Evaluating treatment benefit predictors using observational data from a COPD cohort

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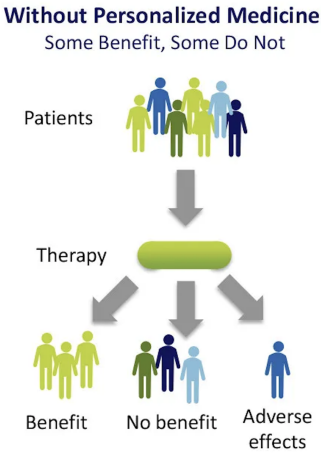
Background

Tailored treatment decisions



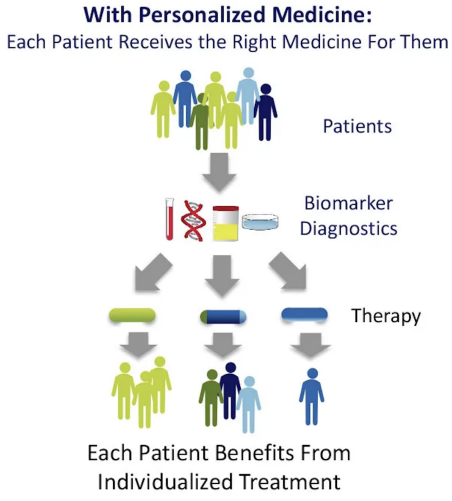
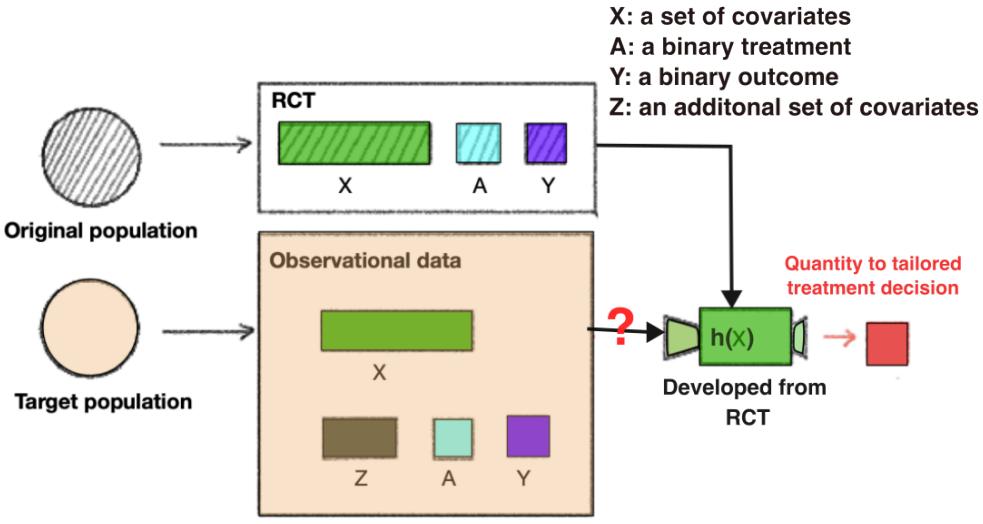


Image credit: Bayer Healthcare, "Personalized Medicine."

Problem setup



Treatment benefit

Treatment benefits

Hypothetically, each individual in the target population can be described by $(Y(0), Y(1), A, X, Z) \sim \mathbb{P}$, and define:

$$\begin{aligned} \text{Individual treatment benefit:} \quad & B = Y(0) - Y(1), \\ \text{(Subgroup) treatment benefit:} \quad & \tau_0(x) = \mathbb{E}[B \mid X = x], \\ \text{(Smaller subgroup) treatment benefit:} \quad & \tau(x, z) = \mathbb{E}[B \mid X = x, Z = z]. \end{aligned}$$

Assumptions

- No interference: Potiental outcome $Y(a)$ of an individual does not depend on what treatment other patient receive.
- Consistency: $Y = Y(1)A + Y(0)(1 - A)$.
- Unconfoundedness: $Y(1), Y(0) \perp\!\!\!\perp A \mid X, Z$.

Treatment benefit predictor

Treatment benefit predictor

A treatment benefit predictor (TBP) is any function $h(x)$ such that

$$h : \mathcal{X} \to \mathbb{R} \text{ that aims to approximate } \tau_0(x) := \mathbb{E}[B \mid X = x],$$

where $X \in \mathcal{X}$. We denote the treatment benefit prediction as $H := h(X)$.

How to evaluate a pre-specified TBP on the target population $(Y, A, X, Z) \sim \mathbb{P}_{obs}$, using observational data?

Predictive performance metrics

Predictive performance metrics

Moderate calibration curve

For a given TBP, $h(x)$, if $\mathbb{E}[B \mid H = h] = h$, it is moderately calibrated. The estimand of moderate calibration curve for $h(x)$ is

$$\mathbb{E}[B \mid H = h] = \mathbb{E}[\tau(X, Z) \mid H = h].$$

How to estimate a specific estimand, describing the predictive performance of $h(x)$?

1. Estimate $\mathbb{E}[Y \mid A = a, X = x, Z = z]$.
2. Predict $\tau(x, z) = \hat{\mathbb{E}}[Y \mid A = 0, X = x, Z = z] - \hat{\mathbb{E}}[Y \mid A = 1, X = x, Z = z]$.
3. Estimate the specific estimand.

Bayesian additive regression tree

We use Bayesian additive regression tree (BART) to estimate $\mathbb{E}[Y \mid A = a, X = x, Z = z]$ and then predict $\tau(x, z)$.

Why BART?

- BART allow us to draw samples $\tau_j^*,\ j = 1, \cdots, D$ from posterior distribution of $\tau(X, Z)$.
- With the second stage estimation, we can draw samples from posterior distribution of $\mathbb{E}[\hat{\tau}(X, Z) \mid H = h]$ for each h.

1. Estimate $\mathbb{E}[Y \mid A = a, X = x, Z = z]$

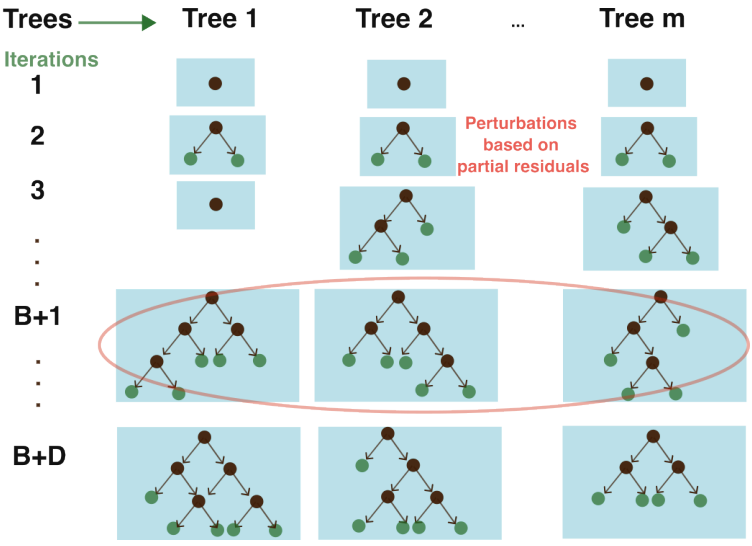
Bayesian additive regression tree

Bayesian additive regression tree (BART) is an ensemble of regression trees in a Bayesian framework. Let $Y^* = \sum_{j=1}^{m} g(a, x, z; T_j, M_j) + \varepsilon$ and $Y = I(Y^* > 0)$, then

$$\mathbb{E}[Y \mid A = a, X = x, Z = z] = \Phi\left(\sum_{j=1}^{m} g(a, x, z; T_j, M_j)\right).$$

- $g(a, x, z; T_j, M_j)$ is a regression tree with structure T_j and leaf values M_j,
- m is the number of trees,
- $\epsilon \sim N(0, \sigma^2)$,
- $I(\cdot)$ is the indicator function,
- Φ is the cumulative distribution function of $N(0, 1)$.

2. Predict $\tau(x, z)$



- Create $2n$ augmented data: one copy with $A = 0$, one with $A = 1$.
- Predict $\hat{\tau}(x, z)$ on augmented data, which outputs

$$\begin{pmatrix} \tau_1^*(x_1, z_1) & \cdots & \tau_1^*(x_n, z_n) \\ \vdots & \vdots & \vdots \\ \tau_D^*(x_1, z_1) & \cdots & \tau_D^*(x_n, z_n) \end{pmatrix}$$

3. Estimate the specific estimand

With predicted $\tau_j^*(x_i, z_i)$, $i = 1, \cdots, n,\ j = 1, \cdots, D$, Nadaraya-Watson kernel smoothing estimator is adopted to estimate $\mathbb{E}[\hat{\tau}(X, Z) \mid H = h]$. That is,

$$\hat{\mathbb{E}}[\hat{\tau}(X, Z) \mid H = h] = \sum_{i=1}^{n} \frac{K\left((h - H_i)/d\right))}{\sum_{i=1}^{n} K\left((h - H_i)/d\right)} \tau_j^*(X_i, Z_i),$$

where $K(\cdot)$ is a kernel smoothing function and d is the bandwidth.

Evaluating a TBP on observational data

Chronic obstructive pulmonary disease (COPD) observational data

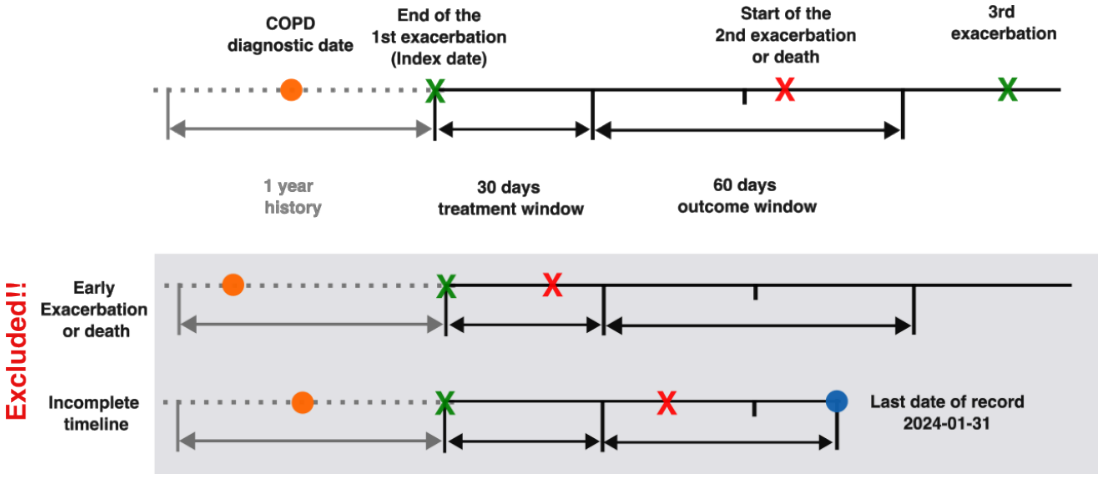
A cohort of newly diagnosed COPD patients is derived from UK's Clinical Practice Research Datalink (CPRD): (1) CPRD Aurum and (2) Linked data: hospital records and death registration.

- Treatment: Azithromycin
- Outcome: Death or the recurrence of acute exacerbation

Inclusion criteria (GOLD2023):

- Aged 40 years or older at the time of initial COPD diagnosis
- Spirometry-confirmed COPD
- Current or former smokers

Timelines of study design



Pre-specified treatment benefit predictor

The treatment benefit for the 2-month window can be defined as

$$\begin{aligned}\tau_0(X) &= \mathrm{P}(Y = 1 \mid A = 0, X = x) - \mathrm{P}(Y = 1 \mid A = 1, X = x) \\ &= \mathrm{P}(T \leq 1/6 \mid A = 0, X = x) - \mathrm{P}(T \leq 1/6 \mid A = 1, X = x),\end{aligned}$$

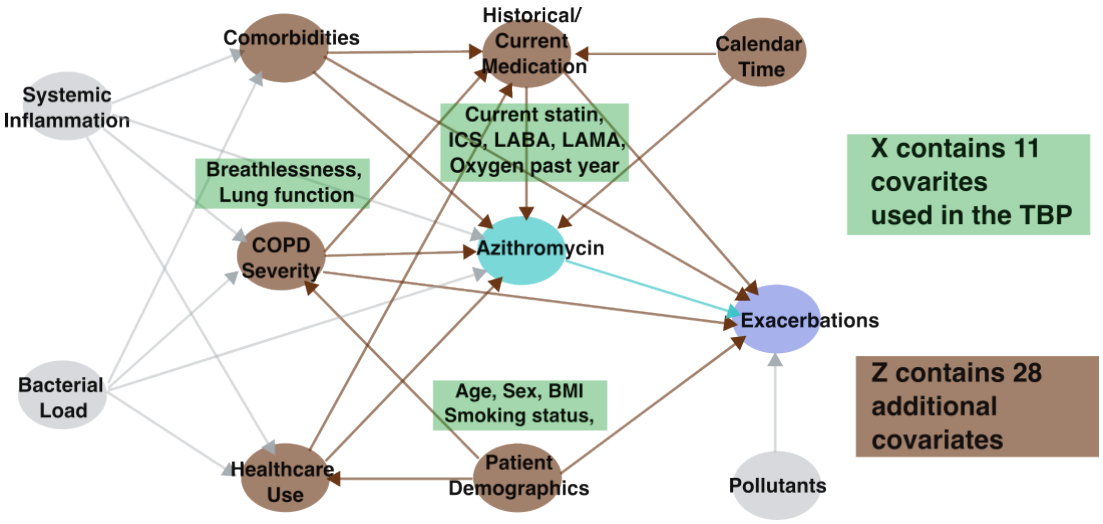
where T is the time to exacerbation, measured in years. Thus, the TBP is

$$h(x) = (1 - S(T = 1 \mid A = 0, X = x))^{1/6} - \left(1 - S(T = 1 \mid A = 0, X = x)^{\mathrm{HR}=0.73}\right)^{1/6},$$

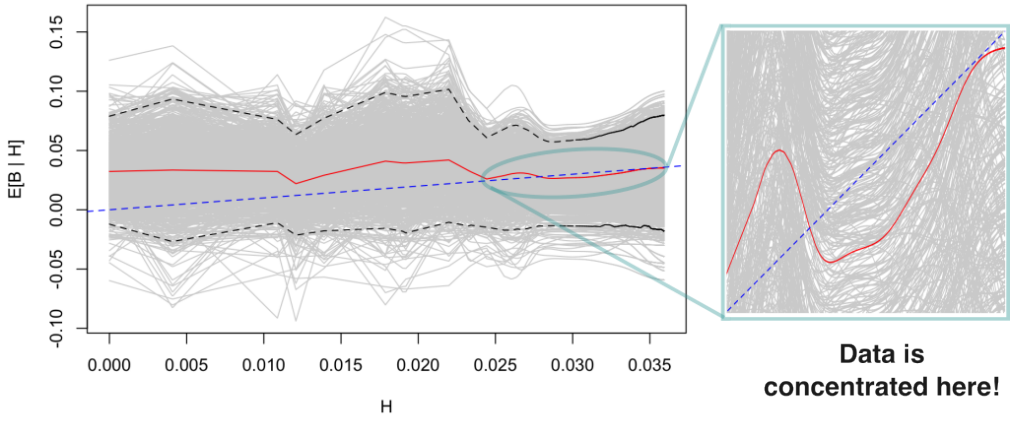
where

- $S(T = t \mid A = 0, X = x)$ is the survival function per patient-year estimated from ACCEPT algorithm [Adibi et al., 2020],
- and HR is a hazard ratio of 0.73 for experiencing an acute exacerbation of COPD per patient-year in the azithromycin group [Albert et al., 2011].

Directed acyclic graph



TBP evaluation results



The TBP is moderately calibrated.

Take home messages

- TBPs support personalized treatment decisions and must be evaluated in the target population before use.
- We demonstrated how to evaluate TBPs using observational data, leveraging BART to estimate conditional average treatment effects and draw samples from the posterior distribution of the estimand that describes the predictive performance of TBPs.
- Checked the calibration of a realistic TBP that predicts the benefit of Azithromycin in a newly diagnosed COPD cohort.

Thank you!

References I

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