

Web-based Supplementary Materials for "Evaluating Marker-Guided Treatment Selection Strategies"

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APPENDIX

Web Appendix A: Asymptotic Properties of $\widehat{\mathbb{V}}_{\widehat{\mathcal{I}}_{\text{calib}}}$ and $\widehat{\mathcal{I}}_{\text{calib}}$

Although the working models could be semi-parametric and $\widehat{\boldsymbol{\beta}}$ could be infinite dimensional, for the derivation of the asymptotic theory, we focus on the case when $\widehat{\boldsymbol{\beta}}$ is finite dimensional. Throughout we use notation $g'(x) = dg(x)/dx$ and $\mathbf{g}'_k(\mathbf{x}_1, \dots, \mathbf{x}_K) = \partial g(\mathbf{x}_1, \dots, \mathbf{x}_K)/\partial \mathbf{x}_k$. We assume that the covariates are bounded, $\bar{\boldsymbol{\beta}}$ is an interior point of a compact parameter space, $D(\bar{\boldsymbol{\beta}}, \mathbf{X})$ is a continuous random variable which has a continuously differentiable density function $f_D(\cdot)$ bounded away from 0 with finite support $[\tau_l, \tau_r]$, and $Y^{(k)} \mid D(\bar{\boldsymbol{\beta}}, \mathbf{X})$ has a finite second moment for any $D(\bar{\boldsymbol{\beta}}, \mathbf{X}) \in [\tau_l, \tau_r]$. We require the regularity condition that $\widehat{\boldsymbol{\beta}} \rightarrow \bar{\boldsymbol{\beta}} = (\bar{\boldsymbol{\beta}}_0^\top, \bar{\boldsymbol{\beta}}_1^\top)^\top$ for $\bar{\boldsymbol{\beta}}$ and $\widehat{\mathcal{W}}_{\boldsymbol{\beta}} = n^{\frac{1}{2}}(\widehat{\boldsymbol{\beta}} - \bar{\boldsymbol{\beta}}) = n^{-\frac{1}{2}} \sum_{i=1}^n \Psi_{\boldsymbol{\beta}i} + o_p(1)$ which converges weakly in distribution to a multivariate normal. We consider that $\bar{\Delta}(\cdot)$ is continuously differentiable with $|\bar{\Delta}'(s)| \leq b_{\bar{\Delta}} < \infty$. We also assume that there are at most $K_0 < \infty$ number of solutions to $\bar{\Delta}'(s) = 0$, there exists intervals $\tau_l = s_1 < \dots < s_{K_0+1} = \tau_r$ such that $\bar{\Delta}(s)$ is monotone in $[s_k, s_{k+1}]$, for $k = 1, \dots, K_0$; and hence $\bar{\Delta}(s) = \xi$ has at most K_0 roots. Furthermore, when at least one solution to $\bar{\Delta}(s) = \xi$ exists, we denote by $\{\mathbf{s}_{k_r} \in (s_{k_r}, s_{k_r+1}) : r = 1, \dots, R_0\}$ all the solutions and assume that $|\bar{\Delta}'(\mathbf{s}_{k_r})| \geq L_{\bar{\Delta}} > 0$. This regularity condition ensures that the total variation of $\mathfrak{J}(s) = I\{\bar{\Delta}(s) \geq \xi\}$ is bounded by K_0 .

We next derive the convergence properties of $\widehat{\mathbb{V}}_{\widehat{\mathcal{I}}_{\text{calib}}} = \widehat{\mathbb{V}}_a(\widehat{\Delta}, \widehat{\boldsymbol{\beta}}) + \bar{Y}_0$ to $\mathbb{V}_{\mathcal{I}_{\text{calib}}} = \mathbb{V}_a(\bar{\Delta}, \bar{\boldsymbol{\beta}}) + \mu_0$, where $\bar{Y}_0 = n_0^{-1} \sum_{i=1}^n Y_i I(G_i = 0)$, $\mu_0 = E(Y^{(0)})$,

$$\widehat{\mathbb{V}}_a(\Delta, \boldsymbol{\beta}) = n^{-1} \sum_{i=1}^n I[\Delta\{D(\boldsymbol{\beta}, \mathbf{X}_i)\} \geq \xi] \widehat{\mathcal{Y}}_{\xi_i}, \quad \mathbb{V}_a(\Delta, \boldsymbol{\beta}) = E(I[\Delta\{D(\boldsymbol{\beta}, \mathbf{X}_i)\} \geq \xi] \mathcal{Y}_{\xi_i})$$

$$\widehat{\mathcal{Y}}_{\xi_i} = (Y_i - \xi)I(G_i = 1)/\widehat{\pi}_1 - Y_i I(G_i = 0)/\widehat{\pi}_0 \text{ and } \mathcal{Y}_{\xi_i} = (Y_i - \xi)I(G_i = 1)/\pi_1 - Y_i I(G_i = 0)/\pi_0.$$

To decompose various sources of variation, we define $\widehat{\mathbb{W}}_{\mathbb{V}}$ as

$$\widehat{\mathbb{W}}_{\mathbb{V}} \equiv \widehat{\mathbb{V}}_{\widehat{\mathcal{I}}_{\text{calib}}} - \mathbb{V}_{\mathcal{I}_{\text{calib}}} = \widehat{\mathbb{W}}_{\Delta} + \widehat{\mathbb{V}}_a(\bar{\Delta}, \widehat{\boldsymbol{\beta}}) - \widehat{\mathbb{V}}_a(\bar{\Delta}, \bar{\boldsymbol{\beta}}) + \widehat{\mathbb{V}}_a(\bar{\Delta}, \bar{\boldsymbol{\beta}}) + \bar{Y}_0 - \mathbb{V}_{\mathcal{I}_{\text{calib}}}$$

where $\widehat{W}_\Delta \equiv \widehat{V}_a(\widehat{\Delta}, \widehat{\beta}) - \widehat{V}_a(\bar{\Delta}, \widehat{\beta}) = \widehat{W}_{\Delta 1} + \widehat{W}_{\Delta 2}$ with

$$\begin{aligned}\widehat{W}_{\Delta 1} &= \int [I\{\widehat{\Delta}_\xi(s) \geq 0\} - I\{\Delta_\xi(s) \geq 0\}] \widehat{H}(\widehat{\beta}; ds) \\ \widehat{W}_{\Delta 2} &= \int [I\{\widehat{\Delta}_\xi(s) \geq 0\} - I\{\Delta_\xi(s) \geq 0\}] \Delta_\xi(s) \widehat{F}(\widehat{\beta}; ds),\end{aligned}$$

and $\widehat{H}(\beta; s) = n^{-1} \sum_{i=1}^n I\{D(\beta, \mathbf{X}_i) \leq s\} [\widehat{\mathcal{Y}}_{\xi_i} - \Delta_\xi\{D(\beta, \mathbf{X}_i)\}]$, $\widehat{\Delta}_\xi(d) = \widehat{\Delta}(d) - \xi$, $\Delta_\xi(d) =$

$E(\mathcal{Y}_{\xi_i} \mid D(\bar{\beta}, \mathbf{X})_i = d) = \bar{\Delta}(d) - \xi$, and $\widehat{F}(\beta; s) = n^{-1} \sum_{i=1}^n I\{D(\beta, \mathbf{X}_i) \leq s\}$.

From $\sup_{\mathbf{x}} |D(\widehat{\beta}, \mathbf{x}) - D(\bar{\beta}, \mathbf{x})| = O_p(n^{-\frac{1}{2}})$ and similar arguments in Cai et al. (2011),

$$\widehat{\epsilon}_\Delta = \sup_s |\widehat{\Delta}(s) - \bar{\Delta}(s)| = o_p\{(nh)^{-1/2} \log(n)\}.$$

Now consider $\widehat{W}_{\Delta 1}$. Note that $n^{\frac{1}{2}} \left\{ \widehat{H}(\beta; s) - H(\beta; s) \right\} = n^{-\frac{1}{2}} \sum_{i=1}^n H_i(\beta; s) + o_p(1)$, where $H_i(\beta; s) = I\{D(\beta, \mathbf{X}_i) \leq s\} [\mathcal{Y}_{\xi_i} - \Delta_\xi\{D(\beta, \mathbf{X}_i)\}] - m_1(\beta, s) \{I(G_i = 1)/\pi_1 - 1\} + m_0(\beta, s) \{I(G_i = 0)/\pi_0 - 1\}$ and $H(\beta; s) = E[H_i(\beta; s)]$, $m_j(\beta; s) = E[I\{D(\beta, \mathbf{X}_i) \leq s\} \mathcal{Y}_{\xi_i} \mid G_i = j]$. It follows from a functional central limit theorem that $n^{\frac{1}{2}} \left\{ \widehat{H}(\beta; s) - H(\beta; s) \right\}$ converges weakly to a gaussian process and hence is equicontinuous in β . Hence, $n^{\frac{1}{2}} \widehat{H}(\widehat{\beta}; s) = n^{\frac{1}{2}} \{ \widehat{H}(\widehat{\beta}; s) - H(\bar{\beta}; s) \} = n^{\frac{1}{2}} \left\{ \widehat{H}(\bar{\beta}; s) - H(\bar{\beta}; s) \right\} + \dot{\mathbf{H}}_1(\bar{\beta}; s)^\top n^{\frac{1}{2}} (\widehat{\beta} - \bar{\beta})$ which converges weakly to a zero-mean gaussian process. Therefore, for any $\delta = o_p(1)$,

$$\widehat{\epsilon}_H(\delta) = \sup_s \left| \widehat{H}(\widehat{\beta}; s) - \widehat{H}(\widehat{\beta}; s + \delta) \right| = o_p(n^{-\frac{1}{2}}),$$

and consequently $|\widehat{W}_{\Delta 1}| \leq \int I\{\bar{\Delta}(s) - \xi \in [-\widehat{\epsilon}_\Delta, \widehat{\epsilon}_\Delta]\} |\widehat{H}(\widehat{\beta}; ds)|$. If $\inf_s |\bar{\Delta}(s) - \xi| \geq \delta_0 > 0$, then the equation $\bar{\Delta}(s) = \xi$ has no solution. This implies that $P\{\inf_s |\bar{\Delta}(s) - \xi| \geq \delta_0/2\} \rightarrow 1$ and $I\{\bar{\Delta}(s) - \xi \in [-\widehat{\epsilon}_\Delta, \widehat{\epsilon}_\Delta]\} \xrightarrow{P} 0$ in probability. Thus, $P(\widehat{W}_{\Delta 1} = 0) \rightarrow 1$ and $n^{\frac{1}{2}} \widehat{W}_{\Delta 1} \xrightarrow{P} 0$.

For the setting where the solution to $\bar{\Delta}(s) = \xi$ exists, we have,

$$\begin{aligned}|\widehat{W}_{\Delta 1}| &\leq \sum_{r=1}^{R_0} \int_{s_{k_r}}^{s_{k_r+1}} I\{s \in [\bar{\Delta}_{k_r}^{-1}(\xi - \widehat{\epsilon}_\Delta), \bar{\Delta}_{k_r}^{-1}(\xi + \widehat{\epsilon}_\Delta)]\} \left| \widehat{H}(\widehat{\beta}; ds) \right| \\ &\leq \sum_{r=1}^{R_0} \widehat{\epsilon}_H \left\{ \left| \bar{\Delta}_{k_r}^{-1}(\xi - \widehat{\epsilon}_\Delta) - \bar{\Delta}_{k_r}^{-1}(\xi + \widehat{\epsilon}_\Delta) \right| \right\}\end{aligned}$$

where $\bar{\Delta}_{k_r}^{-1}(\cdot)$ denotes the inverse function of $\bar{\Delta}$ within $[s_{k_r}, s_{k_r+1}]$. Given that $|\bar{\Delta}'(\mathbf{s}_{k_r})| \geq L_{\Delta}$ and $\hat{\epsilon}_{\Delta} = o_p(1)$, $\bar{\Delta}_{k_r}^{-1}(\xi - \hat{\epsilon}_{\Delta}) - \bar{\Delta}_{k_r}^{-1}(\xi + \hat{\epsilon}_{\Delta}) = o_p(1)$, we have $\widehat{W}_{\Delta 1} = o_p(n^{-\frac{1}{2}})$.

For $\widehat{W}_{\Delta 2}$, since $\widehat{F}(\boldsymbol{\beta}; s)$ is a monotone function in s ,

$$\begin{aligned} |\widehat{W}_{\Delta 2}| &\leq \int \left| I\{\widehat{\Delta}_{\xi}(s) \geq 0\} - I\{\Delta_{\xi}(s) < 0\} \right| |\Delta_{\xi}(s)| \widehat{F}(\widehat{\boldsymbol{\beta}}; ds) \\ &\leq \int I\{\Delta_{\xi}(s) \in [-\hat{\epsilon}_{\Delta}, \hat{\epsilon}_{\Delta}]\} \hat{\epsilon}_{\Delta} \widehat{F}(\widehat{\boldsymbol{\beta}}; ds) = \hat{\epsilon}_{\Delta} \left\{ \widehat{F}_{\Delta}(\widehat{\boldsymbol{\beta}}; \hat{\epsilon}_{\Delta}) - \widehat{F}_{\Delta}(\widehat{\boldsymbol{\beta}}; -\hat{\epsilon}_{\Delta}) \right\} \end{aligned}$$

where $\widehat{F}_{\Delta}(\boldsymbol{\beta}; d) = n^{-1} \sum_{i=1}^n I[\Delta\{D(\boldsymbol{\beta}, \mathbf{X}_i)\} \leq d]$.

It follows from a functional central limit theorem that $n^{\frac{1}{2}}\{\widehat{F}_{\Delta}(\boldsymbol{\beta}; d) - F_{\Delta}(\boldsymbol{\beta}; d)\}$ converges to a zero-mean Gaussian process and hence is equicontinuous in $\boldsymbol{\beta}$ and d . We have $\widehat{F}_{\Delta}(\widehat{\boldsymbol{\beta}}; \hat{\epsilon}_{\Delta}) - \widehat{F}_{\Delta}(\widehat{\boldsymbol{\beta}}; -\hat{\epsilon}_{\Delta}) = F_{\Delta}(\bar{\boldsymbol{\beta}}; \hat{\epsilon}_{\Delta}) - F_{\Delta}(\bar{\boldsymbol{\beta}}; -\hat{\epsilon}_{\Delta}) + o_p(n^{-\frac{1}{2}})$. This implies $|\widehat{W}_{\Delta 2}| \leq 2\hat{\epsilon}_{\Delta}^2 \sup_s |f_{\Delta}(\bar{\boldsymbol{\beta}}; s)| + o_p(n^{-\frac{1}{2}})$. Provided that $\hat{\epsilon}_{\Delta} = o_p(n^{-1/4})$, we have $\widehat{W}_{\Delta 2} = o_p(n^{-\frac{1}{2}})$. Hence, $\widehat{W}_{\Delta} = o_p(n^{-\frac{1}{2}})$. The above results also indicate that $P\{\widehat{\mathcal{I}}_{\text{calib}}(\mathbf{X}) \neq \mathcal{I}_{\text{calib}}(\mathbf{X})\} \rightarrow 0$.

Next, we establish the asymptotic convergence of $\widehat{\mathbb{V}}_{\widehat{\mathcal{I}}_{\text{calib}}}$ to $\mathbb{V}_{\mathcal{I}_{\text{calib}}}$. By the law of large numbers, $\widehat{\mathbb{V}}_a(\bar{\Delta}, \widehat{\boldsymbol{\beta}}) + \bar{Y}_0 - \mathbb{V}_{\mathcal{I}_{\text{calib}}} \xrightarrow{P} 0$. It remains to show that $\widehat{\mathbb{V}}_a(\bar{\Delta}, \widehat{\boldsymbol{\beta}}) - \widehat{\mathbb{V}}_a(\bar{\Delta}, \bar{\boldsymbol{\beta}}) = o_p(1)$. It follows from similar arguments as given for the convergence of $\widehat{H}(\boldsymbol{\beta}; s)$ that $n^{\frac{1}{2}}\{\widehat{\mathbb{V}}_a(\bar{\Delta}, \boldsymbol{\beta}) - \mathbb{V}_a(\bar{\Delta}, \boldsymbol{\beta})\} = n^{-\frac{1}{2}} \sum_{i=1}^n \Psi_{ai}(\boldsymbol{\beta}) + o_p(1)$, which converges weakly to a zero-mean Gaussian process, where

$$\Psi_{ai}(\boldsymbol{\beta}) = I[\bar{\Delta}_{\xi}\{D(\boldsymbol{\beta}; \mathbf{X}_i)\} \geq 0] \mathcal{Y}_{\xi_i} - m_{\Delta 1}(\boldsymbol{\beta}) \frac{I(G_i=1)}{\pi_1} - m_{\Delta 0}(\boldsymbol{\beta}) \frac{I(G_i=0)}{\pi_0}$$

and $m_{\Delta j}(\boldsymbol{\beta}) = E(I[\bar{\Delta}_{\xi}\{D(\boldsymbol{\beta}; \mathbf{X}_i)\} \geq 0] \mathcal{Y}_{\xi_i} | G_i = j)$. Hence,

$$\widehat{\mathbb{V}}_a(\bar{\Delta}, \widehat{\boldsymbol{\beta}}) - \widehat{\mathbb{V}}_a(\bar{\Delta}, \bar{\boldsymbol{\beta}}) = \mathbb{V}_a(\bar{\Delta}, \widehat{\boldsymbol{\beta}}) - \mathbb{V}_a(\bar{\Delta}, \bar{\boldsymbol{\beta}}) + o_p(n^{-\frac{1}{2}}) = \mathcal{V}'_{a2}(\bar{\Delta}, \boldsymbol{\beta})^{\top} (\widehat{\boldsymbol{\beta}} - \bar{\boldsymbol{\beta}}) + o_p(n^{-\frac{1}{2}}).$$

Therefore, $\widehat{\mathbb{V}}_a(\bar{\Delta}, \widehat{\boldsymbol{\beta}}) - \widehat{\mathbb{V}}_a(\bar{\Delta}, \bar{\boldsymbol{\beta}}) = o_p(1)$ and thus $\widehat{\mathbb{W}}_{\mathbb{V}} = o_p(1)$, indicating the consistency of $\widehat{\mathbb{V}}_{\widehat{\mathcal{I}}_{\text{calib}}}$ for $\mathbb{V}_{\mathcal{I}_{\text{calib}}}$. For the weak convergence of $\widehat{\mathbb{V}}_{\widehat{\mathcal{I}}_{\text{calib}}}$, we note from the above expansions that

$$\begin{aligned} n^{\frac{1}{2}}(\widehat{\mathbb{V}}_{\widehat{\mathcal{I}}_{\text{calib}}} - \mathbb{V}_{\mathcal{I}_{\text{calib}}}) &= n^{\frac{1}{2}} \mathcal{V}'_{a2}(\bar{\Delta}, \boldsymbol{\beta})^{\top} (\widehat{\boldsymbol{\beta}} - \bar{\boldsymbol{\beta}}) + n^{\frac{1}{2}} \{\widehat{\mathbb{V}}_a(\bar{\Delta}, \bar{\boldsymbol{\beta}}) + \bar{Y}_0 - \mathbb{V}_{\mathcal{I}_{\text{calib}}}\} + o_p(1) \\ &= n^{-\frac{1}{2}} \sum_{i=1}^n \Psi_{\mathcal{V}i} + o_p(1), \end{aligned}$$

where

$$\Psi_{\mathcal{V}_i} = \mathcal{V}'_{a2}(\bar{\Delta}, \boldsymbol{\beta})^\top \Psi_{\beta_i} + \Psi_{ai}(\bar{\boldsymbol{\beta}}) + (Y_i - \mu_0) \frac{I(G_i = 0)}{\pi_0}. \quad (\text{A.1})$$

It then follows from a central limit theorem that $n^{\frac{1}{2}}(\widehat{\mathbb{V}}_{\widehat{I}_c} - \mathbb{V}_{I_c})$ converges in distribution to a normal with mean 0 and variance $\sigma_{\mathbb{V}}^2 = E(\Psi_{\mathcal{V}_i}^2)$.

Web Appendix B: Asymptotic Properties of \widehat{c} , \widehat{c} , and $\widehat{\mathbb{V}}_{\widehat{I}_c}$ when $\bar{\Delta}$ is increasing

In this section, we assume that $\bar{\Delta}(c)$ is monotone and there exists c_0 such that $\bar{\Delta}(c_0) = \xi$ and $\bar{\Delta}'(c_0) > 0$. The monotonicity implies that $V\{F^{-1}(u)\} = \mu_0 + \int_0^u \bar{\Delta}\{F^{-1}(v)\} dv$ is convex in u . Moreover, $\bar{\Delta}'(c_0)F'(c_0) > 0$ implies that \mathbb{V}_{I_c} has a unique maximizer at c_0 , where $I_c = I\{D(\bar{\boldsymbol{\beta}}; \mathbf{X}) \geq c\}$. From Newey and McFadden (1994), to show the consistency of \widehat{c} , it suffices to show that $\widehat{\mathbb{V}}_{\widehat{I}_c} \xrightarrow{P} \mathbb{V}_{I_c}$ uniformly in c . To this end, note that $\widehat{\mathbb{V}}(c, \boldsymbol{\beta}) = \widehat{\mathbb{V}}_a(c, \boldsymbol{\beta}) + \bar{Y}_0$, and $\widehat{\mathbb{V}}_a(c, \boldsymbol{\beta}) = n^{-1} \sum_{i=1}^n I\{D(\boldsymbol{\beta}; \mathbf{X}_i) \geq c\} \widehat{\mathcal{Y}}_{\xi_i}$. We have $\widehat{\mathbb{V}}_{\widehat{I}_c} = \widehat{\mathbb{V}}(c; \widehat{\boldsymbol{\beta}})$. It follows from the uniform law of large numbers (Pollard, 1990) that $\widehat{\mathbb{V}}(c; \boldsymbol{\beta})$ converges to $\mathbb{V}(c; \boldsymbol{\beta})$ uniformly in $\{\boldsymbol{\beta}, c\}$, where $\mathbb{V}(c; \boldsymbol{\beta}) = E[I\{D(\boldsymbol{\beta}; \mathbf{X}) \geq c\} \mathcal{Y}_\xi] + \mu_0$. Furthermore, by the functional central limit theorem (Pollard, 1990), $n^{\frac{1}{2}}\{\widehat{\mathbb{V}}(c, \boldsymbol{\beta}) - \mathbb{V}(c; \boldsymbol{\beta})\}$ converges weakly to a Gaussian process in $\boldsymbol{\beta}$ and c .

These results, together with the weak convergence of $n^{\frac{1}{2}}(\widehat{\boldsymbol{\beta}} - \bar{\boldsymbol{\beta}})$, imply that

$$\sup_c \left| n^{\frac{1}{2}} \{ \widehat{\mathbb{V}}_{\widehat{I}_c} - \mathbb{V}_{I_c} \} \right| = O_p(1) \quad (\text{B.1})$$

The consistency of \widehat{c} immediately follows from the monotonicity of $\bar{\Delta}(c)$, $\bar{\Delta}'(c_0) > 0$.

We next show that $\widehat{c} - c^o = O_p(n^{-1/3})$ following the cubic-root asymptotic theory from Kim and Pollard (1990). For the ease of presentation, we assume that $\bar{\boldsymbol{\beta}}$ is known and hence

$$\widehat{c} = \underset{c}{\operatorname{argmax}} \widehat{\mathbb{V}}_{\widehat{I}_c} = \underset{c}{\operatorname{argmax}} \{ \widehat{\mathbb{V}}_{\widehat{I}_c} - \bar{Y}_0 \} = n^{-1} \sum_{i=1}^n \mathbb{Y}_i I(D(\bar{\boldsymbol{\beta}}, \mathbf{X}_i) \geq c) + O_p(n^{-1})$$

where $\mathbb{Y}_i = \mathcal{Y}_{\xi_i} - \mu_1\{I(G_i = 1)/\pi_1 - 1\} + \mu_0\{I(G_i = 0)/\pi_0 - 1\}$. To verify the regularity conditions of the main theorem in §1.1 of Kim and Pollard (1990), we let $\eta_i = (\mathbb{Y}_i, D(\bar{\boldsymbol{\beta}}, \mathbf{X}_i))$, $g(\eta, c) = \mathbb{Y}_i I(D(\bar{\boldsymbol{\beta}}, \mathbf{X}_i) \geq c)$ and hence $n^{-1} \sum_{i=1}^n \mathbb{Y}_i I(D(\bar{\boldsymbol{\beta}}, \mathbf{X}_i) \geq c) = n^{-1} \sum_{i=1}^n g(\eta_i, c)$.

The main condition involves an envelope function for $g(\xi, c)$

$$\begin{aligned} G_R(\eta) &= \sup\{g(\eta, c) : |c - c^o| \leq R\} \\ &= \sup_{|c - c^o| \leq R} [\mathbb{Y}\{I(D(\bar{\boldsymbol{\beta}}, \mathbf{X}) \geq c) - I(D(\bar{\boldsymbol{\beta}}, \mathbf{X}) \geq c^o)\}] = |\mathbb{Y}|I(|D(\bar{\boldsymbol{\beta}}, \mathbf{X}) - c^o| < R) \end{aligned}$$

It is easy to see that $E\{G_R(\eta_i)\} = E\{|\mathbb{Y}|I(|D(\bar{\boldsymbol{\beta}}, \mathbf{X}) - c^o| < R)\} = O(R)$ as $R \rightarrow 0$ and

$$\begin{aligned} E[G_R(\eta_i)I\{G_R(\eta_i) > \mathcal{K}\}] &\leq E\{I(|D(\bar{\boldsymbol{\beta}}, \mathbf{X}) - c^o| < R)\mathbb{Y}^2I(|\mathbb{Y}| > \mathcal{K})\} \\ &\leq R [\max\{f_D(\cdot)\}E\{\mathbb{Y}^2I(|\mathbb{Y}| > \mathcal{K}) \mid c^o - R < D(\bar{\boldsymbol{\beta}}, \mathbf{X}) < c^o + R\}]. \end{aligned}$$

Since $Y^{(k)}$ has a finite second moment given $D(\bar{\boldsymbol{\beta}}, \mathbf{X})$, $E\{\mathbb{Y}^2I(|\mathbb{Y}| > \mathcal{K}) \mid c^o - R < D(\bar{\boldsymbol{\beta}}, \mathbf{X}) < c^o + R\} \rightarrow 0$ as $\mathcal{K} \rightarrow \infty$ and hence condition (vi) of Theorem §1.1 is verified. The rest of the regularity conditions follow mainly from the smoothness of $\Delta(\cdot)$ and f_D .

To derive the distribution of \hat{c} , note that $\hat{\Delta}_\xi(\hat{c}; \hat{\boldsymbol{\beta}}) = 0$, where $\hat{\Delta}_\xi(c; \boldsymbol{\beta}) = \sum_{i=1}^n K_h\{D(\boldsymbol{\beta}; \mathbf{X}_i) - c\}\hat{\mathcal{Y}}_{\xi_i}/[\sum_{i=1}^n K_h\{D(\boldsymbol{\beta}; \mathbf{X}_i)\}]$. From arguments as given in Cai et al. (2011), $\sup_c |\hat{\Delta}_\xi(c; \hat{\boldsymbol{\beta}}) - \hat{\Delta}_\xi(c; \bar{\boldsymbol{\beta}})| = O_p(n^{-\frac{1}{2}})$ and $\sup_c |\hat{\Delta}_\xi(c; \bar{\boldsymbol{\beta}}) - \bar{\Delta}_\xi(c; \bar{\boldsymbol{\beta}})| = O_p\{(nh)^{-1/2} \log(n)\}$. Then, by a Taylor series expansion, $0 = \hat{\Delta}_\xi(\hat{c}; \hat{\boldsymbol{\beta}}) = \hat{\Delta}_\xi(\hat{c}; \bar{\boldsymbol{\beta}}) + O_p(n^{-\frac{1}{2}}) = \hat{\Delta}_\xi(c_0; \bar{\boldsymbol{\beta}}) + (\hat{c} - c_0)\hat{\Delta}'_\xi(c_0; \bar{\boldsymbol{\beta}}) + O_p\{n^{-\frac{1}{2}} + (nh)^{-1} \log(n)^2\}$. It follows that

$$\hat{c} - c_0 = \hat{\Delta}_\xi(c_0; \bar{\boldsymbol{\beta}}) + o_p\{(nh)^{-1/2} + h^2\} = n^{-1} \sum_{i=1}^n K_h\{D(\boldsymbol{\beta}; \mathbf{X}_i) - c\} \frac{\mathcal{Y}_{\xi_i} - \bar{\Delta}_\xi(c_0; \bar{\boldsymbol{\beta}})}{F'(c)}$$

which is asymptotically normal as a typical kernel smoothed estimator.

For the asymptotic distribution of $\hat{\mathbb{V}}_{\hat{c}} = \hat{\mathbb{V}}(\hat{c}, \hat{\boldsymbol{\beta}})$, using similar arguments as given above, we can show that $\hat{\mathbb{V}}(\hat{c}, \hat{\boldsymbol{\beta}}) - \hat{\mathbb{V}}(c_0, \hat{\boldsymbol{\beta}}) = o_p(n^{-\frac{1}{2}})$ and $\hat{\mathbb{V}}(c_0; \hat{\boldsymbol{\beta}}) - \hat{\mathbb{V}}(c_0; \bar{\boldsymbol{\beta}}) = \mathbb{V}(c_0; \hat{\boldsymbol{\beta}}) - \mathbb{V}(c_0; \bar{\boldsymbol{\beta}}) + o_p(n^{-\frac{1}{2}})$. Therefore,

$$\begin{aligned} \hat{\mathbb{V}}_{\hat{c}} - \mathbb{V}_{\mathcal{I}_{\text{calib}}} &= \mathbb{V}(c_0; \hat{\boldsymbol{\beta}}) - \mathbb{V}(c_0; \bar{\boldsymbol{\beta}}) + \hat{\mathbb{V}}(c_0; \bar{\boldsymbol{\beta}}) - \mathbb{V}_{\mathcal{I}_{\text{calib}}} + o_p(n^{-\frac{1}{2}}) \\ &= \mathbf{V}'_2(c_0; \bar{\boldsymbol{\beta}})^\top (\hat{\boldsymbol{\beta}} - \bar{\boldsymbol{\beta}}) + \hat{\mathbb{V}}(c_0; \bar{\boldsymbol{\beta}}) - \mathbb{V}_{\mathcal{I}_{\text{calib}}} + o_p(n^{-\frac{1}{2}}) = n^{-1} \sum_{i=1}^n \boldsymbol{\Psi}_{V_i}(c_0) + o_p(n^{-\frac{1}{2}}) \end{aligned}$$

where $\boldsymbol{\Psi}_{V_i}(c_0) = \mathbf{V}'_2(c_0; \bar{\boldsymbol{\beta}})^\top \boldsymbol{\Psi}_{\boldsymbol{\beta}_i} + I(D_i \geq c_0)\mathcal{Y}_{\xi_i} - m_{\Delta_1}(\bar{\boldsymbol{\beta}})I(G_i = 1)/\pi_1 + m_{\Delta_0}(\bar{\boldsymbol{\beta}})I(G_i =$

$0)/\pi_0 + (Y_i - \mu_0)I(G_i = 0)/\pi_0$. Under the monotonicity of $\bar{\Delta}(\cdot)$, we see that $\Psi_{V_i}(c_0) = \Psi_{V_i}$ and hence $\widehat{V}_{\widehat{I}_{\widehat{c}}} - \widehat{V}_{\widehat{I}_{\text{calib}}} = o_p(n^{-\frac{1}{2}})$.

References

- Cai, T., Tian, L., Wong, P., and Wei, L. (2011). Analysis of randomized comparative clinical trial data for personalized treatment selections. *Biostatistics* **12**, 270–282.
- Kim, J. and Pollard, D. (1990). Cube root asymptotics. *The Annals of Statistics* pages 191–219.
- Newey, W. K. and McFadden, D. (1994). Large sample estimation and hypothesis testing. *Handbook of econometrics* **4**, 2111–2245.
- Pollard, D. (1990). Empirical processes: theory and applications. In *NSF-CBMS regional conference series in probability and statistics*. JSTOR.