Estimating the Optimal Individualized Treatment Rule from A Cost-Effectiveness Perspective

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INTRODUCTION

- **Background**: Optimal individualized treatment rules (ITRs) provide customized treatment recommendations based on subject characteristics which optimize clinical benefit in accordance with the objectives in precision medicine. As a result, there has been growing interest in developing statistical tools for estimating optimal ITRs in evidence-based research.
- **Motivation**: From a health economic perspective, policy makers consider the trade-off between health gains and added upfront costs of the intervention to set priorities and allocate resources. However, most work on ITRs has focused on maximizing the effectiveness of a treatment without considering the contribution of cost to the preferred decision.
- **Objective**: We jointly consider the impact of treatment decisions on both cost and effectiveness and extend the concept of ITRs to a composite-outcome setting, so that we identify the most cost-effective ITR that accounts for individual-level heterogeneity through direct optimization.
- **Innovation**:
  i. We introduce the existing direct optimization approach to the problem of estimating the optimal cost-effective ITR;
  ii. We propose a new estimator for the reward function in terms of estimates of the *net monetary benefit* so that the classification process is guided jointly by cost and effectiveness;
  iii. We provide several approaches to estimating the newly proposed reward and summarize practical suggestions on implementing these methods by comparing their performance in simulation studies.

METHODS

Notations	Indications	Notations	Indications
Y	Net monetary benefit (NMB), $Y = \lambda \times T - M$	$\Delta\mathbf{Y} = Y^{(1)} - Y^{(0)}$	Incremental NMB, or treatment effects on NMB
T	Restricted survival time	$\Delta\mathbf{T} = T^{(1)} - T^{(0)}$	Treatment effects on T
M	Cumulative cost	$\Delta\mathbf{M} = M^{(1)} - M^{(0)}$	Treatment effects on M
λ	Willingness-to-pay	g^{opt}	Optimal treatment rule
$X^{(1)}, X^{(0)}$	Counterfactual outcomes under treatment and control, respectively	$Y^{g(X)}$	NMB under a specific treatment decision $g(X)$

Step I: A Weighted Classification Procedure

- The optimal CE ITR is defined as the treatment rule that maximizes the mean NMB:

$$g^{opt} = \mathbf{argmax}\, E\left[Y^{g(X)}\right] \Leftrightarrow \mathbf{argmax}\, E[\mathbf{g(X)}\Delta Y]$$

- **Extend the direct optimization approach (Zhang 2012) to estimating the optimal CE ITR:**

$$g^{opt} = \mathbf{argmax}\, E[g(X)\Delta Y] = \mathbf{argmin}\, E\left[|\Delta Y|[I\{\Delta Y > 0\} - g(X)]^2\right] \quad (1)$$

(Optimal ITR; Arbitrary ITR; Classification weights; Classification Error)

- Equation (1) has a standard set-up of a classification problem.
- A decision tree method is implemented for the classification procedure using *rpart* in R package. Tuning parameters are carefully selected to prevent overfitting (CP=0.01, minsplit=10, xval=10).

Step II: Estimation Approaches for the Classification Weights

1) **Regression Modeling**

- **Reg-naïve**: $\Delta\hat{Y}_i^{\text{Reg-based}} = \lambda\Delta\hat{T}_i^{\text{Reg-based}} - \Delta\hat{M}_i^{\text{Reg-based}}$, and $\hat{g}^{opt} = I\left\{\Delta\hat{Y}_i^{\text{Reg-based}} > 0\right\}$.
- **Reg-based**: use $\Delta\hat{Y}_i^{\text{Reg-based}}$ as the classification weights, and $\hat{g}^{opt} \xleftarrow{\text{predicted by}}$ Decision Tree (DT)

2) **Inverse-Probability-Weighting-Based Approaches**

- $\Delta\widehat{Y}_i^{\text{AIPW}} = \boldsymbol{\lambda}\left[\left\{\frac{A_i U_i \delta_i}{\hat{e}_i^T \hat{K}_{A_i}(U_i)} - \frac{(A_i - \hat{e}_i^T)\hat{h}_1(X_i)\delta_i}{\hat{e}_i^T \hat{K}_{A_i}(U_i)}\right\} - \left\{\frac{(1-A_i)U_i\delta_i}{(1-\hat{e}_i^T)\hat{K}_{A_i}(U_i)} + \frac{(A_i - \hat{e}_i^T)\hat{h}_0(X_i)\delta_i}{(1-\hat{e}_i^T)\hat{K}_{A_i}(U_i)}\right\}\right]$

(Observed follow-up time; Estimated survival time outcomes; Censoring indicator)

$$-\left[\left\{\frac{A_i M_i \delta_i}{\hat{e}_i^M \hat{K}_{A_i}(U_i)} - \frac{(A_i - \hat{e}_i^M)\hat{m}_1(X_i)\delta_i}{\hat{e}_i^M \hat{K}_{A_i}(U_i)}\right\} - \left\{\frac{(1-A_i)M_i\delta_i}{(1-\hat{e}_i^M)\hat{K}_{A_i}(U_i)} + \frac{(A_i - \hat{e}_i^M)\hat{m}_0(X_i)\delta_i}{(1-\hat{e}_i^M)\hat{K}_{A_i}(U_i)}\right\}\right]$$

(Observed cumulative cost; Estimated cumulative cost outcomes; Censoring weight; Augmentation terms; Propensity score; Augmentation terms)

- **Outcome Weighted Learning (OWL)** method: The original classification weights are simple transformations of the IPWE, and we further **modified** them to account for the censoring issue.
- **Inverse Probability Weighting Estimator (IPWE)**: Omit the augmentation terms (colored) in the AIPWE.
- **Augmented Inverse Probability Weighting Estimator (AIPWE)**: 1) robust to model misspecification; 2) provide efficient estimators when both PS and outcome models are correct (Doubly robust property).

Appendix: Additional results may be found by request. Data and R code are available at https://github.com/CrystalXuR/CEAOptimalITR.

SIMULATION STUDY

Simulation schemes:

- Survival times $t^{*(a)}$ are simulated using an exponential PH model.
- Cumulative costs are simulated using a Gamma distribution: initial cost, monthly cost, death-related cost.
- Eight different simulation cases that are defined by 3 parameters:
  1) Presence/absence of effect modification on the rate ratio scale for cost;
  2) Medium/large effect modification on the hazard ratio scale for survival time
  3) WTP: \$50K/\$100K.

Evaluation metrics:

1) The Correct Classification Rate (CCR) evaluates the accuracy of an estimated optimal ITR $\hat{g}^{opt}$; where the accuracy is defined as the proportion of subjects that are classified to the correct treatment group based on the true optimal ITR;
2) The Estimated Mean Outcome (EMO) assesses how closely the mean NMB under an estimated optimal ITR $\hat{g}^{opt}$ estimates the mean NMB under the true optimum treatment regime g^{opt}, i.e., $\mathbf{EMO} = E[Y^{(1)}\hat{g}^{opt} + Y^{(0)}(1 - \hat{g}^{opt})]$. (See Appendix)

Table 1. Comparison of Correct Classification Rate (CCR) under Estimated Optimal ITRs. "SM=1": both of the PS model and the two outcome models are correct; "SM=2": only the PS model is correct; "SM=3": all models are incorrect. Effect modifications (EM) present on both survival time and cost.

SM	EM	HTE	WTP	Reg-naive	Reg-based	OWL	IPW	AIPW
1	T, M	M	50K	0.92 (0.02)	0.86 (0.03)	0.52 (0.06)	0.80 (0.03)	0.83 (0.03)
1	T, M	L	50K	0.96 (0.01)	0.88 (0.02)	0.53 (0.07)	0.85 (0.03)	0.86 (0.03)
1	T, M	M	100K	0.94 (0.02)	0.88 (0.02)	0.54 (0.06)	0.81 (0.03)	0.85 (0.02)
1	T, M	L	100K	0.96 (0.01)	0.91 (0.02)	0.54 (0.07)	0.85 (0.03)	0.87 (0.02)
2	T, M	M	50K	0.76 (0.02)	0.74 (0.02)	0.53 (0.06)	0.80 (0.03)	0.84 (0.03)
2	T, M	L	50K	0.77 (0.02)	0.76 (0.02)	0.53 (0.06)	0.85 (0.02)	0.87 (0.02)
2	T, M	M	100K	0.77 (0.02)	0.76 (0.02)	0.53 (0.07)	0.82 (0.03)	0.86 (0.02)
2	T, M	L	100K	0.78 (0.02)	0.78 (0.02)	0.53 (0.07)	0.86 (0.03)	0.88 (0.02)
3	T, M	M	50K	0.75 (0.02)	0.74 (0.02)	0.63 (0.03)	0.76 (0.03)	0.81 (0.03)
3	T, M	L	50K	0.77 (0.02)	0.76 (0.02)	0.66 (0.04)	0.80 (0.03)	0.80 (0.04)
3	T, M	M	100K	0.77 (0.02)	0.76 (0.02)	0.66 (0.03)	0.78 (0.03)	0.82 (0.03)
3	T, M	L	100K	0.78 (0.02)	0.78 (0.02)	0.67 (0.04)	0.81 (0.04)	0.82 (0.04)

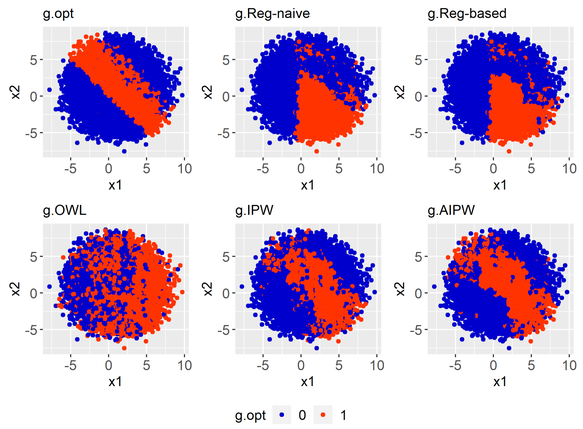

Figure 1. Comparison of Decision Boundaries of Estimated Optimal ITRs. The effect modification on the rate ratio scale for cost is present and the outcome models are misspecified. The very first figure shows the true decision boundary (gold standard), and the rest five display the estimated decision boundaries that are given by 5 different methods.

CONCLUSIONS/DISCUSSIONS

1. **Highlights:**
   i. We extend the ideas of the optimal ITR to health economic evaluations and identify the most cost-effective ITR;
   ii. We propose to use flexible machine learning methods for classification due to the data complexity in CEAs and non-linear mapping of the decision rules.
2. **Limitations:**
   i. Reg-naïve and Reg-based estimators heavily rely on correct model specification;
   ii. Inverse-weighting-based methods may have limited efficiency: 1) Extreme classification weights; 2) Information loss -- only using uncensored subjects; 3) Use a decision tree method.
3. **Future extensions:**
   i. Estimation of the optimal dynamic treatment regime (DTR) from a CE perspective;
   ii. Situations with multiple treatment arms;
   iii. Other health economic analyses: cost-utility analysis (CUA) and cost-benefit analysis (CBA).
   iv. Costs vary across different levels of health status, locations, and time – sensitivity analyses.

DATA ANALYSES

Apply the proposed **AIPW-based CE ITR** approach to the Systolic Blood Pressure Intervention Trial (SPRINT):

- Background: SPRINT compared the impact of two systolic blood-pressure controls on lowering the risk of death and cardiovascular disease: **Standard** – target, <140 mm Hg; **Intensive** – target, <120 mm Hg.
- Inclusion criteria: SBP≥130 mm Hg and at least 1 CVD risk factor (SPRINT Protocol Version 4.0)
- Aim: Identify the optimal individualized treatment rule that maximizes the mean net monetary benefit.
- Data construction:
  † We extracted **8779** completed cases, and **46%** were censored;
  † Cost data was constructed using a micro simulation model (Bress et al, 2017).

- Analyses:
  † 25 covariates were pre-selected based on expert knowledge;
  † We used GLMs to estimate survival and cost outcomes.
  † We implemented a regularized decision tree for classification.
- Results:
  † Table 2 shows that the AIPW-based CE ITR provides a significantly larger NMB on average than uniform treatment decisions, which implies that there is heterogeneity among subjects in response to treatments, thus, it is necessary to consider individualized regime for maximizing NMB.
  † Figure 2 indicates that Gout, HDL, and Sodium are the top 3 important covariates for predicting the optimal CE ITR.

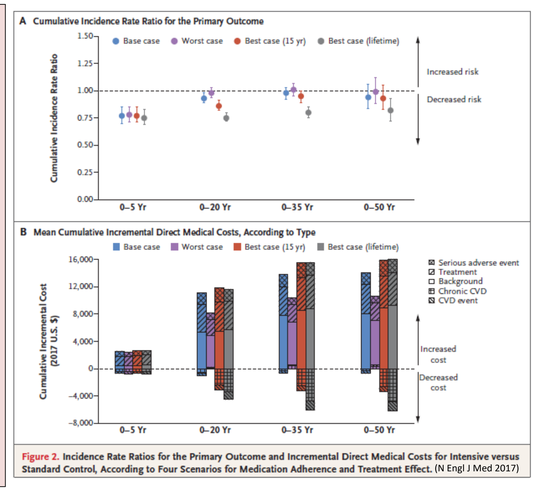

Figure 2. Incidence Rate Ratios for the Primary Outcome and Incremental Direct Medical Costs for Intensive versus Standard Control, According to Four Scenarios for Medication Adherence and Treatment Effect. (N Engl J Med 2017)

Table 2. The Proportions of Treated and Estimated Mean Outcomes in SPRINT from the AIPW-based CE ITR Analyses and the Conventional CE Analyses. The 95% CI is computed using bootstrapping, and 10-fold cross validation is conducted to avoid overfitting.

	WTP	All patients assigned to intensive SBP control[a]	All patients assigned to standard SBP control	AIPW-based CE ITR (95% CI)
Proportion of Treated	50K	1	0	0.82 (0.81, 0.82)
	100K	1	0	0.89 (0.89, 0.90)
Mean NMB Outcome	50K	167656	167185.6	168986 (168431, 169540)
	100K	342861	341442.2	343406 (342326, 344487)

[a]The rule of assigning all patients to intensive SBP control is the optimal rule from a conventional cost-effectiveness analysis based on the average treatment effect on NMB across the full study population.

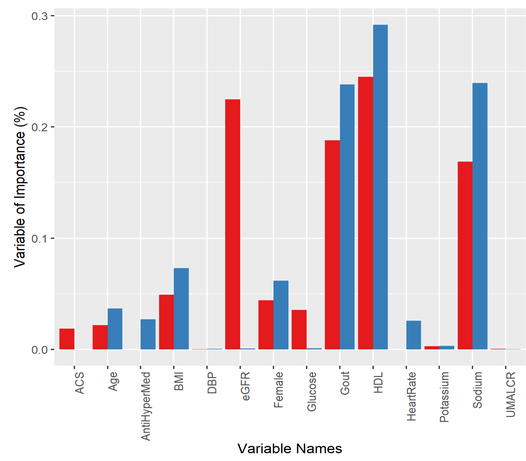

Figure 2. The Importance of Variables Given by the Proposed Method. The variable of importance is computed as the importance of each variable divided by the total importance of all variables. Abbreviations: ACS – acute coronary syndrome; AntiHyperMed – number of antihypertensive medications; UMALCR – urine albumin / creatinine ratio.

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