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Statistical Inference when using Data Adaptive Estimators of Nuisance Parameters

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Abstract

In order to be concrete we focus on estimation of the treatment specific mean, controlling for all measured baseline covariates, based on observing n independent and identically distributed copies of a random variable consisting of baseline covariates, a subsequently assigned binary treatment, and a final outcome. The statistical model only assumes possible restrictions on the conditional distribution of treatment, given the covariates, the so called propensity score. Estimators of the treatment specific mean involve estimation of the propensity score and/or estimation of the conditional mean of the outcome, given the treatment and covariates. In order to make these estimators asymptotically unbiased at any data distribution in the statistical model, it is essential to use data adaptive estimators of these nuisance parameters such as ensemble learning, and specifically super-learning. Because such estimators involve optimal trade-off of bias and variance w.r.t. the infinite dimensional nuisance parameter itself, they result in a sub-optimal bias/variance trade-off for the resulting real valued estimator of the estimand. We demonstrate that additional targeting of the estimators of these nuisance parameters guarantees that this bias for the estimand is second order, and thereby allows us to prove theorems thatestablish asymptotic linearity of the estimator of the treatment specific mean under regularity conditions. These insights result in novel targeted maximum likelihood estimators (TMLE) that use ensemble learning withadditional targeted bias reduction to construct estimators of the nuisance parameters. In particular, we construct collaborative targeted maximum likelihood estimators (CTMLE) with known influence curve allowing for statistical inference, even though these CTMLEs involve variable selection for the propensity score based on a criterion that measures how effective the resulting fit of the propensity score is in removing bias for the estimand. As a particular special case, we also demonstrate the required targeting of the propensity score for

the inverse probability of treatment weighted estimator using super-learning to fit the propensity score.

1 Introduction

Suppose we observe n independent and identically distributed copies of a random variable O with probability distribution P_0. In addition, assume that it is known that P_0 is an element of a statistical model $\mathcal{M}$, and that we want to estimate $\psi_0 = \Psi(P_0)$ for a given target parameter mapping $\Psi : \mathcal{M} \rightarrow \mathbb{R}$. Since such correctly specified models only incorporate real knowledge, such models $\mathcal{M}$ are always very large and, in particular, are infinite dimensional. We assume that the target parameter mapping is path-wise differentiable and let $D^*(P)$ be the canonical gradient of the path-wise derivative of Ψ at $P \in \mathcal{M}$ (Bickel et al., 1997). An estimator $\psi_n = \hat{\Psi}(P_n)$ is a functional $\hat{\Psi}$ applied to the empirical distribution P_n of $O_1, \ldots, O_n$ into the parameter space, and can thus be represented as a mapping $\hat{\Psi} : \mathcal{M}_{NP} \rightarrow \mathbb{R}$ from the nonparametric statistical model $\mathcal{M}_{NP}$ into the real line. An estimator $\hat{\Psi}$ is efficient if and only if it is asymptotically linear with influence curve $D^*(P_0)$:

$$\psi_n - \psi_0 = \frac{1}{n} \sum_{i=1}^{n} D^*(P_0)(O_i) + o_P(1/\sqrt{n}).$$

The empirical mean of the influence curve $D^*(P_0)$ represent the first order linear approximation of the estimator as a functional of the empirical distribution, and the derivation of the influence curve is a by-product of the application of the so called functional delta-method for statistical inference based on functionals (i.e., $\hat{\Psi}$) of the empirical distribution (Gill, 1989; van der Vaart and Wellner, 1996; Gill et al., 1995).

Suppose that $\Psi(P)$ only depends on P through a parameter $Q(P)$ and that the canonical gradient depends on P only through $Q(P)$ and a nuisance parameter $g(P)$. The construction of an efficient estimator requires the construction of estimators Q_n and g_n of these nuisance parameters Q_0 and g_0, respectively. Targeted maximum likelihood estimation (TMLE) represents a method for construction of efficient substitution estimators $\Psi(Q_n^*)$, where Q_n^* is an update of Q_n that relies on the estimator g_n(van der Laan and Rubin, 2006; van der Laan, 2008; van der Laan and Rose, 2012). The bias of such an estimator will be second order in terms of the bias of $(Q_n - Q_0)$ and $(g_n - g_0)$. As a consequence, TMLE will only have a chance of being asymptotically linear if at least one of the nuisance parameter estimators is consistent, thereby requiring nonparametric adaptive estimation such as super-learning (van der Laan and Dudoit, 2003; van der Laan et al., 2007; van der Vaart et al., 2006). If only one of the nuisance parameter estimators is consistent, then it follows that the bias is of the same order as the bias of the consistent nuisance parameter estimator. Thus, in that case the estimator of the target parameter is still having the same order of bias as the consistent nuisance parameter estimator, and thus be overly biased. Therefore it is essential that the consistent nuisance parameter estimator is targeted towards the estimand so that the bias for the estimand becomes second order. Even if both estimators Q_n, g_n are consistent, but one might be converging at a faster rate than the other, this targeting of the nuisance parameter estimator will help to remove finite sample bias for the estimand. The same arguments applies to other double robust estimators, such as estimating equation based estimators and inverse probability of treatment weighted (IPTW) estimators (see e.g., Robins and Rotnitzky (1992, 1995); van der Laan and Robins (2003); Robins et al. (2000); Robins (2000); Robins and Rotnitzky (2001)). The current article concerns the construction of such targeted IPTW and TMLE that are asymptotically linear under regularity conditions, even when only one of the nuisance parameters is consistent and the estimators of the nuisance parameters are highly data adaptive.

In order to be concrete in this article we will focus on a particular example. Let $O = (W, A, Y) \sim P_0$, W baseline covariates, A a binary treatment, and Y a final outcome. Let $\mathcal{M}$ be a model that makes at most some assumptions about the conditional distribution of A, given W, but leaves the marginal distribution of W and the conditional distribution of Y, given A, W, unspecified. Let $\Psi : \mathcal{M} \rightarrow \mathbb{R}$ be defined as $\Psi(P) = E_P E_P(Y \mid A = 1, W)$, the so called treatment specific mean controlling for the baseline covariates. The canonical gradient, also called the efficient influence curve, of Ψ at P is given by $D^*(P)(O) = A/g(1 \mid W)(Y - \bar{Q}(1, W)) + \bar{Q}(1, W) - \Psi(P)$, where $g(1 \mid W) = P(A = 1 \mid W)$ is the propensity score, and $\bar{Q}(a, W) = E_P(Y \mid A = a, W)$ is the outcome regression (e.g., (van der Laan and Robins, 2003). Let $Q = (Q_W, \bar{Q})$, where Q_W is the marginal distribution of W, and note that $\Psi(P)$ only depends on P through $Q = Q(P)$. For convenience, we will denote the target parameter with $\Psi(Q)$ in order to not have to introduce additional notation. A targeted maximum likelihood estimator is a plug-in estimator $\Psi(Q_n^*)$, where Q_n^* is an update of an initial estimator Q_n that relies on an estimator g_n of g_0, and it has the property that it solves $P_n D^*(Q_n^*, g_n) = 0$, where we used the notation $Pf = \int f(o) dP(o)$.

For this example, such targeted maximum likelihood estimators are presented in Scharfstein et al. (1999); van der Laan and Rubin (2006); Bembom et al. (2009); Gruber and van der Laan (2010a,c,d); Rosenblum and van der Laan (2010); Sekhon et al. (2011); van der Laan and Rose (2012); Gruber and van der Laan (2012c). Since $P_0 D^*(Q, g) = \psi_0 - \Psi(Q) + P_0(\bar{Q}_0 - \bar{Q})(\bar{g}_0 - \bar{g})/\bar{g}$ (e.g, Zheng and van der Laan (2010, 2011)), where we use the notation $\bar{g}(W) =$

$g(1 \mid W)$ and $\bar{Q}(W) = \bar{Q}(1, W)$, this results in the identity:

$$\Psi(Q_n^*) - \psi_0 = (P_n - P_0)D^*(Q_n^*, g_n) + P_0(\bar{Q}_0 - \bar{Q}_n^*)(\bar{g}_0 - \bar{g}_n)/\bar{g}_n.$$

The first term equals $(P_n - P_0)D^*(Q, g) + o_P(1/\sqrt{n})$ if $D^*(Q_n^*, g_n)$ falls in a P_0-Donsker class with probability tending to 1, and $P_0\{D^*(Q_n^*, g_n) - D^*(Q, g)\}^2 \to 0$ in probability as $n \to \infty$ (van der Vaart and Wellner (1996); van der Vaart (1998)). If $\bar{Q}_n^*$ and $\bar{g}_n$ are consistent for the true $\bar{Q}_0$ and $\bar{g}_0$, respectively, then the remainder is a second order term. If one now assumes that this second order term is $o_P(1/\sqrt{n})$, it has been proven that the TMLE is asymptotically efficient. However, if only one of these nuisance parameter estimators is consistent, then this remainder is still a first order term, and it remains to establish that it is also asymptotically linear with a second order remainder. For sake of discussion, suppose that $\bar{Q}_n^*$ converges to a wrong $\bar{Q}$ while $\bar{g}_n$ is consistent. In that case, this remainder behaves in first order as $P_0(\bar{Q}_0 - \bar{Q})(\bar{g}_n - \bar{g}_0)/\bar{g}_0$. To establish that such a term (e.g., $\bar{g}_n$ is a super-learner) is asymptotically linear requires that $\bar{g}_n$ solves the necessary estimating equations, and thereby needs to be targeted: that is, $\bar{g}_n$ needs to be a TMLE itself targeting the required smooth functional of g_0.

In this article, we present TMLE that also target g_n and allow us to prove the desired asymptotic linearity of the remainder when either $\bar{g}_n$ or $\bar{Q}_n$ is consistent, under conditions that require second order terms to be $o_P(1/\sqrt{n})$. The latter type of regularity conditions are typical for the construction of asymptotically linear estimators and are therefore considered appropriate for the sake of this article. Though it is of interest to study cases in which these second order terms cannot be assumed to be $o_P(1/\sqrt{n})$, this is beyond the scope of this article.

The organization of this paper is as follows. In the next section 2 we introduce a targeted IPTW estimator that relies on an adaptive consistent estimator of g_0, and we establish its asymptotic linearity. In the remainder of the article we focus on asymptotic linearity of the TMLE. In Section 3 we introduce a novel TMLE that assumes that the targeted adaptive estimator g_n is consistent for g_0, and we establish its asymptotic linearity. In Section 4 we introduce a novel TMLE that only assumes that either the targeted $\bar{Q}_n^*$ or the targeted $\bar{g}_n^*$ is consistent, and we establish its asymptotic linearity. This result thus allows statistical inference in the statistical model that only assumes that one of the estimators is consistent, and we refer to this as "double robust statistical inference". Even though double robust estimators have been extensively presented in the current literature, double robust statistical inference in these large semi-parametric models has been a difficult topic. In Section

5 we extend our results to collaborative targeted maximum likelihood estimators (CTMLE) in which the estimator g_n is construction w.r.t. a criterion that measures how well the corresponding TMLE improves bias for the estimand of interest (van der Laan and Gruber, 2010; Gruber and van der Laan, 2010c, 2011; Stitelman and van der Laan, 2010; Porter et al., 2011; Gruber and van der Laan, 2012a; van der Laan and Rose, 2011; Wang et al., 2011). Specifically, we present a novel CTMLE for which we can establish asymptotic linearity and thereby statistical inference. Again, even though CTMLEs have been presented in the current literature, statistical inference based on the CTMLEs has been another difficult topic. We conclude this article with a discussion. The proofs of the theorems are presented in the Appendix.

2 Statistical inference for IPTW-estimator when using super learning to fit treatment mechanism.

We consider a simple IPTW estimator $\hat{\Psi}(P_n) = P_n D(\hat{g}(P_n))$, where $D(g)(O) = YI(A=1)/\bar{g}(W)$, and $\hat{g} : \mathcal{M}_{np} \rightarrow \mathcal{G}$ is an adaptive estimator of g_0 based on the log-likelihood loss function. For a general presentation of an IPTW estimator we refer to Robins and Rotnitzky (1992); van der Laan and Robins (2003); Hernan et al. (2000). We wish to establish conditions under which reliable statistical inference based on this estimator of ψ_0 can be obtained.

One might wish to estimate g_0 with ensemble learning, and, in particular, super learning in which cross-validation (Györfi et al., 2002) is used to determine the best weighted combination of a library of candidate estimators: van der Laan and Dudoit (2003); van der Laan et al. (2006); van der Vaart et al. (2006); van der Laan et al. (2004); Dudoit and van der Laan (2005); Polley et al. (2011); Polley and van der Laan (2010); van der Laan et al. (2007); van der Laan and Petersen (2012). We will start with presenting a succinct description of a super-learner. Consider a library of estimators $\hat{g}_j : \mathcal{M}_{np} \rightarrow \mathcal{G}$, $j = 1, \ldots, J$, and a family of weighted (on logistic scale) combinations of these estimators $\mathrm{Logit}\hat{g}_\alpha(1 \mid W) = \sum_{j=1}^J \alpha_j \mathrm{Logit}\hat{g}_j(1 \mid W)$, indexed by vectors α for which $\alpha_j \in [0,1]$ and $\sum_j \alpha_j = 1$. Given a random sample split $B_n \in \{0,1\}^n$ into a training sample $\{i : B_n(i) = 0\}$ of size $n(1-p)$ and validation sample $\{i : B_n(i) = 1\}$ of size np, let

$$\alpha_n = \arg\min_\alpha E_{B_n} P^1_{n,B_n} L(\hat{g}_\alpha(P^0_{n,B_n})) = \arg\min_\alpha E_{B_n} \frac{1}{np} \sum_{i:B_n(i)=1} L(\hat{g}_\alpha(P^0_{n,B_n}))(O_i)$$

be the choice of estimator that minimizes cross-validated risk, where $L(g)(O) = -\{A \log g(1 \mid W) + (1-A) \log(1-g(1 \mid W))\}$ is the log-likelihood loss function for g_0. The super-learner of g_0 is defined as the estimator $\hat{g}(P_n) = \hat{g}_{\alpha_n}(P_n)$.

The next theorem presents an IPTW-estimator that uses a targeted fit g_n^* of g_0, involving the updating of an initial estimator g_n, and conditions under which this IPTW estimator of ψ_0 is asymptotically linear. For example, g_n could be defined as the super-learner presented above. In spite of the fact that such an IPTW estimator uses a very adaptive hard to understand estimator g_n, this theorem shows that its influence curve is known and can be well estimated.

Theorem 1 *Suppose $O = (W, A, Y) \sim P_0 \in \mathcal{M}$, the model $\mathcal{M}$ makes only assumptions about g_0, and our target parameter $\Psi : \mathcal{M} \to \mathbb{R}$ is defined as $\Psi(P) = E_P E_P(Y \mid A = 1, W)$. Let $\bar{g}(W) = g(1 \mid W)$, $\bar{Q}(W) = \bar{Q}(1, W)$. We consider a simple IPTW estimator $\hat{\Psi}(P_n) = P_n D(\hat{g}(P_n))$, where $D(g) = YI(A=1)/g(A|W)$, and $\hat{g} : \mathcal{M}_{np} \to \mathcal{G}$ is an estimator of g_0.*

Let g_n^* be an update of $g_n = \hat{g}(P_n)$ defined as follows:

Definition of targeted estimator g_n^*: *Define $\bar{Q}_0^r = E_0(Y \mid A = 1, \bar{g}_0(W))$, and $H_0^r \equiv \bar{Q}_0^r/\bar{g}_0$.Let $\bar{Q}_n^r$ be obtained by nonparametric estimation of the regression function $E_0(Y \mid A = 1, \bar{g}_n(W))$ treating $\bar{g}_n$ as a fixed covariate (i.e., function of W). This yields an estimator $H_n^r \equiv \bar{Q}_n^r/\bar{g}_n$ of H_0^r. Consider the submodel $Logit\bar{g}_n(\epsilon) = Logit\bar{g}_n + \epsilon H_n^r$, and fit ϵ with the MLE*

$$\epsilon_n = \arg\max_{\epsilon} P_n \log g_n(\epsilon).$$

We define $g_n^* = g_n(\epsilon_n)$ as the corresponding targeted update of g_n. This TMLE g_n^* satisfies

$$P_n D_{H_n^r}(\bar{g}_n^*) = 0,$$

where $D_H(\bar{g}) \equiv H(W)(A - \bar{g}(W))$.

Empirical Process condition:

Assume that $D(g_n^*), D_{H_n^r}(\bar{g}_n^*)$ fall in a P_0-Donsker clas with probability tending to 1.

Consistency condition: *Assume*

$$\begin{aligned} P_0\{D(g_n^*) - D(g_0)\}^2 &= o_P(1) \\ P_0\{D_{H_n^r}(\bar{g}_n^*) - D_{H_0^r}(\bar{g}_0)\}^2 &= o_P(1) \end{aligned}$$

Negligibility of second order terms: *Define $\bar{Q}_{0,n}^r \equiv E_0(Y \mid A = 1, \bar{g}_0(W), \bar{g}_n(W))$.*

Assume

$$\begin{aligned} P_0 \frac{\bar{Q}_0}{\bar{g}_0 \bar{g}_n^*}(\bar{g}_0 - \bar{g}_n^*)^2 &= o_P(1/\sqrt{n}) \\ P_0(\bar{Q}_{0,n}^r - \bar{Q}_0^r)\frac{\bar{g}_0 - \bar{g}_n^*}{\bar{g}_0} &= o_P(1/\sqrt{n}) \\ P_0(H_n^r - H_0^r)(\bar{g}_0 - \bar{g}_n^*) &= o_P(1/\sqrt{n}). \end{aligned}$$

Then,

$$\hat{\Psi}(P_n) - \psi_0 = (P_n - P_0)IC(P_0) + o_P(1/\sqrt{n}),$$

where $IC(P_0) = YI(A = 1)/g_0(A \mid W) - \psi_0 + H_0^r(W)(A - \bar{g}_0(W))$.

Regarding the displayed second order term conditions, we note that the first condition is satisfied if $\bar{g}_n^* - \bar{g}_0$ converges to zero w.r.t. $L^2(P_0)$-norm at rate $o_P(n^{-1/4})$, and $\bar{g}_n^* > \delta > 0$ for some $\delta > 0$ with probability tending to 1 as $n \to \infty$. The second and third condition again require that $\bar{g}_n^*$ converges to $\bar{g}_0$ at fast enough rate $o(n^{-1/4})$ so that the products of the two terms is $o_P(1/\sqrt{n})$. The two consistency conditions only require consistency of $\bar{g}_n^*$ and H_n^r to $\bar{g}_0$ and H_0^r, respectively.

An example of a Donsker class is the class of multivariate real valued functions with uniform sectional variation norm bounded by a universal constant (van der Laan (1996)). It is important to note that if each estimator in the library falls in such a class, then also the convex combinations fall in that same class(van der Vaart and Wellner, 1996). So this Donsker condition will hold if it holds for each of the candidate estimators in the library of the super learner. The obvious important implication of this theorem is that, under appropriate regularity conditions, even if we use a very adaptive estimator g_n of g_0, the resulting IPTW-estimator is asymptotically normally distributed with a variance $\sigma^2 = P_0 IC(P_0)^2$ that can be consistently estimated with

$$\sigma_n^2 = \frac{1}{n}\sum_{i=1}^n IC_n^2(O_i),$$

where IC_n is the plug-in estimator of the influence curve $IC(P_0)$ obtained by plugging in g_n or g_n^* for g_0 and $\bar{Q}_n^r$ for $\bar{Q}_0^r$.

2.1 Comparison with IPTW using parametric model.

Consider an IPTW estimator using a MLE g_n^1 according to a parametric model for g_0, and let's contrast this IPTW estimator with an IPTW estimator defined in the above theorem based on an initial super learner g_n that includes g_n^1 as an element of the library of estimators. Let's first consider the case that the parametric model is correctly specified. In that case g_n^1 converges to g_0 at a parametric rate $1/\sqrt{n}$. From the oracle inequality for cross-validation (van der Laan and Dudoit, 2003; van der Laan et al., 2006; van der Vaart et al., 2006), it follows that g_n also converges at the rate $1/\sqrt{n}$ to g_0 possibly up to a $\sqrt{logn}$-factor in case the number of algorithms in the library is of the order n^p for some fixed p. As a consequence, all the consistency and second order term conditions for the IPTW-estimator using a targeted g_n^* based on g_n hold. If one uses estimators in the library of algorithms that have a uniform sectional variation norm smaller than a $M < \infty$ wit probability tending to 1, then also a weighted average of these estimators will have uniform sectional variation norm smaller than $M < \infty$ with probability tending to 1. Thus, in that case we will also have that $D(g_n^*), D_{H_n^r}(\bar{g}_n^*)$ fall in a P_0-Donsker class. Examples of estimators that control the uniform sectional variation norm are any parametric model with fewer than K main terms that themselves have a uniform sectional variation norm, but also penalized least-squares estimators (e.g., Lasso) using basis functions with bounded uniform sectional variation norm, and one could map any estimator into this space of functions with universally bounded uniform sectional variation norm through a smoothing operation. Thus, under this restriction on the library, the IPTW-estimator using the super-learner is asymptotically linear with influence curve $IC(P_0) = YI(A=1)/g_0(A \mid W) - \psi_0 + H_0^r(W)(A - \bar{g}_0(W))$, where $H_0^r(W) = E_0(Y \mid A = 1, \bar{g}_0(W))/\bar{g}_0(W)$. We note that $IC(P_0)$ is the efficient influence curve for the target parameter $E_0Y(1)$ if the observed data is given by $O = (\bar{g}_0(W), A, Y)$ instead of $O = (W, A, Y)$.

The parametric IPTW-estimator is asymptotically linear with influence curve $YI(A=1)/g_0(A \mid W) - \psi_0 - \Pi(YI(A=1)/\bar{g}_0(W) \mid T_g)$, where T_g is the tangent space of the parametric model for g_0, and $\Pi(f \mid T_g)$ denotes the projection of f onto T_g in the Hilbert space $L_0^2(P_0)$ (van der Laan and Robins, 2003). This IPTW estimator could be less or more efficient than the IPTW-estimator using the super-learner depending on the actual tangent space of the parametric model. For example, if the parametric model happens to have a score equal to $\bar{Q}_0(W)(A/\bar{g}_0(W) - 1)$, then the parametric IPTW-estimator would be asymptotically efficient. Of course, a standard parametric model is not tailored to correspond with such optimal scores, but it shows that we cannot claim superiority of one versus the other in the case that the parametric model for g_0 is correctly specified.

If, on the other hand, the parametric model is misspecified, then the IPTW estimator using g_n^1 is inconsistent. However, the super-learner g_n will be consistent if the library contains a nonparametric adaptive estimator, and performs asymptotically as well as the oracle selector among all the weighted combinations of the algorithms in the library. To conclude, the IPTW estimator using super-learning to estimate g_0 will be as good as the IPTW-estimator using a correctly specified parametric model (included in the library of the super-learner), but it remains consistent and asymptotically linear in a much larger model than the parametric IPTW-estimator relying on the true g_0 being an element of the parametric model.

3 Statistical inference for TMLE when using super learning to consistently fit treatment mechanism.

In this section we extend the result for the IPTW estimator of the previous section to TMLE. Since TMLE also relies on an estimator of $\bar{Q}_0$, the targeting of the estimator of g_0 is by necessity iterative in order to establish the desired asymptotic linearity of the TMLE of ψ_0 under second order conditions. The following theorem presents a novel TMLE and corresponding asymptotic linearity with specified influence curve, where we rely on on consistent estimation of g_0. The TMLE still uses the same updating step for the estimator of $\bar{Q}_0$, but uses a novel targeting step for the estimator of g_0, analogue to the targeting step of the IPTW-estimator in the previous section.

Theorem 2 *Let $O = (W, A, Y)$, and $Y \in \{0, 1\}$ or Y is continuous with values in $(0, 1)$. Let P_0 be the true probability distribution of O, and let $\mathcal{M}$ be a statistical model that only puts restrictions on the conditional distribution of A, given W. Let $D^*(Q, g)(O) = A/\bar{g}(W)(Y - \bar{Q}(A, W)) + \bar{Q}(1, W) - \Psi(Q)$ be the efficient influence curve of $\Psi : \mathcal{M} \to \mathbb{R}$.*
Definition of terms: *Consider the following definitions:*

$$\begin{aligned}
&\bar{Q}^r_{0,n}(W) \equiv E_0(Y - \bar{Q}(1, W) \mid A = 1, \bar{g}^*_n(W), \bar{g}_0(W))\\
&\bar{Q}^r_0(W) \equiv E_0(Y - \bar{Q}(1, W) \mid A = 1, \bar{g}_0(W))\\
&H_g(A, W) \equiv A/\bar{g}(W)\\
&H^r_{0,n} = \bar{Q}^r_{0,n}/\bar{g}^*_n\\
&H_{0,r} = \bar{Q}^r_0/\bar{g}_0\\
&D_H(\bar{g})(A, W) \equiv H(W)(A - \bar{g}(W)),
\end{aligned}$$

where $\bar{g}^*_n(W)$ is treated as a fixed covariate (i.e., function of W) in the conditional expectation $\bar{Q}^r_{0,n}$.
Iterative targeted MLE of ψ_0:

Definitions: *Given $\bar{Q}, \bar{g}$, let $\bar{Q}_n^r(\bar{Q}, \bar{g})$ be a consistent estimator of the regression of $(Y - \bar{Q})$ on $\bar{g}(W)$ and $A = 1$. Let $H_n^r(\bar{Q}, \bar{g}) = \bar{Q}_n^r(\bar{Q}, \bar{g})/\bar{g}$. Let $g_n, \bar{Q}_n$ be an initial estimator of $g_0, \bar{Q}_0$.*

Initialization: *Let $g_n^0 = g_n, \bar{Q}_n^0 = \bar{Q}_n$ and let $k = 0$.*

Updating step for g_n^k: *Consider the submodel $Logit\bar{g}_n^k(\epsilon) = Logit\bar{g}_n^k + \epsilon H_n^r(\bar{Q}_n^k, \bar{g}_n^k)$, and fit ϵ with the MLE*

$$\epsilon_n = \arg\max_{\epsilon} P_n \log g_n^k(\epsilon).$$

We define $g_n^{k+1} = g_n^k(\epsilon_n)$ as the corresponding targeted update of g_n^k. This g_n^{k+1} satisfies

$$P_n D_{H_n^r(\bar{Q}_n^k, \bar{g}_n^k)}(\bar{g}_n^{k+1}) = \frac{1}{n} \sum_i H_n^r(\bar{Q}_n^k, \bar{g}_n^k)(W_i)(A_i - \bar{g}_n^{k+1}(W_i)) = 0.$$

Updating step for $\bar{Q}_n^k$: *Let $-L(\bar{Q})(O) = Y \log \bar{Q}(A, W) + (1 - Y)\log(1 - \bar{Q}(A, W))$ be the log-likelihood loss-function for $\bar{Q}_0$. Define the submodel $Logit\bar{Q}_n^k(\epsilon) = Logit\bar{Q}_n^k + \epsilon H_{g_n^k}$, and let $\epsilon_n = \arg\max_\epsilon P_n L(\bar{Q}_n^k(\epsilon))$. Define $\bar{Q}_n^{k+1} = \bar{Q}_n^k(\epsilon_n)$ as the resulting update.*

Iterating till convergence: *Now, set $k = k + 1$, and iterate this updating process mapping a $(g_n^k, \bar{Q}_n^k)$ into $(g_n^{k+1}, \bar{Q}_n^{k+1})$ till convergence or till large enough K so that the estimating equations (1) below are solved up till an $o_P(1/\sqrt{n})$-term. Denote the limit of this iterative procedure with $g_n^*, \bar{Q}_n^*$.*

Plug-in estimator: *Let $Q_n^* = (Q_{W,n}, \bar{Q}_n^*)$, where $Q_{W,n}$ is the empirical distribution estimator of $Q_{W,0}$. The TMLE of ψ_0 is defined as $\Psi(Q_n^*)$.*

Estimating equations solved by TMLE: *This TMLE (Q_n^*, g_n^*) solves*

$$\begin{aligned} P_n D^*(Q_n^*, g_n^*) &= 0 \\ P_n D_{H_n^r(\bar{Q}_n^*, \bar{g}_n^*)}(\bar{g}_n^*) &= 0 \end{aligned} \tag{1}$$

Empirical process condition: *Let $H_n^r = H_n^r(\bar{Q}_n^*, \bar{g}_n^*)$. Assume that $D^*(Q_n^*, g_n^*)$, $D_{H_n^r}(g_n^*)$ fall in a P_0-Donsker class with probability tending to 1 as $n \to \infty$.*

Consistency condition:

$$P_0\{D^*(Q_n^*, g_n^*) - D^*(Q, g_0)\}^2 = o_P(1)$$
$$P_0(D_{H_n^r}(\bar{g}_n^*) - D_{H_0^r}(\bar{g}_0))^2 = o_P(1)$$

Negligibility of second order terms:

$$P_0(H_{g_n^*} - H_{g_0})(\bar{Q}_n^* - \bar{Q}) = o_P(1/\sqrt{n})$$
$$P_0(H_{0,n}^r - H_0^r)(\bar{g}_n^* - \bar{g}_0) = o_P(1/\sqrt{n})$$
$$P_0(H_n^r - H_0^r)(\bar{g}_n^* - \bar{g}_0) = o_P(1/\sqrt{n}).$$

Then,

$$\Psi(Q_n^*) - \Psi(Q_0) = (P_n - P_0)IC(P_0) + o_P(1/\sqrt{n}),$$

where $IC(P_0) = D^*(Q, g_0) - D_{H_0^r}(\bar{g}_0)$.

4 Double robust statistical inference for TMLE when using super learning to fit outcome regression and treatment mechanism

In this section our aim is to present a TMLE whose influence curve is known if either g_0 or Q_0 is consistently estimated, but we do not need to know which one. Again, this requires a novel way of targeting the nuisance parameters in order to arrange that the relevant smooth functionals of the nuisance parameter estimators are indeed asymptotically linear under second order term conditions. In this case, we also need to augment the targeting operation for the estimator of $\bar{Q}_0$ with another clever covariate.

Theorem 3 *Let* $O = (W, A, Y)$*, and* $Y \in \{0, 1\}$ *or* Y *is continuous with values in* $(0, 1)$*. Let* $\mathcal{M}$ *be a statistical model for the true distribution of* O *that only puts restrictions on the conditional distribution* g_0 *of* A*, given* W*. Let* $D^*(Q, g)(O) = A/\bar{g}(W)(Y - \bar{Q}(A, W)) + \bar{Q}(1, W) - \Psi(Q)$ *be the efficient influence curve of* $\Psi : \mathcal{M} \rightarrow \mathbb{R}$ *at* $P \in \mathcal{M}$*, where* $Q = (Q_W, \bar{Q})$*,* Q_W *is probability distribution of* W *under* P*, and* $\bar{Q}(W) = E_P(Y \mid A = 1, W)$*.*

Definitions:

$$\bar{Q}_0^r = \bar{Q}_0^r(\bar{g}, \bar{Q}) = E_0(Y - \bar{Q} \mid A = 1, \bar{g})$$
$$\bar{g}_0^r = \bar{g}_0^r(\bar{g}, \bar{Q}) = E_0(A \mid \bar{Q}, \bar{g})$$
$$\bar{Q}_{0,n}^r = E_0(Y - \bar{Q} \mid A = 1, \bar{g}, \bar{g}_n)$$
$$\bar{g}_{0,n}^r = E_0(A \mid \bar{g}, \bar{Q}, \bar{Q}_n^*)$$
$$H_A(\bar{g}, \bar{Q}_0^r) \equiv \frac{\bar{Q}_0^r}{\bar{g}}$$
$$H_Y(\bar{g}_0^r, \bar{g}) \equiv \frac{A}{\bar{g}_0^r}\frac{\bar{g}_0^r - \bar{g}}{\bar{g}}$$
$$D_A(\bar{g}, \bar{Q}_0^r) = H_A(\bar{g}, \bar{Q}_0^r)(A - \bar{g})$$
$$D_Y(\bar{g}_0^r, \bar{g}, \bar{Q}) = H_Y(\bar{g}_0^r, \bar{g})(Y - \bar{Q})$$
$$H_g(A, W) \equiv \frac{A}{\bar{g}(W)}.$$

For any given $\bar{g}, \bar{Q}$, let $\bar{g}_n^r(\bar{g}, \bar{Q})$ and $\bar{Q}_n^r(\bar{g}, \bar{Q})$ be consistent estimators of $\bar{g}_0^r(\bar{g}, \bar{Q})$ and $\bar{Q}_0^r(\bar{g}, \bar{Q})$, respectively (e.g., using a super learner or other non-parametric adaptive regression algorithm). Let $\bar{Q}_n^r = \bar{Q}_n^r(\bar{g}_n^*, \bar{Q}_n^*)$ and $\bar{g}_n^r = \bar{g}_n^r(\bar{g}_n^*, \bar{Q}_n^*)$ denote these estimators applied to $(\bar{g}_n^*, \bar{Q}_n^*)$.

Iterative targeted MLE of ψ_0:

Initialization: *Let g_n, $\bar{Q}_n$ be an initial estimator of g_0, $\bar{Q}_0$. Let $g_n^0 = g_n$, $\bar{Q}_n^0 = \bar{Q}_n$ and let $k = 0$.*

Updating step: *Let $\bar{g}_n^{r,k} = \bar{g}_n^r(\bar{g}_n^k, \bar{Q}_n^k)$ be obtained by non parametrically regressing A on $\bar{Q}_n^k, \bar{g}_n^k$. Let $\bar{Q}_n^{r,k} = \bar{Q}_n^r(\bar{g}_n^k, \bar{Q}_n^k)$ be obtained by non parametrically regressing $Y - \bar{Q}_n^k$ on $A = 1, \bar{g}_n^k$. Consider the submodel $Logit\bar{g}_n^k(\epsilon) = Logit\bar{g}_n^k + \epsilon H_A(\bar{g}_n^k, \bar{Q}_n^{r,k})$, and fit ϵ with the MLE*

$$\epsilon_{A,n} = \arg\max_{\epsilon} P_n \log g_n^k(\epsilon).$$

Let $-L(\bar{Q})(O) = Y \log \bar{Q}(A,W) + (1-Y)\log(1 - \bar{Q}(A,W))$ be the log-likelihood loss for $\bar{Q}_0$. Define the submodel $Logit\bar{Q}_n^k(\epsilon) = Logit\bar{Q}_n^k + \epsilon_1 H_{g_n^k} + \epsilon_2 H_Y(\bar{g}_n^{r,k}, \bar{g}_n^k)$, and let $\epsilon_{Y,n} = \arg\max_\epsilon P_n L(\bar{Q}_n^k(\epsilon))$ be the MLE. We define $g_n^{k+1} = g_n^k(\epsilon_{A,n})$ as the corresponding targeted update of g_n^k, and $\bar{Q}_n^{k+1} = \bar{Q}_n^k(\epsilon_{Y,n})$ as the corresponding update of $\bar{Q}_n^k$.

Iterate till convergence: *Now, set $k = k + 1$, and iterate this updating process mapping a $(g_n^k, \bar{Q}_n^k)$ into $(g_n^{k+1}, \bar{Q}_n^{k+1})$ till convergence or till large enough K so that the following three estimating equations are solved up till an $o_P(1/\sqrt{n})$-term:*

$$\begin{aligned}
o_P(1/\sqrt{n}) &= P_n D^*(g_n^K, Q_n^K) \\
o_P(1/\sqrt{n}) &= P_n D_A(\bar{g}_n^K, \bar{Q}_n^{r,K}) \\
o_P(1/\sqrt{n}) &= P_n D_Y(\bar{g}_n^{r,K}, \bar{g}_n^K, \bar{Q}_n^K).
\end{aligned}$$

Final substitution estimator: *Denote these limits of this iterative procedure with $\bar{Q}_n^r, \bar{g}_n^r, g_n^*, \bar{Q}_n^*$. Let $Q_n^* = (Q_{W,n}, \bar{Q}_n^*)$, where $Q_{W,n}$ is the empirical distribution estimator of $Q_{W,0}$. The TMLE of ψ_0 is defined as $\Psi(Q_n^*)$.*

Equations solved by TMLE:

$$\begin{aligned}
o_P(1/\sqrt{n}) &= P_n D^*(g_n^*, Q_n^*) \\
o_P(1/\sqrt{n}) &= P_n D_A(\bar{g}_n^*, \bar{Q}_n^r) \\
o_P(1/\sqrt{n}) &= P_n D_Y(\bar{g}_n^r, \bar{g}_n^*, \bar{Q}_n^*).
\end{aligned}$$

Empirical process condition: *Assume that* $D^*(g_n^*, Q_n^*)$, $D_A(\bar{g}_n^*, \bar{Q}_n^r)$, $D_Y(\bar{g}_n^r, \bar{g}_n^*, \bar{Q}_n^*)$ *fall in a* P_0*-Donsker class with probability tending to 1 as* $n \to \infty$.
Consistency condition: $\bar{Q}_n^r, \bar{g}_n^r, \bar{g}_n^*, \bar{Q}_n^*$ *are consistent for* $\bar{Q}_0^r, \bar{g}_0^r, \bar{g}, \bar{Q}$ *in the following sense:*

$$
\begin{aligned}
&P_0\{D^*(g_n^*, Q_n^*) - D^*(g, Q)\}^2 = o_P(1) \\
&P_0\{D_A(\bar{g}_n^*, \bar{Q}_n^r) - D_A(\bar{g}, \bar{Q}_0^r\}^2 = o_P(1) \\
&P_0\{D_Y(\bar{g}_n^r, \bar{g}_n^*, \bar{Q}_n^*) - D_Y(\bar{g}_0^r, \bar{g}, \bar{Q})\}^2 = o_P(1) \\
&\bar{Q} = \bar{Q}_0 \ \textit{or} \ \bar{g} = \bar{g}_0.
\end{aligned}
$$

Negligibility of Second order terms: *We assume that the following second order terms are* $o_P(1/\sqrt{n})$*:*

$$
\begin{aligned}
&P_0(H_{g_n^*} - H_g)(\bar{Q}_n^* - \bar{Q}) = o_P(1/\sqrt{n}) \\
&P_0(\bar{Q}_n^* - \bar{Q}_0))(\bar{g}_n^* - \bar{g}_0)\frac{\bar{g}_n^* - \bar{g}}{\bar{g}\bar{g}_n^*} = o_P(1/\sqrt{n}) \\
&P_0(\bar{Q}_n^* - \bar{Q})\frac{\bar{g}_n^* - \bar{g}}{\bar{g}} = o_P(1/\sqrt{n}) \\
&P_0\frac{\bar{Q}_{0,n}^r - \bar{Q}_0^r}{\bar{g}}(\bar{g}_n^* - \bar{g}) = o_P(1/\sqrt{n}) \\
&P_0(H_A(\bar{g}_n^*, \bar{Q}_n^r) - H_A(\bar{g}, \bar{Q}_0^r)(\bar{g}_n^* - \bar{g}) = o_P(1/\sqrt{n}) \\
&P_0\{H_Y(\bar{g}_0^r, \bar{g}) - H_Y(\bar{g}_n^r, \bar{g}_n^*)(\bar{Q} - \bar{Q}_n^*)\} = o_P(1/\sqrt{n}) \\
&P_0\{H_Y(\bar{g}_{0,n}^r, \bar{g}) - H_Y(\bar{g}_0^r, \bar{g})(\bar{Q} - \bar{Q}_n^*)\} = o_P(1/\sqrt{n}).
\end{aligned}
$$

Then,

$$
\Psi(Q_n^*) - \Psi(Q_0) = (P_n - P_0)IC(P_0) + o_P(1/\sqrt{n}),
$$

where

$$
IC(P_0) = D^*(g, Q) - D_A(\bar{g}, \bar{Q}_0^r) + D_Y(\bar{g}_0^r, \bar{g}, \bar{Q}).
$$

Note that consistent estimation of the influence curve $IC(P_0)$ relies on consistency of $\bar{g}_n^r, \bar{Q}_n^r$ as estimators of $\bar{g}_0^r, \bar{Q}_0^r$, and estimators $\bar{Q}_n^*, \bar{g}_n^*$ converging to a $\bar{Q}, \bar{g}$ for which either $\bar{Q} = \bar{Q}_0$ or $\bar{g} = \bar{g}_0$.

If $\bar{g} = \bar{g}_0$, then $E_0(A \mid \bar{g}, \bar{Q}) = \bar{g}$, and therefore $D_Y(\bar{g}_0^r, \bar{g}, \bar{Q}) = 0$ for all $\bar{Q}$. If $\bar{Q} = \bar{Q}_0$, then it follows that $\bar{Q}_0^r = 0$, and thus that $D_A(\bar{g}, \bar{Q}_0^r) = 0$ for all $\bar{g}$. In particular, if both $\bar{g} = \bar{g}_0$ and $\bar{Q} = \bar{Q}_0$, then $IC(P_0) = D^*(g_0, Q_0)$. We also note that if $\bar{g} \neq \bar{g}_0$, but $\bar{g}$ is a true conditional distribution of A, given some function W^r of W for which $\bar{Q}(W)$ is only a function of W^r, then it follows that $E_0(A \mid \bar{g}, \bar{Q}) = \bar{g}$ and thus $D_Y = 0$.

5 Collaborative double robust inference for C-TMLE when using super learning to fit outcome regression and reduced treatment mechanism

We note that $P_0 D^*(Q,g) = P_0 \frac{A}{\bar{g}}(\bar{Q}_0 - \bar{Q}) + \bar{Q} - \Psi(Q)$. If $Q_W = Q_{W,0}$, this reduces to $P_0 D^*(Q,g) = P_0 \frac{A}{\bar{g}}(\bar{Q}_0 - \bar{Q})$. Let $\mathcal{G}$ be the class of all possible distributions of A, given W, and let $g_0 \in \mathcal{G}$ be the true conditional distribution of A given W. We define the set $\mathcal{G}(P_0, Q) \equiv \{g :\in \mathcal{G} : 0 = P_0(A - \bar{g})\frac{\bar{Q}_0 - \bar{Q}}{\bar{g}}\}$. For any $g \in \mathcal{G}(P_0, \bar{Q})$, we have $P_0 D^*(Q,g) = \Psi(Q_0) - \Psi(Q)$. We note that $\mathcal{G}(P_0, \bar{Q})$ contains the true conditional distributions g_0^r of A, given W^r, for which $(\bar{Q} - \bar{Q}_0)/\bar{g}_0^r$ is a function of W^r. We refer to such distributions as reduced treatment mechanisms. However, it contains many more conditional distributions since any conditional distribution g for which $(A - \bar{g}(W))$ is orthogonal to $(\bar{Q}_0 - \bar{Q})/\bar{g}$ in $L_0^2(P_0)$ is an element of $\mathcal{G}(P_0, Q)$. The general collaborative TMLE introduced in (van der Laan and Gruber, 2010) provides a template for construction of a TMLE $(g_n^*, \bar{Q}_n^*)$ satisfying $P_n D^*(g_n^*, Q_n^*) = 0$ and that converges to a $(g, \bar{Q})$ with $g \in \mathcal{G}(P_0, \bar{Q})$ so that $P_0 D^*(g, Q) = 0$ and thereby $\Psi(Q) - \Psi(Q_0) = 0$. Thus C-TMLE provides a template for construction of targeted MLEs that exploit the collaborative double robustness of TMLEs in the sense that a TMLE will be consistent as long as Q_n^*, g_n^* converge to a (Q, g) for which $g \in \mathcal{G}(P_0, \bar{Q})$. The goal is not to estimate the true treatment mechanism, but instead the goal is to construct a g_n^* that converges to a conditional distribution given a reduction W^r of W that is an element of $\mathcal{G}(P_0, \bar{Q})$. We could state that, just as the propensity score provides a sufficient dimension reduction for the outcome regression, so does, given $\bar{Q}$, $(\bar{Q} - \bar{Q}_0)$ provide a sufficient dimension reduction for the propensity score regression in the TMLE. The current literature appears to agree that propensity score estimators are best evaluated with respect to their effect on estimation of the causal effect of interest, not by metrics such as likelihoods or classification rates (Lee et al., 2009; Schneeweiss et al., 2009; Westreich et al., 2011; Vansteelandt et al., 2010), and the above stated general collaborative double robustness provides a formal foundation for such claims.

The general collaborative targeted maximum likelihood estimator (C-TMLE) has been implemented and applied to point treatment and longitudinal data (Porter et al., 2011; Stitelman and van der Laan, 2010; van der Laan and Gruber, 2010; Gruber and van der Laan, 2010c; Wang et al., 2011; Gruber and van der Laan, 2012a, 2011). A C-TMLE algorithm relies on a TMLE algorithm that maps an initial $(\bar{Q}_n, g_n)$ into a TMLE $(\bar{Q}_n^*, g_n^*)$, and uses this algorithm in combination with a targeted variable selection algorithm for generating candidate models for the propensity score to generate a sequence of candidate TMLEs $(g_n^k, \bar{Q}_n^k)$, increasingly nonparametric in k, and finally uses cross-validation to select the best TMLE among these candidates estimators of $\bar{Q}_0$.

In particular, the CTMLE algorithm in (van der Laan and Gruber, 2010; Gruber and van der Laan, 2010b,c) is tailored to determine a g_n that adjusts for $\bar{Q} - \bar{Q}_0$, where $\bar{Q}$ denotes the limit of the resulting CTMLE of $\bar{Q}_0$. For example, if one runs the CTMLE with initial estimator of $\bar{Q}_0$ the intercept, then the resulting g_n involves adjustment for a function close to $\bar{Q}_0$. Note that the conditional distribution of A, given $\bar{Q}(W), \bar{Q}_0 - \bar{Q}$, is by no means close to the true g_0 that was used in the data generating experiment.

The C-TMLE algorithm can be thought of as a targeted variable selection algorithm for selecting variables in the model for the propensity score, whose resulting fit is then used in the TMLE for $\bar{Q}_0$. This variable selection algorithm avoids selection of instrumental variables but prioritizes the variables that provide the most important bias reduction for the target parameter when the resulting fit of the propensity score is used in the TMLE for $\bar{Q}_0$. It results in estimators of the conditional distribution of A, given W^r, for a function W^r of W. Just as with the IPTW and TMLE analyzed in the previous sections, to establish that the C-TMLE is asymptotically linear at misspecified $\bar{Q}_n^*$, it will be necessary that certain smooth functionals of $\bar{Q}_n^*, \bar{g}_n^*$ are asymptotically linear. This will thus again require a further targeting.

In this section we wish to establish a C-TMLE with known influence curve under regularity conditions, generalizing our theorem in the previous section by also allowing that both $\bar{Q}, \bar{g}$ are misspecified, but $g \in \mathcal{G}(Q, P_0)$. Our next theorem presents a TMLE algorithm and a corresponding influence curve under the assumption that the propensity score correctly adjusts for the possibly misspecified $\bar{Q}$ and $\bar{Q} - \bar{Q}_0$. The presented TMLE algorithm already arranges that this TMLE indeed non parametrically adjusts for $\bar{Q}$. In the next subsection we will present an actual C-TMLE algorithm that generates a TMLE for which the propensity score is targeted to adjust for $\bar{Q} - \bar{Q}_0$, so that this theorem can be applied.

Theorem 4 *Let $O = (W, A, Y)$, and $Y \in \{0, 1\}$ or Y is continuous with values in $(0, 1)$. Let $\mathcal{M}$ be a statistical model for the true distribution of O that only puts restrictions on the conditional distribution g_0 of A, given W. Let $D^*(Q, g)(O) = A/\bar{g}(W)(Y - \bar{Q}(A, W)) + \bar{Q}(1, W) - \Psi(Q)$ be the efficient influence curve of $\Psi : \mathcal{M} \rightarrow \mathbb{R}$ at $P \in \mathcal{M}$, where $Q = (Q_W, \bar{Q})$, Q_W is*

probability distribution of W under P, and $\bar{Q}(W) = E_P(Y \mid A = 1, W)$.
Definitions: *We define*

$$\begin{aligned}
&\bar{Q}_0^r = \bar{Q}_0^r(\bar{g}, \bar{Q}) = E_0(Y - \bar{Q} \mid A = 1, \bar{g}) \\
&\bar{g}_0^r = \bar{g}_0^r(\bar{g}, \bar{Q}) = E_0(A \mid \bar{Q}, \bar{g}) \\
&H_A(\bar{g}, \bar{Q}_0^r) \equiv \tfrac{\bar{Q}_0^r}{\bar{g}} \\
&D_A(\bar{g}, \bar{Q}_0^r) = H_A(\bar{g}, \bar{Q}_0^r)(A - \bar{g}) \\
&H_g(A, W) \equiv \tfrac{A}{\bar{g}} \\
&\bar{Q}_{0,n}^r = E_0(Y - \bar{Q} \mid A = 1, \bar{g}, \bar{g}_n^*) \\
&\bar{g}_{0,n}^r = E_0(A \mid \bar{g}, \bar{Q}, \bar{Q}_n^*) \\
&H(\bar{g}_{0,n}^r, \bar{g}) \equiv \tfrac{\bar{g}_{0,n}^r - \bar{g}}{\bar{g}}.
\end{aligned}$$

Estimators: *Let $\bar{Q}_n^*, \bar{g}_n^*$ be estimators that are consistent for $\bar{Q}$, $\bar{g}$. For any given $\bar{g}, \bar{Q}$, let $\bar{g}_n^r(\bar{g}, \bar{Q})$ and $\bar{Q}_n^r(\bar{g}, \bar{Q})$ be consistent estimators of $\bar{g}_0^r(\bar{g}, \bar{Q})$ and $\bar{Q}_0^r(\bar{g}, \bar{Q})$, respectively (e.g., using a super learner or other nonparametric adaptive regression algorithm). Let $\bar{Q}_n^r = \bar{Q}_n^r(\bar{g}_n^*, \bar{Q}_n^*)$ and $\bar{g}_n^r = \bar{g}_n^r(\bar{g}_n^*, \bar{Q}_n^*)$ denote these estimators applied to $(\bar{g}_n^*, \bar{Q}_n^*)$.*
"Score" equations the TMLE should solve: *Below, we describe an iterative TMLE algorithm that results in estimators $\bar{g}_n^r, \bar{Q}_n^r$, g_n^*, $\bar{Q}_n^*$ that solve the following equations:*

$$\begin{aligned}
0 &= P_n D^*(g_n^*, Q_n^*) \\
0 &= P_n D_A(\bar{g}_n^*, \bar{Q}_n^r)
\end{aligned}$$

Iterative targeted MLE of ψ_0:

Initialization: *Let g_n, $\bar{Q}_n$ be an initial estimator of g, $\bar{Q}$.*

Let $g_n^0 = g_n$, $\bar{Q}_n^0 = \bar{Q}_n$ and let $k = 0$.

Updating step: *Let $\bar{g}_n^{new} = \bar{g}_n^r(\bar{g}_n^k, \bar{Q}_n^k)$ be obtained by non parametrically regressing A on $\bar{Q}_n^k, \bar{g}_n^k$. Let $\bar{Q}_n^{r,k} = \bar{Q}_n^r(\bar{g}_n^k, \bar{Q}_n^k)$ be obtained by non parametrically regressing $Y - \bar{Q}_n^k$ on $A = 1, \bar{g}_n^k$. Redefine $g_n^k = \bar{g}_n^{new}$.*

Consider the submodel $Logit\bar{g}_n^k(\epsilon) = Logit\bar{g}_n^k + \epsilon H_A(\bar{g}_n^k, \bar{Q}_n^{r,k})$, and fit ϵ with the MLE

$$\epsilon_{A,n} = \arg\max_{\epsilon} P_n \log g_n^k(\epsilon).$$

Let $-L(\bar{Q})(O) = Y \log \bar{Q}(A, W) + (1 - Y) \log(1 - \bar{Q}(A, W))$ be the log-likelihood loss for $\bar{Q}_0$. Define the submodel $Logit\bar{Q}_n^k(\epsilon) = Logit\bar{Q}_n^k + \epsilon_1 H_{g_n^k}$. Let $\epsilon_{Y,n} = \arg\max_\epsilon P_n L(\bar{Q}_n^k(\epsilon))$ be the MLE.

We define $g_n^{k+1} = g_n^k(\epsilon_{A,n})$ as the corresponding targeted update of g_n^k, and $\bar{Q}_n^{k+1} = \bar{Q}_n^k(\epsilon_{Y,n})$ as the corresponding update of $\bar{Q}_n^k$.

Iterating till convergence: *Now, set $k = k + 1$, and iterate this updating process mapping a $(g_n^k, \bar{Q}_n^k)$ into $(g_n^{k+1}, \bar{Q}_n^{k+1})$ till convergence or till large enough K so that the following estimating equations are solved up till an $o_P(1/\sqrt{n})$-term:*

$$\begin{aligned} o_P(1/\sqrt{n}) &= P_n D^*(g_n^k, Q_n^k) \\ o_P(1/\sqrt{n}) &= P_n D_A(\bar{g}_n^k, \bar{Q}_n^{r,k}). \end{aligned}$$

Final substitution estimator: *Denote these limits of this iterative procedure with $\bar{Q}_n^r, \bar{g}_n^r, g_n^*, \bar{Q}_n^*, \gamma_n^*$, where $\bar{g}_n^r = \bar{g}_n^*$ at convergence. Let $Q_n^* = (Q_{W,n}, \bar{Q}_n^*)$, where $Q_{W,n}$ is the empirical distribution estimator of $Q_{W,0}$. The TMLE of ψ_0 is defined as $\Psi(Q_n^*)$.*

Assumption on limit $\bar{g}$ of $\bar{g}_n^*$: *We assume that $\bar{g}(W) = E_0(A \mid W^r)$ for some function $W^r(W)$ of W for which $\bar{Q}, (\bar{Q}_0 - \bar{Q})(W)$ is a function of W^r: i.e., $\bar{g}_n^*$ involves nonparametric adjustment by $\bar{Q}, \bar{Q}_0$. As a consequence, $\bar{g}_0^r = \bar{g}$.*

Empirical process condition: *Assume that $D^*(g_n^*, Q_n^*)$, $D_A(\bar{g}_n^*, \bar{Q}_n^r)$ fall in a P_0-Donsker class with probability tending to 1 as $n \to \infty$.*

Consistency condition: *Assume that $\bar{Q}_n^r, \bar{g}_n^r, \bar{g}_n^*, \bar{Q}_n^*$ are consistent for $\bar{Q}_0^r, \bar{g}_0^r, \bar{g}, \bar{Q}$, where $\bar{g}_0^r = \bar{g}$, in the following sense:*

$$\begin{aligned} P_0\{D^*(g_n^*, Q_n^*) - D^*(g, Q)\}^2 &= o_P(1) \\ P_0\{D_A(\bar{g}_n^*, \bar{Q}_n^r) - D_A(\bar{g}, \bar{Q}_0^r\}^2 &= o_P(1) \end{aligned}$$

Second order conditions: *Define $H_1(\bar{g}_n^*) \equiv E_0(\bar{Q} - Y \mid A = 1, \bar{g}, \bar{g}_n^*) \frac{E_0(A \mid \bar{g}, \bar{g}_n^*)}{\bar{g}^2}$. We assume*

$$\begin{aligned} &P_0(\bar{Q} - \bar{Q}_0)(\bar{g} - \bar{g}_0)\tfrac{(\bar{g}_n^* - \bar{g})^2}{\bar{g}^2 \bar{g}_n^*} = o_P(1/\sqrt{n}) \\ &P_0(H_1(\bar{g}_n^*) - H_1(\bar{g}))(\bar{g}_n^* - \bar{g}) = o_P(1/\sqrt{n}) \\ &P_0(\bar{Q}_n^* - \bar{Q})\tfrac{(\bar{g}_n^* - \bar{g})}{\bar{g}} = o_P(1/\sqrt{n}) \\ &P_0\tfrac{(\bar{Q}_{0,n}^r - \bar{Q}_0^r)}{\bar{g}}(\bar{g}_n^* - \bar{g}) = o_P(1/\sqrt{n}) \\ &P_0(H_A(\bar{g}_n^*, \bar{Q}_n^r) - H_A(\bar{g}, \bar{Q}_0^r))(\bar{g}_n^* - \bar{g}) = o_P(1/\sqrt{n}) \\ &P_0\tfrac{(\bar{g}_{0,n}^r - \bar{g})}{\bar{g}}(\bar{Q}_n^* - \bar{Q}) = o_P(1/\sqrt{n}). \end{aligned}$$

Then,

$$\Psi(Q_n^*) - \Psi(Q_0) = (P_n - P_0)IC(P_0) + o_P(1/\sqrt{n}),$$

where

$$IC(P_0) = D^*(g, Q) - D_A(\bar{g}, \bar{Q}_0^r).$$

Note that consistent estimation of the influence curve $IC(P_0)$ relies on consistency of $\bar{Q}_n^r$ as an estimator of $\bar{Q}_0^r$, and estimators $\bar{Q}_n^*, \bar{g}_n^*$ converging to a $\bar{Q}, \bar{g} = \bar{g}_0^r$ for which $\bar{g}$ equals a true conditional mean of A, given W^r, and $\bar{Q}_0 - \bar{Q}, \bar{Q}$ only depend on W through W^r.

5.1 A C-TMLE algorithm

The TMLE algorithm presented in Theorem 4 maps an initial estimator Q_n^0, g_n^0 into an updated estimator Q_n^*, g_n^* that solves the two estimating equations, allowing for statistical inference with known influence curve. The updating algorithm results in a g_n^* that non-parametrically adjusts for $\bar{Q}_n^*$ itself, and thus for its limit $\bar{Q}$ in the limit. The condition on the limit g was that it should not only non parametrically adjust for $\bar{Q}$ but also for $\bar{Q} - \bar{Q}_0$. If the initial estimator g_n^0 already adjusted for an approximation of $\bar{Q}_n^0 - \bar{Q}_0$, for example, g_n^0, Q_n^0 is already a C-TMLE, then this condition might hold approximately. Nonetheless, we want to present a C-TMLE algorithm that simultaneously fits g in response to $\bar{Q} - \bar{Q}_0$, but also carries out the nonparametric adjustment by $\bar{Q}$. The latter is normally not part of the C-TMLE algorithm, but we want to enforce this in order to be able to apply Theorem 3. We achieve this goal in this subsection by applying the C-TMLE algorithm as presented in van der Laan and Gruber (2009) to the particular TMLE-algorithm presented in Theorem 4.

Firstly, we compute a set of K univariate covariates $W_1, \ldots, W_K$, i.e., functions of W, which we will refer to as main terms, even though a term could be an interaction term or a super learning fit of the regression of A on a subset of the components of W. Let $\Omega = \{W_1, \ldots, W_K\}$ be the full collection of main terms. In the previous subsection we defined an algorithm that maps an initial (Q, g) into a TMLE (Q^*, g^*). Let $L(Q)(O)$ be the loss function for Q_0.

Globally, given a TMLE algorithm that maps any initial (Q, g) into a TMLE (Q^*, g^*), the C-TMLE algorithm generates a sequence of increasing sets $\mathcal{S}^k \subset \Omega$ of k main terms, where each set $\mathcal{S}^k$ has an associated estimator g^k of g_0, and simultaneously it generates a corresponding sequence of Q^k, $k = 1, \ldots, K$. This sequence (g^k, Q^k) maps into a corresponding sequence of TMLEs (g^{k*}, Q^{k*}) that is increasingly nonparametric in k, $k = 1, \ldots, K$, using the TMLE-algorithm presented in Theorem 4.

In this variable selection algorithm the choice of the next main term to add, mapping $\mathcal{S}^k$ into $\mathcal{S}^{k+1}$, is based on how much the TMLE using the g-fit implied by $\mathcal{S}^{k+1}$, using Q^k as initial estimator, improves the fit of the corresponding TMLE Q^{k*} for Q_0. Cross-validation is used to select k among these candidate TMLEs Q^{k*}, $k = 1, \ldots, K$, where the last TMLE Q^{K*} uses the most aggressive bias reduction by being based on the most nonparametric estimator g^K implied by Ω.

In order to present a precise C-TMLE algorithm we will first introduce some notation. For a given subset of main terms $\mathcal{S} \subset \Omega$, let $\mathcal{S}^c$ be its complement within Ω. In the C-TMLE algorithm we use a forward selection algorithm that augments a given set $\mathcal{S}^k$ into a next set $\mathcal{S}^{k+1}$ obtained by adding the best main term among all main terms in the complement $\mathcal{S}^{k,c}$ of $\mathcal{S}^k$. Each choice $\mathcal{S}$ corresponds with an estimator of g_0. In other words, the algorithm iteratively updates a current estimate g^k into a new estimate g^{k+1}, but the criterion for g does not measure how well g fits g_0; it measures how well the TMLE of Q_0 that uses this g (and as initial estimator Q^k) fits Q_0.

Given a set $\mathcal{S}^k$, an initial g^{k-1}, Q^{k-1}, we define a corresponding g^k obtained by fitting

$$\text{Logit}\bar{g}^k = \text{Logit}\bar{g}^r(\bar{g}^{k-1}, \bar{Q}^{k-1}) + \sum_{j \in \mathcal{S}^k} \beta_j W_j.$$

Thus, this estimator g^k involves nonparametric adjustment by $\bar{g}^{k-1}, \bar{Q}^{k-1}$, augmented with a linear regression component implied by $\mathcal{S}^k$. This function mapping $\mathcal{S}^k, g^{k-1}, Q^{k-1}$ into a fit g^k will be denoted with $g(\mathcal{S}^k, g^{k-1}, Q^{k-1})$. This also allows us to define a mapping from $(Q^k, \mathcal{S}^k, Q^{k-1}, g^{k-1})$ into a TMLE (Q^{k*}, g^{k*}) defined by the TMLE algorithm of Theorem 4 applied to initial Q^k and $g^k = g(\mathcal{S}^k, g^{k-1}, Q^{k-1})$. We will denote this mapping into Q^{k*} with TMLE$(Q^k, \mathcal{S}^k, Q^{k-1}, g^{k-1})$.

The C-TMLE algorithm defined below generates a sequence $(Q^k, \mathcal{S}^k)$ and thereby corresponding TMLEs (Q^{k*}, g^{k*}), $k = 0, \ldots, K$, where Q^k represents an initial estimate, $\mathcal{S}^k$ a subset of main terms that defines g^k, and Q^{k*}, g^{k*} the corresponding TMLE that starts with (Q^k, g^k). These TMLEs Q^{k*} represent subsequent updates of the initial estimator Q^0. The corresponding main term set $\mathcal{S}^k$ that defines g^k in this k-specific TMLE, increases in k, one unit at a time: $\mathcal{S}^0$ is empty, $\mid \mathcal{S}^{k+1} \mid = \mid \mathcal{S}^k \mid +1$, $\mathcal{S}^K = \Omega$. The C-TMLE uses cross-validation to select k, and thereby to select the TMLE Q^{k*} that yields the best fit of Q_0 among the $K+1$ k-specific TMLEs $(Q^{k*} : k = 0, \ldots, K)$ that are increasingly aggressive in their bias-reduction effort. This C-TMLE algorithm is defined as follows, and uses the same format as presented in (Wang et al., 2011):

Initiate algorithm: Set initial TMLE. Let $k = 0$, and $Q^k = Q^0$, g^{start} be an initial estimate of Q_0, g_0, and let $\mathcal{S}^0$ be the empty set. Let $g^k = g(\mathcal{S}^0, Q^0, g^{start})$. This defines an initial TMLE $Q^{0*} = \text{TMLE}(Q^0, \mathcal{S}^0, Q^0, g^0)$.

Determine next TMLE. Determine the next best main term to add:

$$\mathcal{S}^{k+1,cand} = \arg \min_{\{\mathcal{S}^k \cup W_j : W_j \in \mathcal{S}^{k,c}\}} P_n L(\text{TMLE}(Q^k, \mathcal{S}^k \cup W_j, Q^{k-1}, g^{k-1})).$$

If

$$P_n L(\text{TMLE}(Q^k, \mathcal{S}^{k+1,cand}, Q^{k-1}, g^{k-1})) \leq P_n L(Q^{k*}),$$

then $(\mathcal{S}^{k+1} = \mathcal{S}^{k+1,cand}, Q^{k+1} = Q^k)$, else $Q^{k+1} = Q^{k*}$, and

$$\mathcal{S}^{k+1} = \arg \min_{\{\mathcal{S}^k \cup W_j : W_j \in \mathcal{S}^{k,c}\}} P_n L(\text{TMLE}(Q^{k*}, \mathcal{S}^k \cup W_j, Q^{k-1}, g^{k-1})).$$

[In words: If the next best main term added to the fit of $E_0(A \mid W)$ yields a TMLE of $E_0(Y \mid A, W)$ that improves upon the previous TMLE Q^{k*}, then we accept this best main term, and we have our next $(Q^{k+1}, \mathcal{S}^{k+1})$ and corresponding TMLE Q^{k+1*}, g^{k+1*} (which still uses the same initial estimate of Q_0 as Q^{k*} uses). Otherwise, reject this best main term, update the initial estimate in the candidate TMLEs to the previous TMLE Q^{k*} of $E_0(Y \mid A, W)$, and determine the best main term to add again. This best main term will now always result in an improved fit of the corresponding TMLE of Q_0, so that we now have our next TMLE Q^{k+1*}, g^{k+1} (which now uses a different initial estimate than Q^{k*} used).]

Iterate. Run this from $k = 1$ to K at which point $\mathcal{S}^K = \Omega$. This yields a sequence (Q^k, g^k) and corresponding TMLE Q^{k*}, $k = 0, \ldots, K$.

This sequence of candidate TMLEs Q^{k*} of Q_0 has the following property: the estimates g^k are increasingly nonparametric in k and $P_n L(Q^{k*})$ is decreasing in k, $k = 0, \ldots, K$. It remains to select k. For that purpose we use V-fold cross-validation. That is, for each of the V splits of the sample in a training and validation sample, we apply the above algorithm for generating a sequence of candidate estimates $(Q^{k*} : k)$ to a training sample, and we evaluate the empirical mean of the loss function at the resulting Q^{k*} over the validation sample, for each $k = 0, \ldots, K$. For each k we take the average over the V-splits of the k-specific performance measure over the validation sample, which is called the cross-validated risk of the k-specific TMLE. We select the k that has the best cross-validated risk, which we denote with k_n. Our final C-TMLE of Q_0 is now defined as $Q_n^* = Q^{k_n*}$, and the TMLE of ψ_0 is defined as $\psi_n^* = \Psi(Q_n^*)$.

Fast version of above C-TMLE: We could carry out the above C-TMLE algorithm but replacing the TMLE that maps an initial (Q, g) into Q^*, g^* replaced by the first-step of the TMLE that maps (Q, g) into Q^1, g^1. In that manner, the selection of the sets $\mathcal{S}^k$ is based on the bias reduction achieved in a first step of the TMLE algorithm, and most bias reduction occurs in the first step. After having selected the final one-step TMLE $Q^{k_n 1}$ and corresponding g^{k_n}, one should still carry out the full TMLE algorithm so that the final $Q_n^* = Q^{k_n*}, g^{k_n*}$ is a real TMLE solving the estimating equations of Theorem 4.

Statistical inference for C-TMLE: Let $\bar{Q}_n^r = \bar{Q}_n^r(\bar{g}_n^*, \bar{Q}_n^*)$ be the final estimator of $\bar{Q}_0^r = \bar{Q}_0^r(\bar{g}, \bar{Q}) = E_0(Y - \bar{Q} \mid A = 1, \bar{g})$, a by-product of the TMLE-algorithm. Let $H_A(\bar{g}_n^*, \bar{Q}_n^r) = \frac{\bar{Q}_n^r(W)}{\bar{g}_n^*(W)}$, and $D_A(\bar{g}_n, \bar{Q}_n^r) = H_A(\bar{g}_n^*, \bar{Q}_n^r)(W)(A - \bar{g}_n^*(W))$. An estimate of the influence curve of ψ_n^* is now given by

$$IC_n = D^*(Q_n^*, \bar{g}_n^*) - D_A(\bar{g}_n^*, \bar{Q}_n^r).$$

The asymptotic variance of $\sqrt{n}(\psi_n^* - \psi_0)$ can thus be estimated with $\sigma_n^2 = 1/n \sum_{i=1}^n IC_n(O_i)^2$. An asymptotically valid 0.95-confidence interval for ψ_0 is given by $\psi_n^* \pm 1.96\sigma_n^*/\sqrt{n}$.

6 Discussion

Targeted minimum loss-based estimation allows us to construct plug-in estimators $\Psi(Q_n^*)$ of a path-wise differentiable parameter $\Psi(Q_0)$ utilizing the state of the art in ensemble learning such as super-learning, while guaranteeing that the estimator Q_n^*, and an estimator g_n^* of the nuisance parameter the TMLE utilizes in its targeting step, solve a set of user-supplied estimating equations, empirical means of estimating functions. These estimating functions can be selected so that the resulting TMLE of ψ_0 has certain statistical properties such as being efficient, or guaranteed to be more efficient than a given user supplied estimator (Rotnitzky et al., 2012; Gruber and van der Laan, 2012b), and so on. However, most importantly, these estimating equations are necessary to make the TMLE asymptotically linear, i.e. to make the TMLE unbiased enough so that the first order linear expansion can be used for statistical inference. For example, by selecting the estimating functions to be equal to the canonical gradient of $\Psi : \mathcal{M} \to \mathbb{R}$ one arranges that $\Psi(Q_n^*)$ is asymptotically efficient under conditions that assume consistency of Q_n^* and g_n^*.

However, we noted that this level of targeting is insufficient if one only relies on consistency of g_n^*, even when that suffices for consistency of $\Psi(Q_n^*)$. Under such weaker assumptions, additional targeting is necessary so that a specific smooth functional of g_n^* is asymptotically linear, which requires that that smooth function of g_n^* is itself a TMLE. The joint targeting of Q_n^* and g_n^* is achieved by a TMLE that solves these extra equations, allowing one to establish asymptotic linearity of $\Psi(Q_n^*)$ under milder conditions that assume that the second order terms are negligible relative to the first order linear approximation.

In this article we also pushed this additional level of targeting to a new level by demonstrating how it allows for double robust statistical inference, and that even if we estimate the nuisance parameter in a complicated manner that is based on a criterion that cares about how it helps the estimator to fit ψ_0, as used by the C-TMLE, we can still determine a set of additional estimating equations that need to be targeted by the TMLE in order to establish asymptotic linearity and thereby valid statistical inference based on the central limit theorem. This allows us now to use the sophisticated but often necessary C-TMLE while still preserving valid statistical inference under regularity conditions.

It remains to evaluate the practical benefit of the modifications of TMLE and C-TMLE as presented in this article. We plan to address this in future research. At least, we feel that it is useful to now have an actual influence curve for C-TMLE while in our general theorems so far (see e.g., Appendix van der Laan and Rose (2011)) our suggested influence curve relied on the influence curve of a smooth functional of Q_n^* that is typically unknown to the user if Q_n^* was a complicated estimator.

Even though we focussed in this article on a particular concrete estimation problem, TMLE is a general tool and our theorems can be generalized to general statistical models and path-wise differentiable statistical target parameters.

We note that this targeting of nuisance parameter estimators in the TMLE is not only necessary to get a known influence curve, but it is necessary to make the TMLE asymptotically linear. So it does not simply suffice to run a bootstrap as an alternative of influence curve based inference, since the bootstrap only works if the estimator is asymptotically linear so that it has an existing limit distribution. In addition, the established asymptotic linearity with known influence curve has the important by-product that one now obtains statistical inference with no extra computational cost. This is particularly important in these large semi-parametric models that require the utilization of aggressive machine learning methods in order to cover the model-space, making the estimators by necessity very computer intensive, so that a bootstrap method might simply be too computer extensive.

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Appendix

Proof of Theorem 1.

To start with we note:

$$\begin{aligned}&P_nD(g_n^*) - P_0D(g_0) = (P_n - P_0)D(g_0) + P_n(D(g_n^*) - D(g_0))\\&= (P_n - P_0)(D(g_0) - \psi_0) + P_0(D(g_n^*) - D(g_0)) + (P_n - P_0)(D(g_n^*) - D(g_0)).\end{aligned}$$

Since g_n^* falls in Donsker class the last second term is $o_P(1/\sqrt{n})$ if $P_0(D(g_n^*) - D(g_0))^2 \to 0$ in probability. So it remains to analyze $P_0(D(g_n) - D(g_0))$. We now note

$$\begin{aligned}&P_0YA\{1/g_n^* - 1/g_0\} = P_0YA\{(g_0 - g_n^*)/(g_n^* g_0)\}\\&= P_0YA\{g_0 - g_n^*\}/g_0^2 + P_0YA\{g_0 - g_n^*)^2\}/(g_0^2 g_n^*).\end{aligned}$$

We assumed that the last term

$$P_0YA\{g_0 - g_n^*)^2/g_0^2 g_n^* = P_0\bar{Q}_0(\bar{g}_n^* - \bar{g}_0)^2/(\bar{g}_0\bar{g}_n^*) = o_P(1/\sqrt{n}).$$

So it remains to study:

$$P_0 YA\{g_0 - g_n^*\}/g_0^2 = P_0\bar{Q}_0(\bar{g}_0 - \bar{g}_n^*)/\bar{g}_0.$$

We now use the following lemma.

Lemma 1 *Define* $\bar{Q}_{0,n}^r \equiv E_0(Y \mid A = 1, \bar{g}_0(W), \bar{g}_n^*(W))$, $\bar{Q}_0^r = E_0(Y \mid A = 1, \bar{g}_0(W))$, *where* $\bar{g}_n^*(W)$ *is treated as a fixed function of* W *when calculating the conditional expectation. Assume*

$$R_{1,n} \equiv P_0(\bar{Q}_{0,n}^r - \bar{Q}_0^r)(\bar{g}_0 - \bar{g}_n^*)/\bar{g}_0 = o_P(1/\sqrt{n}).$$

Define $\Psi_1(g) = P_0\frac{\bar{Q}_0}{\bar{g}_0}\bar{g}$. *Define* $\Psi_1^r(g) = P_0\frac{\bar{Q}_0^r}{\bar{g}_0}\bar{g}$. *Then,*

$$\begin{aligned}\Psi_1(g_n^*) - \Psi_1(g_0) &= P_0\bar{Q}_0(\bar{g}_n^* - \bar{g}_0)/\bar{g}_0\\ &= P_0\bar{Q}_0^r(\bar{g}_n^* - \bar{g}_0)/\bar{g}_0 + P_0(\bar{Q}_{0,n}^r - \bar{Q}_0^r)(\bar{g}_n^* - \bar{g}_0)/\bar{g}_0\\ &= \Psi_1^r(\bar{g}_n^*) - \Psi_1^r(\bar{g}_0) + R_{1,n}.\end{aligned}$$

Proof of Lemma 1: Note that

$$\begin{aligned}\Psi_1(g_n^*) - \Psi_1(g_0) &= P_0 YA\{g_0 - g_n^*\}/g_0^2\\ &= P_0\bar{Q}_{0,n}^r A\{g_0 - g_n^*\}/g_0^2\\ &= P_0\bar{Q}_{0,n}^r(\bar{g}_0 - \bar{g}_n^*)/\bar{g}_0\\ &= P_0\bar{Q}_0^r(\bar{g}_0 - \bar{g}_n^*)/\bar{g}_0 + P_0(\bar{Q}_{0,n}^r - \bar{Q}_0^r)(\bar{g}_0 - \bar{g}_n^*)/\bar{g}_0.\square\end{aligned}$$

Thus, it remains to prove that $\Psi_1^r(g_n^*) - \Psi_1^r(g_0) = P_0\bar{Q}_0^r(\bar{g}_0 - \bar{g}_n^*)/\bar{g}_0$ is asymptotically linear. Let $D_H(g) = H(W)(A - \bar{g}(W))$, and let $H_0^r = \bar{Q}_0^r/\bar{g}_0$. Let $H_n^r = \bar{Q}_n^r/\bar{g}_n^*$, where $\bar{Q}_n^r$ is obtained by regressing Y on $\bar{g}_n(W)$ (initial estimator $\bar{g}_n^*$ is based on) and $A = 1$. We have $P_n D_{H_n^r}(\bar{g}_n^*) = 1/n\sum_i H_n^r(W_i)(A_i - \bar{g}_n^*(W_i)) = 0$. Thus,

$$\begin{aligned}&P_0 D_{H_n^r}(\bar{g}_n^*) = P_0(D_{H_n^r} - D_{H_0^r})(\bar{g}_n^*) + P_0 D_{H_0^r}(\bar{g}_n^*)\\ &= \int(H_n^r - H_0^r)(W)(A - \bar{g}_n^*(W))dP_0(W, A) + P_0 D_{H_0^r}(\bar{g}_n^*)\\ &= \int(H_n^r - H_0^r)(W)(\bar{g}_0 - \bar{g}_n^*)(W)dP_0(W) + P_0 D_{H_0^r}(\bar{g}_n^*)\\ &\equiv R_{2,n} + P_0 D_{H_0^r}(\bar{g}_n^*).\end{aligned}$$

We now note that

$$\begin{aligned}&P_0 D_{H_0^r}(\bar{g}_n^*) = \int H_0^r(W)(A - \bar{g}_n^*(W))dP_0(A, W)\\ &= \int H_0^r(W)\bar{g}_0(W)dP_0(W) - \int H_0^r(W)\bar{g}_n^*(W)dP_0(W)\\ &\equiv \Psi_1^r(\bar{g}_0) - \Psi_1^r(\bar{g}_n^*).\end{aligned}$$

Thus, we have

$$-P_0 D_{H_n^r}(\bar{g}_n^*) = \Psi_1^r(\bar{g}_n^*) - \Psi_1^r(\bar{g}_0) - R_{2,n}.$$

Thus,

$$\begin{aligned} \Psi_1^r(\bar{g}_n^*) - \Psi_1^r(\bar{g}_0) &= -P_0 D_{H_n^r}(\bar{g}_n^*) + R_{2,n} \\ &= (P_n - P_0) D_{H_n^r}(\bar{g}_n^*) + R_{2,n} \\ &= (P_n - P_0) D_{H_0^r}(\bar{g}_0) + R_{2,n} + R_{3,n}, \end{aligned}$$

where we defined

$$R_{3,n} = (P_n - P_0)(D_{H_n^r}(\bar{g}_n^*) - D_{H_0^r}(\bar{g}_0)).$$

This yields the following lemma.

Lemma 2 *Define $\Psi_1(g) = \int H_0(W)\bar{g}(W)dP_0(W)$, where $H_0 = \bar{Q}_0(W)/\bar{g}_0(W)$. Let $\Psi_1^r(g) = \int H_0^r(W)\bar{g}(W)dP_0(W)$, where $H_0^r = \bar{Q}_0^r(W)/\bar{g}_0(W)$. Let g_n^* satisfy $P_n D_{H_n^r}(\bar{g}_n^*) = 0$, where $H_n^r = \bar{Q}_n^r/\bar{g}_n$ for some estimator g_n (not necessarily equal to g_n^*) and estimator $\bar{Q}_n^r$ of $E_0(Y \mid A = 1, \bar{g}_0(W))$. Assume that*

$$\begin{aligned} R_{1,n} &\equiv P_0(\bar{Q}_n^r - \bar{Q}_0^r)(\bar{g}_0 - \bar{g}_n^*)/\bar{g}_0 = o_P(1/\sqrt{n}) \\ R_{2,n} &= P_0(H_n^r - H_0^r)(\bar{g}_0 - \bar{g}_n^*) = o_P(1/\sqrt{n}) \\ R_{3,n} &= (P_n - P_0)\{D_{H_n^r}(\bar{g}_n^*) - D_{H_0^r}(\bar{g}_0)\} = o_P(1/\sqrt{n}). \end{aligned}$$

Then,

$$\Psi_1(g_n^*) - \Psi_1(g_0) = (P_n - P_0) D_{H_0^r}(\bar{g}_0) + R_{1,n} + R_{2,n} + R_{3,n}.$$

Under the conditions on $\bar{Q}_n^r$, g_n and g_n^* that $R_{1,n}, R_{2,n}, R_{3,n}$ are all $o_P(1/\sqrt{n})$, we now have that $\Psi_1(g_n^*) - \Psi_1(g_0) = (P_n - P_0) D_{H_0^r}(\bar{g}_0)$. This completes the proof of the theorem. □

Proof of Theorem 2.

We have

$$\begin{aligned} &\Psi(Q_n^*) - \Psi(Q_0) = -P_0 D^*(Q_n^*, g_0) \\ &= -P_0 D^*(Q_n^*, g_n^*) + P_0\{D^*(Q_n^*, g_n^*) - D(Q_n^*, g_0)\} \\ &= (P_n - P_0) D^*(Q_n^*, g_n^*) + P_0\{D^*(Q_n^*, g_n^*) - D(Q_n^*, g_0)\}. \end{aligned}$$

If $D^*(Q_n^*, g_n^*)$ falls in a P_0-Donsker class and $P_0\{D^*(Q_n^*, g_n^*) - D^*(Q, g_0)\}^2 = o_P(1)$, then the first term on the right-hand side equals $(P_n - P_0)D^*(Q, g_0) + o_P(1/\sqrt{n})$. The second term can be written as

$$P_0\left(\{D^*(Q_n^*, g_n^*) - D^*(Q_n^*, g_0)\} - \{D^*(Q, g_n^*) - D^*(Q, g_0)\}\right) + P_0\{D^*(Q, g_n^*) - D^*(Q, g_0)\}.$$

The first term equals

$$P_0(H_{g_n^*} - H_{g_0})(\bar{Q}_n^* - \bar{Q}),$$

where $H_g(A, W) = A/\bar{g}(W)$. We assumed that this term is $o_P(1/\sqrt{n})$. Thus, it remains to establish asymptotic linearity of $\Psi_1(g_n^*) = P_0 D^*(Q, g_n^*)$ as an estimator of $\Psi_1(g_0) = P_0 D^*(Q, g_0)$. We have

$$\begin{aligned}
&\Psi_1(g_n^*) - \Psi_1(g_0) = -P_0(Y - \bar{Q})\tfrac{A}{\bar{g}_n^* \bar{g}_0}(\bar{g}_n^* - \bar{g}_0) \\
&= -P_0 \bar{Q}_{0,n}^r \tfrac{A}{\bar{g}_n^* \bar{g}_0}(\bar{g}_n^* - \bar{g}_0) \\
&= -P_0 \bar{Q}_{0,n}^r \tfrac{1}{\bar{g}_n^*}(\bar{g}_n^* - \bar{g}_0).
\end{aligned}$$

Let $H_{0,n}^r = \bar{Q}_{0,n}^r/\bar{g}_n^*$ and $H_0^r = \bar{Q}_0^r/\bar{g}_0$, where $\bar{Q}_0^r = E_0(Y - \bar{Q}(W) \mid A = 1, \bar{g}_0(W))$. The last term can be written as

$$-P_0 H_0^r(\bar{g}_n^* - \bar{g}_0) - P_0(H_{0,n}^r - H_0^r)(\bar{g}_n^* - \bar{g}_0).$$

We assumed that the second term is $o_P(1/\sqrt{n})$. Thus, in order to establish asymptotic linearity of $\Psi_1(g_n^*)$, it remains to establish asymptotic linearity of $\Psi_1^r(\bar{g}_n^*) = P_0 H_0^r \bar{g}_n^*$ as an estimator of $\Psi_1^r(\bar{g}_0) = P_0 H_0^r \bar{g}_0$.

Let $D_H(g) = H(W)(A - \bar{g}(W))$. Let $H_n^r = \bar{Q}_n^r/\bar{g}_n^*$. Our targeted estimator g_n^* solves $P_n D_{H_n^r}(\bar{g}_n^*) = 1/n \sum_i H_n^r(W_i)(A_i - \bar{g}_n^*(W_i)) = 0$. We now note that

$$\begin{aligned}
&P_0 D_{H_0^r}(\bar{g}_n^*) = \int H_0^r(W)(A - \bar{g}_n^*(W))dP_0(A, W) \\
&= \int H_0^r(W)\bar{g}_0(W)dP_0(W) - \int H_0^r(W)\bar{g}_n^*(W)dP_0(W) \\
&\equiv \Psi_1^r(\bar{g}_0) - \Psi_1^r(\bar{g}_n^*).
\end{aligned}$$

Thus, we can focus on establishing the asymptotic linearity of $P_0 D_{H_0^r}(\bar{g}_n^*)$. We have

$$\begin{aligned}
&P_0 D_{H_n^r}(\bar{g}_n^*) = P_0(D_{H_n^r} - D_{H_0^r})(\bar{g}_n^*) + P_0 D_{H_0^r}(\bar{g}_n^*) \\
&= \int (H_n^r - H_0^r)(W)(A - \bar{g}_n^*(W))dP_0(W, A) + P_0 D_{H_0^r}(\bar{g}_n^*) \\
&= \int (H_n^r - H_0^r)(W)(\bar{g}_0 - \bar{g}_n^*(W))dP_0(W) + P_0 D_{H_0^r}(\bar{g}_n^*) \equiv R_{2,n} + P_0 D_{H_0^r}(\bar{g}_n^*),
\end{aligned}$$

where $R_{2,n} = o_P(1/\sqrt{n})$, by assumption. Thus, we have

$$-P_0 D_{H_n^r}(\bar{g}_n^*) = \Psi_1^r(\bar{g}_n^*) - \Psi_1^r(\bar{g}_0) + R_{2,n}.$$

We now proceed as follows:

$$\begin{aligned}
\Psi_1^r(\bar{g}_n^*) - \Psi_1^r(\bar{g}_0) &= -P_0 D_{H_n^r}(\bar{g}_n^*) - R_{2,n} \\
&= (P_n - P_0)D_{H_n^r}(\bar{g}_n^*) - R_{2,n} \\
&= (P_n - P_0)D_{H_0^r}(\bar{g}_0) - R_{2,n} + R_{3,n},
\end{aligned}$$

where we defined

$$R_{3,n} = (P_n - P_0)(D_{H_n^r}(\bar{g}_n^*) - D_{H_0^r}(\bar{g}_0)).$$

We have that $R_{3,n} = o_P(1/\sqrt{n})$ if $D_{H_n^r}(\bar{g}_n^*) - D_{H_0^r}(\bar{g}_0)$ falls in a P_0-Donsker class with probability tending to 1, and $P_0\{D_{H_n^r}(\bar{g}_n^*) - D_{H_0^r}(\bar{g}_0)\}^2 \to 0$ in probability as $n \to \infty$. Thus we have proven that $\Psi_1(g_n^*) - \Psi_1(g_0) = -(P_n - P_0)D_{H_0^r}(\bar{g}_0)$. This completes the proof of the theorem. $\Box$

Proof of Theorem 3.

If $P_n D^*(Q_n^*, g_n^*) = 0$, then

$$\begin{aligned}
&\Psi(Q_n^*) - \Psi(Q_0) = -P_0 D^*(Q_n^*, g_n^*) + P_0(\bar{Q}_0 - \bar{Q}_n^*)\tfrac{\bar{g}_0 - \bar{g}_n^*}{\bar{g}_n^*} \\
&= (P_n - P_0)D^*(Q_n^*, g_n^*) + P_0(\bar{Q}_0 - \bar{Q}_n^*)\tfrac{\bar{g}_0 - \bar{g}_n^*}{\bar{g}_n^*} \\
&= (P_n - P_0)D^*(Q, g) + P_0(\bar{Q}_n^* - \bar{Q}_0)\tfrac{\bar{g}_n^* - \bar{g}_0}{\bar{g}_n^*} + o_P(1/\sqrt{n}).
\end{aligned}$$

Here we used that the latter term is indeed $o_P(1/\sqrt{n})$, if $D^*(Q_n^*, g_n^*)$ falls in a Donsker class with probability tending to 1, and $P_0\{D^*(Q_n^*, g_n^*) - D^*(Q, g)\}^2 \to 0$ in probability as $n \to \infty$.

It remains to analyze the second term. Firstly, we note that

$$P_0(\bar{Q}_0 - \bar{Q}_n^*)\frac{\bar{g}_0 - \bar{g}_n^*}{\bar{g}_n^*} = P_0(\bar{Q}_0 - \bar{Q}_n^*)\frac{\bar{g}_0 - \bar{g}_n^*}{\bar{g}} + R_{1,n},$$

where

$$R_{1,n} = P_0(\bar{Q}_n^* - \bar{Q}_0))(\bar{g}_n^* - \bar{g}_0)\frac{\bar{g}_n^* - \bar{g}}{\bar{g}\bar{g}_n^*}.$$

We assumed that $R_{1,n} = o_P(1/\sqrt{n})$.

Now, we note

$$\begin{aligned}
&P_0(\bar{Q}_n^* - \bar{Q}_0)\tfrac{\bar{g}_n^* - \bar{g}_0}{\bar{g}} = P_0(\bar{Q}_n^* - \bar{Q} + \bar{Q} - \bar{Q}_0)\tfrac{\bar{g}_n^* - \bar{g} + \bar{g} - \bar{g}_0}{\bar{g}} \\
&= P_0(\bar{Q}_n^* - \bar{Q})\tfrac{\bar{g}_n^* - \bar{g}}{\bar{g}} + P_0(\bar{Q}_n^* - \bar{Q})\tfrac{\bar{g} - \bar{g}_0}{\bar{g}} \\
&+ P_0(\bar{Q} - \bar{Q}_0)\tfrac{\bar{g}_n^* - \bar{g}}{\bar{g}} + P_0(\bar{Q} - \bar{Q}_0)\tfrac{\bar{g} - \bar{g}_0}{\bar{g}}.
\end{aligned}$$

Let's denote the first term with $R_{2,n} = P_0(\bar{Q}_n^* - \bar{Q})\frac{\bar{g}_n^* - \bar{g}}{\bar{g}}$. We assumed $R_{2,n} = o_P(1/\sqrt{n})$. The last term equals zero by assumption. So it remains to analyze the second and third term.

In order to represent the second and third term we define

$$\begin{aligned}
&\Psi_{2,\bar{g},\bar{g}_0}(\bar{Q}_n^*) = P_0 \bar{Q}_n^* \tfrac{\bar{g} - \bar{g}_0}{\bar{g}} \\
&\Psi_{1,\bar{g},\bar{Q},\bar{Q}_0}(\bar{g}_n^*) = P_0 \tfrac{\bar{Q} - \bar{Q}_0}{\bar{g}} \bar{g}_n^*.
\end{aligned}$$

Note that the second and third term can now be represented as:

$$\begin{array}{l} I(\bar{Q}=\bar{Q}_0)\left\{\Psi_{2,\bar{g},\bar{g}_0}(\bar{Q}_n^*)-\Psi_{2,\bar{g},\bar{g}_0}(\bar{Q})\right\} \\ +I(\bar{g}=\bar{g}_0)\left\{\Psi_{1,\bar{g},\bar{Q},\bar{Q}_0}(\bar{g}_n^*)-\Psi_{1,\bar{g},\bar{Q},\bar{Q}_0}(\bar{g})\right\}. \end{array}$$

For notational convenience, we will suppress the dependence of these mappings on the unknown quantities, and thus use Ψ_1, Ψ_2.

Analysis of $\Psi_1(\bar{g}_n^*)$ if $\bar{g}=\bar{g}_0$: If $\bar{g}=\bar{g}_0$, $H_0^r=\bar{Q}_0^r/\bar{g}_0$, $H_n^r=\bar{Q}_n^r/\bar{g}_n^*$, and $P_n H_n^r(A-\bar{g}_n^*)=0$, then

$$\begin{array}{l} \Psi_1(\bar{g}_n^*)-\Psi_1(\bar{g})=P_0\frac{\bar{Q}-\bar{Q}_0}{\bar{g}_0}(\bar{g}_n^*-\bar{g}_0) \\ =-P_0(Y-\bar{Q})\frac{A}{\bar{g}_0^2}(\bar{g}_n^*-\bar{g}_0) \\ =-P_0\frac{E_0(Y-\bar{Q}|A=1,\bar{g}_0,\bar{g}_n^*)}{\bar{g}_0}(\bar{g}_n^*-\bar{g}_0) \\ =-P_0\frac{\bar{Q}_{0,n}^r}{\bar{g}_0}(\bar{g}_n^*-\bar{g}_0) \\ =-P_0\frac{\bar{Q}_{0,n}^r-\bar{Q}_0^r}{\bar{g}_0}(\bar{g}_n^*-\bar{g}_0)+-P_0\frac{\bar{Q}_0^r}{\bar{g}_0}(\bar{g}_n^*-\bar{g}_0). \end{array}$$

We assumed

$$R_{3,n}\equiv P_0\frac{\bar{Q}_{0,n}^r-\bar{Q}_0^r}{\bar{g}_0}(\bar{g}_n^*-\bar{g}_0)=o_P(1/\sqrt{n}).$$

Using notation $H_0^r=\bar{Q}_0^r/\bar{g}_0$, we proceed as follows:

$$\begin{array}{l} P_0H_0^r(\bar{g}_n^*-\bar{g}_0) \\ =P_0H_n^r(\bar{g}_n^*-\bar{g}_0)+P_0(H_0^r-H_n^r)(\bar{g}_n^*-\bar{g}_0) \\ \equiv P_0H_n^r(\bar{g}_n^*-\bar{g}_0)+R_{4,n} \\ =-P_0H_n^r(A-\bar{g}_n^*)+R_{4,n} \\ =-(P_n-P_0)H_n^r(A-\bar{g}_n^*)+R_{4,n} \\ =-(P_n-P_0)H_0^r(A-\bar{g}_0)+R_{4,n}+R_{5,n}, \end{array}$$

where $R_{5,n}=o_P(1/\sqrt{n})$ if $P_0(D_A(\bar{g}_n^*,\bar{Q}_n^r)-D_A(\bar{g},\bar{Q}_0^r)^2=o_P(1)$ and $D_A(\bar{g}_n^*,\bar{Q}_n^r)$ falls in a Donsker class with probability tending to 1. We also assumed

$$R_{4,n}=P_0(H_n^r-H_0^r)(\bar{g}_n^*-\bar{g}_0)=o_P(1/\sqrt{n}).$$

This proves that, if $\bar{g}=\bar{g}_0$, then $\Psi_1(\bar{g}_n^*)-\Psi_1(\bar{g}_0)=-(P_n-P_0)D_A(\bar{g},\bar{Q}_0^r)+o_P(1/\sqrt{n})$.

Analysis of $\Psi_2(\bar{Q}_n^*)$ if $\bar{Q}=\bar{Q}_0$: If $\bar{Q}=\bar{Q}_0$, $\bar{g}_{0,n}^r=E_0(A\mid\bar{g},\bar{Q}_n^*,\bar{Q})$, and recall that $\bar{g}_n^r$ is estimator of $\bar{g}_0^r = E_0(A \mid \bar{g}, \bar{Q})$, $P_n H_Y(\bar{g}_n^r, \bar{g}_n^*)(Y - \bar{Q}_n^*) = 0$, then

$$\begin{aligned}
&\Psi_2(\bar{Q}_n^*) - \Psi_2(\bar{Q}_0) = P_0 \tfrac{\bar{g}-\bar{g}_0}{\bar{g}}(\bar{Q}_n^* - \bar{Q}_0) \\
&= -P_0 \tfrac{A-\bar{g}}{\bar{g}}(\bar{Q}_n^* - \bar{Q}_0) \\
&= -P_0 \tfrac{\bar{g}_{0,n}^r-\bar{g}}{\bar{g}}(\bar{Q}_n^* - \bar{Q}_0) \\
&= P_0 \tfrac{A}{\bar{g}_{0,n}^r} \tfrac{\bar{g}_{0,n}^r-\bar{g}}{\bar{g}}(Y - \bar{Q}_n^*) \\
&= P_0 H_Y(\bar{g}_{0,n}^r, \bar{g})(Y - \bar{Q}_n^*) \\
&= P_0 H_Y(\bar{g}_n^r, \bar{g}_n^*)(Y - \bar{Q}_n^*) + \\
&P_0\{H_Y(\bar{g}_{0,n}^r, \bar{g})(Y - \bar{Q}_n^*) - H_Y(\bar{g}_n^r, \bar{g}_n^*)(\bar{Q}_0 - \bar{Q}_n^*)\}
\end{aligned}$$

We assumed that the last term is $o_P(1/\sqrt{n})$. We now proceed as follows:

$$\begin{aligned}
&P_0 H_Y(\bar{g}_n^r, \bar{g}_n^*)(Y - \bar{Q}_n^*) = (P_n - P_0) H_Y(\bar{g}_n^r, \bar{g}_n^*)(Y - \bar{Q}_n^*) \\
&= (P_n - P_0) H_Y(\bar{g}_0^r, \bar{g})(Y - \bar{Q}),
\end{aligned}$$

where we assumed that $H_Y(\bar{g}_n^r, \bar{g}_n^*)(Y - \bar{Q}_n^*)$ falls in a Donsker class with probability tending to 1, and $P_0\{H_Y(\bar{g}_n^r, \bar{g}_n^*) - H_Y(\bar{g}_0^r, \bar{g})(Y - \bar{Q})\}^2 \to 0$ in probability. This proves $\Psi_2(\bar{Q}_n^*) - \Psi_2(\bar{Q}_0) = (P_n - P_0) D_Y(\bar{g}_0^r, \bar{g}, \bar{Q}) + o_P(1/\sqrt{n})$. This completes the proof of the theorem. $\Box$

Proof of Theorem 4.

If $P_n D^*(Q_n^*, g_n^*) = 0$, then

$$\begin{aligned}
&\Psi(Q_n^*) - \Psi(Q_0) = -P_0 D^*(Q_n^*, g_n^*) + P_0(\bar{Q}_0 - \bar{Q}_n^*) \tfrac{\bar{g}_0 - \bar{g}_n^*}{\bar{g}_n^*} \\
&= (P_n - P_0) D^*(Q_n^*, g_n^*) + P_0(\bar{Q}_0 - \bar{Q}_n^*) \tfrac{\bar{g}_0 - \bar{g}_n^*}{\bar{g}_n^*} \\
&= (P_n - P_0) D^*(Q, g) + P_0(\bar{Q}_n^* - \bar{Q}_0) \tfrac{\bar{g}_n^* - \bar{g}_0}{\bar{g}_n^*} + o_P(1/\sqrt{n}),
\end{aligned}$$

if $D^*(Q_n^*, g_n^*)$ falls in a Donsker class with probability tending to 1, and $P_0\{D^*(Q_n^*, g_n^*) - D^*(Q, g)\}^2 \to 0$ in probability as $n \to \infty$.

Now, we note

$$\begin{aligned}
&P_0(\bar{Q}_n^* - \bar{Q}_0) \tfrac{\bar{g}_n^* - \bar{g}_0}{\bar{g}_n^*} = P_0(\bar{Q}_n^* - \bar{Q} + \bar{Q} - \bar{Q}_0) \tfrac{\bar{g}_n^* - \bar{g} + \bar{g} - \bar{g}_0}{\bar{g}_n^*} \\
&= P_0(\bar{Q}_n^* - \bar{Q}) \tfrac{\bar{g}_n^* - \bar{g}}{\bar{g}_n^*} + P_0(\bar{Q}_n^* - \bar{Q}) \tfrac{\bar{g} - \bar{g}_0}{\bar{g}_n^*} \\
&+ P_0(\bar{Q} - \bar{Q}_0) \tfrac{\bar{g}_n^* - \bar{g}}{\bar{g}_n^*} + P_0(\bar{Q} - \bar{Q}_0) \tfrac{\bar{g} - \bar{g}_0}{\bar{g}_n^*},
\end{aligned}$$

resulting in four terms, which we will denote with Term 1,2,3,4, respectively.

Term 4: This last term equals:

$$\begin{aligned}
&P_0(\bar{Q} - \bar{Q}_0)(\bar{g} - \bar{g}_0) \tfrac{(\bar{g}_n^* - \bar{g})}{\bar{g}_n^* \bar{g}} \\
&= P_0(\bar{Q} - \bar{Q}_0)(\bar{g} - \bar{g}_0) \tfrac{(\bar{g}_n^* - \bar{g})}{\bar{g}^2} + R_{1,n},
\end{aligned}$$

where

$$R_{1,n} = P_0(\bar{Q} - \bar{Q}_0)(\bar{g} - \bar{g}_0)\frac{(\bar{g}_n^* - \bar{g})^2}{\bar{g}^2\bar{g}_n^*} = o_P(1/\sqrt{n}),$$

by assumption. We proceed as follows:

$$\begin{aligned} & P_0(\bar{Q} - \bar{Q}_0)(\bar{g} - \bar{g}_0)\tfrac{(\bar{g}_n^* - \bar{g})}{\bar{g}^2} \\ & = P_0(\bar{Q} - \bar{Q}_0)(\bar{g} - A)\tfrac{(\bar{g}_n^* - \bar{g})}{\bar{g}^2} \\ & = P_0\tfrac{(\bar{Q} - \bar{Q}_0)}{\bar{g}}(\bar{g}_n^* - \bar{g}) - P_0(\bar{Q} - \bar{Q}_0)\tfrac{A}{\bar{g}^2}(\bar{g}_n^* - \bar{g}). \end{aligned}$$

The first term is identical to Term 3 analyzed below, and is shown to be asymptotically linear with influence curve $-D_A(\bar{g}, \bar{Q}_0^r)$. The second term equals

$$\begin{aligned} & -P_0(\bar{Q} - \bar{Q}_0)\tfrac{A}{\bar{g}^2}(\bar{g}_n^* - \bar{g}) = -P_0(\bar{Q} - Y)\tfrac{A}{\bar{g}^2}(\bar{g}_n^* - \bar{g}) \\ & = -P_0E_0(\bar{Q} - Y \mid A = 1, \bar{g}, \bar{g}_n^*)\tfrac{A}{\bar{g}^2}(\bar{g}_n^* - \bar{g}) \\ & = -P_0E_0(\bar{Q} - Y \mid A = 1, \bar{g}, \bar{g}_n^*)\tfrac{E_0(A|\bar{g},\bar{g}_n^*)}{\bar{g}^2}(\bar{g}_n^* - \bar{g}) \\ & = -P_0E_0(\bar{Q} - Y \mid A = 1, \bar{g})\tfrac{E_0(A|\bar{g})}{\bar{g}^2}(\bar{g}_n^* - \bar{g}) - P_0(H_1(\bar{g}_n^*) - H_1(\bar{g}))(\bar{g}_n^* - \bar{g}), \end{aligned}$$

where $H_1(\bar{g}_n^*) \equiv E_0(\bar{Q} - Y \mid A = 1, \bar{g}, \bar{g}_n^*)\frac{E_0(A|\bar{g},\bar{g}_n^*)}{\bar{g}^2}$ which approximates $H_1(\bar{g}) = E_0(\bar{Q} - Y \mid A = 1, \bar{g})\frac{E_0(A|\bar{g})}{\bar{g}^2}$. We assume that

$$R_{2,n} = -P_0(H_1(\bar{g}_n^*) - H_1(\bar{g}))(\bar{g}_n^* - \bar{g}) = o_P(1/\sqrt{n}).$$

We also have that $E_0(A \mid \bar{g}) = \bar{g}$, by the fact that $\bar{g} = E_0(A \mid W^r)$ for some function W^r of W. Thus, it remains to analyze

$$P_0\frac{E_0(Y - \bar{Q} \mid A = 1, \bar{g})}{\bar{g}}(\bar{g}_n^* - \bar{g}).$$

This term is analyzed below under Term 3, and it is shown that this term equals

$$(P_n - P_0)D_A(\bar{g}, \bar{Q}_0^r) + o_P(1/\sqrt{n}),$$

which cancels with the above mentioned $-(P_n - P_0)D_A(\bar{g}, \bar{Q}_0^r)$. To conclude, we have shown that

$$P_0(\bar{Q} - \bar{Q}_0)(\bar{g} - \bar{g}_0)\frac{(\bar{g}_n^* - \bar{g})}{\bar{g}_n^*\bar{g}} = o_P(1/\sqrt{n}).$$

Term 1: The first term $P_0(\bar{Q}_n^* - \bar{Q})\frac{\bar{g}_n^* - \bar{g}}{\bar{g}} = o_P(1/\sqrt{n})$, by assumption.

So it remains to analyze the second and third term. In order to represent the second and third term we define

$$\begin{aligned} \Psi_{2,\bar{g},\bar{g}_0}(\bar{Q}_n^*) &= P_0\bar{Q}_n^*\tfrac{\bar{g} - \bar{g}_0}{\bar{g}} \\ \Psi_{1,\bar{g},\bar{Q},\bar{Q}_0}(\bar{g}_n^*) &= P_0\tfrac{\bar{Q} - \bar{Q}_0}{\bar{g}}\bar{g}_n^*. \end{aligned}$$

Note that the sum of second and third term can now be represented as:

$$\begin{array}{l}\left\{\Psi_{2,\bar{g},\bar{g}_0}(\bar{Q}_n^*) - \Psi_{2,\bar{g},\bar{g}_0}(\bar{Q})\right\} \\ + \left\{\Psi_{1,\bar{g},\bar{Q},\bar{Q}_0}(\bar{g}_n^*) - \Psi_{1,\bar{g},\bar{Q},\bar{Q}_0}(\bar{g})\right\}.\end{array}$$

For notational convenience, we will suppress the dependence of these mappings on the unknown quantities, and thus use Ψ_1, Ψ_2 instead.

Analysis of Term 3: If $H_0^r = \bar{Q}_0^r/\bar{g}$, $H_n^r = \bar{Q}_n^r/\bar{g}_n^*$, $P_n H_n^r(A - \bar{g}_n^*) = 0$, then

$$\begin{array}{l}\Psi_1(\bar{g}_n^*) - \Psi_1(\bar{g}) = P_0 \frac{\bar{Q}-\bar{Q}_0}{\bar{g}}(\bar{g}_n^* - \bar{g}) \\ = -P_0(Y - \bar{Q})\frac{A}{\bar{g}_{0,n}^*\bar{g}}(\bar{g}_n^* - \bar{g}),\end{array}$$

where

$$\bar{g}_{0,n}^* \equiv E_0(A \mid \bar{Q}_0 - \bar{Q}, \bar{g}_n^*, \bar{g}) = E_0(A \mid \bar{g}_n^*, \bar{g}),$$

where latter equality follows since $\bar{Q}_0 - \bar{Q}$ is a function of W^r and $\bar{g} = E_0(A \mid W^r)$. We note that $\bar{g}_{0,n}^*$ converges to $\bar{g}$. So we used the following lemma.

Lemma 3 *Suppose $\bar{g} = E_0(A \mid W^r)$ and $\bar{Q}_0 - \bar{Q}$ depends on W only through W^r. Then $E_0(A \mid \bar{Q}_0 - \bar{Q}, \bar{g}) = \bar{g}$.*

Proof lemma: In general, $E_0(A \mid E_0(A \mid Z)) = E_0(A \mid Z)$. Thus, $E_0(A \mid E_0(A \mid W^r)) = E_0(A \mid W^r)$. If $\bar{Q}_0 - \bar{Q}$ is a function of W^r, then $E_0(A \mid E_0(A \mid W^r), \bar{Q}_0 - \bar{Q}) = E_0(A \mid W^r) = \bar{g}$. $\square$

We define $\bar{Q}_{0,n}^r = E_0(Y - \bar{Q} \mid A = 1, \bar{g}_{0,n}^*, \bar{g}, \bar{g}_n^*)$, and $\bar{Q}_0^r = E_0(Y - \bar{Q} \mid A = 1, \bar{g})$. Since $\bar{g}_n^*, \bar{g}_{0,n}^*$ both converge to $\bar{g}$, we have that $\bar{Q}_{0,n}^r$ will converge to $\bar{Q}_0^r$. We now proceed as follows:

$$\begin{array}{l}-P_0(Y - \bar{Q})\frac{A}{\bar{g}_{0,n}^*\bar{g}}(\bar{g}_n^* - \bar{g}) = -P_0 E_0(Y - \bar{Q} \mid A = 1, \bar{g}_{0,n}^*, \bar{g}, \bar{g}_n^*)\frac{A}{\bar{g}_{0,n}^*\bar{g}}(\bar{g}_n^* - \bar{g}) \\ \equiv -P_0 \frac{\bar{Q}_{0,n}^r}{\bar{g}} \frac{E_0(A|\bar{g},\bar{g}_n^*)}{\bar{g}_{0,n}^*}(\bar{g}_n^* - \bar{g}) \\ = -P_0 \frac{\bar{Q}_{0,n}^r}{\bar{g}}(\bar{g}_n^* - \bar{g}) \\ = -P_0 \frac{\bar{Q}_{0,n}^r - \bar{Q}_0^r}{\bar{g}}(\bar{g}_n^* - \bar{g}) - P_0 \frac{\bar{Q}_0^r}{\bar{g}}(\bar{g}_n^* - \bar{g}),\end{array}$$

where we used that $\bar{g}_{0,n}^* = E_0(A \mid \bar{g}_n^*, \bar{g})$. We assumed

$$R_{3,n} \equiv P_0 \frac{\bar{Q}_{0,n}^r - \bar{Q}_0^r}{\bar{g}}(\bar{g}_n^* - \bar{g}) = o_P(1/\sqrt{n}).$$

It remains to analyze $-P_0\frac{\bar{Q}_0^r}{\bar{g}}(\bar{g}_n^* - \bar{g})$. We will use the notation $H_0^r = \bar{Q}_0^r/\bar{g}$.

Let $H_n^r = \bar{Q}_n^r / \bar{g}_n^*$. We have

$$
\begin{array}{l}
-P_0 H_0^r(\bar{g}_n^* - \bar{g}) \\
= -P_0 H_n^r(\bar{g}_n^* - \bar{g}) - P_0(H_0^r - H_n^r)(\bar{g}_n^* - \bar{g}) \\
\equiv -P_0 H_n^r(\bar{g}_n^* - \bar{g}) + R_{4,n} \\
= P_0 H_n^r(A - \bar{g}_n^*) + R_{4,n} \\
= -(P_n - P_0) H_n^r(A - \bar{g}_n^*) + R_{4,n} \\
= -(P_n - P_0) H_0^r(A - \bar{g}) + R_{4,n} + R_{5,n},
\end{array}
$$

where $R_{5,n} = o_P(1/\sqrt{n})$ if $P_0(D_A(\bar{g}_n^*, \bar{Q}_n^r) - D_A(\bar{g}, \bar{Q}_0^r)^2 = o_P(1)$ and $D_A(\bar{g}_n^*, \bar{Q}_n^r)$ falls in a Donsker class with probability tending to 1, and we are reminded that $D_A(\bar{g}, \bar{Q}_0^r) = H_0^r(A - \bar{g})$. We also assumed that

$$R_{4,n} = P_0(H_n^r - H_0^r)(\bar{g}_n^* - \bar{g}) = o_P(1/\sqrt{n}).$$

This proves that, $\Psi_1(\bar{g}_n^*) - \Psi_1(\bar{g}) = -(P_n - P_0) D_A(\bar{g}, \bar{Q}_0^r) + o_P(1/\sqrt{n})$.
Analysis of term 2: We have

$$
\begin{array}{l}
\Psi_2(\bar{Q}_n^*) - \Psi_2(\bar{Q}) = P_0 \frac{\bar{g} - \bar{g}_0}{\bar{g}}(\bar{Q}_n^* - \bar{Q}) \\
= -P_0 \frac{A - \bar{g}}{\bar{g}}(\bar{Q}_n^* - \bar{Q}) \\
= -P_0 \frac{E_0(A \mid \bar{g}, \bar{Q}_n^*, \bar{Q}) - \bar{g}}{\bar{g}}(\bar{Q}_n^* - \bar{Q}).
\end{array}
$$

By assumption, we have that $\bar{g} = E_0(A \mid \bar{Q}, W^r)$ since $\bar{Q}$ is a function of W^r. In that case, we have

$$E_0(A \mid \bar{g}, \bar{Q}) = E_0(E_0(A \mid \bar{Q}, W^r) \mid \bar{g}, \bar{Q}) = \bar{g}.$$

Let $\bar{g}_{0,n}^r = E_0(A \mid \bar{g}, \bar{Q}_n^*, \bar{Q})$, and we assumed that

$$P_0 \frac{\bar{g}_{0,n}^r - \bar{g}}{\bar{g}}(\bar{Q}_n^* - \bar{Q}) = o_P(1/\sqrt{n}).$$

This proves that $\Psi_1(\bar{Q}_n^*) - \Psi_2(\bar{Q}) = o_P(1/\sqrt{n})$.

This completes the proof of the theorem. □