
GUIDANCE ON INDIVIDUALIZED TREATMENT RULE ESTIMATION IN HIGH DIMENSIONS

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ABSTRACT

Individualized treatment rules, cornerstones of precision medicine, inform patient treatment decisions with the goal of optimizing patient outcomes. These rules are generally unknown functions of patients' pre-treatment covariates, meaning they must be estimated from clinical or observational study data. Myriad methods have been developed to learn these rules, and these procedures are demonstrably successful in traditional asymptotic settings with moderate number of covariates. The finite-sample performance of these methods in high-dimensional covariate settings, which are increasingly the norm in modern clinical trials, has not been well characterized, however. We perform a comprehensive comparison of state-of-the-art individualized treatment rule estimators, assessing performance on the basis of the estimators' rule quality, interpretability, and computational efficiency. Sixteen data-generating processes with continuous outcomes and binary treatment assignments are considered, reflecting a diversity of randomized and observational studies. We summarize our findings and provide succinct advice to practitioners needing to estimate individualized treatment rules in high dimensions. Owing to these estimators' poor interpretability, we propose a novel pre-treatment covariate filtering procedure based on recent work for uncovering treatment effect modifiers. We show that it improves estimators' rule quality and interpretability. All code is made publicly available, facilitating modifications and extensions to our simulation study.

Keywords clinical trials · heterogeneous treatment effects · observational studies · precision medicine

1 Introduction

Broadly, clinical trials are performed to evaluate the efficacy and safety of novel therapies relative to the standard of care. Efficacy is generally assessed by performing inference on a pre-defined marginal parameter, like the average treatment effect. The rise of personalized medicine is however partially at odds with this approach, especially when the patient population is large and diverse. Seemingly similar patients' response to a given treatment can vary widely, which is often attributable to the existence of unknown patient subpopulations. Identifying these patient subgroups is therefore required to maximize patient outcomes and optimize trial success rates.

These subpopulations are generally defined as an unknown function of patient characteristics, like age, sex-at-birth, or genetic mutations. Certain pre-treatment covariates are therefore said to modify the effect of a treatment. These variables are referred to as *treatment effect modifiers* (TEMs).

Individualized treatment rules (ITRs) may in turn be defined using these TEMs. Much effort has been dedicated to developing statistical methods for learning ITRs, and in particular *optimal* ITRs [see Robins, 2004, Qian and Murphy, 2011, Zhang et al., 2012a,b, Tian et al., 2014, Luedtke and van der Laan, 2016, Künzel et al., 2019, to name but a few]. Here, an optimal rule refers to that which optimizes the average clinical outcome in the patient population. Note too that ITRs may be inferred from clinical trial and observational study data alike.

Beyond informing patient treatment decisions, estimated ITRs may provide some insight on the biological functioning of therapies by classifying pre-treatment covariates as TEMs. TEM classification generally requires that the rules be inferred using “interpretable” methods [see Murdoch et al., 2019, for a discussion on interpretability in machine learning]. Examples include penalized linear modeling procedures and decision trees, methods capable of communicating which covariates are believed to interact with the treatment in order to predict outcomes. Importantly, rules estimated by interpretable ITR estimators can be vetted by domain experts, possibly increasing the rules trustworthiness from the perspective of patients and healthcare providers alike.

While many approaches can successfully estimate the optimal ITR in randomized settings where the number of pre-treatment covariates is small relative to the number of patients, it is not necessarily the case when there are more pre-treatment covariates than observations. The challenge is even greater when estimating this rule from observational study data due to possible confounding. As in many high-dimensional settings, simplifying assumptions about the complexity of the estimand must be made to ensure consistent estimation and therefore reliable predictive performance. Examples include sparsity, such as subpopulation-specific expression of a particular biomarker [Qian and Murphy, 2011, Tian et al., 2014, Chen et al., 2017, Zhao et al., 2017, Bahamyiroo et al., 2022], or that the outcome is a (partially) linear function of the covariates and treatment [Tian et al., 2014, Chen et al., 2017]. To the best of our knowledge, there neither exists a comprehensive comparison of popular ITR estimators in high-dimensional settings or an analysis of these methods’ sensitivity to violations of their assumptions.

Recent developments for uncovering TEMs in high-dimensional data have been proposed by Boileau et al. [2022, 2024] that might partially alleviate the difficulty of estimating optimal ITRs in these settings. These authors define a formal statistical framework for treatment effect modifier variable importance parameters (TEM-VIPs), permitting the reliable classification of individual pre-treatment covariates as TEMs. The TEM classification methods of Boileau et al. [2022, 2024] control the false positive rate at the nominal level while maintaining elevated power in high-dimensional data-generating processes (DGPs).

In the same way that variables can be filtered prior to fitting traditional regression methods to improve interpretability and predictive performance, we posit that these TEM-VIP inference procedures may be used with any of the existing ITR estimators to a similar effect. We refer to this procedure as *TEM-VIP-based filtering*. Pre-treatment covariates are classified as TEMs or non-effect modifiers. Inferred TEMs — in addition to all other variables known to be clinically relevant — are then be used by an ITR estimator to learn the treatment rule. This filtering strategy may be particularly useful when combined with black-box ITR methods, which generally provide greater predictive performance than more rigid parametric methods at the expense of opaqueness.

Our contributions to the ITR estimation literature are hence two-fold:

1. Provide practical guidance to applied scientists on ITR estimation in high-dimensional settings, and
2. Assess the impact of TEM-VIP-based filtering on ITR estimation.

A comprehensive simulation study using a variety of DGPs representative of randomized controlled trials (RCTs) and observational studies with continuous outcomes, binary treatment variables, and high-dimensional covariates is performed to accomplish both tasks. As part of this simulation study, ITR estimators, with and without TEM-VIP-based filtering, are compared on the basis of rule quality, interpretability, and computational efficiency.

2 Problem Formulation

We begin by formally outlining the statistical problem. Consider n independent and identically distributed (i.i.d.) random vectors $X_i = (W_i, A_i, Y_i^{(0)}, Y_i^{(1)}) \sim P_{X,0} \in \mathcal{M}_X$ for, $i = 1, \dots, n$, representing the full, partially-unobserved data. Indices are omitted for convenience where possible throughout the remainder of the text. In the full-data random vector, X , W is a vector of p pre-treatment covariates, A is a binary indicator of treatment assignment, and $Y^{(0)}$ and $Y^{(1)}$ are random variables representing observations’ potential outcomes under assignment to the control and treatment groups, respectively [Rubin, 1974]. We assume that p is approximately equal to or larger than n . Further, $Y^{(0)}$ and $Y^{(1)}$ are either continuous or binary and it is assumed that large values of Y are beneficial; this has no bearing on the definition of the estimand, the optimal ITR. The true full-data DGP $P_{X,0}$ is typically unknown and is a member of the nonparametric statistical model \mathcal{M}_X , the collection of all possible full-data DGPs.

Only one of the potential outcomes is generally observed for any given participant; the full data are censored by the treatment assignment mechanism. However, this characterization of the full-data random vectors permits a rigorous definition of the optimal ITR and related quantities.

In particular, an intermediate parameter for performing inference about the optimal ITR is the conditional average treatment effect (CATE):

$$\Gamma_{X,0}(W) \equiv \mathbb{E}_{P_{X,0}} [Y^{(1)} - Y^{(0)} | W]. \quad (1)$$

This functional corresponds to the expected difference of individuals' potential outcomes conditional on pre-treatment covariates. For any given participant with $W = w$, a $\Gamma_{X,0}(w)$ larger than zero indicates that, on average, participants with the same pre-treatment covariates benefit more from being assigned to the treatment group than to the control group. The opposite is true when $\Gamma_{X,0}(w)$ is less than zero.

With the CATE in hand, we define the optimal ITR as follows:

$$\Psi_{X,0}(W) \equiv I(\Gamma_{X,0}(W) > 0). \quad (2)$$

That is, the optimal ITR is an indicator function that equals one when the CATE is larger than zero and zero otherwise. Proposition 1 follows:

Proposition 1. *Let Ψ_X be the collection of all possible ITRs for the full-data model, i.e., the set of all functions from the covariate space into $\{0, 1\}$. Then*

$$\Psi_{X,0} = \arg \max_{\Psi \in \Psi_X} \mathbb{E}_{P_{X,0}} [Y^{(\Psi(W))}] .$$

Proof.

$$\begin{aligned} \Psi_{X,0} &= \arg \max_{\Psi \in \Psi_X} \mathbb{E}_{P_{X,0}} [Y^{(\Psi(W))}] \\ &= \arg \max_{\Psi \in \Psi_X} \mathbb{E}_{P_{X,0}} [\mathbb{E}_{P_{X,0}} [Y^{(1)}\Psi(W) + Y^{(0)}(1 - \Psi(W)) | W]] \\ &= \arg \max_{\Psi \in \Psi_X} \mathbb{E}_{P_{X,0}} [\Psi(W)\mathbb{E}_{P_{X,0}} [Y^{(1)} - Y^{(0)} | W]] \\ &= \arg \max_{\Psi \in \Psi_X} \mathbb{E}_{P_{X,0}} [\Psi(W)\Gamma_{X,0}(W)]. \end{aligned}$$

□

$\Psi_{X,0}$ is therefore optimal in the sense that it maximizes the expected outcome under an ITR from among all possible ITRs. Note too that it is not necessarily unique.

Now, as previously mentioned, only one of the potential outcomes is observed for a given random unit. In place of $\{X_i\}_{i=1}^n$, we observe n i.i.d. random vectors $O = (W, A, Y) \sim P_0 \in \mathcal{M}$, where W and A are defined as above, and $Y = AY^{(1)} + (1 - A)Y^{(0)}$. P_0 is defined as the unknown observed-data DGP, and is fully determined by $P_{X,0}$. This treatment assignment mechanism is denoted by $\pi_0(W) \equiv \mathbb{P}_{P_0}[A = 1 | W]$ throughout the text. Note that this treatment assignment mechanism is known in RCTs and is unknown in observational studies. Additionally, we refer to the conditional expected outcome $\mathbb{E}_{P_0}[Y | A, W]$ by $\mu_0(W, A)$.

Regrettably, performing inference about the parameters of Equations (1) and (2) using the observed data in place of the full data is generally not possible without making additional assumptions. Identifiability conditions linking parameters of the observed data DGP to the desired parameters of the full data DGP are provided in Proposition 2.

Proposition 2. *Under the assumptions of no unmeasured confounding between the treatment and the outcome conditional on W , i.e., $A \perp Y^{(a)} | W$ for $a \in \{0, 1\}$, and that the probability of receiving treatment conditional on W is bounded away from zero, i.e., $\pi_0(W) > 0$:*

$$\begin{aligned} \Gamma_0(W) &\equiv \mu_0(W, 1) - \mu_0(W, 0) \\ &= \Gamma_{X,0}(W), \end{aligned}$$

and

$$\begin{aligned} \Psi_0(W) &\equiv I(\Gamma_0(W) > 0) \\ &= \Psi_{X,0}(W). \end{aligned}$$

Proof. This result follows immediately from the fact that $\mu_0(W, a) = \mathbb{E}_{P_{X,0}}[Y^{(a)} | W]$ for $a \in \{0, 1\}$ under the stated assumptions. □

Proposition 2 establishes that the optimal ITR is estimable from the observed data in the continuous and binary outcome setting. Its assumptions are satisfied in RCTs: randomization ensures that (1) there are no treatment–outcome confounders, (2) the treatment assignment mechanism is known, and (3) the probability of receiving treatment, conditional on covariates, is generally bounded away from zero. In observational studies accounting for confounders, these assumptions are such that the data may be considered as if generated by a stratified RCT but with an unknown treatment assignment mechanism.

We note that, when the confounding variables and treatment effect modifiers are known a priori, they can be used to define the CATE and the optimal ITR instead of the entire pre-treatment covariates vector W . It is straightforward to show that a result analogous to Proposition 2 can be obtained using this (possibly) reduced collection of variables. When identifiability conditions are satisfied, the CATE only depends on the set of treatment effect modifiers. In practice, however, the relevant subset of pre-treatment covariates is generally unknown. Using numerous pre-treatment covariates is therefore encouraged to ensure that Proposition 2 is satisfied and that many treatment effect modifiers are considered.

Assuming Proposition 2 is satisfied, we take as target of inference the optimal ITR, $\Psi_0(W)$, which, as a preliminary step, requires the estimation of the CATE, $\Gamma_0(W)$. Possible estimators are presented and discussed in Section 3.

3 Methods

Myriad methods have been developed for estimating the CATE and therefore the optimal ITR. We review a subset of these approaches capable of performing inference about the latter in the high-dimensional, binary treatment setting. We begin with the simplest parametric approach and end with state-of-the-art nonparametric methods. Throughout, we represent estimators of $\Gamma_0(W)$, $\Psi_0(W)$, $\mu_0(W, A)$, and $\pi_0(W)$ fit using the empirical distribution P_n by $\Gamma_n(W)$, $\Psi_n(W)$, $\mu_n(W, A)$, and $\pi_n(W)$, respectively.

3.1 Plug-In Estimators

The most straightforward approach for estimating Γ_0 is to assume that the conditional expected outcome admits a parametric form, like that of a generalized linear model (GLM). For example, we might assume that $\mu_0(W, A) = l^{-1}(\alpha_0 + \beta_0 A + \gamma_0^\top W + \delta_0^\top WA)$ for some link function $l(\cdot)$. Here, α_0 and β_0 are intercept terms, and γ_0 and δ_0 are p -length vectors. Letting the outcome be continuous and using the identity link, $l(x) = x$, $\mu_0(W, A)$ could be estimated using penalized regression methods, like the LASSO [Tibshirani, 1996] or the elastic net [Zou and Hastie, 2005], to produce coefficient estimates $\alpha_n, \beta_n, \gamma_n$, and δ_n . Note that, when the pre-treatment covariates are centered such that $\mathbb{E}_{P_0}[W] = 0$, $\alpha_0 = \mathbb{E}_{P_{X,0}}[Y^{(0)}]$ and $\beta_0 = \mathbb{E}_{P_{X,0}}[Y^{(1)} - Y^{(0)}]$ — the average treatment effect — under the identity link.

The plug-in CATE estimator under this linear model is given by

$$\begin{aligned}\Gamma_n(W) &\equiv \mu_n(W, 1) - \mu_n(W, 0) \\ &= \beta_n + \delta_n^\top W.\end{aligned}\tag{3}$$

This plug-in estimator can then be used to construct an optimal ITR estimator under this linear model:

$$\Psi_n(W) \equiv \mathbf{I}(\Gamma_n(W) > 0).\tag{4}$$

Analogous estimators can be constructed for scenarios with binary outcomes using penalized logistic regression to estimate the conditional expected outcome.

While computationally efficient implementations can be painlessly constructed in standard software, like the R language and environment for statistical computing [R Core Team, 2021], and resulting estimators are generally interpretable, this approach may be hampered by its reliance on strong parametric assumptions about the functional form of the CATE. When the parametric form of the conditional expected outcome is misspecified, the estimator of Equation (3) could be biased, and so too could be the corresponding ITR estimator of Equation (4). Further, when the covariates are correlated, the covariates classified as TEMs by penalized regression methods like the LASSO—variables whose corresponding treatment interaction coefficient estimates in δ_n are non-zero—may be unreliable [Zhao and Yu, 2006].

We might instead estimate $\mu_0(W, A)$ using more flexible machine learning procedures, like Random Forests [Breiman, 2001] or XGBoost [Chen and Guestrin, 2016]. In fact, $\mu_0(W, 0)$ and $\mu_0(W, 1)$ can even be estimated individually on observations in control and treatment conditions, respectively, using possibly different estimators. Estimators of the CATE and the accompanying optimal ITR are then constructed similarly to those of Equations (3) and (4).

These flexible plug-in estimators share similar limitations to their parametric counterparts, however: if the estimators of $\mu_0(W, 0)$ and $\mu_0(W, 1)$ are not consistent, then neither will their associated CATE estimator. If estimated using black-box methods, then they may also be less interpretable and computationally efficient than plug-in estimators obtained from parametric modeling procedures.

3.2 (Augmented) Modified Covariates Estimators

In part motivated by the limitations of the parametric plug-in estimator, [Tian et al., 2014] developed a semiparametric framework for estimating the CATE in RCTs. Assume for now that the outcome is a continuous variable and let

$$\mu_0(W, A) = \gamma_0^\top f(W) + \delta_0^\top h(W) \frac{2A - 1}{2}, \quad (5)$$

where f and h are some functions of the covariates. For simplicity of presentation, we let $f(W) = h(W) = W$ such that γ_0 and δ_0 are p -length coefficient vectors. It follows that $\Gamma_0(W) = \mathbb{E}_{P_0}[2Y(2A - 1)|W] = \delta_0^\top W$. Dubbed the *modified outcome* method, this approach permits a straightforward estimation of the CATE using standard ordinary least squares or penalized methods like the LASSO and elastic net. As [Tian et al., 2014] note, however, this framework does not easily generalize to DGPs with other kinds of outcome variables.

They instead propose the more general *modified covariates* method, which relies on GLMs or the proportional hazards model. Again, first assuming a continuous outcome and positing the following working model,

$$\mu_0(W, A) = \delta_0^\top h(W) \frac{2A - 1}{2}, \quad (6)$$

Tian et al. [2014] show that the δ_0 s of Equations (5) and (6) share identical interpretations and can be estimated in the same manner. We again let $h(W) = W$. The resulting CATE estimator in this model therefore takes the form of

$$\Gamma_n(W) \equiv \delta_n^\top W,$$

where δ_n is again estimated via (penalized) linear methods. The accompanying optimal ITR estimator take the same form as the estimator of Equation (4).

GLMs can be used to apply this approach to other kinds of outcomes. When Y is binary, the conditional outcome regression can be represented by the following logistic regression model:

$$\mu_0(W, A) = \frac{\exp(\delta_0^\top h(W)(2A - 1)/2)}{1 + \exp(\delta_0^\top h(W)(2A - 1)/2)}. \quad (7)$$

When this working model is well-specified,

$$\Gamma_0(W) = \frac{\exp(\delta_0^\top h(W)/2) - 1}{\exp(\delta_0^\top h(W)/2) + 1}.$$

Estimates of δ_0 are again obtained by fitting the working model for the conditional expected outcome using standard (penalized) regression approaches. An optimal ITR estimator under this model is constructed as in Equation (4).

While the modified covariates framework is more flexible than the parametric approaches based on GLMs, it is generally inefficient. Tian et al. [2014] therefore proposed an “augmented” modified covariates framework that can be used to construct CATE estimators with generally smaller variance but which are asymptotically equivalent. In the continuous outcome scenario with $h(W) = W$, the resulting CATE estimator is equivalent to $\Gamma_n(W)$ of Equation (3). This simplicity is not shared with non-linear working models like that of Equation (7), however [Tian et al., 2014].

Chen et al. [2017] generalized the (augmented) modified covariates methodology through a loss-based estimation procedure relying on loss functions incorporating the propensity score. For a continuous outcome, the non-augmented CATE estimator is defined as

$$\Gamma_n(W) \equiv \arg \min_{\Gamma \in \Gamma_n} \sum_{i=1}^n \frac{(Y_i - (2A_i - 1)\Gamma(W_i))^2}{(2A_i - 1)\pi_0(W_i) + 1 - A_i},$$

where Γ_n is the set of possible CATE estimators and $\pi_0(W)$ must be replaced by $\pi_n(W)$ in observational studies. This generalized framework also permits more flexible estimation of $\mu_0(W, A)$ using machine learning methods like with XGBoost. More efficient estimation of the CATE and the ITR is therefore made possible using this modified covariates model in observational studies, assuming that $\mu_n(W, A)$ and $\pi_n(W)$ are consistent. Readers interested in the augmented version of this weighted CATE estimator are invited to review Chen et al. [2017].

Like the parametric plug-in estimators, these approaches result in biased CATE estimators when their models are misspecified. This may result in a biased ITR estimator, too. When the difference in expected outcomes is estimated using more complex methods, like XGBoost, or penalized GLMs are used but covariates are correlated [Zhao and Yu, 2006], the interpretability of the resulting ITR estimate is reduced, too.

A computationally efficient implementations of this methodology is made available in the `personalized` R package [Huling and Yu, 2021]. We use it throughout the simulation studies in Sections 4.

3.3 Nonparametric Approaches

Much work in the nonparametric estimation literature has been dedicated to developing estimators of the CATE and the optimal ITR; see Robins [2004], Robins et al. [2008], Zhang et al. [2012a,b], van der Laan and Luedtke [2015], Luedtke and van der Laan [2016], Zhao et al. [2017], Bahamyiroo et al. [2022], Kennedy [2022]. These estimators, typically relying on nuisance parameters like $\mu_0(W, A)$ and $\pi_0(W)$, are generally doubly-robust. That is, these ITR estimators are consistent estimators under mild regularity conditions and so long as either $\mu_n(W, A)$ or $\pi_n(W)$ is consistent. Given that the treatment assignment rule $\pi_0(W)$ is typically known in a clinical trial, these nonparametric estimators are guaranteed to be consistent in these settings.

3.3.1 Estimators Based on the Augmented Inverse Probability Weighted Transform

We briefly present the approach inspired by Luedtke and van der Laan [2016]. It relies on the Augmented Inverse Probability Weighted (AIPW) transform, defined as

$$T(O; \mu_n, \pi_n) = \frac{2A - 1}{A\pi_n(W) + (1 - A)(1 - \pi_n(W))} (Y - \mu_n(W, A)) + \mu_n(W, 1) - \mu_n(W, 0),$$

and also referred to as the *pseudo-outcome difference*.

A nonparametric, “AIPW-based” ITR estimator can then be defined as follows:

$$\Gamma_n(W) \equiv \arg \min_{\Gamma \in \Gamma_n} \sum_{i=1}^n (\Gamma(W_i) - T(O_i; \mu_n, \pi_n))^2.$$

That is, $\Gamma_n(W)$ is the squared AIPW-transform error risk minimizer from among the set of possible CATE estimators. $\Gamma_n(W)$ can be constructed by regressing the pseudo-outcome differences given by $T(O; \mu_n, \pi_n)$ on the covariates W . This estimator is a consistent estimator of $\Gamma_0(W)$ when either $\mu_n(W, A)$ or $\pi_n(W)$ are consistent [Luedtke and van der Laan, 2016]. The accompanying optimal ITR estimator is constructed similarly to the ITR estimators of Equation (4).

This nonparametric approach makes minimal assumptions about the DGP and is made all the more attractive by the possible use of flexible machine learning algorithms to both estimate nuisance parameters and the CATE, curbing the risk of model misspecification and potentially translating to increased finite sample precision. We recommend using an estimator based on the Super Learner framework of van der Laan et al. [2007]. Building upon the theory of cross-validated loss-based estimation [Dudoit and van der Laan, 2003, van der Laan and Dudoit, 2003, Dudoit and van der Laan, 2005, van der Vaart et al., 2006], a Super Learner constructs a convex combination of estimators from a pre-specified library that minimizes the cross-validated risk of a pre-defined loss. This collection of estimators can be made up of modern machine learning algorithms, avoiding the need to make strong parametric assumptions about the target parameter. The resulting estimator converges in probability to the oracle asymptotically. The oracle corresponds to the estimator that would be selected for the given dataset if P_0 were in fact known. The Super Learner is conveniently implemented in the `s13` R package [Coyle et al., 2021], which we use in the subsequent simulation study.

This flexibility of this estimation procedure comes at the cost of computational efficiency, however. Whether the aforementioned asymptotic properties lead to improved performance in the high-dimensional settings considered here remains uncertain, too.

The resulting CATE estimator’s level of interpretability also largely depends on the method used to regress pseudo-outcome differences on the covariates. A compromise between flexibility and finite sample precision might be achieved by fitting the pseudo-outcome differences as a function of the covariates using penalized GLMs [Zhao et al., 2017, Bahamyiroo et al., 2022]. If interpretability is not a concern, then a Super Learner composed of flexible machine learning algorithms will likely provide the best finite sample performance.

3.3.2 Causal Random Forests

An alternative but related nonparametric approach is that of Causal Random Forests [Wager and Athey, 2018, Athey et al., 2019]. Like the Random Forests algorithm proposed by Breiman [2001], a large number of decision trees are

constructed on random subsamples of the data. Whereas traditional Random Forests generate branches in any given tree by maximizing the variance of the outcome within subgroups formed across random selections of covariates, the causal version attempts to maximize the variance of the estimated treatment effects. The CATE is then constructed using a weighted Robinson's residual-on-residual regression [Robinson, 1988]. This methodology is implemented in the `grf` R package [Tibshirani et al., 2022], which we use in the simulation study of Section 4.

Similar to the previously described nonparametric CATE estimator, $\mu_n(W, A)$ and $\pi_n(W)$ must be fit. This is typically done using traditional Random Forests. If either estimator is consistent, then so too is the CATE estimator given by the Causal Random Forests under mild conditions on the DGP. Reliably recovering TEMs is however not possible in high dimensions.

3.4 Feature Selection using Treatment Effect Modifier Variable Importance Parameters

Recent work by Boileau et al. [2022, 2024] discussed and demonstrated how CATE-based methods aiming to uncover TEMs in high-dimensional RCTs and observational studies generally fail to reliably uncover true TEMs. This has been reported elsewhere as well [for example, see the simulation studies of Tian et al., 2014, Bahamyrou et al., 2022]. This suggests that the previously reviewed CATE estimators may needlessly incorporate uninformative covariates in their estimation procedures, potentially decreasing their rule quality and diminishing their interpretability.

Motivated by the need for reliable TEM discovery methodology applicable to high-dimensional data, Boileau et al. [2022, 2024] proposed a nonparametric framework for defining TEM-VIPs based on any pathwise differentiable treatment effect and for subsequently constructing regular asymptotically linear (RAL) estimators of these parameters. This framework provides formal statistical guarantees, like Type I error rate control.

Of particular relevance is the absolute TEM-VIP based on the average treatment effect (ATE), and therefore related to the CATE. Assuming that the expected value of $\mu_0(W, 1) - \mu_0(W, 0)$ conditional on any given W_j is linear in W_j , this TEM-VIP is defined as the simple linear regression coefficient obtained by regressing the difference in conditional expected potential outcomes on a single covariate. For the j^{th} pre-treatment covariate W_j , this parameter is given by

$$\frac{\text{Cov}_{P_0} [\mu_0(W, 1) - \mu_0(W, 0), W_j]}{\text{Var}_{P_0}[W_j]}.$$

Though the true relationship between this expected outcome difference and the covariate conditional on said covariate is unlikely to be linear, this parameter is an informative measure of treatment effect modification: any value greater than zero is indicative of effect modification, and the magnitude and sign of the TEM-VIP summarize, respectively, the strength and direction of the effect.

Boileau et al. [2022, 2024] provide one-step, estimating equation, and targeted maximum likelihood (TML) estimators of this TEM-VIP that possess $\mu_0(W, A)$ and $\pi_0(W)$ as nuisance parameters, and prove that these estimators are doubly-robust and efficient in nonparametric models. Assuming $\mu_n(W, A)$ and $\pi_n(W)$ converge to $\mu_0(W, A)$ and $\pi_0(W)$, respectively, at the appropriate nonparametric rate, $o_P(n^{-1/4})$, these TEM-VIP estimators are shown to be RAL. In RCTs, these estimators are guaranteed to be RAL by virtue of $\pi_0(W)$ being known. Recall that RAL estimators' sampling distributions are asymptotically Normal, permitting computationally efficient hypothesis testing. Inference procedures for this TEM-VIP are implemented in the `unihtee` R package. We use this software in the simulation studies.

We propose to use these TEM-VIP estimators in a two-stage CATE estimation procedure. First, the TEM-VIPs are estimated for each covariate, and a hypothesis test about their modification status is performed. Covariates classified as TEMs based on a predefined null hypothesis and level of significance are then used to estimate the CATE.

As previously mentioned, decreasing the number of covariates used by CATE estimators in the second stage may decrease said estimators' variance and bias. The two-stage procedure may also be more computationally efficient than fitting an estimator using the entire set of covariates. Ranking the estimated TEM-VIPs also adds a layer of interpretability to the resulting CATE estimate, regardless of the CATE estimation strategy used in the second stage.

4 Simulation Study

4.1 Data-Generating Processes and Simulation Details

Recall that, in a continuous outcome setting, we have access to realizations of $O = (W, A, Y)$, where W is a p -dimensional vector of pre-treatment covariates (and possible confounders), A is a binary treatment indicator, and Y is

the observed continuous outcome. We consider generative models based on the template below:

$$\begin{aligned} W &\sim N(0, \Sigma) \\ A|W &\sim \text{Bernoulli}(\pi(W)) \\ Y^{(A)}|W &\sim N(\mu(W, A), 1) \\ Y &= AY^{(1)} + (1 - A)Y^{(0)}. \end{aligned}$$

Here, Σ is some $p \times p$ covariance matrix and $\pi(W)$ and $\mu(W, A)$ are generic propensity score and conditional expected outcome functions, respectively.

Setting $p = 500$, we define 16 DGPs using every possible combination of the following factors:

$$\begin{array}{ccc} \Sigma_1 = I_{500 \times 500} & \times & \pi_1(W) = \frac{1}{2} \\ \Sigma_2 = \text{Block diagonal} & \times & \pi_2(W) = \text{logit}^{-1}\left(\frac{W_1 + W_2 + W_3 + W_4}{5}\right) \end{array} \quad \begin{array}{c} \mu_1(A, W) = A + \gamma^\top W + (\delta^{(10)})^\top WA \\ \mu_2(A, W) = A + \gamma^\top W + (\delta^{(50)})^\top WA \\ \mu_3(A, W) = \gamma^\top W + 2 \arctan\left\{(\delta^{(10)})^\top WA\right\} \\ \mu_4(A, W) = \gamma^\top W + 2 \arctan\left\{(\delta^{(50)})^\top WA\right\} \end{array}$$

where $\gamma_1 = \dots = \gamma_5 = 2$, $\gamma_6 = \dots = \gamma_{500} = 0$, $\delta_1^{(10)} = \dots = \delta_{10}^{(10)} = 2$, $\delta_{11}^{(10)} = \dots = \delta_{500}^{(10)} = 0$, $\delta_1^{(50)} = \dots = \delta_{50}^{(50)} = 1/2$, and $\delta_{51}^{(50)} = \dots = \delta_{500}^{(50)} = 0$. Σ_2 is constructed by randomly generating 50 positive definite square symmetric matrices with diagonal elements equal to one. Details on the generation of these matrices are provided in the accompanying code.

We note that DGPs using π_1 are treated as observational studies in that the treatment assignment mechanism is unknown. DGPs with π_2 mimic an RCT, where π_2 is treated as known. We also highlight that $\delta^{(10)}$ and $\delta^{(50)}$ permit the evaluation of methods in DGPs where the number of TEMs is sparse and non-sparse, respectively. The effect sizes associated with each TEM also vary in terms of the conditional expected outcome function: μ_1 produces TEMs with the largest effect sizes, followed by μ_3 , μ_2 , and μ_4 in decreasing order. Finally, DGPs using μ_1 and μ_2 rely on linear models to produce the outcome, whereas DGPs using μ_3 and μ_4 use non-linear models to generate outcomes as a function of treatment assignment and pre-treatment covariates.

One hundred learning datasets made up of $n = 250, 500$ and 1,000 observations are generated for each DGP. The potential outcomes $Y^{(0)}$ and $Y^{(1)}$ are unobserved in these datasets. Accompanying each learning set is a test set made up of $n' = 100$ observations. These data contain the potential outcomes for evaluation purposes. The learning datasets are used to fit the considered CATE and ITR estimators which are subsequently assessed using the test sets. The size of the learning and test datasets were chosen to resemble the sample sizes typically observed in Phase 2 and 3 oncology trials, as well those of observational studies investigating ITRs in moderate-to-small patient populations. Additionally, the considered learning set sample sizes produce datasets with a variety of p/n ratios, offering insights into the benchmarked methods' performance across many high-dimensional regimes.

4.2 Estimators

The CATE-based ITR estimators considered in this simulation study are listed in Table 1. Owing to the many possible implementations of the estimation approaches discussed in Section 3, we restrict our benchmarks to ITR estimators relying on familiar nuisance parameter estimators capable of handling high-dimensional data that are easily implemented with standard statistical software. While an exhaustive benchmarking of ITR estimators is infeasible, we believe that this analysis provides valuable insights into ITR estimation in high dimensions. Additionally, this simulation study provides a foundation for bespoke investigations.

Details on the ITR estimators' fitting procedures are provided in Table 1, as is a column indicating whether they provide built-in TEM classification. That is, whether the CATE estimates underlying the ITRs explicitly distinguish between predicted TEMs and non-TEMs. Among the considered estimators, only those relying solely on the LASSO to estimate the conditional expected outcome possess this ability: covariates with non-zero estimated treatment-covariate interaction coefficients are categorized as TEMs, others as non-TEMs. We emphasize that while the LASSO-based ITR estimators provide built-in TEM classification, the resulting classifications may produce many false positives and negatives. Built-in TEM classification may be misleading and could therefore be considered an undesirable property in settings where the LASSO's assumptions are violated. Note that all methods employing the LASSO select the regularization hyperparameter by minimizing the 10-fold cross-validated mean squared error.

A TEM-VIP-based filtered version of each estimator outlined in Table 1 is also included in this benchmark. As previously described in Section 3, inference about TEM-VIPs is performed to identify TEMs in each learning dataset replicate. These predicted TEMs are then used to train the CATE-based ITR estimators.

CATE Estimator	Details	Built-in TEM Classification
Plug-In LASSO	A plug-in estimator, where $\mu(W, A)$ is estimated using the LASSO. Linear model coefficients for the treatment indicator, the pre-treatment covariates, and the treatment-covariates interactions are considered.	Yes
Plug-In XGBoost	A plug-in estimator, where XGBoost [Chen and Guestrin, 2016] is used to estimate $\mu(W, A)$.	No
Modified Covariates LASSO	A modified covariates estimator, where $\mu(W, A)$ is estimated with a LASSO linear regression. $\pi(W)$ is estimated in non-randomized DGPs with a logistic LASSO regression.	Yes
Modified Covariates XGBoost	A modified covariates estimator, where $\mu(W, A)$ is estimated with XGBoost. $\pi(W)$ is estimated in non-randomized DGPs with a logistic LASSO regression.	No
Augmented Modified Covariates LASSO	An augmented modified covariates estimator, where $\mu(W, A)$ is estimated with a LASSO linear regression. $\pi(W)$ is estimated in non-randomized DGPs with a logistic LASSO regression.	Yes
Augmented Modified Covariates XGBoost	An augmented modified covariates estimator, where $\mu(W, A)$ is estimated with XGBoost. $\pi(W)$ is estimated in non-randomized DGPs with a logistic LASSO regression.	No
AIPW-based LASSO	An AIPW-based estimator, where a Super Learner comprised of penalized linear regression (LASSO, ridge, elastic net), Random Forests, and XGBoost is used to estimate $\mu(W, A)$. A Super Learner comprised of penalized logistic regressions (LASSO, ridge, elastic net), Random Forests, and XGBoost is used to estimate $\pi(W)$ when necessary. The difference in predicted pseudo-outcomes is regressed on the covariates using a LASSO linear regression.	Yes
AIPW-based Super Learner	An AIPW-based estimator, where a Super Learner comprised of penalized linear regression (LASSO, ridge, elastic net), Random Forests, and XGBoost is used to estimate $\mu(W, A)$. A Super Learner comprised of penalized logistic regressions (LASSO, ridge, elastic net), Random Forests, and XGBoost is used to estimate $\pi(W)$ when necessary. The difference in predicted pseudo-outcomes is regressed on the covariates using a Super Learner identical to that used to estimate the conditional expected outcomes.	No
Causal Random Forests	A Causal Random Forests estimator, where Random Forests are used to estimate $\mu(W, A)$ and, when necessary, $\pi(W)$.	No

Table 1: CATE-based ITR estimators benchmarked in simulation study.

We use the nonparametric doubly-robust one-step estimator to perform inference about the absolute ATE-based TEM-VIPs [Boileau et al., 2022, 2024]. Recall that in observational studies, this filtering procedure requires that two nuisance parameters be estimated: $\mu(W, A)$ and $\pi(W)$. They are fit in the observational study DGPs considered here with the same Super Learners used by the AIPW-based estimators listed in Table 1. In the RCT-like DGPs, $\pi(W)$ need not be estimated, and $\mu(W, A)$ is estimated with a LASSO regression that includes main terms for the treatment and covariates, as well as all possible treatment-covariate interaction terms. Again, regardless of whether a DGP mimics an observational study or an RCT, this one-step estimator is asymptotically Normal under mild conditions. Wald-type confidence intervals are constructed for each pre-treatment covariate's TEM-VIP, and any variable with an Benjamini-Hochberg FDR-adjusted p -value [Benjamini and Hochberg, 1995] lower than 5% is classified as a TEM.

4.3 Estimator Performance Metrics

Estimators are evaluated using three metrics: quality of the resulting ITR-based classification on new data, accurate interpretability, and computational efficiency.

Rule Quality: For a generic ITR estimate $\psi_b(W)$ produced by fitting a generic ITR estimator $\Psi_n(W)$ to the b^{th} learning dataset, we compute the mean outcome over the b^{th} test set based on the resulting estimate's classification as

$$\frac{1}{n'} \sum_{i=1}^{n'} Y_i^{(\psi_b(W_i))},$$

where, recall, each test set is made up of $n' = 100$ observations. $\Psi_n(W)$'s performance across the $B = 100$ test set replicates is then summarized as

$$\frac{1}{B} \sum_{b=1}^B \left(\frac{1}{n'} \sum_{i=1}^{n'} Y_i^{(\psi_b(W_i))} \right).$$

This metric, corresponding to the empirical mean of the potential outcomes under the ITR $\Psi_n(W)$, is therefore an estimator of $\mathbb{E}_{P_{X,0}}[Y^{(\Psi_{X,0}(W))}]$, assuming the conditions of Proposition 2 are satisfied. ITR estimators that produce the largest value are said to be “high-quality”—their treatment assignments empirically optimize, relative to all considered ITRs, the observations’ average outcomes.

Accurate Interpretability: The non-zero entries in $\delta^{(10)}$ and $\delta^{(50)}$ correspond to the TEMs of their respective DGPs, and are therefore the driving force behind heterogeneous treatment effects. For any given learning set replicate, the false discovery, true negative, and true positive proportions with respect to TEM status are computed for all estimators capable of classifying pre-treatment covariates. These proportions are then averaged across replicates to produce the empirical false discovery rate (FDR), true negative rate (TNR), and true positive rate (TPR). ITR estimators are deemed accurately interpretable if the empirical false discovery rate (FDR) approximately achieves the nominal Type I error rate of 5% while producing TNRs and TPRs near 100%.

Computational Efficiency: The time to fit each estimator, using a single core, to each learning dataset is recorded and considered a surrogate for overall computational efficiency. The mean fit time is then computed across sample sizes and DGPs. Smaller times indicate improved computational efficiency. We note that some of the estimators implementations permit parallelization, which generally decreases the required time. We nevertheless fit all estimators in serial to ensure a comparison that is relevant and informative for an audience with access to a diverse set of computing environments.

4.4 Results

Due to the many DGPs and estimators considered, a representative subset of results is presented in Figure 1. A comprehensive report of all estimators’ performance with respect to the previously introduced metrics are provided in Tables A1-A16 of the Appendix, stratified by DGP. These results are also illustrated in Figures A1, A2, A3, A4, and A5. We summarize our findings below.

Rule Quality: No estimator uniformly dominates the others (Figure A1). In the DGPs with sparse TEMs—regardless of whether treatment is randomized or of the covariates’ correlation structure—the filtered and non-filtered versions of the LASSO-based plug-in, AIPW-based, and augmented modified covariates estimators are the top performers (Figure 1A). These estimators produce empirical means that are approximately equal to the population mean under the optimal ITR in the linear model DGPs at all sample sizes and in the non-linear DGPs when $n = 1,000$. The optimal ITR is defined in Proposition 1, which is approximated using a Monte Carlo procedure for each DGP. When $n = 250$, the non-filtered versions of these estimators generally perform marginally better than their filtered counterparts. The reverse is true as sample size increases.

In the non-sparse settings, the non-filtered plug-in LASSO, AIPW-based, and LASSO-based augmented modified covariates estimators produce the best empirical mean outcomes on average (Figures A1). The empirical means obtained under these estimators are near the population mean under the optimal ITRs as sample size increases. The performance of the filtered versions of these estimators’ generally converges with increasing sample size to that of their non-filtered counterparts. An exception to this trend is observed in the DGPs with non-linear conditional expected outcomes and whose covariates’ covariance matrix is $I_{500 \times 500}$.

The XGBoost-based plug-in, modified covariates, and Causal Random Forest estimators are generally of lower rule quality than other estimators considered here, though their performance is improved by the covariate filtering procedure.

Accurate Interpretability: As illustrated in Boileau et al. [2022, 2024], only ITR estimators employing the TEM-VIP-based filtering procedure reliably control the FDR near the nominal 5% level regardless of the treatment assignment mechanism (Figures 1C and A2). Indeed, these estimators produce empirical FDRs near $\approx 5\%$ in all DGPs as sample sizes increase. All other estimators capable of classifying TEMs produce empirical FDRs ranging from 40% to 80%. However, we find that this FDR control sometimes results in a worse empirical TPR in non-sparse settings (Figure A3). This is not the case in DGPs with sparse conditional expected outcome models (Figure 1D). With respect to the empirical TNR, only the filtered estimators produce near-perfect results, and this regardless of sample size (Figure A4).

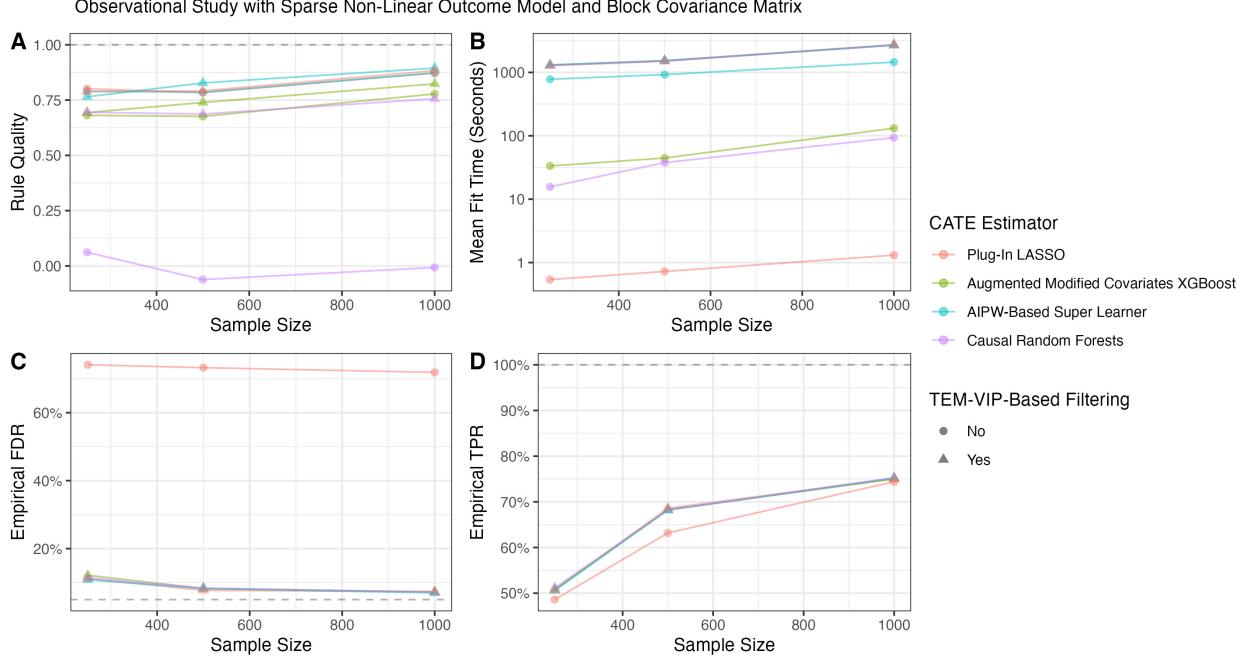


Figure 1: Simulation Study Results Summary: The results of select estimators in the simulated observational study with sparse non-linear conditional expected outcome and a block covariance matrix are presented. These results are representative of the general findings of the simulation study. **(A)** The relative rule quality computed over the 100 test set replicates. Rule quality is defined as the mean ITR outcome divided by the optimal ITR, given in Proposition 1, which is approximated using a Monte Carlo procedure for each DGP. The dotted line corresponds to the idealized relative rule quality. **(B)** The mean fit time in seconds computed over the 100 learning set replicates. Note the y-axis's log scale. **(C)** The empirical FDR computed over the 100 learning set replicates. The dotted line corresponds to desired nominal Type I error rate of 5%. **(D)** The empirical TPR computed over the 100 learning set replicates. The dotted line corresponds to the desired TPR of 100%.

Computational Efficiency: In RCT DGPs, the non-filtered LASSO-based plug-in estimator generally has the lowest mean fit time across all sample sizes and DGPs, followed closely by the non-filtered (augmented) modified covariates estimators using the LASSO and the non-filtered XGBoost plug-in estimator (Figure A5). The non-filtered AIPW-based estimators are the slowest estimators to produce a rule in all DGPs and sample sizes. All estimators using the TEM-VIP-based filtering procedure exhibit similar mean fit times that are several orders of magnitude larger than that of the non-filtered LASSO-based plug-in estimator. These filtered estimators' mean fit times are sometimes similar, however, to their non-filtered counterparts when $n = 1,000$, as is the case with Causal Random Forests and the augmented modified covariates estimators using XGBoost. Further, the filtered AIPW-based estimators have lower mean fit times than their non-filtered versions.

Similar patterns are observed in the observational study DGPs' simulations (Figure 1B). The non-filtered plug-in estimator using the LASSO is again the most computationally efficient procedure, followed by the non-filtered plug-in estimator using XGBoost (Figure A5). The non-filtered (augmented) modified covariates estimators and non-filtered the Causal Random Forests exhibit similar mean fit times which are approximately two orders of magnitude larger than the fastest estimator. The nonparametric AIPW-based estimators are again the slowest of the non-filtered estimators, though they produce estimated rules more quickly than any of the estimators relying on the TEM-VIP-based filtering strategy.

5 Discussion

The simulation results suggest that no ITR estimator uniformly dominates all others with respect to rule quality, accurate interpretability, and computational efficiency in the continuous outcome, binary treatment setting. We posit that the same is true in binary outcome, binary treatment settings. A trade-off must therefore be made when selecting a method with which to learn a treatment rule. Given that the primary goal of learning an ITR is to optimize patient benefit—that

is, to learn the optimal ITR—we hold that only high-quality estimators should be considered. Selecting a procedure therefore comes down to favoring either accurate interpretability or computational efficiency as a secondary goal.

If more importance is placed on accurate interpretability than computational efficiency, the TEM-VIP-based filtering procedure is a virtual necessity. None of the non-filtered estimators considered here reliably control the empirical FDR or produce near-perfect empirical TPRs (Figures A2, A4). Even when empirical TPR optimization is required, filtered estimators generally perform as well as non-filtered estimators (Figure A3). In sparse TEM scenarios, high-quality estimators are generally filtered. In non-sparse TEM settings, the filtered LASSO-based plug-in and AIPW-based estimators are typically only marginally worse than the non-filtered estimators with the highest rule quality.

However, the use of this filtering procedure may be constrained by available computing power. In RCTs, this filtering procedure makes fitting ITR estimators slower than their non-filtered versions in small sample sizes (Figure A5)—with the exception of nonparametric ITR estimators. This gap decreases in larger sample sizes: the mean fit times for the filtered estimators are approximately constant, while the non-filtered estimators’ fit times follow an approximately exponential function of sample size. In observational studies, where more computationally intensive nuisance parameter estimators are generally required to ensure accurate TEM classification, the filtered estimators are generally several orders of magnitude slower than their non-filtered counterparts.

When there is limited time, effort, or computing resources available to learn an ITR, the simulation study results suggest that the non-filtered LASSO-based plug-in estimator or the non-filtered augmented modified covariates approach using XGBoost should be used for analyzing data collected in an RCT. In observational studies, the LASSO-based plug-in estimator is the most computationally efficient of the estimators with sufficiently elevated rule quality. We again emphasize, however, that the computational efficiency of these procedures comes at the cost of accurate interpretability: these estimators cannot reliably distinguish TEMs from non-modifiers.

6 Recommendations

We summarize our discussion of the simulation results with concise recommendations about the choice of ITR estimators based on desired operating characteristics.

High-quality and accurately interpretable: The filtered LASSO-based plug-in and AIPW-based estimators generally produce high-quality ITR estimates while accurately recovering TEMs. These estimators are computationally intensive, however. When computational resources are available, parallelized implementations of these estimators will decrease the time required to produce a treatment rule estimate.

High-quality and computationally efficient: The LASSO-based plug-in estimator is among the most high-quality in our simulation study, providing empirical evidence that it is robust to model misspecification while being exceptionally computationally efficient. However, as previously mentioned, this estimator’s built-in feature selection capabilities should not be used for TEM discovery.

We emphasize that while this simulation study is comprehensive, practitioners may benefit from performing bespoke benchmarks of their own. Code used to generate the simulations results of Section 4, found on GitHub, may serve as foundation for extensions and modifications. This code relies on the `simChef` R package, which provides a general framework for building reproducible and computationally efficient simulation studies Duncan et al. [2024].

Code

Code used to generate the results is available in the PhilBoileau/pub_guidance-on-ITR-estimation-in-HD GitHub repository.

Acknowledgments.

P.B. gratefully acknowledges the support of the Fonds de recherche du Québec - Nature et technologies and the Natural Sciences and Engineering Research Council of Canada.

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Appendix

CATE Estimator	Metric	Unfiltered			TEM-VIP-Based Filtering		
		n = 250	n = 500	n = 1000	n = 250	n = 500	n = 1000
Plug-In LASSO	Rule quality	0.99	1.00	0.95	0.95	1.00	0.95
	Empirical FDR (%)	54.88	51.82	53.33	5.41	4.60	4.84
	Empirical TPR (%)	100.00	100.00	100.00	91.60	99.90	100.00
	Empirical TNR (%)	97.28	97.56	97.42	99.88	99.89	99.89
Plug-In XGBoost	Mean fit time (sec.)	0.51	0.66	1.08	67.43	75.54	87.46
	Rule quality	0.34	0.54	0.63	0.67	0.79	0.80
	Empirical FDR (%)	NA	NA	NA	5.34	4.69	4.77
	Empirical TPR (%)	NA	NA	NA	91.50	99.90	100.00
Modified Covariates LASSO	Empirical TNR (%)	NA	NA	NA	99.88	99.89	99.89
	Mean fit time (sec.)	2.18	5.21	14.19	66.17	74.09	86.73
	Rule quality	0.47	0.69	0.84	0.84	0.95	0.92
	Empirical FDR (%)	57.72	64.50	71.96	5.42	4.69	4.77
Modified Covariates XGBoost	Empirical TPR (%)	40.50	74.40	98.40	91.60	99.90	100.00
	Empirical TNR (%)	97.20	95.72	93.91	99.88	99.89	99.89
	Mean fit time (sec.)	0.44	0.86	0.93	65.80	73.78	85.99
	Rule quality	0.31	0.44	0.58	0.66	0.79	0.82
Augmented Modified Covariates LASSO	Empirical FDR (%)	NA	NA	NA	5.35	4.76	4.77
	Empirical TPR (%)	NA	NA	NA	91.50	99.90	100.00
	Empirical TNR (%)	NA	NA	NA	99.88	99.89	99.89
	Mean fit time (sec.)	10.26	16.26	32.96	74.98	85.32	101.38
Augmented Modified Covariates XGBoost	Rule quality	0.98	0.99	0.95	0.94	1.00	0.95
	Empirical FDR (%)	77.63	75.85	73.33	5.18	4.69	4.84
	Empirical TPR (%)	100.00	100.00	100.00	91.40	99.90	100.00
	Empirical TNR (%)	91.72	92.65	93.67	99.89	99.89	99.89
AIPW-Based LASSO	Mean fit time (sec.)	1.17	1.67	2.81	67.30	75.87	88.60
	Rule quality	0.83	0.93	0.91	0.88	0.97	0.93
	Empirical FDR (%)	NA	NA	NA	5.42	4.60	4.77
	Empirical TPR (%)	NA	NA	NA	91.60	99.90	100.00
AIPW-Based Super Learner	Empirical TNR (%)	NA	NA	NA	99.88	99.89	99.89
	Mean fit time (sec.)	86.46	114.07	154.01	102.34	122.81	138.76
	Rule quality	0.98	0.99	0.95	0.94	1.00	0.95
	Empirical FDR (%)	68.27	66.45	63.50	5.41	4.69	4.69
Causal Random Forests	Empirical TPR (%)	100.00	100.00	100.00	91.50	99.90	100.00
	Empirical TNR (%)	94.91	95.28	95.93	99.88	99.89	99.89
	Mean fit time (sec.)	718.99	803.38	977.49	77.62	88.79	106.51
	Rule quality	0.98	0.99	0.95	0.94	1.00	0.95
	Empirical FDR (%)	NA	NA	NA	5.28	4.69	4.75
	Empirical TPR (%)	NA	NA	NA	91.50	99.90	100.00
	Empirical TNR (%)	NA	NA	NA	99.88	99.89	99.89
	Mean fit time (sec.)	749.06	857.28	1092.48	88.86	99.19	123.61
	Rule quality	0.28	0.35	0.35	0.73	0.85	0.83
	Empirical FDR (%)	NA	NA	NA	5.53	4.69	4.77
	Empirical TPR (%)	NA	NA	NA	91.50	99.90	100.00
	Empirical TNR (%)	NA	NA	NA	99.88	99.89	99.89
	Mean fit time (sec.)	11.64	31.43	79.28	72.61	87.78	111.26

Table A1: Simulation results: RCT with Sparse Linear Outcome Model and Identity Covariance Matrix

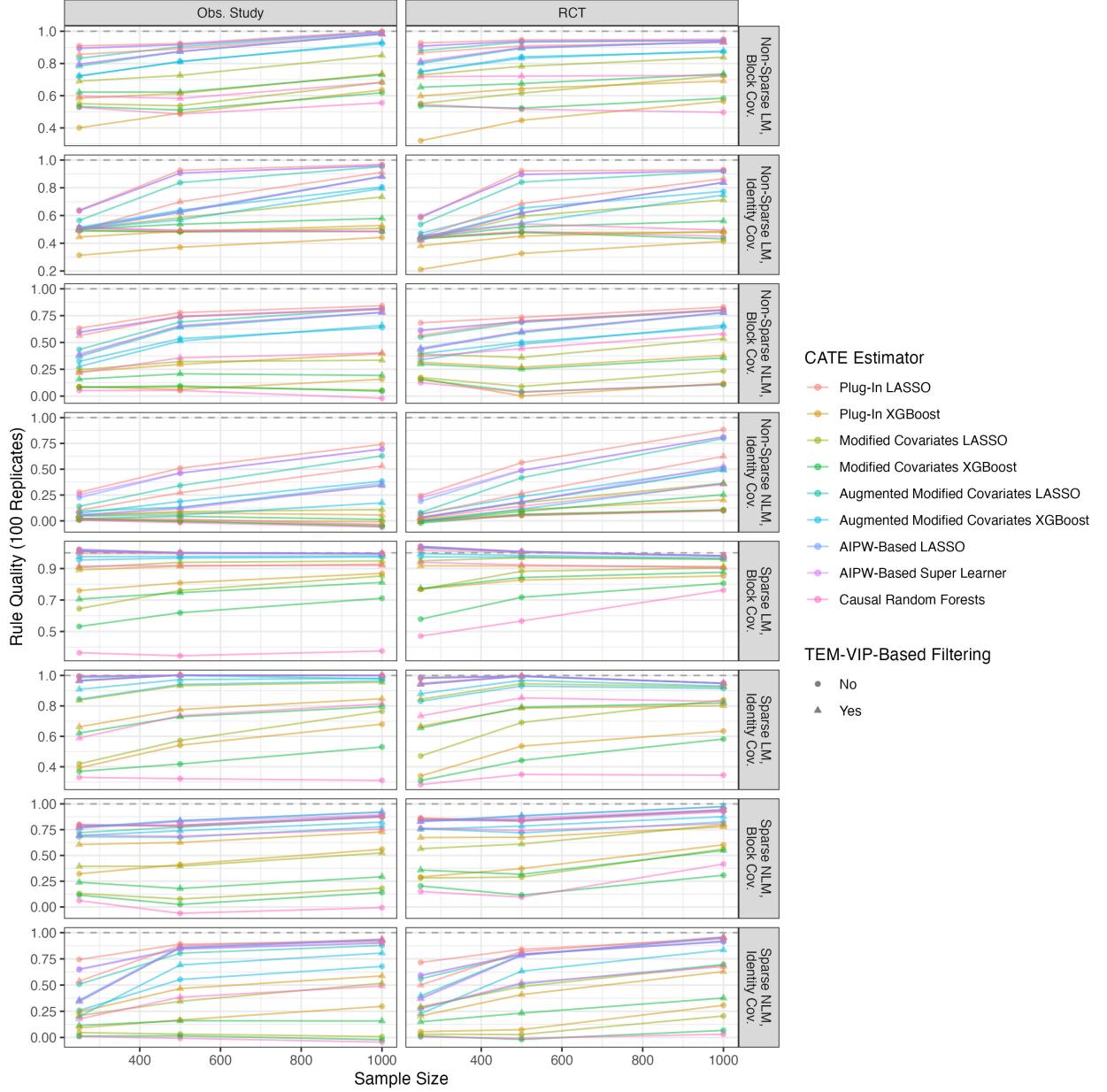


Figure A1: *Rule Quality*: The relative rule quality computed over the 100 test set replicates vs. sample size, for each combination of DGP. Relative rule quality is defined as the mean ITR outcome divided by the optimal ITR defined in Proposition 1, which is approximated using a Monte Carlo procedure for each DGP. The dotted line corresponds to the idealized relative rule quality.

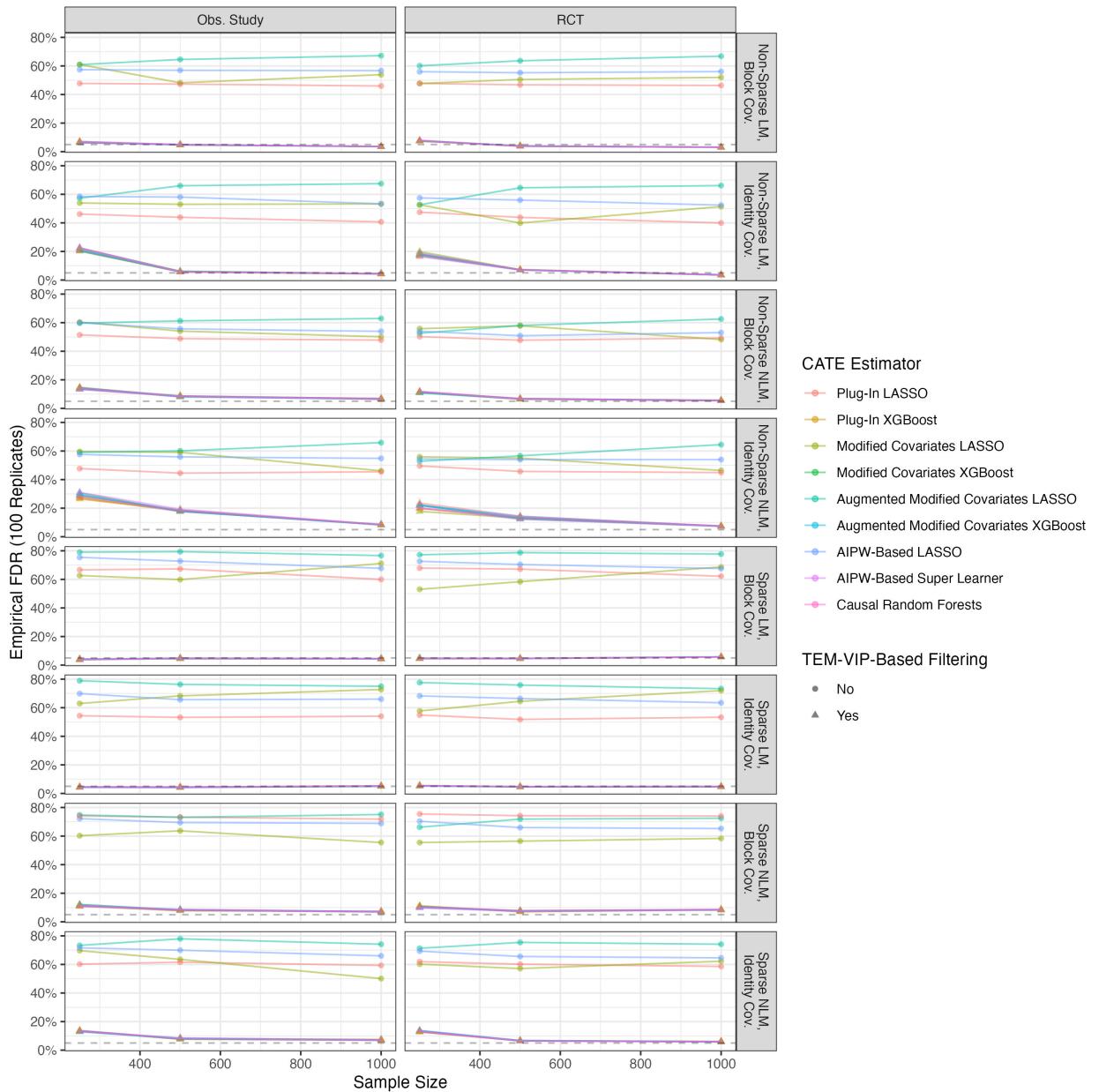


Figure A2: *Accurate Interpretability, FDR*: Empirical FDR computed over the 100 learning set replicates vs. sample size for each combination of DGP. The dotted line corresponds to desired nominal Type I error rate of 5%.

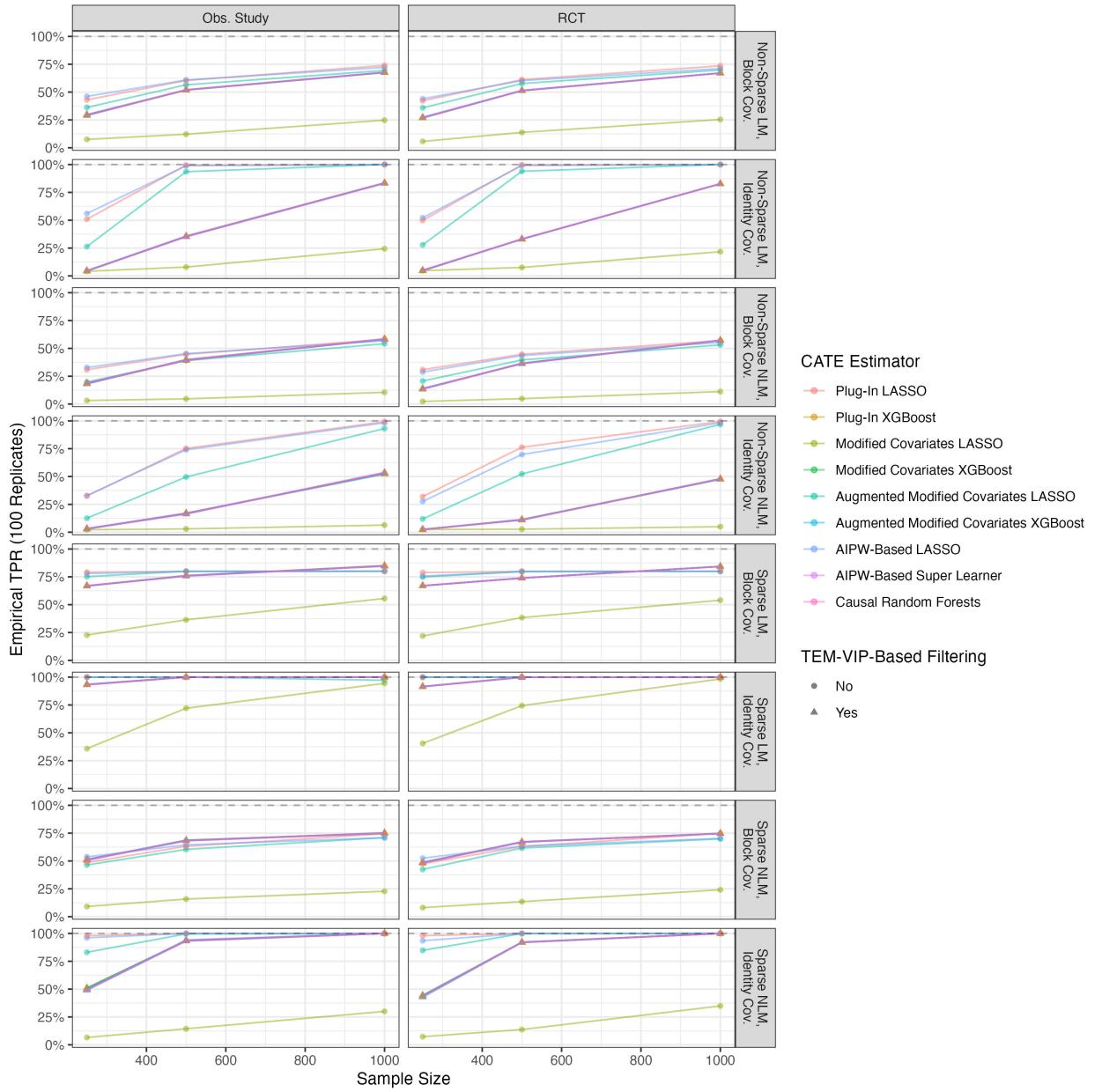


Figure A3: *Accurate Interpretability, TPR:* Empirical TPR computed over the 100 learning set replicates vs. sample size for each combination of DGP. The dotted line corresponds to desired TPR of 100%.

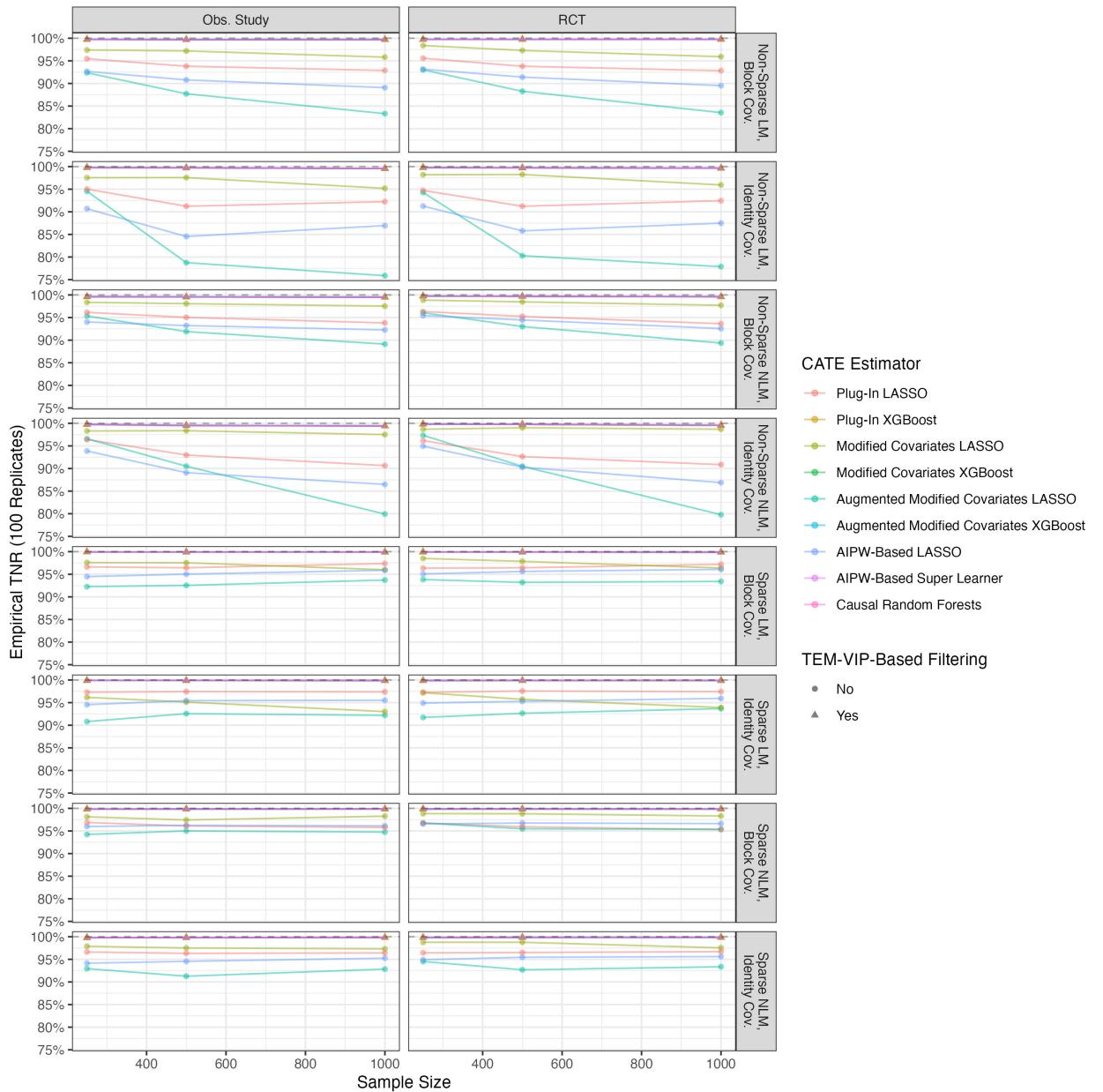


Figure A4: *Accurate Interpretability, TNR:* Empirical TNR computed over the 100 learning set replicates vs. sample size for each combination of DGP. The dotted line corresponds to desired TNR of 100%.

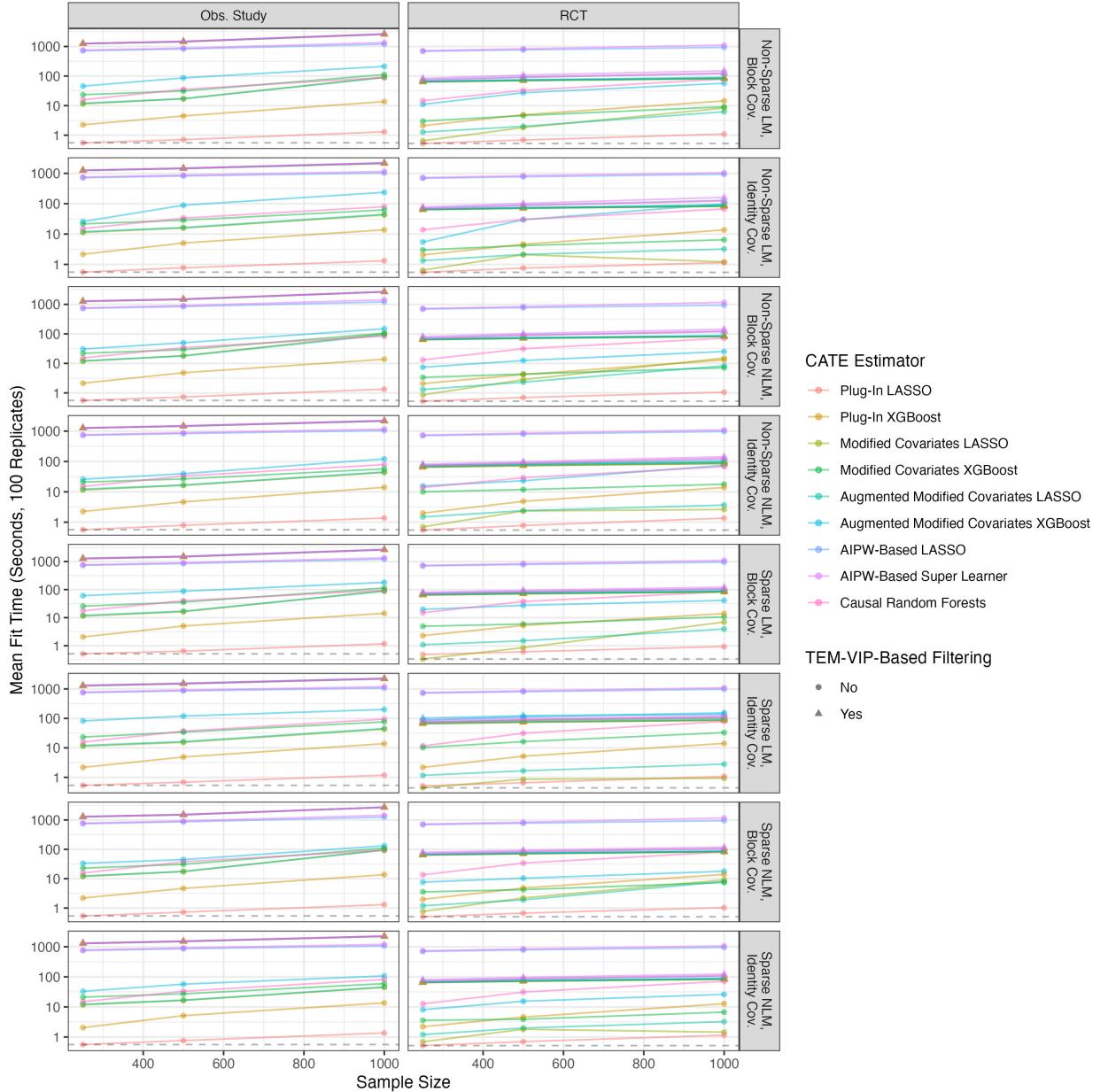


Figure A5: *Computational Efficiency*: Fit time computed over the 100 learning set replicates vs. sample size for each combination of DGP. The dotted line corresponds to the minimum mean fit time observed in each DGP.

CATE Estimator	Metric	Unfiltered			TEM-VIP-Based Filtering		
		n = 250	n = 500	n = 1000	n = 250	n = 500	n = 1000
Plug-In LASSO	Rule quality	1.00	1.00	1.00	0.97	1.00	1.00
	Empirical FDR (%)	54.39	53.24	54.06	4.58	4.57	5.25
	Empirical TPR (%)	100.00	100.00	100.00	93.30	100.00	100.00
	Empirical TNR (%)	97.30	97.44	97.38	99.90	99.89	99.88
	Mean fit time (sec.)	0.54	0.69	1.19	1285.98	1498.31	2196.98
Plug-In XGBoost	Rule quality	0.39	0.54	0.68	0.66	0.78	0.85
	Empirical FDR (%)	NA	NA	NA	4.32	4.33	5.10
	Empirical TPR (%)	NA	NA	NA	93.20	100.00	100.00
	Empirical TNR (%)	NA	NA	NA	99.90	99.90	99.88
	Mean fit time (sec.)	2.18	4.89	13.88	1278.96	1495.74	2200.38
Modified Covariates LASSO	Rule quality	0.42	0.57	0.76	0.84	0.93	0.96
	Empirical FDR (%)	62.96	68.30	72.76	4.46	4.33	5.10
	Empirical TPR (%)	35.80	72.10	94.40	93.50	100.00	100.00
	Empirical TNR (%)	96.17	95.13	93.01	99.90	99.90	99.88
	Mean fit time (sec.)	11.43	15.38	43.12	1284.50	1501.51	2213.89
Modified Covariates XGBoost	Rule quality	0.37	0.42	0.53	0.62	0.73	0.80
	Empirical FDR (%)	NA	NA	NA	4.48	4.33	5.02
	Empirical TPR (%)	NA	NA	NA	93.30	100.00	100.00
	Empirical TNR (%)	NA	NA	NA	99.90	99.90	99.88
	Mean fit time (sec.)	23.32	34.35	76.25	1299.77	1517.25	2235.83
Augmented Modified Covariates LASSO	Rule quality	0.99	1.00	0.98	0.97	1.00	1.00
	Empirical FDR (%)	78.89	76.33	75.00	4.56	4.31	5.25
	Empirical TPR (%)	100.00	100.00	97.20	93.40	100.00	100.00
	Empirical TNR (%)	90.81	92.56	92.18	99.90	99.90	99.88
	Mean fit time (sec.)	12.05	16.35	45.18	1286.57	1503.82	2212.27
Augmented Modified Covariates XGBoost	Rule quality	0.84	0.94	0.96	0.91	0.97	0.98
	Empirical FDR (%)	NA	NA	NA	4.33	4.16	5.02
	Empirical TPR (%)	NA	NA	NA	93.50	100.00	100.00
	Empirical TNR (%)	NA	NA	NA	99.90	99.90	99.88
	Mean fit time (sec.)	82.00	120.08	200.47	1316.34	1552.06	2283.46
AIPW-Based LASSO	Rule quality	0.99	1.00	1.00	0.97	1.00	1.00
	Empirical FDR (%)	69.89	65.64	66.02	4.30	4.25	5.15
	Empirical TPR (%)	100.00	100.00	100.00	93.40	100.00	100.00
	Empirical TNR (%)	94.54	95.44	95.51	99.90	99.90	99.88
	Mean fit time (sec.)	747.79	856.14	1072.22	1301.05	1522.12	2233.43
AIPW-Based Super Learner	Rule quality	0.99	1.00	1.00	0.96	1.00	1.00
	Empirical FDR (%)	NA	NA	NA	4.47	4.50	5.09
	Empirical TPR (%)	NA	NA	NA	93.30	100.00	100.00
	Empirical TNR (%)	NA	NA	NA	99.90	99.89	99.88
	Mean fit time (sec.)	774.92	909.20	1187.28	1310.44	1534.90	2244.74
Causal Random Forests	Rule quality	0.33	0.32	0.31	0.59	0.74	0.81
	Empirical FDR (%)	NA	NA	NA	4.50	4.22	5.32
	Empirical TPR (%)	NA	NA	NA	93.10	100.00	100.00
	Empirical TNR (%)	NA	NA	NA	99.90	99.90	99.87
	Mean fit time (sec.)	15.72	36.77	94.67	1290.28	1514.75	2236.92

Table A2: Simulation results: Observational Study with Sparse Linear Outcome Model and Identity Covariance Matrix

CATE Estimator	Metric	Unfiltered			TEM-VIP-Based Filtering		
		n = 250	n = 500	n = 1000	n = 250	n = 500	n = 1000
Plug-In LASSO	Rule quality	1.04	1.01	0.98	1.02	1.00	0.98
	Empirical FDR (%)	67.91	67.18	62.19	4.60	4.59	5.73
	Empirical TPR (%)	78.80	80.00	80.00	67.00	73.90	84.30
	Empirical TNR (%)	96.34	96.43	97.20	99.92	99.91	99.88
	Mean fit time (sec.)	0.49	0.61	0.93	65.01	72.45	84.75
Plug-In XGBoost	Rule quality	0.77	0.83	0.85	0.92	0.92	0.91
	Empirical FDR (%)	NA	NA	NA	4.60	4.59	5.73
	Empirical TPR (%)	NA	NA	NA	67.00	73.90	84.30
	Empirical TNR (%)	NA	NA	NA	99.92	99.91	99.88
	Mean fit time (sec.)	2.29	5.30	13.97	64.05	70.93	82.80
Modified Covariates LASSO	Rule quality	0.77	0.88	0.90	0.95	0.97	0.96
	Empirical FDR (%)	53.05	58.37	68.66	4.73	4.64	5.73
	Empirical TPR (%)	21.90	38.40	54.00	67.00	73.90	84.30
	Empirical TNR (%)	98.50	97.85	96.38	99.92	99.91	99.88
	Mean fit time (sec.)	0.34	0.85	6.98	63.89	70.72	82.19
Modified Covariates XGBoost	Rule quality	0.58	0.72	0.81	0.77	0.84	0.88
	Empirical FDR (%)	NA	NA	NA	4.74	4.68	5.73
	Empirical TPR (%)	NA	NA	NA	67.00	73.90	84.30
	Empirical TNR (%)	NA	NA	NA	99.92	99.91	99.88
	Mean fit time (sec.)	4.94	5.93	10.65	67.24	73.92	85.77
Augmented Modified Covariates LASSO	Rule quality	1.04	1.01	0.98	1.03	1.01	0.98
	Empirical FDR (%)	77.21	78.71	77.73	4.51	4.59	5.73
	Empirical TPR (%)	74.90	79.70	80.00	67.00	73.90	84.30
	Empirical TNR (%)	93.83	93.20	93.41	99.92	99.91	99.88
	Mean fit time (sec.)	1.09	1.50	3.95	64.85	72.83	84.60
Augmented Modified Covariates XGBoost	Rule quality	0.97	0.97	0.96	1.00	0.98	0.97
	Empirical FDR (%)	NA	NA	NA	4.76	4.59	5.73
	Empirical TPR (%)	NA	NA	NA	67.00	73.90	84.30
	Empirical TNR (%)	NA	NA	NA	99.92	99.91	99.88
	Mean fit time (sec.)	19.69	27.49	40.98	72.08	79.84	92.87
AIPW-Based LASSO	Rule quality	1.04	1.01	0.98	1.03	1.01	0.98
	Empirical FDR (%)	72.64	70.42	67.60	4.87	4.59	5.73
	Empirical TPR (%)	75.70	79.70	80.00	67.00	73.90	84.30
	Empirical TNR (%)	95.07	95.62	96.07	99.92	99.91	99.88
	Mean fit time (sec.)	698.37	781.89	946.50	73.84	84.93	105.01
AIPW-Based Super Learner	Rule quality	1.04	1.01	0.98	1.03	1.01	0.98
	Empirical FDR (%)	NA	NA	NA	4.62	4.59	5.73
	Empirical TPR (%)	NA	NA	NA	67.00	73.90	84.30
	Empirical TNR (%)	NA	NA	NA	99.92	99.91	99.88
	Mean fit time (sec.)	727.38	838.27	1097.19	80.72	94.42	121.68
Causal Random Forests	Rule quality	0.47	0.57	0.76	0.94	0.92	0.91
	Empirical FDR (%)	NA	NA	NA	4.64	4.59	5.73
	Empirical TPR (%)	NA	NA	NA	67.00	73.90	84.30
	Empirical TNR (%)	NA	NA	NA	99.92	99.91	99.88
	Mean fit time (sec.)	15.01	37.68	83.47	69.82	82.87	106.72

Table A3: Simulation results: RCT with Sparse Linear Outcome Model and Block Covariance Matrix

CATE Estimator	Metric	Unfiltered			TEM-VIP-Based Filtering		
		n = 250	n = 500	n = 1000	n = 250	n = 500	n = 1000
Plug-In LASSO	Rule quality	1.02	1.00	1.00	1.00	1.00	0.99
	Empirical FDR (%)	66.68	67.32	59.96	4.09	4.59	4.42
	Empirical TPR (%)	79.20	80.00	80.00	67.00	75.90	84.90
	Empirical TNR (%)	96.62	96.44	97.38	99.93	99.92	99.91
	Mean fit time (sec.)	0.52	0.64	1.17	1268.36	1480.99	2614.30
Plug-In XGBoost	Rule quality	0.76	0.81	0.87	0.89	0.92	0.93
	Empirical FDR (%)	NA	NA	NA	4.22	4.53	4.48
	Empirical TPR (%)	NA	NA	NA	66.90	76.00	85.20
	Empirical TNR (%)	NA	NA	NA	99.93	99.92	99.91
	Mean fit time (sec.)	2.06	5.05	14.30	1266.69	1478.83	2625.31
Modified Covariates LASSO	Rule quality	0.64	0.76	0.85	0.91	0.94	0.95
	Empirical FDR (%)	62.69	59.85	71.13	3.72	4.65	4.35
	Empirical TPR (%)	22.70	36.40	55.60	66.90	75.90	84.80
	Empirical TNR (%)	97.59	97.54	96.00	99.94	99.91	99.91
	Mean fit time (sec.)	11.43	16.29	91.10	1271.48	1485.92	2640.70
Modified Covariates XGBoost	Rule quality	0.53	0.62	0.71	0.71	0.75	0.81
	Empirical FDR (%)	NA	NA	NA	3.97	4.88	4.41
	Empirical TPR (%)	NA	NA	NA	66.80	76.20	84.60
	Empirical TNR (%)	NA	NA	NA	99.94	99.91	99.91
	Mean fit time (sec.)	25.78	35.77	114.26	1279.80	1505.50	2652.49
Augmented Modified Covariates LASSO	Rule quality	1.01	1.00	1.00	1.01	1.00	1.00
	Empirical FDR (%)	79.01	79.40	76.66	4.09	4.46	4.53
	Empirical TPR (%)	75.20	80.00	80.10	66.80	76.00	84.90
	Empirical TNR (%)	92.26	92.54	93.71	99.93	99.92	99.91
	Mean fit time (sec.)	12.01	17.02	87.90	1268.95	1490.85	2639.48
Augmented Modified Covariates XGBoost	Rule quality	0.95	0.97	0.97	0.98	0.98	0.98
	Empirical FDR (%)	NA	NA	NA	4.22	4.72	4.33
	Empirical TPR (%)	NA	NA	NA	66.80	75.70	84.90
	Empirical TNR (%)	NA	NA	NA	99.93	99.91	99.91
	Mean fit time (sec.)	60.73	87.24	181.10	1294.77	1527.59	2690.81
AIPW-Based LASSO	Rule quality	1.02	1.00	1.00	1.01	1.00	1.00
	Empirical FDR (%)	75.42	72.76	67.76	3.97	4.58	4.59
	Empirical TPR (%)	78.00	79.80	80.00	67.00	75.90	84.70
	Empirical TNR (%)	94.48	95.02	95.88	99.94	99.91	99.90
	Mean fit time (sec.)	735.33	848.68	1220.28	1280.04	1505.40	2635.82
AIPW-Based Super Learner	Rule quality	1.02	1.00	1.00	1.01	1.00	1.00
	Empirical FDR (%)	NA	NA	NA	3.99	4.74	4.34
	Empirical TPR (%)	NA	NA	NA	66.80	75.70	84.80
	Empirical TNR (%)	NA	NA	NA	99.94	99.91	99.91
	Mean fit time (sec.)	762.44	898.22	1355.78	1287.77	1513.87	2628.08
Causal Random Forests	Rule quality	0.36	0.35	0.38	0.92	0.92	0.92
	Empirical FDR (%)	NA	NA	NA	3.72	4.77	4.48
	Empirical TPR (%)	NA	NA	NA	67.00	76.00	84.90
	Empirical TNR (%)	NA	NA	NA	99.94	99.91	99.91
	Mean fit time (sec.)	17.57	40.15	94.69	1271.76	1497.79	2647.69

Table A4: Simulation results: Observational Study with Sparse Linear Outcome Model and Block Covariance Matrix

CATE Estimator	Metric	Unfiltered			TEM-VIP-Based Filtering		
		n = 250	n = 500	n = 1000	n = 250	n = 500	n = 1000
Plug-In LASSO	Rule quality	0.72	0.84	0.94	0.50	0.82	0.96
	Empirical FDR (%)	61.95	60.18	58.60	12.97	6.63	5.82
	Empirical TPR (%)	98.00	100.00	100.00	43.50	92.00	100.00
	Empirical TNR (%)	96.43	96.50	96.70	99.82	99.85	99.86
Plug-In XGBoost	Mean fit time (sec.)	0.52	0.70	1.15	65.26	72.65	84.65
	Rule quality	0.06	0.07	0.31	0.21	0.41	0.63
	Empirical FDR (%)	NA	NA	NA	13.12	6.58	6.04
	Empirical TPR (%)	NA	NA	NA	44.10	91.90	100.00
Modified Covariates LASSO	Empirical TNR (%)	NA	NA	NA	99.82	99.85	99.85
	Mean fit time (sec.)	2.21	4.59	12.83	64.29	71.34	83.58
	Rule quality	0.03	0.03	0.20	0.29	0.48	0.69
	Empirical FDR (%)	60.20	57.12	62.25	12.75	6.60	6.12
Modified Covariates XGBoost	Empirical TPR (%)	7.30	13.70	34.90	44.40	92.10	100.00
	Empirical TNR (%)	98.77	98.77	97.54	99.82	99.85	99.85
	Mean fit time (sec.)	0.69	1.81	1.45	64.16	71.11	82.74
	Rule quality	0.01	-0.02	0.07	0.15	0.23	0.38
Augmented Modified Covariates LASSO	Empirical FDR (%)	NA	NA	NA	13.44	6.61	5.97
	Empirical TPR (%)	NA	NA	NA	44.00	92.30	100.00
	Empirical TNR (%)	NA	NA	NA	99.81	99.85	99.86
	Mean fit time (sec.)	3.59	3.90	6.71	66.92	73.79	85.85
Augmented Modified Covariates XGBoost	Rule quality	0.56	0.79	0.92	0.40	0.79	0.95
	Empirical FDR (%)	71.30	75.42	74.15	13.58	6.72	5.71
	Empirical TPR (%)	84.80	99.90	100.00	42.60	92.00	100.00
	Empirical TNR (%)	94.52	92.69	93.35	99.82	99.85	99.86
AIPW-Based LASSO	Mean fit time (sec.)	1.21	1.99	3.24	65.05	73.01	84.89
	Rule quality	0.28	0.51	0.70	0.23	0.63	0.84
	Empirical FDR (%)	NA	NA	NA	13.77	6.73	5.92
	Empirical TPR (%)	NA	NA	NA	44.50	92.00	100.00
AIPW-Based Super Learner	Empirical TNR (%)	NA	NA	NA	99.81	99.85	99.86
	Mean fit time (sec.)	8.06	15.47	26.13	67.35	75.95	89.19
	Rule quality	0.59	0.79	0.91	0.38	0.79	0.95
	Empirical FDR (%)	69.33	65.56	64.59	13.57	6.39	5.96
Causal Random Forests	Empirical TPR (%)	93.50	99.90	100.00	43.50	91.90	100.00
	Empirical TNR (%)	94.91	95.46	95.61	99.82	99.86	99.86
	Mean fit time (sec.)	700.71	784.39	945.12	73.57	86.15	105.23
	Rule quality	0.59	0.80	0.91	0.37	0.78	0.95
	Empirical FDR (%)	NA	NA	NA	13.58	6.52	5.89
	Empirical TPR (%)	NA	NA	NA	43.90	92.00	100.00
	Empirical TNR (%)	NA	NA	NA	99.82	99.85	99.86
	Mean fit time (sec.)	732.22	846.29	1072.01	80.19	95.97	123.03
	Rule quality	0.01	-0.01	0.03	0.28	0.52	0.68
	Empirical FDR (%)	NA	NA	NA	12.77	6.53	6.00
	Empirical TPR (%)	NA	NA	NA	43.60	92.00	100.00
	Empirical TNR (%)	NA	NA	NA	99.82	99.85	99.86
	Mean fit time (sec.)	12.68	31.26	71.44	69.46	84.65	109.05

Table A5: Simulation results: RCT with Sparse Non-Linear Outcome Model and Identity Covariance Matrix

CATE Estimator	Metric	Unfiltered			TEM-VIP-Based Filtering		
		n = 250	n = 500	n = 1000	n = 250	n = 500	n = 1000
Plug-In LASSO	Rule quality	0.74	0.89	0.92	0.54	0.88	0.94
	Empirical FDR (%)	60.20	61.57	59.33	13.61	8.02	6.84
	Empirical TPR (%)	98.00	100.00	100.00	50.40	93.20	100.00
	Empirical TNR (%)	96.62	96.32	96.42	99.79	99.81	99.84
Plug-In XGBoost	Mean fit time (sec.)	0.56	0.76	1.36	1288.48	1498.63	2214.52
	Rule quality	0.09	0.17	0.30	0.24	0.47	0.59
	Empirical FDR (%)	NA	NA	NA	13.34	7.87	7.07
	Empirical TPR (%)	NA	NA	NA	50.80	93.50	100.00
Modified Covariates LASSO	Empirical TNR (%)	NA	NA	NA	99.80	99.81	99.83
	Mean fit time (sec.)	2.05	5.14	13.65	1287.49	1498.99	2222.88
	Rule quality	0.05	0.03	0.01	0.21	0.35	0.52
	Empirical FDR (%)	69.66	63.56	50.09	13.71	7.96	7.51
Modified Covariates XGBoost	Empirical TPR (%)	6.60	14.40	30.00	49.80	93.80	100.00
	Empirical TNR (%)	97.88	97.51	97.31	99.79	99.81	99.82
	Mean fit time (sec.)	11.71	16.45	44.60	1291.44	1504.89	2222.43
	Rule quality	0.01	0.02	-0.02	0.11	0.16	0.16
Augmented Modified Covariates LASSO	Empirical FDR (%)	NA	NA	NA	13.32	7.67	7.04
	Empirical TPR (%)	NA	NA	NA	51.10	93.60	100.00
	Empirical TNR (%)	NA	NA	NA	99.79	99.82	99.83
	Mean fit time (sec.)	21.17	27.25	59.50	1301.96	1515.93	2244.15
Augmented Modified Covariates XGBoost	Rule quality	0.51	0.80	0.88	0.35	0.85	0.93
	Empirical FDR (%)	73.34	77.93	74.15	13.59	8.24	7.12
	Empirical TPR (%)	83.10	99.60	99.80	50.60	93.50	100.00
	Empirical TNR (%)	92.94	91.27	92.84	99.80	99.80	99.82
AIPW-Based LASSO	Mean fit time (sec.)	12.29	16.82	45.95	1293.00	1508.69	2229.23
	Rule quality	0.26	0.55	0.68	0.20	0.69	0.81
	Empirical FDR (%)	NA	NA	NA	12.97	8.04	7.04
	Empirical TPR (%)	NA	NA	NA	49.00	93.40	100.00
AIPW-Based Super Learner	Empirical TNR (%)	NA	NA	NA	99.80	99.81	99.83
	Mean fit time (sec.)	33.07	57.02	107.41	1303.81	1527.92	2252.42
	Rule quality	0.65	0.85	0.90	0.36	0.86	0.93
	Empirical FDR (%)	71.60	69.97	66.02	12.92	8.60	7.17
Causal Random Forests	Empirical TPR (%)	96.10	100.00	100.00	49.20	94.30	100.00
	Empirical TNR (%)	94.14	94.55	95.26	99.80	99.80	99.82
	Mean fit time (sec.)	750.51	859.28	1071.85	1303.96	1527.14	2242.93
	Rule quality	0.65	0.84	0.90	0.34	0.86	0.93
	Empirical FDR (%)	NA	NA	NA	13.69	8.07	7.22
	Empirical TPR (%)	NA	NA	NA	49.60	93.70	100.00
	Empirical TNR (%)	NA	NA	NA	99.79	99.81	99.82
	Mean fit time (sec.)	779.20	916.65	1201.11	1313.50	1537.09	2262.57
	Rule quality	0.01	-0.01	-0.04	0.18	0.38	0.49
	Empirical FDR (%)	NA	NA	NA	13.42	8.06	7.24
	Empirical TPR (%)	NA	NA	NA	49.20	93.20	100.00
	Empirical TNR (%)	NA	NA	NA	99.79	99.81	99.83
	Mean fit time (sec.)	14.93	33.12	82.13	1293.04	1518.81	2252.98

Table A6: Simulation results: Observational Study with Sparse Non-Linear Outcome Model and Identity Covariance Matrix

CATE Estimator	Metric	Unfiltered			TEM-VIP-Based Filtering		
		n = 250	n = 500	n = 1000	n = 250	n = 500	n = 1000
Plug-In LASSO	Rule quality	0.86	0.84	0.93	0.86	0.84	0.94
	Empirical FDR (%)	75.47	74.26	74.03	10.65	7.68	8.24
	Empirical TPR (%)	47.50	63.00	74.80	48.80	67.20	74.70
	Empirical TNR (%)	96.77	95.93	95.32	99.86	99.86	99.84
Plug-In XGBoost	Mean fit time (sec.)	0.51	0.67	1.03	64.74	72.23	85.61
	Rule quality	0.29	0.37	0.60	0.67	0.68	0.78
	Empirical FDR (%)	NA	NA	NA	11.23	7.02	8.41
	Empirical TPR (%)	NA	NA	NA	48.50	66.90	74.70
Modified Covariates LASSO	Empirical TNR (%)	NA	NA	NA	99.86	99.87	99.84
	Mean fit time (sec.)	1.98	4.80	13.95	63.80	70.77	82.57
	Rule quality	0.28	0.29	0.56	0.57	0.61	0.80
	Empirical FDR (%)	55.51	56.47	58.35	10.83	7.25	8.46
Modified Covariates XGBoost	Empirical TPR (%)	8.10	13.50	24.10	48.20	67.00	74.60
	Empirical TNR (%)	98.83	98.82	98.31	99.85	99.87	99.84
	Mean fit time (sec.)	0.76	2.21	9.11	63.66	70.63	81.69
	Rule quality	0.20	0.11	0.31	0.36	0.32	0.55
Augmented Modified Covariates LASSO	Empirical FDR (%)	NA	NA	NA	10.11	7.74	8.35
	Empirical TPR (%)	NA	NA	NA	48.70	67.10	74.60
	Empirical TNR (%)	NA	NA	NA	99.86	99.86	99.84
	Mean fit time (sec.)	3.56	4.22	7.44	66.41	73.30	85.21
Augmented Modified Covariates XGBoost	Rule quality	0.84	0.84	0.94	0.83	0.88	0.97
	Empirical FDR (%)	66.22	71.88	72.49	10.69	7.35	8.44
	Empirical TPR (%)	42.40	61.60	69.80	48.30	66.90	74.80
	Empirical TNR (%)	96.75	95.48	95.37	99.86	99.87	99.84
AIPW-Based LASSO	Mean fit time (sec.)	1.20	1.89	7.98	64.70	72.54	84.36
	Rule quality	0.76	0.72	0.83	0.75	0.79	0.88
	Empirical FDR (%)	NA	NA	NA	10.55	7.60	8.53
	Empirical TPR (%)	NA	NA	NA	48.80	67.10	74.70
AIPW-Based Super Learner	Empirical TNR (%)	NA	NA	NA	99.85	99.86	99.84
	Mean fit time (sec.)	7.64	10.37	17.87	67.10	74.71	87.00
	Rule quality	0.85	0.84	0.94	0.83	0.89	0.97
	Empirical FDR (%)	70.39	65.97	65.27	10.09	7.55	8.43
Causal Random Forests	Empirical TPR (%)	52.50	63.40	70.30	48.10	67.30	74.60
	Empirical TNR (%)	96.57	96.75	96.63	99.86	99.86	99.84
	Mean fit time (sec.)	695.05	778.12	945.00	72.96	84.03	102.92
	Rule quality	0.85	0.83	0.92	0.83	0.86	0.94
	Empirical FDR (%)	NA	NA	NA	9.66	7.39	8.31
	Empirical TPR (%)	NA	NA	NA	48.10	66.90	74.70
	Empirical TNR (%)	NA	NA	NA	99.87	99.87	99.84
	Mean fit time (sec.)	725.98	839.18	1168.98	79.53	93.16	119.29
	Rule quality	0.15	0.10	0.42	0.77	0.74	0.81
	Empirical FDR (%)	NA	NA	NA	10.51	7.82	8.65
	Empirical TPR (%)	NA	NA	NA	48.60	67.00	74.60
	Empirical TNR (%)	NA	NA	NA	99.86	99.86	99.84
	Mean fit time (sec.)	13.52	34.10	80.81	69.20	82.56	105.42

Table A7: Simulation results: RCT with Sparse Non-Linear Outcome Model and Block Covariance Matrix

CATE Estimator	Metric	Unfiltered			TEM-VIP-Based Filtering		
		n = 250	n = 500	n = 1000	n = 250	n = 500	n = 1000
Plug-In LASSO	Rule quality	0.80	0.78	0.87	0.79	0.79	0.88
	Empirical FDR (%)	74.10	73.25	71.86	11.16	7.73	7.34
	Empirical TPR (%)	48.60	63.20	74.40	50.70	68.60	75.10
	Empirical TNR (%)	96.88	96.11	95.79	99.83	99.86	99.86
	Mean fit time (sec.)	0.54	0.72	1.31	1285.60	1501.50	2708.36
Plug-In XGBoost	Rule quality	0.32	0.41	0.56	0.61	0.63	0.73
	Empirical FDR (%)	NA	NA	NA	10.83	8.01	7.11
	Empirical TPR (%)	NA	NA	NA	51.50	68.10	74.80
	Empirical TNR (%)	NA	NA	NA	99.84	99.85	99.87
	Mean fit time (sec.)	2.19	4.66	13.72	1284.61	1502.65	2716.66
Modified Covariates LASSO	Rule quality	0.13	0.08	0.18	0.39	0.40	0.52
	Empirical FDR (%)	60.29	63.69	55.52	12.06	8.37	7.10
	Empirical TPR (%)	9.10	15.80	22.80	51.00	68.30	75.30
	Empirical TNR (%)	98.14	97.44	98.27	99.82	99.85	99.87
	Mean fit time (sec.)	11.92	17.43	95.63	1286.64	1507.44	2709.83
Modified Covariates XGBoost	Rule quality	0.12	0.02	0.14	0.24	0.18	0.29
	Empirical FDR (%)	NA	NA	NA	11.25	8.11	7.21
	Empirical TPR (%)	NA	NA	NA	51.00	68.70	74.90
	Empirical TNR (%)	NA	NA	NA	99.84	99.85	99.86
	Mean fit time (sec.)	22.86	30.89	109.89	1295.73	1518.52	2725.34
Augmented Modified Covariates LASSO	Rule quality	0.72	0.78	0.88	0.77	0.84	0.92
	Empirical FDR (%)	74.77	73.13	75.10	11.36	8.36	6.87
	Empirical TPR (%)	46.40	60.40	71.00	51.20	68.40	75.00
	Empirical TNR (%)	94.23	95.01	94.74	99.83	99.84	99.87
	Mean fit time (sec.)	12.30	17.69	94.37	1288.82	1512.12	2706.51
Augmented Modified Covariates XGBoost	Rule quality	0.68	0.68	0.78	0.69	0.74	0.82
	Empirical FDR (%)	NA	NA	NA	12.15	8.26	7.25
	Empirical TPR (%)	NA	NA	NA	50.80	68.30	75.00
	Empirical TNR (%)	NA	NA	NA	99.82	99.85	99.86
	Mean fit time (sec.)	33.46	44.63	131.79	1304.42	1524.95	2726.26
AIPW-Based LASSO	Rule quality	0.79	0.79	0.89	0.77	0.84	0.92
	Empirical FDR (%)	72.21	69.47	68.88	11.18	8.77	7.08
	Empirical TPR (%)	53.70	64.50	70.90	51.50	68.50	75.10
	Empirical TNR (%)	95.99	96.25	96.14	99.83	99.84	99.87
	Mean fit time (sec.)	749.21	865.50	1247.68	1303.10	1525.92	2690.73
AIPW-Based Super Learner	Rule quality	0.79	0.79	0.87	0.76	0.83	0.89
	Empirical FDR (%)	NA	NA	NA	10.83	8.28	6.97
	Empirical TPR (%)	NA	NA	NA	50.60	68.20	75.20
	Empirical TNR (%)	NA	NA	NA	99.84	99.85	99.87
	Mean fit time (sec.)	779.23	924.56	1452.27	1312.20	1537.01	2679.75
Causal Random Forests	Rule quality	0.06	-0.06	-0.01	0.69	0.69	0.76
	Empirical FDR (%)	NA	NA	NA	11.42	8.37	7.21
	Empirical TPR (%)	NA	NA	NA	51.20	68.20	75.30
	Empirical TNR (%)	NA	NA	NA	99.83	99.85	99.86
	Mean fit time (sec.)	15.66	37.75	93.58	1290.05	1519.02	2705.30

Table A8: Simulation results: Observational Study with Sparse Non-Linear Outcome Model and Block Covariance Matrix

CATE Estimator	Metric	Unfiltered			TEM-VIP-Based Filtering		
		n = 250	n = 500	n = 1000	n = 250	n = 500	n = 1000
Plug-In LASSO	Rule quality	0.58	0.92	0.93	0.45	0.69	0.87
	Empirical FDR (%)	47.50	43.85	39.97	18.48	7.14	3.58
	Empirical TPR (%)	49.82	99.68	100.00	4.68	33.04	82.70
	Empirical TNR (%)	94.72	91.23	92.45	99.80	99.72	99.65
Plug-In XGBoost	Mean fit time (sec.)	0.55	0.76	1.15	64.45	71.90	83.55
	Rule quality	0.21	0.33	0.41	0.38	0.45	0.49
	Empirical FDR (%)	NA	NA	NA	16.82	7.28	3.61
	Empirical TPR (%)	NA	NA	NA	4.66	33.08	82.74
Modified Covariates LASSO	Empirical TNR (%)	NA	NA	NA	99.81	99.72	99.64
	Mean fit time (sec.)	2.05	4.60	13.69	63.43	70.61	83.51
	Rule quality	0.43	0.48	0.48	0.42	0.59	0.71
	Empirical FDR (%)	52.64	39.92	51.37	19.90	7.25	3.64
Modified Covariates XGBoost	Empirical TPR (%)	4.72	7.60	21.74	4.88	32.96	82.80
	Empirical TNR (%)	98.20	98.25	95.94	99.78	99.72	99.64
	Mean fit time (sec.)	0.65	2.10	1.21	63.30	70.41	81.51
	Rule quality	0.44	0.48	0.43	0.44	0.52	0.56
Augmented Modified Covariates LASSO	Empirical FDR (%)	NA	NA	NA	17.79	7.12	3.60
	Empirical TPR (%)	NA	NA	NA	4.84	33.04	82.68
	Empirical TNR (%)	NA	NA	NA	99.79	99.72	99.64
	Mean fit time (sec.)	3.00	4.19	6.49	65.58	72.94	85.37
Augmented Modified Covariates XGBoost	Rule quality	0.54	0.84	0.92	0.43	0.62	0.84
	Empirical FDR (%)	52.67	64.58	66.10	17.92	7.11	3.60
	Empirical TPR (%)	27.84	93.98	100.00	4.74	33.16	82.68
	Empirical TNR (%)	94.28	80.28	77.87	99.79	99.72	99.64
AIPW-Based LASSO	Mean fit time (sec.)	1.34	2.14	3.20	64.45	72.22	83.43
	Rule quality	0.47	0.65	0.77	0.45	0.54	0.75
	Empirical FDR (%)	NA	NA	NA	17.43	7.05	3.55
	Empirical TPR (%)	NA	NA	NA	4.74	33.02	82.74
AIPW-Based Super Learner	Empirical TNR (%)	NA	NA	NA	99.78	99.73	99.65
	Mean fit time (sec.)	5.47	29.67	98.29	65.78	73.61	93.18
	Rule quality	0.59	0.90	0.92	0.44	0.62	0.84
	Empirical FDR (%)	57.47	55.96	52.43	18.89	7.21	3.55
Causal Random Forests	Empirical TPR (%)	52.16	99.12	100.00	5.04	33.18	82.72
	Empirical TNR (%)	91.27	85.78	87.49	99.76	99.72	99.65
	Mean fit time (sec.)	690.79	771.17	926.92	71.76	89.88	129.04
	Rule quality	0.59	0.90	0.92	0.42	0.62	0.84
	Empirical FDR (%)	NA	NA	NA	16.44	7.03	3.64
	Empirical TPR (%)	NA	NA	NA	5.08	33.12	82.80
	Empirical TNR (%)	NA	NA	NA	99.79	99.72	99.64
	Mean fit time (sec.)	723.86	835.28	1050.34	77.39	102.05	161.40
	Rule quality	0.44	0.49	0.45	0.45	0.54	0.49
	Empirical FDR (%)	NA	NA	NA	18.12	7.18	3.56
	Empirical TPR (%)	NA	NA	NA	4.84	33.16	82.76
	Empirical TNR (%)	NA	NA	NA	99.80	99.72	99.65
	Mean fit time (sec.)	13.88	30.26	67.22	68.61	86.01	123.85

Table A9: Simulation results: RCT with Non-Sparse Linear Outcome Model and Identity Covariance Matrix

CATE Estimator	Metric	Unfiltered			TEM-VIP-Based Filtering		
		n = 250	n = 500	n = 1000	n = 250	n = 500	n = 1000
Plug-In LASSO	Rule quality	0.64	0.93	0.97	0.49	0.70	0.91
	Empirical FDR (%)	46.18	43.92	40.70	20.28	5.84	4.31
	Empirical TPR (%)	50.94	99.42	100.00	4.26	35.76	83.50
	Empirical TNR (%)	95.02	91.23	92.24	99.81	99.73	99.57
	Mean fit time (sec.)	0.56	0.78	1.32	1244.32	1450.47	2129.83
Plug-In XGBoost	Rule quality	0.31	0.37	0.44	0.45	0.49	0.53
	Empirical FDR (%)	NA	NA	NA	21.00	5.69	4.22
	Empirical TPR (%)	NA	NA	NA	4.54	35.60	83.44
	Empirical TNR (%)	NA	NA	NA	99.78	99.73	99.58
	Mean fit time (sec.)	2.16	5.05	13.83	1244.99	1446.94	2138.34
Modified Covariates LASSO	Rule quality	0.49	0.48	0.51	0.50	0.58	0.73
	Empirical FDR (%)	53.91	53.01	53.24	22.05	6.22	4.35
	Empirical TPR (%)	4.16	7.94	24.36	4.46	35.36	83.44
	Empirical TNR (%)	97.54	97.56	95.19	99.79	99.71	99.57
	Mean fit time (sec.)	11.32	15.79	42.52	1247.94	1447.56	2139.97
Modified Covariates XGBoost	Rule quality	0.49	0.48	0.49	0.50	0.54	0.58
	Empirical FDR (%)	NA	NA	NA	20.34	5.69	4.45
	Empirical TPR (%)	NA	NA	NA	4.36	35.30	83.48
	Empirical TNR (%)	NA	NA	NA	99.81	99.74	99.56
	Mean fit time (sec.)	21.67	28.57	62.41	1256.05	1462.82	2162.50
Augmented Modified Covariates LASSO	Rule quality	0.56	0.84	0.95	0.51	0.62	0.88
	Empirical FDR (%)	57.28	65.98	67.46	22.56	6.00	4.41
	Empirical TPR (%)	26.32	93.62	100.00	4.48	35.52	83.14
	Empirical TNR (%)	94.55	78.76	75.88	99.79	99.72	99.56
	Mean fit time (sec.)	11.95	16.38	44.77	1250.36	1449.69	2140.68
Augmented Modified Covariates XGBoost	Rule quality	0.52	0.64	0.81	0.50	0.57	0.80
	Empirical FDR (%)	NA	NA	NA	21.05	5.91	4.36
	Empirical TPR (%)	NA	NA	NA	4.78	35.60	83.48
	Empirical TNR (%)	NA	NA	NA	99.78	99.73	99.57
	Mean fit time (sec.)	25.82	89.09	236.97	1258.51	1466.26	2194.13
AIPW-Based LASSO	Rule quality	0.64	0.91	0.96	0.51	0.63	0.88
	Empirical FDR (%)	58.46	58.06	53.37	21.07	5.82	4.46
	Empirical TPR (%)	56.00	98.96	100.00	4.46	35.28	83.48
	Empirical TNR (%)	90.68	84.54	86.95	99.79	99.73	99.56
	Mean fit time (sec.)	719.46	817.62	1027.26	1257.46	1470.86	2199.02
AIPW-Based Super Learner	Rule quality	0.63	0.91	0.96	0.49	0.62	0.88
	Empirical FDR (%)	NA	NA	NA	22.45	5.81	4.35
	Empirical TPR (%)	NA	NA	NA	4.56	35.10	83.10
	Empirical TNR (%)	NA	NA	NA	99.78	99.74	99.57
	Mean fit time (sec.)	748.58	875.43	1154.68	1259.41	1483.30	2220.65
Causal Random Forests	Rule quality	0.51	0.49	0.49	0.51	0.49	0.49
	Empirical FDR (%)	NA	NA	NA	22.46	5.65	4.44
	Empirical TPR (%)	NA	NA	NA	4.50	35.56	83.40
	Empirical TNR (%)	NA	NA	NA	99.78	99.74	99.56
	Mean fit time (sec.)	15.10	33.61	79.68	1244.90	1467.12	2185.54

Table A10: Simulation results: Observational Study with Non-Sparse Linear Outcome Model and Identity Covariance Matrix

CATE Estimator	Metric	Unfiltered			TEM-VIP-Based Filtering		
		n = 250	n = 500	n = 1000	n = 250	n = 500	n = 1000
Plug-In LASSO	Rule quality	0.93	0.95	0.95	0.87	0.91	0.93
	Empirical FDR (%)	47.78	46.78	46.36	7.62	3.96	3.12
	Empirical TPR (%)	42.16	61.14	73.58	26.80	51.36	67.10
	Empirical TNR (%)	95.57	93.80	92.82	99.75	99.75	99.75
Plug-In XGBoost	Mean fit time (sec.)	0.53	0.69	1.09	64.13	71.02	84.58
	Rule quality	0.32	0.45	0.57	0.60	0.64	0.69
	Empirical FDR (%)	NA	NA	NA	7.31	3.92	3.12
	Empirical TPR (%)	NA	NA	NA	26.92	51.32	67.10
Modified Covariates LASSO	Empirical TNR (%)	NA	NA	NA	99.75	99.75	99.75
	Mean fit time (sec.)	2.10	4.91	14.47	63.25	70.53	83.11
	Rule quality	0.55	0.62	0.73	0.73	0.78	0.84
	Empirical FDR (%)	47.74	50.53	51.99	7.55	3.89	3.13
Modified Covariates XGBoost	Empirical TPR (%)	5.72	13.80	25.38	26.94	51.26	67.02
	Empirical TNR (%)	98.39	97.29	95.92	99.74	99.76	99.75
	Mean fit time (sec.)	0.65	1.81	8.31	63.07	70.43	81.39
	Rule quality	0.54	0.52	0.58	0.65	0.68	0.73
Augmented Modified Covariates LASSO	Empirical FDR (%)	NA	NA	NA	7.60	4.07	3.07
	Empirical TPR (%)	NA	NA	NA	26.84	51.44	67.08
	Empirical TNR (%)	NA	NA	NA	99.74	99.74	99.76
	Mean fit time (sec.)	3.00	4.61	9.14	65.59	72.82	84.71
Augmented Modified Covariates XGBoost	Rule quality	0.88	0.93	0.94	0.80	0.89	0.94
	Empirical FDR (%)	60.10	63.63	66.83	7.73	4.03	3.12
	Empirical TPR (%)	35.88	57.70	69.82	26.88	51.34	67.06
	Empirical TNR (%)	93.01	88.26	83.55	99.74	99.75	99.75
AIPW-Based LASSO	Mean fit time (sec.)	1.27	2.00	6.20	64.33	71.79	82.71
	Rule quality	0.75	0.84	0.87	0.75	0.83	0.88
	Empirical FDR (%)	NA	NA	NA	7.60	3.91	3.12
	Empirical TPR (%)	NA	NA	NA	27.46	51.36	67.10
AIPW-Based Super Learner	Empirical TNR (%)	NA	NA	NA	99.74	99.75	99.75
	Mean fit time (sec.)	11.03	27.33	57.07	66.36	74.97	90.38
	Rule quality	0.91	0.94	0.94	0.81	0.90	0.94
	Empirical FDR (%)	55.98	55.23	56.07	7.78	3.94	3.09
Causal Random Forests	Empirical TPR (%)	44.00	60.26	71.14	26.84	51.22	67.08
	Empirical TNR (%)	93.16	91.40	89.51	99.74	99.75	99.76
	Mean fit time (sec.)	690.17	770.09	930.39	75.74	93.21	121.72
	Rule quality	0.91	0.94	0.94	0.81	0.90	0.93
	Empirical FDR (%)	NA	NA	NA	7.73	3.84	3.09
	Empirical TPR (%)	NA	NA	NA	27.10	51.44	67.08
	Empirical TNR (%)	NA	NA	NA	99.74	99.76	99.76
	Mean fit time (sec.)	723.10	833.32	1115.03	83.23	107.56	150.30
	Rule quality	0.55	0.52	0.50	0.72	0.72	0.73
	Empirical FDR (%)	NA	NA	NA	7.93	3.85	3.12
	Empirical TPR (%)	NA	NA	NA	27.12	51.36	67.08
	Empirical TNR (%)	NA	NA	NA	99.73	99.76	99.75
	Mean fit time (sec.)	14.71	32.72	79.30	71.31	89.65	124.53

Table A11: Simulation results: RCT with Non-Sparse Linear Outcome Model and Block Covariance Matrix

CATE Estimator	Metric	Unfiltered			TEM-VIP-Based Filtering		
		n = 250	n = 500	n = 1000	n = 250	n = 500	n = 1000
Plug-In LASSO	Rule quality	0.91	0.92	1.00	0.86	0.89	0.98
	Empirical FDR (%)	47.76	47.30	45.99	6.55	4.92	3.61
	Empirical TPR (%)	43.06	60.40	73.98	29.50	51.86	67.64
	Empirical TNR (%)	95.46	93.80	92.87	99.75	99.68	99.71
	Mean fit time (sec.)	0.55	0.71	1.30	1245.84	1454.06	2593.35
Plug-In XGBoost	Rule quality	0.40	0.49	0.64	0.58	0.61	0.74
	Empirical FDR (%)	NA	NA	NA	7.07	4.72	3.61
	Empirical TPR (%)	NA	NA	NA	29.30	51.70	67.66
	Empirical TNR (%)	NA	NA	NA	99.72	99.70	99.71
	Mean fit time (sec.)	2.25	4.48	13.69	1243.62	1446.91	2596.23
Modified Covariates LASSO	Rule quality	0.55	0.54	0.68	0.69	0.73	0.85
	Empirical FDR (%)	60.98	48.19	53.87	6.43	4.89	3.62
	Empirical TPR (%)	7.52	12.16	24.78	29.06	52.02	67.70
	Empirical TNR (%)	97.39	97.19	95.81	99.76	99.68	99.71
	Mean fit time (sec.)	11.46	17.08	91.95	1250.49	1457.11	2599.80
Modified Covariates XGBoost	Rule quality	0.53	0.51	0.62	0.62	0.62	0.73
	Empirical FDR (%)	NA	NA	NA	6.26	4.90	3.60
	Empirical TPR (%)	NA	NA	NA	29.24	51.90	67.52
	Empirical TNR (%)	NA	NA	NA	99.76	99.68	99.71
	Mean fit time (sec.)	23.46	31.15	112.34	1256.65	1468.72	2624.43
Augmented Modified Covariates LASSO	Rule quality	0.83	0.90	0.99	0.78	0.87	0.98
	Empirical FDR (%)	60.93	64.53	67.19	6.77	4.74	3.61
	Empirical TPR (%)	36.20	56.52	69.42	29.84	51.90	67.64
	Empirical TNR (%)	92.36	87.72	83.32	99.73	99.70	99.71
	Mean fit time (sec.)	12.07	17.10	89.35	1247.60	1457.27	2605.49
Augmented Modified Covariates XGBoost	Rule quality	0.72	0.81	0.92	0.72	0.81	0.93
	Empirical FDR (%)	NA	NA	NA	6.49	4.92	3.56
	Empirical TPR (%)	NA	NA	NA	29.18	51.98	67.66
	Empirical TNR (%)	NA	NA	NA	99.75	99.68	99.71
	Mean fit time (sec.)	45.71	86.56	212.64	1258.50	1478.16	2654.82
AIPW-Based LASSO	Rule quality	0.89	0.92	0.99	0.80	0.87	0.98
	Empirical FDR (%)	57.39	56.95	56.70	6.54	4.81	3.63
	Empirical TPR (%)	46.14	60.86	72.20	29.68	52.04	67.64
	Empirical TNR (%)	92.66	90.78	89.08	99.74	99.69	99.70
	Mean fit time (sec.)	719.27	824.58	1195.33	1257.30	1481.06	2634.83
AIPW-Based Super Learner	Rule quality	0.90	0.92	0.99	0.80	0.88	0.98
	Empirical FDR (%)	NA	NA	NA	7.17	5.03	3.60
	Empirical TPR (%)	NA	NA	NA	29.70	51.96	67.70
	Empirical TNR (%)	NA	NA	NA	99.73	99.68	99.71
	Mean fit time (sec.)	747.26	881.33	1357.61	1266.63	1488.79	2636.36
Causal Random Forests	Rule quality	0.53	0.49	0.56	0.60	0.58	0.68
	Empirical FDR (%)	NA	NA	NA	6.41	4.90	3.62
	Empirical TPR (%)	NA	NA	NA	28.96	52.12	67.86
	Empirical TNR (%)	NA	NA	NA	99.76	99.68	99.70
	Mean fit time (sec.)	15.71	35.59	90.24	1250.24	1470.02	2642.60

Table A12: Simulation results: Observational Study with Non-Sparse Linear Outcome Model and Block Covariance Matrix

CATE Estimator	Metric	Unfiltered			TEM-VIP-Based Filtering		
		n = 250	n = 500	n = 1000	n = 250	n = 500	n = 1000
Plug-In LASSO	Rule quality	0.24	0.56	0.88	0.06	0.27	0.62
	Empirical FDR (%)	49.56	45.71	44.93	23.52	14.31	7.42
	Empirical TPR (%)	32.00	76.30	99.42	2.48	11.18	47.74
	Empirical TNR (%)	96.16	92.64	90.86	99.79	99.76	99.56
	Mean fit time (sec.)	0.55	0.78	1.36	65.97	74.40	86.94
Plug-In XGBoost	Rule quality	-0.01	0.05	0.10	0.02	0.11	0.20
	Empirical FDR (%)	NA	NA	NA	19.73	13.22	7.43
	Empirical TPR (%)	NA	NA	NA	2.28	11.20	47.88
	Empirical TNR (%)	NA	NA	NA	99.84	99.78	99.55
	Mean fit time (sec.)	1.98	4.86	13.89	64.78	72.69	85.90
Modified Covariates LASSO	Rule quality	0.01	0.06	0.11	0.03	0.17	0.36
	Empirical FDR (%)	55.94	55.01	46.40	17.73	13.05	7.43
	Empirical TPR (%)	2.40	2.70	4.94	2.40	10.92	47.60
	Empirical TNR (%)	98.68	99.00	98.69	99.86	99.78	99.56
	Mean fit time (sec.)	0.70	2.34	2.62	64.78	72.51	85.18
Modified Covariates XGBoost	Rule quality	-0.02	0.06	0.10	0.00	0.09	0.25
	Empirical FDR (%)	NA	NA	NA	21.94	12.43	7.37
	Empirical TPR (%)	NA	NA	NA	2.46	11.38	47.90
	Empirical TNR (%)	NA	NA	NA	99.83	99.78	99.56
	Mean fit time (sec.)	10.02	11.86	17.79	72.03	81.80	96.96
Augmented Modified Covariates LASSO	Rule quality	0.08	0.42	0.80	0.03	0.18	0.49
	Empirical FDR (%)	52.84	56.62	64.47	22.28	13.53	7.35
	Empirical TPR (%)	11.92	52.34	96.80	2.50	11.26	47.52
	Empirical TNR (%)	97.35	90.48	79.80	99.82	99.78	99.56
	Mean fit time (sec.)	1.49	2.40	3.66	65.77	75.59	88.95
Augmented Modified Covariates XGBoost	Rule quality	0.07	0.23	0.51	0.00	0.11	0.36
	Empirical FDR (%)	NA	NA	NA	22.09	13.06	7.41
	Empirical TPR (%)	NA	NA	NA	2.50	11.32	47.62
	Empirical TNR (%)	NA	NA	NA	99.81	99.77	99.56
	Mean fit time (sec.)	15.59	23.18	75.12	72.71	81.47	100.49
AIPW-Based LASSO	Rule quality	0.19	0.49	0.81	0.04	0.18	0.50
	Empirical FDR (%)	54.44	54.00	53.99	21.95	14.37	7.36
	Empirical TPR (%)	27.70	69.78	98.24	2.50	10.98	48.02
	Empirical TNR (%)	94.94	90.29	86.88	99.80	99.77	99.56
	Mean fit time (sec.)	709.70	796.43	970.79	75.40	88.13	117.51
AIPW-Based Super Learner	Rule quality	0.22	0.49	0.81	0.03	0.18	0.53
	Empirical FDR (%)	NA	NA	NA	20.33	12.28	7.33
	Empirical TPR (%)	NA	NA	NA	2.44	11.20	47.84
	Empirical TNR (%)	NA	NA	NA	99.83	99.79	99.56
	Mean fit time (sec.)	742.66	856.73	1098.70	81.30	98.50	143.29
Causal Random Forests	Rule quality	0.00	0.05	0.10	0.03	0.14	0.35
	Empirical FDR (%)	NA	NA	NA	19.93	13.72	7.59
	Empirical TPR (%)	NA	NA	NA	2.42	11.06	48.04
	Empirical TNR (%)	NA	NA	NA	99.83	99.78	99.54
	Mean fit time (sec.)	13.87	29.14	68.09	72.10	86.70	127.29

Table A13: Simulation results: RCT with Non-Sparse Non-Linear Outcome Model and Identity Covariance Matrix

CATE Estimator	Metric	Unfiltered			TEM-VIP-Based Filtering		
		n = 250	n = 500	n = 1000	n = 250	n = 500	n = 1000
Plug-In LASSO	Rule quality	0.28	0.51	0.74	0.10	0.27	0.53
	Empirical FDR (%)	47.71	44.51	45.48	27.09	17.74	8.42
	Empirical TPR (%)	32.66	75.22	99.26	3.12	17.14	52.74
	Empirical TNR (%)	96.41	92.99	90.64	99.77	99.52	99.42
	Mean fit time (sec.)	0.56	0.79	1.37	1264.10	1464.83	2152.27
Plug-In XGBoost	Rule quality	0.02	0.01	-0.01	0.05	0.08	0.06
	Empirical FDR (%)	NA	NA	NA	26.45	18.62	8.26
	Empirical TPR (%)	NA	NA	NA	3.14	17.08	52.16
	Empirical TNR (%)	NA	NA	NA	99.76	99.52	99.44
	Mean fit time (sec.)	2.26	4.65	14.03	1262.08	1458.83	2154.81
Modified Covariates LASSO	Rule quality	0.02	0.00	-0.04	0.05	0.09	0.11
	Empirical FDR (%)	59.57	59.08	46.13	27.80	18.13	8.39
	Empirical TPR (%)	2.22	2.96	6.40	2.96	16.68	52.76
	Empirical TNR (%)	98.30	98.36	97.51	99.77	99.51	99.42
	Mean fit time (sec.)	11.50	16.41	43.46	1264.86	1465.85	2166.97
Modified Covariates XGBoost	Rule quality	0.01	-0.01	-0.05	0.02	0.04	0.01
	Empirical FDR (%)	NA	NA	NA	30.73	17.68	8.60
	Empirical TPR (%)	NA	NA	NA	2.96	16.86	53.26
	Empirical TNR (%)	NA	NA	NA	99.76	99.54	99.41
	Mean fit time (sec.)	20.91	26.58	57.12	1271.27	1474.22	2177.19
Augmented Modified Covariates LASSO	Rule quality	0.14	0.34	0.63	0.09	0.13	0.34
	Empirical FDR (%)	59.12	60.10	65.89	28.96	18.57	8.45
	Empirical TPR (%)	12.56	49.62	93.10	3.34	16.68	53.16
	Empirical TNR (%)	96.57	90.51	79.93	99.73	99.50	99.42
	Mean fit time (sec.)	12.24	16.68	45.01	1260.81	1465.51	2168.90
Augmented Modified Covariates XGBoost	Rule quality	0.07	0.19	0.38	0.05	0.06	0.17
	Empirical FDR (%)	NA	NA	NA	29.46	17.87	8.31
	Empirical TPR (%)	NA	NA	NA	3.04	17.04	52.44
	Empirical TNR (%)	NA	NA	NA	99.75	99.54	99.43
	Mean fit time (sec.)	26.00	39.51	121.43	1269.92	1473.57	2183.60
AIPW-Based LASSO	Rule quality	0.23	0.46	0.69	0.06	0.13	0.36
	Empirical FDR (%)	57.64	55.89	54.84	29.34	17.82	8.33
	Empirical TPR (%)	32.78	74.06	98.22	2.90	16.62	52.88
	Empirical TNR (%)	93.88	89.08	86.49	99.78	99.53	99.42
	Mean fit time (sec.)	729.03	829.63	1045.16	1268.48	1483.21	2209.84
AIPW-Based Super Learner	Rule quality	0.25	0.46	0.69	0.06	0.12	0.34
	Empirical FDR (%)	NA	NA	NA	31.00	19.25	8.55
	Empirical TPR (%)	NA	NA	NA	3.34	16.96	53.18
	Empirical TNR (%)	NA	NA	NA	99.72	99.48	99.41
	Mean fit time (sec.)	757.21	884.50	1166.49	1274.90	1494.74	2225.23
Causal Random Forests	Rule quality	0.01	-0.02	-0.06	0.02	0.02	-0.03
	Empirical FDR (%)	NA	NA	NA	28.34	18.25	8.53
	Empirical TPR (%)	NA	NA	NA	3.10	16.24	53.90
	Empirical TNR (%)	NA	NA	NA	99.74	99.53	99.40
	Mean fit time (sec.)	14.96	33.27	78.61	1259.24	1473.02	2204.43

Table A14: Simulation results: Observational Study with Non-Sparse Non-Linear Outcome Model and Identity Covariance Matrix

CATE Estimator	Metric	Unfiltered			TEM-VIP-Based Filtering		
		n = 250	n = 500	n = 1000	n = 250	n = 500	n = 1000
Plug-In LASSO	Rule quality	0.68	0.73	0.83	0.57	0.70	0.80
	Empirical FDR (%)	50.24	47.74	49.22	11.53	6.96	5.59
	Empirical TPR (%)	30.84	44.68	57.02	13.72	36.56	57.18
	Empirical TNR (%)	96.33	95.26	93.64	99.76	99.67	99.61
Plug-In XGBoost	Mean fit time (sec.)	0.52	0.70	1.06	64.46	72.09	84.93
	Rule quality	0.16	0.00	0.12	0.32	0.27	0.38
	Empirical FDR (%)	NA	NA	NA	11.61	6.67	5.63
	Empirical TPR (%)	NA	NA	NA	13.62	36.66	57.14
Modified Covariates LASSO	Empirical TNR (%)	NA	NA	NA	99.74	99.69	99.60
	Mean fit time (sec.)	2.07	4.19	13.06	63.38	70.78	81.83
	Rule quality	0.17	0.09	0.23	0.39	0.36	0.53
	Empirical FDR (%)	55.78	57.79	48.19	11.11	6.35	5.63
Modified Covariates XGBoost	Empirical TPR (%)	2.36	4.86	11.20	13.56	36.50	57.04
	Empirical TNR (%)	98.86	98.47	97.72	99.77	99.70	99.60
	Mean fit time (sec.)	0.86	2.82	15.14	63.26	70.11	80.43
	Rule quality	0.15	0.04	0.11	0.30	0.25	0.36
Augmented Modified Covariates LASSO	Empirical FDR (%)	NA	NA	NA	11.26	6.67	5.58
	Empirical TPR (%)	NA	NA	NA	13.58	36.56	57.26
	Empirical TNR (%)	NA	NA	NA	99.76	99.70	99.60
	Mean fit time (sec.)	3.36	4.35	7.10	65.68	73.23	84.44
Augmented Modified Covariates XGBoost	Rule quality	0.55	0.69	0.80	0.44	0.59	0.78
	Empirical FDR (%)	52.56	58.05	62.54	10.81	6.69	5.58
	Empirical TPR (%)	20.72	39.60	53.12	14.00	36.28	57.18
	Empirical TNR (%)	96.06	93.01	89.37	99.75	99.69	99.61
AIPW-Based LASSO	Mean fit time (sec.)	1.30	2.33	8.29	64.37	72.30	83.50
	Rule quality	0.40	0.50	0.64	0.34	0.48	0.66
	Empirical FDR (%)	NA	NA	NA	11.62	6.79	5.41
	Empirical TPR (%)	NA	NA	NA	13.92	36.20	57.22
AIPW-Based Super Learner	Empirical TNR (%)	NA	NA	NA	99.75	99.69	99.62
	Mean fit time (sec.)	7.43	12.51	25.32	66.30	74.08	86.95
	Rule quality	0.61	0.70	0.81	0.45	0.60	0.78
	Empirical FDR (%)	53.98	50.87	53.03	11.24	6.65	5.48
Causal Random Forests	Empirical TPR (%)	28.78	43.62	55.22	13.74	36.54	57.20
	Empirical TNR (%)	95.42	94.46	92.57	99.76	99.69	99.62
	Mean fit time (sec.)	691.70	773.56	936.19	73.93	90.07	118.82
	Rule quality	0.61	0.69	0.80	0.43	0.60	0.78
	Empirical FDR (%)	NA	NA	NA	11.83	6.69	5.45
	Empirical TPR (%)	NA	NA	NA	13.68	36.64	57.24
	Empirical TNR (%)	NA	NA	NA	99.75	99.69	99.62
	Mean fit time (sec.)	722.40	838.81	1164.73	80.88	101.80	143.47
	Rule quality	0.12	0.04	0.11	0.37	0.44	0.58
	Empirical FDR (%)	NA	NA	NA	11.75	6.62	5.36
	Empirical TPR (%)	NA	NA	NA	13.32	36.32	57.30
	Empirical TNR (%)	NA	NA	NA	99.75	99.70	99.62
	Mean fit time (sec.)	13.13	31.45	71.31	69.51	88.07	123.80

Table A15: Simulation results: RCT with Non-Sparse Non-Linear Outcome Model and Block Covariance Matrix

CATE Estimator	Metric	Unfiltered			TEM-VIP-Based Filtering		
		n = 250	n = 500	n = 1000	n = 250	n = 500	n = 1000
Plug-In LASSO	Rule quality	0.63	0.78	0.84	0.56	0.74	0.81
	Empirical FDR (%)	51.46	48.81	47.81	13.67	8.29	7.00
	Empirical TPR (%)	30.84	44.66	58.12	18.72	39.18	58.44
	Empirical TNR (%)	96.15	95.04	93.82	99.61	99.58	99.48
	Mean fit time (sec.)	0.56	0.73	1.34	1266.36	1470.17	2634.34
Plug-In XGBoost	Rule quality	0.09	0.06	0.16	0.23	0.29	0.40
	Empirical FDR (%)	NA	NA	NA	14.72	8.31	6.49
	Empirical TPR (%)	NA	NA	NA	18.40	39.24	58.18
	Empirical TNR (%)	NA	NA	NA	99.59	99.58	99.52
	Mean fit time (sec.)	2.13	4.82	13.82	1265.64	1470.82	2646.84
Modified Covariates LASSO	Rule quality	0.08	0.08	0.06	0.24	0.32	0.33
	Empirical FDR (%)	60.38	54.08	50.15	14.05	8.72	6.75
	Empirical TPR (%)	3.18	4.68	10.54	18.60	39.40	58.56
	Empirical TNR (%)	98.37	98.07	97.54	99.60	99.55	99.50
	Mean fit time (sec.)	11.82	18.33	99.27	1271.48	1481.43	2650.73
Modified Covariates XGBoost	Rule quality	0.08	0.09	0.05	0.16	0.21	0.19
	Empirical FDR (%)	NA	NA	NA	13.70	8.50	6.37
	Empirical TPR (%)	NA	NA	NA	18.66	39.68	58.04
	Empirical TNR (%)	NA	NA	NA	99.62	99.56	99.53
	Mean fit time (sec.)	21.97	29.19	104.87	1278.55	1489.49	2667.57
Augmented Modified Covariates LASSO	Rule quality	0.43	0.69	0.81	0.37	0.64	0.78
	Empirical FDR (%)	59.66	61.26	62.93	14.35	8.68	6.75
	Empirical TPR (%)	19.78	39.04	54.18	18.06	39.90	58.14
	Empirical TNR (%)	95.35	91.90	89.12	99.62	99.55	99.50
	Mean fit time (sec.)	12.23	17.80	92.71	1268.55	1481.57	2658.96
Augmented Modified Covariates XGBoost	Rule quality	0.32	0.54	0.64	0.28	0.51	0.66
	Empirical FDR (%)	NA	NA	NA	14.47	7.97	6.77
	Empirical TPR (%)	NA	NA	NA	18.64	39.42	58.32
	Empirical TNR (%)	NA	NA	NA	99.59	99.59	99.50
	Mean fit time (sec.)	30.63	49.91	149.00	1276.58	1498.14	2680.37
AIPW-Based LASSO	Rule quality	0.60	0.74	0.82	0.39	0.65	0.78
	Empirical FDR (%)	60.04	55.65	53.91	13.37	8.29	6.59
	Empirical TPR (%)	32.82	45.30	56.80	18.72	39.82	58.24
	Empirical TNR (%)	94.02	93.23	92.27	99.62	99.57	99.51
	Mean fit time (sec.)	731.78	843.97	1211.56	1276.14	1502.32	2674.74
AIPW-Based Super Learner	Rule quality	0.59	0.74	0.82	0.38	0.66	0.78
	Empirical FDR (%)	NA	NA	NA	14.32	8.37	6.56
	Empirical TPR (%)	NA	NA	NA	18.92	39.50	58.26
	Empirical TNR (%)	NA	NA	NA	99.60	99.57	99.52
	Mean fit time (sec.)	759.28	901.83	1430.13	1285.08	1514.52	2663.28
Causal Random Forests	Rule quality	0.05	0.05	-0.02	0.22	0.36	0.40
	Empirical FDR (%)	NA	NA	NA	13.37	8.62	6.74
	Empirical TPR (%)	NA	NA	NA	18.24	39.76	58.58
	Empirical TNR (%)	NA	NA	NA	99.61	99.56	99.50
	Mean fit time (sec.)	15.22	34.23	84.13	1268.99	1494.08	2682.33

Table A16: Simulation results: Observational Study with Non-Sparse Non-Linear Outcome Model and Block Covariance Matrix