A1c or fasting glucose – but in the DPP study,
  - Highest-risk quartile: 25% had A1c < 6.0
  - Lowest-risk quartile: 15% had A1c ≥ 6.0

Providers want guidance for shared decision-making

- Multivariate model can be more informative than any single lab result
- Multiple display modes:
  - “Accompaniment” to A1c or fasting glucose indicating pre-diabetes
  - Alert – fires no more than once for a new screening result indicating pre-diabetes

Pre-diabetes: A1c 5.7 – 6.4
**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
Translational Research: Evaluation → Spread to Practice

- Implement in EHRs
- Small-scale trial at each organization
- Refine design
- Broader implementation within each organization
  - 6 month trial
- Follow-up questionnaire: RE-AIM framework
  - Patients
  - Providers
- Spread to other AMGA members participating in T2G

PCORI-funded study of HTE (re-analyze RCTs) → PCORI-funded D&I study (dissemination and implementation)

REACH
- Effectiveness
- Adoption
- Implementation
- Maintenance
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All statements in this presentation, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee.
Thank You!

David M. Kent, MD, MS
Director, Predictive Analytics and Comparative Effectiveness (PACE) Center
Tufts Medical Center
dkent1@tuftsmmedicalcenter.org

John Cuddeback, MD, PhD
Chief Medical Informatics Officer
AMGA
jcuddeback@amga.org