ADDITIONAL APPENDIX to "A Precision Medicine Approach to Develop and Internally Validate Optimal Exercise and Weight Loss Treatments for Overweight and Obese Adults with Knee Osteoarthritis *Data from the Intensive Diet and Exercise for Arthritis (IDEA) Trial*" **Jiang et al. 2020**

B. Theorem 1 and its proof. Theorem 1: Consistency of the jackknife estimator.

Assume

(A1) $\mathbb{E}[P_{\boldsymbol{X}}(\hat{d}_n(\boldsymbol{X}) \neq \hat{d}_{n-1}(\boldsymbol{X}))] \to 0$,

(A2) $\mathbb{E}\left[\frac{Y^2}{P^2(A|\boldsymbol{X})} + \frac{1}{P^2(A|\boldsymbol{X})}\right] < \infty$.

Then

$$\frac{\sum_{i=1}^{n} \frac{Y_i\, 1\{A_i = \hat{d}_n^{(-i)}(\boldsymbol{X}_i)\}}{P(A_i|\boldsymbol{X}_i)}}{\sum_{i=1}^{n} \frac{1\{A_i = \hat{d}_n^{(-i)}(\boldsymbol{X}_i)\}}{P(A_i|\boldsymbol{X}_i)}} - \mathbb{E}\left[Y \middle| A = \hat{d}_n(\boldsymbol{X})\right] \underset{p}{\rightarrow} 0$$

It is reasonable to assume (A1) because the training sets of size n and $n-1$ are asymptotically equal, which implies that the decision functions estimated from these two training sets eventually converge as sample size grows to infinity. Assumption (A2) requires a finite second moment of the outcome adjusted by the propensity score and thus a finite variance of the adjusted outcome, which is easily satisfied for clinical data where the outcome itself is finite and is usually contained in a range. The second term in (A2) is automatically satisfied because propensity scores are bounded between 0 and 1, and it is used in the analogous proof of W_n. Given the two weak assumptions, Theorem 1 can be proved as follows.

<u>Proof of Theorem 1.</u>

Let $U_i = \frac{Y_i\, 1\{A_i = \hat{d}_n^{(-i)}(\boldsymbol{X}_i)\}}{P(A_i|\boldsymbol{X}_i)}$, $W_i = \frac{1\{A_i = \hat{d}_n^{(-i)}(\boldsymbol{X}_i)\}}{P(A_i|\boldsymbol{X}_i)}$, $U_n = n^{-1}\sum_{i=1}^{n} U_i$, and $W_n = n^{-1}\sum_{i=1}^{n} W_i$.

First,

$$\mu_n = \mathbb{E}[U_n] = n^{-1}\sum_{i=1}^{n} \mathbb{E}\left[\frac{Y_i 1\{A_i = \hat{d}_n^{(-i)}(\boldsymbol{X}_i)\}}{P(A_i|\, \boldsymbol{X}_i)}\right] = \mathbb{E}\left[\frac{Y 1\{A = \hat{d}_{n-1}(\boldsymbol{X})\}}{P(A|\boldsymbol{X})}\right].$$

Denote $\tilde{\mu}_n = \mathbb{E}\left[\frac{Y 1\{A = \hat{d}_n(\boldsymbol{X})\}}{P(A|\boldsymbol{X})}\right]$, then

$$\begin{aligned}\mu_n - \tilde{\mu}_n &= \mathbb{E}\left[\frac{Y}{P(A|\boldsymbol{X})}\left(1\{A = \hat{d}_{n-1}(\boldsymbol{X})\} - 1\{A = \hat{d}_n(\boldsymbol{X})\}\right)\right] \\ &\leq M\, \mathbb{E}\left[1\{A = \hat{d}_{n-1}(\boldsymbol{X})\} - 1\{A = \hat{d}_n(\boldsymbol{X})\}\right] \\ &\quad + \mathbb{E}\left[\frac{|Y|}{P(A|\boldsymbol{X})} 1\left\{\frac{|Y|}{P(A|\boldsymbol{X})} > M\right\}\right] \to 0,\end{aligned}$$

where the convergence is based on (A1) for the first term in the inequality and (A2), which implies finite first moment, for the second term in the inequality. Given the first term in (A2), we have the following property of the variance

$$Var[U_n] = n^{-1}Var\left[\sum\nolimits_{i=1}^{n} U_i\right] = n^{-2} \sum_{i=1}^{n}\sum_{j=1}^{n}\left[\mathbb{E}(U_iU_j) - \mathbb{E}(U_i)\mathbb{E}(U_j)\right]$$
$$= n^{-2}\sum_{i=1}^{n}\sum_{j=1}^{n}\left[\mathbb{E}\left(\frac{Y_iY_j\, 1\left\{A_i = \hat{d}_n{}^{(-i)}(\boldsymbol{X}_i)\right\} 1\left\{A_j = \hat{d}_n{}^{(-j)}(\boldsymbol{X}_j)\right\}}{P(A_i|\boldsymbol{X}_i)P(A_j|\boldsymbol{X}_j)}\right) - \mu_n^2\right]$$
$$\to n^{-2}\sum_{i=1}^{n}\sum_{j=1}^{n}\left[\mathbb{E}\left(\frac{Y_iY_j\, 1\{A_i = \hat{d}_n{}^{(-i,-j)}(\boldsymbol{X}_i)\}1\{A_j = \hat{d}_n{}^{(-i,-j)}(\boldsymbol{X}_j)\}}{P(A_i|\boldsymbol{X}_i)P(A_j|\boldsymbol{X}_j)}\right) - \mu_n^2\right]$$
$$= n^{-2}\sum_{i=1}^{n}\sum_{j=1}^{n}\left\{\left[\mathbb{E}\left(\frac{Y1\{A = \hat{d}_{n-2}(\boldsymbol{X})\}}{P(A|\boldsymbol{X})}\right)\right]^2 - \mu_n^2\right\} \to n^{-2}\sum_{i=1}^{n}\sum_{j=1}^{n}(\mu_n^2 - \mu_n^2) = 0,$$

here both convergences are based on (A1). Thus, we have shown that

$$\mathbb{E}[U_n] - \tilde{\mu}_n \to 0$$
$$Var[U_n] \to 0$$

Applying the same arguments as above to W_n with assumptions (A1) and the second term in (A2), we have

$$\tau_n = \mathbb{E}[W_n] = \mathbb{E}\left[\frac{1\{A=\hat{d}_{n-1}(\boldsymbol{X})\}}{P(A|\boldsymbol{X})}\right],$$
$$\tilde{\tau}_n = \mathbb{E}\left[\frac{1\{A = \hat{d}_n(\boldsymbol{X})\}}{P(A|\boldsymbol{X})}\right] = \mathbb{E}\left\{\mathbb{E}\left[\left.\frac{1\{A = \hat{d}_n(\boldsymbol{X})\}}{P(A = \hat{d}_n(\boldsymbol{X})|\boldsymbol{X})}\right| \boldsymbol{X}\right]\right\} = 1,$$

and similarly

$$\mathbb{E}[W_n] - 1 \to 0$$
$$Var[W_n] \to 0$$

Thus, by the weak law of large numbers (WLLN),

$$U_n - \tilde{\mu}_n \underset{p}{\to} 0 \quad \text{and} \quad W_n - 1 \underset{p}{\to} 0,$$

which yields

$$\frac{U_n}{W_n} - \tilde{\mu}_n \underset{p}{\to} 0$$

by the multivariate continuous mapping theorem. This completes the proof because

$$\tilde{\mu}_n = \mathbb{E}\left[\frac{Y1\{A=\hat{d}_n(\boldsymbol{X})\}}{P(A|\boldsymbol{X})}\right] = \mathbb{E}\left[Y^{\hat{d}_n(\boldsymbol{X})}\right] = \mathbb{E}\left[Y|A = \hat{d}_n(\boldsymbol{X})\right]$$

This equation is derived by applying a version of Radon-Nikodym derivative (i.e. $dP^d/dP = 1\{a = d(\boldsymbol{x})\}/P(a|\boldsymbol{x})$ where P denotes the distribution of $(\boldsymbol{X}, A, Y)$ and P^d denotes the distribution of $(\boldsymbol{X}, A, Y)$ under the decision rule d (1)) and

$$\frac{\sum_{i=1}^{n} \frac{Y_i\, 1\{A_i = \hat{d}_n^{(-i)}(X_i)\}}{P(A_i|X_i)}}{\sum_{i=1}^{n} \frac{1\{A_i = \hat{d}_n^{(-i)}(X_i)\}}{P(A_i|X_i)}} - \mathbb{E}\left[Y \middle| A = \hat{d}_n(\boldsymbol{X})\right] = \frac{U_n}{W_n} - \tilde{\mu}_n. \square$$

REFERENCES

1. Qian M, Murphy SA. Performance guarantees for individualized treatment rules. *Ann Stat* 2011;39:1180–1210.