A Conditional Random Forest Approach to Estimating the Most Cost-Effective Individualized Treatment Rule

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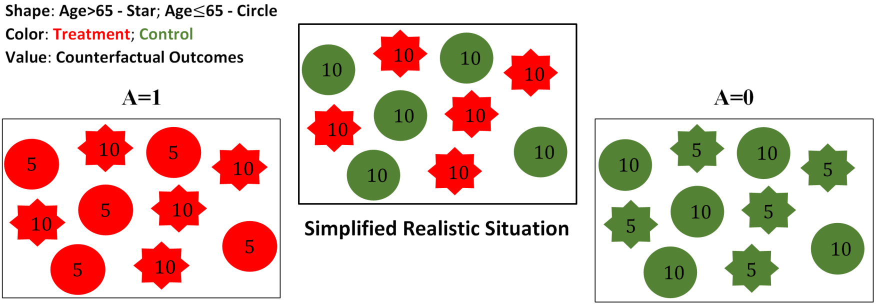
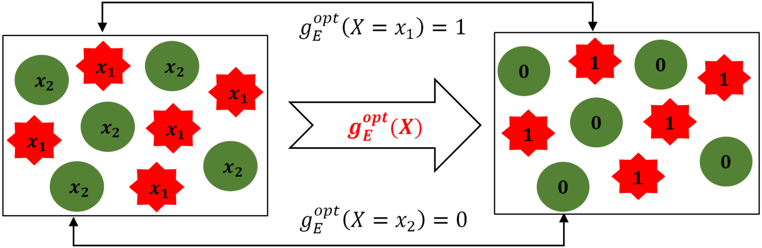
Outline

Importance of Personalized Treatment



- The view of precision medicine: subjects' varied response to treatment
- One-size-fits-all treatment fails to maximize average health benefits
- Treatment needs to be tailored to individual heterogeneity

The Optimal ITR for A Single Health Outcome



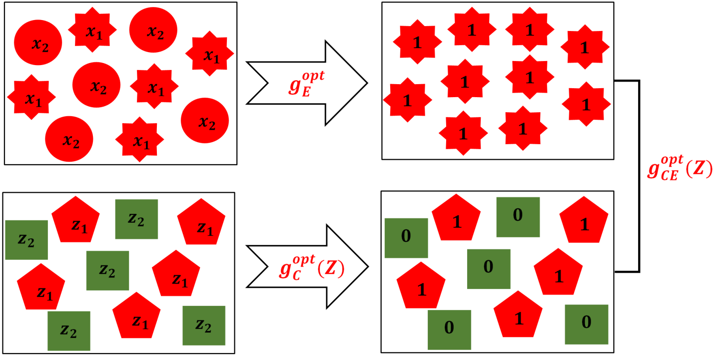
- The optimal individualized treatment rule (ITR) g^{opt} is a map from patients' characteristics (e.g., demographics, health status) to the optimal treatment decision
- Methods for estimating ITR have been developed for clinical outcomes[1], but how to directly apply them to health economic evaluations?

[1] OWL[1, 6], tree-based[3, 2, 5, 4]

The Optimal ITR Concerning Two Outcomes – Scenario 1

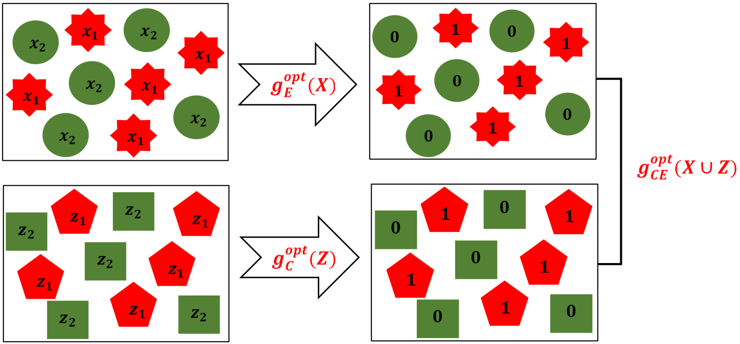
No. Health economic evaluations weigh health gains against added cost:

S1: Constant health benefit (> 0) and heterogeneous incremental cost



The Optimal ITR Concerning Two Outcomes – Scenario 2

S2: Heterogeneous health benefit and incremental cost



Research Gap:

- Lack of methods for estimating ITRs in health economic evaluations
- Causal inference methods are not widely used in CE analyses

Outline

ITR for A Single Health Outcome

Let T^* be the survival time and τ as the restriction time of the study; then, the effectiveness outcome of interest is the restricted survival time $T = \min(T^*, \tau)$.

SID	T^1	T^0	g_T^{opt}	$T^{g_T^{\text{opt}}}$
1	8	3	1	8
2	7	2	1	7
3	5	11	0	11
4	5.5	5	1	5.5
5	4.5	4	1	4.5
$E[T]$	6	5		7.2

How to determine the optimal ITR also with consideration of cost?

ITR Concerning Both Effectiveness and Cost

- Cost outcome: $M_i(S)$ is the accumulated cost up to time S
- Treatment effects: $\Delta T = T^1 - T^0$ and $\Delta M = M^1 - M^0$
- We may have some intuitive ideas about the optimal CE ITR by comparing ΔT and ΔM

SID	T^1	T^0	$M(T^1)$	$M(T^0)$	Comment	g_{CE}^{opt}
1	8	3	\$600K	\$50K	High ΔT, high ΔM	1 or 0
2	7	2	\$250K	\$150K	High ΔT, low ΔM	highly likely 1
3	5	11	\$250K	\$200K	Negative ΔT, low ΔM	0
4	5.5	5	\$200K	\$100K	Low ΔT, low ΔM	1 or 0
5	4.5	4	\$400K	\$100K	Low ΔT, moderate ΔM	likely 0
$E[T]$	6	5	\$340K	\$120K	–	–

How can we capture the concept of the trade-off between effectiveness and cost with one outcome?

Cost-Effectiveness Analysis

- Commonly used outcomes:
  - Net Monetary Benefit (NMB): $Y = \lambda T - M$, $\lambda = \$100K/\text{life-year}$: willingness to pay parameter
  - Incremental Cost-Effectiveness Ratio: $\mathrm{ICER} = \Delta M / \Delta T$
  - CE Acceptability Curve: $P(\Delta Y > 0)$ for different λ
- Treatment effect on NMB: incremental NMB

$$\Delta Y = Y^1 - Y^0 = \lambda \Delta T - \Delta M$$

The Optimal ITR for the NMB Outcome

SID	T^1	T^0	$M(T^1)$	$M(T^0)$	Y^1	Y^0	g_T^{opt}	g_{CE}^{opt}	$Y^{g_{CE}^{\text{opt}}}$
1	8	3	\$600K	\$50K	200K	250K	1	0	250K
2	7	2	\$250K	\$150K	450K	50K	1	1	450K
3	5	11	\$250K	\$200K	250K	900K	0	0	900K
4	5.5	5	\$200K	\$100K	350K	400K	1	0	400K
5	4.5	4	\$400K	\$100K	50K	300K	1	0	300K
$E[T]$	6	5	\$340K	\$120K	260K	380K	–	–	460K

- g_T^{opt} maximizes $E[T^{g_T^{\text{opt}}}]$
- $g_T^{\text{opt}} \neq g_{CE}^{\text{opt}}$
- g_{CE}^{opt} maximizes $E[Y^{g_{CE}^{\text{opt}}}]$

Assumptions for Identifying Causal Estimates with Observational Data

We denote treatment assignment as $A_i \in \{0, 1\}$

1. Stable unit-treatment value assumption (SUTVA): $T_i^{(a)} \perp a_j$ and $M_i^{(a)} \perp a_j$, where $i \neq j$;
2. Consistency: $T_i = A_i T_i^{(1)} + (1 - A_i) T_i^{(0)}$ and $M_i = A_i M_i^{(1)} + (1 - A_i) M_i^{(0)}$;
3. Positivity: $P(A_i|X_i) > \epsilon$ for some positive value of ϵ ;
4. Ignorability: $T_i^{(a)} \perp A_i|X_i$ and $M_i^{(a)} \perp A_i|X_i$, for $a \in \{0, 1\}$.
5. Conditional non-informative censoring: $T_i^{(a)} \perp C_i|X_i$.

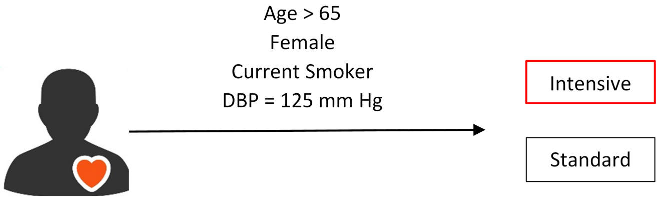
Outline

Definition of the Optimal ITR in A CE Analysis

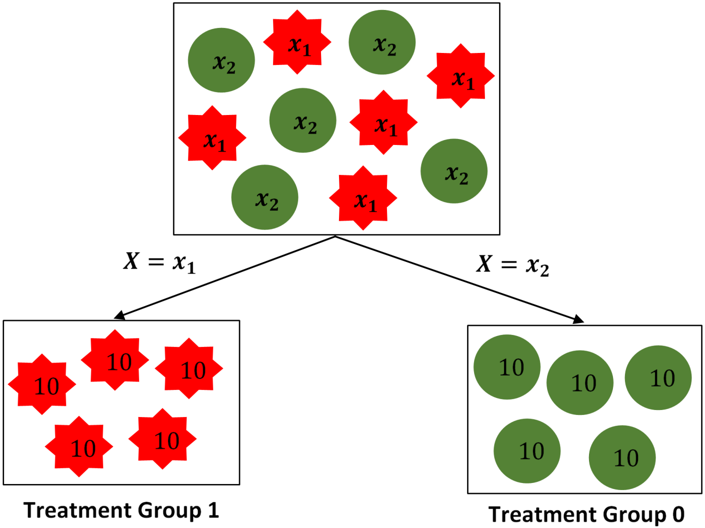
Optimal ITR

Let $Y^{g(X)}$ represents the counterfactual NMB when each subject follows an arbitrary treatment rule $g(X)$, then the optimal ITR is the treatment rule that maximizes the mean NMB, i.e.,

$$g^{opt}(X) \equiv \arg\max_{g \in \mathcal{G}} E_X[Y^{g(X)}]$$



Estimating the Optimal ITR As A Classification Problem



Classification Reformulations

$$g^{\text{opt}}(X) = \text{argmin}_{g\in\mathcal{G}} E_X \left[\underbrace{Y^{(A)}}_{\text{Classification weight } |W_1|} I\{\underbrace{A}_{\text{Class label } Z_1} \neq g(X)\}\right] \quad (1)$$

$$g^{\text{opt}}(X) = \text{argmin}_{g\in\mathcal{G}} E_X \left[\underbrace{|\Delta Y|}_{\text{Classification weight } |W_2|} I\{\underbrace{I\{\Delta Y > 0\}}_{\text{Class label } Z_2} \neq g(X)\}\right] \quad (2)$$

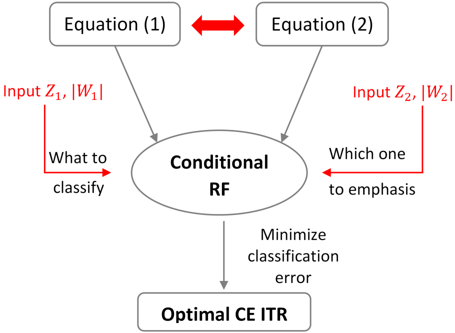
- Equation (1) directly classifies the treatment group A [1]
  - g^{opt} minimizes the misclassification error induced by failing to assign patients to the treatment group that yields the larger NMBs
- Equation (2) classifies whether the treatment effect is positive: cost-effective [2] v.s. not cost-effective [2]
  - g^{opt} minimizes the misclassification error induced by failing to assign patients to the treatment when it is cost-effective, or failing to not assign patients to the treatment when it is not cost-effective

[2] health benefits are gained at a cost that is under the maximum one is willing to pay

A Two-step Procedure

- Step I: Estimate the NMB-based classification weights using the proposed estimators
  - Partitioned IPW/AIPW estimators
- Step II: Feed these weight estimates to a classification algorithm to estimate the optimal treatment rule
  - A conditional random forest (RF) approach via R package **party**

A conditional RF Classification

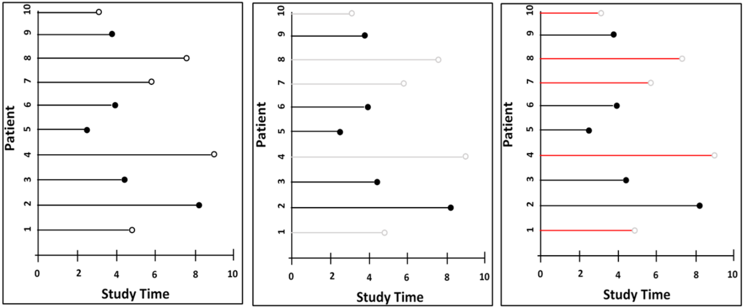


- An ensemble of conditional inference trees that built using unbiased recursive partitioning algorithms
- Employing a conditional permutation scheme for variable importance calculation
- Unbiased even with predictors in various types or correlated variables

Issue: Z_2, $|W_1|$, and $|W_2|$ are counterfactual quantities that we do not know in real studies.

Using Partitioned Weight Estimators

- Goal: Censored subjects also contribute the data from pre-censoring intervals to our estimation
- How: Estimating the incremental cost for each partitioned subinterval then summing them up to compute the total additional cost



Partitioned IPW Estimator for Cost

Cost accrued from the j^{th} subinterval

Whether or not censored by the j^{th} subinterval

$$\Delta \hat{M}_i^{\text{IPW-P}} = \sum_{j=1}^{J} \frac{A_i M_i^j \delta_i^j}{\hat{e}_i^M \hat{K}(U_i^j)} - \frac{(1-A_i) M_i^j \delta_i^j}{(1-\hat{e}_i^M)\hat{K}(U_i^j)},$$

$U_i^j = \min(U_i, t_j, C_i)$

- For pre-censoring subintervals, censored subjects use their own cost data M_i^j, and they are represented by **others** after censored
- The later the subjects are censored (e.g., year 10 v.s year 1), the more cost data and more efficiency may be gained compared to employing a non-partitioned (NP) estimator
- The higher the censoring rate is (e.g., 50% versus 10%), the more efficiency may be gained

What Else Do We Gain? – Estimation Accuracy

Suppose Subject 1 and Subject 2 share the most similar characteristics

	Subject 1	Subject 2	Subject 3
C^1	1	1	1
C^2	0	1	1
C^3	0	1	1
C^4	0	1	1
C^5	0	0	1

- With a NP-E, Subject 1 can only be represented by Subject 3 for subintervals 2-5
- With a P-E, Subject 1 can be represented by Subject 2 for subintervals 2-4 and be accounted by Subject 3 for subinterval 5
- Higher-quality matching scheme improves estimation accuracy and incorporating cost data from censored subjects enhances efficiency

Partitioned IPW Estimator for NMB

To ensure every subject has a classification weight, we propose the estimator of ΔT_i as:

$$
\begin{aligned}
\Delta\hat{T}_i^{\text{IPW-R}} &= \delta_i \left[\frac{A_i U_i}{\hat{e}_i^T} - \frac{(1-A_i)U_i}{(1-\hat{e}_i^T)}\right] + (1-\delta_i)\left[A_i h_1(X_i;\hat{\alpha}) - (1-A_i)h_0(X_i;\hat{\alpha})\right] \\
\hat{W}_i^{\text{IPW-P}} &= \lambda\Delta\hat{T}_i^{\text{IPW-R}} - \Delta\hat{M}_i^{\text{IPW-P}}
\end{aligned}
$$

Partitioned AIPW Estimator

$$\Delta \hat{M}_i^{\text{AIPW-P}} = \sum_{j=1}^{J} \left[\frac{A_i M_i^j \delta_i^j}{\hat{e}_i^M \hat{K}(U_i^j)} - \frac{(A_i - \hat{e}_i^M) m_1^j(X_i; \hat{\beta}) \delta_i^j}{\hat{e}_i^M \hat{K}(U_i^j)} \right] - \left[\frac{(1-A_i) M_i^j \delta_i^j}{(1-\hat{e}_i^M) \hat{K}(U_i^j)} + \frac{(A_i - \hat{e}_i^M) m_0^j(X_i; \hat{\beta}) \delta_i^j}{(1-\hat{e}_i^M) \hat{K}(U_i^j)} \right],$$

$$\Delta \hat{T}_i^{\text{AIPW-R}} = \delta_i \left[\left\{ \frac{A_i U_i}{\hat{e}_i^T} - \frac{(A_i - \hat{e}_i^T) h_1(X_i; \hat{\alpha})}{\hat{e}_i^T} \right\} - \left\{ \frac{(1-A_i) U_i}{(1-\hat{e}_i^T)} + \frac{(A_i - \hat{e}_i^T) h_0(X_i; \hat{\alpha})}{(1-\hat{e}_i^T)} \right\} \right] + (1-\delta_i) \left[A_i h_1(X_i; \hat{\alpha}) - (1-A_i) h_0(X_i; \hat{\alpha}) \right],$$

- **Double information gain**: utilizes both the cost data of censored and outcome models to improve efficiency
- High censoring rates may affect the prediction accuracy of outcome models in augmented terms
- Model misspecification in outcome models also increases the risk of making poor inferences

Outline

Simulation Results

Table 1: Comparison of Classification Accuracies (%) of Estimated Optimal ITRs. Effect modification exists on both survival time and cost. Only the outcome models are misspecified.

CR	WTP	HTE	Reg-naive	DT-AIPW-NP[1]	DT-IPW-P	DT-AIPW-P	RF-AIPW-NP	RF-IPW-P	RF-AIPW-P
20%	50K	S	72.0 (2.1)	89.5 (2.6)	89.9 (1.7)	92.4 (1.2)	91.2 (1.7)	91.5 (1.2)	**92.8** (1.0)
		L	71.4 (2.5)	89.0 (3.0)	91.0 (1.6)	93.2 (1.1)	91.2 (2.0)	92.3 (1.2)	**93.5** (0.9)
	100K	S	75.1 (1.4)	92.9 (1.2)	91.3 (1.5)	93.0 (1.2)	93.5 (0.9)	92.5 (1.1)	**93.5** (1.0)
		L	75.0 (1.5)	93.6 (1.3)	92.0 (1.4)	93.6 (1.1)	94.0 (0.9)	93.1 (1.1)	**94.0** (1.0)
50%	50K	S	75.4 (1.7)	87.7 (3.2)	76.4 (4.2)	92.5 (1.2)	90.9 (1.5)	81.3 (4.4)	**92.7** (1.0)
		L	75.3 (1.7)	87.9 (3.4)	77.0 (4.5)	93.2 (1.1)	91.4 (1.5)	81.8 (4.3)	**93.3** (1.0)
	100K	S	75.6 (1.5)	92.5 (1.6)	89.2 (2.1)	93.2 (1.2)	93.1 (1.0)	91.0 (1.5)	**93.3** (1.0)
		L	75.4 (1.5)	93.1 (1.5)	89.9 (2.1)	93.7 (1.2)	93.7 (1.0)	91.5 (1.4)	**93.8** (1.0)

- The classification-based approaches resulted in higher accuracies
- The partitioned AIPW weight estimators outperformed the other estimators
- The conditional RF classification method outperformed the decision tree
- The accuracies dropped when the censoring rate was high

Simulation Results

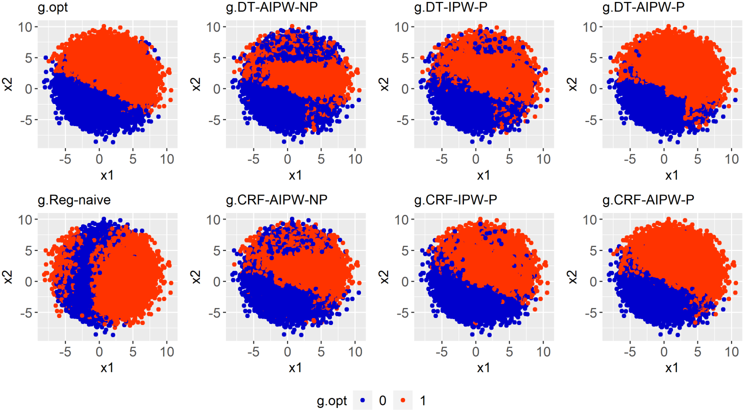


Figure 1: Comparison of the Decision Boundaries of the Estimated Optimal ITRs. Effect modification exists on both survival time and cost. Only the outcome models are misspecified. WTP=$50K, Large HTE, CR=20%.

Data Analysis

- Aim: Estimating the most cost-effective and personalized SBP control strategy in SPRINT [4]
- Data: 10,000 patients generated from microsimulation model based on SPRINT participants [5]
  - Follow-up time: 15 year
  - Outcome: projected NMB: restricted life-years and total cost (medication, hospitalization, background costs)
  - Treatment: intensive control v.s. standard control
  - Assumption: adherence and treatment effects decrease after the first 5 years of follow-up
- Analysis:
  - The top-performing approach is applied: AIPWE + DT
  - 17 pre-selected covariates are used to model each outcome
  - 10-fold CV - overfitting; bootstrapped 95% CI - estimates uncertainty.

Data Analysis Results

Table 2: The Proportions of Treated and Estimated Mean Outcomes in A SPRINT-Eligible Cohort.

	WTP	All patients assigned to intensive SBP control	All patients assigned to standard SBP control	AIPW-based CE ITR (95% CI)
Proportion of Treated	50K	1	0	69% (49%, 84%)
	100K	1	0	74% (54%, 87%)
Mean NMB Outcome	50K	437212	429848	438166 (4339245, 442638)
	100K	1059798	1037198	1060619 (1053006, 1068140)

- Average treatment effect on NMB $> 0 \rightarrow$ conventional CE analysis recommends to treat everyone
- Individualized CE ITR yielded higher mean NMBs than the uniform rules across both WTP thresholds

Outline

Innovations

1. Estimate the most cost-effective treatment rule as a weighted classification problem
   - By defining the weights using a net-monetary-benefit (NMB) outcome
2. Propose two partitioned estimators
   - Maximize the use of censored data
   - Provide more flexible matching scheme for IPCW
   - Estimate the NMB-based classification weight as two components: effectiveness and cost
   - Estimate the NMB-based classification weight as a function of individual characteristics
3. Data-driven estimation approaches relieve the concerns of model misspecification
4. Our methods can be applied to both randomized trials and observational studies

Contributions

1. Introduce the idea of individualized treatment rules to health economic evaluations
    - Emphasize the treatment rules that maximize a clinical outcome do not necessarily maximize CE due to the non-trivial contribution of cost
2. Encourage healthcare policy makers to consider personalized interventions from a CE perspective
    - Propose partitioned weight estimators to enhance estimation accuracy and efficiency
    - Provide several flexible classification approaches with straightforward implementation

Future Extensions

- Estimating the optimal dynamic treatment regime as a sequence of ITRs
- Extensions to situations with multiple treatment arms
- Extensions to other health economic evaluations, e.g., cost-benefit analysis and cost-utility analysis

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Thank you!

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