Towards Optimal Use of Surrogate Markers to Improve Power

Xuan Wang  
*Department of Biostatistics, Harvard University, Boston, MA 02115 U.S.A.*

Layla Parast  
*Department of Statistics and Data Sciences, University of Texas at Austin, Austin, TX 78712 U.S.A.*

Lu Tian  
*Department of Biomedical Data Science, Stanford University, Stanford, CA 94305 U.S.A.*

Tianxi Cai  
*Department of Biostatistics and Department of Biomedical Informatics, Harvard University, Boston, MA 02115 U.S.A.*

**Summary**

Motivated by increasing pressure for decision makers to shorten the time required to evaluate the efficacy of a treatment such that treatments deemed safe and effective can be made publicly available, there has been substantial recent interest in using an earlier or easier to measure surrogate marker, \( S \), in place of the primary outcome, \( Y \). To validate the utility of a surrogate marker in these settings, a commonly advocated measure is the proportion of treatment effect on the primary outcome that is explained by the treatment effect on the surrogate marker (PTE). Model based and model free estimators for PTE have also been developed. While this measure is very intuitive, it does not directly address the important questions of how \( S \) can be used to make inference of the unavailable \( Y \) in the next phase clinical trials. In this paper, to optimally use the information of surrogate \( S \), we provide a framework for deriving an optimal transformation of \( S \), \( g_{\text{opt}}(S) \), such that the treatment effect on \( g_{\text{opt}}(S) \) maximally approximates the treatment effect on \( Y \) in a certain sense. Based on the optimally transformed surrogate, \( g_{\text{opt}}(S) \), we propose a new measure to quantify surrogacy, the relative power (RP), and demonstrate how RP can be used to make decisions with \( S \) instead of \( Y \) for next phase trials. We propose nonparametric estimation procedures, derive asymptotic properties, and compare the RP measure with the PTE measure. Finite sample performance of our estimators is assessed via a simulation study. We illustrate our proposed procedures using an application to the Diabetes Prevention Program (DPP) clinical trial to evaluate the utility of hemoglobin A1c and fasting plasma glucose as surrogate markers for diabetes.

**Keywords:** clinical trial; surrogate marker; relative power; nonparametric estimation; proportion of treatment effect explained
Motivated by increasing pressure for decision makers to shorten the time required to evaluate the efficacy of a treatment such that treatments deemed safe and effective can be made publicly available, there has been substantial recent interest in using an earlier or easier to measure surrogate marker in place of a primary outcome. The development and testing of clinical treatments, including vaccines, often require years of research and participants follow-up. Though strict and regulated testing is essential to guarantee that treatments are safe and effective, early indications about the effectiveness of the treatment based on a surrogate marker could potentially be used to make inference about the treatment effect on the primary outcome. The use of a surrogate marker in this way may allow for early testing of a treatment effect and lead to reduced follow up time and/or costs. For example, during the COVID-19 public health emergency in 2020, the Food and Drug Administration issued guidance allowing for an emergency use authorization for vaccines demonstrating efficacy with respect to a surrogate marker that is “reasonably likely to predict” protection against COVID-19 (Avorn & Kesselheim, 2020; FDA, 2020). These urgent needs highlight the importance of developing methods to identify valid surrogate markers such that they may be used in future studies.

For decades, the statistical, epidemiological, and clinical research communities have made substantial progress by proposing and evaluating methods to assess the value of potential surrogate markers (Prentice, 1989; Molenberghs et al., 2002; Alonso et al., 2004; Burzykowski et al., 2005; Frangakis & Rubin, 2002; Gilbert & Hudgens, 2008; Huang & Gilbert, 2011; VanderWeele, 2013; Price et al., 2018). A formal definition for a valid surrogate marker was proposed in Prentice (1989) and since then, numerous methods have been proposed to validate surrogate markers or quantify the surrogacy of such surrogate markers. For example, Freedman et al. (1992) proposed a measure for the proportion of treatment effect on the primary outcome that is explained by the treatment effect on the surrogate (PTE) by examining the change in the treatment coefficient in a regression model predicting the primary outcome from the treatment with vs. without the surrogate marker included in the model. As a more flexible alternative, Wang & Taylor (2002) proposed to quantify the PTE by evaluating what the treatment would be if the surrogate marker in the treatment group had the same distribution as the surrogate in the control group. While useful, these methods are model based and lead to biased estimates of the PTE under model misspecification. A robust nonparametric model free estimation method was proposed by Parast et al. (2016) to estimate the PTE defined by Wang & Taylor (2002). However, this method requires a monotone relationship between the outcome and the surrogate marker. Recently, Wang et al. (2020) proposed a model free strategy to quantify PTE that involves identifying an optimal transformation of the surrogate marker that best predicts the treatment effect on the primary outcome. This method is very robust and provides a way to infer the treatment effect on the primary outcome by using the optimally transformed surrogate marker. The derivation of the optimal transformation function relies on an working independence assumption, though the forms of the optimal transformation and PTE are not sensitive to the departure of the assumption. Note that these quantities were proposed for a single study setting, different from a meta
analytic setting where multiple studies are available to investigate the surrogate marker and alternative measures have been developed to validate surrogacy (Daniels & Hughes, 1997; Buyse & Molenberghs, 1998; Burzykowski et al., 2005).

In this paper, to avoid the working independence assumption that may be questioned, we derive an optimal transformation of the surrogate, $g_{\text{opt}}(\cdot)$, such that the treatment effect on $g_{\text{opt}}(S)$ maximally approximates the treatment effect on the primary outcome from another different aspect but as a supplementary to the optimal transformation in Wang et al. (2020). The form of $g_{\text{opt}}(S)$ is analogous to the optimal transformation derived in Wang et al. (2020). Simulation studies show that these two optimal transformations performs similarly. This also justify the robustness of the optimal transformation function in Wang et al. (2020), which is relatively easier to implement. For simplicity we use notation $g_{\text{opt}}(S)$ for the optimal transformation in this paper, same as that in Wang et al. (2020).

The PTE quantity based on the proposed optimal transformation of the surrogate can provide useful information regarding the strength of a potential surrogate within, for example, a Phase 2 clinical trial, where testing is often conducted in a small number of patients in order to assess safety, monitor how a drug is metabolized, and gather initial data on efficacy. In the next clinical trial, such as Phase 3 clinical trial which is a large trial in patients to test efficacy and safety that provide the key data on efficacy in submissions for regulatory approval, one may be interested in understanding how this surrogate marker can be used to make inference about the treatment effect on the primary outcome. That is, knowing that a particular surrogate marker explains, for example, 90% of the treatment effect in an existing trial (Phase 2), what can be expected in a future trial (Phase 3) with respect to effect size and power, if that surrogate is used to make inference about the treatment effect instead of the primary outcome? With respect to using a surrogate marker to test for a treatment effect, useful methods have been proposed to improve power through the use of the surrogate marker information, when combined with the primary outcome (Pepe, 1992; Robins & Rotnitzky, 1992; Rotnitzky & Robins, 1995; Venkatraman & Begg, 1999; Parast et al., 2014). Some recent work has addressed the question of how one can use a surrogate marker to replace a primary outcome in a future study. For example, in a setting with multiple surrogate markers, Athey et al. (2019) proposed a model-based approach to combining surrogate markers into a surrogate index that can be used to predict a treatment effect on the primary outcome. In a survival setting, Parast et al. (2019) proposed a testing procedure to test for a treatment effect using a single surrogate marker measured earlier in time. Importantly, this testing procedure requires a similar monotonicity assumption as Parast et al. (2016), discussed earlier.

In this paper, we propose the relative power (RP) measure as an alternative measure of surrogacy, and discuss how this measure compared to existing approaches/measures. Our proposed measure aims to quantify the feasibility of using surrogate marker information to make inference about the primary outcome in a subsequent study. In addition, we demonstrate how this quantity can be used to inform future trial design.

We propose robust nonparametric estimation procedures for $g_{\text{opt}}(\cdot)$, PTE and the RP measures and derive asymptotic properties of our estimators. Simulation results suggest
that the proposed estimators perform well in finite sample. We illustrate our approach using an application to the Diabetes Prevention Program (DPP) study where we examine two potential surrogate markers for diabetes, hemoglobin A1c and fasting plasma glucose.

2 Identifying and Estimating an Optimal Transformation

2.1 Notation, Setting, and Assumptions

Let $Y$ denote the primary outcome and $S$ be the surrogate marker such that $S$ can either be measured earlier than $Y$ or at the same time as $Y$ but with less cost or patient burden. The surrogate marker $S$ can be discrete or continuous; we treat $S$ as continuous for conciseness of presentation but the proposed methods can be easily modified to accommodate discrete $S$. Under the standard causal inference framework, let $Y(a)$ and $S(a)$ denote the respective potential outcome and potential surrogate under treatment $A = a \in \{0, 1\}$. In practice, $(Y(1), S(1))$ and $(Y(0), S(0))$ cannot both be observed for the same subject. We assume that treatment assignment is random and without loss of generality $P(A = a) = 0.5$. The observable data for analysis consist of $n$ sets of independent and identically distributed random vectors $\mathcal{D} = \{D_i = (Y_i, S_i, A_i)^T, i = 1, ..., n\}$, where $Y_i = Y_i(1)A_i + Y_i(0)(1 - A_i)$, $S_i = S_i(1)A_i + S_i(0)(1 - A_i)$ and $n$ is the sample size. The treatment effect on the primary outcome, $\Delta$ is defined as:

$$\Delta = \mu_1 - \mu_0, \quad \text{where} \quad \mu_a = \mathbb{E}(Y(a)).$$

Without loss of generality, we assume $\Delta \geq 0$, which can always be realized by switching the two different treatment groups for analytic purposes if needed.

2.2 Identifying $g_{opt}$

It is desirable to identify an optimal prediction function such that the resulting $g(s)$ maximally predicts $Y$ while ensuring that $\Delta_g \leq \Delta$ to maintain a desirable interpretation of $\Delta_g$, which is the treatment effect on $g(S)$, $\Delta_g = \mu_{g,1} - \mu_{g,0} = \mathbb{E}\{g(S(1)) - \mathbb{E}\{g(S(0))\}\}$. Wang et al. (2020) identified an optimal $g$ that minimizes the mean squared error:

$$\mathcal{L}_{oracle}(g) = \mathbb{E} \left[ (Y(1) - Y(0)) - \{g(S(1)) - g(S(0))\} \right]^2$$

under the working independence assumption $(Y(1), S(1)) \perp (Y(0), S(0))$. This assumption is needed because the correlation between $(Y(1), S(1))$ and $(Y(0), S(0))$ is not identifiable. Although the inference procedures proposed in Wang et al. (2020) for quantifying the PTE of $g(S)$ do not require this assumption to hold and the form of the optimal transformation is not sensitive to the departure of the assumption, the optimality of the resulting transformation may not hold when the working independence assumption is violated.

To overcome this challenge, we propose in this paper an alternative optimal $g$ that does not rely on this assumption. To this end, we note that maximizing $\text{PTE}_g = \frac{\Delta_g}{\Delta}$ under the constraint of $\text{PTE}_g \leq 1$ is equivalent to minimizing $\epsilon_g \equiv \Delta - \Delta_g \equiv \mathbb{E}\{Y(1) - Y(0)\} - \mathbb{E}\{g(S(1)) - g(S(0))\}$.
that the following

\[
E\{g(S^{(1)}) - g(S^{(0)})\} \text{ with respect to } g \text{ under the constraint that } \epsilon_g \geq 0. \text{ Since } g \text{ is not location identifiable, one may constrain the minimization under both } E\{Y^{(0)} - g(S^{(0)})\} = 0 \text{ and } \epsilon_g \geq 0, \text{ which leads to the equivalent minimization problem of }
\]

\[
e^2_g = [E\{Y^{(1)} - g(S^{(1)})\}]^2 \text{ s.t. } E\{Y^{(0)} - g(S^{(0)})\} = 0 \text{ and } \epsilon_g \geq 0.
\]

By Jensen’s inequality \(e^2_g = [E\{Y^{(1)} - g(S^{(1)})\}]^2 \leq E\{Y^{(1)} - g(S^{(1)})\}^2\). If we can find a \(g\) function such that the loss function \(E\{Y^{(1)} - g(S^{(1)})\}^2\) is very small, then the loss \(e^2_g\) will automatically be very small. To this end, as an alternative strategy, we minimize

\[
L(g) = E\{Y^{(1)} - g(S^{(1)})\}^2 \text{ s.t. } E\{Y^{(0)} - g(S^{(0)})\} = 0. \tag{2.1}
\]

Note that we have also dropped the constraint that \(\epsilon_g \geq 0\) since it is satisfied automatically with the solution to the optimization problem (C.3) under minor conditions that can be empirically checked with observed data, will be shown later. However, \(g_{opt}(s)\) optimizing (C.3) is not uniquely identifiable for \(s \in D_0 = \Omega_0 \setminus \Omega_1\), where \(\Omega_a\) denotes the support of \(S^{(a)}\) for \(a = 0, 1\). For identifiability, we let \(g_{opt}(s) = m_0(s) + c\) for \(s \in D_0\), where \(m_0(s) = E\{Y^{(0)} | S^{(0)} = s\}\) and \(c\) is an unknown constant to be determined. Under this constraint, we show in Appendix B that the following \(g_{opt}\) minimizes (C.3):

\[
g_{opt}(s) = \begin{cases} 
  m_1(s) + \lambda \ r(s), & s \in \Omega_1 = D_c \cup D_1 \\
  m_0(s) + c, & s \in D_0 
\end{cases} \tag{2.2}
\]

where \(D_c \equiv \Omega_1 \cap \Omega_0\), \(D_1 = \Omega_1 \setminus \Omega_0\), \(m_a(s) = E\{Y^{(a)} | S^{(a)} = s\}\), \(f_a(s) = dF_a(s)/ds\) is the conditional density of \(S^{(a)}\) with \(F_a(s) = P(S^{(a)} \leq s)\), \(r(s) = f_0(s)/f_1(s)\) is the density ratio,

\[
\lambda = \{K_2 + K_1 r(s^*)\}^{-1} \left[ \int_{D_c} \Delta_{01}(s)f_0(s)ds + K_1 \Delta_{01}(s^*) \right],
\]

\[
c = \{K_2 + K_1 r(s^*)\}^{-1} \left[ r(s^*) \int_{D_c} \Delta_{01}(s)f_0(s)ds - K_2 \Delta_{01}(s^*) \right]
\]

with \(\Delta_{01}(s) = m_0(s) - m_1(s)\), \(K_1 = \int_{D_0} f_0(s)ds\), \(K_2 = \int_{D_c} r(s)f_0(s)ds\) and \(s^*\) being the intersection point of \(D_c\) and \(D_0\). When \(\Omega_0 \subseteq \Omega_1\), \(D_0\) is empty, \(K_1 = 0\), and \(g_{opt}\) is reduced to

\[
g_{opt}(s) = m_1(s) + \lambda \ r(s), \text{ where } \lambda = K_2^{-1} \int_{D_c} \Delta_{01}(s)f_0(s)ds. \tag{2.3}
\]

**Remark 1** With the aim of predicting \(Y\), a natural choice of \(g_{opt}(s)\) for \(s \in D_0\) is \(m_0(s)\) as in \(D_0\), there are only observations from group 0 with the surrogate marker and thus, \(m_0(s) = m(s) = E[Y | S = s]\) for \(s \in D_0\) is the best prediction function of \(S\) for \(Y\). However, an additional constant \(c\) is needed to make the function \(g_{opt}(s)\) to satisfy the constraint, and,
at the same time, to be continuous at the intersection point \( s^* \), where

\[
g_{\text{opt}}(s^*) = \frac{r(s^*)}{K_2 + K_1 r(s^*)} \left[ \int_{D^c} \Delta_{01}(s) f_0(s) ds + K_1 \Delta_{01}(s^*) \right] + m_1(s^*),
\]

which is well defined even if \( f_1(s^*) = 0 \).

**Remark 2** From the forms of \( \lambda \) and \( c \), it can be seen that if \( m_0(s) = m_1(s) = m(s) \) for \( s \in D_c \) (a perfect surrogate), then \( \lambda = 0 \), and \( g_{\text{opt}}(s) = m(s) \) for the whole domain. Therefore, 
\[
\Delta_{g_{\text{opt}}} = E[g_{\text{opt}}(S^{(1)}) - g_{\text{opt}}(S^{(0)})] = E[m(S^{(1)}) - m(S^{(0)})] = \int m(s) f_1(s) ds - \int m(s) f_0(s) ds = \int m_1(s) f_1(s) ds - \int m_0(s) f_0(s) ds = \Delta. \]
That is, \( \text{PTE} = 1 \), which is as would be expected for a perfect surrogate.

### 2.3 Estimating \( g_{\text{opt}} \)

We propose to estimate \( g_{\text{opt}} \) non-parametrically by first estimating \( f_a(s) \), \( m_a(s) \) and \( \lambda \) as

\[
\hat{f}_a(s) = n^{-1} \sum_{A_i=a} K_h(S_i - s), \quad \hat{m}_a(s) = \sum_{A_i=a} K_h(S_i - s) Y_i / \sum_{A_i=a} K_h(S_i - s), \quad \hat{\Delta}_{01}(s) = \hat{m}_0(s) - \hat{m}_1(s)
\]

\[
\hat{\lambda} = \left\{ \hat{K}_2 + \hat{K}_1 \hat{r}(s^*) \right\}^{-1} \left\{ \int_{D^c} \hat{\Delta}_{01}(s) \hat{f}_0(s) ds + \hat{K}_1 \hat{\Delta}_{01}(s^*) \right\},
\]

\[
\hat{\vartheta} = \left\{ \hat{K}_2 + \hat{K}_1 \hat{r}(s^*) \right\}^{-1} \left\{ \hat{r}(s^*) \int_{D^c} \hat{\Delta}_{01}(s) \hat{f}_0(s) ds - \hat{K}_2 \hat{\Delta}_{01}(s^*) \right\},
\]

where \( \hat{r}(s) = \hat{f}_0(s)/\hat{f}_1(s) \), \( \hat{K}_1 = \int_{D_0} \hat{f}_0(s) ds \), \( \hat{K}_2 = \int_{D^c} \hat{r}(s) \hat{f}_0(s) ds \), \( K_h(\cdot) = K(\cdot/h)/h \) is a symmetric kernel function with bandwidth \( h = O(n^{-\nu}) \), \( \nu \in (1/5,1/2) \). Based on these quantities, we may construct a plug-in estimate for \( g_{\text{opt}} \), denoted by \( \hat{g} \), as follows

\[
\hat{g}(s) = \begin{cases} 
\hat{m}_1(s) + \hat{\lambda} \hat{r}_0(s), & s \in D_c \cup D_1 \\
\hat{m}_0(s) + \hat{\vartheta}, & s \in D_0.
\end{cases}
\]

In Appendix D, we show that \( (nh)^{\nu/2} \{ \hat{g}(s) - g_{\text{opt}}(s) \} \) converges in distribution to a normal distribution with mean 0 and variance-covariance \( \Sigma^2(s) \).

The resulting PTE for \( g_{\text{opt}}(S) \) can be obtained as \( \text{PTE}_{g_{\text{opt}}} = \Delta_{g_{\text{opt}}}/\Delta \) and estimated as

\[
\hat{\text{PTE}}_{\hat{g}} = \hat{\Delta}_{\hat{g}}/\hat{\Delta},
\]

where \( \hat{\Delta} = \hat{\mu}_1 - \hat{\mu}_0, \hat{\Delta}_g = \hat{\mu}_{g,1} - \hat{\mu}_{g,0}, \hat{\mu}_a = n_a^{-1} \sum_{i=1}^n I(A_i = a) Y_i, n_a = \sum_{i=1}^n I(A_i = a), \hat{\mu}_{g,a} = n_a^{-1} \sum_{i=1}^n I(A_i = a) g(S_i) \). With respect to PTE, Parast et al. (2017) proposed a class of surrogacy measures based on the PTE to evaluate a surrogate marker, \( \text{PTE}_L \), indexed by a reference distribution of the surrogate marker. We show in Appendix C that \( \text{PTE}_{g_{\text{opt}}} \) is approximately equivalent to \( \text{PTE}_L \) with a particular reference distribution uniquely defined
by $g_{\text{opt}}(\cdot)$ and $\Delta_{g_{\text{opt}}(S)}$. In addition, this PTE$_{g_{\text{opt}}}$ only requires the following conditions (C1) and (C2) to guarantee that PTE$_{g_{\text{opt}}}$ is between 0 and 1.

(C1) $S_1(u) \geq S_0(u)$ for all $u$,

(C2) $M_1(u) \geq M_0(u)$ for all $u$ in the common support of $g_{\text{opt}}(S^{(1)})$ and $g_{\text{opt}}(S^{(0)})$,

where $S_a(u) = P\{g(S^{(a)}) > u \mid A = a\}$, $M_a(u) = E\{Y^{(a)} \mid g(S^{(a)}) = u\}$, for $a = 0, 1$. These assumptions can be verified based on the observed data and are more likely to hold as $g_{\text{opt}}(S)$ is chosen to be close to $Y$, compared with the four assumptions in Parast et al. (2017).

3 Evaluating Surrogacy Using Relative Power

3.1 Relative Power Measure

Our goal is to evaluate the surrogacy of $S$ for the primary outcome $Y$. For any $g$ such that $0 \leq \Delta_g \leq \Delta$, such as $g_{\text{opt}}$ in Section 2, it would be valid to test for the treatment effect $H_0 : \Delta = 0$ based on $\Delta_g$. We propose to quantify the surrogacy of $g(S)$ based on the extent to which the estimated $\Delta_g$ can be used to detect the target treatment effect $\Delta$. To this end, consider a pair of regular asymptotically normal estimators $\hat{\Delta}$ and $\hat{\Delta}_g$ for $\Delta$ and $\Delta_g$ such that

\[ n^{1/2}(\hat{\Delta} - \Delta) \to N(0, \sigma^2), \quad \text{and} \quad n^{1/2}(\hat{\Delta}_g - \Delta_g) \to N(0, \sigma_g^2). \]

Then we may define the effect sizes for $Y$ and $g(S)$ as $\Delta/\sigma$ and $\Delta_g/\sigma_g$, which directly indicate the potential power of a study in detecting treatment difference $H_0 : \Delta = 0$ using $Y$ versus using $g(S)$ with a given sample size $\bar{n}$. Thus, we propose to measure the surrogacy of $g(S)$ based on the relative power (RP):

\[ \text{RP}_g(\bar{n}) := \text{RP}_g(\bar{n}, \bar{n}), \quad \text{where} \quad \text{RP}_g(n_1, n_2) = \frac{P(\Delta_g/\sigma_g, n_1)}{P(\Delta/\sigma, n_2)}, \]

where $P(\Delta_g/\sigma_g, n_1) = 1 - \Phi(1.96 - \sqrt{n_1 \Delta_g/\sigma_g})$, $P(\Delta/\sigma, n_2) = 1 - \Phi(1.96 - \sqrt{n_2 \Delta/\sigma})$, the testing powers based on $g(S)$ and $Y$, respectively. A good surrogate marker will have $\text{RP}_g(\bar{n})$ close to or greater than 1 while $\text{RP}_g(\bar{n})$ being much less than 1 would indicate a poor surrogate. Importantly, while PTE$_g \equiv \Delta_g/\Delta \leq 1$ is true with the class of $g$ of interest, it is not necessarily the case that $\text{RP}_g(\bar{n}) \leq 1$. If the variance of $\hat{\Delta}_g$ is sufficiently smaller than that of $\hat{\Delta}$, $\text{RP}_g(\bar{n})$ may be larger than 1, indicating greater power and efficiency when the effect size is calculated using the surrogate information due to the reduction in variation. Compared with PTE$_g$, $\text{RP}_g(\bar{n})$ considers variation in estimating $\Delta_g$ and provides more direct information on the power of the study if $g(S)$ is used instead of $Y$. We examine both $\text{RP}_g(\bar{n})$ and PTE$_g$ in our numerical studies.
3.2 Estimation of RP

To estimate $RP_g(\bar{n})$ for a given $g$, we estimate $\Delta$ and $\Delta_g$, respectively, by

$$\hat{\Delta} = \hat{\mu} - \mu_0 \quad \text{and} \quad \hat{\Delta}_g = \hat{\mu}_{g,1} - \hat{\mu}_{g,0},$$

where. In Appendix A, we show that $\sqrt{n}(\hat{\Delta} - \Delta)$ and $\sqrt{n}(\hat{\Delta}_g - \Delta_g)$ respectively converge in distribution to $N(0, \sigma^2)$ and $N(0, \sigma_g^2)$, where $\sigma^2 = E\{\psi_i^2\}$ and $\sigma_g^2 = E\{\psi_{g,i}^2\}$ can be respectively estimated by $\hat{\sigma}^2 = n^{-1}\sum_{i=1}^n \hat{\psi}_i^2$ and $\hat{\sigma}_g^2 = n^{-1}\sum_{i=1}^n \hat{\psi}_{g,i}^2$. $\psi_i$ and $\hat{\psi}_{g,i}$ are influence functions and their estimates. Their rigorous definitions are given in Appendix A. With these estimators, we may construct a plug-in estimator for $RP_g(\bar{n})$ as

$$\hat{RP}_g(\bar{n}) := \hat{RP}_g(\bar{n}, \bar{n}) \quad \text{where} \quad \hat{RP}_g(n_1, n_2) = \frac{P(\hat{\Delta}_g/\hat{\sigma}_g, n_1)}{P(\hat{\Delta}/\hat{\sigma}, n_2)}.$$ 

To assess the variability of $\hat{RP}_g(n_1, n_2)$, one can show that $\sqrt{n}\{\hat{RP}_g(n_1, n_2) - RP_g(n_1, n_2)\}$ converges in distribution to a zero-mean normal distribution with variance $\sigma_{RP_g}^2(n_1, n_2)$ based on the weak convergence of the random vector $\sqrt{n}(\hat{\Delta} - \Delta, \hat{\Delta}_g - \Delta_g, \hat{\sigma}^2 - \sigma^2, \hat{\sigma}_g^2 - \sigma_g^2)^T$. In practice, we may approximate $\sigma_{RP_g}^2(n_1, n_2)$ via the standard perturbation resampling procedures (Park & Wei, 2003; Cai et al., 2005, e.g.).

With $g_{opt}(\cdot)$ estimated as $\hat{g}(\cdot)$, we may estimate $\Delta_{g_{opt}}$ as $\hat{\Delta}_{g_{opt}}$ and $\sigma_{g_{opt}}^2$ as $\hat{\sigma}_{g_{opt}}^2 = n^{-1}\sum_{i=1}^n \hat{\psi}_{g,i}^2$. A plug-in estimate for $RP_{g_{opt}}(\bar{n})$ can be constructed accordingly, denoted as $\hat{RP}_{g_{opt}}(\bar{n})$, whose asymptotic variance can be estimated by perturbation resampling procedures similarly.

3.3 Using RP to Design a Future Trial

With a surrogate marker identified in an existing trial (Phase 2 trial), it is possible to use our estimate of RP to inform the design of a new trial (Phase 3 trial) wherein one would use the treatment effect on the surrogate information to predict or test for the treatment effect on the primary outcome. We assume the transportability of $\Delta_g/\sigma_g$ between the existing trial and the future trial, which is generally reasonable in the Phase 2 trial and Phase 3 trial setting since these trials usually have the same inclusion-exclusion criteria. Under this assumption, we may consider relative power between a future trial and an existing trial as:

$$RP_g(n^*, \bar{n}) = \frac{P(\Delta_g/\sigma_g, n^*)}{P(\Delta/\sigma, \bar{n})}, \quad (3.1)$$

where $n^*$ is the sample size in the future trial. $RP_g(n^*, \bar{n})$ can be interpreted approximately as the power ratio of

$$\Delta_g/\text{se}(\hat{\Delta}_g^*) \quad \text{vs.} \quad \Delta/\text{se}(\hat{\Delta}),$$

where $\hat{\Delta}_g^*$ is the estimator of $\Delta_g$ in the future trial with sample size $n^*$ and $\hat{\Delta}$ is the estimator of $\Delta$ in the existing trial with sample size $\bar{n}$. Of course, (3.1) can be re-written such that
we can use the expression to determine the needed sample size \( n^* \) for the future trial given a desired \( \text{RP}_g(n^*, \bar{n}) \) in the future trial.

Alternatively, one could consider selecting \( n^* \) such that it is ensured that the lower bound of the one-sided \( 100(1 - \alpha)\% \) confidence interval (CI) for \( \text{RP}_g(n^*, \bar{n}) \) exceeds a desired threshold value \( \kappa \).

4 Final Estimation and Inference for RP with Estimated \( g_{opt}() \)

Using the same dataset to estimate both \( g_{opt} \) and its corresponding \( \text{RP}(\bar{n}) = \text{RP}_{g_{opt}}(\bar{n}) \) may lead to overfitting bias as in standard prediction settings. Therefore, we employ cross-validation (CV) wherein we split the data randomly into two subsets and estimate \( g_{opt} \) with one subset, and estimate \( \text{RP}_g(\bar{n}) \) given \( g \) using a separate subset.

Specifically, denote \( \mathcal{I}_k \) and \( \mathcal{I}_{-k} = \{1, ..., n\} \setminus \mathcal{I}_k \), \( k = 1, ..., K \), be a random partition of the index set \( \{1, ..., n\} \) of equal sizes, and let \( \mathcal{D}_I = \{D_i, i \in \mathcal{I}\} \). Let \( \hat{g}_{\mathcal{I}_k} \) denote \( g_{opt} \) estimated based on \( \mathcal{D}_I \). Given \( \hat{g}_{\mathcal{I}_k} \), \( \text{RP}_{g_{opt}}(\bar{n}) \) is estimated using data in \( \mathcal{D}_{\mathcal{I}_{-k}} \), and denoted by \( \hat{\text{RP}}_{g_{\mathcal{I}_k}}(\bar{n}) \).

Then, we define the CV-based estimator of \( \text{RP}_{g_{opt}}(\bar{n}) \) as

\[
\hat{\text{RP}}_{CV}(\bar{n}) = K^{-1} \sum_{k=1}^{K} \hat{\text{RP}}_{g_{\mathcal{I}_k}}(\bar{n}).
\]

The consistency of \( \hat{g}_{\mathcal{I}_k} \) to \( g_{opt} \) and that of \( \hat{\text{RP}}_{g_{\mathcal{I}_k}}(\bar{n}) \) to \( \text{RP}_g(\bar{n}) \) guarantee the consistency of \( \hat{\text{RP}}_{CV}(\bar{n}) \) to \( \text{RP}(\bar{n}) \). The asymptotic distribution of \( \hat{\text{RP}}_{CV}(\bar{n}) - \text{RP}(\bar{n}) \) can be obtained from the asymptotic expansions of \( \hat{g}_{\mathcal{I}_k} - g_{opt} \) and \( \hat{\text{RP}}_{g_{\mathcal{I}_k}}(\bar{n}) - \text{RP}_g(\bar{n}) \). Specifically, when \( h = O(n^{-\nu}) \) with \( \nu \in (1/4, 1/2) \),

\[
n^{1/2} \{\hat{\text{RP}}_{CV}(\bar{n}) - \text{RP}_{g_{opt}}(\bar{n})\} = n^{-1/2} \sum_{i=1}^{n} \psi_{g_{opt},i}(\bar{n}) + o_p(1),
\]

which converges in distribution to a normal with mean 0 and variance \( \tau^2_{g_{opt}}(\bar{n}) = E\{\psi^2_{g_{opt},i}(\bar{n})\} \). Similar to \( \sigma_{g_{opt}}(\bar{n}) \), it is difficult to construct explicit estimation of \( \tau^2_{g_{opt}}(\bar{n}) \) and we instead employ resampling methods. Estimation and inference for \( \text{PTE} = \text{PTE}_{g_{opt}} \), whose estimate we denote as \( \hat{\text{PTE}}_{g_{opt}} \), can be derived similarly.

5 Simulation studies

5.1 Simulation Goals

We conducted simulation studies to: (1) evaluate the finite sample performance of the proposed estimation and inference procedures for \( \text{RP}(\bar{n}), \bar{n} = 50, 100, 150 \), with respect to bias, accuracy of standard error estimates, and coverage probabilities in a variety of settings, (2) compare estimates of \( \text{RP}(\bar{n}) \) and \( \text{PTE} \), and (3) compare \( \text{PTE} \) of our proposed optimal
transformation with existing PTE methods. Specifically, for comparison of PTEs, we include PTE estimate from the methods of (i) Wang et al. (2020), denoted as \( \text{PTE}_{W_{2020}} \); (ii) Parast et al. (2016), denoted as \( \text{PTE}_{L} \); (iii) Wang & Taylor (2002), denoted as \( \text{PTE}_{W} \); and (iv) Freedman et al. (1992), denoted as \( \text{PTE}_{F} \).

5.2 Simulation Setup

We examined five simulation settings; settings were selected in an effort to examine settings with varying surrogate strength (e.g. weak vs. moderate vs. strong surrogate) and settings that violate certain assumptions required by existing comparator methods. Throughout, we let \( n = 2000 \), variances were estimated using perturbation resampling, a normal density was used for the kernel function, and we chose the bandwidth \( h = h_{\text{opt}}n^{-c_0} \) with \( c_0 = 0.06 \) to ensure under-smoothing needed for \( \text{RP}(\bar{n}) \) estimation, where \( h_{\text{opt}} \) is obtained using the procedure of Scott (1992). For settings \( k = 1, 2, 3 \), we generate

\[
S^{(1)} \sim \text{Gamma}(\text{shape} = a_k^{(1)}, \text{scale} = b_k^{(1)}), \quad S^{(0)} \sim \text{Gamma}(\text{shape} = a_k^{(0)}, \text{scale} = b_k^{(0)}),
\]

\[
Y^{(1)} = I\{E^{(1)}/(0.2G_k^{(1)}(S^{(1)})) > t\}, \quad Y^{(0)} = I\{E^{(0)}/(0.2 + 0.22G_k^{(0)}(S^{(0)})) > t\},
\]

where \( E^{(0)} \) and \( E^{(1)} \) follow the unit exponential distribution, and we let

- \( a_1^{(1)} = 2, \ b_1^{(1)} = 2, \ a_1^{(0)} = 9, \ b_1^{(0)} = 0.5, \ G_1^{(1)}(s) = s, \ G_1^{(0)}(s) = s; \)
- \( a_2^{(1)} = 2, \ b_2^{(1)} = 2, \ a_2^{(0)} = 9, \ b_2^{(0)} = 0.5, \ G_2^{(1)}(s) = s - 3\log(s), \ G_2^{(0)}(s) = 3; \)
- \( a_3^{(1)} = 5, \ b_3^{(1)} = 1, \ a_3^{(0)} = 9, \ b_3^{(0)} = 0.5, \ G_3^{(1)}(s) = s/2, \ G_3^{(0)}(s) = 9/11 + s. \)

In setting (4), \( S^{(1)} \sim \text{Uniform}(1, 3), \ S^{(0)} \sim \text{Uniform}(2, 4), \ G_5^{(1)}(s) = G_5^{(0)}(s) = s, \) and \( Y^{(1)}, Y^{(0)} \) are generated as above. In setting (5), we generated

\[
\begin{bmatrix} S^{(1)} \\ S^{(0)} \end{bmatrix} \sim \mathcal{N} \left( \begin{bmatrix} 5 \\ 5 \end{bmatrix}, \begin{bmatrix} 2 & 1 \\ 1 & 1 \end{bmatrix} \right),
\]

and \( Y^{(1)} \) and \( Y^{(0)} \) from

\[
P(Y^{(1)} \mid S^{(0)}, S^{(1)}) = \exp\{-1 - 0.1S^{(1)}\}, \quad \text{and} \quad P(Y^{(0)} \mid S^{(0)}, S^{(1)}) = \exp\{-4 - 0.1S^{(0)}\}.
\]

In setting (1), all assumptions required by Parast et al. (2016) are satisfied. However, in settings (2), the effect of \( S \) on \( Y \) is non-monotone and in settings (3) and (4), \( S^{(0)} \) and \( S^{(1)} \) have rather different supports; thus, in these settings, the assumptions required by Parast et al. (2016) do not hold. The working independence assumption of Wang et al. (2020) holds in settings (1)-(4) but not in setting (5).

5.3 Simulation Results

Simulation results are shown in Table 1 and Table 2, for PTE and RP, respectively. All results are summarized based on 500 replications for each setting. Across all settings, the point
estimates for our proposed RP measure using $g_{\text{opt}}$ have negligible bias, estimated standard errors are close to the empirical standard errors, and coverage probabilities of the confidence intervals are close to their nominal level 0.95. Similar results are observed for the PTE estimate using our proposed $g_{\text{opt}}$. With respect to comparing RP and PTE, in setting (1) and (4), where the estimates of PTE$_{g_{\text{opt}}}$ are relatively higher (above 0.5) than other settings, the estimates of RP$_{g_{\text{opt}}}$ ($\bar{n}$) are above 1, so PTE and RP are consistent in indicating the surrogacy of a surrogate marker. This also suggests that although the estimated $\Delta_{g_{\text{opt}}}$ is slightly smaller compared to $\Delta$, the variation of $\hat{\Delta}_{g_{\text{opt}}}$ is substantially smaller than the corresponding variation of $\hat{\Delta}$, leading to higher power if the study were to be based on $g_{\text{opt}}(S)$ rather than the outcome $Y$ itself. This illustrates the advantage of using RP for quantifying surrogacy since it is more closely tied to study power and effect size compared to PTE alone.

Table 1 also summarizes the results of other PTE estimators. Across all settings, the methods of Wang & Taylor (2002) and Freedman et al. (1992) misspecify the underlying model and as a result, PTE$_W$ and PTE$_{F}$ estimates differ substantially from the nonparametric estimates of PTE (using $g_{\text{opt}}$), PTE$_{W2020}$ and PTE$_L$. For setting (2), where we have introduced a deviation from the monotone increasing assumption for $E(Y \mid S = s)$, we observe that except for our proposed PTE and PTE$_{W2020}$ estimates, the other methods yield PTE estimates negative or close to zero. This is due to the fact that the monotone assumption fails in this case and our proposed PTE and PTE$_{W2020}$ evaluate the PTE for $g_{\text{opt}}(S)$ rather than $S$, thus demonstrating the robustness of the proposed PTE and PTE$_{W2020}$. In setting (3), PTE$_L$, PTE$_W$ and PTE$_F$ all fail with their estimates being negative. This may be due to the supports of the treatment and control groups being quite different. In contrast, the proposed PTE and PTE$_{W2020}$ perform well here. In setting (4), both our proposed PTE and PTE$_{W2020}$ estimates identify this setting as one with strong surrogacy while the comparison methods fail to do so. Across all settings, the proposed PTE estimates are comparable or a little bit larger than corresponding estimates of PTE$_{W2020}$, so both estimators are relatively robust and comparable.

6 Application to the Diabetes Prevention Program Study

To illustrate our proposed RP measure, we apply our procedures to the Diabetes Prevention Program (DPP) study which was a randomized trial investigating the effect of several prevention strategies for reducing the risk of type 2 diabetes (T2D) among high risk individuals with pre-diabetes (Diabetes Prevention Program Group, 1999, 2002). DPP data are publicly available through the the National Institute of Diabetes and Digestive and Kidney Diseases Central Repository. The participants were randomized to one of four treatment groups: placebo, lifestyle intervention, metformin and troglitazone. The primary endpoint of the trial was time to T2D onset and the participants were followed up to 5 years with a mean follow up of 2.8 years. Both lifestyle intervention and metformin were shown to significantly reduce T2D risk among participants.

For illustration, we focused on the comparison of the lifestyle intervention group ($n_1 = 1007$) versus the placebo group ($n_0 = 1010$) with respect to diabetes risk at $t = 1, 2, 3, 4$. 
years. Our goal is to investigate to what extent surrogate information on hemoglobin A1C (HbA1c) or fasting glucose at $t_0 = 0.5$ years (i.e., 6 months), can be used to predict treatment effect on diabetes risk at $t = 1, 2, 3$ or 4 years. Only 10 patients developed T2D before $t_0$ and were excluded from this analyses. We evaluate the surrogacy potential of these markers based on the proposed RP measure primary, and also calculate PTE for comparison.

Results are shown in Table 3 and Table 4. Examining RP first, for both HbA1c and glucose, RP is highest when $t = 1$ and generally decreases as $t$ gets further from $t_0 = 0.5$. For comparison, we provide the other PTE estimates as well; the PTE estimate with the proposed $g_{opt}$ is generally larger than or comparable to corresponding estimates of $\text{PTE}_{W2020}$, $\text{PTE}_L$, $\text{PTE}_W$ and $\text{PTE}_F$, which is similar to what was observed in simulations meaning that the proposed transformed surrogate explains a larger proportion of the treatment effect on the outcome than the untransformed surrogate. In addition, using either PTE or RP, fasting glucose appears to be a stronger surrogate compared to HbA1C.

To illustrate how these estimates can be used to design a future trial, consider the estimated RP($n^*, 50$) in (3.1) for the primary outcome at $t = 2$ for fasting glucose. To ensure a 95% lower bound of $\hat{\text{RP}}(n^*, 50)$ above 1, we obtain a needed sample size $n^* \geq 50$. This suggests that with a future sample size $n^* \geq 50$, the power of a future 0.5-year trial based on $g_{opt}(S)$ could be at least as high as the power of the DPP study with sample size 50 based on the diabetes onset information collected up to 2 years.

7 Discussion

We derive an optimal transformation of the surrogate marker such that we avoid the requirement of a working independence assumption in Wang et al. (2020). Our methods has the advantage of both being model-free and requiring flexible assumptions about the surrogate marker distribution and its relationship with the outcome. Numerical studies show good performance of this optimal transformation. Both the proposed optimal transformation and the optimal transformation of Wang et al. (2020) are robust to various scenarios and have comparable performances. So the proposed one is a good alternative to the one in Wang et al. (2020) if one is not confident in the validity of the working independence assumption for a specific dataset under analysis.

We propose a relative power measure to quantify the utility of a potential surrogate marker which is measured either earlier than the primary outcome or with less burden/cost compared to the primary outcome. Unlike the commonly used proportion of treatment effect explained measure, the RP measure provides a direct link to the expected power of subsequent phase trials and can be used to inform their design. Specifically, it directly reflects the expected gain or loss in power when considering the use of a surrogate marker in a future trial relative relying on the primary outcome. Through the calculation of a sample size, and if desired, a confidence interval lower bound, actionable information to determine needed study size and duration can be obtained. We have provided a nonparametric inference approach for the optimal transformation and the corresponding RP, which demonstrated good finite sample performance.
Importantly, the ability to calculate a sample size to inform the design of a future trial relies on the assumption of transportability of the quantity $\Delta_g/\sigma_g$ from the existing trial to a future trial. This is reasonable for different phases of trials as these trials often use parallel inclusion criteria of participants. But using surrogate to inform different future studies needs caution. According to our knowledge, the transportability is unavoidable in studying surrogate markers. We choose to assume the transportability of $\Delta_g/\sigma_g$ instead of, for example, the complete joint distribution of outcome and surrogate marker. Transportability of information learned about a surrogate marker in a previous study is a complex and interesting issue and is an active area of research (Wang et al., 2020; Price et al., 2018; Athey et al., 2016). Of course, the ultimate goal underlying surrogate marker research is that if they can be identified, they can be used in future trials, and reduce follow-up time and costs, but successfully achieving this goal strongly relies on the assumption of transportability. Violations of this transportability assumption could have important consequences and future work in this area is warranted.

Our work has some limitations. Given our nonparametric estimation approach, we require a relatively large sample size such that the kernel smoothing will behave properly. Our methods would likely not be a reasonable option for studies with a very small sample size and in those cases, a parametric approach may need to be considered. In addition, we can address the issue of drop-out, censoring, or staggered entry into the study similarly to Wang et al. (2021). Each of these issues would introduce additional complexities that warrant future work. Lastly, we focus on evaluating and using a single surrogate marker. Often, studies have multiple potential surrogate markers and/or a surrogate marker measured repeatedly over time i.e., a longitudinal marker (Wang et al., 2022). While methods have been developed to evaluate surrogate in these settings, this area of research would benefit from further development of methods that address the issue of how to design future clinical trial studies that would use such markers to replace the primary outcome (Parast et al., 2020; Athey et al., 2019; Agniel & Parast, 2021).

The DPP data used in this paper is not available to the public. The authors can provide information on application for the dataset.
Table 1: Estimates (Est) of PTE (using our proposed $g_{opt}$), $PTE_{W2020}$, $PTE_L$, $PTE_W$, and $PTE_F$ along with their empirical standard errors (ESE) under settings (1)-(5); for PTE estimates using our proposed $g_{opt}$, we also present the averages of the estimate standard errors (ASE, shown in subscript) along with the empirical coverage probabilities (CP) of the 95% confidence intervals.

|           | True | Est  | ESEASE | CP   | Est  | ESE | Est  | ESE | Est  | ESE | Est  | ESE |
|-----------|------|------|--------|------|------|-----|------|-----|------|-----|------|-----|
| (1)       | .657 | .666 | .073   | .956 | .616 | .060| .374 | .078| .195 | .043| .189 | .041|
| (2)       | .188 | .207 | .057   | .968 | .140 | .049| -.226| .060| .075 | .020| .059 | .016|
| (3)       | .095 | .092 | .023   | .972 | .077 | .015| -.042 | .013| -.049 | .011| -.037 | .008|
| (4)       | .772 | .794 | .056   | .942 | .806 | .033| .382 | .280| .546 | .118| .463 | .086|
| (5)       | .301 | .308 | .080   | .986 | .244 | .057| .177 | .065| .001 | .039| .001 | .027|

Table 2: Estimates (Est) of $RP(\bar{n})$ (using our proposed $g_{opt}$), with their empirical standard errors (ESE), the averages of the estimate standard errors (ASE, shown in subscript) and the empirical coverage probabilities (CP) of the 95% confidence intervals under settings (1)-(5).

|           | True | Est  | ESEASE | CP   | Est  | ESE | Est  | ESE | Est  | ESE | Est  | ESE |
|-----------|------|------|--------|------|------|-----|------|-----|------|-----|------|-----|
| (1)       | RP(50)| 2.005| 2.117 | .415 | .934 | RP(100)| 1.710 | 1.792 | .360 | .952 | RP(150)| 1.432 | 1.501 | .277 | .964 |
|           | RP(50)| .631 | .707 | .253 | .974 | RP(100)| .615 | .679 | .251 | .980 | RP(150)| .631 | .673 | .231 | .976 |
| (3)       | RP(50)| .216 | .200 | .054 | .919 | RP(100)| .378 | .344 | .099 | .913 | RP(150)| .521 | .469 | .127 | .921 |
| (4)       | RP(50)| 2.231| 2.337 | .374 | .962 | RP(100)| 1.361| 1.421 | .174 | .972 | RP(150)| 1.128| 1.167 | .095 | .984 |
| (5)       | RP(50)| .783 | .737 | .184 | .938 | RP(100)| .759 | .705 | .210 | .938 | RP(150)| .761 | .700 | .215 | .932 |

Table 2: Estimates (Est) of $RP(\bar{n})$ (using our proposed $g_{opt}$), with their empirical standard errors (ESE), the averages of the estimate standard errors (ASE, shown in subscript) and the empirical coverage probabilities (CP) of the 95% confidence intervals under settings (1)-(5).
|       | HBA1c | Fasting glucose |
|-------|-------|-----------------|
|       | PTE   | PTE\(_{W,2020}\) | PTE\(_{L}\) | PTE\(_{W}\) | PTE\(_{F}\) |
| \(t = 1\) | .264,066 | .240,034 | .241,011 | .163,007 | .195,004 |
| \(t = 2\) | .331,076 | .250,025 | .179,005 | .155,003 | .208,003 |
| \(t = 3\) | .295,055 | .248,020 | .186,004 | .137,002 | .176,002 |
| \(t = 4\) | .286,060 | .240,021 | .169,004 | .139,003 | .175,002 |

|       | PTE   | PTE\(_{W,2020}\) | PTE\(_{L}\) | PTE\(_{W}\) | PTE\(_{F}\) |
|-------|-------|-----------------|------------|------------|------------|
| \(t = 1\) | .558,067 | .475,044 | .337,018 | .267,015 | .478,014 |
| \(t = 2\) | .570,067 | .535,035 | .603,021 | .449,014 | .536,013 |
| \(t = 3\) | .564,061 | .515,029 | .495,011 | .382,008 | .478,008 |
| \(t = 4\) | .576,068 | .521,030 | .479,012 | .377,010 | .481,010 |

Table 3: Estimates of PTE using the proposed \(g_{opt}\), and PTE\(_{W,2020}\), PTE\(_{L}\), PTE\(_{W}\), PTE\(_{F}\), along with the estimated standard errors (shown in subscript).

|       | HBA1c | Fasting glucose |
|-------|-------|-----------------|
|       | RP(50) | RP(100) | RP(150) |
| \(t = 1\) | 1.054,305 | 1.065,369 | 1.067,379 |
| \(t = 2\) | .921,268 | .924,309 | .930,306 |
| \(t = 3\) | .702,185 | .694,196 | .717,188 |
| \(t = 4\) | .770,227 | .758,246 | .772,239 |

|       | Fasting glucose |
|-------|-----------------|
|       | RP(50) | RP(100) | RP(150) |
| \(t = 1\) | 1.756,375 | 1.808,418 | 1.728,397 |
| \(t = 2\) | 1.486,294 | 1.488,304 | 1.417,272 |
| \(t = 3\) | 1.296,248 | 1.267,240 | 1.208,204 |
| \(t = 4\) | 1.466,297 | 1.431,295 | 1.341,254 |

Table 4: Estimates of RP using the proposed \(g_{opt}\) along with the estimated standard errors (shown in subscript).
A Influence functions of $\hat{\Delta}$, $\hat{\Delta}_g$, $\hat{\sigma}$ and $\hat{\sigma}_g^2$

We derive asymptotic distributions for $\hat{\Delta}$ and $\hat{\Delta}_g$. To this end, we first write

$$\hat{\mu}_a - \mu_a = \frac{\sum_{i=1}^n I(A_i = a)Y_i}{\sum_{i=1}^n I(A_i = a)} - \mu_a = \frac{\sum_{i=1}^n I(A_i = a)(Y_i - \mu_a)}{\sum_{i=1}^n I(A_i = a)} := n^{-1} \sum_{i=1}^n \psi_{a,i} + o_p(n^{-1/2}),$$

where $\psi_{a,i} = 2I(A_i = a)(Y_i - \mu_a)$. It follows that

$$\sqrt{n}(\hat{\Delta} - \Delta) = n^{-1/2} \sum_{i=1}^n (\psi_{1,i} - \psi_{0,i}) + o_p(1) := n^{-1/2} \sum_{i=1}^n \psi_i + o_p(1).$$

By the central limit theorem we have that $\sqrt{n}(\hat{\Delta} - \Delta)$ converges in distribution to a normal distribution $N(0, \sigma^2)$ with $\sigma^2 = E[\psi_i^2]$.

Similarly, we have

$$\hat{\mu}_{g,a} - \mu_{g,a} = \frac{\sum_{A_i=a} g(S_i)}{\sum_{A_i=a} 1} - \mu_{g,a} = \frac{\sum_{A_i=a} \{g(S_i) - \mu_{g,a}\}}{\sum_{A_i=a} 1} := n^{-1} \sum_{i=1}^n \psi_{g,a,i} + o_p(n^{-1/2}).$$

It follows that

$$\sqrt{n}(\hat{\Delta}_g - \Delta_g) = n^{-1/2} \sum_{i=1}^n (\psi_{g,1,i} - \psi_{g,0,i}) + o_p(1) := n^{-1/2} \sum_{i=1}^n \psi_{g,i} + o_p(1).$$

By the central limit theorem we have that $\sqrt{n}(\hat{\Delta}_g - \Delta_g)$ converges in distribution to a normal distribution $N(0, \sigma_g^2)$ with $\sigma_g^2 = E[\psi_{g,i}^2]$.

We next derive estimators for the asymptotic variances $\sigma^2$ and $\sigma_g^2$. To this end, we first note that the variance of $\psi_{a,i}$ is

$$E\psi_{a,i}^2 = E[4I(A_i = a)(Y_i - \mu_a)^2],$$

which can be estimated by

$$\hat{\Sigma}_a = n^{-1} \sum_{i=1}^n 4I(A_i = a)(Y_i - \hat{\mu}_a)^2.$$

Therefore, the asymptotic variance of $\sqrt{n}(\hat{\Delta} - \Delta)$, $\sigma^2$, can be estimated by $\hat{\sigma}^2 := \hat{\Sigma} := \hat{\Sigma}_1 + \hat{\Sigma}_0$. 

It follows from the above formulas that $n^{1/2}(\hat{\sigma}^2 - \sigma^2)$ can be written as the form

$$n^{1/2}(\hat{\sigma}^2 - \sigma^2) = n^{-1/2} \sum_{i=1}^{n} \psi_{\sigma^2,i} + o_p(1).$$

Similarly, we can get the estimate for the asymptotic variance of $\sqrt{n}(\hat{\Delta}_g - \Delta_g)$, $\hat{\sigma}_g^2$, with a given $g$, and

$$n^{1/2}(\hat{\sigma}_g^2 - \sigma_g^2) = n^{-1} \sum_{i=1}^{n} \psi_{\sigma_g^2,i} + o_p(1).$$

With the above influence functions for $\hat{\sigma}^2$ and $\hat{\sigma}_g^2$, the variance estimates for $\hat{\sigma}^2$ and $\hat{\sigma}_g^2$ can be obtained by perturbation resampling method.

**B Derivations of the optimal $g$**

In this section, we derive the specific form for the optimal transformation function of the surrogate information, $g_{opt}(\cdot)$. We aim to solve the following problem for $g$:

$$\min_{g} L(g) = E\{Y^{(1)} - g(S^{(1)})\}^2, \quad \text{given} \quad E\{Y^{(0)} - g(S^{(0)})\} = 0$$

with $g(s) = m_0(s) + c, s \in D_0$ and $g(s)$ is continuous.

Without loss of generality, we assume that $S$ is continuous with conditional densities given $A = a$, $F_a(s) := f_a(s)$, with respect to the Lebesgue measure. Similar arguments as given below can be used to derive $g_{opt}$ when $S$ is discrete. It can be shown that

$$E\{Y^{(1)} - g(S^{(1)})\}^2 \propto E[g^2(S^{(1)})] - 2E[Y^{(1)} g(S^{(1)})] = E[g^2(S^{(1)})] - 2E[m_1(S^{(1)}) g(S^{(1)})].$$

And thus the problem is equivalent to finding a function $g_{opt}(\cdot)$ such that

$$\min_{g} \frac{1}{2} E[g^2(S^{(1)})] - E[m_1(S^{(1)}) g(S^{(1)})] \quad \text{given} \quad E[g(S)|A = 0] = \mu_0.$$ 

Our optimization problem is thus,

$$\min_{g} \int \frac{1}{2} g^2(s) f_1(s) ds - \int m_1(s) g(s) f_1(s) ds \quad \text{given that} \quad \int g(s) f_0(s) ds = \mu_0,$$

which is equivalent to

$$\min_{g} \mathcal{L}(g), \quad \text{given that} \quad \mathcal{G}(g) = \mu_0,$$

where we used the functional notation

$$\mathcal{L}(g) = \int \frac{1}{2} g^2(s) f_1(s) ds - \int m_1(s) g(s) f_1(s) ds, \quad \text{and} \quad \mathcal{G}(g) = \int g(s) f_0(s) ds.$$
Taking the Frechet derivatives of the functionals, we have that for all measurable \( h \) such that \( \int h^2(s)f_1(s)ds < \infty \),
\[
\frac{d}{dg} \left[ \mathcal{L}(g) - \lambda \mathcal{G}(g) \right](h) = \int g_{opt}(s)h(s)f_1(s)ds - \int g_{opt}(s)h(s)m_1(s)f_1(s)ds - \lambda \int h(s)f_0(s)ds = 0.
\]

Setting \( h = \delta(s) \), this implies that
\[
g_{opt}(s) = m_1(s) + \lambda f_0(s) / f_1(s) = m_1(s) + \lambda r(s), \quad s \in D_c \cup D_1.
\]
By the constraint \( \int_{D_c} \{ m_1(s) + \lambda r(s) \} f_0(s)ds + \int_{D_0} \{ m_0(s) + c \} f_0(s)ds = \mu_0 = \int m_0(s)ds \) and \( g_{opt}(s) \) is continuous at \( s^* \), or \( m_1(s^*) + \lambda r(s^*) = m_0(s^*) + c \), we have
\[
\lambda = \{ K_2 + K_1 r(s^*) \}^{-1} \int_{D_c} \Delta_{01}(s)f_0(s)ds + K_1 \{ K_2 + K_1 r(s^*) \}^{-1} \Delta_{01}(s^*),
\]
\[
c = \{ K_2 + r(s^*)K_1 \}^{-1} \left[ -K_2 \Delta_{01}(s^*) + r(s^*) \int_{D_c} \Delta_{01}(s)f_0(s)ds \right]
\]
with \( \Delta_{01}(s) = m_0(s) - m_1(s) \), \( K_1 = \int_{D_0} f_0(s)ds \), \( K_2 = \int_{D_c} f_0(s)f_1(s)ds = \int_{D_c} r(s)f_0(s)ds \).

Finally, the optimal function \( g_{opt}(\cdot) \) can be expressed as
\[
g_{opt}(s) = \begin{cases} m_1(s) + \lambda r(s), & s \in D_c \cup D_1 \\ m_0(s) + c, & s \in D_0. \end{cases}
\]

C  Relationship between PTE and PTE\(_L\)

In this section, we show the relationship between our proposed PTE and the PTE of Parast et al. (2016). To this end, let \( \Delta_{rte} \) denote the “residual treatment effect” defined in Parast et al. (2016) as:
\[
\Delta_{rte} = \int E(Y^{(1)} - Y^{(0)} | S^{(1)} = S^{(0)} = s) d\mathcal{F}(s) = \int \{ m_1(s) - m_0(s) \} d\mathcal{F}(s),
\]
where \( \mathcal{F}(\cdot) \) is a reference distribution function. It follows that
\[
\Delta_L = \Delta - \Delta_{rte} = \int m_1(s) \{ dF_1(s) - d\mathcal{F}(s) \} - \int m_0(s) \{ dF_0(s) - d\mathcal{F}(s) \}.
\]
and PTE\(_L = \Delta_L/\Delta\).
To relate $\Delta_{L}$ to $\Delta_{g_{\text{opt}}(s)}$, recall that

$$g_{\text{opt}}(s) = m_1(s) + \lambda f_0(s)/f_1(s), \quad s \in D_c \cup D_1,$$

$$g_{\text{opt}}(s) = m_0(s) + c, \quad s \in D_0,$$

$$\lambda = \left\{ K_2 + K_1 \frac{f_0(s^*)}{f_1(s^*)} \right\}^{-1} \int_{D_c} \{m_0(s) - m_1(s)\} f_0(s) ds + K_1 \left\{ K_2 + K_1 \frac{f_0(s^*)}{f_1(s^*)} \right\}^{-1} \{m_0(s^*) - m_1(s^*)\},$$

$$c = \left\{ 1 + \frac{f_0(s^*)}{f_1(s^*)} K_2 \right\}^{-1} \left[ m_1(s^*) - m_0(s^*) + \frac{f_0(s^*)}{f_1(s^*)} K_2 \int_{D_c} \{m_0(s) - m_1(s)\} f_0(s) ds \right]$$

and

$$\Delta_{g_{\text{opt}}(s)} = E\{g_{\text{opt}}(S^{(1)}) - g_{\text{opt}}(S^{(0)})\}.$$

Therefore,

$$\Delta_{g_{\text{opt}}(s)} = \int_{D_c} m_1(s) f_1(s) ds + \int_{D_c} \{m_1(s) + \lambda f_0(s)/f_1(s)\} f_1(s) ds - \mu_0$$

$$= \int_{D_c \cup D_c} m_1(s) f_1(s) ds - \int_{D_0 \cup D_c} m_0(s) f_0(s) ds + \int_{D_c} f_0(s) ds$$

$$\times \left[ \left\{ K_2 + K_1 \frac{f_0(s^*)}{f_1(s^*)} \right\}^{-1} \int_{D_c} \{m_0(s) - m_1(s)\} f_0(s) ds + K_1 \left\{ K_2 + K_1 \frac{f_0(s^*)}{f_1(s^*)} \right\}^{-1} \{m_0(s^*) - m_1(s^*)\} \right]$$

$$= \int_{D_c} m_1(s) f_1(s) ds + \int_{D_c} m_1(s) \left[ f_1(s) - f_0(s) \frac{\int_{D_c} f_0(s) ds}{K_2 + K_1 f_0(s^*) / f_1(s^*)} \right] ds$$

$$- \int_{D_0} m_0(s) f_0(s) ds - \int_{D_c} m_0(s) \left[ f_0(s) - f_0(s) \frac{\int_{D_c} f_0(s) ds}{K_2 + K_1 f_0(s^*) / f_1(s^*)} \right] ds$$

$$+ \int_{D_c} f_0(s) ds K_1 \left\{ K_2 + K_1 \frac{f_0(s^*)}{f_1(s^*)} \right\}^{-1} \{m_0(s^*) - m_1(s^*)\}$$

$$:= \int_{D_c} \{dF_1(s) - d\mathcal{F}_{\text{new}}(s)\} - \int_{D_0} m_0(s) \{dF_0(s) - d\mathcal{F}_{\text{new}}(s)\}$$

$$+ \int_{D_c} f_0(s) ds K_1 \left\{ K_2 + K_1 \frac{f_0(s^*)}{f_1(s^*)} \right\}^{-1} \{m_0(s^*) - m_1(s^*)\}$$

where

$$\mathcal{F}_{\text{new}}(s) = \int_{D_c} \{dF_1(s) - d\mathcal{F}_{\text{new}}(s)\} \frac{\int_{D_c} f_0(s) ds}{K_2 + K_1 f_0(s^*) / f_1(s^*)}. \quad (C.2)$$

If $\mathcal{F}(s)$ in (C.1) is replaced by $\mathcal{F}_{\text{new}}(s)$, then $\Delta_{g_{\text{opt}}(s)} = \Delta_{L} + \int_{D_c} f_0(s) ds K_1 \left\{ K_2 + K_1 \frac{f_0(s^*)}{f_1(s^*)} \right\}^{-1} \{m_0(s^*) - m_1(s^*)\}$; and thus, when $D_0$ is empty ($K_1=0$), or $m_0(s^*) = m_1(s^*)$ we have $\text{PTE} \equiv \text{PTE}_{L}$.

We next show that only assumptions (C1) and (C2) are required to ensure that the
proposed PTE is between 0 and 1.

(C1) \( S_1(u) \geq S_0(u) \) for all \( u \),

(C2) \( M_1(u) \geq M_0(u) \) for all \( u \) in the common support of \( g_{\text{opt}}(S^{(1)}) \) and \( g_{\text{opt}}(S^{(0)}) \),

where \( S_a(u) = P\{g_{\text{opt}}(S^{(a)}) > u \mid A = a\} \), \( M_a(u) = E\{Y^{(a)} \mid g_{\text{opt}}(S^{(a)}) = u\} \), \( a = 0, 1 \), which are assumed to be continuous functions. Following arguments given in Appendices A and B, we have

\[
\Delta = E\{Y^{(1)}\} - E\{Y^{(0)}\} = \int M_1(u)dF_1(u) - \int M_0(u)dF_0(u),
\]

\[
\Delta_{g_{\text{opt}}} = \int M_1(u)\{dF_1(u) - d\hat{F}_\text{new}(u)\} - \int M_0(u)\{dF_0(u) - d\hat{F}_\text{new}(u)\} + H(u^*\{M_0(u^*) - M_1(u^*)\},
\]

\[
\Delta - \Delta_{g_{\text{opt}}} = \int_{\mathbb{D}_c}\{M_1(u) - M_0(u)\}|\hat{F}_\text{new}(u)du + H(u^*\{M_1(u^*) - M_0(u^*)\}
\]

(C-3)

where \( H(u^*) \) is a non-negative function of \( u^\star \), \( \hat{F}_a(u) = 1 - S_a(u) \), \( \hat{F}_\text{new}(u) = d\hat{F}_a(u)/du \), and \( \hat{F}_\text{new}(u) \) is similarly defined as (C-2) but for \( g_{\text{opt}}(S) \) instead of \( S \) and \( \mathbb{D}_c \) is the common support of \( g_{\text{opt}}(S^{(1)}) \) and \( g_{\text{opt}}(S^{(0)}) \). It is also straightforward to see from an integration by parts that

\[
\Delta_{g_{\text{opt}}}(S) = \int u\ dF_1(u) - \int u\ dF_0(u) = \int (S_1(u) - S_0(u))du.
\]

Thus, from condition (C1), we have \( \Delta_{g_{\text{opt}}}(S) \geq 0 \). On the other hand, since \( \hat{F}_\text{new}(u) \geq 0 \), we see from (C-3) that \( \Delta - \Delta_{g_{\text{opt}}}(S) \geq 0 \) under condition (C2). It follows that PTE \( \in [0, 1] \) under conditions (C1) and (C2). Furthermore, \( \Delta_{g_{\text{opt}}}(S) = 0 \) when \( \Delta = 0 \).

### D Asymptotic properties for \( \hat{g}(\cdot) \)

Throughout, we assume that \( m_a(s), a = 0, 1 \) is continuously differentiable. In addition, we assume that \( f_a(s), a = 0, 1 \) is continuously differentiable with finite support. For inference, we require under-smoothing with \( h = o_p(n^{-1/5}) \) for interval estimation of \( g_{\text{opt}} \) and \( h = o_p(n^{-1/4}) \) for the interval estimation of RE and PTE. Since \( \hat{m}_a(s) \) and \( \hat{f}_a(s), a = 0, 1 \) are standard kernel estimators, we have that they are consistent w.r.t their true values with rate \( (\log n)^{\frac{1}{2}}(nh)^{-\frac{1}{2}} + h^2 \). It follows immediately that \( |\hat{g}(s) - g_{\text{opt}}(s)| = O_p\{[\log n]^{\frac{1}{2}}(nh)^{-\frac{1}{2}} + h^2\} \).

We firstly derive the influence functions for each estimator in Section 2.3. The influence functions can be derived following exactly the derivations of \( \hat{\mu}_a - \mu_a \) and \( \hat{\mu}_{g,a} - \hat{\mu}_{g,a} \). Direct
calculations show that

\[
\hat{f}_a(s) - f_a(s) = \frac{n^{-1} \sum_{A_i=a} \{K_h(S_i - s) - f_a(s)\}}{n^{-1} \sum_{A_i=a} 1}
\]

\[
\hat{m}_a(s) - m_a(s) = \frac{\sum_{i=1}^n I(A_i = a)K_h(S_i - s)\{Y_i - m_a(s)\}}{\sum_{i=1}^n I(A_i = a)K_h(S_i - s)}
\]

\[
\hat{K}_1 - K_1 = \int_{D_0} \{\hat{f}_0(s) - f_0(s)\}ds = n^{-1} \sum_{i=1}^n 2I(A_i = 0)I(S_i \in D_0) - \int_{D_0} f_0(s)ds
\]

\[
\hat{K}_2 - K_2 = \int_{D_c} 2\frac{f_0(s)}{f_1(s)}\{\hat{f}_0(s) - f_0(s)\}ds - \int_{D_c} \frac{f_0^2(s)}{f_1(s)}\{\hat{f}_1(s) - f_1(s)\}ds
\]

\[
= n^{-1} \sum_{i=1}^n 2I(A_i = 0)I(S_i \in D_0)\frac{f_0(S_i)}{f_1(S_i)} - \int_{D_c} \frac{f_0^2(s)}{f_1(s)}ds
\]

\[
- \left\{ n^{-1} \sum_{i=1}^n 2I(A_i = 1)I(S_i \in D_c)\frac{f_0^2(S_i)}{f_1^2(S_i)} - \int_{D_c} \frac{f_0^2(s)}{f_1(s)}ds \right\}
\]

\[
= n^{-1} \sum_{i=1}^n \phi_{K_2,i} + o_p\{n^{-1/2}\}.
\]
Furthermore,
\[
\hat{\lambda} - \lambda = \frac{\int_{D_c} \{\hat{m}_0(s) - \hat{m}_1(s)\} d\hat{F}_0(s)}{K_2 + K_1 f_0(s^*)/f_1(s^*)} + K_1 \frac{\hat{m}_0(s^*) - \hat{m}_1(s^*)}{K_2 + K_1 f_0(s^*)/f_1(s^*)} - \int_{D_c} \{m_0(s) - m_1(s)\} dF_0(s) - K_1 \frac{m_0(s^*) - m_1(s^*)}{K_2 + K_1 f_0(s^*)/f_1(s^*)}
\]
\[
= \frac{\int_{D_c} \{\hat{m}_0(s) - m_0(s) - m_1(s)\} f_0(s) ds + \int_{D_c} \{m_0(s) - m_1(s)\} \{\hat{f}_0(s) - f_0(s)\} ds}{K_2 + K_1 f_0(s^*)/f_1(s^*)}
\]
\[
+ K_1 \frac{\hat{m}_0(s^*) - m_0(s^*) - \hat{m}_1(s^*) + m_1(s^*)}{K_2 + K_1 f_0(s^*)/f_1(s^*)} + \frac{m_0(s^*) - m_1(s^*)}{K_2 + K_1 f_0(s^*)/f_1(s^*)} n^{-1} \sum_{i=1}^{n} \phi_{K_1,i} 
\]
\[
- \int_{D_c} \{m_0(s) - m_1(s)\} dF_0(s) + K_1 \{m_0(s^*) - m_1(s^*)\}
\]
\[
\times \left[ \frac{1}{n} \sum_{i=1}^{n} \phi_{K_2,i} + \frac{1}{n} \sum_{i=1}^{n} \phi_{K_1,i} \frac{f_0(s^*)}{f_1(s^*)} + (nh)^{-1} \left\{ \sum_{i=1}^{n} \phi_{0,i}(s^*) - \frac{f_0(s^*)}{f_1(s^*)} \sum_{i=1}^{n} \phi_{1,i}(s^*) \right\} \right]
\]
\[
+ o_p\{(nh)^{-1/2}\}
\]
\[
= \frac{1}{K_2 + K_1 f_0(s^*)/f_1(s^*)} \left[ n^{-1} \sum_{i=1}^{n} 2I(A_i = 0) Y_i I(S_i \in D_c) - \int_{D_c} m_0(s) f_0(s) ds 
\]
\[
- n^{-1} \sum_{i=1}^{n} 2I(A_i = 1) Y_i I(S_i \in D_c) f_0(S_i)/f_1(S_i) + \int_{D_c} m_1(s) f_0(s) ds 
\]
\[
+ n^{-1} \sum_{i=1}^{n} 2I(A_i = 0) I(S_i \in D_c) \{m_0(S_i) - m_1(S_i)\} - \int_{D_c} \{m_0(s) - m_1(s)\} f_0(s) ds 
\]
\[
+ \frac{K_1}{K_2 + K_1 f_0(s^*)/f_1(s^*)} (nh)^{-1} \sum_{i=1}^{n} \{\phi_{m_0,i}(s^*) - \phi_{m_1,i}(s^*)\} 
\]
\[
+ \frac{m_0(s^*) - m_1(s^*)}{K_2 + K_1 f_0(s^*)/f_1(s^*)} n^{-1} \sum_{i=1}^{n} \phi_{K_1,i} + o_p\{(nh)^{-1/2}\} 
\]
\[
- \int_{D_c} \{m_0(s) - m_1(s)\} dF_0(s) + K_1 \{m_0(s^*) - m_1(s^*)\}
\]
\[
\times \left[ \frac{1}{n} \sum_{i=1}^{n} \phi_{K_2,i} + \frac{1}{n} \sum_{i=1}^{n} \phi_{K_1,i} \frac{f_0(s^*)}{f_1(s^*)} + (nh)^{-1} \left\{ \sum_{i=1}^{n} \phi_{0,i}(s^*) - \frac{f_0(s^*)}{f_1(s^*)} \sum_{i=1}^{n} \phi_{1,i}(s^*) \right\} \right]
\]
\[
:= \left( nh \right)^{-1} \sum_{i=1}^{n} \phi_{\lambda,i} + o_p\{(nh)^{-1/2}\}.
\]

Similarly, we can get \( \hat{c} - c = (nh)^{-1} \sum_{i=1}^{n} \phi_{c,i} + o_p\{(nh)^{-1/2}\} \).

Using above results we can obtain the influence functions for the optimal transformation
function estimators by coupling delta method with the fact that

\[ g_{\text{opt}}(s) = \tilde{G}(m_0(s), m_1(s), f_0(s), f_1(s), \lambda, c) \]
and \( \hat{g}(s) = \tilde{G}(\hat{m}_0(s), \hat{m}_1(s), \hat{f}_0(s), \hat{f}_1(s), \hat{\lambda}, \hat{c}) \).

Specifically, we can show that

\[ \hat{g}(s) - g_{\text{opt}}(s) = (nh)^{-1} \sum_{i=1}^{n} \phi_{g,i}(s) + o_p\{(nh)^{-1/2}\}, \]

where \( E(\phi_{g,i}^2(s)) < \infty \).
REFERENCES

AGNIEL, D. & PARAST, L. (2021). Evaluation of longitudinal surrogate markers. *Biometrics* **77**, 477–489.

ALONSO, A., GEYS, H., MOLENBERGHS, G., KENWARD, M. G. & VANGENEUGDEN, T. (2004). Validation of surrogate markers in multiple randomized clinical trials with repeated measurements: canonical correlation approach. *Biometrics* **60**, 845–853.

ATEHY, S., CHETTY, R., IMBENS, G. & KANG, H. (2016). Estimating treatment effects using multiple surrogates: The role of the surrogate score and the surrogate index. *arXiv preprint arXiv:1603.09326*.

ATEHY, S., CHETTY, R., IMBENS, G. W. & KANG, H. (2019). The surrogate index: Combining short-term proxies to estimate long-term treatment effects more rapidly and precisely. Technical report, National Bureau of Economic Research.

AVORN, J. & KESSELHEIM, A. S. (2020). Up is down—pharmaceutical industry caution vs. federal acceleration of covid-19 vaccine approval. *New England Journal of Medicine* **383**, 1706–1708.

BURZYZKOWSKI, T., MOLENBERGHS, G. & BUYSE, M. (2005). *The evaluation of surrogate endpoints*. Springer.

BUYSE, M. & MOLENBERGHS, G. (1998). Criteria for the validation of surrogate endpoints in randomized experiments. *Biometrics* pages 1014–1029.

CAI, T., TIAN, L. & WEI, L. J. (2005). Semiparametric box-cox power transformation models for censored survival observations. *Biometrika* **92**, 619–632.

DANIELS, M. J. & HUGHES, M. D. (1997). Meta-analysis for the evaluation of potential surrogate markers. *Statistics in medicine* **16**, 1965–1982.

DIABETES PREVENTION PROGRAM GROUP (1999). The diabetes prevention program: design and methods for a clinical trial in the prevention of Type 2 diabetes. *Diabetes Care* **22**, 623–634.

DIABETES PREVENTION PROGRAM GROUP (2002). Reduction in the incidence of Type 2 diabetes with lifestyle intervention or Metformin. *New England Journal of Medicine* **346**, 393–403.

FDA (2020). Development and licensure of vaccines to prevent covid-19: Guidance for industry. *U.S. Department of Health and Human Services Food and Drug Administration*.

FRANGAKIS, C. E. & RUBIN, D. B. (2002). Principal stratification in causal inference. *Biometrics* **58**, 21–29.

FREEDMAN, L. S., GRAUBARD, B. I. & SCHATZKIN, A. (1992). Statistical validation of intermediate endpoints for chronic diseases. *Statistics in Medicine* **11**, 167–178.

GILBERT, P. B. & HUDGENS, M. G. (2008). Evaluating candidate principal surrogate endpoints. *Biometrics* **64**, 1146–1154.

HUANG, Y. & GILBERT, P. B. (2011). Comparing biomarkers as principal surrogate endpoints. *Biometrics* **67**, 1442–1451.

MOLENBERGHS, G., BUYSE, M., GEYS, H., RENARD, D., BURZYZKOWSKI, T. & ALONSO, A. (2002). Statistical challenges in the evaluation of surrogate endpoints in
randomized trials. *Controlled Clinical Trials* **23**, 607–625.

Parast, L., Cai, T. & Tian, L. (2017). Evaluating surrogate marker information using censored data. *Statistics in medicine* **36**, 1767–1782.

Parast, L., Cai, T. & Tian, L. (2019). Using a surrogate marker for early testing of a treatment effect. *Biometrics* **75**, 1253–1263.

Parast, L., Cai, T. & Tian, L. (2020). Evaluating multiple surrogate markers with censored data. *Biometrics*.

Parast, L., McDermott, M. M. & Tian, L. (2016). Robust estimation of the proportion of treatment effect explained by surrogate marker information. *Statistics in medicine* **35**, 1637–1653.

Parast, L., Tian, L. & Cai, T. (2014). Landmark estimation of survival and treatment effect in a randomized clinical trial. *Journal of the American Statistical Association* **109**, 384–394.

Park, Y. & Wei, L. J. (2003). Estimating subject-specific survival functions under the accelerated failure time model. *Biometrika* **90**, 717–723.

Pepe, M. S. (1992). Inference using surrogate outcome data and a validation sample. *Biometrika* **79**, 355–365.

Prentice, R. L. (1989). Surrogate endpoints in clinical trials: definition and operational criteria. *Statistics in Medicine* **8**, 431–440.

Price, B. L., Gilbert, P. B. & Van der Laan, M. J. (2018). Estimation of the optimal surrogate based on a randomized trial. *Biometrics*.

Robins, J. M. & Rotnitzky, A. (1992). Recovery of information and adjustment for dependent censoring using surrogate markers. In *AIDS epidemiology*, pages 297–331. Springer.

Rotnitzky, A. & Robins, J. M. (1995). Semiparametric regression estimation in the presence of dependent censoring. *Biometrika* **82**, 805–820.

Scott, D. (1992). Multivariate density estimation. *Multivariate Density Estimation, Wiley, New York, 1992* 1.

VanderWeele, T. J. (2013). Surrogate measures and consistent surrogates. *Biometrics* **69**, 561–565.

Venkatraman, E. & Begg, C. B. (1999). Properties of a nonparametric test for early comparison of treatments in clinical trials in the presence of surrogate endpoints. *Biometrics* **55**, 1171–1176.

Wang, X., Cai, T., Tian, L., Bourgeois, F. & Parast, L. (2021). Quantifying the feasibility of shortening clinical trial duration using surrogate markers. *Statistics in Medicine* **40**, 6321–6343.

Wang, X., Parast, L., Han, L., Tian, L. & Cai, T. (2022). Robust approach to combining multiple markers to improve surrogacy. *Biometrics*.

Wang, X., Parast, L., Tian, L. & Cai, T. (2020). Model-free approach to quantifying the proportion of treatment effect explained by a surrogate marker. *Biometrika* **107**, 107–122.

Wang, Y. & Taylor, J. M. (2002). A measure of the proportion of treatment effect
explained by a surrogate marker. *Biometrics* **58**, 803–812.