

# Statistical Practices and Research for Interdisciplinary Sciences (**SPRIS**)

## Lecture 7: Machine Learning and Precision Medicine

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# Precision Medicine

An innovative approach to tailoring disease prevention and treatment that takes into account differences in people's genes, environments, and lifestyles<sup>1</sup>.

Targeted therapies: Drugs or biologics intended for use with a genomic, proteomic, or other biomarker/tool that

- ▶ Identifies patients who are eligible for treatment
- ▶ Assist determining the appropriate dosage
- ▶ Allows for monitoring of response to individualize therapy

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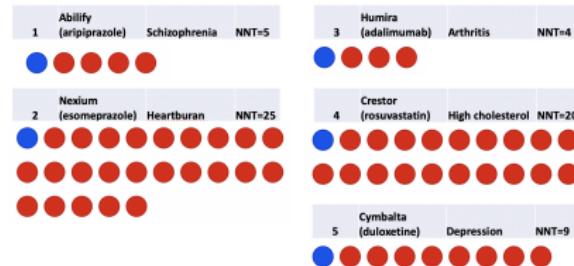
<sup>1</sup>Precision Medicine. US FDA.

# Why Precision Medicine?

Past: Population-based, “One Size Fits Many” care models:

- Diseases are diagnosed based on symptoms. Treating patients who suffered from a broad category of diseases is inefficient and costly.

Figure. Numbers Needed To Treat (NNT) for Top Five High-Grossing Drugs in the US<sup>2</sup>



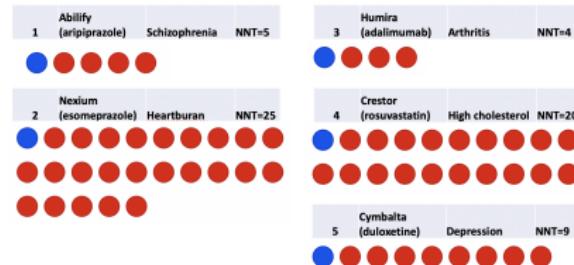
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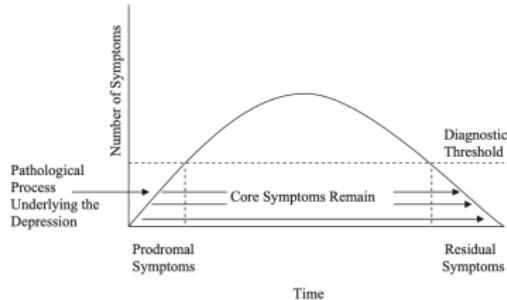


- Ignores sources of variation: (a) Heterogeneity of diseases; (b) Heterogeneity between patients and over time.

<sup>2</sup>Schork. *Nature*. 520, 609–611; 2015

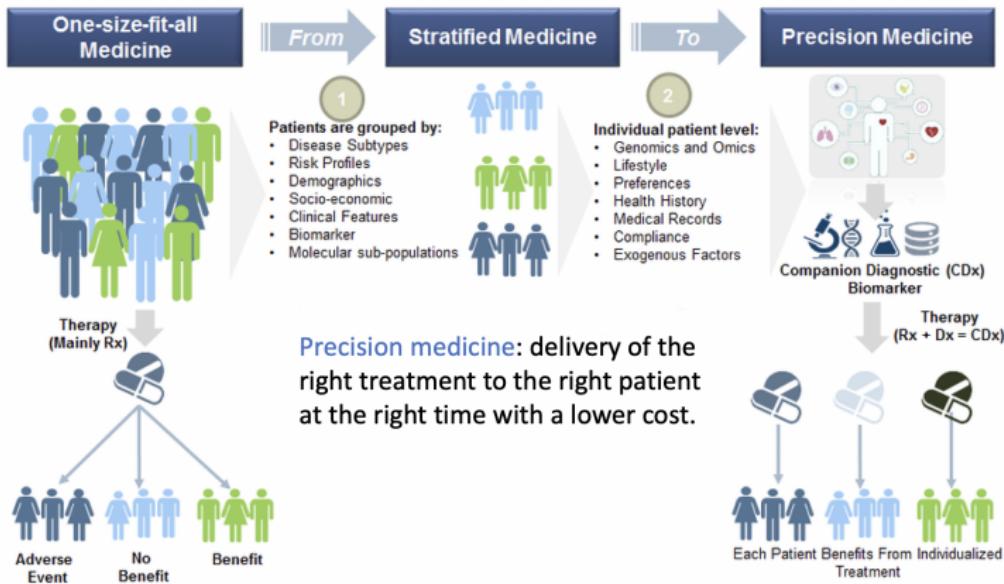
# Evidence for Heterogeneity of Depression

- ▶ Current DSM-5 diagnosis of major depressive disorder (MDD) requires 5 out of 9 symptoms: depressed mood; anhedonia; hypersomnia/insomnia; weight gain/loss; psychomotor retardation; fatigue; guilt/ worthlessness/helplessness; indecisiveness, concentration difficulties suicidality
- ▶ 140 ( $2^8!/(4!^4!)$ ) ways of meeting the DSM-5 criteria
- ▶ Polygenic: more than 150 risk genes (Wray et al. 2018; *Nature Genet*)
- ▶ Heterogeneous clinical course of depression (Iacoviello et al., 2010)



- ▶ Differential treatment response across patients (response rate 33% single treatment) and within patients (50% relapse rate; APA 2000)

# The Paradigm of Precision Medicine<sup>3</sup>



**Disentangle heterogeneity of disease:** measure diseases more precisely; target and diagnose illnesses on a biological level.

**Heterogeneity of patients:** better measurements of patient's behavioral, biological, psychosocial factors; (dynamically) target treatment strategies accordingly

<sup>3</sup>Source: Frost & Sullivan

# FDA Approved Targeted Therapies

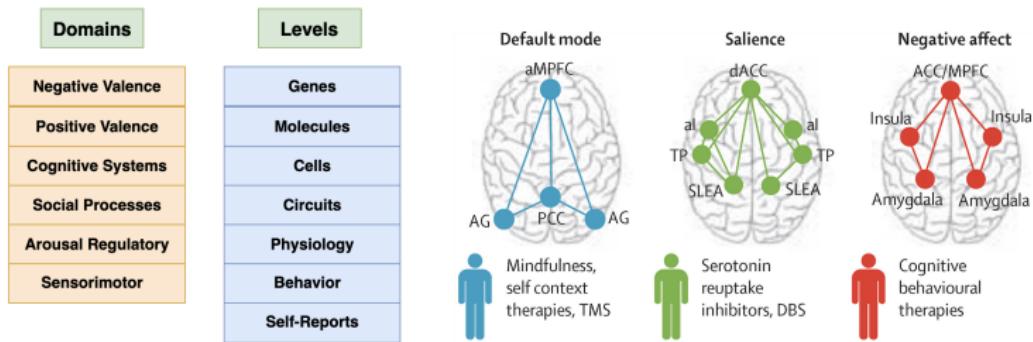
## Medical Products and Biomarkers Selected CDER Drug Approvals in 2022 (of 37 new molecular entities)



Drug	Disease or Condition	Biomarker	Use
Tebentafusp-tebn	Uveal melanoma	<i>HLA-A*02:01</i> †	Selection (subset)
Lutetium Lu 177 vipivotide tetraxetan	Prostate cancer	Prostate-specific membrane antigen	Selection (subset)
Futibatinib	Cholangiocarcinoma	<i>FGFR2</i> gene fusions or other rearrangements	Selection (subset)
Mirvetuximab soravtansine-gynx	Ovarian, fallopian tube, primary peritoneal cancer	Folate receptor alpha†	Selection (subset)
Olutasidenib	Acute myeloid leukemia	<i>IDH1</i> mutations†	Selection (subset)
Adagrasib	Non-small cell lung cancer	<i>KRAS G12C</i> mutation†	Selection (subset)
Abrocitinib	Atopic dermatitis	<i>CYP2C19</i> variants	Dosage
Mitapivat	Pyruvate kinase deficiency	<i>PKLR</i> variants	Selection (diagnosis)
Vutrisiran	Transthyretin amyloidosis polyneuropathy	<i>TTR</i> variants	Selection (diagnosis)
Olipudase alfa-rpcp	Acid sphingomyelinase deficiency	<i>SMPD1</i> variants	Selection (diagnosis)

# Precision Psychiatry: RDoC & Conceptual Model<sup>4</sup>

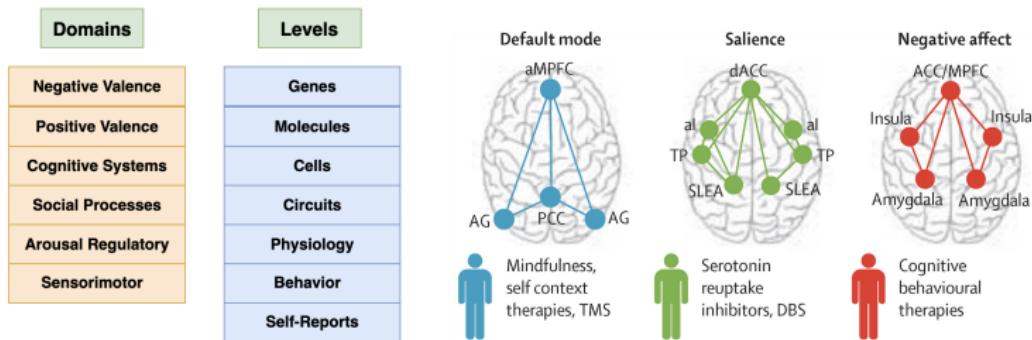
(a) RDoC: research framework to characterize mental disorders based on biological, behavioral, psychosocial measures; (b) target treatment strategies.



<sup>4</sup>Williams, *Lancet Psychiatry*, 2016; 3(5): 472-480

# Precision Psychiatry: RDoC & Conceptual Model<sup>4</sup>

(a) RDoC: research framework to characterize mental disorders based on biological, behavioral, psychosocial measures; (b) target treatment strategies.



Empirical studies to generate evidence for optimizing treatments:



Review article

Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC): Rationale and design

Madhukar H. Trivedi <sup>a,\*</sup>, Patrick J. McGrath <sup>b</sup>, Maurizio Fava <sup>c</sup>, Ramin V. Parsey <sup>d</sup>, Benji T. Kurian <sup>a</sup>, Mary L. Phillips <sup>e</sup>, Maria A. Oquendo <sup>b</sup>, Gerard Bruder <sup>b</sup>, Diego Pizzagalli <sup>f</sup>

<sup>4</sup>Williams, *Lancet Psychiatry*, 2016; 3(5): 472-480

# Paradigms of Precision Medicine

Two frameworks:

- ▶ Identifying right subjects for a given treatment (salvaging strategy for therapy with minimal overall population benefit)
- ▶ Identifying the right treatment for a given subpopulation or a given subject

Two broad types of methods:

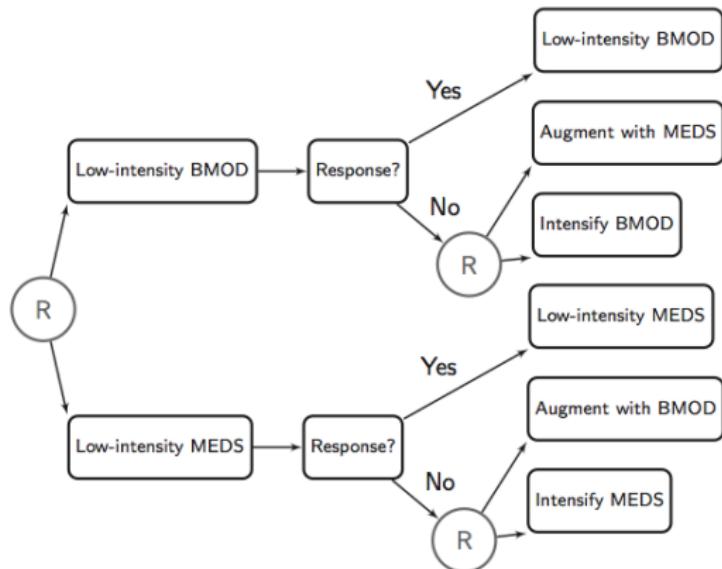
- ▶ Guideline-based: test treatment heterogeneity in pre-defined subgroups (Brookes 2001; Rothwell 2005)
- ▶ Data-driven: emphasize discovery process (interaction tree, Negassa et al. 2005, Su et al. 2009, Qiu & Wang 2019; modified covariate, Tian et al. 2012; virtue twins, Foster et al. 2012; Q-learning, Qian and Murphy 2011; O-learning, Zhao et al. 2012)

# Using RCTs for Precision Medicine Research

- ▶ Data collected from one or more randomized, parallel group, single-stage clinical trials
- ▶ Data collected from sequential randomization trials
  - ▶ Adaptive Pharmacological and Behavioral treatments for ADHD (Pelham et al., 2008)
  - ▶ Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) (Rush, et al., 2004)
  - ▶ CATIE for schizophrenia (Schneider, et al., 2003)
  - ▶ ExTEND for alcohol dependence (Oslin, 2005)
  - ▶ Adaptive therapy for androgen independent prostate cancer (Thall et al. 2007)
- ▶ Trial evidence provides valid assessment of treatment effects.

# Sequential Multiple Assignment Randomized Trial

Figure. Design of Adaptive Pharmacological Behavioral Treatments for Children with ADHD Trial (Pelham, 2008)



Excellent resources to learn about optimizing intervention and SMART trials at [University of Michigan d3Center](#).

# Advantages and Limitations with RCT

## Advantages:

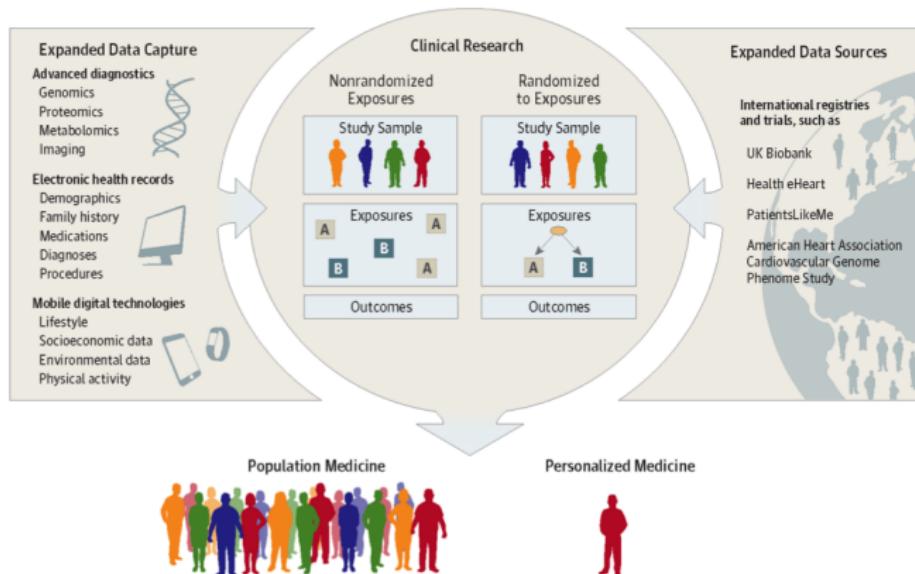
- ▶ Free of unmeasured confounding
- ▶ Carefully conducted and monitored
- ▶ Scheduled visits and follow ups

## Limitations:

- ▶ Trial data are limited in sample sizes so are usually lack of statistical power for detecting subgroup effects.
- ▶ Trials are usually not designed for personalizing treatments.
- ▶ Insufficient follow up time for adverse events
- ▶ The generalizability to a broad population is questioned.

# Observational Data for Precision Medicine

- Rich data sources provide patient information: Demographics, Co-morbidity, Stage of disease, Genomic (oncology), Imaging (psychiatry), Mobile technology (neurology, psychiatry), Electronic health records (*JAMA* 2014;312(19):1969-1970)



# 1 M Patient Cohort Being Prepared to Fuel Precision Medicine

Access to the data will be managed through the program's Data and Research Support Center which is expected to build an active community of researchers who can learn from the information and propose new research initiatives.

May 18, 2017



- EHR data resources contain massive information: CUIMC clinical data warehouse (CDW) contains 20 years of health information for about 4.5 million patients with diverse ethnicity

# Challenges with Large-Scale Observational Data

- ▶ Presence of (unobserved) confounders can lead to invalid results.
- ▶ Selection bias
- ▶ High-dimensional or dynamic tailoring variables
- ▶ Intensively measured outcomes (mobile health technologies)
- ▶ Noisy and poor data quality (measurement errors, missing data)
- ▶ Large number of treatment options
- ▶ Large data size

# Machine Learning Approaches to Tackle Some Challenges

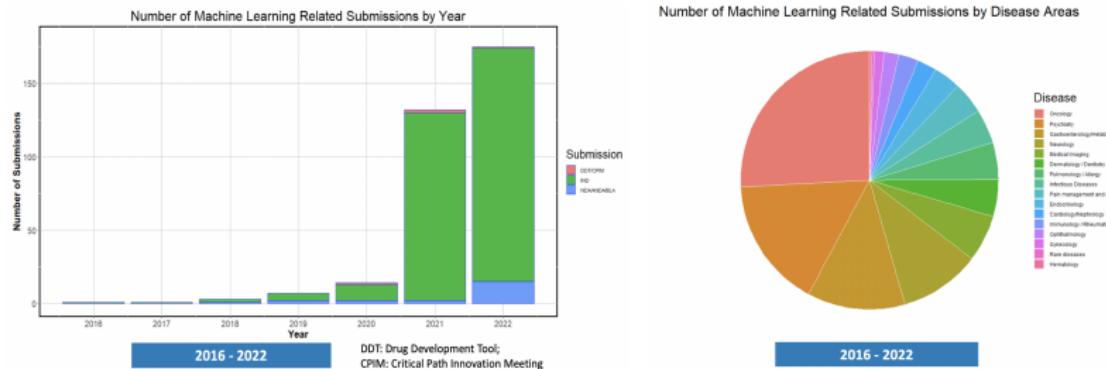
- ▶ Powerful to estimate nonparametric treatment decision functions/complex interactions
- ▶ Powerful to handle large, diverse health data
- ▶ Goal-oriented towards an objective function
- ▶ Recent major advances in machine learning
  - ▶ Modern computational techniques (e.g. regularized regressions, feed-forward neural nets, variants of SGD)
  - ▶ Available high-quality open source softwares for implementation

## But, machine learning approaches are not panacea

- ▶ Many of the research questions are causal
  - ▶ Direct use of machine learning for prediction is insufficient
- ▶ Applications with high impacts on human health
  - ▶ Robustness, generalizability, and reproducibility are important
- ▶ ML can only ever be as good as the underlying data:
  - ▶ Lack of high-quality, large-scale, and fit-for-purpose datasets for development and testing
  - ▶ Identification and mitigation of bias in datasets
  - ▶ Poor generalization due to dataset shift, to overfitting to confounders
- ▶ Data can be expensive (e.g., neuroimaging) and many studies with small to moderate size (randomized trials)
- ▶ Balancing interpretability, flexibility and accuracy (black-box undesirable)

# AI or ML Submissions to the FDA

Figure. Regulatory submissions to the Center for Drug Evaluation and Research (CDER) that included artificial intelligence or machine learning, US FDA from 2016 to 2021<sup>5</sup>.



<sup>5</sup> Qi Liu, R. H., Julie Hsieh, Hao Zhu, Mo Tiwari, Guansheng Liu, Daphney Jean, M. Khair ElZarrad, Tala Fakhouri, Steven Berman, Billy Dunn, Matthew Diamond, and Shiew-Mei Huang (2022). Landscape Analysis of the Application of Artificial Intelligence and Machine Learning in Regulatory Submissions for Drug Development from 2016 to 2021. *Clinical Pharmacology & Therapeutics*.

# Potential Outcome Framework

# Potential Outcome Framework in Precision Medicine

For single-stage trials with only two treatment options  $\{-1, 1\}$  and a single outcome  $R$  (assuming a larger outcome is desirable)

- ▶ **Potential outcome**  $R(a)$  refers to the outcome if treated by  $a \in \{1, -1\}$ .
- ▶ The goals of precision medicine are to determine whether  $R(1)$  is larger than  $R(-1)$  and the size of  $R(1) - R(-1)$  for each subject.

For two treatment stages and one single outcome  $R$

- ▶ **Potential outcome**  $R(a_1, a_2)$  refers the outcome if treated by  $a_1$  in the first stage and  $a_2$  in the second stage.
- ▶ The goal is to compare  $R(a_1, a_2)$  under different options of  $a_1, a_2$ .

# Fundamental Problem of Causal Inference

In general, consider any treatment sequence  $(a_1, a_2, \dots)$ . Let  $R(a_1, a_2, \dots)$  be the corresponding potential outcome, we aim to estimate the difference among potential outcomes from data.

- ▶ Cannot observe all sequences of potential outcomes: only the potential outcome under one possible sequence of treatments is observed for a given individual
- ▶ So in theory, comparing individual treatment effect is impossible!
- ▶ Solution: use other individuals' outcomes to "impute" unobserved potential outcomes; however, imputation depends on strong assumptions due to unobserved differences between individuals.

# Practical Solutions

- ▶ Instead of seeking individual effects, aim for the average effects from groups of individuals with similar feature variables (e.g., covariates).
- ▶ Overall average treatment effects (ATE):

$$E[R(1)] - E[R(-1)], \quad E[R(a_1, a_2)] - E[R(a'_1, a'_2)].$$

- ▶ Feature-specific conditional average treatment effects (CATE):

$$E[R(1) - R(-1)|X], \quad E[R(a_1, a_2) - R(a'_1, a'_2)|X]$$

where  $X$  is a pre-specified feature variable.

# Practical Solutions

- We can consider other transformations for discrete outcomes (e.g., odds ratio, relative risk)
- We can compare treatment decision rules  $D_1(X), D_2(X)$

$$E[R(D_1(X))] - E[R(D_2(X))],$$

where  $D_1$  and  $D_2$  are decision functions that map  $X$ 's domain into  $\{-1, 1\}$ :

$$D : \text{domain of } X \rightarrow \{-1, 1\}.$$

- This can assist making evidence-based treatment decision/health policy decision.

# From Fixed Treatment Options to Treatment Strategies

- ▶ Overall average treatment effects compares fixed treatment options, i.e., what if we apply treatment option  $a_1$  or  $a_2$  to everyone in the study population.
- ▶ Essentially, we are comparing two treatment strategies:
  - Strategy 1: Everyone is treated by  $a_1$ .
  - Strategy 2: Everyone is treated by  $a_2$ .
- ▶ This is referred as **one-size-fits-all strategy** or **universal strategy**.
- ▶ Similarly, the subgroup comparison is comparing two fixed treatment strategies within **pre-defined** subgroups.
- ▶ In contrast, precision medicine estimates even broader (dynamic) treatment strategies that **depends on interim outcomes**, so it is not pre-defined!

# Tailoring Treatments using ITR

Individualized treatment rules (ITRs): decision rules prescribing medical treatment/therapy for patients in a given state.

Mathematically, it is a mapping from currently available pre-treatment state variables (e.g., biomarker, intermediate outcomes) into the space of possible decisions (e.g., switch to an alternative treatment).

Example: Healing Emotion After Loss (HEAL, Shear et al. 2016; *JAMA Psychiatry*)

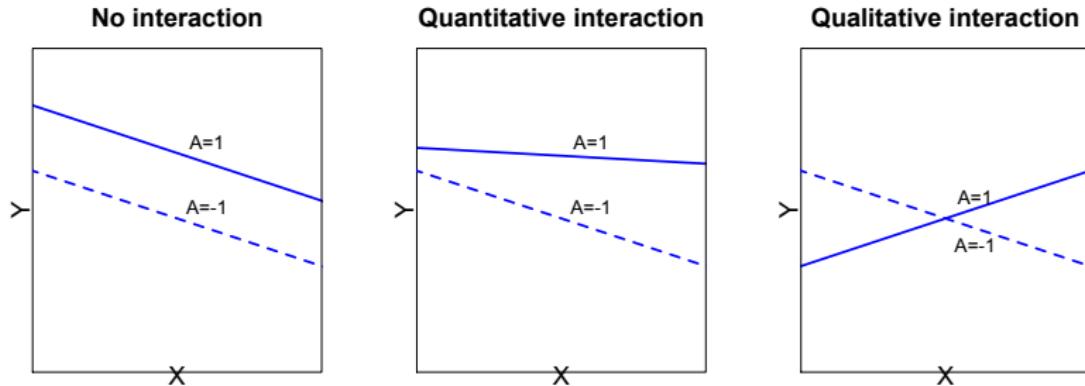
- ▶ Administer clinical management as the initial treatment; **if a patient responds** then continue; **if** a patient does not respond within 12 weeks then offer an anti-depressant (Citalopram).

**Original Investigation**

## Optimizing Treatment of Complicated Grief A Randomized Clinical Trial

M. Katherine Shear, MD; Charles F. Reynolds III, MD; Naomi M. Simon, MD, MSc; Sidney Zisook, MD; Yuanjia Wang, PhD; Christine Mauro, PhD; Naihua Duan, PhD; Barry Lebowitz, PhD; Natalia Skritskaya, PhD

# Types of Variables for Tailoring Treatments



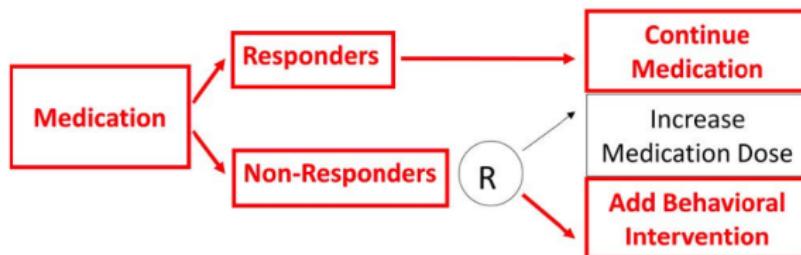
Three types of state variables (pre-treatment covariates):

- ▶ prognostic variables (associated with clinical outcomes, no interaction with treatment  $A$ )
- ▶ predictive variables (quantitative interaction)
- ▶ prescriptive variables (qualitative interaction; Gunter et al. 2011)  
**Tailoring variables**

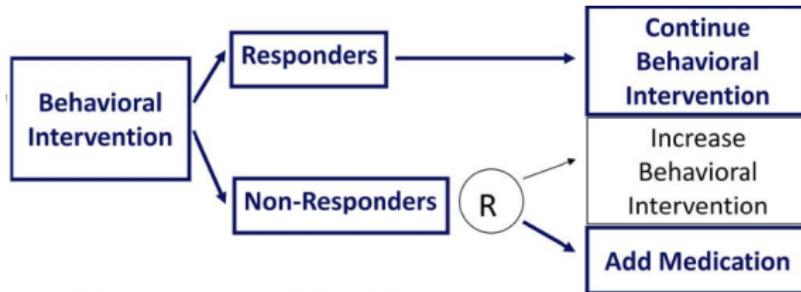
# Dynamic Treatment Strategies

Treatment strategies can be dynamic (e.g., adapts to patient's intermediate outcomes):

- ▶ Example 1:



- ▶ Example 2:



# Dynamic Treatment Strategies

- ▶ The average potential outcomes cannot be quantified in terms of constant treatment options, since the treatment choices depend on the intermediate outcomes for different individuals.
- ▶ The examples are two different treatment strategies and they are dynamic in nature.
- ▶ Also referred as **dynamic treatment regimes**, **dynamic treatment rules**, **dynamic treatment policies**, **adaptive treatment strategies**, or **adaptive interventions**.

# Goals for Precision Medicine Research

- ▶ **Design** studies to test (dynamic) treatment strategy.
- ▶ **Estimate effects or compare** different treatment strategies.
- ▶ **Discover** the optimal treatment strategies.
- ▶ **Implement** a treatment strategy (implementation science).
- ▶ **Validate** a treatment strategy (external validation studies).

Consider designs, assumptions, and practical constraints to achieve these goals.

# Estimation from RCTs and Observational Data

## Single-stage Randomized Trials

- ▶ For simplicity, consider 2 treatment options  $\{-1, 1\}$ .
- ▶ In randomized trials, patients are randomized into one of the treatment arms.
- ▶ The randomization probability can be different for each patient, i.e.,

$$\pi(a|x) \equiv P(A = a|X = x) \text{ can be a function of } x,$$

where  $X$  denotes covariates and  $A$  is treatment.

- ▶ Note that  $\pi(a|x)$  is known by the design.

# Virtue of Randomization

- ▶ It removes all **observed and unobserved** confounders ( $R(a) \perp A$ ) so that the observed difference between two arms is purely due to their treatment assignments
- ▶ It can provide an unbiased estimator for the average treatment effect (ATE)

$$E[R(1)] - E[R(-1)].$$

- ▶ It also gives an unbiased estimator for the feature-specific conditional average treatment effect (CATE)

$$E[R(1)|X = x] - E[R(-1)|X = x].$$

# Assumptions and Justification

- ▶ Ignorability/no unobserved confounder condition (NUC):  
 $A$  is independent of  $\{R(a) : a = 1, -1\}$  conditional on  $X$ .  
Thus,

$$E[R(a)|X = x] = E[R(a)|A = a, X = x].$$

- ▶ Stable Unit Treatment Value Assumption (SUTVA):

$$R = R(a) \text{ when } A = a.$$

- ▶ The first condition: the treatment assignment is independent of all potential outcomes given  $X$ .
- ▶ The second condition: the observed outcome is the same as the potential outcome for the given treatment (no treatment interference).

## Discussion of Assumptions

- ▶ The first condition holds in randomized trials unless randomization is compromised.
- ▶ The second condition is natural but may not hold when there are treatment interference or non-compliance.
- ▶ NUC may not hold due to the nature of observational studies.
- ▶ In practice, if we can collect additional auxiliary covariates (patient's disease history, biomarkers, social economical status), denoted as  $Z$ , assume the following 'Generalized NUC' condition:

$A$  is conditionally independent of  $\{R(a)\}$  given  $X$  and  $Z$ .

# Justification of Estimating Causal Effects from RCTs

- The first key relationship:

$$E[R(a)|X = x] = E[R(a)|A = a, X = x].$$

- The second key relationship:

$$R(a) = R \text{ when } A = a.$$

- These two equations yield

$$E[R(a)|X = x] = E[R|A = a, X = x]$$

which ensures that causal effects can be estimated unbiasedly from RCT data.

# Estimation under the (Generalized) NUC Condition

- ▶ Together with SUTVA, the same argument shows that we can unbiasedly estimate

$$E[R(1)|X, Z] - E[R(-1)|X, Z]$$

using  $E[R|X, Z, A = 1] - E[R|X, Z, A = -1]$

- ▶ Obtain  $E[R(1)|X] - E[R(-1)|X]$  and  $E[R(1)] - E[R(-1)]$  by marginalization:

- ▶ Estimate  $E[R|X, Z, A = a]$  using either semiparametric regression models or nonparametrically.
- ▶ Estimate the conditional distribution of  $f(Z|X, A = a)$  semiparametrically or nonparametrically.
- ▶ Compute  
$$E[R|X, A = a] = \int E[R|X, Z, A = a]f(Z|X, A = a)dZ.$$

- ▶ This is the essence of **G-computation** in causal inference.

# Alternative IPW Estimation

- We estimate  $E[R(a)|X]$  using the inverse probability weighted (IPW) expectation of  $R$  among subjects with  $A = a$

$$\frac{1}{n} \sum_i \frac{R_i I(A_i = a)}{P(A_i = a | X_i, Z_i)}$$

- Inverse probability weighted (IPW) mean:

$$\begin{aligned} E \left[ \frac{RI(A = a)}{P(A = a | X, Z)} \middle| X \right] &= E \left[ \frac{R(a)I(A = a)}{P(A = a | X, Z)} \middle| X \right] \\ &= E \left[ E[R(a) | X, Z] \frac{E[I(A = a) | X, Z]}{P(A = a | X, Z)} \middle| X \right] \\ &= E [R(a) | X] . \end{aligned}$$

# Positivity Assumption

- ▶ One implicit assumption is  $P(A = a|X, Z) > 0$ .
- ▶ Note that this assumption holds in randomized trials if randomization probabilities are positive.
- ▶ Inverse probability weighted augmentation estimators can be further constructed to achieve double robustness and local efficiency using semiparametric efficiency theory.

# Estimation Approaches for Conditional Average Treatment Effects (CATE)

# Double Robust Estimation Approaches for CATE

Denote treatment by  $A = 0, 1$ . Conditional average treatment effect:  $\text{CATE} = E[R(1) - R(0)|X]$ .

Two important components:

- ▶ Propensity scores:  $\pi(x) = P(A = 1|X = x)$
- ▶ Outcome regression:  $\mu_a(X) = E(R|X = x, A = a)$

Under consistency, positivity and exchangeability:

$$E[R(1) - R(0)|X] = \mu_1(x) - \mu_0(x).$$

Why not estimate outcome regressions in each group and take the difference? This method is referred to as “**plug-in estimator**” or “T-learner” ([Kunzel et al. 2019](#)).

## Motivating Example of Limitations of “T-learner”

Simulated example in [Kennedy \(2020\)](#): covariates uniform [-1,1],  $\mu_a(x)$  piecewise polynomial function,

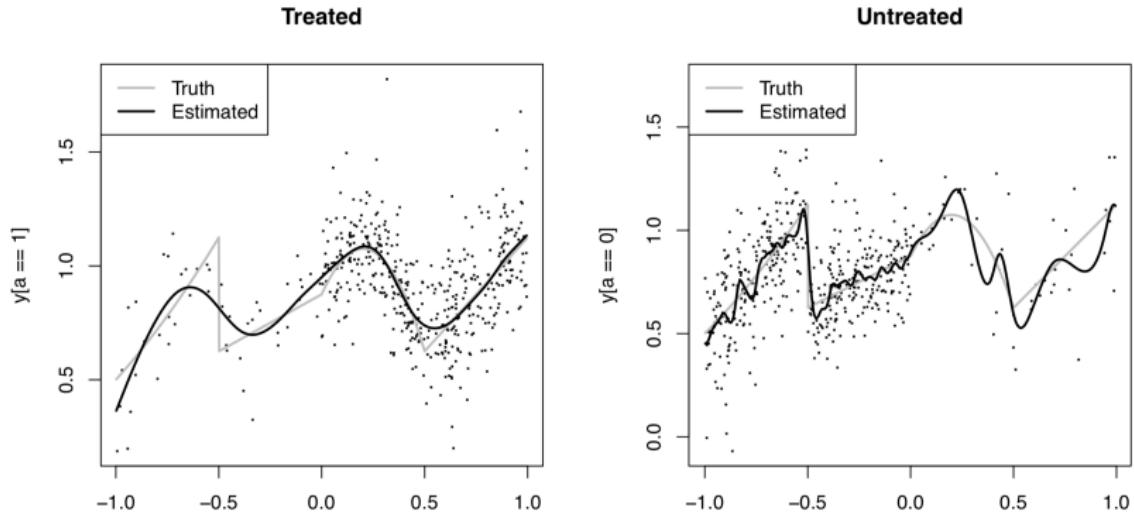
$$\mu_1(x) = \mu_0(x), \pi(x) = 0.5 + 0.4 \times \text{sign}(x).$$

- ▶ Individual outcome regressions are non-smooth and difficult to estimate (piecewise polynomial)
- ▶ CATE= 0! Easy!

In this case, plug-in estimator is heavily impacted by the data generating process and outcome regression estimation, and performs poorly.

# Motivating Example

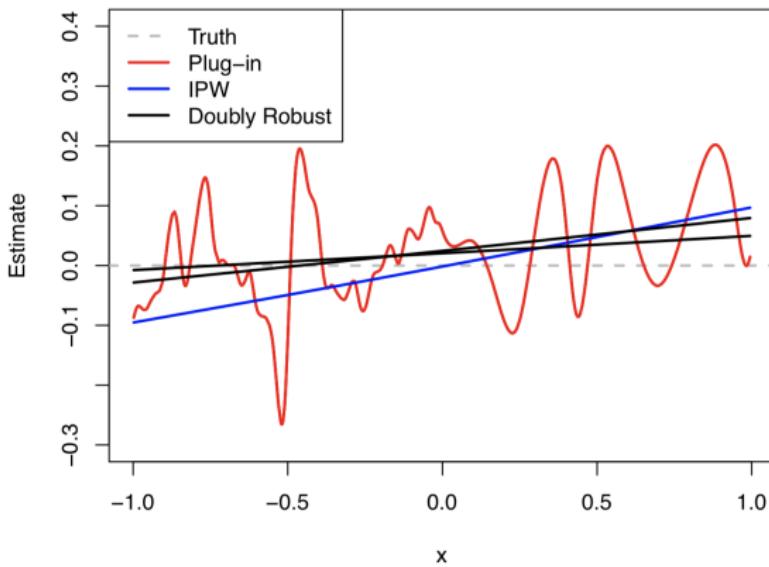
Figure. Simulated outcomes in treated and untreated population<sup>6</sup>



<sup>6</sup>Kennedy (2020). <https://arxiv.org/pdf/2004.14497.pdf>

# Motivating Example of Limitations of “T-learner”

Figure. Comparison of Several Estimators<sup>7</sup>



<sup>7</sup>Kennedy (2020). <https://arxiv.org/pdf/2004.14497.pdf>

## Alternative: Doubly Robust Estimator

Key observation: define

$$Y = \frac{(A - \pi)R}{\pi(1 - \pi)},$$

then under assumptions

$$E(Y|X = x) = E(R(1) - R(0)|X = x) = CATE(x)$$

# Alternative: Doubly Robust Estimator

DR-learner (van der Lann, 2013; Luektke & van der Laan, 2016):  
Divide data  $(X, A, R)$  into 3 folds  $(D_{1a}, D_{1b}, D_2)$ .

Step 1. Nuisance training:

- Construct estimates  $\hat{\pi}$  for propensity scores using  $D_{1a}$
- Construct estimates for outcome models  $\hat{\mu}_1(x), \hat{\mu}_0(x)$  using  $D_{1b}$

Step 2. Construct the pseudo-outcome

$$\widehat{\psi}(Z) = \frac{A - \hat{\pi}(X)}{\hat{\pi}(X)(1 - \hat{\pi}(X))} \{R - \hat{\mu}_A(X)\} + \hat{\mu}_1(x) - \hat{\mu}_0(x)$$

and regress it on  $X$  in the test sample  $D_2$  to obtain

$$\widehat{CATE}(x) = \widehat{E}_n\{\widehat{\psi}(Z)|X = x\}$$

# Estimation Approaches for Treatment Rules

# Single-Stage Decision: Notation and Data

- ▶ Observe independently and identically distributed training data  $(X_i, A_i, R_i), i = 1, \dots, n.$   
 $X$ : baseline variables,  $X \in \mathbb{R}^d$ ,  
 $A$ : binary treatment options,  $A \in \{-1, 1\}$ ,  
 $R$ : outcome (or reward; assuming larger is better),  
 $R \in \mathbb{R}^+$ ,  $R$  is bounded.
- ▶ Randomized study with known randomization probability of the treatment.
- ▶ Construct **individualized treatment rule (ITR)**

$$\mathcal{D}(X) : \mathbb{R}^d \rightarrow \{-1, 1\}.$$

Goal:

Maximize the expected outcome (or reward) if the ITR is implemented in a future target population.

# Value Function and Optimal ITR

1. The value function of  $\mathcal{D}$  is

$$\mathcal{V}(\mathcal{D}) = E^{\mathcal{D}}(R) = \int R dP^{\mathcal{D}} = \int R \frac{dP^{\mathcal{D}}}{dP} dP = E \left[ \frac{I(A = \mathcal{D}(X))}{P(A|X)} R \right].$$

2. Optimal Individualized Treatment Rule:

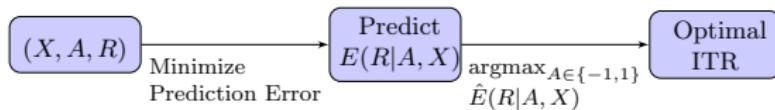
$$\mathcal{D}^* \in \operatorname{argmax}_{\mathcal{D}} \mathcal{V}(\mathcal{D}).$$

$$E(R|X, A = 1) > E(R|X, A = -1) \Rightarrow \mathcal{D}^*(X) = 1$$

$$E(R|X, A = 1) < E(R|X, A = -1) \Rightarrow \mathcal{D}^*(X) = -1$$

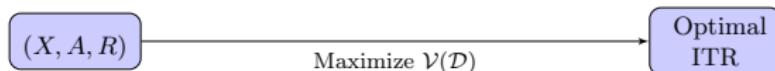
# Estimating Optimal ITRs

Regression-based approach:



**Problem:** mismatch between minimizing the prediction error and maximizing the value function.

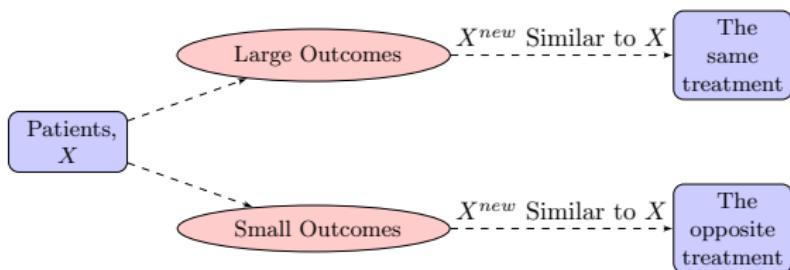
Can we directly maximize the value function?



# The Classification Perspective

Given a new subject with  $X^*$ , predict the optimal treatment label  $\mathcal{D}^*$ .

- ▶ No direct information on the true class labels,  $\mathcal{D}^*$ .
- ▶ Can we assign the right treatment based on the observed information?



# Outcome Weighted Learning (O-Learning)<sup>8</sup>

## Optimal Individualized Treatment Rule $\mathcal{D}^*$

Maximize the value

Minimize the risk

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

- ▶ For any rule  $\mathcal{D}$ ,  $\mathcal{D}(X) = \text{sign}(f(X))$  for some function  $f$ .  
Empirical approximation to the risk function:  
 $n^{-1} \sum_{i=1}^n \frac{R_i}{P(A_i|X_i)} I(A_i \neq \text{sign}(f(X_i)))$ .
- ▶ Computational challenges: non-convexity and discontinuity of 0-1 loss.
- ▶ Solution: use convex surrogate loss (e.g., hinge loss for SVM or binomial deviance for logistic regression)

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<sup>8</sup>Zhao et al. (2012). Estimating Individualized Treatment Rules Using Outcome Weighted Learning. JASA. 107(449)

# Outcome Weighted Learning (O-Learning)

- Objective Function: Regularization Framework

$$\min_f \left\{ \frac{1}{n} \sum_{i=1}^n \frac{R_i}{P(A_i|X_i)} \phi(A_i f(X_i)) + \lambda_n \|f\|^2 \right\}.$$

- $\|f\|$  is the norm for  $f$ . For a linear decision rule:  
 $f(X) = X^T \beta + \beta_0$  with  $\|f\|$  as the Euclidean norm of  $\beta$ .
- Estimation uses **weighted classification algorithms**.  
Estimated individualized treatment rule:

$$\hat{\mathcal{D}}_n = \text{sign}(\hat{f}_n(X)),$$

where  $\hat{f}_n$  is the solution.

- Improve efficiency by removing main effects on  $R^9$ .

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<sup>9</sup>Liu et al. (2018). Augmented outcome-weighted learning for estimating optimal dynamic treatment regimens. *Statistics in medicine*, 37(26), 3776-3788.

# Summary

Machine learning techniques can be used for precision medicine research. O-learning based methods transforms optimizing ITR/DTRs into sequential classification problems.

Extensions:

- ▶ More interpretable rules: incorporate tree model, identify high-benefit subgroups.
- ▶ Integrate information from multiple sources (e.g., RCT and EHRs)
- ▶ Handle multivariate outcomes; Latent outcomes (Case study)
- ▶ Design studies better suited for testing or building ITRs

Future directions:

- ▶ **Precision medicine**: incorporate genomic data, environmental risk factors, EHRs, social and behavioral variables.
- ▶ **From finite stage decisions to real-time decisions**: mobile health

## Case Study: Towards Deep Learning Models for Precision Medicine<sup>10,11</sup>

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<sup>10</sup>Chen et al. Learning Individualized Treatment Rules for Multiple-Domain Latent Outcomes. *J American Statistical Association*; 2021. 116:533, 269- 282.

<sup>11</sup>Chen et al., Representation Learning for Integrating Multi- domain Outcomes to Optimize Individualized Treatments. *Advances in Neural Information Processing Systems (NeurIPS)*, 2020.