

# Self-Matched Learning with Electronic Health Records for Precision Medicine<sup>1,2</sup>

Yuanjia Wang, Ph.D.

Department of Biostatistics, Mailman School of Public Health  
Columbia University  
& Department of Psychiatry, Columbia University



Columbia University  
MAILMAN SCHOOL  
OF PUBLIC HEALTH



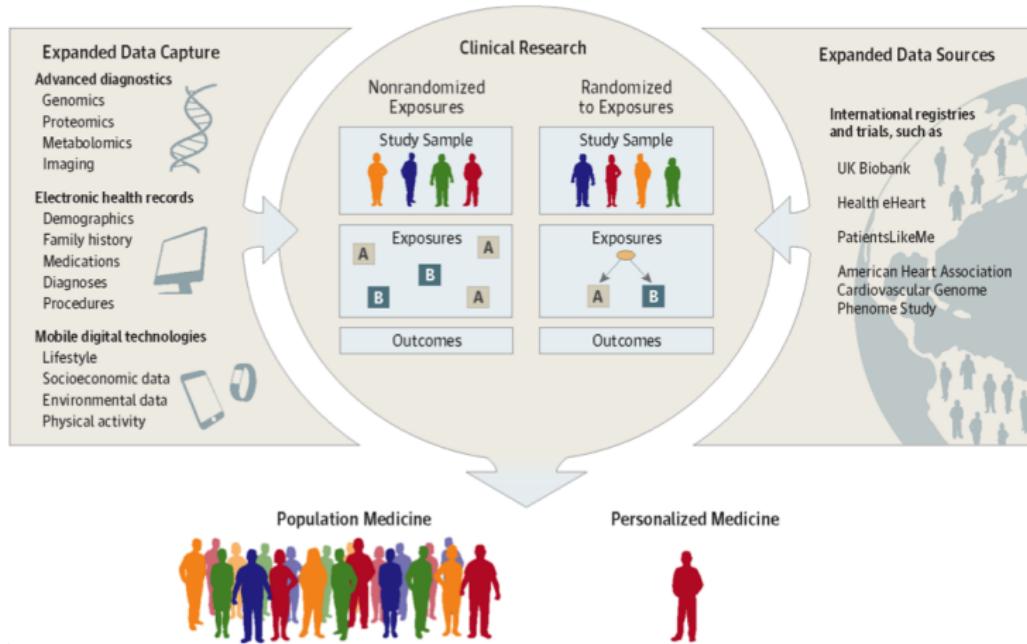
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<sup>1</sup>Wu et al. (2020). Matched Learning for Optimizing Individualized Treatment Strategies Using Electronic Health Records. JASA. 115:529, 380-392.

<sup>2</sup>Xu et al. (2022). Self-Matched Learning to Construct Treatment Decision Rules from Electronic Health Records. Stat Med. 41(17): 3434-3447.

# Precision Medicine

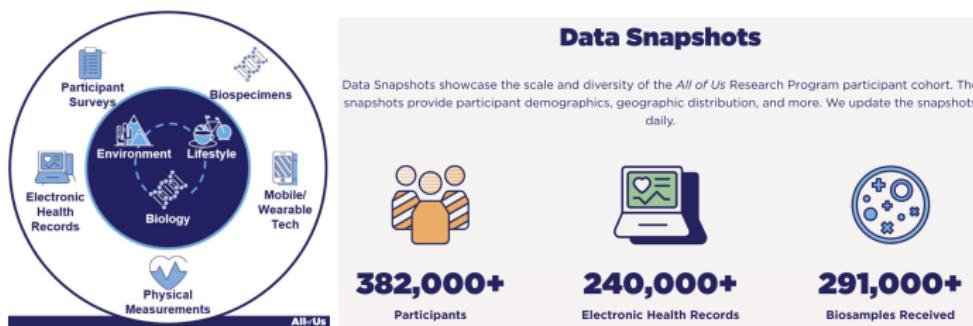
Disentangle heterogeneity of disease and patients, tailor treatments according to patient's behavioral, biological, psychosocial factors<sup>3</sup>.



<sup>3</sup>Mega et al. *JAMA*. 2014;312(19):1969-1970).

# Real World Data (RWD)

Precision Medicine Initiative ([AllofUs Study](#)): launched in 2015 to provide diverse digital health data for 1 million cohort<sup>4</sup>



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1 M Patient Cohort Being Prepared to Fuel Precision...

## 1 M Patient Cohort Being Prepared to Fuel Precision Medicine

Access to the data will be managed through the program's Data and Research

# RCT versus RWD

RCT characteristics:

- High internal validity but lacks generalizability
- Stringent inclusion/exclusion criteria (e.g., excluding comorbidities) (Weng et al. 2011; Lawrence et al. 2023)
- Strict standardization of treatment procedures (e.g., treatment protocols based on manuals)
- Broad range of real-world medication use patterns not captured by RCTs were observed in EHRs (Hripcsak et al., 2016)
- Lacks long-term outcomes or adverse events

EHR characteristics:

- Greater variability in outcomes in naturalistic settings
- More modest treatment effect sizes (Gibbons et al. 2010)

# Generalizability of RCTs of Depression

Our study on the eligibility of CUIMC emergency psychiatry patients for depression trials (Lawrence et al. 2023):

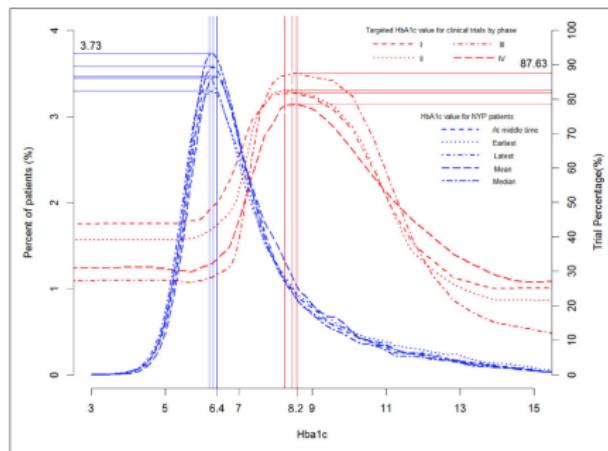
Table: Prevalence of common exclusion criteria among a sample of patients in the Emergency Department with Depression (N=184)			
Exclusion Criteria	N	%	Definitions and coding details
High suicide risk	137	74.5	Presentations involved suicide attempt, suicide ideation, suicidal statements (even if later recanted), self-harm, or overdose
Substance use (prior 2 weeks)	112	60.9	Excludes nicotine, caffeine, benzodiazepines, and social alcohol use not leading to intoxication and unrelated to the presentation. Includes use of prescribed controlled substances (e.g., opioids) and cannabis and related products.
Schizophrenia, Schizoaffective, Other Psychosis	92	50.0	Other psychosis included substance induced psychosis and mood disorders with psychotic features.

- Eligibility rate after applying top 3 exclusion criteria: **6.5%** (95% CI: 3.4%-11.1%)
- Eligibility rate after applying 9 remaining exclusion criteria: **3.3%** (95% CI: 1.2%-7.0%)

Presented to ER but not eligible

# Generalizability of RCTs of T2D

Figure: Comparing 1,761 T2D clinical trials and the EHRs of 26,120 patients with T2D who visited CUIMC/NYP (Weng et al. 2011). **RCT populations has worse baseline.**



**Fig. 1** For each HbA<sub>1c</sub> value on X, the red lines indicate the percentage of trials of different phases whose eligibility criteria include that value and the blue lines indicate the percentage of patients whose earliest, latest, mean, median, or middle- collection-time HbA<sub>1c</sub> was that value.

Columbia University Medical Center/New-York Presbyterian Hospital contains 20 years health information on 4.5 million patients; Provides infrastructure for the 1-million volunteer **Precision Medicine Initiative Cohort Program**

# RCT versus RWD

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EHR characteristics:

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# Challenges with Learning ITRs from EHRs

Develop individualized treatment rules (ITRs) to guide treatment decision:

- Data quality: studies of CUIMC EHR assessed completeness, correctness, concordance, plausibility and timeliness (Weiskopf et al. 2013).
- Need to address statistical challenges: confounding bias, selection bias (Hripcsak and Albers 2013) when learning treatment rules.
- Many existing methods express the objective function through inverse probability weighting (IPW) of propensity scores (PS) based on observed covariates (Kosorok and Moodie 2015).

# Inverse Weighting and Matching

Value function through IPW of PS:  $\mathcal{V}(\mathcal{D}) = E_{\mathcal{D}}(Y) = E \left( \frac{YI(A=\mathcal{D}(H))}{P(A|H)} \right)$ .

- IPW needs a model for PS, adjusts for observed confounding.
- Unstable with small weights especially with **multiple treatments or combination of treatments in EHRs**
- Ensures similar distribution of confounders at the group average level.

Extensive literature comparing matching<sup>5</sup> and weighting:

- Direct control over achieving covariates balance and overlap, useful for EHR applications.
- Matching by prognostic scores can improve efficiency.
- Within-subject matching to control for **unobserved time-invariant confounding**.

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<sup>5</sup>Stuart E. *Stat Sci.* 2010; 25: 1–21.

# Methods

## Notation

- Data are collected from  $n$  patients
- $H_i$ : covariates for matching or tailoring treatment
- $A_i$ : treatment taking values in  $\mathcal{A} = \{1, 2, \dots, K\}$
- $Y_i$  or  $R_i$ : a real-valued post-treatment outcome (also referred as the “reward”)
- An ITR ( $D(H_i)$ ) is a deterministic decision rule mapping  $\mathcal{H}$  into  $\mathcal{A}$ .

# Augmented Outcome-Weighted Learning<sup>6</sup>

Heuristics:

Maximize the value

Minimize the risk

$$E \left[ \frac{I(A = \mathcal{D}(H))}{P(A|H)} Y \right] \quad E \left[ \frac{I(A \neq \mathcal{D}(H))}{P(A|H)} Y \right]$$

- Subjects with large response: more likely  $\mathcal{D}(H)$  would be the **same** as the assigned treatment.
- Subjects with little response: more likely  $\mathcal{D}(H)$  would be the **opposite** of the assigned treatment.

Optimization reduces to a weighted classification problem with **modified outcomes (subtracting main effect of treatment)** as weights and minimizes an empirical risk function.

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<sup>6</sup>Liu et al. (2018). Augmented Outcome-weighted Learning for Estimating Optimal Dynamic Treatment Regimens. *Stat Med.* 37:3776-3788.

# Matching-based Learning (M-Learning)

## Matching-based value function:

$$V_n(\mathcal{D}; g) = \sum_{i=1}^n |\mathcal{M}_i|^{-1} \sum_{j \in \mathcal{M}_i} \{I(Y_j \leq Y_i, \mathcal{D}(H_i) = A_i) + I(Y_j \geq Y_i, \mathcal{D}(H_i) = -A_i)\} g(|Y_j - Y_i|)$$

$\mathcal{M}_i$ : matching set;  $g(\cdot)$ : monotone increasing function to weight different matched pairs.

## Heuristics of M-learning value function<sup>7</sup>:

- Two subjects who are matched on confounders and receive different treatments, the treatment with a larger clinical outcome more likely to be optimal.

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<sup>7</sup>Wu et al. (2020). Matched Learning for Optimizing Individualized Treatment Strategies Using Electronic Health Records. *JASA*. 115:529, 380-392.

# Matched Learning (M-learning)

## Matching-based value function:

$$V_n(\mathcal{D}; g) = \sum_{i=1}^n |\mathcal{M}_i|^{-1} \sum_{j \in \mathcal{M}_i} \{I(Y_j \leq Y_i, \mathcal{D}(H_i) = A_i) + I(Y_j \geq Y_i, \mathcal{D}(H_i) = -A_i)\} g(|Y_j - Y_i|)$$

### Heuristics of M-learning value function (continued):

- Allow subjects to be matched with themselves, replace  $Y_j$  by predicted average outcome across treatments and use 1/PS as weights, M-learning reduces to augmented O-learning.
- M-learning compares individual outcomes when treatment assignment is approximately “random” given  $H_i$  but received treatments are opposite.
- Accommodates discrete, ordinal, and continuous outcomes.
- More robust to error in outcomes due to using the relative ranking. Useful for EHR applications.

## M-Learning Algorithm

Maximizing matching-based value function is equivalent to minimizing empirical risk function

$$V_n(f; g) = n^{-1} \sum_{i=1}^n |\mathcal{M}_i|^{-1} \sum_{j \in \mathcal{M}_i} I(f(H_i) A_i \text{sign}(Y_i - Y_j) \leq 0) g(|Y_i - Y_j|)$$

where  $\mathcal{D}(H) = \text{sign}(f(H))$ .

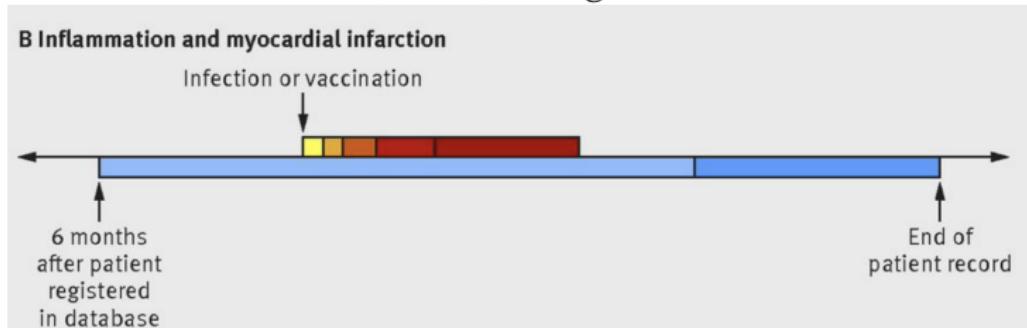
Learning ITR:

- Replacing zero-one loss in the empirical risk function by a surrogate loss
- Computational algorithm: under hinge-loss implemented by weighted SVM with paired observations
- Other classification tools can be used

M-learning requires all confounding variables to be measured.

# Self-matched Learning

## Self-controlled cases series (SCCS) design<sup>8</sup>.

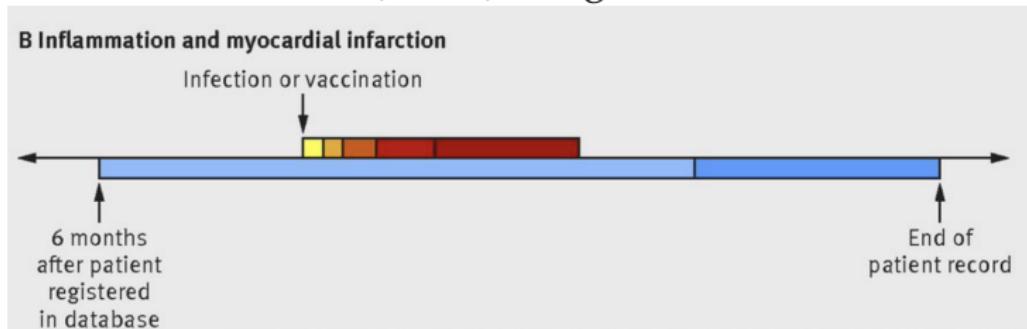


<sup>8</sup>Peterson et al. BMJ 2016;354: i4515

<sup>9</sup>Xu et al. (2022). Self-Matched Learning to Construct Treatment Decision Rules from Electronic Health Records. *Stat Med.* 41(17): 3434-3447.

# Self-matched Learning

Self-controlled cases series (SCCS) design<sup>8</sup>.



We propose **self-matched learning**<sup>9</sup> inspired by the SCCS:

- Can alleviate both observed and unobserved time-invariant confounders in EHRs
- Targets within-subject personalized effect

<sup>8</sup>Peterson et al. BMJ 2016;354: i4515

<sup>9</sup>Xu et al. (2022). Self-Matched Learning to Construct Treatment Decision Rules from Electronic Health Records. *Stat Med.* 41(17): 3434-3447.

## Matched Set

- $\mathcal{M}_{ij}$ : matched set of subject  $i$  at visit  $j$
- The matched set consists of periods with different treatments from the same subject

$$\mathcal{M}_{ij} = \{k : A_{ik} \neq A_{ij}, d(H_{ik}, H_{ij}) \leq \delta_i\},$$

- ▶  $H_{ij}$ : observed time-varying confounders
- ▶  $d(\cdot, \cdot)$ : a metric defined in the feature space measuring similarity between treatment periods
- ▶  $\delta_i$ : a pre-specified threshold to determine the size of the matched set.

## Self-Matched Value Function

- $f_{r,s} : H \mapsto \{r, s\}$  is a binary decision rule that chooses the better treatment among options  $r$  and  $s$
- The kernel-weighted self-matching value function:

$$V_n(D) = \frac{1}{n} \sum_{1 \leq r < s \leq K} V'_n(r, s),$$

$$\begin{aligned} V'_n(r, s) = & \sum_{i=1}^n \frac{1}{|\mathcal{M}_i|} \sum_{j=1}^{n_i} \sum_{\substack{A_{ij}, A_{ik} \in \{r, s\} \\ k \in \mathcal{M}_{ij}}} \left\{ I(R_{ik} \geq R_{ij}, f_{r,s}(H_{ik}) = A_{ik}) \right. \\ & \left. + I(R_{ik} \leq R_{ij}, f_{r,s}(H_{ik}) = A_{ij}) \right\} w(|R_{ij} - R_{ik}|) k \{d(H_{ij}, H_{ik})\}. \end{aligned}$$

- Optimization by weighted classification.

# Theoretical Justification

- Assume the following additive model for the potential outcome

$$R_{ij}^{(a)} = f(H_{ij}, U_i) + \frac{1}{2}g(H_{ij})a + \epsilon_{ij}^{(a)},$$

- ▶  $f$  and  $g$  are unspecified nonparametric functions
- ▶  $U_i$ : unmeasured confounding,  $\epsilon_{ij}^{(a)}$  random measurement error

## Theorem

Under the following assumptions:

(a) Stable unit treatment values assumption (SUTVA):

$$R_{ij} = R_{ij}^{(1)}I(A_{ij} = 1) + R_{ij}^{(-1)}I(A_{ij} = -1)$$

(b) No unmeasured time-varying confounding

$$(\epsilon_{ij}^{(a)}, \epsilon_{ik}^{(a)}) \perp\!\!\!\perp A_{ij}, A_{ik} | H_{ij}, H_{ik}, \textcolor{blue}{U}_i,$$

self-matched learning is **Fisher consistent**. That is, the ITR that maximizes the self-matched value function is the true optimal ITR,  $\operatorname{argmax}_{a=1,-1} E(R^{(a)} | H = h)$ .

# Simulation Results

# Simulation Designs

We considered four simulation designs:

- ① Propensity score model is correctly specified
- ② Propensity score model is misspecified
- ③ Presence of unmeasured confounder
- ④ Presence of unmeasured confounder that interacts with treatments

Comparison methods and details:

- Q-learning by random forest; Augmented O-Learning; Subject matching; Self-matched learning.
- 1 : 1 nearest neighbor matching with replacement using Euclidean distance for M-learning.
- Complete match weighted by kernel distance for self-matched learning.
- Repeated 100 times with 5-fold CV tuning and tested on a large independent testing set.

## Simulation Designs

Adverse event outcome model  $R \sim \text{Poisson}(e^{0.04\mu})$ , where

- ①  $\mu = 40 - H_1 + 0.1H_2 + 0.003(H_3^2 - H_4^2 + 82^2)I(A = 2) - 10H_5 \cdot I(A = 3)$
- ②  $\mu = 150 + (H_1 - 0.1H_2 + 11) \cdot I(A = 1) + 0.003(H_3^2 - H_4^2 + 82^2) \cdot I(A = 2) - 10H_5 \cdot I(A = 3) - 0.01U_1^2 + 2U_2.$
- ③  $\mu = 40 - H_1 + 0.1H_2 + 0.003(H_3^2 - H_4^2 + U_1^2)I(A = 2) - 7(H_5 + 0.1U_2) \cdot I(A = 3).$

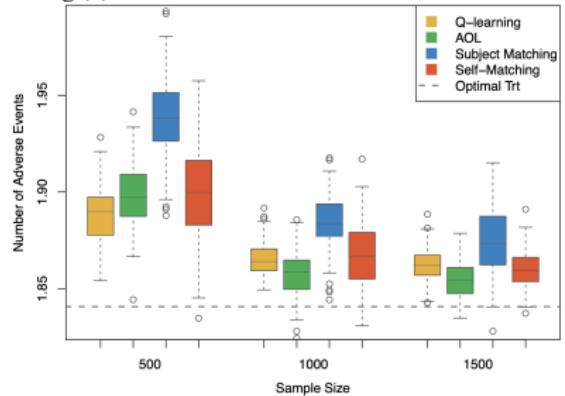
Treatment assignment model:

- ①  $\log \left\{ \frac{\Pr(A=1|H)}{\Pr(A=3|H)} \right\} = H_5, \log \left\{ \frac{\Pr(A=2|H)}{\Pr(A=3|H)} \right\} = 3.8 - 0.4H_1$
- ②  $\log \left\{ \frac{\Pr(A=1|H)}{\Pr(A=3|H)} \right\} = -1.5 + \log(0.1H_3), \log \left\{ \frac{\Pr(A=2|H)}{\Pr(A=3|H)} \right\} = 5 - \sqrt[3]{H_2}$
- ③  $\log \left\{ \frac{\Pr(A=1|H,U)}{\Pr(A=3|H,U)} \right\} = \log(u) - 1.2 + H_5 + I(U_1 > 50),$   
 $\log \left\{ \frac{\Pr(A=2|H,U)}{\Pr(A=3|H,U)} \right\} = \log(u) - 0.5 + 0.1H_1 - 0.1U_2.$

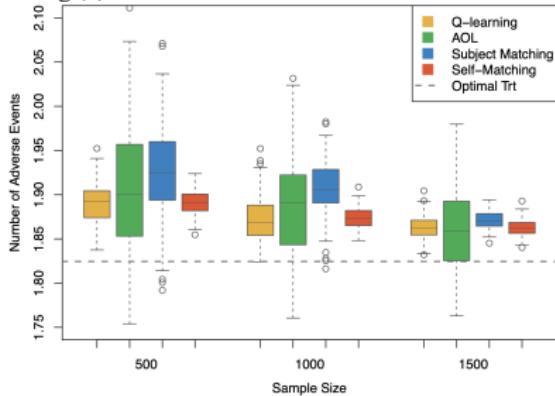
# No Unmeasured Confounding

Setting (1): PS model correct. Setting (2): PS model misspecified

Setting (1):



Setting (2):

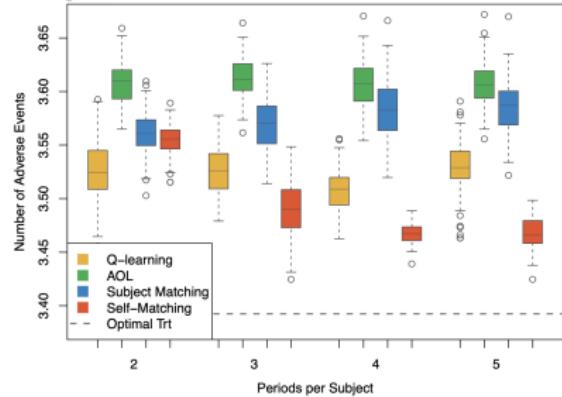


Augmented O-learning performs well when PS is correctly specified;  
Self-matched learning not affected by the misspecification of PS.

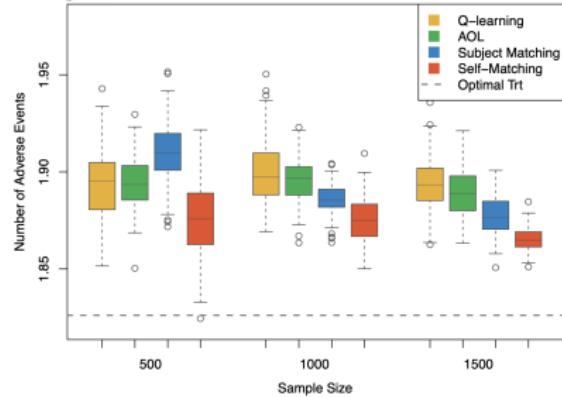
# Presence of Unmeasured Confounding

Setting (3): Unmeasured confounding  $U$  in treatment-free model only  
Setting (4):  $U$  interacts with treatment

Setting (3):



Setting (4):



In (4), none of methods can recover optimal value; Self-matched learning closest to optimal in nonlinear setting.

# Applications to EHRs

# Application to NYP Hospital EHRs<sup>10</sup>

- EHRs of T2D patients from a clinical data warehouse (CDW) at New York Presbyterian (NYP) hospital
- Three treatment options: monotherapy basal insulin, combination therapy of insulin and metformin, and monotherapy metformin
- Response: count the total ICDs related to diabetes comorbidities/adverse events (hypoglycemia, hypertension, hyperlipidemia)

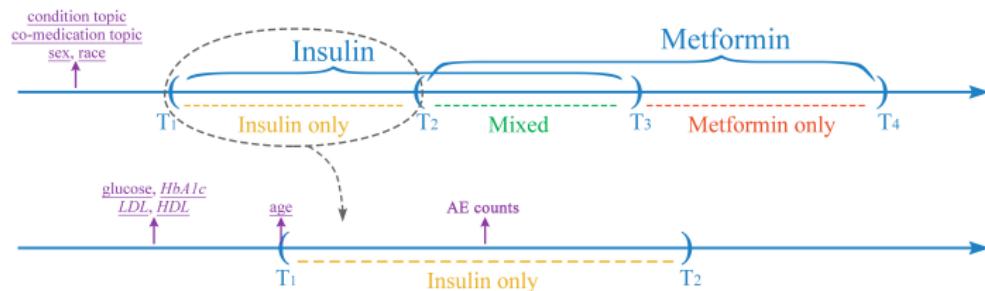
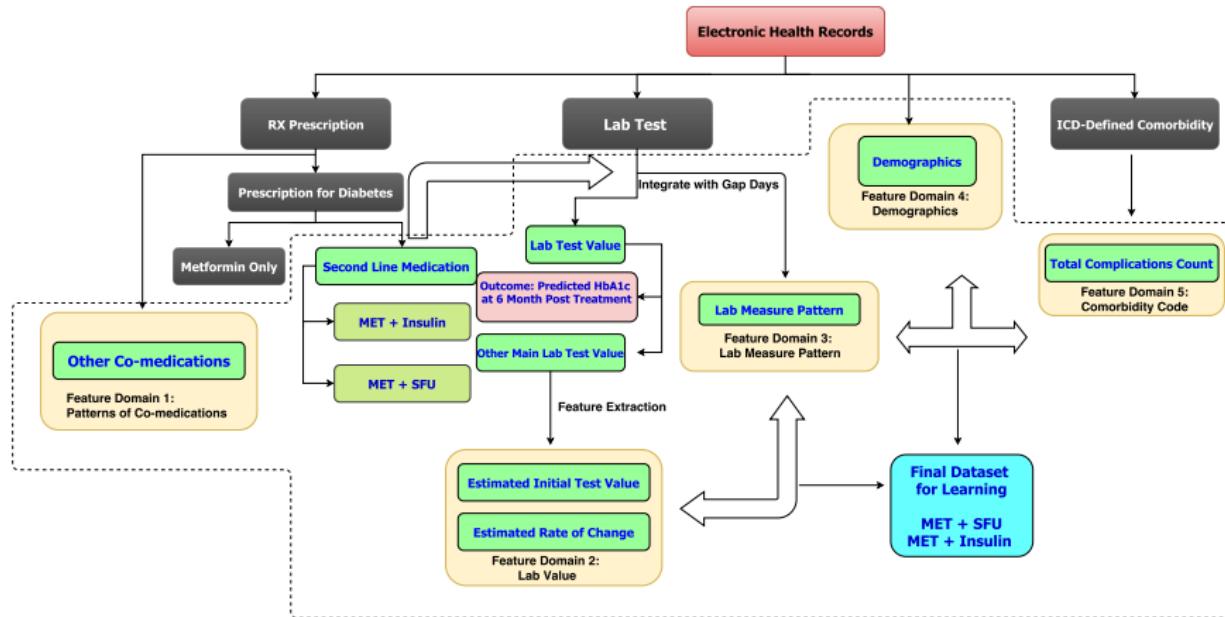


Figure: SCCS study design. Italic variables are matching variables and underlined variables are **feature variables**.

<sup>10</sup>Xu et al. (2022). *Statistics in Medicine*. 41(17): 3434-3447.

# Information Captured in CDW EHRs

Figure: Schematics of EHR Data Processing Procedures<sup>11</sup>

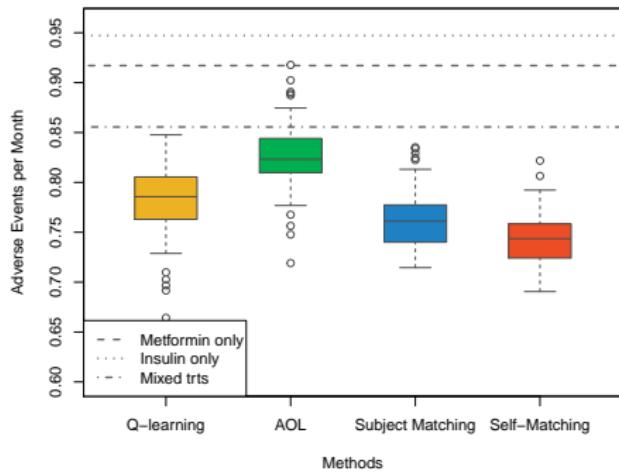


$n = 3,002$  (1623 metformin only, 900 insulin only, 479 combination therapy;  
median observation period 231 days)

<sup>11</sup>Wu et al. (2020). JASA. 115:529, 380-392.

# Application – Result

Figure: Empirical value function of the number of diabetes complications per month of ITRs estimated from NYP patient EHRs (lower value more desirable).



- 51% combination therapy remains to be predicted as optimal
- 34% of insulin, 35% of metformin recommended to combination therapy
- Combination therapy can be beneficial in controlling diabetes-related complications.

# Application – Result

Topic modeling used. Condition topic 2: chronic kidney disease, hypertensive renal disease, congestive heart failure, and atrial fibrillation. Comedication topic 4: lisinopril (high BP), carvedilol (heart failure).

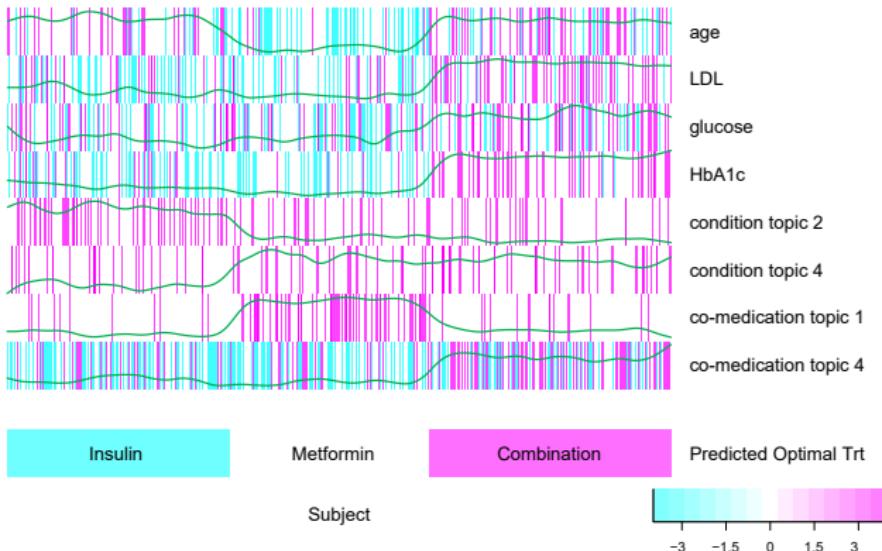


Figure: Heatmap of baseline features by recommended optimal treatments

## Second Example: SCCS Design for Time-to-Event Outcomes

- Adverse effect of stimulant use on cardiovascular risks and death
- Two data sources:
  - ▶ a retrospective observational analysis using the FDA Adverse Event Reporting System (FAERS; 2,730 drugs and 14,544 events<sup>12</sup>)
  - ▶ a longitudinal EHRs obtained from 2004 to October 2019 at the NYP (number of records: 77,778)



Figure: Exposure period: 90 days after exposure is the 'risk' period. Endpoint: all-cause mortality, which can occur during the 'risk' period or outside.

<sup>12</sup>Tatonetti (2012). *Science Translational medicine* 4, 125ra31– 125ra31.

## SCCS Assumptions<sup>13</sup>

- The event of interest (i.e., death) must be rare in the study population over the observation period of interesting.
  - ▶ systematic bias,  $p$  calibration using negative controls
- The duration of the risk periods must be known (90 days).
- It must be possible to define a nominal end of observation for each case (age 30-75).
  - ▶ alleviate the issue of event-dependent observation periods.
- Estimation and inference based on estimating equations.

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<sup>13</sup>Farrington et al. (2018). Self-controlled case series studies: a modeling guide with R.

## $p$ -Calibration with Negative Controls<sup>14</sup>

- Assume log-relative risk (LRR) for negative controls:

$$LRR_i \sim N(\theta_i, \tau_i^2), \quad \theta_i \sim N(\mu, \sigma^2).$$

- Estimate  $\mu$  and  $\sigma^2$  by MLE based on the negative controls:

$$\ln L(LRR) = \text{Constant} + \sum_{i=1}^n \left\{ -\frac{1}{2} \ln(\tau_i^2 + \sigma^2) - \frac{(LRR_i - \mu)^2}{2(\tau_i^2 + \sigma^2)} \right\}.$$

- For both negative controls and stimulants, compute the calibrated  $p$ -values from the estimated empirical null distribution

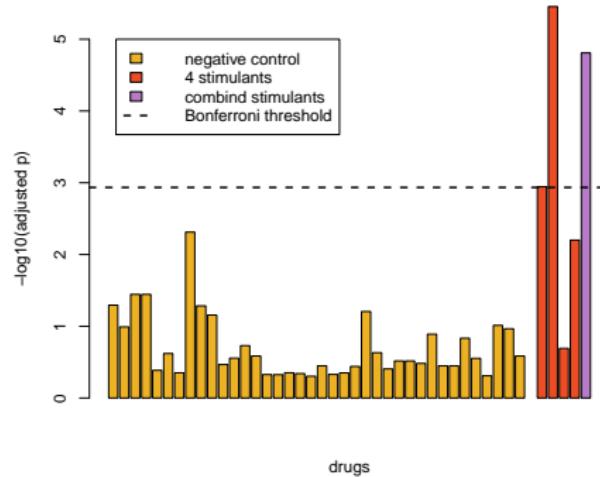
$$\text{adjusted } p = \Phi \left( \frac{-|LRR_i - \hat{\mu}|}{\sqrt{\hat{\sigma}^2 + \tau_i^2}} \right).$$

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<sup>14</sup>Schuemie et al. (2014). *Stat in Med.* 33, 209–218.

# Results

(a) FAERS:



(b) SCCS:

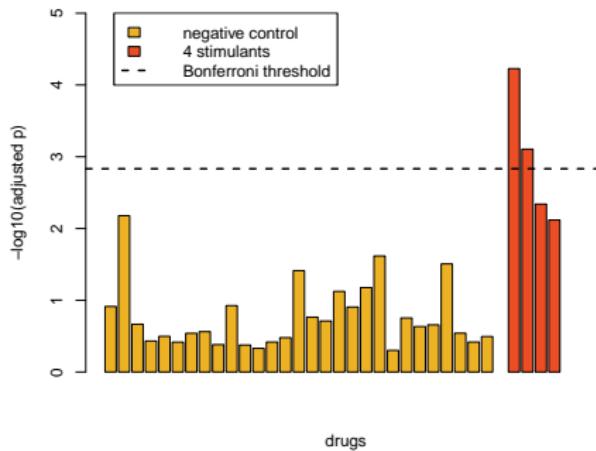
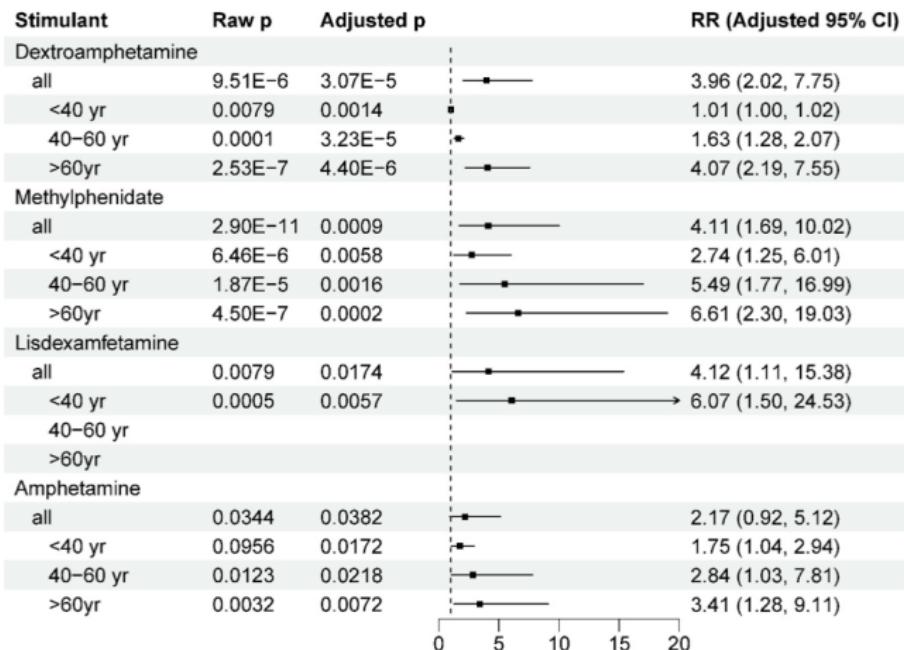


Figure: Manhattan plot of adjusted  $p$ -values. Red bars are for four stimulants (Dextroamphetamine, Methylphenidate, Lisdexamfetamine, Amphetamine in order); the purple bar is the combined relative risk  $p$ -value. The dashed line is the Bonferroni alpha.

# Relative Risks



# Final Remarks

# Conclusions

Proposed matching-based learning methods to optimize ITRs using EHRs:

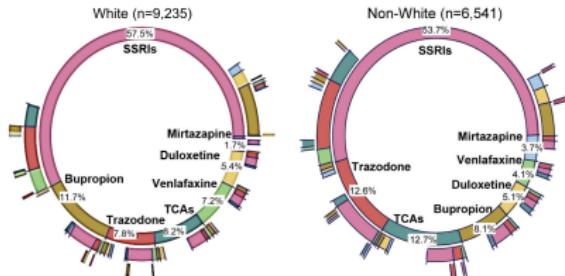
- Feasible to use EHRs for precision medicine research.

Future directions:

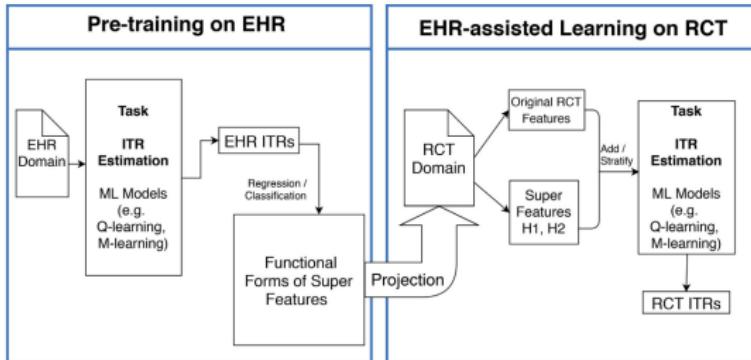
- Better feature extraction (e.g., jointly model lab measurement patterns) to adjust for confounding and selection bias
- Dynamic multi-stage decisions
- Integrate information from multiple sources (e.g., other EHR databases; RCT and EHRs)
- Precision medicine: incorporates EHRs and genomic data, environmental risk factors, social and behavioral measures.

# Transfer Learning and EBM+

- External validation with real world data (CUIMC EHRs; AllofUs PMI)



- Integrate RWD and RCT<sup>15</sup> (e.g., transfer learning).



<sup>15</sup>Wu et al. (2020). *Biometrics*. 76:1075–1086

## References and Acknowledgments

- Wu et al. (2020). Matched Learning for Optimizing Individualized Treatment Strategies Using Electronic Health Records. *Journal of the American Statistical Association*. 115:529, 380-392.
- Xu et al. (2022). Self-Matched Learning to Construct Treatment Decision Rules from Electronic Health Records. *Statistics in Medicine*. 41(17): 3434-3447.
- Informatics and psychiatry department: Timothy Walsh, Nick Tatonetti, Undina Gisladottir, John Morrow.
- Codes: <https://CRAN.R-project.org/package=WeightSVM>.
- Research support:
  - ▶ NIH (NS073671, GM124104, MH123487)

**THANK YOU!**