Heterogeneity of Treatment Effect

*We tend to assume that anyone who would have qualified for a clinical trial will experience the average treatment effect seen in the trial.*

But in most trials, some patients benefit, and some don’t—heterogeneity of treatment effect.

Can we predict, using information available at the beginning of the trial, the likelihood that an individual patient will benefit?

Population perspective → Can we risk-stratify?

From the outset, some patients are at higher risk of the outcome—heterogeneity of baseline risk.

Likelihood of benefit from an intervention depends on individual’s baseline risk for the outcome.
Predicted Risk Distribution in DPP Study

Includes all participants in the DPP Study—placebo arm, plus both intervention arms.
Predicted Risk Distributions in 36 Clinical Trials
Absolute Risk Reduction Seen in DPP Study

Intensive Lifestyle Intervention

Metformin

Average: 14.2
Average: 28.3
Average: 7.1
Average: 21.4

Risk Group

Risk Group

From the predictive model

http://www.pcori.org/research-in-action/moving-beyond-averages
Re-develop Risk Model using Typical EHR Data

Model from DPP Study Data
- HbA1c
- Fasting glucose
- Triglycerides
- History of elevated glucose
- Height
- Waist circumference
- Waist:hip ratio

Average risk in placebo arm 30.2%

Adapted Model for Use in EHR
- HbA1c
- Fasting glucose
- Triglycerides
- Age
- Gender
- Race
- BMI
- Smoking status
- Systolic blood pressure
- Hypertension diagnosis
- HDL cholesterol (“good cholesterol”)

Average baseline risk 7.04%

Reflects tests currently used to detect prediabetes and diabetes
Accommodates missing data (imputed values for most model data elements)

Longitudinal data for over 2 million people with prediabetes
Use Model to Apply Learning from DPP Study in Current Practice

• Confirm that new EHR-based model works...
  – On a separate dataset representing current EHR data
  – On the placebo arm of the DPP Study (all the new variables were measured in the DPP Study)

• Then, for people with prediabetes, use this model to estimate their individual risk of developing type 2 diabetes over 3 years

  Multivariable model is a better predictor than any single parameter:
  In the lowest-risk quartile, about 15% of patients have A1c ≥ 6.0
  In the highest-risk quartile, more than 25% of patients have A1c < 6.0

• Apply risk-specific estimates of the effects of the two interventions in the DPP Study
  – Consistent benefit for the lifestyle program (58% relative risk reduction, across all levels of risk)
  – Benefit from taking metformin is concentrated in high-risk individuals
Premier Medical Associates

- Eastern suburbs of Pittsburgh, PA
- Formed 1993
- ~100 providers
- Part of Highmark Health–Allegheny Health Network (Integrated Delivery and Financing System)

IDFS – Integrated Delivery and Financing System
Intensive Lifestyle Intervention

- DPP Programs are Resource-Intensive
  - 16 core sessions: one-to-one, in person
  - 2 monthly maintenance phone contacts
  - Exercise facilities at no extra cost

- For every 1 kg of weight loss, diabetes incidence drops by 16 percent.
Utilization Savings

✓ CMS Office of the Actuary estimates $2,650 in net cost savings for a Medicare beneficiary over 15 months, by participating in a DPP

✓ Intermountain: Avoiding or delaying progression to diabetes saves Intermountain’s Health Plan $3,500 per patient per year

✓ DPP participation costs about $600

Data retrieved from EHR, displayed in the EHR for validation and editing by the clinician, at Premier Medical Associates

eCalcs add-in for Allscripts TouchWorks EHR

Galen Healthcare Solutions

Premier Medical Associates

<tufts dpp risk estimator v20180418>

- Sex: Female
- Race: Black
- Smoking Status: Former Smoker
- Hypertension: True

Height: 64 in
Weight: 160 lb

BMI: 27.46 kg/m²
Systolic Blood Pressure: 138 mmHg
HDL Cholesterol: 38 mg/dL
Triglycerides: 160 mg/dL
A1C: 6.2 %
Fasting Blood Glucose: 118 mg/dL

Drawn in same timeframe as fasting labs, so assumed to be a fasting blood glucose.
Predictive model results, as displayed in the EHR for shared decision-making, at Premier Medical Associates

Note: This example was prior to recalibration of the model for current EHR data (OptumLabs)
## PMA Experience—Reach of Project

<table>
<thead>
<tr>
<th></th>
<th>5/1/18 – 8/31/19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total prediabetes</td>
<td>2,518</td>
</tr>
<tr>
<td>Calculation completed</td>
<td>1,881</td>
</tr>
<tr>
<td>Percent with calculation</td>
<td>74.7%</td>
</tr>
</tbody>
</table>
## Interventions vs. Risk

<table>
<thead>
<tr>
<th>Risk stratification</th>
<th>Intervention ordered</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>75.2%</td>
</tr>
<tr>
<td>Medium risk</td>
<td>20.6%</td>
</tr>
<tr>
<td>Low risk</td>
<td>7.3%</td>
</tr>
</tbody>
</table>

During the 15 months, 97 patients were identified as having diabetes, through timely screening.
Provider Surveys: How confident are you in your ability to estimate the average risk of diabetes progression for your patients with prediabetes?
Personalized Risk Estimates at the Point of Care

Two approaches to implementing the model in the EHR:

Build predictive model into EHR — Premier Medical Associates

- Calculator add-in for Allscripts TouchWorks: Galen eCalcs
- Provider needs to access the calculator, but eCalcs obtains data elements from patient’s record and displays them for validation or editing

“Subscribe” to a cloud-hosted SMART app, using FHIR resources — Mercy

- Emerging EHR interoperability standards—Office of the National Coordinator for Health IT (ONC)
- EHR vendors are exposing data elements as “FHIR resources” and enabling integration of cloud-hosted apps
- CDS Hooks can trigger the calculation automatically, upon opening a patient’s record or posting a lab result that suggests prediabetes
- EHR vendors charge a small transaction fee, each time the model is used

EHR — Electronic health record (Premier uses Allscripts, with Galen eCalcs; Mercy uses Epic)
SMART — Substitutable Medical Apps and Reusable Technology
FHIR — Fast Healthcare Interoperability Resources, an HL7 standard
CDS Hooks — Clinical Decision Support Hooks
SMART App

Cloud-hosted SMART app implemented in Epic at Mercy

This is the Clinician View, showing data values retrieved for this patient from the EHR, for validation/editing

Model results are displayed at the top of the screen
SMART App

Cloud-hosted SMART app implemented in Epic at Mercy

This is the Clinician View, showing data values retrieved for this patient from the EHR, for validation/editing

Model results are displayed at the top of the screen

DPP lifestyle intervention yields a 7.3% absolute reduction in risk of diabetes at 3 years, from 12.7% to 5.4%, which corresponds to an NNT of 14

For this intermediate-risk patient, taking metformin yields only a 1.5% absolute reduction in risk, from 12.7% to 11.2%, which corresponds to an NNT of 57
SMART App

Cloud-hosted SMART app implemented in Epic at Mercy

This is the Clinician View, showing data values retrieved for this patient from the EHR, for validation/editing

Model results are displayed at the top of the screen

Changing Smoking Status to Current increases baseline risk to 14.2%, placing this patient into the high-risk group (top quartile of risk)
SMART App

Cloud-hosted SMART app implemented in Epic at Mercy

This is the Clinician View, showing data values retrieved for this patient from the EHR, for validation/editing.

Model results are displayed at the top of the screen.

Changing Smoking Status to Current increases baseline risk to 14.2%, placing this patient into the high-risk group (top quartile of risk).

Acknowledging a Diagnosis of Hypertension (even though it isn’t yet on the patient’s problem list in the EHR) further increases baseline risk to 17.2%.
SMART App

Cloud-hosted SMART app implemented in Epic at Mercy

This is the Clinician View, showing data values retrieved for this patient from the EHR, for validation/editing

Model results are displayed at the top of the screen

Now, DPP lifestyle intervention yields a 10.0% absolute reduction in risk of diabetes at 3 years, from 17.2% to 7.2%, which corresponds to an NNT of 11

At this higher level of baseline risk, taking metformin yields a 4.0% absolute reduction in risk, from 17.2% to 13.2%, which corresponds to an NNT of 27
SMART App

This is the Patient View tab, displaying model results graphically, at the top of the screen.

There are sliders and radio buttons only for attributes that the patient might target changing, to explore “what-if” scenarios.

The next slide illustrates a discussion about reducing the patient’s risk by quitting smoking, losing weight, and improving blood pressure control.
SMART App

Adjustments to model parameters:
• Former smoker instead of current
• 7% weight loss (Δ BMI from 29 to 27)
• Systolic blood pressure 125 mmHg, rather than 135

But... Interpretation is important:

The updated model values correspond to putting the patient into a group of people with a different baseline risk (and also a different estimated benefit from the DPP).

They do NOT reflect the prospective effect on the risk of diabetes if the patient were to make a change (e.g., quitting smoking, losing weight, or lowering blood pressure). That has not been studied.
These three changes yield a lower estimate of baseline risk, from 17.2% to 14.7%.

But recall that with the initial parameters, the DPP lifestyle intervention lowered the patient’s risk from 17.2% to 7.2%.

In most cases, the estimated benefit of the DPP lifestyle program substantially exceeds the reduction in baseline risk corresponding to the changes in parameters (e.g., quitting smoking, losing weight, and lowering BP) that are typically achieved by participating in the program.

This may reflect the value of nutrition education, emphasis on exercise, and group activities. For the DPP lifestyle program, the whole is more than the sum of its parts.