

Targeted Machine Learning for Causal Inference Based on Real-World Data

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Plenary Session II

Joint work with Maya Petersen

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Outline

- 1 Roadmap for Statistical Learning: Targeted Learning
- 2 Ingredients of Targeted Learning: Causal Framework, Super-learning, Targeting (TMLE)
- 3 Example: Nonparametric estimation of the Average Treatment Effect
- 4 Super Learning and Highly Adaptive Lasso
- 5 TMLE
- 6 Objective simulation with HAL-TMLE of ATE
- 7 Targeted learning for analyzing RCTs
- 8 Targeted learning for adaptive trial design
- 9 Targeted learning in complex longitudinal observational studies
 - Targeted learning in complex observational study of diabetes (Neugebauer et al.)
- 10 Inference with TMLE
- 11 Collaborative TMLE for effective/targeted estimation of propensity score.
- 12 Preparing SAP based on TMLE
- 13 Concluding Remarks

Roadmap of Statistical Learning

- **Observed data:** Realization of a random variable $O^n = (O_1, \dots, O_n)$ with a probability distribution (say) P_0^n on n units.
- **Model stochastic system of observed data realistically:** Statistical model \mathcal{M}^n is set of possible probability distributions of the data.
- **Define query about stochastic system:** Function Ψ from model \mathcal{M}^n to real line, where $\Psi(P_0^n)$ is the true answer to query about our stochastic system. **Estimand is chosen so that it best approximates the answer to causal question of interest.**
- **Estimator:** An a priori-specified algorithm that takes the observed data O^n and returns an estimate ψ_n to the *true answer to query*. Benchmarked by a dissimilarity-measure (e.g., MSE) w.r.t true answer to query.
- **Confidence interval for true answer to query:** Establish approximate sampling probability distribution of the estimator (e.g., based on CLT), and corresponding statistical inference.

Targeted Learning (TL)

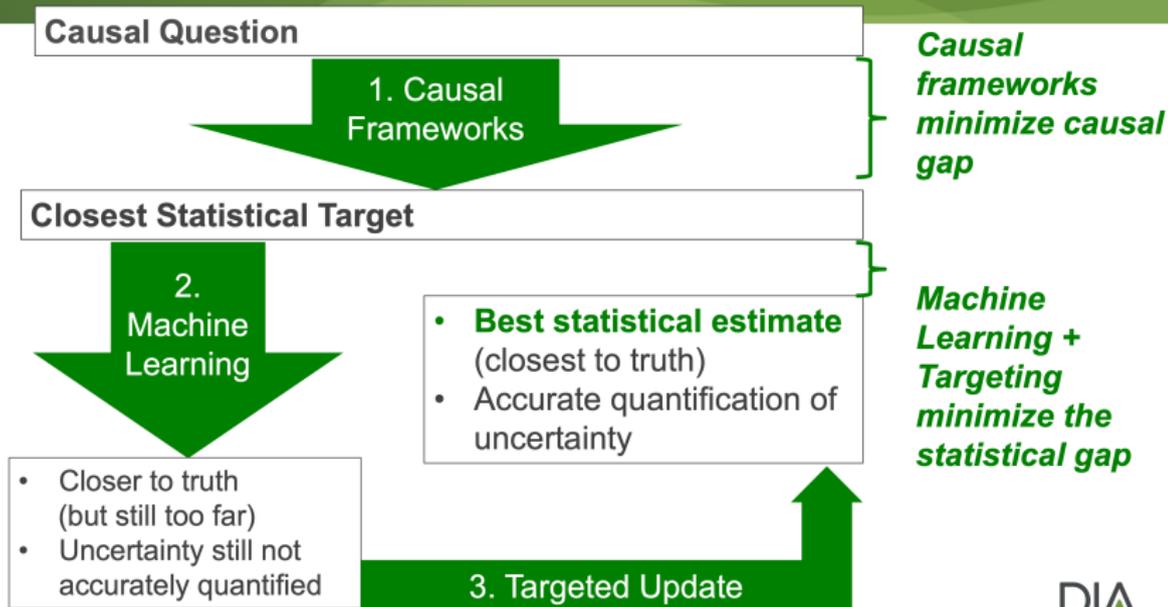
is the subfield of statistics concerned with development of (targeted ML) estimators of the data distribution based on observed data with corresponding plug-in estimates and **confidence intervals** for the desired estimand, **based on realistic statistical models**.

By necessity, TL involves highly data adaptive estimation (i.e., ensemble machine learning) to estimate the relevant complex stochastic relations between the different observed variables.

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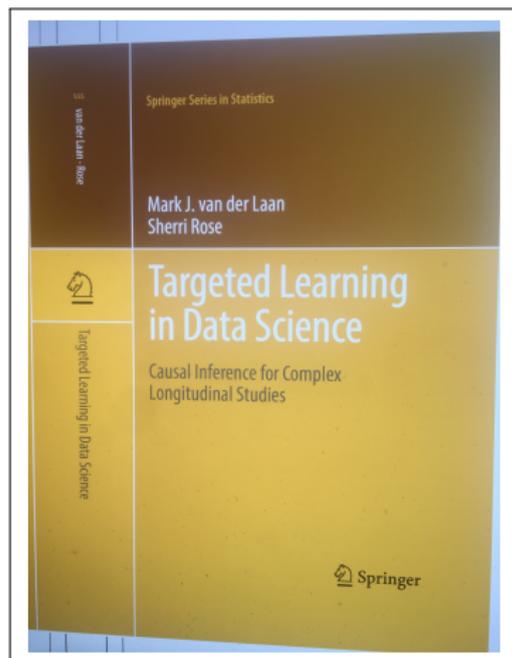
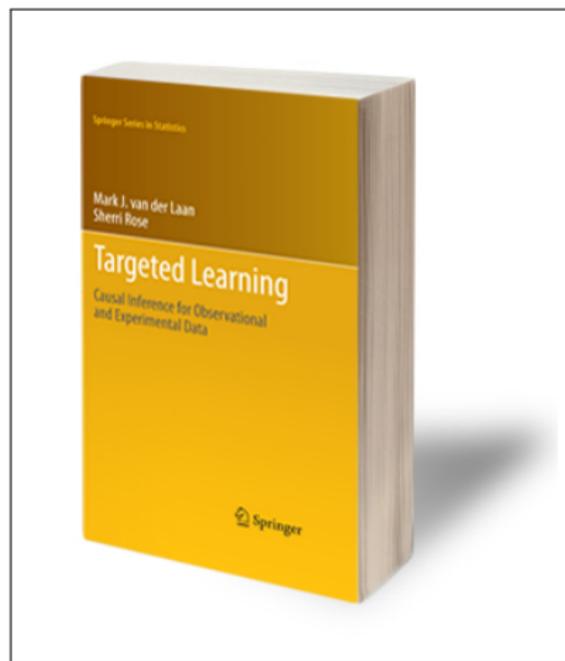
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Targeted Learning



DIA

Targeted Learning (<https://vanderlaan-lab.org>)



van der Laan & Rose, *Targeted Learning: Causal Inference for Observational and Experimental Data*. New York: Springer, 2011.

Short Course, Targeted Learning

December 4-6, **75-th Annual Deming Conference**, Atlantic City, NJ

Targeted Learning in Data Science: Causal Inference for Observational and Experimental Data

Professor Mark J. van der Laan, University of California at Berkeley
Moderator: Bill Wang

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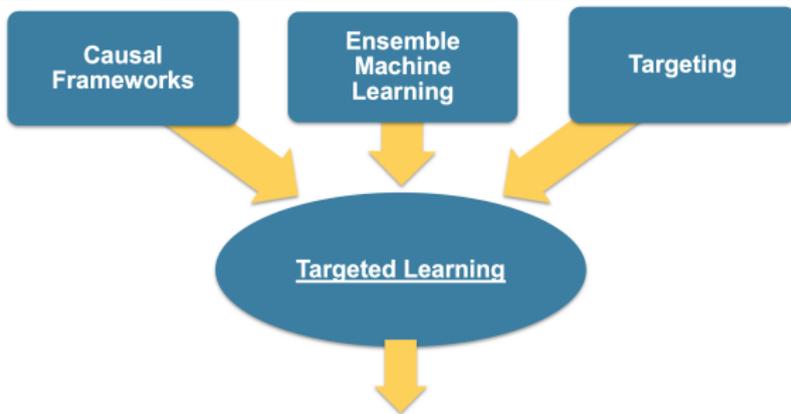
Example: Nonparametric Estimation of Average Treatment Effect

- Unit (i.i.d.) data $O \sim P_0$ consists of baseline covariates W , binary treatment A , and final binary outcome Y .
- Statistical model for the data distribution P_0 is nonparametric.
- Statistical target parameter:

$$\Psi(P) = E_P\{P(Y = 1 \mid A = 1, W) - P(Y = 1 \mid A = 0, W)\}.$$

- Under causal model, randomization assumption, and positivity assumption, $\Psi(P) = E(Y_1 - Y_0)$ is the ATE.
- A TMLE will estimate $P(Y = 1 \mid A, W)$ with **ensemble machine learning** and a subsequent **Targeting step** using logistic regression with off-set initial fit, and clever covariate $(2A - 1)/\hat{P}(A|W)$.

Targeted Learning



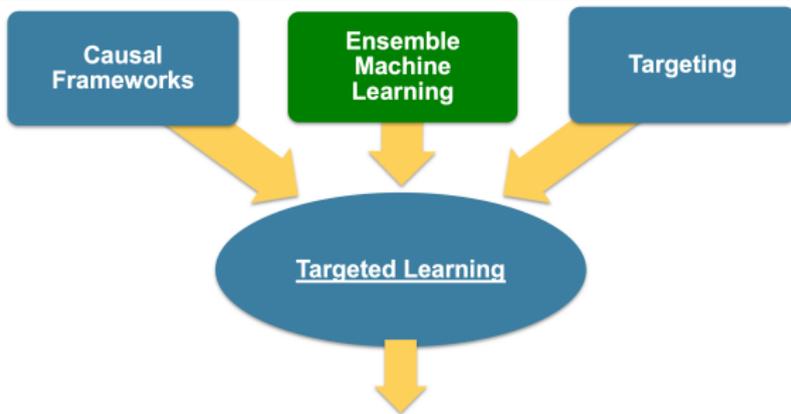
Better (more precise) **answers** to **causal** (actionable) **questions** with **accurate quantification of uncertainty** (signal from noise)

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Targeted Learning

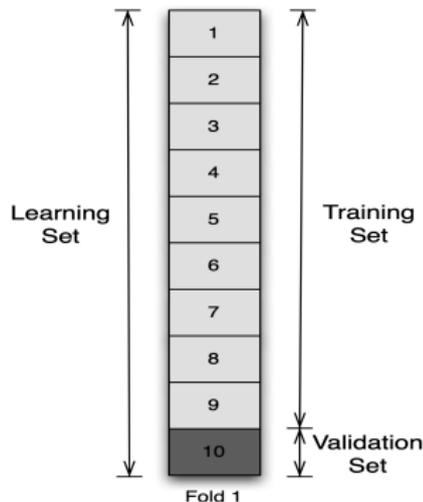


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Super Learning: Ensemble Machine Learning

- “Competition” of algorithms
 - Parametric models
 - Data-adaptive (ex. Random forest, Neural nets)
- Best “team” wins
 - Convex combination of algorithms
- Performance judged on independent data
 - V-fold cross validation (Internal data splits)
- Customizable optimality criterion
 - Standard loss function
 - Minimize false negatives with bounded false positives
 - Respect resource constraints



Van der Laan, Polley, 2007

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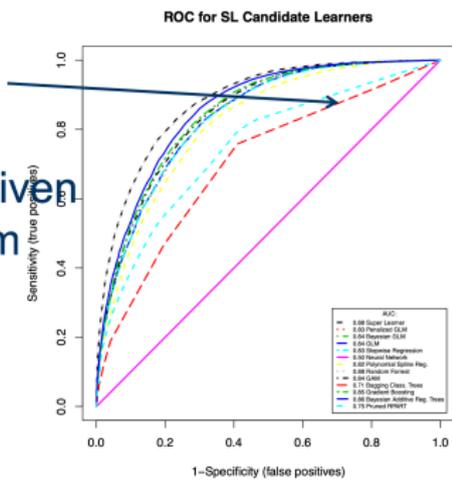
V-fold Cross Validation

1	1	1	1	1	1	1	1	1	1	1
2	2	2	2	2	2	2	2	2	2	2
3	3	3	3	3	3	3	3	3	3	3
4	4	4	4	4	4	4	4	4	4	4
5	5	5	5	5	5	5	5	5	5	5
6	6	6	6	6	6	6	6	6	6	6
7	7	7	7	7	7	7	7	7	7	7
8	8	8	8	8	8	8	8	8	8	8
9	9	9	9	9	9	9	9	9	9	9
10	10	10	10	10	10	10	10	10	10	10
Fold 1	Fold 2	Fold 3	Fold 4	Fold 5	Fold 6	Fold 7	Fold 8	Fold 9	Fold 10	

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Ex. Mortality prediction for ICU patients

Super Learner:
Best weighted combination of algorithms for a given prediction problem



Pirracchio, Lancet Resp Med 2015



Cross-validation is optimal for selection among estimators

- We established an oracle inequality for the cross-validation selector among a collection of candidate estimators (e.g, van der Laan, Dudoit, 03, van der Vaart et al 06).
- Oracle selector chooses the estimator closest to the true function w.r.t. loss-based dissimilarity.
- It establishes that the loss-based dissimilarity with truth of the cross-validated selected estimator divided by the loss-based dissimilarity of the oracle selected estimator converges to 1, even as the number of candidate estimators converges to infinity as a polynomial in sample size.
- Only condition is that loss-function is uniformly bounded.

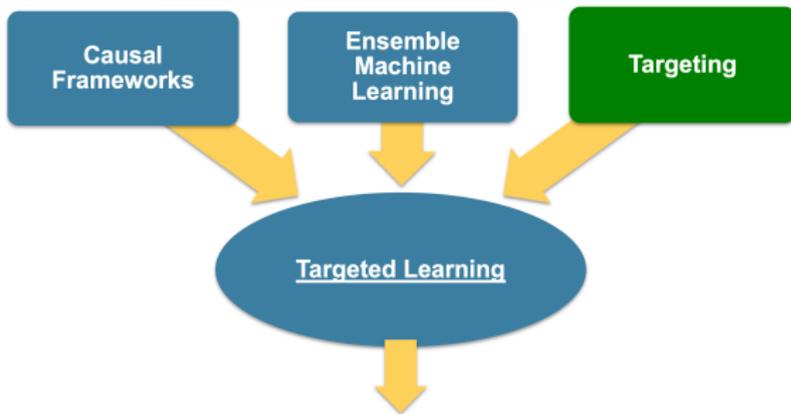
Highly Adaptive Lasso (HAL)

- This is a machine learning algorithm that estimates functionals (e.g. outcome regression and propensity score) by approximating them with linear model in **tensor product of spline basis functions** and constraining the L_1 -norm of the coefficients.
- Can be computed with **Lasso**-software implementations.
- Guaranteed to converge to truth at rate $n^{-1/3}$ (up till $\log n$ -factors) in sample size n .
- When used in super-learner library, TMLE (targeted learning) is guaranteed **consistent, (double robust) asymptotically normal and efficient**: one only needs to assume *strong positivity assumption*.

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Targeted Learning



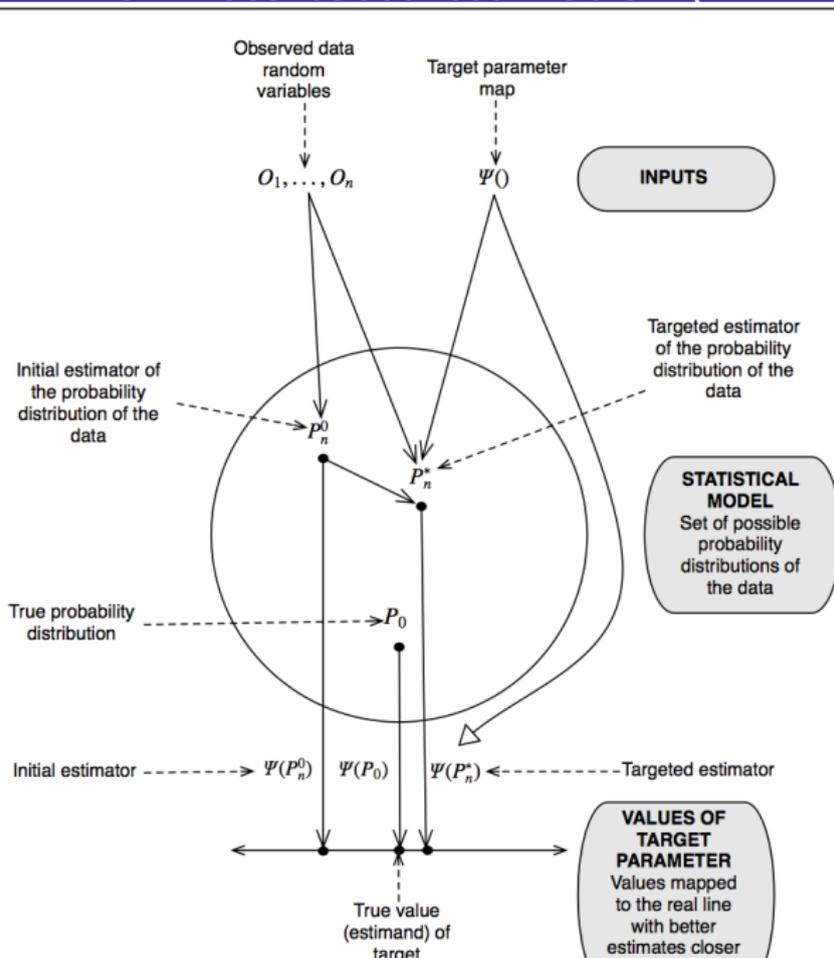
Better (more precise) **answers** to **causal** (actionable) **questions** with **accurate quantification of uncertainty** (signal from noise)

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Targeted Update of Machine Learning

- Don't try to do a good job for all questions at once.
- Focus estimation where it matters most for question at hand.
- ① Less bias (closer to truth).
- ② Sampling distribution approximately normal, more accurate quantification of uncertainty.

Targeted minimum loss based estimation (TMLE)



Targeted Minimum Loss Based Estimation (TMLE)

- Super learning provides an initial estimator \mathbf{P}_n of stochastic system P_0 .
- Determine mathematically the fluctuation strategy (least favorable submodel) $\mathbf{P}_{n,\epsilon}$ of the super-learner fit \mathbf{P}_n with tuning parameter ϵ **so that a small change in ϵ corresponds with a maximal small change** in estimated answer $\Psi(\mathbf{P}_{n,\epsilon})$ to query $\Psi(P_0)$: i.e., score equals canonical gradient/**efficient influence curve** $D^*(\mathbf{P}_n)$.
- Determine the optimal amount ϵ_n of fluctuation based on the data (e.g., maximum likelihood estimation).
- The resulting update $\mathbf{P}_n^* = \mathbf{P}_{n,\epsilon_n}$ of the initial estimator of stochastic system is the TMLE of P_0 and it implies the TMLE $\Psi(\mathbf{P}_n^*)$ of the answer to query.
- Thanks to TMLE-update, TMLE solves optimal score equation $P_n D^*(\mathbf{P}_n^*) \approx 0$, and is asymptotically normally distributed around true answer to query with minimal asymptotic variance.

Three general methods for efficient estimation in literature

Three general methods result in asymptotically efficient estimators, given good initial estimator \mathbf{P}_n of data distribution P_0 , using canonical gradient $D^*(P)$ of target estimand as ingredient:

- **One-step estimator:** $\psi_n^1 = \Psi(\mathbf{P}_n) + P_n D^*(\mathbf{P}_n)$.
- **Estimating equation estimator:** Assume estimating function representation $D^*(P) = D^*(\psi, \eta(P))$; let ψ_n solution of $P_n D^*(\psi, \eta(\mathbf{P}_n)) = 0$.
- **TMLE:** $\mathbf{P}_{n,\epsilon}$ least favorable submodel through initial \mathbf{P}_n ; ϵ_n MLE; $P_n^* = \mathbf{P}_{n,\epsilon_n}$; TMLE is $\Psi(P_n^*)$.
- TMLE is general method that updates initial \mathbf{P}_n into improved fit \mathbf{P}_n^* that solves **user supplied set of equations** $P_n D(\mathbf{P}_n^*) \approx 0$, allowing for various additional statistical properties beyond asymptotic efficiency.

Each one of the methods has a sample splitting analogue removing Donsker class condition.

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Simulation design for ATE example

We repeatedly sampled random data generating mechanisms and simulated samples of size $n \in \{100, 500, 1000, 2000\}$ for a total of 25,000 different data generating mechanisms of (W, A, Y) .

We computed TMLEs of the ATE based on different estimators of $E_0(Y | A, W)$ and $P_0(A = 1 | W)$.

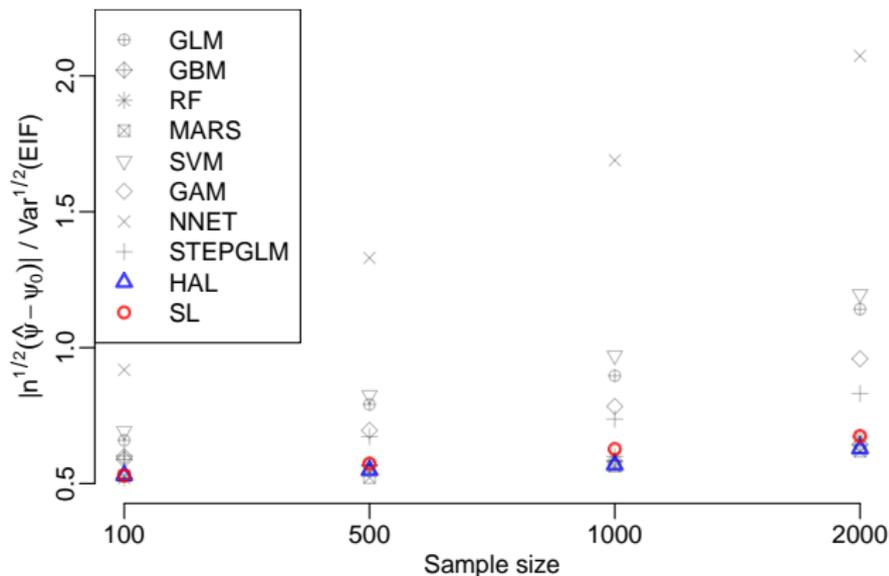
- GLM, Bayes GLM, stepwise GLM (AIC), stepwise GLM (p-value), stepwise GLM with two-way interactions, intercept-only GLM, GAM, GBM*, random forest*, linear SVM*, neural nets*, regression trees*, HAL
- Super Learner (based on these algorithms)
- * = tuning parameters selected via cross-validation

Estimators compared on their absolute error (relative to best achievable SE) and coverage probability of 95% oracle confidence intervals.

Results – absolute error by sample size

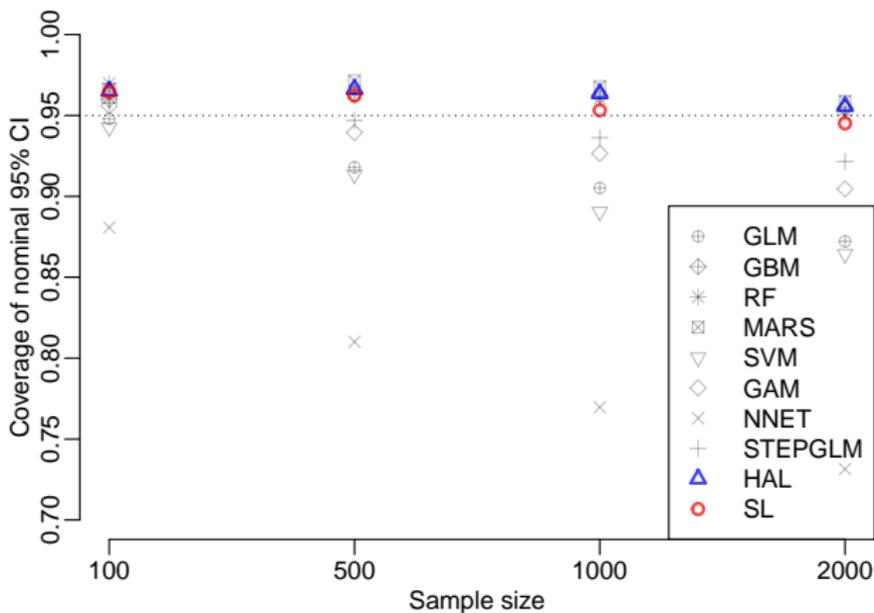
HAL-TMLE exhibited excellent accuracy relative to competitors.

Mean absolute error



Results – coverage by sample size

HAL-TMLE achieves approximate Normality in reasonable sample sizes.

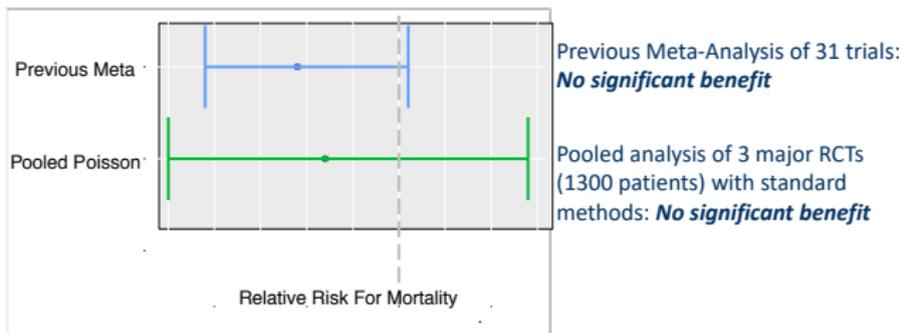


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1 Better, cheaper trials

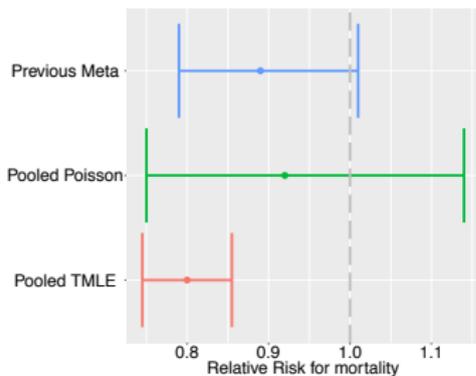
Do corticosteroids reduce mortality for adults with septic shock?



Pirracchio 2016

Better, cheaper trials

Do corticosteroids reduce mortality for adults with septic shock?



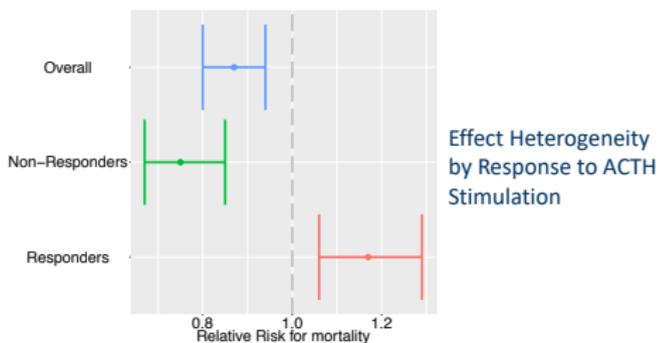
Previous Meta-Analysis of 31 trials:
No significant benefit

Pooled analysis of 3 major RCTs
(1300 patients) with standard
methods: **No significant benefit**

***Pooled analysis of 3 major RCTs
using Targeted Learning: significant
reduction of mortality.***

Not just is there an effect, but for whom?

- In Sepsis re-analysis: Targeted Learning showed **all benefit** occurred in a key subgroup
 - Heterogeneity in patient populations one cause of inconsistent results

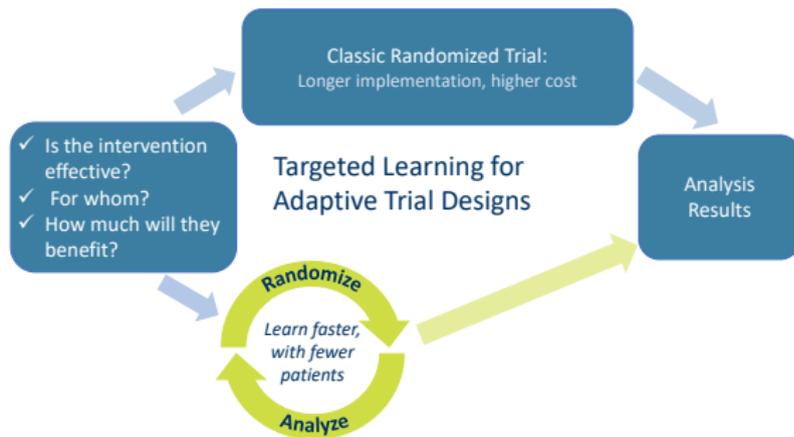


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Robust estimation and inference for sequential designs adapting intervention allocation probabilities based on learning from past

Optimal intervention allocation: “Learn as you go”



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General Longitudinal Data Structure for Complex Observational Studies

We observe n i.i.d. copies of a longitudinal data structure

$$O = (L(0), A(0), \dots, L(K), A(K), Y = L(K + 1)),$$

where $A(t)$ denotes a discrete valued **intervention node** whose effect we desire to evaluate, $L(t)$ is an intermediate covariate and outcome realized in between intervention nodes $A(t - 1)$ and $A(t)$, $t = 0, \dots, K$, and Y is a final **outcome** of interest.

Survival outcome example: For example,

$$A(t) = (A_1(t), A_2(t))$$

$$A_1(t) = \text{Indicator of being treated at time } t$$

$$A_2(t) = \text{Indicator of being right-censored at time } t$$

$$Y(t) = \text{Indicator of observing a failure by time } t$$

$$L(t) \quad \text{Vector of time-dependent measurements}$$

$$Y(t) \subset L(t) \text{ and } Y = Y(K + 1).$$

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A real-world CER study comparing different rules for treatment intensification for diabetes

- Data extracted from diabetes registries of 7 HMO research network sites:
 - Kaiser Permanente
 - Group Health Cooperative
 - HealthPartners
- Enrollment period: Jan 1st 2001 to Jun 30th 2009

Enrollment criteria:

- past A1c < 7% (glucose level) while on 2+ oral agents or basal insulin
- $7\% \leq \text{latest A1c} \leq 8.5\%$ (study entry when glycemia was no longer reined in)

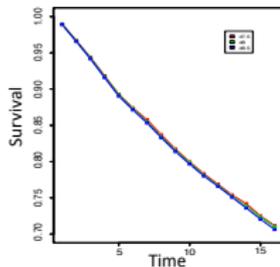
Longitudinal data

- Follow-up til the earliest of Jun 30th 2010, death, health plan disenrollment, or the failure date
- Failure defined as onset/progression of albuminuria (a microvascular complication)
- Treatment is the indicator being on "treatment intensification" (TI)
- $n \approx 51,000$ with a median follow-up of 2.5 years.

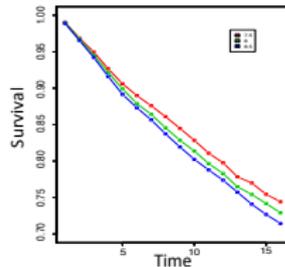
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Better clinical decisions from observational data

- When to intensify treatment for diabetic patients?
 - How best to respond to a series of biomarker measures?
 - 51,000 patients from 7 HMO diabetes registries



Standard methods: No benefit to more aggressive intensification strategy



Targeted Learning: More aggressive intensification protocols result in better outcomes

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Inference with TMLE

- TMLE is **asymptotically linear with influence curve the canonical gradient**, so that Wald-type confidence intervals are based on estimating variance of its influence curve.
- The simple sample variance of influence curve can underestimate the variance if initial estimator is very adaptive or lack of positivity.
- Robust estimation of this variance by using sample splitting, or TMLE plug-in estimator corrects for this finite sample bias, and can be important (Tran et al, 19).
- One can also use the nonparametric bootstrap if one uses HAL as initial estimator (Cai, vdL, 19), resulting in better finite sample coverage by also picking up higher order behavior.

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Advancing the vanilla TMLE: C-TMLE and extra targeting

- The least favorable parametric fluctuation model often depends on nuisance parameter (e.g., propensity score).
- C-TMLE targets estimation of this nuisance parameter based on criterion how well TMLE fits target estimand.
- Important for observational studies (vdL, Gruber, 2010 etc).
- By adding additional parameters to fluctuation model TMLE solves additional score equations that can be chosen to target second order remainder, and thereby improve finite sample performance.
- This has resulted in higher-order TMLE, double robust inference TMLE, etc (vdL, 14, Benkeser et al., Carone et al).

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Preparing SAP based on TMLE

- **Prior** data or **outcome blind** data can be used to decide on **target estimand** supported by data.
- Prior data can also be used to set up **realistic simulation** to benchmark *specifications* of TMLE implementation, where benchmarks includes confidence interval coverage and type I error control.
- These **specifications of TMLE** include deciding on library of SL; sample splitting version; C-TMLE for nuisance parameter; adaptive truncation; TMLE-update step (e.g, possible extra targeting).
- Once one commits, it freezes the **a priori-specified estimator** that can be submitted as part of SAP for FDA approval.

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Concluding Remarks

- **Targeted Learning** *optimally estimates* a causal impact of multiple time point intervention on an outcome for complex observational or randomized studies involving *random monitoring, time-dependent treatment, informative drop-out and missingness*.
- It integrates **causal inference, machine learning, statistical theory**.
- The estimate is accompanied with **confidence interval and p-value** for testing.
- The possible *gap between the estimand and causal quantity* due to violation of identification assumptions (e.g., no unmeasured confounder assumption) can be acknowledged through a **sensitivity analysis**.
- We have developed an ongoing targeted learning software environment **tlverse()** with growing number of tools.