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# Selecting Optimal Treatments Based on Predictive Factors

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## 19.1 Introduction

With the increasing interest in individualized medicine there is a greater need for robust statistical methods for prediction of optimal treatment based on the patient's characteristics. When evaluating two treatments, one treatment may not be uniformly superior to the other treatment for all patients. A patient characteristic may interact with one of the treatments and change the effect of the treatment on the response. Clinical trials are also collecting more information on the patient. This additional information on the patients combined with the state-of-the-art in model selection allows researchers to build better optimal treatment algorithms.

In this chapter we introduce a methodology for predicting optimal treatment. The methodology is demonstrated first on a simulation and then on a phase III clinical trial in neuro-oncology.

## 19.2 Predicting Optimal Treatment Based on Baseline Factors

Start with a randomized controlled trial where patients are assigned to one of two treatme [illegible] $= 1) = \Pi_A$. The main outcome for the trial is defined at [illegible] $T > t)$ where $T$ is the survival time. For example, the ma [illegible] nth progression-free rate and $T$ is the progression time. Al [illegible] the trial is a set of baseline covariates $W$. The baseline co [illegible] n of continuous and categorical variables. The baseline co [illegible] stic and predictive factors. Prognostic factors are patient ch [illegible] d with the outcome independent of the treatment given, wh [illegible] characteristics which interact with the treatment in their as [illegible] determine the optimal treatment, a model for how the pr [illegible] e related to the outcome needs to be estimated.

The observed data is $O_i = (W_i, A_i, Y_i = \mathrm{I}(T_i > t)) \sim P$ for $i = 1, \ldots, n$. For now assume $Y$ is observed for all patients in the trial but this assumption is relaxed in the next section.

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The optimal treatment given a set of baseline variables is found using the $W$-specific variable importance parameter:

$$\Psi(W) = \mathrm{E}(Y|A=1,W) - \mathrm{E}(Y|A=0,W) \tag{19.1}$$

$\Psi(W)$ is the additive risk difference of treatment $A$ for a specific level of the prognostic variables $W$. The conditional distribution of $Y$ given $W$ is defined as $\{Y|W\} \sim \text{Bernoulli}(\pi_Y)$. The subscript $W$ is assumed on $\pi_Y$ and left off for clarity of the notation. Adding the treatment variable $A$ into the conditioning statement we define $\{Y|A=1,W\} \sim \text{Bernoulli}(\pi_{+1})$ and $\{Y|A=0,W\} \sim \text{Bernoulli}(\pi_{-1})$. Again the subscript $W$ is dropped for clarity but assumed throughout the paper. The parameter of interest can be expressed as $\Psi(W) = \pi_{+1} - \pi_{-1}$. For a given value of $W$, $\Psi(W)$ will fall into one of three intervals with each interval leading to a different treatment decision. The three intervals for $\Psi(W)$ are:

1. $\Psi(W) > 0$ : indicating a beneficial effect of the intervention $A = 1$.
2. $\Psi(W) = 0$ : indicating no effect of the intervention $A$.
3. $\Psi(W) < 0$ : indicating a harmful effect of the intervention $A = 1$.

Knowledge of $\Psi(W)$ directly relates to knowledge of the optimal treatment.

f interest can be expressed as:

$$\left.\left(\frac{\mathrm{I}(A=1)}{\Pi_A} - \frac{\mathrm{I}(A=0)}{1-\Pi_A}\right) Y|W\right). \tag{19.2}$$

W xpectation in equation (19.2) can be modeled with the

re . Let $Z = Y(A-(1-A))$ and since $A$ and $Y$ are binary

va

$$\begin{cases} +1 & \text{if } Y=1 \;\&\; A=1 \\ 0 & \text{if } Y=0 \\ -1 & \text{if } Y=1 \;\&\; A=0 \end{cases}$$

The observed values of $Z$ follow a multinomial distribution. The parameter $\Psi(W)$ will be high dimensional in most settings and the components of $\Psi(W)$ are effect modifications between $W$ and the treatment $A$ on the response $Y$. The parameter can be estimated with a model $\Psi(W) = m(W|\beta)$. The functional form of $m(W|\beta)$ can be specified *a priori*, but since the components of the model represent effect modifications, knowledge of a reasonable model may not be available and we recommend a flexible approach called the super learner (described in the next section) for estimating $\Psi(W)$. In many cases a simple linear model may work well for $m(W|\beta)$, but as the true functional form of $\Psi(W)$ becomes more complex, the super learner gives the researcher flexibility in modeling the optimal treatment function. With the squared error loss function for a specific model $m(W|\beta)$, the parameter estimates are:

$$\beta_n = \arg\min_{\beta} \sum_{i=1}^{n} \left(Z_i - m(W_i|\beta)\right)^2 \tag{19.3}$$

The treatment decision for a new individual with covariates $W = w$ is to treat with $A = 1$ if $m(w|\beta_n) > 0$, otherwise treat with $A = 0$.

A normal super learner model for $m(W|\beta)$ would allow for a flexible relationship between $W$ and $Z$ but these models do not respect the fact that $\Psi(W)$ is bounded between $-1$ and $+1$. The regression of $Z$ on $W$ does not use the information that the parameter $\Psi(W) = \pi_{+1} - \pi_{-1}$ is bounded between $-1$ and $+1$. The estimates in equation (19.3) have a nice interpretation since the model predicts the additive difference in survival probabilities. In proposing an alternative method, we wanted to retain the interpretation of an additive effect measure but in distributions. Starting with the parameter of interest in eq alue based on the conditional distribution of $Y$ given $W$ as

$$\frac{= 1, W) - \mathrm{E}_P(Y|A = 0, W)}{\mathrm{E}_P(Y|W)} = \frac{\pi_{+1} - \pi_{-1}}{\pi_Y} \tag{19.4}$$

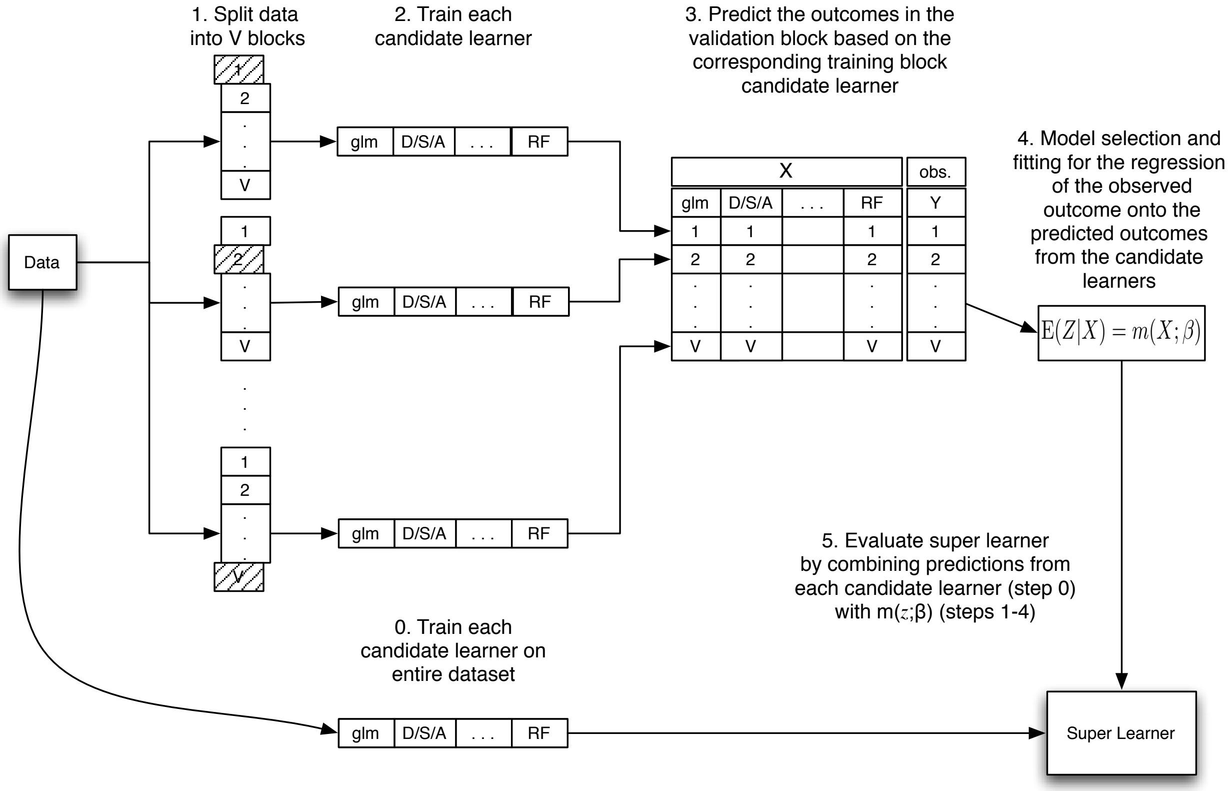
Si $\neq 0|W)$, the new parameter $\Psi'(W) = \mathrm{E}(Z|Z \neq 0, W)$. W cases with $Z \neq 0$ (i.e. $Y = 1$) the outcome becomes a ession methods can be implemented. For example, the log

$$(Z = 1|Z \neq 0, W)) = m'(W_i|\beta) \tag{19.5}$$

The treatment decision is based on $m'(W_i|\beta_n) > 0$ where $\beta_n$ is the maximum likelihood estimate for the logistic regression model. With the binary regression setting, we are now incorporating the distribution information in creating the prediction model, but losing information by working on a subset of the data. These trade-offs depend on the probability $\pi_Y$ and we will evaluate both methods on the trial example below. In the next section we propose a data-adaptive method for estimating $\Psi(W)$.

## 19.3 Super Learner

Many methods exist for prediction, but for any given data set it is not known which method will give the best prediction. A good prediction algorithm should be flexible to the true data generating distribution. One such algorithm is the super learner [2]. The super learner is applied to predict the optimal treatment based on the observed data. The super learner algorithm starts with the researcher selecting a set of candidate prediction algorithms (candidate learners). This list of candidate learners should be selected to cover a wide range of basis functions. The candidate learners are selected prior to analyzing the data; selection of the candidates based on performance on the observed data may introduce bias in the final prediction model. A flow diagram for the super learner algorithm is provided in figure 19.1. With the candidate learners selected and the data collected, the initial step is s on the entire data set and save the predicted values for $\Psi_r$ exes the candidate learners. The data is then split into $V$ sive sets as is typically done for V-fold cross-validation. Pa l to as the $v^{th}$ validation set, and all patients not in the $v^{th}$ training set. For the $v^{th}$ fold, each candidate learner is fit ing set and the predicted values for $\Psi(W) = m_j(W|\beta_n)$ foi on set are saved. This process of training the candidate lea and saving the predicted values in the fold is repeated foi m all $V$ folds are stacked together in a new data matrix $X^v$ ess the observed outcome $Z$ on the columns of $X^v$, which rej for each candidate learner. This regression step selects weights for each candidate learner to minimize the cross-validated risk. With the estimates, $\beta_n$, from the model $\mathrm{E}(Z|X^v) = m(X|\beta)$ the super learner only saves the weights ($\beta_n$) and the functional form of the model. The super learner prediction is then based on combining the predictions from each candidate learner on the entire data set with the weights from the cross-validation step.


1. Split data into V blocks
2. Train each candidate learner
3. Predict the outcomes in the validation block based on the corresponding training block candidate learner
4. Model selection and fitting for the regression of the observed outcome onto the predicted outcomes from the candidate learners
5. Evaluate super learner by combining predictions from each candidate learner (step 0) with m(z;β) (steps 1-4)
0. Train each candidate learner on entire dataset
Data
1
2
V
glm
D/S/A
. . .
RF
X
obs.
Y
E(Z|X) = m(X;β)
Super Learner

: Flow diagram for super learner

## 1 sored Data

ay be subject to right censoring. In both methods above, rig ne $Z$ being missing. The data structure is extended to in the outcome. Let $C$ be the censoring time (for individua set $C = \infty$). Define $\Delta = \mathrm{I}(C > t)$. $\Delta = 1$ when the ou ıen the outcome is missing. The observed data is the set $(W, A, \Delta, Y\Delta)$. For the first method, we propose using the doubly robust censoring unbiased transformation [3]. The doubly robust censoring unbiased transformation generates a new

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variable $Z^*$ which is a function of the observed data but has the additional property:

$$\mathrm{E}\left(Z^*|W,\Delta=1\right)=\mathrm{E}\left(Z|W\right)$$

The transformation allows estimation of the parameter $\Psi(W)$ by applying the super learner on the uncensored observations with the transformed variable $Z^*$ as the outcome. The doubly robust censoring unbiased transformation is:

$$Z^*=\frac{Z\Delta}{\pi(W)}-\frac{\Delta}{\pi(W)}Q(W)+Q(W), \tag{19.6}$$

where $\pi(W)=\Pr(\Delta=1|W)$ and $Q(W)=\mathrm{E}(Z|W,\Delta=1)$. Both $\pi(W)$ and $Q(W)$ need to be estimated from the data. If either $\pi(W)$ or $Q(W)$ is consistently estimated, then the prediction function $\mathrm{E}(Z^*|W,\Delta=1)=m(W|\beta_n)$ is an unbiased estimate for the true parameter $\Psi(W)$. The censoring mechanism $\pi(W)$ can be estimated with a logistic regression model or a binary super learner on the entire data set. Similarly, $Q(W)$ may be fit with a linear regression model or a super learner, but on the subset of the data with observed values for $Z$.

For the second method which relies on modeling $\mathrm{E}(Z|Z\neq 0,W)$, the main feature was the ability to use the knowledge of the distributions to develop a better model. To retain the binary outcome, the doubly robust censoring unbiased transformation will not work. An alt[illegible]ensoring which will retain the binary outcome would be in[illegible]ghting. Inverse probability of censoring weights uses the sa[illegible] incorporate the other nuisance parameter $Q(W)$. When ap[illegible] for $\mathrm{E}(Z|Z\neq 0,W,\Delta=1)$ the weights $1/\pi(W)$ will be ap[illegible]rners and the V-fold cross-validation steps. The super lea[illegible] loss function.

## 1[illegible]e

We first demonstrate the proposed method on a simulation example where the true value of $\Psi(W)$ is known. The baseline variables were all simulated as normally distributed, $W_j\sim$

$N(0,1)$, $j = 1, \ldots, 10$. The treatment was randomly assigned with $\Pi_A = 0.5$. The true model for the outcome was:

$$\begin{aligned}\Pr(Y = 1|A, W) = g^{-1}(&0.405A - 0.105W_1 + 0.182W_2 + 0.039AW_2 \\ &+0.006AW_2W_3 - 0.357AW_4 - 0.020AW_5W_6 - 0.051AW_6)\end{aligned} \tag{19.7}$$

Where $g^{-1}(\cdot)$ is the inverse logit function and $W_j$ refers to the $j^{th}$ variable in $W$. The true model was selected to include interactions between the treatment and some of the baseline variables. With knowledge of the true model for the outcome $Y$, the true value of $\Psi(W)$ is calculated for every individual.

The first method involves the regression of $Z$ on $W$. We applied the super learner for $m(W|\beta)$. 10-fold cross validation was used for estimating the candidate learner weights in the super learner. The super learner for the first method included five candidate learners. The first candidate was ridge regression [4]. Ridge regression used an internal cross validation to select the penalty parameter. Internal cross validation means the candidate learner performed a V-fold cross validation procedure within the folds for the super learner. Structurally, when the candidate learner also performs cross validation within the super learner cross validation we have nested cross validation; therefore, we refer to the candidate learner cross validation as internal cross validation. The second candidate was random forests [5]. Fo arner, 1000 regression trees were grown. The third candi [6]. An internal 10-fold cross validation procedure was us io of the L1 norm of the coefficient vector compared to th es coefficient vector. The fourth candidate was adaptive re outcome [7]. The final candidate was linear regression. Ta ie R packages implemented for the candidate learners in th

super learner is:

$$+ 1.16(X_n^{rf}) - 0.20(X_n^{lars}) - 7.07(X_n^{lm}) - 0.03(X_n^{mars})$$

Where $X_n^j$ is the predicted value for $Z$ based on the $j^{th}$ candidate learner. $j = ridge$ is the

| Method | R Package | Authors |
|---|---|---|
| Adaptive Regression Splines | polspline | Kooperberg |
| Least Angle Regression | lars | Efron and Hastie |
| Penalized Logistic | stepPlr | Park and Hastie |
| Random Forests | randomForest | Liaw and Wiener |
| Ridge Regression | MASS | Venables and Ripley |

Table 19.1: R Packages for Candidate Learners. R is available at `http://www.r-project.org`

ridge regression model. $j = rf$ is the random forests model. $j = lars$ is the least angle regression model. $j = lm$ is the main effects linear regression model. $j = mars$ is the adaptive regression splines model. The largest weights are for ridge regression and the linear regression model. For example, the estimates for the linear regression model is:

$$\begin{aligned} X_n^{lm} &= 0.06 + 0.02W_1 + 0.01W_2 - 0.03W_3 - 0.07W_4 + 0.01W_5 + 0.05W_6 \\ &\quad - 0.02W_7 - 0.00W_8 - 0.01W_9 - 0.06W_{10}. \end{aligned}$$

The linear regression model has the largest coefficient on $W_4$, which is the variable with the strongest effect modification with the treatment in the true model (equation (19.7)). The second largest coefficient is on $W_{10}$ which is a variable unrelated to the outcome. The super
lea ors by having multiple candidate learners. For example,
$W$ in the ridge regression model. When all the candidates
ar earner prediction model the spurious effect estimates will
oft r predictor. The third largest coefficient from the linear
re is also a strong effect modifier in the true model. To
ev erforming in comparison to the other candidate learners,
ea as a separate estimate. We looked at two risk values,
fir s minimized by each algorithm. For the simulation, the
ris lower bound for the risk $\mathrm{E}(\Psi_n(W) - Z)^2$. Since the true
$\Psi($ the risk $\mathrm{E}(\Psi_n(W) - \Psi(W))^2$ was also evaluated. Table
19 he simulation. The super learner achieved the smallest
$\mathrm{E}(\Psi_n(W) - Z)^2$ and is comparable to MARS and LARS on the risk for the true parameter value $\Psi(W)$.

| | $\mathrm{E}(\Psi_n(W) - \Psi(W))^2$ | $\mathrm{E}(\Psi_n(W) - Z)^2$ |
|---|---|---|
| Super Learner | 0.012 | 0.544 |
| MARS | 0.012 | 0.549 |
| LARS | 0.012 | 0.549 |
| Ridge | 0.026 | 0.558 |
| Linear Model | 0.028 | 0.559 |
| Random Forests | 0.038 | 0.565 |

Table 19.2: Risk for all candidate learners and the super learner

The super learner for the second method included three candidate learners. The first candidate was adaptive regression splines for polychotomous outcomes [8]. The second candidate was the step-wise penalized logistic regression algorithm [9]. The final candidate was main terms logistic regression. The super learner for the second method is:

$$\Psi'_n(W) = -1.20 + 1.43(X_n^{poly}) - 0.50(X_n^{plr}) + 1.61(X_n^{glm})$$

Where $X_n^j$ is the predicted value for $Z$ based on the $j^{th}$ candidate learner. $j = poly$ is the polyclass adaptive spline model. $j = plr$ is the penalized logistic regression model. $j = glm$ is the main effects logistic regression model.

# 19 ion Model on Clinical Trial

ducted to evaluate a novel treatment for brain metastasis.
Th with newly diagnosed brain metastasis and the patients
we andard care ($A = 0$) or the novel treatment ($A = 1$). The
res mining an optimal treatment to maximize the probability
of nt initiation without progression. Of the 554 patients, 246
ar r the 308 patients with an observed 6 month progression
tir ). In addition to the treatment and event time data, the
res nostic and predictive factors on every patient. We apply
th del for selecting the optimal treatment given a patient's
baseline factors. A breakdown of the sample size and treatment allocations available for each method is given in table 19.3.

|  |  | A |  |
|---|---|---|---|
|  | total | 0 | 1 |
| Enrolled | 554 | 275 | 279 |
| Method 1 | 308 | 158 | 150 |
| Method 2 | 130 | 67 | 63 |

Table 19.3: Number of subjects in each treatment arm at enrollment and available for each method.

### 19.6.1 Super learner for optimal treatment decisions

Both methods proposed above were applied to the data. The first method looks for a model of $Z$ on $W$ treating $Z$ as a continuous variable. The second method looks for a model of $Z$ on $W$ conditional on $Z \neq 0$ treating the outcome as binary.

The same super learners from the simulation example above were used here in the trial example. The predicted model for the first method is:

$$\Psi_n(W) = -0.01 + 0.02(X_n^{ridge}) + 1.21(X_n^{rf}) - 0.84(X_n^{lars}) - 0.28(X_n^{lm}) + 0.50(X_n^{mars})$$

Where $X_n^j$ is the predicted value for $Z$ based on the $j^{th}$ candidate learner. $j = ridge$ is the ridge regression model. $j = rf$ is the random forests model. $j = lars$ is the least angle regression model. $j = lm$ is the main effects linear regression model. $j = mars$ is th del. The coefficient estimates for each candidate learner fr preted as a weight for each candidate learner in the final pr has the largest absolute weight. When interpreting the we near collinearity of the columns of $X$. To evaluate the su candidate learners, a 10-fold cross validation of the super le earners themselves was used to estimate $\mathrm{E}(\Psi_n(W) - Z)^2$. Ta es. For the trial example, both the lars algorithm and the m er learner. As observed in the simulation, minimizing the ris relate to minimizing the risk $\mathrm{E}(\Psi_n(W) - \Psi(W))^2$. These cr used to select an optimal final model for the treatment de

The second method evaluates $\mathrm{E}(Z|Z \neq 0, W) = m'(W|\beta)$. The estimated super learner

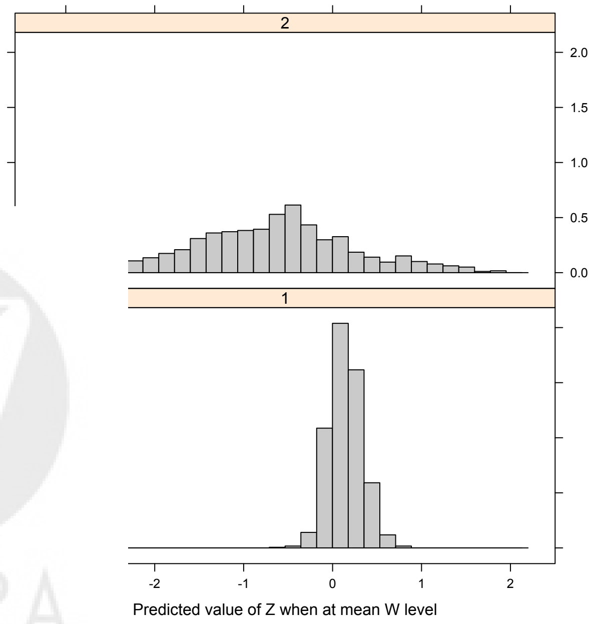
| Method | Risk |
|---|---|
| Lars | 0.426 |
| Mars | 0.426 |
| Super Learner | 0.445 |
| Ridge Regression | 0.505 |
| Random Forests | 0.509 |
| Linear Model | 0.525 |

Table 19.4: 10-fold honest cross validation estimates of $\mathrm{E}(\Psi_n(W) - Z)^2$ for the super learner and each of the candidate learners on their own.

model for the second method is:

$$\Psi'_n(W) = -0.53 - 0.40(X_n^{poly}) + 0.55(X_n^{plr}) + 0.81(X_n^{glm})$$

Where $X_n^j$ is the predicted value for $Z$ based on the $j^{th}$ candidate learner. $j = poly$ is the polyclass adaptive spline model. $j = plr$ is the penalized logistic regression model. $j = glm$ is the main effects logistic regression model. To compare the two methods, we created a confidence interval at the mean vector for $W$. Let $\bar{w}$ be the vector of observed means for the baseline variables using all observations in the trial. Confidence intervals were



Fi bootstrap samples for $\Psi'(W = \bar{w})$ and $\Psi(W = \bar{w})$. The nu e method used.

created based on 1000 bootstrap samples of the entire super learner. The 95% confidence interval for $m(\bar{w}|\beta)$ based on the first method is $(-0.20, 0.52)$. The 95% for $m(\bar{w}|\beta)$ based on the second method is $(-2.23, 1.23)$. Although the second method is able to use the distributional information, the penalty for the smaller sample size is great (308 patients for the first method down to 130 patients for the second method). As can be seen in figure 19.2, the second method has a wide confidence interval compared to the first method.

## 19.7 Variable Importance Measure

An additional feature of having a good prediction model is better variable importance measures. The variables in $\mathrm{E}(Z|W)$ are effect modifications and when applying the targeted maximum likelihood estimation (tMLE) variable importance measure [10] the results will be causal effect modification importance measures. The targeted maximum likelihood effect modification variable importance allows the researcher to focus on each variable in $W$ individually while adjust for the other variables in $W$. An initial variable importance estimate is based on an univariate regression, $Z^* = \beta_{0j} + \beta_{1j}W_j,\ j = 1, \ldots, p$ where $p$ is the number of baseline covariates in $W$. The top 5 baseline variables based on the ranks of the univariate
$p$- . The top unadjusted effect modification variable is an
in lives in the US or Europe, followed by an indicator for
th an indicator for the primary tumor being controlled, an
in is, and finally an indicator for the patient's age greater
th variables from the LARS procedure are similar to those
fr the exception of Squamous cell indicator replacing the
R E variable importance, the effect of $W_j$ on $Z$ is adjusted
by $W_{(-j)}$ be all covariates in $W$ excluding the $j^{th}$ variable.
T variable importance measure as outlined in [11] was then
ap the super learner as the initial estimate of $\mathrm{E}(Z|W)$. The
ta eter is then:

$$\psi_j = \mathrm{E}\left(\mathrm{E}(Z|W_j = 1, W_{(-j)}) - \mathrm{E}(Z|W_j = 0, W_{(-j)})\right),\ j = 1, \ldots, p \tag{19.8}$$

| Method | Baseline Variable | Effect | $p$-value |
|---|---|---|---|
| Univariate Regression | US vs Europe | -0.222 | 0.007 |
| | RPA class 2 | -0.229 | 0.017 |
| | Primary tumor control | 0.165 | 0.052 |
| | Extracranial mets | -0.133 | 0.069 |
| | Age > 65 years | -0.157 | 0.075 |
| LARS | US vs Europe | -0.124 | 0.350 |
| | Primary tumor control | 0.080 | 0.405 |
| | Age > 65 years | -0.050 | 0.412 |
| | Extracranial mets | -0.028 | 0.413 |
| | Squamous cell | 0.034 | 0.419 |
| tMLE | Mets Dx > 6 Mo | 0.864 | <0.001 |
| | Squamous cell | 1.012 | <0.001 |
| | Adeno carcinoma | 0.129 | 0.007 |
| | Extracranial mets | -0.102 | 0.022 |
| | Caucasian | 0.172 | 0.035 |

Table 19.5: Top 5 effect modifiers based on univariate regression, lars, and super learner with targeted maximum likelihood. The standard error was based on a bootstrap with 1,000 samples.

The top 5 baseline variables are presented in table 19.5. The effect estimates from the tMLE procedure can be considered causal effect modifiers. Only extracranial mets appears in both
th ist, although squamous cell indicator does appear in both
th E procedure. The top variable (Mets Dx > 6 Mo) is an
in sis occurring greater than 6 months after prvious cancer.
Th ors for histology of the tumor cells (Squamous and Adeno
ca umor types my respond better to the treatment compared
to importance lists, the indicator for the patient being in
th urope is on top of the list for the univariate regression
an om the tMLE list. There is no biological evidence for
ge ith the treatment in this trial. The variable importance
ba hood is able to appropriately adjust for the confounding
on move the US versus Europe indicator from the list of top
variables. The variable importance list from the tMLE has a better interpretation and is informative as to which patient characteristics have a causal interaction with the treatment.

## 19.8 Discussion

Two methods were proposed for predicting the optimal treatment based on baseline factors. The first method involves modeling $Z$ on $W$ disregarding the knowledge that $\mathrm{E}(Z|W)$ is bounded between $-1$ and $+1$. The second method incorporates the bounds, but does so at a cost in sample size by modeling $\mathrm{E}(Z|Z \neq 0, W)$. The second method predicts a scaled version of the parameter of interest, and so is still valid for making treatment decisions. In the simulation and trial example presented here, the loss of sample size in the second method greatly increased the variability of the final prediction. But both the simulation and trial example had a high fraction of patients with $Z = 0$ (equivalently, $Y = 0$). The second method may outperform the first method in settings where $\Pr(Y = 0)$ is very small. For the examples presented here, no problems were observed with the first method not respecting the bounds on $\mathrm{E}(Z|W)$.

In the trial example, the super learner did perform better than the main terms linear regression based on the estimate of the risk $\mathrm{E}(\Psi_n(W) - Z)^2$. Even though the super learner has shown to have excellent performance across a range of simulations [2, 12] and in various of our data analyses in breast cancer research, there is a risk that the super learner will result in a slight over-fit. In the data analysis we observed that the super learner was ranked third, but competitive with the top two candidate learners, LARS and MARS. We have also pr [illegible] learner outlined here to adaptively select the number of ca [illegible] candidates are not selected, which we believe will protect th [illegible] over-fitting, but this was not implemented in the current da [illegible]

[illegible] in sample size between the two methods may make the se [illegible] mple, but the two methods also differed in the treatment of [illegible] hod incorporated the doubly robust censoring unbiased tra [illegible] thod used the inverse probability of censoring weights. If th [illegible] specified, but the model for the censoring mechanism was no [illegible] the doubly robust estimator would still be unbiased but the inverse probability of censoring weighted method will be biased. Alternatively, if $\pi(W)$ was correctly specified, but $Q(W)$ was inconsistent, then both methods will be unbiased.

The doubly robust transformation gives the researcher two chances to correctly the nuisance parameters, while the inverse weighting method relies solely on the model for $\pi(W)$. When there is uncertainty regarding the model for the censoring mechanism, the doubly robust transformation is preferred.

The methods presented above are not limited to randomized clinical trials. Optimal treatment prediction models could also be estimated from observational or registry data sets. As long as the variables needed to estimate $\Pr(A = 1|W))$ are collected in the study the above methods easily extend to the non-randomized setting. Registry data sets are often larger than randomized trials and therefore have more power to detect the interaction effects necessary for predict optimal treatments.

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