

# Targeted Maximum Likelihood Estimation (TMLE) for Machine Learning: A Gentle Introduction

Mark van der Laan & Rachael Phillips  
Division of Biostatistics, University of California at Berkeley

**Deming Conference on Applied Statistics**  
Session I: 9:00A-12:00P on December 4, 2019

# Schedule

- **9:00A-11:00A:** Overview of Targeted Machine Learning
- **11:00A-12:00P:** TMLE for the Causal Impact of a Single Time-Point Intervention on Survival with Software Exercise in R

## Resources

- The latest version of the presentation slides are available here:  
<https://github.com/tlverse/deming2019-workshop/tree/master/slides>.
- The open source and fully-reproducible electronic vignette for the software tutorials can be found here:  
<https://tlverse.org/deming2019-workshop/>.

# Targeted Machine Learning

## Causal Inference for Real-World Data Science

Mark van der Laan

Division of Biostatistics, University of California at Berkeley

### **Deming Conference on Applied Statistics**

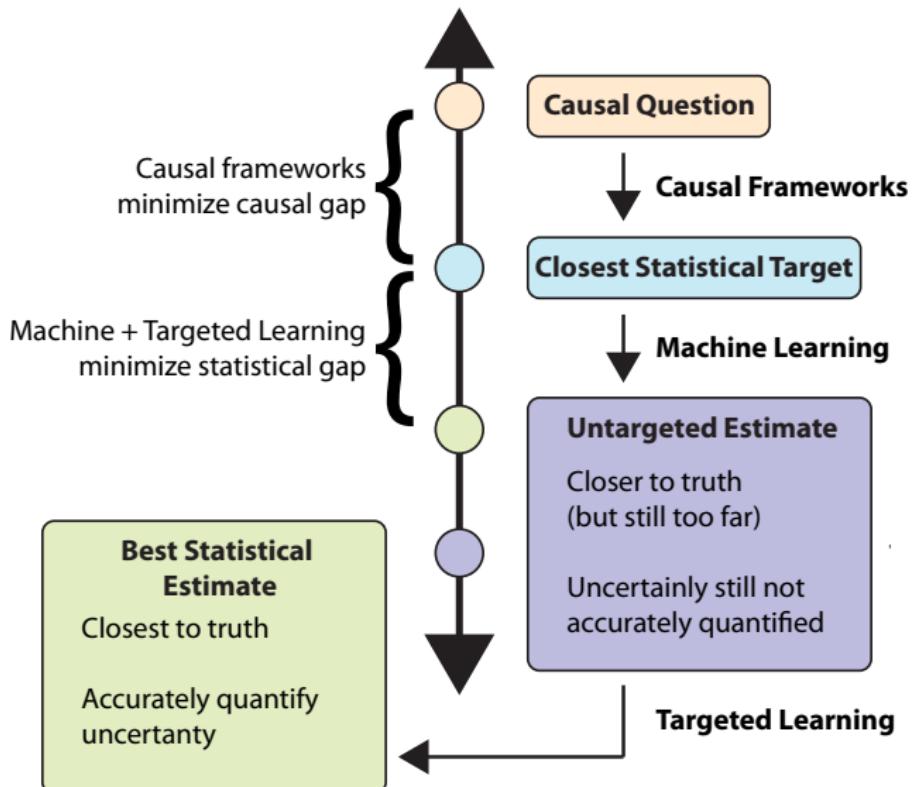
December 4-6 2019, Atlantic City NJ

Various slides from Maya Petersen presentation (NIH R01 AI074345)  
and Bill and Melinda Gates Foundation presentation.

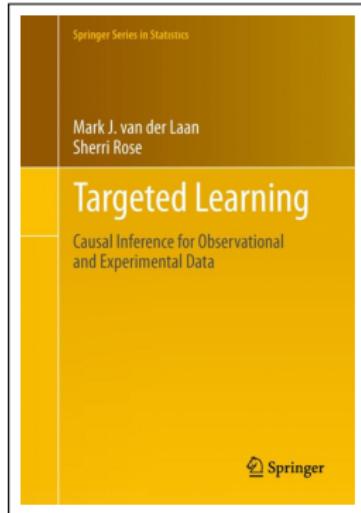
# Outline

- 1 Introduction
- 2 Roadmap for statistical learning
- 3 Nonparametric estimation of the Average Treatment Effect
- 4 Super learning and Highly Adaptive Lasso (HAL)
- 5 Targeted Maximum Likelihood Estimation (TMLE)
- 6 Targeted Learning for analyzing RCTs
- 7 Targeted Learning for adaptive trial design
- 8 Targeted Learning in complex longitudinal observational studies
- 9 Inference with TMLE
- 10 Collaborative TMLE for effective/targeted estimation of propensity score
- 11 Preparing SAP based on TMLE
- 12 Software For Targeted Learning
- 13 Concluding remarks

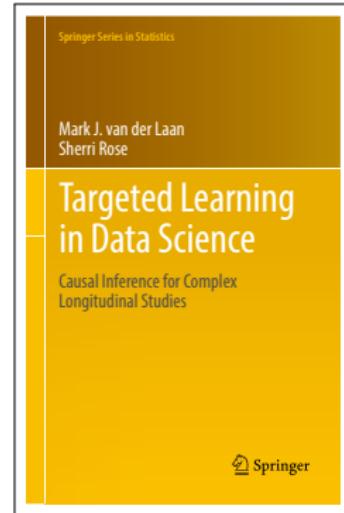
# Targeted Learning fills a much needed gap in machine learning and causal inference



# Targeted Learning is a subfield of statistics



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



van der Laan & Rose, *Targeted Learning in Data Science: Causal Inference for Complex Longitudinal Studies*. New York: Springer, 2018.

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# Roadmap for Statistical Learning

- ① Describe observed data
- ② Specify statistical model
- ③ Define statistical query (e.g., using causal roadmap)
- ④ Construct estimator
- ⑤ Obtain inference

# Roadmap for Statistical Learning

STEP 1:  
DESCRIBE  
OBSERVED DATA

STEP 2:  
SPECIFY  
STATISTICAL MODEL

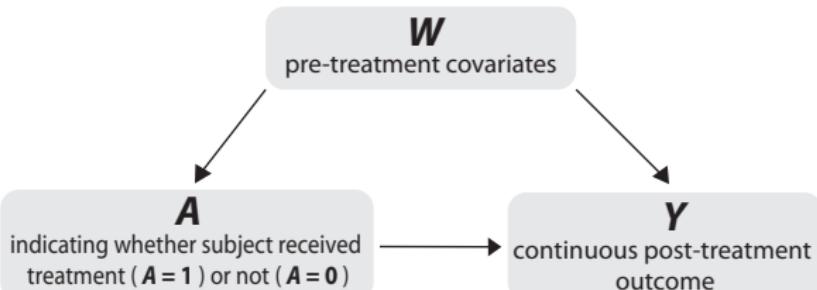
STEP 3:  
DEFINE  
STATISTICAL QUERY

STEP 4:  
CONSTRUCT  
ESTIMATOR

STEP 5:  
OBTAIN INFERENCE

$n = 100$  subjects were sampled independently from each other and from the same population distribution  $P_0$

For each subject, pre-treatment covariates ( $W$ ), treatment ( $A$ ), and outcome ( $Y$ ) vectors were measured



# Roadmap for Statistical Learning

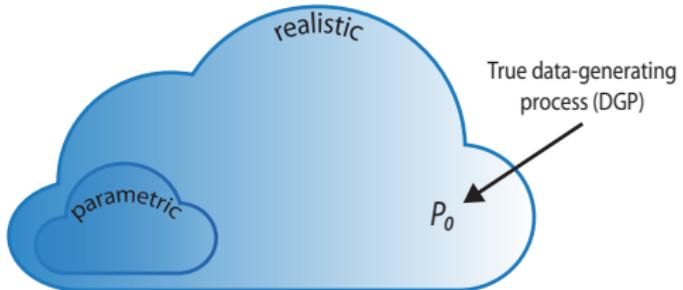
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## Standard Approach

Parametric statistical model

Does not contain  $P_0$ , the DGP  
(i.e., misspecified model)

## Targeted Learning

Realistic semiparametric or  
nonparametric statistical model

Defined to ensure  $P_0$  is  
contained in model

# Roadmap for Statistical Learning

STEP 1:  
DESCRIBE  
OBSERVED DATA

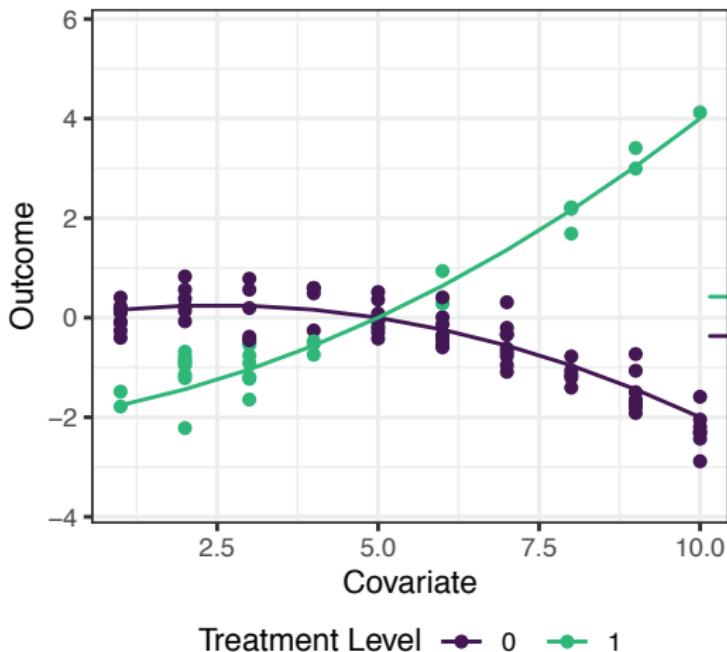
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Example True DGD



# Roadmap for Statistical Learning

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*What is the average difference in outcomes between treatment groups when adjusting for covariates?*

$$\Psi(P_0) = E_0(E_0[Y|A=1, W] - E_0[Y|A=0, W])$$

$\Psi$  is a function that takes as input  $P_0$  and outputs the answer to the question of interest

The **assumption of positivity** is required to estimate of this quantity from the data. That is, it must be possible to observe both levels of treatment for all strata of  $W$ .

Additional assumptions are required to interpret this estimand as causal

# Causal roadmap for obtaining statistical query answering causal question

Step 3 can be carried out using following causal roadmap:

- Define **potential outcomes**  $Y_0, Y_1$  for each subject, representing (counterfactual) outcome we would have seen if subject would have taken treatment 0 and 1, respectively.
- Link desired full-data  $(W, Y_0, Y_1)$  to observed data  $O = (W, A, \mathbf{Y} = \mathbf{Y}_A)$ .
- Define **causal quantity** of interest:  $E(Y_1 - Y_0)$ , called average treatment effect.
- Establish **identification from DGD**: If treatment is independent of potential outcomes, given  $W$ , and positivity holds, then  $E_0(Y_1 - Y_0)$  equals target estimand  $\Psi(P_0)$ .

# Roadmap for Statistical Learning

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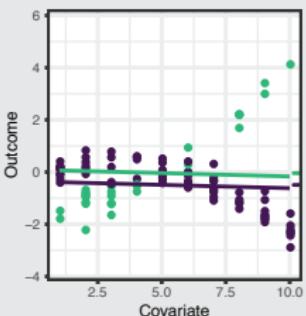
## Standard Approach

Generalized Linear Model (GLM)  
to estimate

$$\mathbf{Y} = \beta_0 + \beta_1 \mathbf{A} + \beta_2 \mathbf{W} + \epsilon$$

Estimated coefficients  
are biased

Cannot detect heterogeneity  
in treatment effect

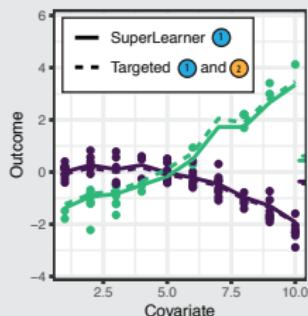


## Targeted Learning

TMLE implements  
a two-step procedure

- 1 initial estimation of  $E_0[Y|A, W]$  with super (machine) learning
- 2 targeting towards optimal bias-variance trade-off for  $\Psi(P_0)$

TMLE estimates are unbiased  
and doubly robust



# Roadmap for Statistical Learning

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## Standard Approach

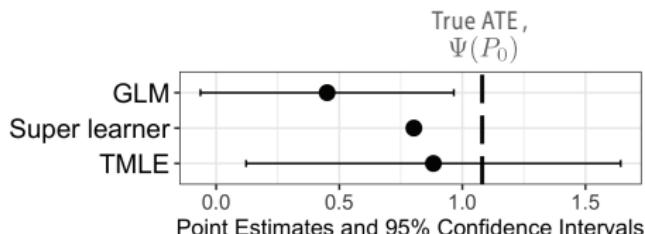
Inference (such as  $p$ -value and confidence interval) assumes parametric model is true

Inference is misleading and erroneous

## Targeted Learning

Targeting (step ②) improves estimate and makes inference possible

Trustworthy inference obtained with efficient influence function



# Roadmap of Statistical Learning Summary

- **Observed data:** Realization of a random variable  $O^n = (O_1, \dots, O_n)$  with a probability distribution (say)  $P_0^n$ , indexed by "sample size"  $n$ .
- **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  $\Psi$  from model  $\mathcal{M}^n$  to real line, where  $\Psi(P_0^n)$  is the true answer to query about our stochastic system.
- **Estimator:** An a priori-specified algorithm that takes the observed data  $O^n$  and returns an estimate  $\psi_n$  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.

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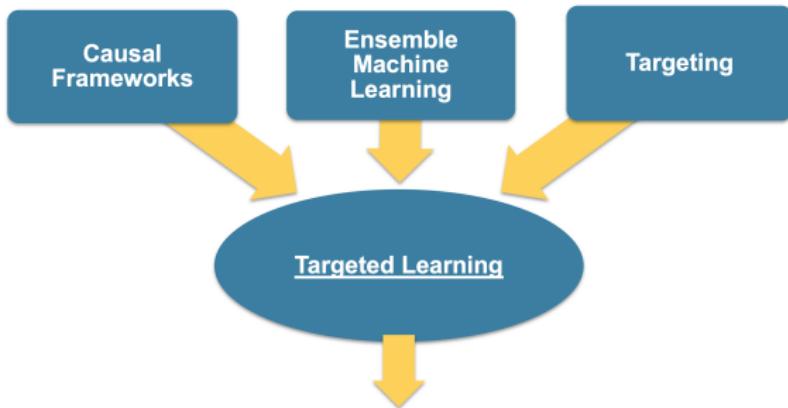
## Example: Nonparametric Estimation of Average Treatment Effect

- 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:

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

- Under causal model, randomization assumption, and positivity assumption,  $\Psi(P) = E(Y_1 - Y_0)$  is the ATE.
- A TMLE will estimate  $P(Y = 1 | A, W)$  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)

DIA

# Identifying contributing factors for health care spending

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DOI: 10.1111/1475-6773.12848

METHODS ARTICLE

## Robust Machine Learning Variable Importance Analyses of Medical Conditions for Health Care Spending

*Sherri Rose* 

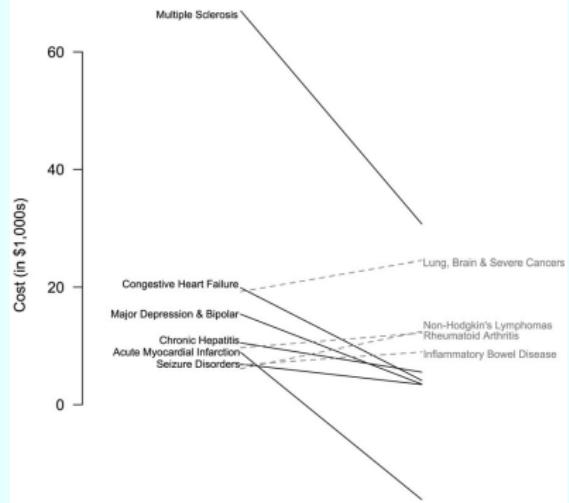
# Identifying contributing factors for health care spending

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DOI: 10.1111/1475-6773.12848  
METHODS ARTICLE

## Robust Machine Learning Variance Importance Analyses of Medication Conditions for Health Care Spending

Sherri Rose 

Figure 4: Top 10 Largest Targeted Learning Effect Estimates



# Average treatment effect in an observational study

International Archives of Occupational and Environmental Health (2019) 92:629–638  
<https://doi.org/10.1007/s00420-018-1397-1>

ORIGINAL ARTICLE



## An educational intervention to improve knowledge about prevention against occupational asthma and allergies using targeted maximum likelihood estimation

Daloha Rodríguez-Molina<sup>1,2</sup> · Swaantje Barth<sup>1</sup> · Ronald Herrera<sup>1</sup> · Constanze Rossmann<sup>3</sup> · Katja Radon<sup>1</sup> · Veronika Karnowski<sup>4</sup>

Received: 15 March 2018 / Accepted: 13 December 2018 / Published online: 14 January 2019  
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**Table 4** Adjusted average treatment effects of the intervention ( $n=116$ ), Bavaria, Germany, 2014

	All six correct measures	At least five correct measures	At least four correct measures
Additive ATE			
Parameter	18.44%	55.53%	29.60%
95% CI	(7.3–29.58%)	(36.96–74.09%)	(12.2–47.0%)
Additive ATT			
Parameter	16.9%	63.07%	62.78%
95% CI	(5.38–28.51%)	(46.02–80.13%)	(41.64–83.93%)
Additive ATC			
Parameter	16.8%	32.28%	18.97%
95% CI	(5.02–28.57%)	(12.84–51.72%)	(1.91–36.02%)

Adjusted for sex, age, education level, smoking status, presence of asthma or rhinoconjunctivitis, riskperception, parental asthma, and knowledge about preventive measures against asthma and allergies before the intervention

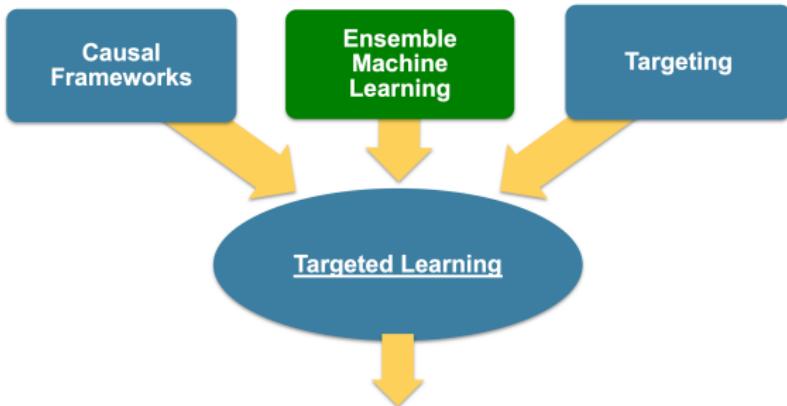
The adjusted model using TMLE allowed including both observed data ( $n=47$ ) and missing values ( $n=69$ ) as parameters

ATE average treatment effect, ATT average treatment effect on the treated, CI confidence interval, ATC average treatment effect on the controls, TMLE targeted maximum likelihood estimation

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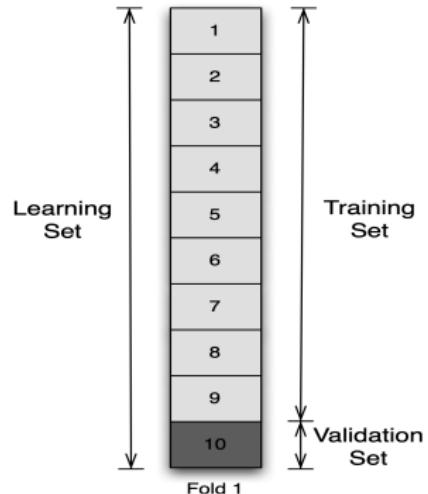
# Targeted Learning



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

# 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

DIA

# V-fold Cross Validation

1	1	1	1	1	1	1	1	1	1
2	2	2	2	2	2	2	2	2	2
3	3	3	3	3	3	3	3	3	3
4	4	4	4	4	4	4	4	4	4
5	5	5	5	5	5	5	5	5	5
6	6	6	6	6	6	6	6	6	6
7	7	7	7	7	7	7	7	7	7
8	8	8	8	8	8	8	8	8	8
9	9	9	9	9	9	9	9	9	9
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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# Improving upon the current standard of predictive analytics in the ICU

## THE LANCET Respiratory Medicine

Volume 3, Issue 1, January 2015, Pages 42-52



### Articles

Mortality prediction in intensive  
care units with the Super ICU  
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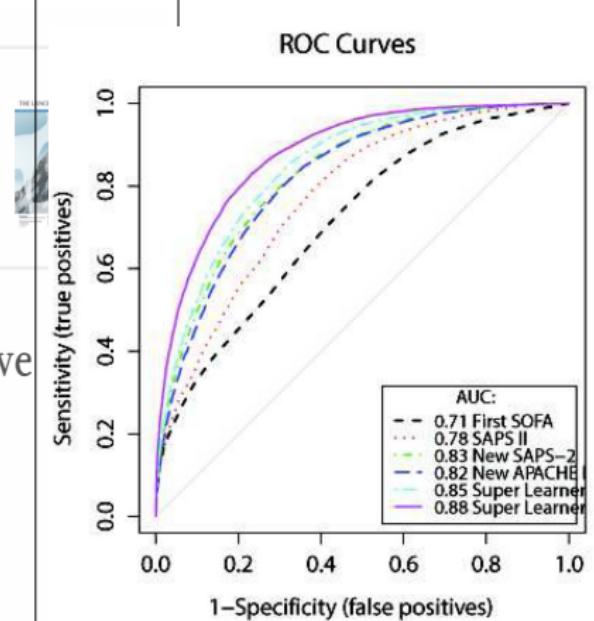
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## Cross-validation is optimal for selection among estimators

- 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.

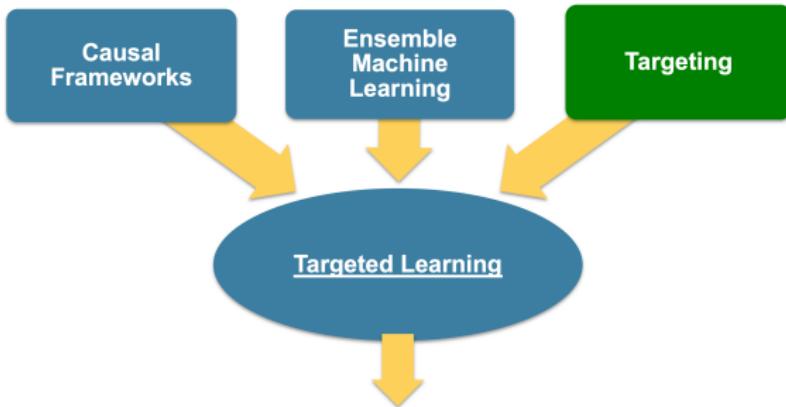
## Highly Adaptive Lasso (HAL)

- 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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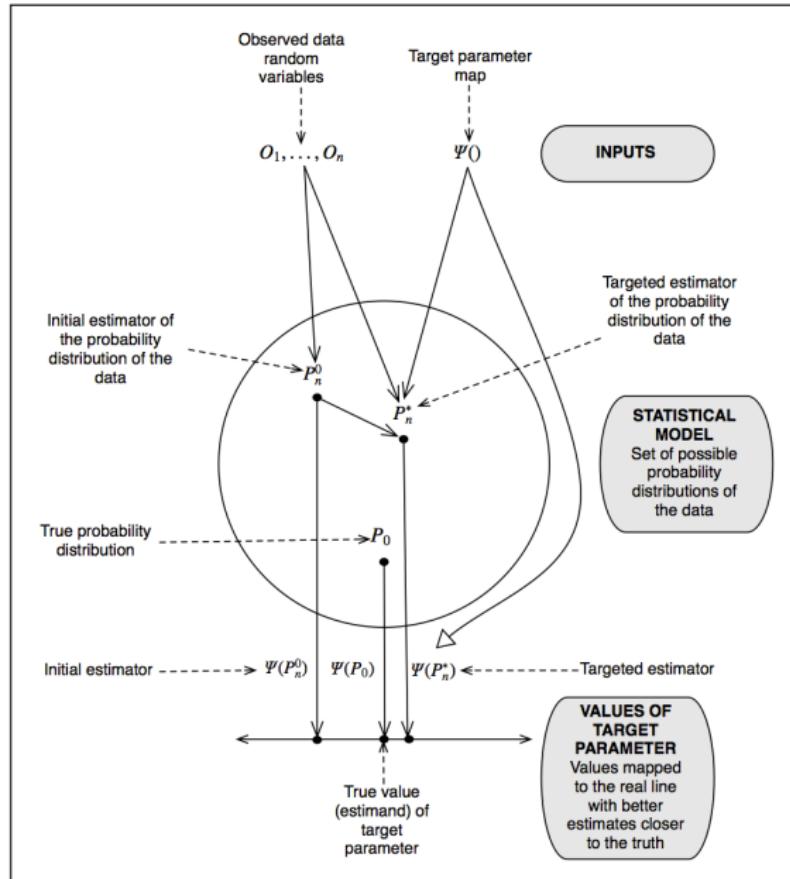


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## Targeted Update of Machine Learning

- Don't try to do a good job for all questions at once.
  - Focus estimation where it matters most for question at hand.
- ➊ Less bias (closer to truth).
  - ➋ 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  $\epsilon$  **so that a small change in  $\epsilon$  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  $\epsilon_n$  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  $\psi_n$  solution of  $P_n D^*(\psi, \eta(\mathbf{P}_n)) = 0$ .
- **TMLE:**  $\mathbf{P}_{n,\epsilon}$  least favorable submodel through initial  $\mathbf{P}_n$ ;  $\epsilon_n$  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.

## Objective simulation with HAL-TMLE of ATE

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.

## Results – coverage by sample size

HAL-TMLE achieves approximate Normality in reasonable sample sizes.

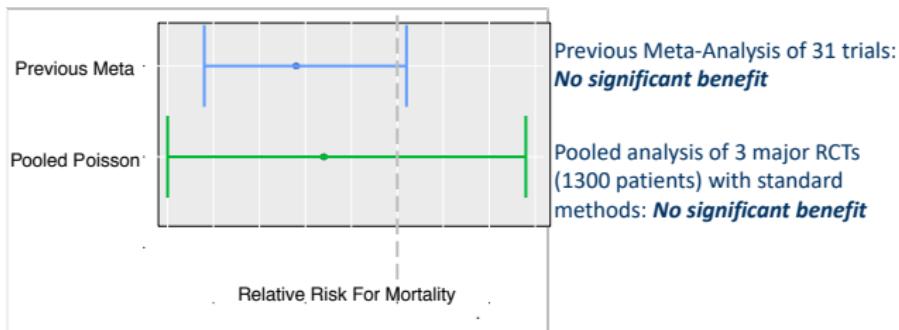
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## 1

## Better, cheaper trials

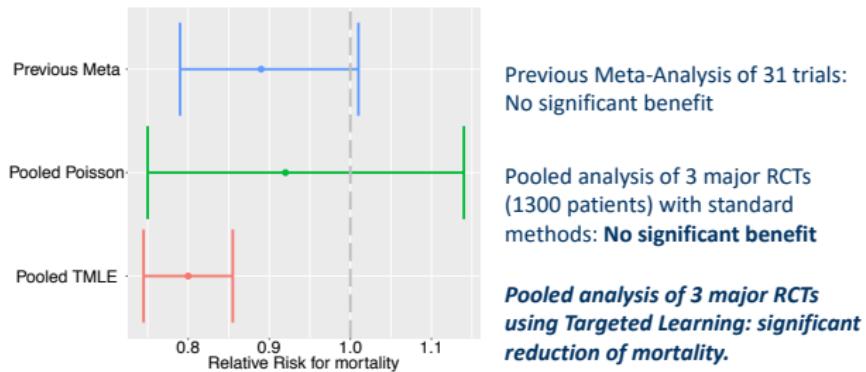
Do corticosteroids reduce mortality for adults with septic shock?



Pirracchio 2016

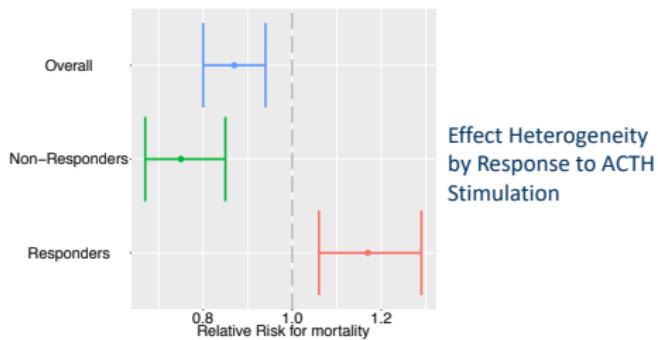
## Better, cheaper trials

Do corticosteroids reduce mortality for adults with septic shock?



## 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



# Estimating the causal effect of a community-level intervention in a clustered RCT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## HIV Testing and Treatment with the Use of a Community Health Approach in Rural Africa

D.V. Havlir, L.B. Balzer, E.D. Charlebois, T.D. Clark, D. Kwarisiima, J. Ayieko,  
J. Kabami, N. Sang, T. Liegler, G. Charmie, C.S. Camlin, V. Jain, K. Kadede,  
M. Atukunda, T. Ruel, S.B. Shade, E. Ssemmondo, D.M. Byonanebye,  
F. Mwangwa, A. Owaranaganise, W. Oolio, D. Black, K. Snyman, R. Burger,  
M. Getahun, J. Achando, B. Awuonda, H. Nakato, J. Kironde, S. Okiror,  
H. Thirumurthy, C. Koss, L. Brown, C. Marquez, J. Schwab, G. Lavoy, A. Plenty,  
E. Mugoma Wafula, P. Omanya, Y.-H. Chen, J.F. Rooney, M. Bacon,  
M. van der Laan, C.R. Cohen, E. Bukusi, M.R. Kamya, and M. Petersen

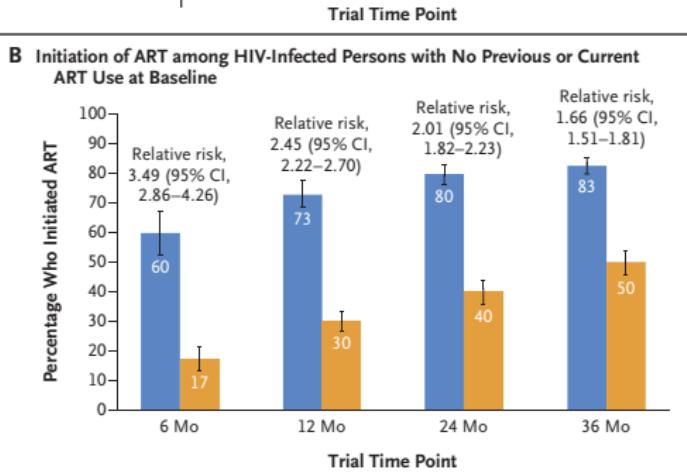
# Estimating the causal effect of a community-level intervention in a clustered RCT

The NEW ENGLAND JOURNAL of MEDICINE

## ORIGINAL ARTICLE

### HIV Testing and Treatment with the Use of a Community Health Approach in Rural Africa

D.V. Havlir, L.B. Balzer, E.D. Charlebois, T.D. Clark, D. Kwarisiima, J. A. J. Kabarni, N. Sang, T. Liegler, G. Charmie, C.S. Camlin, V. Jain, K. Kad M. Atukunda, T. Ruel, S.B. Shade, E. Ssemmondo, D.M. Byonanyiby F. Mwangwa, A. Owaramanise, W. Oolio, D. Black, K. Snyman, R. Burg M. Getahun, J. Achando, B. Awuonda, H. Nakato, J. Kironde, S. Okir H. Thirumurthy, C. Koss, L. Brown, C. Marquez, J. Schwab, G. Lavoy, A. E. Mugoma Wafula, P. Omanya, Y.-H. Chen, J.F. Rooney, M. Bacon M. van der Laan, C.R. Cohen, E. Bukusi, M.R. Kamya, and M. Peters



# Increasing precision and accuracy by accounting for missing data in estimating impacts of HIV treatment program in clustered RCT

Research

JAMA | Original Investigation

## Association of Implementation of a Universal Testing and Treatment Intervention With HIV Diagnosis, Receipt of Antiretroviral Therapy, and Viral Suppression in East Africa

Maya Petersen, MD, PhD; Laura Balzer, PhD; Dalsone Kwartsima, MBChB, MPH; Norton Sang, MA; Gabriel Chamie, MD, MPH; James Ayieko, MBChB, MPH; Jane Kabami, MPH; Asiphas Owaraganise, MBChB; Teri Liegler, PhD; Florence Mwangwa, MBChB; Kevin Kadede, MA; Vivek Jain, MD, MAS; Albert Plenty, MS; Lillian Brown, MD, PhD; Geoff Lavoy; Joshua Schwab, MS; Douglas Black, BA; Mark van der Laan, PhD; Elizabeth A. Bukusi, MBChB, PhD; Craig R. Cohen, MD, MPH; Tamara D. Clark, MHS; Edwin Charlebois, MPH, PhD; Moses Kamya, MMed; Diane Havlir, MD

# Increasing precision and accuracy by accounting for missing data in estimating impacts of HIV treatment program in clustered RCT

Research

JAMA | Original Investigation

## Association of Implementation and Treatment Intervention of Antiretroviral Therapy

Table 2. Postbaseline HIV Viral Suppression in a Closed Cohort of HIV-Positive Stable Residents of 16 SEARCH Intervention Communities in Rural Uganda and Kenya Who Were Diagnosed At or Before Baseline (n = 7108)\*

Baseline Diagnosis, Treatment, and Suppression Status	No. of HIV-Positive Residents (%) <sup>a</sup>	Follow-up Year 1		Follow-up Year 2	
		No. of Residents With Viral Suppression/Total No. of Residents With Measured HIV RNA (%) <sup>a</sup>	Adjusted Proportion, % (95% CI) <sup>a</sup>	No. of Residents With Viral Suppression/Total No. of Residents With Measured HIV RNA (%) <sup>a</sup>	Adjusted Proportion, % (95% CI) <sup>a</sup>
Overall	7108 (100)	4682/5578 (83.9)	79.7 (78.7-80.8)	4602/5215 (88.2)	83.8 (82.8-84.9)
Newly diagnosed (HIV RNA≥500 copies/mL)	2080 (29.3)	963/1321 (72.9)	62.8 (60.4-65.2)	965/1205 (80.1)	68.8 (66.4-71.2)
Previously diagnosed with no ART (HIV RNA≥500 copies/mL)	990 (13.9)	649/812 (79.9)	78.1 (75.3-80.8)	685/778 (88.0)	86.5 (84.2-88.8)
Previous or current ART	4038 (56.8)	3070/3445 (89.1)	88.8 (87.7-89.9)	2952/3232 (91.3)	90.5 (89.4-91.6)
HIV RNA not measured	1063 (15.0)	732/846 (86.5)	86.6 (84.3-88.9)	685/779 (87.9)	87.2 (84.9-89.5)
HIV RNA≥500 copies/mL	426 (6.0)	175/355 (49.3)	49.5 (44.2-54.7)	204/325 (62.8)	62.2 (57.2-67.2)
HIV RNA<500 copies/mL	2549 (35.9)	2163/2244 (96.4)	96.3 (95.6-97.1)	2063/2128 (96.9)	96.8 (96.0-97.6)

Maya Petersen, MD, PhD; Laura Balzer, PhD; Dalsone Kwasimba, MBChB, MPH; Norton Sang, MA; Gabriel Chamie, MD, MPH; James Ayleko, MBChB, MPH; Jane Kabami, MPH; Asiphas Owaraganise, MBChB; Teri Liegler, PhD; Florence Mwangwa, MBChB; Kevin Kadede, MA; Vivek Jain, MD, MAS; Albert Plenty, MS; Lillian Brown, MD, PhD; Geoff Lavoy; Joshua Schwab, MS; Douglas Black, BA; Mark van der Laan, PhD; Elizabeth A. Bukusi, MBChB, PhD; Craig R. Cohen, MD, MPH; Tamara D. Clark, MHS; Edwin Charlebois, MPH, PhD; Moses Kamya, MMed; Diane Havlir, MD

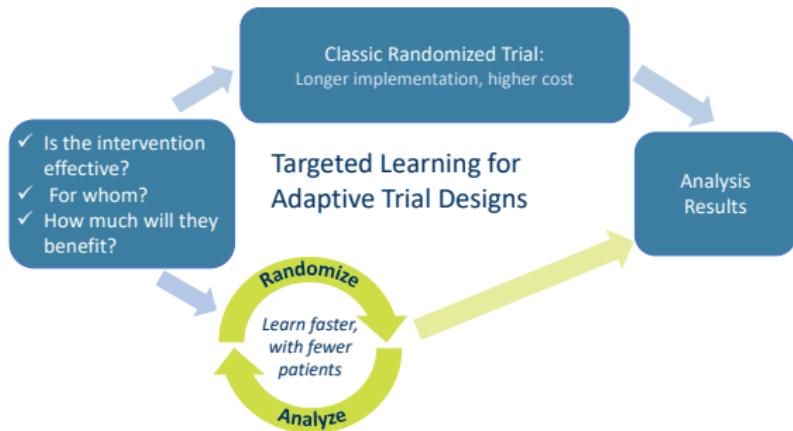


# Outline

- 1 Introduction
- 2 Roadmap for statistical learning
- 3 Nonparametric estimation of the Average Treatment Effect
- 4 Super learning and Highly Adaptive Lasso (HAL)
- 5 Targeted Maximum Likelihood Estimation (TMLE)
- 6 Targeted Learning for analyzing RCTs
- 7 Targeted Learning for adaptive trial design**
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- 12 Software For Targeted Learning
- 13 Concluding remarks

# 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,

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

$A_1(t)$  = Indicator of being treated at time  $t$

$A_2(t)$  = Indicator of being right-censored at time  $t$

$Y(t)$  = Indicator of observing a failure by time  $t$

$L(t)$  Vector of time-dependent measurements

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

# Comparing strategies for diabetes treatment intensification in Comparative Effectiveness Research (CER) study

- Data extracted from diabetes registries of 7 HMO research network sites: Kaiser Permanente, Group Health Cooperative, HealthPartners.
- Enrollment period: Jan 1<sup>st</sup> 2001 to Jun 30<sup>th</sup> 2009
- Enrollment criteria: past A1c < 7% (glucose level) while on 2+ oral agents or basal insulin and  $7\% \leq \text{latest A1c} \leq 8.5\%$  (study entry when glycemia was no longer reined in)

Longitudinal data:

- Follow-up til the earliest of Jun 30<sup>th</sup> 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.

# Comparing strategies for diabetes treatment intensification in Comparative Effectiveness Research (CER) study

Statistics  
in Medicine

Research Article

Received 24 May 2013,

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(wileyonlinelibrary.com) DOI: 10.1002/sim.6099

## Targeted learning in real-world comparative effectiveness research with time-varying interventions

Romain Neugebauer,<sup>a\*†</sup> Julie A. Schmittiel<sup>a</sup> and  
Mark J. van der Laan<sup>b</sup>

# Comparing strategies for diabetes treatment intensification in Comparative Effectiveness Research (CER) study

Statistics  
in Medicine

Research Article

Received 24 May 2013,

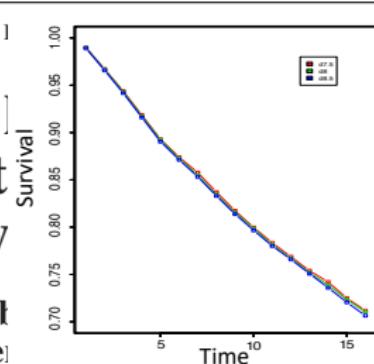
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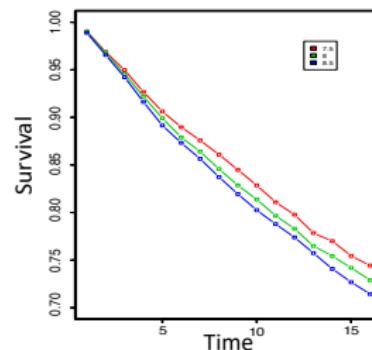
(wileyonlinelibrary.com)

Targeted  
comparat  
time-vary

Romain Neugeb  
Mark J. van de



**Standard methods:** No benefit to more aggressive intensification strategy



**Targeted Learning:** More aggressive intensification protocols result in better outcomes

# Estimating the cumulative, long-term impacts of environmental exposures

ORIGINAL ARTICLE

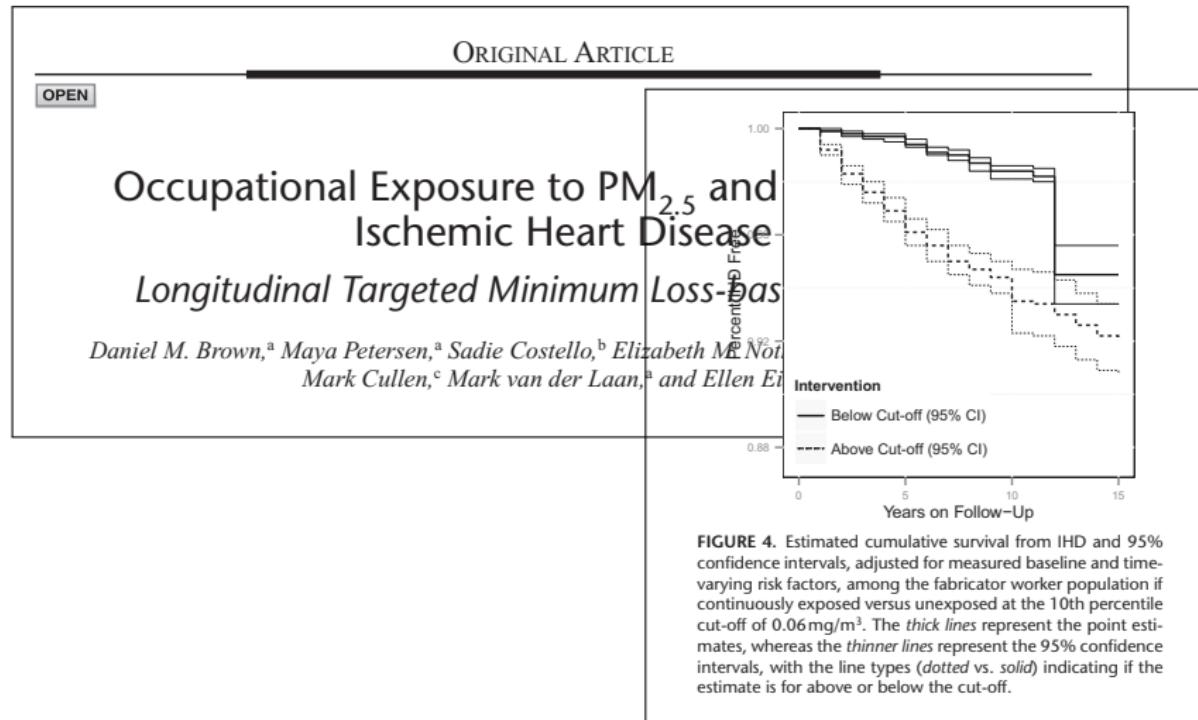
OPEN

## Occupational Exposure to PM<sub>2.5</sub> and Incidence of Ischemic Heart Disease

*Longitudinal Targeted Minimum Loss-based Estimation*

Daniel M. Brown,<sup>a</sup> Maya Petersen,<sup>a</sup> Sadie Costello,<sup>b</sup> Elizabeth M. Noth,<sup>b</sup> Katherine Hammond,<sup>b</sup> Mark Cullen,<sup>c</sup> Mark van der Laan,<sup>a</sup> and Ellen Eisen<sup>b</sup>

# Estimating the cumulative, long-term impacts of environmental exposures



# Estimating the impact of genetic polymorphisms on the efficacy of malaria vaccine on the time to infection

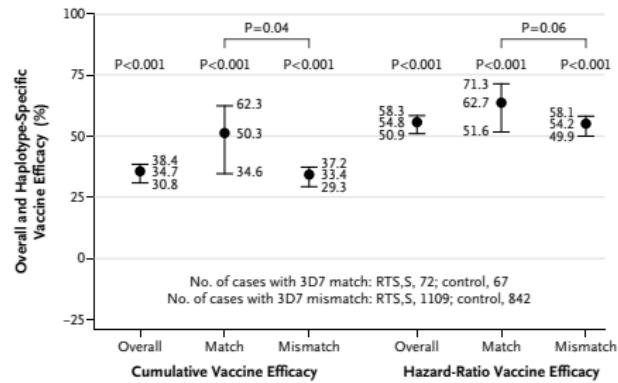
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Genetic Diversity and Protective Efficacy of the RTS,S/AS01 Malaria Vaccine

D.E. Neafsey, M. Juraska, T. Bedford, D. Benkeser, C. Valim, A. Griggs, M. Lievens, S. Abdulla, S. Adjei, T. Agbenyega, S.T. Agnandji, P. Aide, S. Anderson, D. Ansong, J.J. Aponte, K.P. Asante, P. Bejon, A.J. Birkett, M. Bruls, M.K. Connolly, U. D'Alessandro, C. Dobaño, S. Gesase, B. Greenwood, J. Grimesby, H. Tinto, M.J. Hamel, I. Hoffman, P. Kamthunzi, S. Kariuki, P.G. Kremsner, A. Leach, B. Lell, N.J. Lennon, J. Lusingu, K. Marsh, F. Martinson, J.T. Molet, E.L. Moss, P. Njuguna, C.F. Ockenhouse, B. Ragama Ogutu, W. Otieno, L. Otieno, K. Otieno, S. Owusu-Agyei, D.J. Park, K. Pellé, D. Robbins, C. Russ, E.M. Ryan, J. Sacarlal, B. Sogoloff, H. Sorgho, M. Tanner, T. Theander, I. Valea, S.K. Volkman, Q. Yu, D. Lapierre, B.W. Birren, P.B. Gilbert, and D.F. Wirth

### D Cumulative and Hazard-Ratio Vaccine Efficacy



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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 Statistical Analysis Plan 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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## tlverse - Targeted Learning software ecosystem in R

- A curated collection of R packages for Targeted Learning
- Shares a consistent underlying philosophy, grammar, and set of data structures
- Open source
- Designed for generality, usability, and extensibility
- Microwave dinners for machine learning

# tlverse outreach to train and support practitioners

- May 2019 - Atlantic Causal Inference Conference (ACIC) Workshop
- June 2019 - tlverse book →
- October 2019 - University of Pittsburgh School of Public Health Workshop
- November 2019 - Bill & Melinda Gates Foundation Workshop
- December 2019 - Deming Conference on Applied Statistics Workshop



- February 2020 - Conference on Statistical Practice (CSP) Workshop
- March 2020 - Alan Turing Institute Workshop

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## Concluding Remarks

- **Targeted Learning** *optimally estimates* the causal impact of an intervention on an outcome for complex real-world data.
- It integrates **causal inference, machine learning, statistical theory**.
- Targeted Learning learns better answers to causal, actionable questions which result in improved policy, treatments, etc.
- The estimate is accompanied with accurate quantification of uncertainty such as **confidence interval and p-value**.
- We have developed an ongoing targeted learning software environment `tlverse` with growing number of tools and tutorials.

# Targeted Maximum Likelihood Estimation for the Causal Impact of a Single Time-Point Intervention on Survival

Mark van der Laan & Rachael Phillips  
Division of Biostatistics, University of California at Berkeley

**Deming Conference on Applied Statistics**  
Session I: 9:00A-12:00P on December 4, 2019

# Outline

- 1 Causal model for the counterfactual treatment specific survival curve
- 2 Statistical estimation problem
- 3 Super-learner and HAL-MLE of conditional hazard
- 4 One-step TMLE of causal impact of point intervention on survival

## Observed data

- We observe

$$O = (W, A, \tilde{T} = \min(T, C), \Delta = I(T \leq C)) \sim P_0$$

- $W$  baseline covariates.
- $A$  binary treatment.
- $C, T$ , censoring and survival time.

## Causal formulation of observed data

- $T_0, T_1$  potential survival times under control and treatment.
- $C_0, C_1$  potential censoring times under control and treatment.
- $T = T_A, C = C_A, \tilde{T} = \tilde{T}_A, \Delta = \Delta_A$ .
- $O = (W, A, \tilde{T}_A = \min(T_A, C_A), \Delta_A = I(T_A \leq C_A))$ .

## Causal quantity: Treatment specific survival curve

- Let  $W \rightarrow d(W) \in \{0, 1\}$  be a dynamic treatment rule.
- Let  $S_d(t) = P(T_d > t)$ , where  $T_d = T_{d(W)}$  be quantity of interest.

## Coarsening at random assumption on treatment and censoring

- Randomization of treatment: Assume that  $A$  is independent of  $T_d$ , given  $W$ .
- Let  $A_2(t) = I(\tilde{T} \leq t, \Delta = 0)$  is censoring process, jumps at observed censoring time.
- Let  $N(t) = I(\tilde{T} \leq t, \Delta = 1)$  is failure process that jumps at observed failure time.
- $(W, A, \bar{N}(t), \bar{A}_2(t-))$  is available history right before  $A_2(t)$ .
- Non-informative censoring (CAR): Assume that at each time  $t$ ,  $A_2(t)$  is independent of  $T_d$ , given  $(W, A, \bar{N}(t), \bar{A}_2(t-))$ .
- These assumptions are non-testable: put no restrictions on data distribution  $P_0$ .

## Identifiability of treatment specific survival curve

- Under the above CAR assumption we have

$$S_d(t_0) = E_P S(t_0 \mid A = d(W), W).$$

- $S(t_0 \mid A, W) = P(T > t_0 \mid A, W)$  conditional survival curve of  $T$ .
- For any data distribution  $P$ , let  $\Psi(P) = E_P S(t_0 \mid A = d(W), W)$ .

# Outline

- ① Causal model for the counterfactual treatment specific survival curve
- ② Statistical estimation problem
- ③ Super-learner and HAL-MLE of conditional hazard
- ④ One-step TMLE of causal impact of point intervention on survival

## Longitudinal formulation of observed data

- We can represent the observed data as

$$O = (W, A, \bar{A}_2(\tau), \bar{N}(\tau)),$$

where  $\tau$  is a maximal follow up time.

- This data is time-ordered as:

$$O = (W, A, A_2(0), N(1), A_2(1), N(2), \dots, A_2(\tau - 1), N(\tau)).$$

## Conditional probability distributions of data distribution

- Let  $Q_W$  be probability measure of  $W$ .
- Let  $Q_{N(t)}$  be conditional probability measure of  $N(t)$ , given  $W, A, \bar{N}(t-1), \bar{A}_2(t-1)$ .
- Let  $Q_N = (Q_{N(t)} : t)$ .
- Let  $G_1$  be conditional probability measure of  $A$ , given  $W$ .
- Let  $G_{A_2(t)}$  be conditional probability measure of  $A_2(t)$ , given  $W, A, \bar{A}_2(t-1), \bar{N}(t)$ .
- Let  $G_2 = (G_{A_2(t)} : t)$ .

## Density of data distribution

- The density of a data distribution  $P$  of  $O$  can be factorized as: for  $o = (w, a, \bar{a}_2(\tau), \bar{n}(\tau))$ ,

$$p(o) = q_W(w) \prod_{t=0}^{\tau} q_{N(t)}(n(t) | w, a, \bar{a}_2(t-1), \bar{n}(t-1)) \\ g_1(a | W) \prod_{t=0}^{\tau-1} g_{A_2(t)}(a_2(t) | w, a, \bar{a}_2(t-1), \bar{n}(t)).$$

- $g_1(a | W) = P(A = a | W)$  and  $g_{A_2(t)}$  is conditional probability distribution of  $A_2(t)$ , given  $Pa(A_2(t))$ .
- $q_W(w)$  density of  $W$ , and  $q_{N(t)}$  is conditional probability distribution of  $N(t)$  given  $Pa(N(t))$ .

## Conditional densities become degenerate after failure or censoring event

- Note that if  $N(t) = 1$  or  $A_2(t - 1) = 1$ , then the conditional density  $g_{A_2(t)}$  of  $A_2(t)$  is degenerate at 0 or 1, respectively.
- Note that if  $N(t - 1) = 1$  or  $A_2(t - 1) = 1$ , then the conditional density  $q_{N(t)}$  of  $N(t)$  is degenerate at 1 or 0, respectively.
- Thus, the product over  $t$  for  $q_{N(t)}$  only includes  $t$  with  $n(t - 1) = a_2(t - 1) = 0$ .
- The product over  $t$  for  $g_{A_2(t)}$  only includes  $t$  with  $n(t) = a_2(t - 1) = 0$ .

## Hazard of censoring

- The conditional density  $g_{A_2(t)}(1 \mid W, A, A_2(t-1) = N(t) = 0)$  is a conditional hazard  $\lambda_C(t \mid W, A, N(t) = 0)$ .
- Under CAR, this equals conditional hazard  $\lambda_C(t \mid W, A)$ .
- If censoring  $C$  is continuous, we can replace  $g_{A_2(t)}(1 \mid W, A, \bar{A}_2(t-1), \bar{N}(t))$  by an intensity

$$E(dA_2(t) \mid W, A, \bar{A}_2(t-), \bar{N}(t-)) = I(\tilde{T} \geq t) \lambda_C(t \mid W, A) dt.$$

## Hazard of failure

- The conditional density  $q_{N(t)}(1 \mid W, A, A_2(t-1) = N(t-1) = 0)$  is a conditional hazard  $\lambda(t \mid W, A, A_2(t-1) = 0)$ .
- Under CAR, this equals conditional hazard  $\lambda(t \mid W, A)$ .
- If  $T$  is continuous, we can replace  $q_N(1 \mid W, A, \bar{A}_2(t-1), \bar{N}(t-1))$  by an intensity

$$E(dN(t) \mid W, A, \bar{A}_2(t-), \bar{N}(t-)) = I(\tilde{T} \geq t) \lambda(t \mid W, A) dt.$$

## Observed data density in terms of hazards

- Thus,

$$\begin{aligned} p(o) &= q_W(w) \prod_{t=0}^{\tilde{t}} \lambda(t \mid W, A)^{dn(t)} (1 - \lambda(t \mid W, A))^{1-dn(t)} \\ &\quad \times g_1(a \mid W) \prod_{t=0}^{\tilde{t}} \lambda_C(t \mid w, a)^{da_2(t)} (1 - \lambda_C(t \mid w, a))^{1-da_2(t)}. \end{aligned}$$

## Statistical model

- Recall  $P = P_{Q_W, Q_N, G_1, G_2}$ .
- Parameter space for distribution of  $W$  is nonparametric.
- Parameter space for conditional hazard of  $T$  is nonparametric.
- Parameter space  $\mathcal{G}_1$  for  $G_1$  and parameter space  $\mathcal{G}_2$  for  $G_2$  are possibly restricted.
- The statistical model

$$\mathcal{M} = \{P_{Q_W, Q_N, G_1, G_2} : G_1 \in \mathcal{G}_1, G_2 \in \mathcal{G}_2\}.$$

## Statistical estimation problem

- We observe  $n$  i.i.d. copies of  $O \sim P_0$ .
- We know  $P_0 \in \mathcal{M}$ .
- $\Psi : \mathcal{M} \rightarrow \mathbb{R}$  is statistical target parameter,  
 $\Psi(P) = E_P P(T > t \mid A = d(W), W)$ .
- We want to estimate  $\Psi(P_0)$ .

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## Loss function for conditional hazard

- The log-likelihood loss for  $\lambda$  is given by:

$$L(\lambda)(O) = -\log \left\{ \prod_{t \leq \tilde{T}} \lambda(t | A, W)^{dN(t)} (1 - \lambda(t | A, W))^{1-dN(t)} \right\}.$$

- The true failure time hazard

$$\lambda_0 = \arg \min_{\lambda} P_0 L(\lambda).$$

## Estimation of hazard with pooled logistic regression

- $\lambda(t | A, W) = E(dN(t) | A, W, \tilde{T} \geq t)$  is a regression of binary outcome  $dN(t)$  on  $(A, W)$ , given  $\tilde{T} \geq t$ .
- Thus, one can estimate this function with any logistic regression estimator based on pooled data set in which each unit  $i$  has  $\tilde{T}_i$  rows of data with covariates  $(W_i, A_i, t)$  and outcome  $dN(t)$ ,  $t = 1, \dots, \tilde{T}_i$ .
- If  $\tilde{T}$  is continuous, then one could discretize time to create such estimators, or use Cox-proportional hazard regression type estimators.

## Library of candidate estimators of hazard

- Let  $\hat{\lambda}_j : \mathcal{M}_{NP} \rightarrow \sim$  be a candidate estimator,  $j = 1, \dots, J$ .
- This library of  $J$  estimators can include parametric logistic regression, and large variety of machine learning algorithms.

## Cross-validation to evaluate performance of candidate estimators

- Let  $B_n \in \{0, 1\}^n$  be a random split of sample.
- Let  $P_{n, B_n}^1, P_{n, B_n}^0$  be empirical measures for validation sample  $\{O_i : B_n(i) = 1\}$  and training sample  $\{O_i : B_n(i) = 0\}$ , respectively.
- We evaluate performance of  $\hat{\lambda}_j$  with its cross-validated log-likelihood:

$$R(\hat{\lambda}_j, P_n) = E_{B_n} P_{n, B_n}^1 L(\hat{\lambda}_j(P_{n, B_n}^0)).$$

## Super-learner of hazard

- Let

$$J_n = \arg \min_j R(\hat{\lambda}_j, P_n).$$

- The super-learner is defined as

$$\hat{\lambda}_{SL}(P_n) = \hat{\lambda}_{J_n}(P_n).$$

## Oracle inequality

- Let  $\tilde{J}_n(P_0) = \arg \min_j E_{B_n} P_0 L(\hat{\Psi}_j(P_{n,B_n}^0))$  be the oracle selector.
- Let  $d_0(\lambda, \lambda_0) = P_0 L(\lambda) - P_0 L(\lambda_0)$  be the loss-based dissimilarity.
- By the oracle inequality for the cross-validation selector, the super learner is asymptotically equivalent with the oracle selected estimator:

$$\frac{E_0 d_0(\hat{\lambda}_{\tilde{J}_n}(P_{n,B_n}^0), \lambda_0)}{E d_0(\hat{\lambda}_{\tilde{J}_n(P_0)}(P_{n,B_n}^0), P_0)} \rightarrow 1$$

as  $n \rightarrow \infty$ .

- This remains true if the number  $J$  of candidate estimators grows as fast with sample size as  $n^p$  for some finite integer  $p$ .

## HAL-MLE of conditional hazard

- Suppose that  $O = (W, A, \tilde{T} = \min(T, C), \Delta = I(T \leq C))$ , and that we are interested in estimating the conditional hazard  $\lambda(t | A, W)$ .
- Let  $L(\lambda)$  be the log-likelihood loss.
- If  $T$  is continuous, we could parametrize  $\lambda(t | A, W) = \exp(\psi(t, A, W))$ , or, if  $T$  is discrete,  $\text{Logit}\lambda(t | A, W) = \psi(t, A, W)$ .
- We can represent  $\psi = \sum_{s \in \{1, \dots, d\}} \beta_{s,j} \phi_{u_{s,j}}$  as linear combination of indicator basis functions, where  $L^1$ -norm of  $\beta$  represents the sectional variation norm of  $\psi$ .
- Therefore, we can compute the HAL-MLE of  $\lambda$  with either Cox-Lasso or logistic Lasso regression (`glmnet()`).

# Outline

- 1 Causal model for the counterfactual treatment specific survival curve
- 2 Statistical estimation problem
- 3 Super-learner and HAL-MLE of conditional hazard
- 4 One-step TMLE of causal impact of point intervention on survival

# One-step TMLE of treatment specific survival curve

We investigated the performance of one-step TMLE for treatment specific survival curve based on  $O = (W, A, \tilde{T} = \min(T, C), \Delta = I(T \leq C))$ .

## Data structure

- dynamic treatment intervention:  $W \rightarrow d(W)$ .
- $S_d(t)$  is defined by

$$\Psi(P)(t) = E_P [P(T > t | A = d(W), W)]$$

- Focus on  $d(W) = 1$ .

## Efficient influence curve

The efficient influence curve for  $\Psi(P)(t)$  is (Hubbard et al., 2000)

$$\begin{aligned} D_t^*(P) &= \sum_{k \leq t} h_t(g_A, S_{A_c}, S)(k, A, W) \left[ I(\tilde{T} = k, \Delta = 1) - \right. \\ &\quad \left. I(\tilde{T} \geq k) \lambda(k|A = 1, W) \right] + S(t|A = 1, W) - \Psi(P)(t) \\ &\equiv D_{1,t}^*(g_A, S_{A_c}, S) + D_{2,t}^*(P), \end{aligned}$$

where

$$\begin{aligned} h_t(g_A, S_{A_c}, S)(k, A, W) &= \\ -\frac{I(A = 1)I(k \leq t)}{g_A(A = 1|W)S_{A_c}(k|A, W)} \frac{S(t|A, W)}{S(k|A, W)}. \end{aligned}$$

## From local least favorable submodel to universal least favorable submodel

- A local least favorable submodel (LLFM) for  $S_d(t)$  around initial estimator of conditional hazard:

$$\text{logit}(\lambda_{n,\varepsilon}(\cdot|A=1, W)) = \text{logit}(\lambda_n(\cdot|A=1, W)) + \varepsilon h_t.$$

- Similarly, we have this local least favorable submodel for a vector  $(S_d(t) : t)$  by adding vector  $(h_t : t)$  extension.
- These imply, as above, universal least favorable submodels for single and multidimensional survival function.

# Simulations for one-step TMLE of survival curve

We investigated the performance of one-step TMLE for treatment specific survival curve in two simulation settings.

## Data structure

- $O = (W, A, T) \sim P_0$
- $A \in \{0, 1\}$
- treatment intervention:  $W \rightarrow d(W) = 1$
- $S_d(t)$  is defined by

$$\Psi(P)(t) = E_P [P(T > t | A = d(W), W)]$$

# Candidate estimators

- ① Kaplan Meier
- ② Iterative TMLE for each single  $t$  separately
- ③ One-step TMLE targeting the whole survival curve  $S_d$

# Results

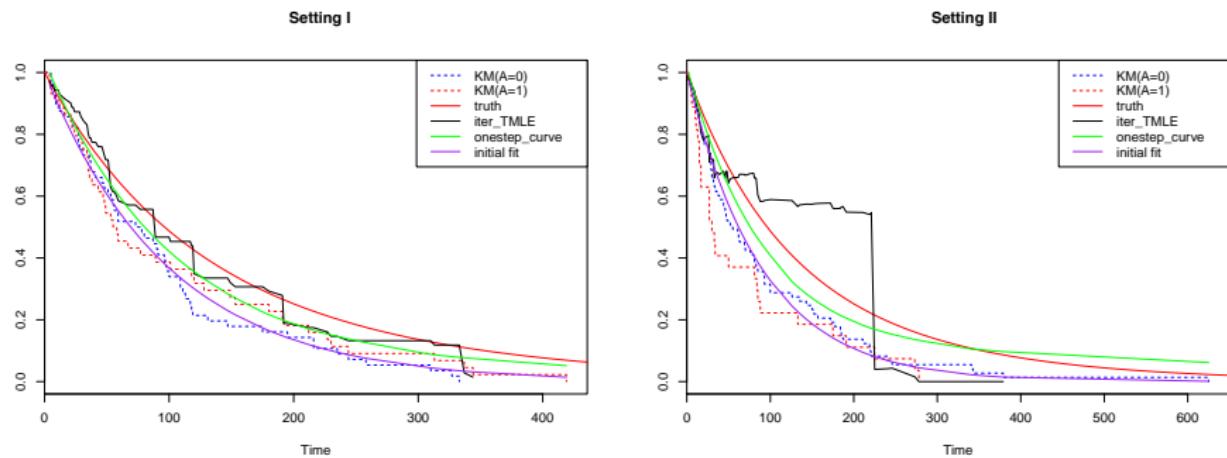


Figure: Based on one data set

# Monte-carlo results ( $n = 100$ )

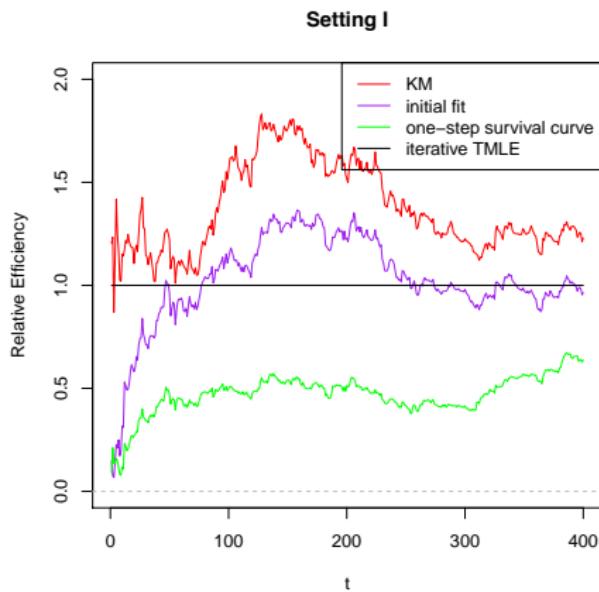


Figure: Relative efficiency against iterative TMLE, as a function of  $t$