

Causal ML for predicting treatment outcomes

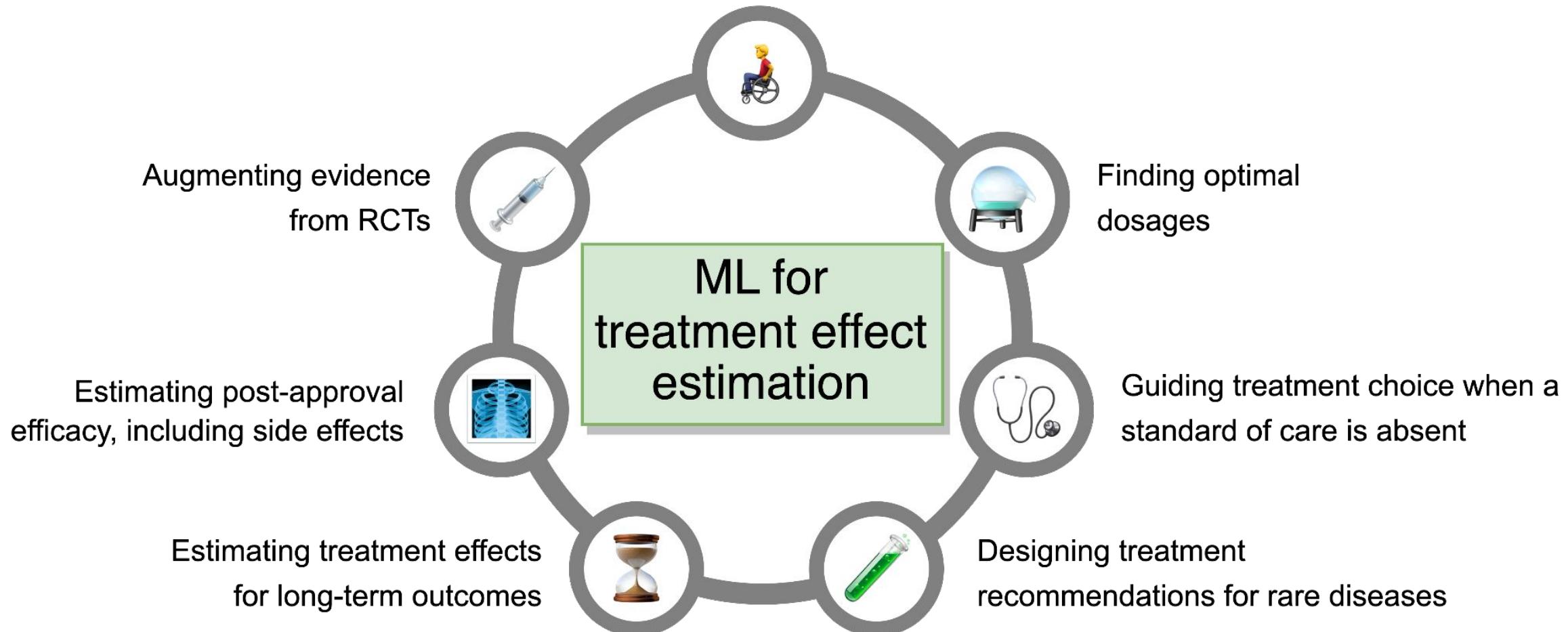
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Valentyn Melnychuk**

**Institute of AI in Management
LMU Munich**
<https://www.ai.bwl.lmu.de>



Promises of Causal ML

Estimating treatment effects for vulnerable groups





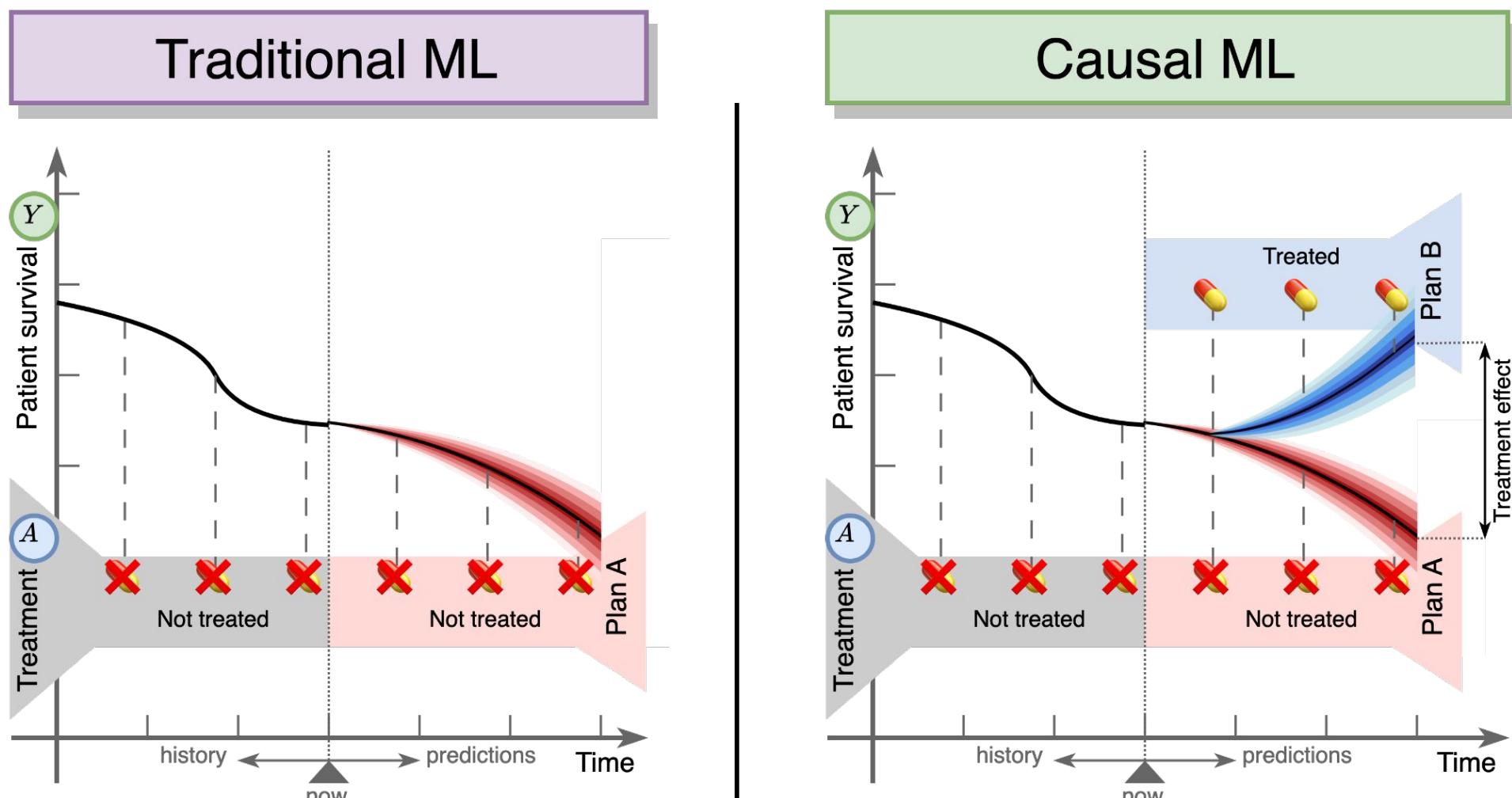
Why do we need Causal ML in medicine?

Reference:

Feuerriegel, S., Frauen, D., Melnychuk, V., Schweisthal, J., Hess, K., Curth, A., Bauer, S., Kilbertus, N., Kohane, I.S. and van der Schaar, M., 2024. Causal machine learning for predicting treatment outcomes. Nature Medicine, 30(4), pp.958-968.

TERMINOLOGY

Moving from diagnostics to therapeutics: Estimating treatment effects with ML



TERMINOLOGY

Real-world data (RWD) vs. real-world evidence (RWE) to support medicine

The US Food and Drug Administration (FDA) defines ^{1,2,3}:



Real-world data (RWD)

- Data relating to patient health status and the delivery of healthcare
- **Examples:** electronic health records (EHRs), claims and billing activities, disease registries, ...
- Naming: observational data (\neq experimental data)



Real-world evidence (RWE)

- Analysis of RWD regarding usage and effectiveness
- Vision: greater personalization of care
- Disclaimer: should not replace but augment RCTs

1) Real-World Evidence — Where Are We Now? <https://www.nejm.org/doi/full/10.1056/NEJMp2200089>

2) Real-World Evidence — What Is It and What Can It Tell Us? <https://www.nejm.org/doi/full/10.1056/nejmsb1609216>

3) Real-World Evidence and Real-World Data for Evaluating Drug Safety and Effectiveness <https://jamanetwork.com/journals/jama/fullarticle/2697359>

TERMINOLOGY

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- Data relating to patient health status and the delivery of healthcare
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- Naming: observational data (\neq experimental data)



Real-world evidence (RWE)

- **Aim:** estimate treatment effectiveness
- **Challenges:** representativeness (selection bias), no proper randomization, ...
- **Custom methodologies:** target trial emulation, **causal machine learning**, ...

- Analysis of RWD regarding usage and effectiveness
- Vision: greater personalization of care
- Disclaimer: should not replace but augment RCTs

1) Real-World Evidence — Where Are We Now? <https://www.nejm.org/doi/full/10.1056/NEJMmp2200089>

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Application scenarios of RWD

RWD helps to guide decision-making (beyond RCTs):

1 ... in the absence of a standard of care

- Specific subtypes of diseases with no standard of care yet (e.g., oncology)
- New or experimental drugs (e.g., orphan drugs, is Biontech vs. Moderna vaccine more effective for subcohort X?)

2 ... in complex, high-dimensional decision problems

- Complex dosaging problems (e.g., chemotherapy, combi-treatments)

3 ... when RCTs are unethical

- Vulnerable populations (pregnant women, children, severely ill, etc.) ¹

4 ... when a greater personalization is desired

- Highly granular subpopulations that cannot be really placed in RCTs (e.g., women, above 60, with comorbidity X, Y & Z or generally specific patient trajectories)
→ maybe a subpopulations responds different for a specific drug, or a second line of treatment is more effective than the first line?
- Personalization based on genome data (e.g., precision medicine)

1) The Effectiveness of Right Heart Catheterization in the Initial Care of Critically Ill Patients <https://jamanetwork.com/journals/jama/article-abstract/407990>

EXAMPLE

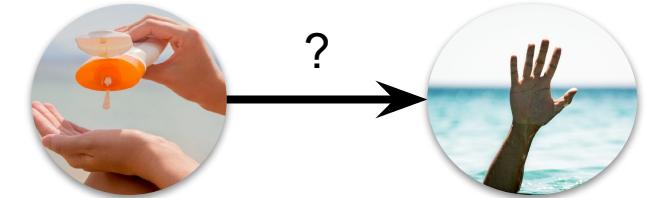
Real-world data (RWD) vs. real-world evidence (RWE) to support medicine

Why is getting a **meaningful** RWE challenging?



Real-world data (RWD)

- Observational data of
 - sunscreen usage (binary treatment)
 - number of drowning-related deaths (outcome)



Real-world evidence (RWE)

- Aim: effect of sunscreen on the chance of drowning

- Evidence: The higher the usage of sunscreen -> the more likely is the chance of drowning
- This is counterintuitive: Is there something we didn't account for?



EXAMPLE

Real-world data (RWD) vs. real-world evidence (RWE) to support medicine

Why is getting a **meaningful RWE** challenging?



Real-world data (RWD)

- Observational data of
 - sunscreen usage (binary treatment)
 - number of drowning-related deaths (outcome)
 - **intensity of sunlight (covariates)**



Real-world evidence (RWE)

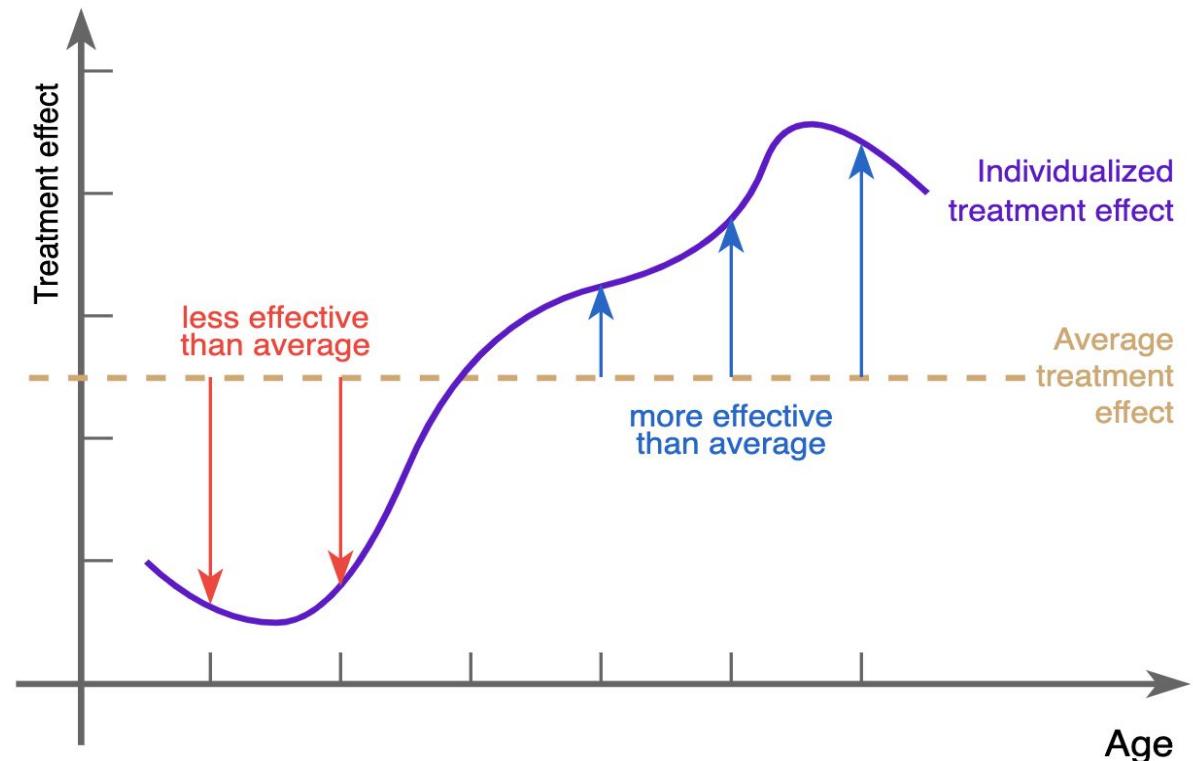
- **Aim:** effect of sunscreen on the chance of drowning for **different intensities of sunlight**



- Evidence: no association between sunscreen usage and chance of drowning in each group of sunlight
- Comparing with the previous slide: Intensity of sunlight is a **confounder**

Understanding heterogeneity in the treatment effect

- Focus is often on **average** treatment effect (ATE)
- ATE is aggregated across the population
- ATE **cannot** tell whether a treatment works for some or not
→ e.g., medication works only for women but not for men, but RCT was done with all patients
- NB: both RCTs and target trial emulation focus on ATEs



To personalize treatment recommendations, we need to understand the **individualized treatment effect (ITE)**



Short introduction to causal machine learning

Reference:

Feuerriegel, S., Frauen, D., Melnychuk, V., Schweisthal, J., Hess, K., Curth, A., Bauer, S., Kilbertus, N., Kohane, I.S. and van der Schaar, M., 2024. Causal machine learning for predicting treatment outcomes. *Nature Medicine*, 30(4), pp.958-968.

Ladder of causation

Pearl's
layers of
causation

Level (Symbol)	Typical Activity	Typical Questions	Examples
1. Association $P(y x)$	Seeing	What is? How would seeing X change my belief in Y ?	What does a symptom tell me about a disease? What does a survey tell us about the election results?
2. Intervention $P(y do(x), z)$	Doing Intervening	What if? What if I do X ?	What if I take aspirin, will my headache be cured? What if we ban cigarettes?
3. Counterfactuals $P(y_x x', y')$	Imagining, Retrospection	Why? Was it X that caused Y ? What if I had acted differently?	Was it the aspirin that stopped my headache? Would Kennedy be alive had Oswald not shot him? What if I had not been smoking the past 2 years?



Causal Hierarchy Theorem: statistical inference for a layer requires the information from the same or higher layer. For the inference from lower layer data, we need to make **additional assumptions**.

¹ Elias Bareinboim et al. "On Pearl's hierarchy and the foundations of causal inference". In: Probabilistic and Causal Inference: The Works of Judea Pearl. Association for Computing Machinery, 2022, pp. 507–556.

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Ladder of causation

Pearl's
layers of
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Level (Symbol)	Typical Activity	Typical Questions	Examples	Traditional ML
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Ladder of causation

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Level (Symbol)	Typical Activity	Typical Questions	Examples
1. Association $P(y x)$	Seeing	What is? How would seeing X change my belief in Y ?	What does a symptom tell me about a disease? What does a stock price tell me about the election?
2. Intervention $P(y do(x), z)$	Doing Intervening	What if? What if I do X ?	What if I take aspirin, will my headache be cured? What if we ban cigarettes?
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Causal ML



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Estimating the potential outcomes of treatments

Problem formulation

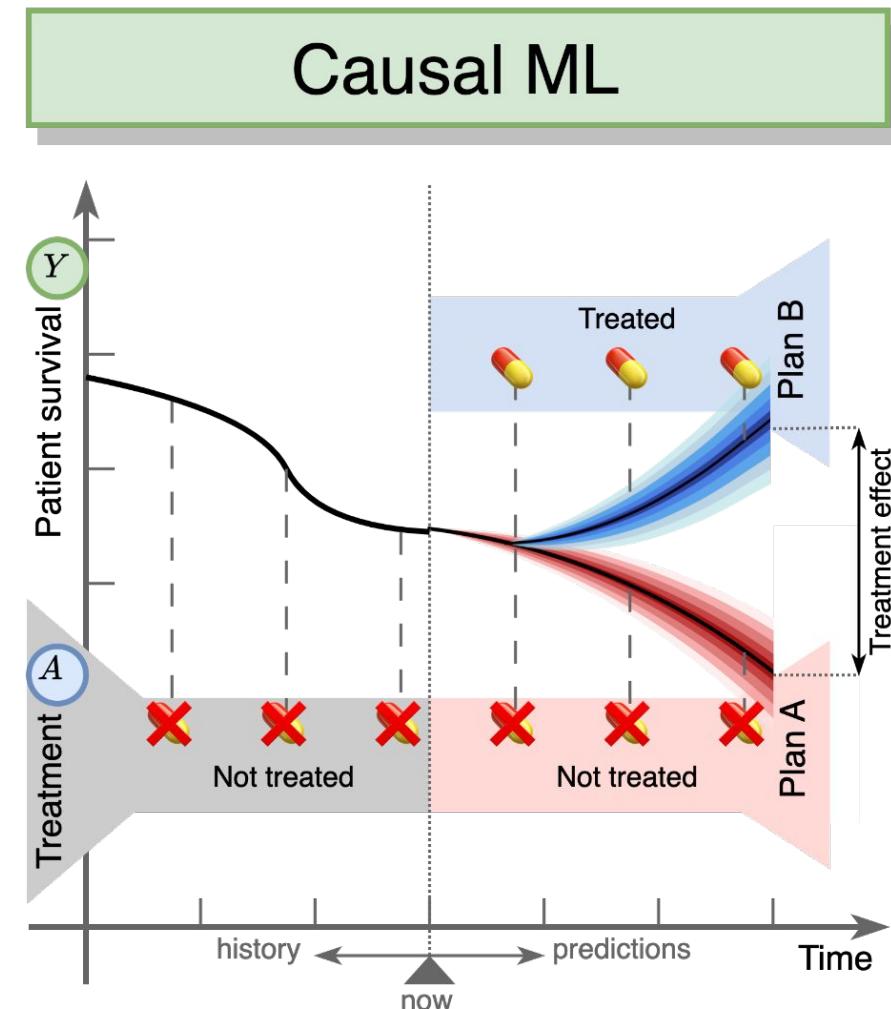
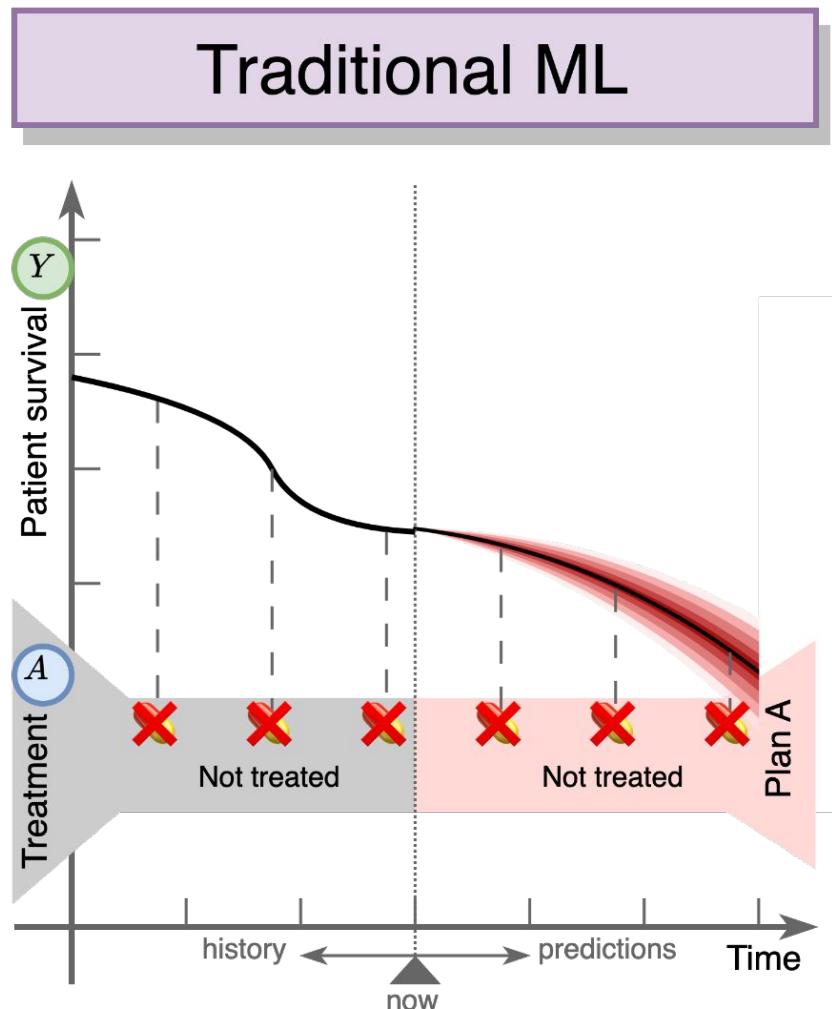
- Given i.i.d. observational dataset $\mathcal{D} = \{x_i, a_i, y_i\}_{i=1}^n \sim \mathbb{P}(X, A, Y)$
 - X covariates
 - A (binary) treatments
 - Y continuous (factual) outcomes
- We want to identify & estimate treatment outcomes:
 - treatment effects** $Y[1] - Y[0]$
 - potential outcomes** (separately) $Y[0]$ $Y[1]$
- Fundamental problem:** never observing both potential outcomes!

Patient	Covariates X	Treatment A	Outcome $Y = Y(0)$	Outcome $Y = Y(1)$
...	...	0	-1.0	
...	...	1		2.3
...	...	1		0.3
...

Patient	Covariates X	Potential outcomes $Y(0)$	Potential outcomes $Y(1)$	Treatment effect $Y(1) - Y(0)$
...	...	?	?	?
...	...	?	?	?
...

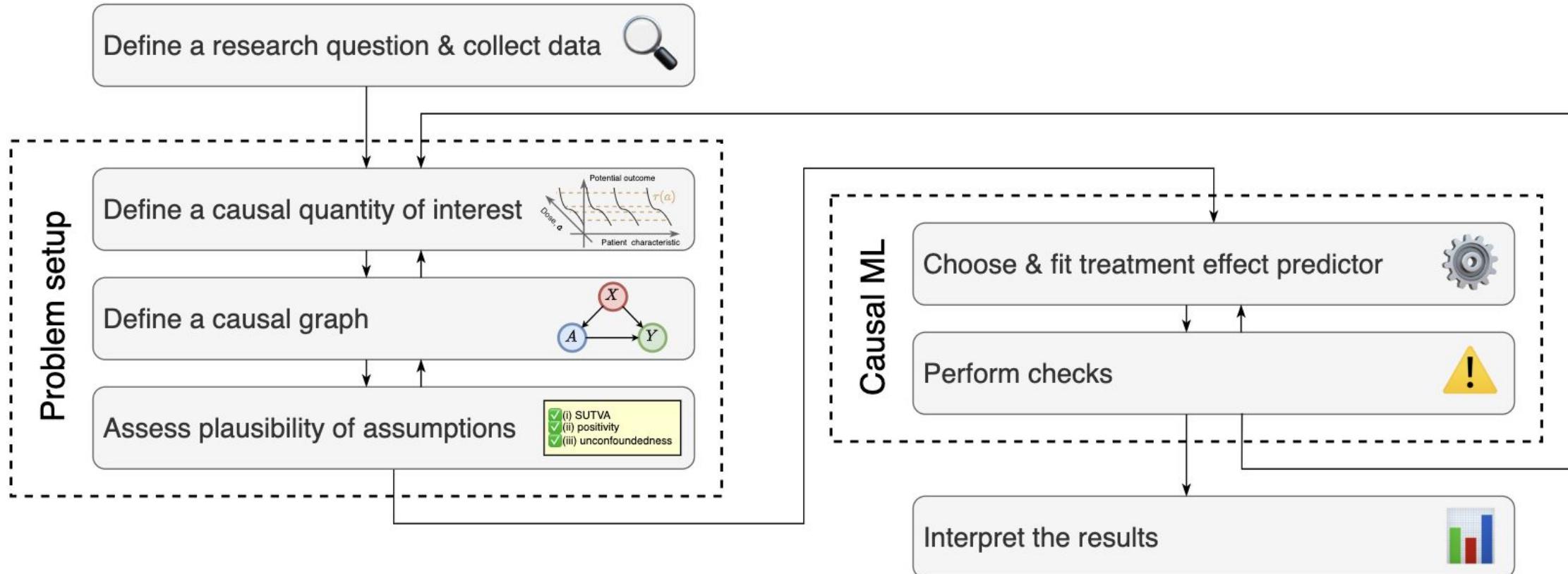
Traditional ML vs. Causal ML

Traditional
ML
vs.
Causal ML



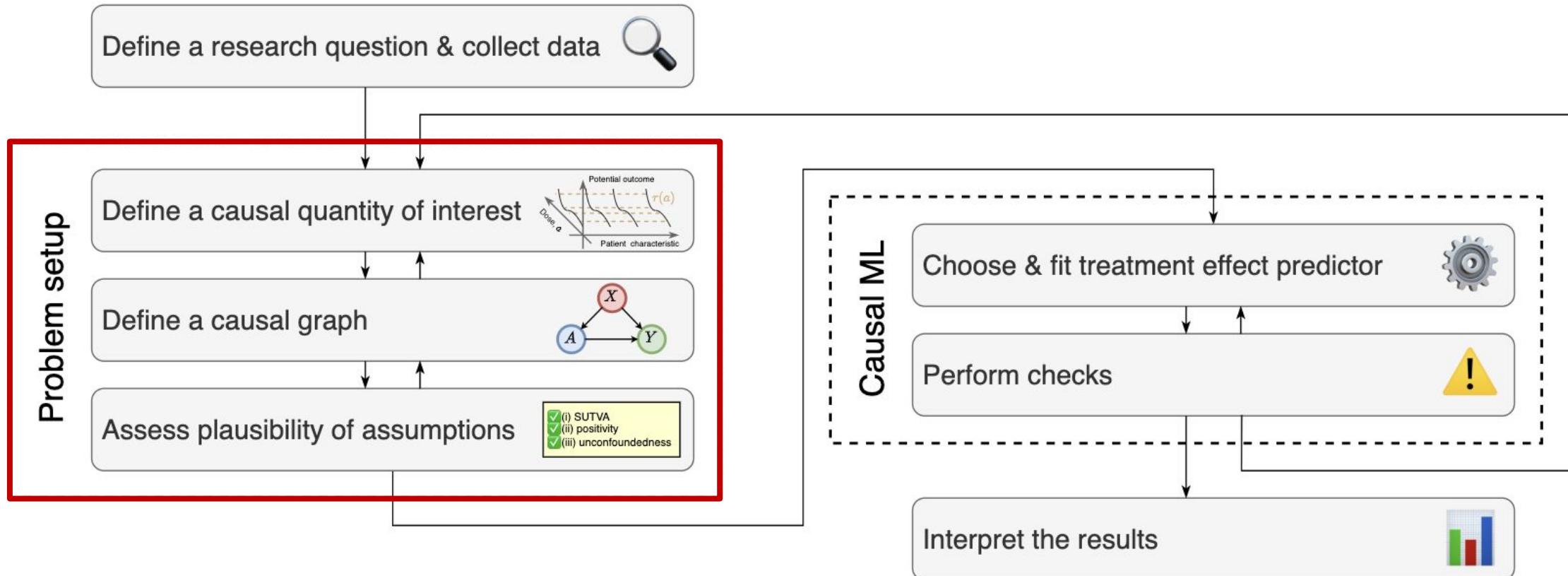
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Causal ML Workflow



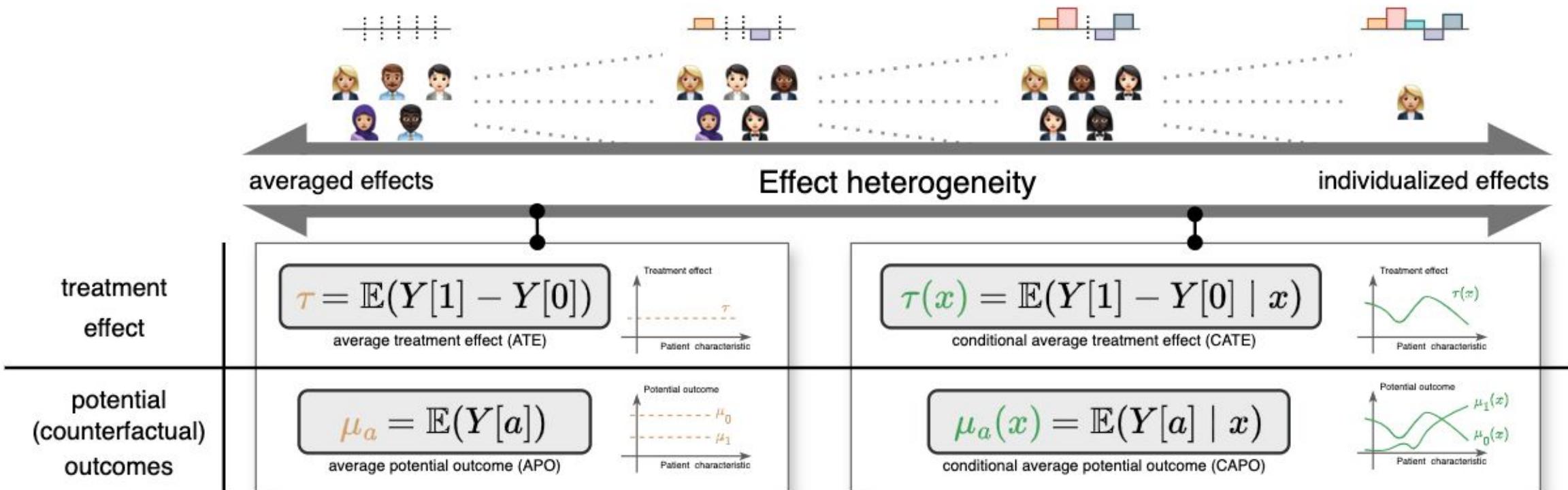
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Causal ML Workflow



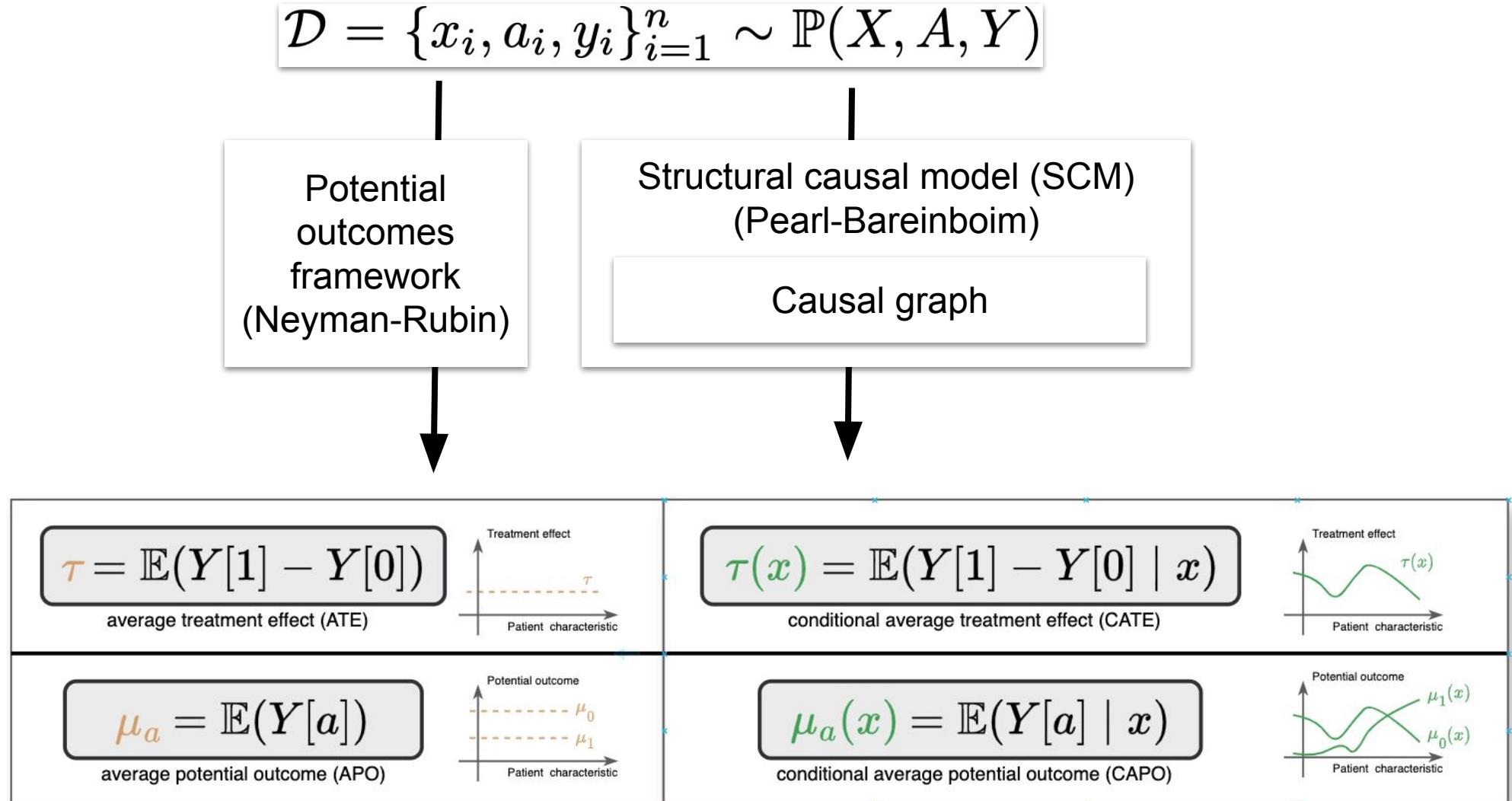
PROBLEM SETUP

Causal quantities of interest



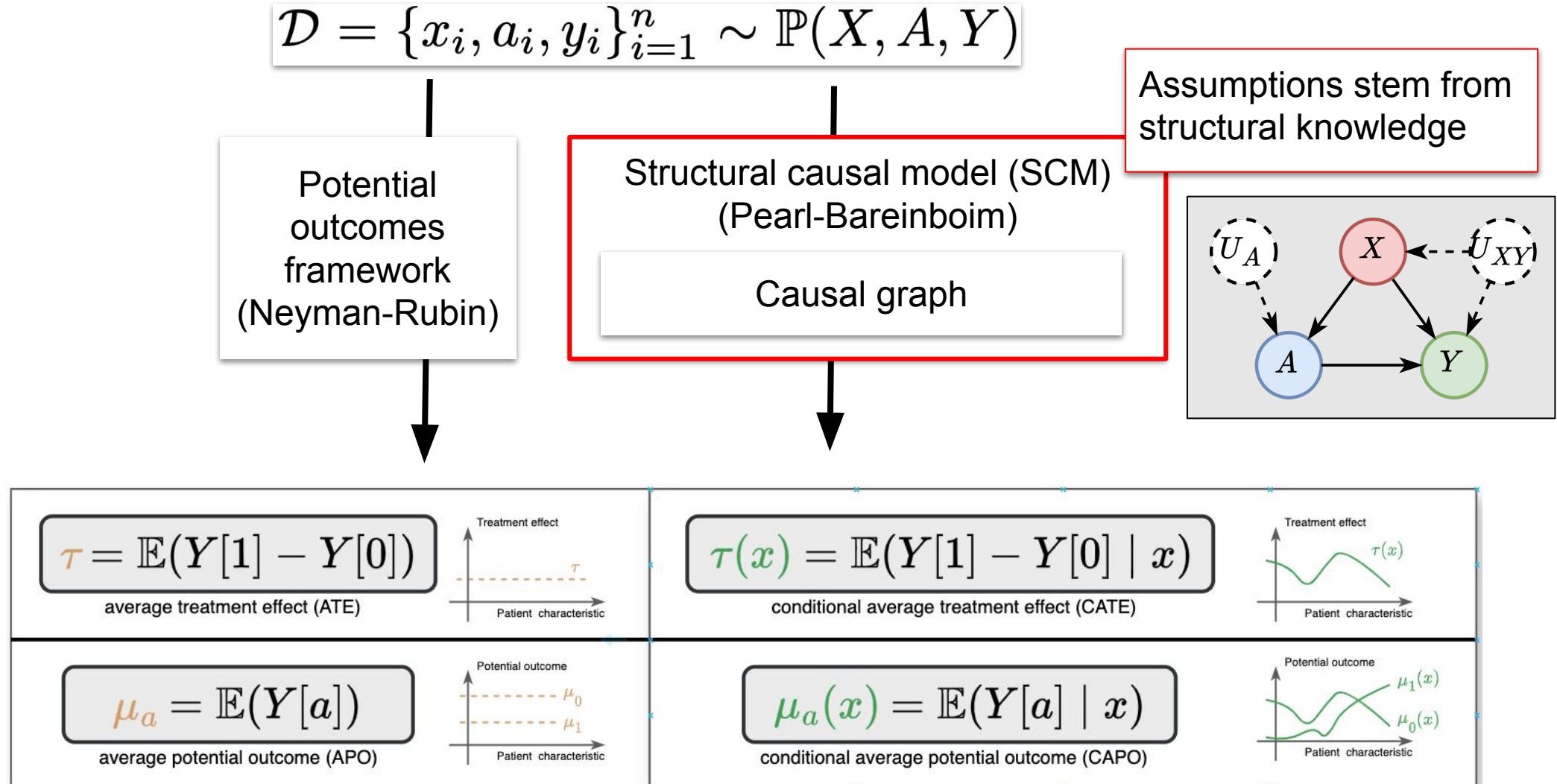
PROBLEM SETUP

Assumption frameworks



PROBLEM SETUP

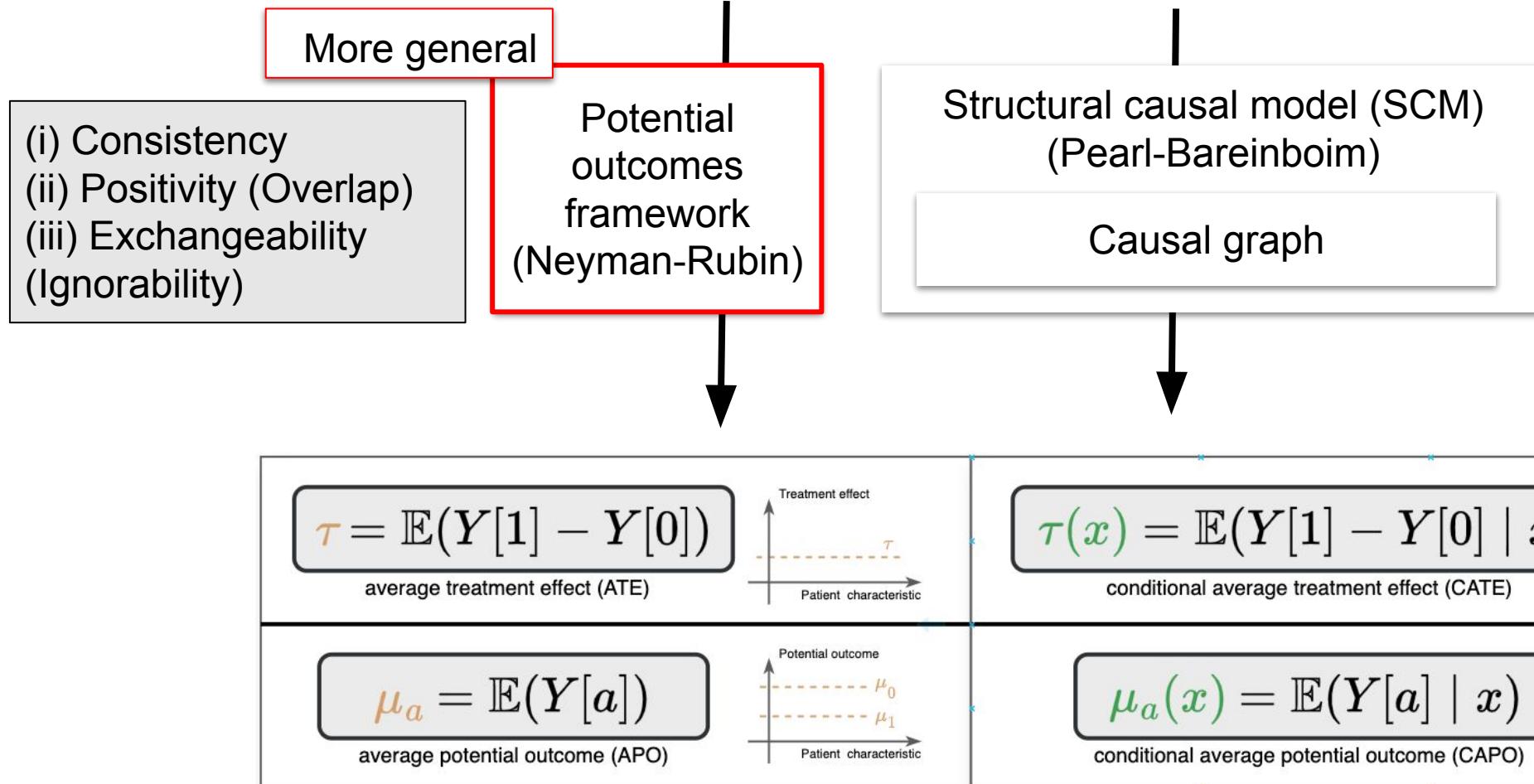
Assumption frameworks: SCMs and causal graphs



PROBLEM SETUP

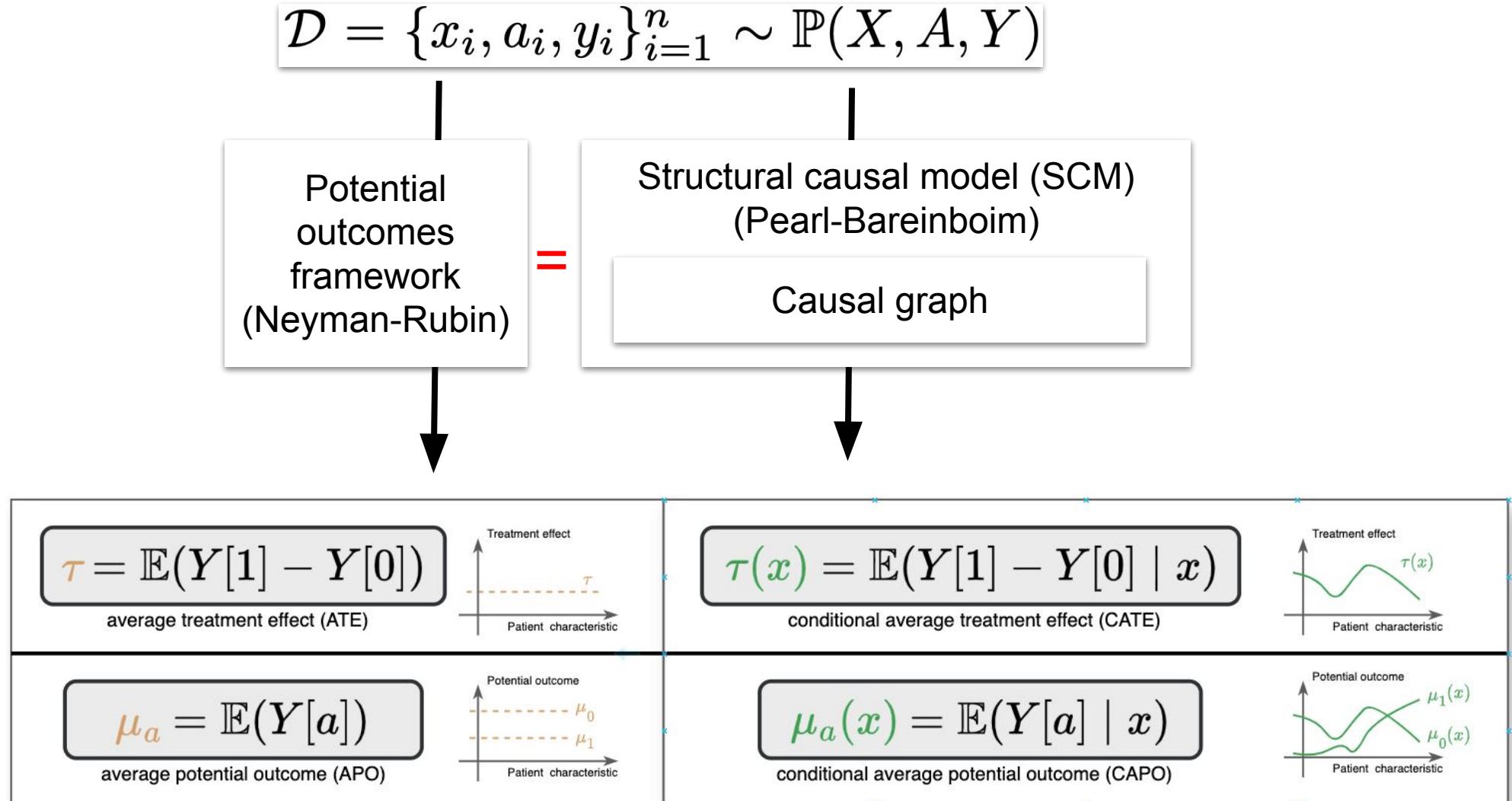
Assumption frameworks: Potential outcomes framework

$$\mathcal{D} = \{x_i, a_i, y_i\}_{i=1}^n \sim \mathbb{P}(X, A, Y)$$



PROBLEM SETUP

Assumption frameworks

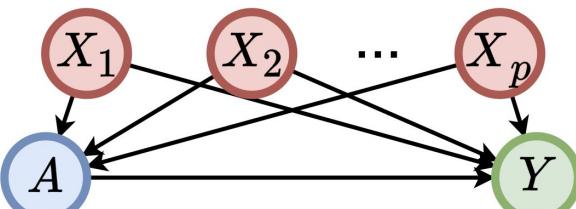


PROBLEM SETUP

Example of a case study

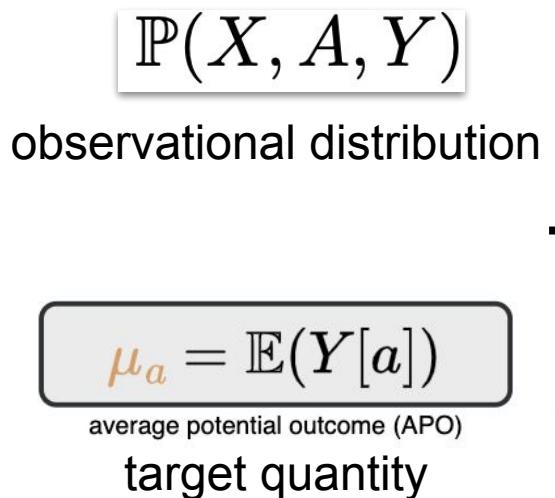
Aim: estimate heterogeneous treatment effect of development aid on SDG outcomes

- **Treatment A:** development aid earmarked to end the HIV/AIDS epidemic
- **Outcome Y:** relative reduction in HIV infection rate
- **Covariates X:** control for differences in country characteristics

Causal graph	Causal quantity of interest	Assumptions
	$\mu_a(x) = \mathbb{E}(Y[a] \mid x)$ <p>conditional average potential outcome (CAPO)</p>	<p>Consistency: $Y = Y(a)$ if $A = a$</p> <p>Positivity: $0 < p(A = a \mid X = x) < 1, \forall a \in \mathcal{A}$</p> <p>Ignorability: $Y(a) \perp\!\!\!\perp A \mid X = x, \forall a \in \mathcal{A}$</p>

Primer: Identification vs. Estimation

**Identification
(infinite data)**



Potential outcomes framework (Neyman-Rubin)

$$\begin{aligned} \mu_a &= \mathbb{E}(\mathbb{E}[Y | a, X]) \\ &\text{back-door adjustment} \\ \mu_a &= \mathbb{E}\left[\frac{1(A=a)}{\pi_a(X)} Y\right] \\ &\text{inverse propensity of treatment weighting (IPTW)} \end{aligned}$$

**Estimation
(finite data)**

$$\mathcal{D} = \{x_i, a_i, y_i\}_{i=1}^n \sim \mathbb{P}(X, A, Y)$$

sample from observational distribution

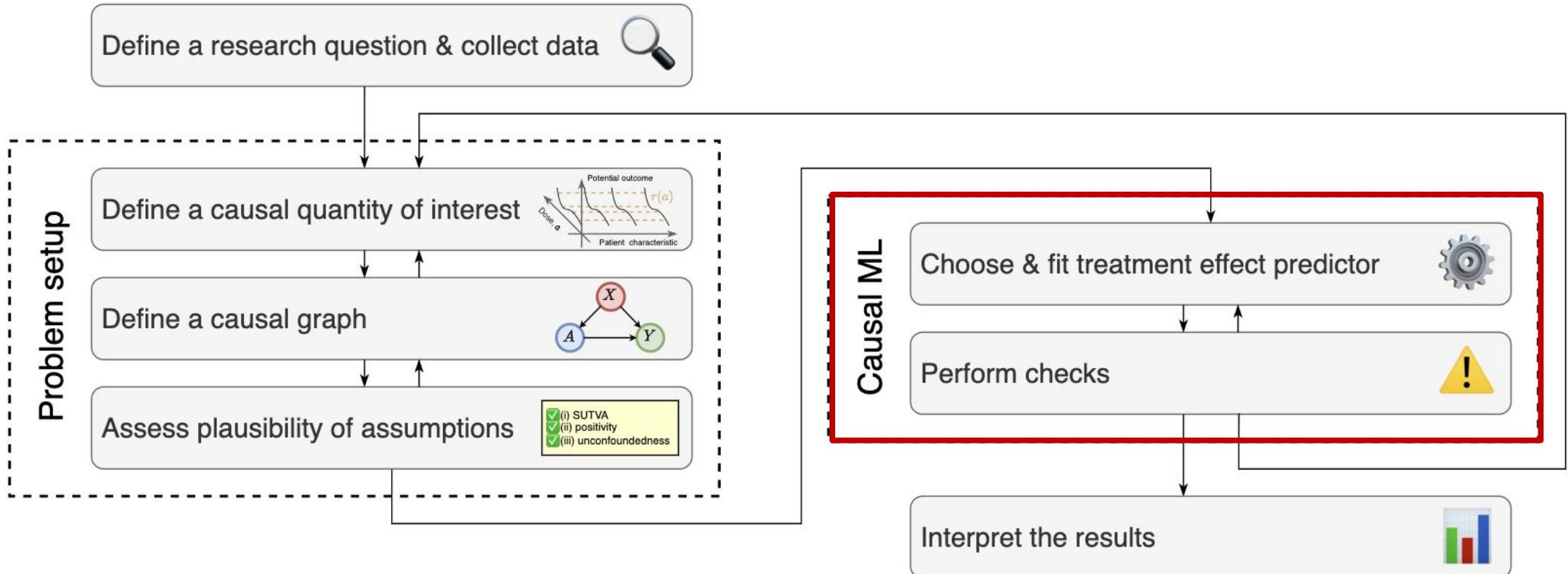
$$\begin{aligned} \mu_a &= \mathbb{E}(\mathbb{E}[Y | a, X]) \\ \mu_a &= \mathbb{E}\left[\frac{1(A=a)}{\pi_a(X)} Y\right] \\ &\text{identification formulas} \end{aligned}$$

Semi-parametric efficiency theory / Orthogonal learning

$$\begin{aligned} \hat{\mu}_{a,\text{A-IPTW}} &= \frac{1}{n} \sum_{i=1}^n \frac{a_i=a}{\hat{\pi}_a(x_i)} \left(y_i - \hat{\mu}_a(x_i) \right) + \hat{\mu}_a(x_i) \\ \hat{\eta} &= \{ \hat{\mu}_a(x) = \hat{\mathbb{E}}[Y | A = a, X = x]; \\ &\quad \hat{\pi}_a(x) = \hat{\mathbb{P}}[A = a | X = x] \} \\ &\text{augmented inverse propensity of treatment weighting (A-IPTW) efficient estimator} \end{aligned}$$

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Causal ML Workflow



Challenges and open questions fitting an ML model

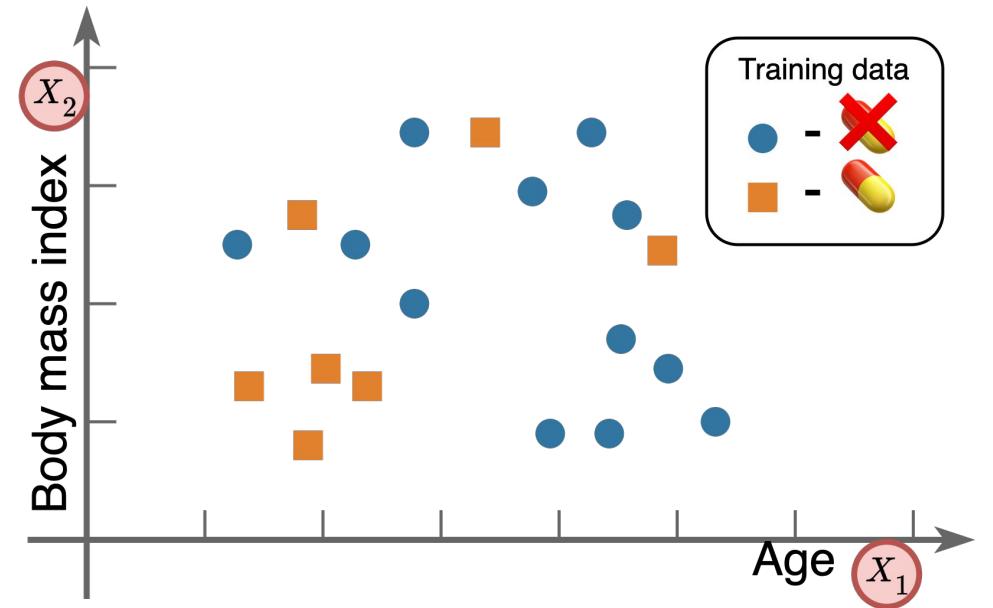
Challenges

$$\mu_a(x) = \mathbb{E}(Y[a] | x)$$

conditional average potential outcome (CAPO)

$$\tau(x) = \mathbb{E}(Y[1] - Y[0] | x)$$

conditional average treatment effect (CATE)



Open
problems

Challenges and open questions fitting an ML model

Challenges

$$\mu_a(x) = \mathbb{E}(Y[a] | x)$$

conditional average potential outcome (CAPO)

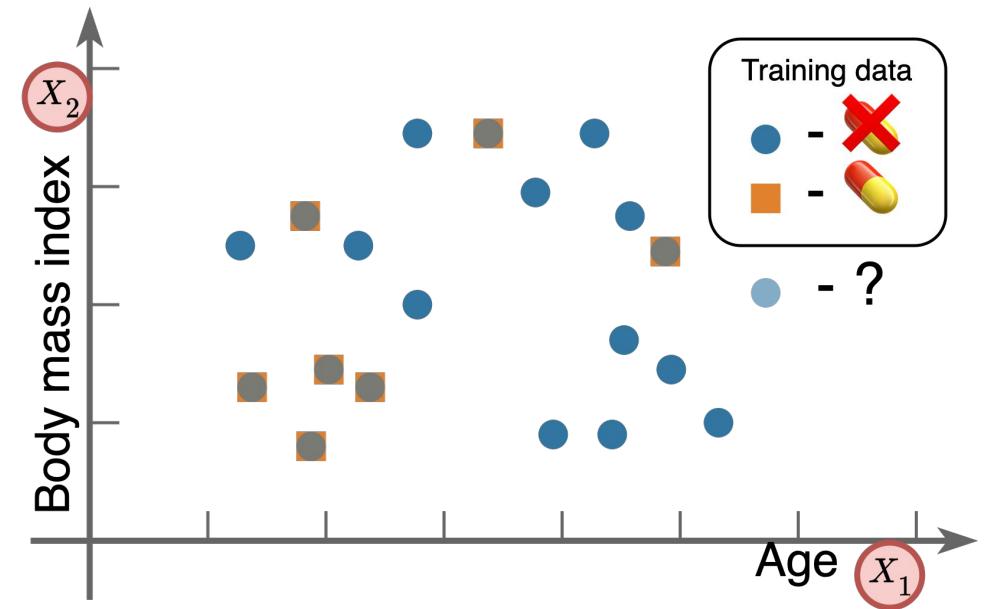
- **Selection bias:** parts of the population rarely gets treated

$$\tau(x) = \mathbb{E}(Y[1] - Y[0] | x)$$

conditional average treatment effect (CATE)

- **Selection bias:** parts of the population rarely gets treated

Open problems



Challenges and open questions fitting an ML model

Challenges

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conditional average potential outcome (CAPO)

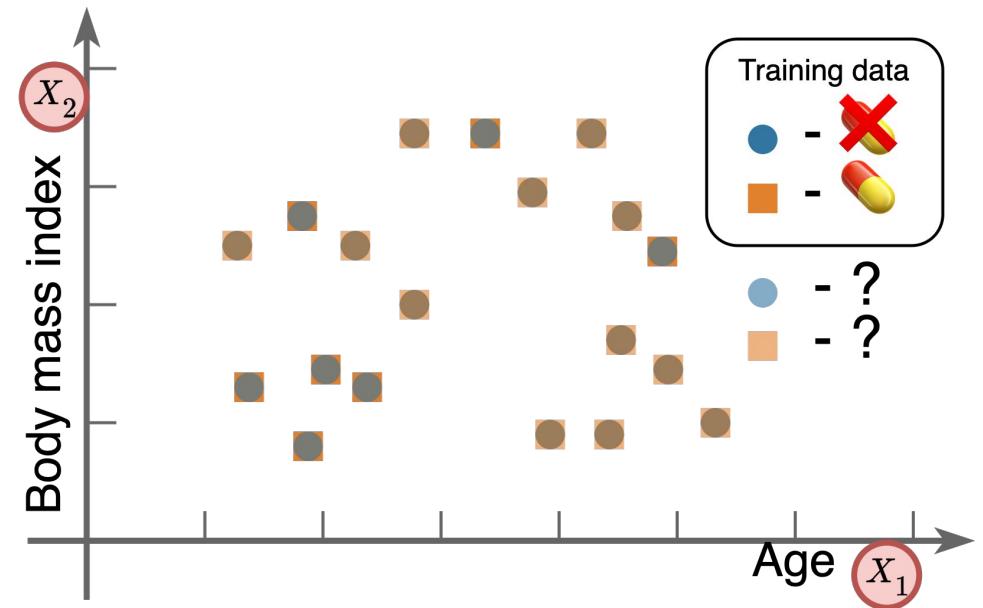
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$$\tau(x) = \mathbb{E}(Y[1] - Y[0] | x)$$

conditional average treatment effect (CATE)

- **Selection bias:** parts of the population rarely gets treated
- **Fundamental problem:** never observing a difference of potential outcomes

Open problems



Challenges and open questions fitting an ML model

Challenges

$$\mu_a(x) = \mathbb{E}(Y[a] | x)$$

conditional average potential outcome (CAPO)

- **Selection bias:** parts of the population rarely gets treated

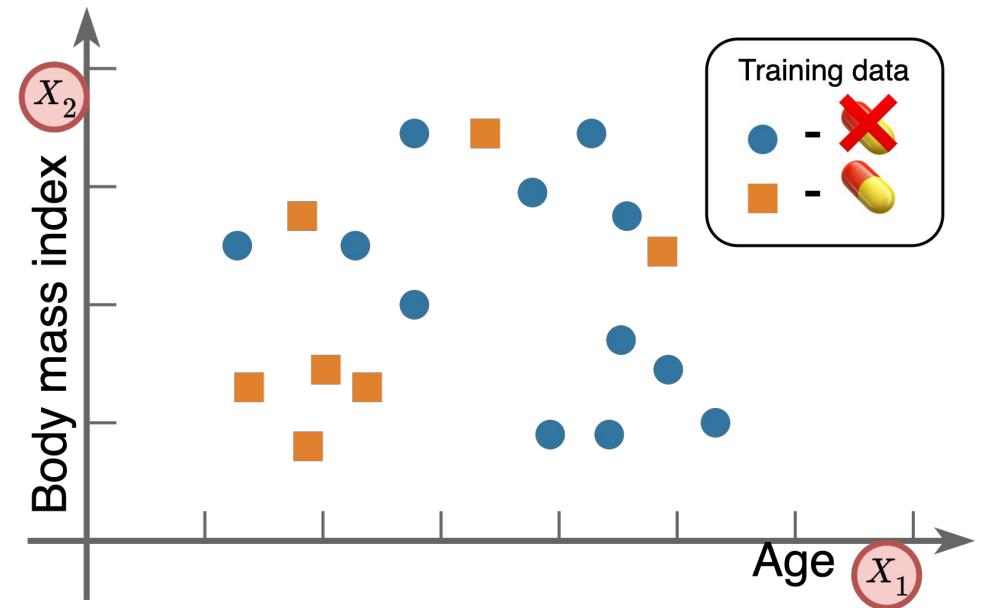
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conditional average treatment effect (CATE)

- **Selection bias:** parts of the population rarely gets treated
- **Fundamental problem:** never observing a difference of potential outcomes

Open problems

- How to effectively address selection bias?
- How to incorporate inductive biases, e.g., regularize CAPO / CATE models?



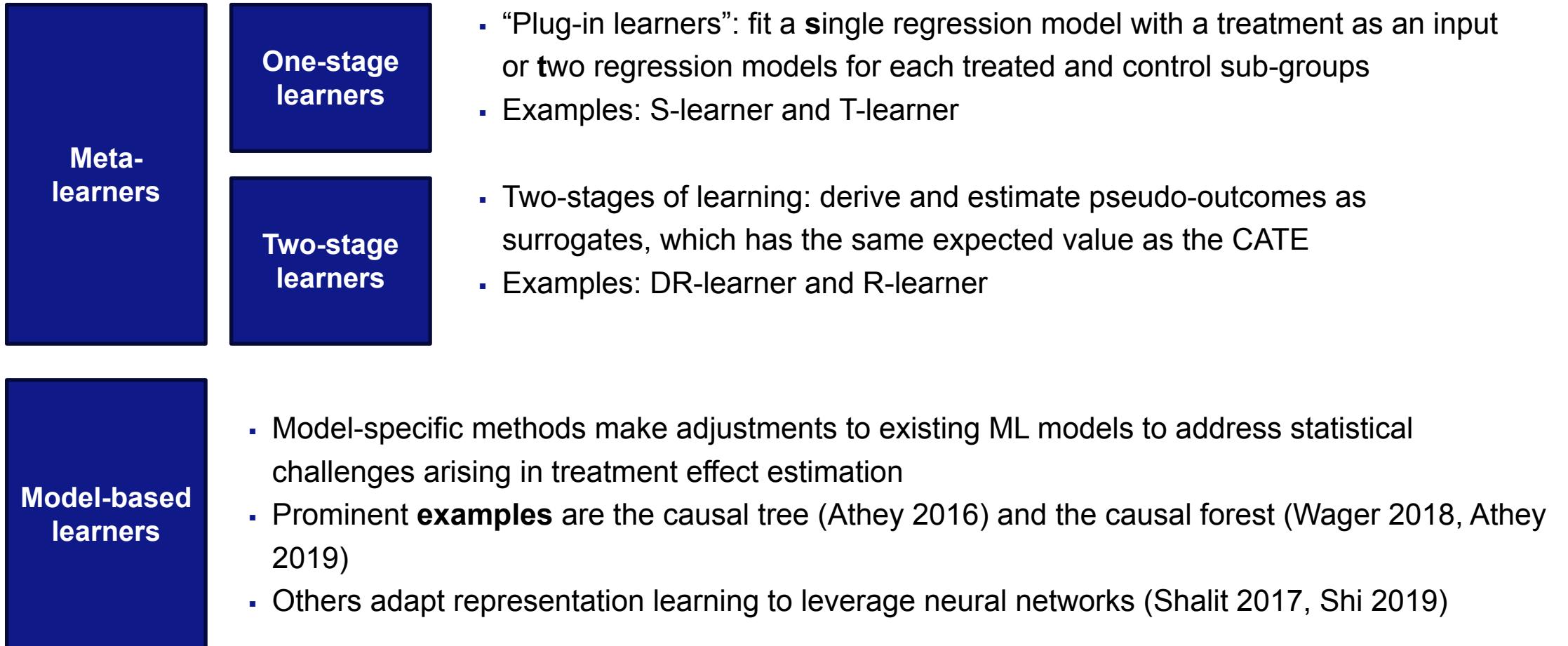
Meta- learners

- Meta-learners (Kunzel 2019) are model-agnostic methods for CATE estimation
- Can be used for treatment effect estimation in combination with an arbitrary ML model of choice (e.g., a decision tree, a neural network)

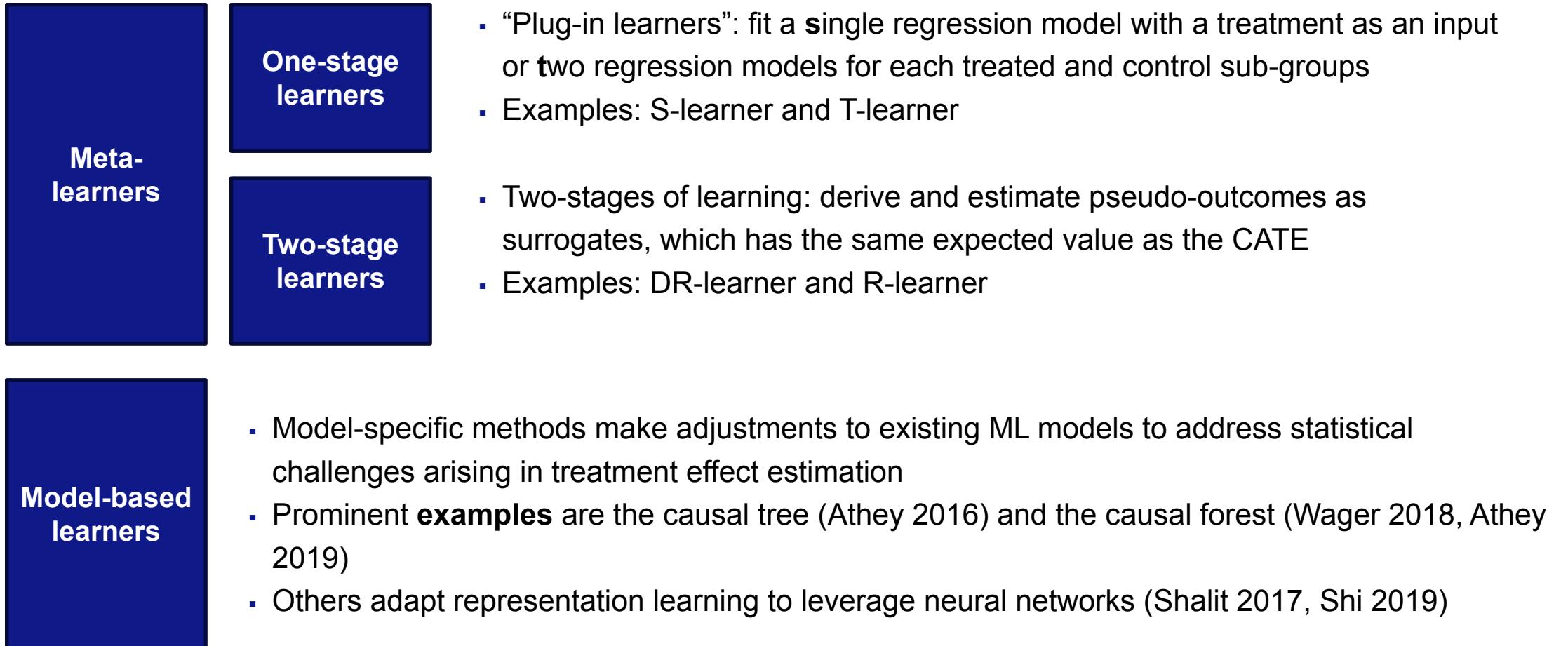
Model-based learners

- Model-specific methods make adjustments to existing ML models to address statistical challenges arising in treatment effect estimation
- Prominent **examples** are the causal tree (Athey 2016) and the causal forest (Wager 2018, Athey 2019)
- Others adapt representation learning to leverage neural networks (Shalit 2017, Shi 2019)

1. Künzel, Sören R., et al. "Metalearners for estimating heterogeneous treatment effects using machine learning." *Proceedings of the national academy of sciences* 116.10 (2019): 4156-4165.
2. Athey, Susan, and Guido Imbens. "Recursive partitioning for heterogeneous causal effects." *Proceedings of the National Academy of Sciences* 113.27 (2016): 7353-7360.
3. Athey, Susan, and Stefan Wager. "Estimating treatment effects with causal forests: An application." *Observational studies* 5.2 (2019): 37-51.
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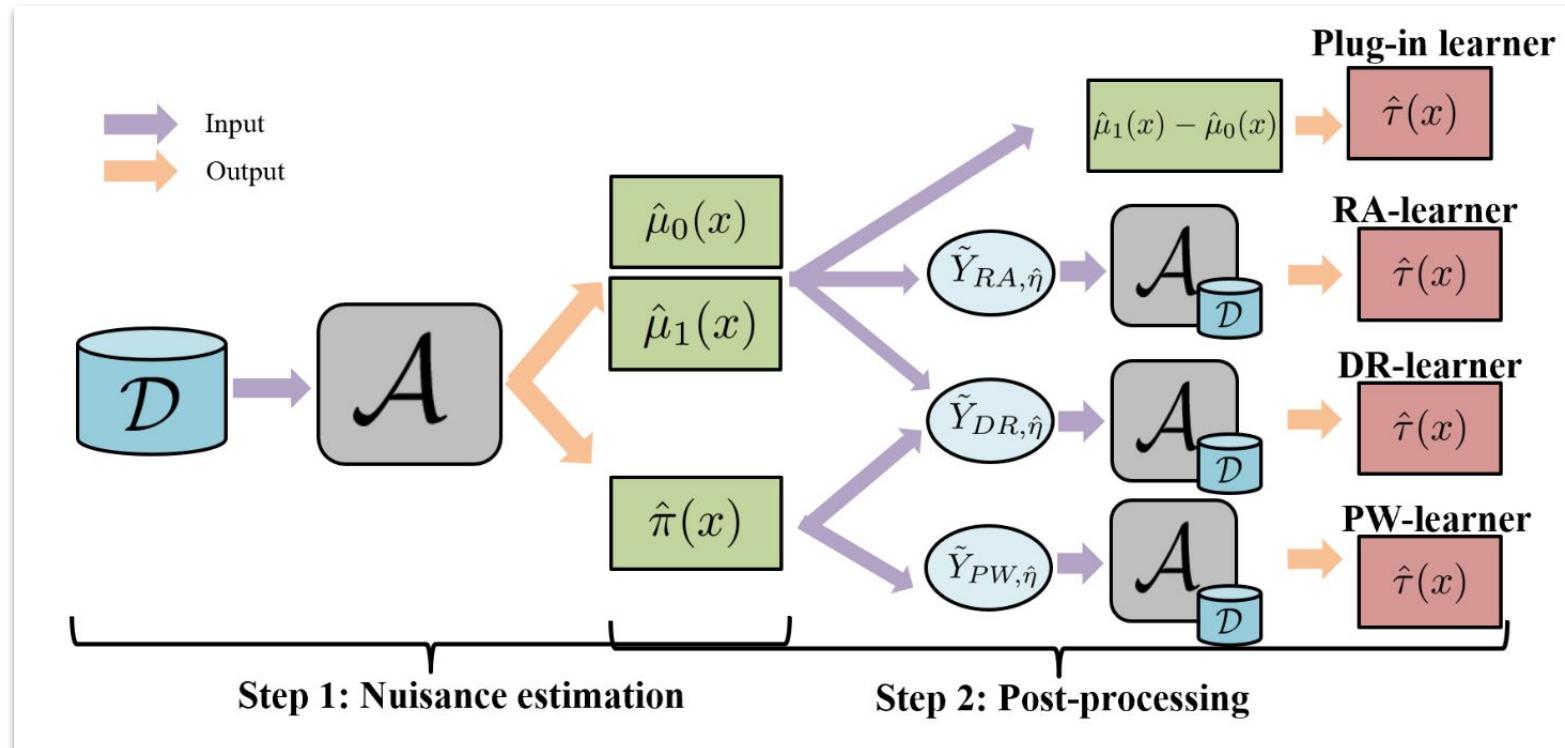
One-stage and two-stage meta-learners

Example: meta-learners for CATE

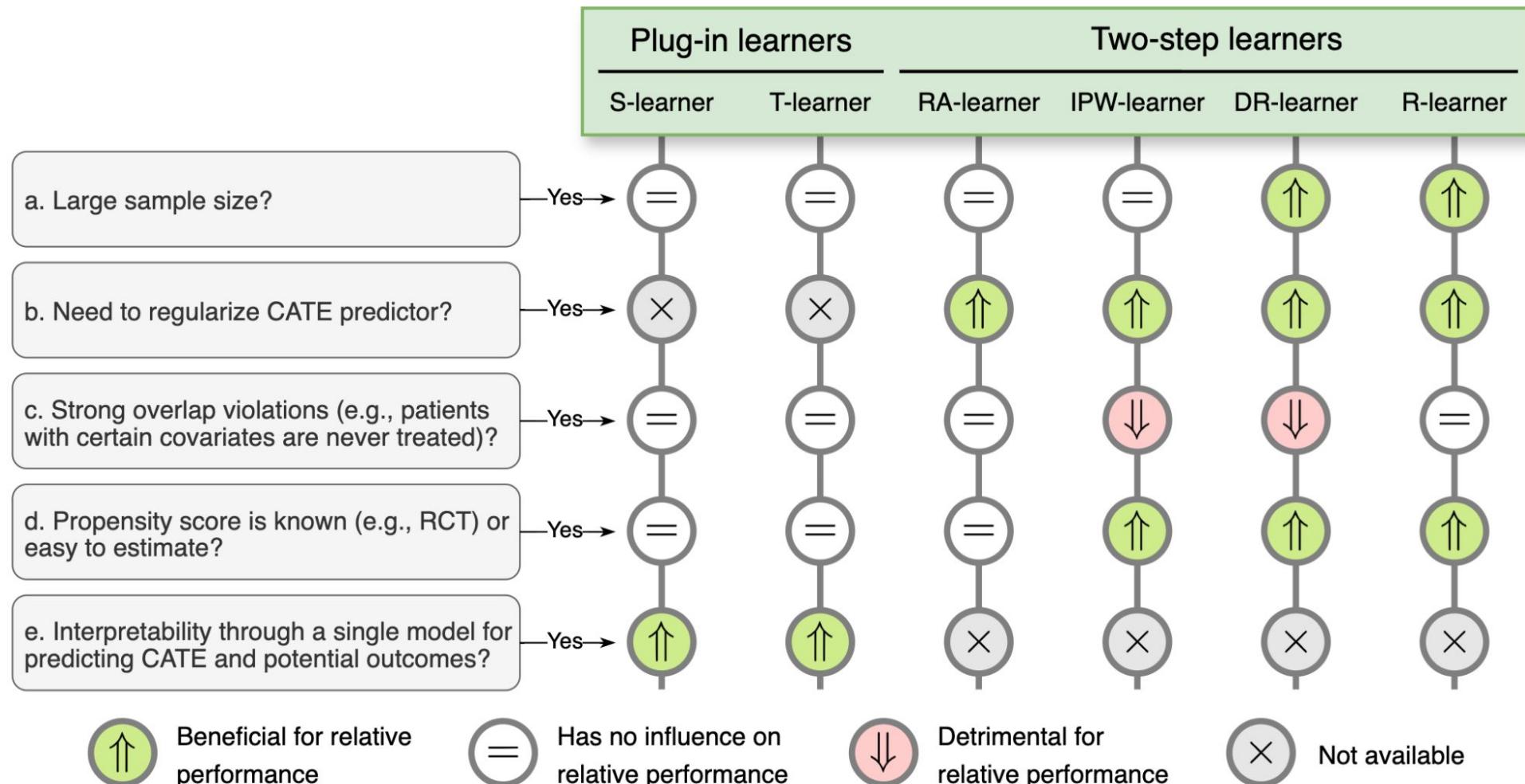
$$\tau(x) = \mathbb{E}(Y[1] - Y[0] \mid x)$$

conditional average treatment effect (CATE)

Method: Using any ML model to fit relevant parts of the observed distribution, namely, **nuisance functions**. Then, we can use the nuisance functions estimators for the final CATE model.



Comparison of meta-learners



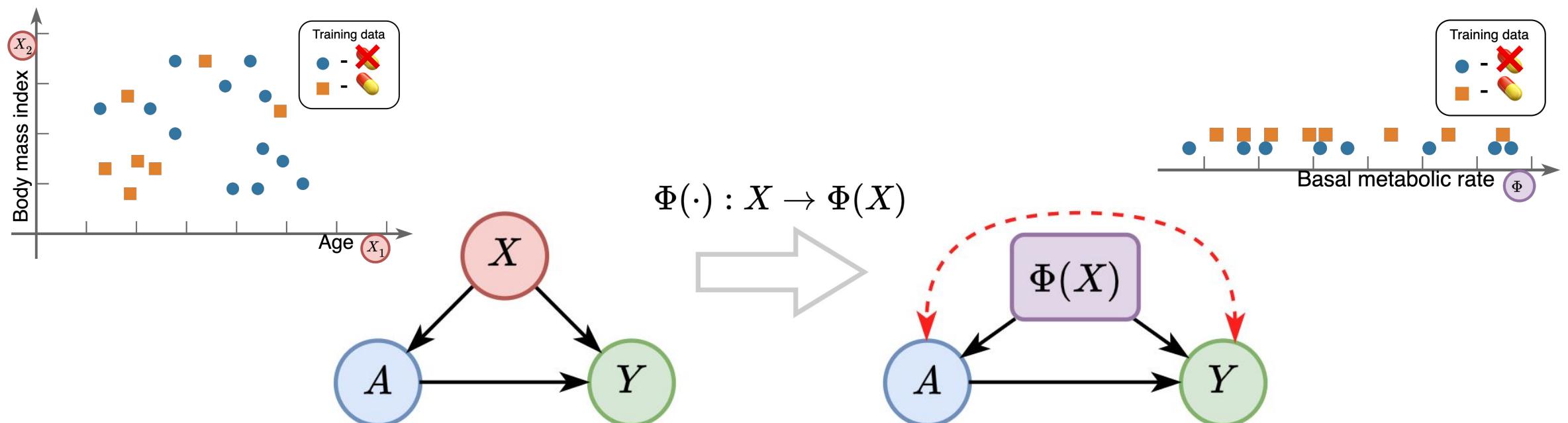
Model-based learners: Representation learning

Example: TarNET / CFRNet for CATE

$$\tau(x) = \mathbb{E}(Y[1] - Y[0] \mid x)$$

conditional average treatment effect (CATE)

Method: Learning a low-dimensional (balanced) representation $\Phi()$ of high-dimensional covariates. Then, we can fit a CATE model based on the representations.



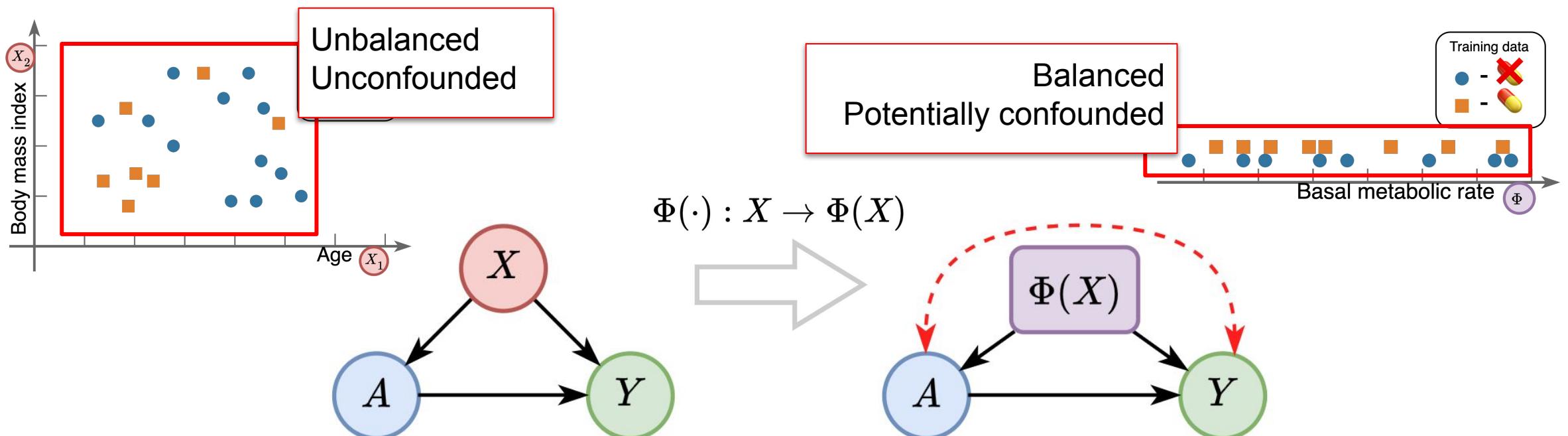
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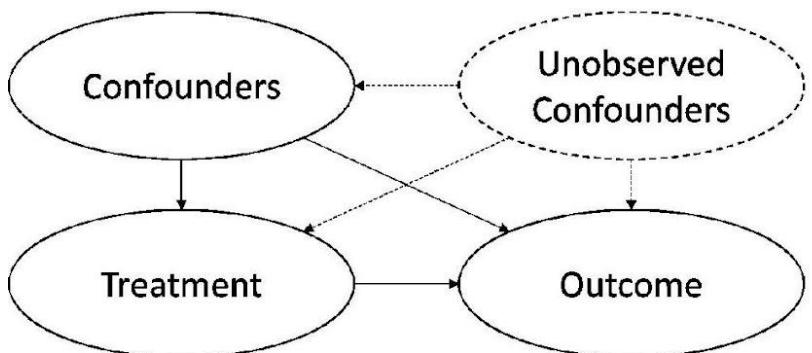
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conditional average treatment effect (CATE)

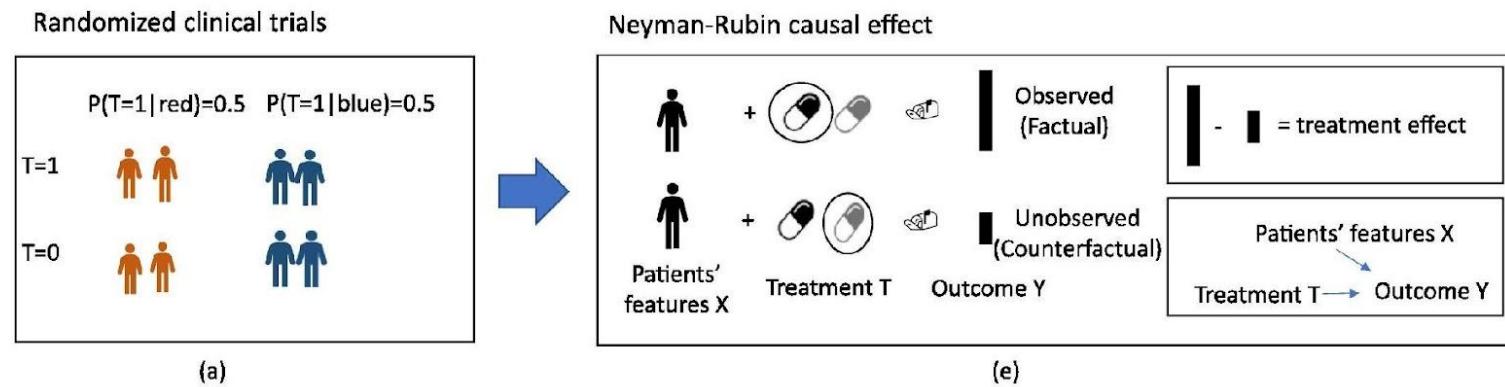
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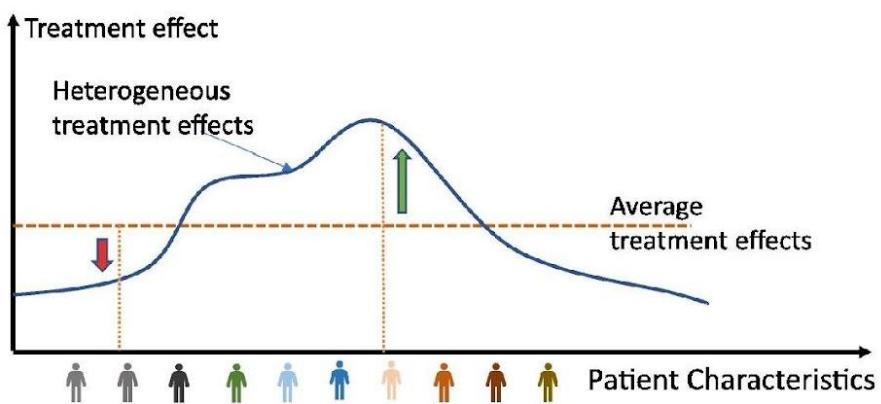
A. An example of treatment effects



B. Comparison between estimating treatment effects from RCTs and from observational data



C. An illustration of heterogeneous treatment effects



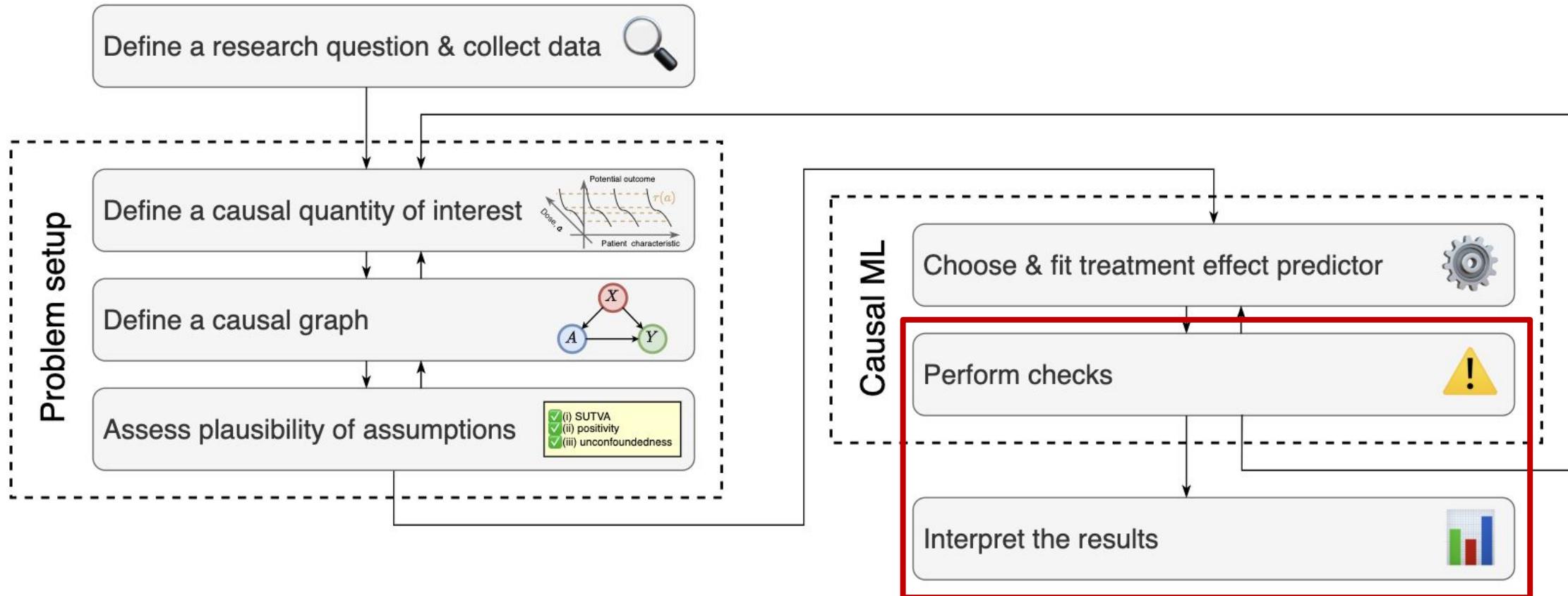


Where we are (and what is still needed): Current state of causal ML research



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Causal ML Workflow



Extensions & Open research problems

1 Model validity

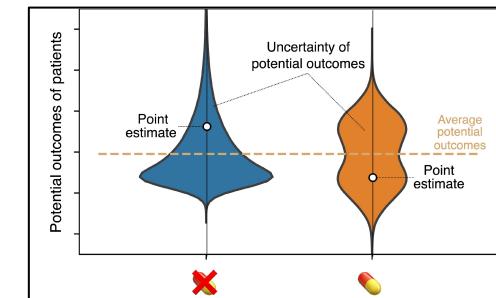
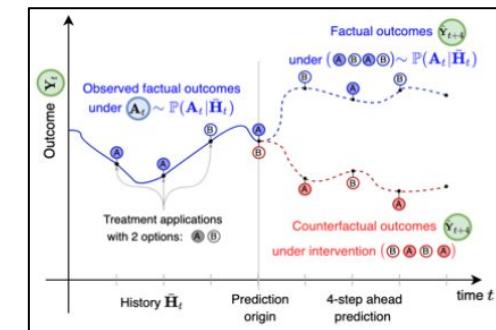
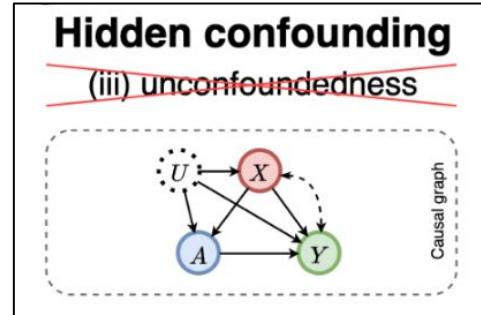
- Selection and validation of CATE models
 - Unlike traditional ML, we do not have a ground truth validation subset
- Robustness checks wrt. violation of assumptions
 - Sensitivity models
 - Spillover effects

2 Flexibility

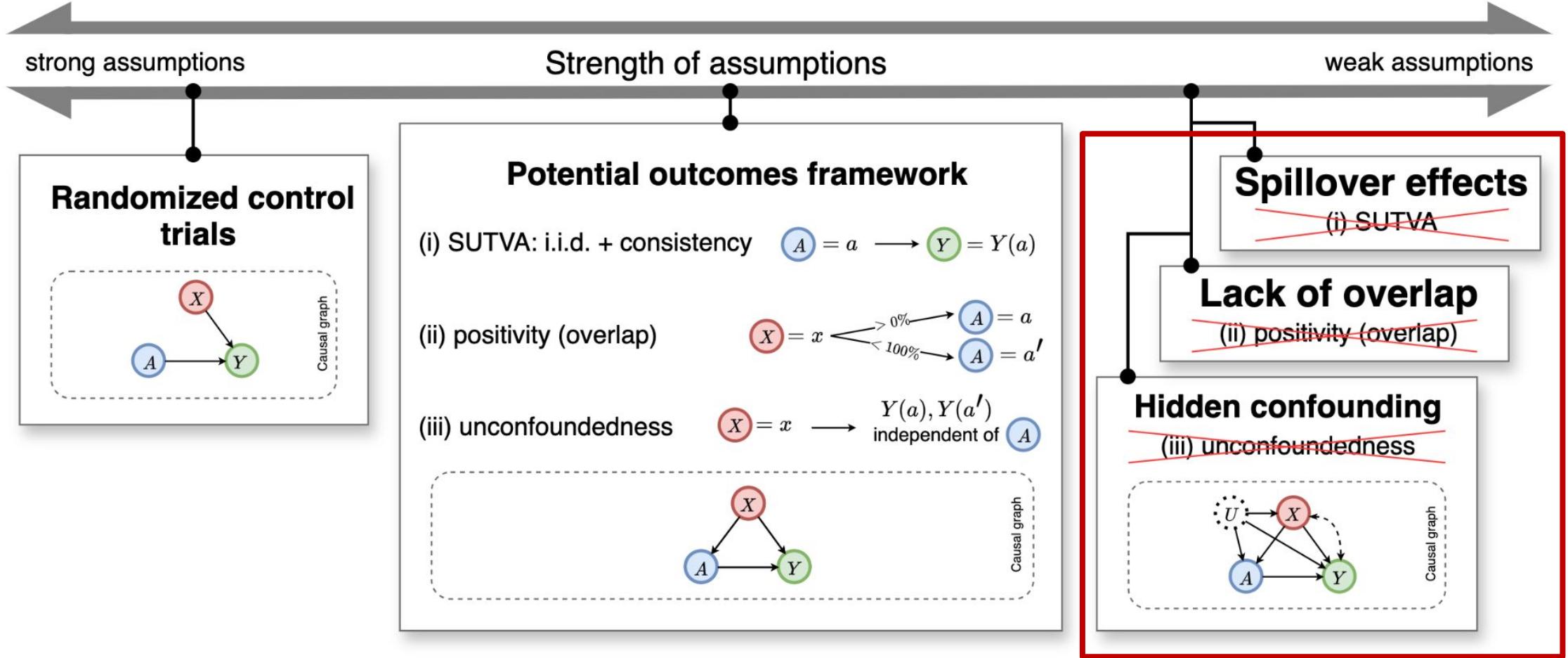
- Extensions to more complicated settings
 - continuous / high-dimensional treatments
 - time-varying potential outcomes and treatment effects
- Data fusion from multiple environments
- Constrained ML: interpretability, privacy enforcement

3 Uncertainty quantification

- Uncertainty quantification
 - uncertainty of estimation (aka confidence intervals)
 - predictive uncertainty (aka predictive intervals)

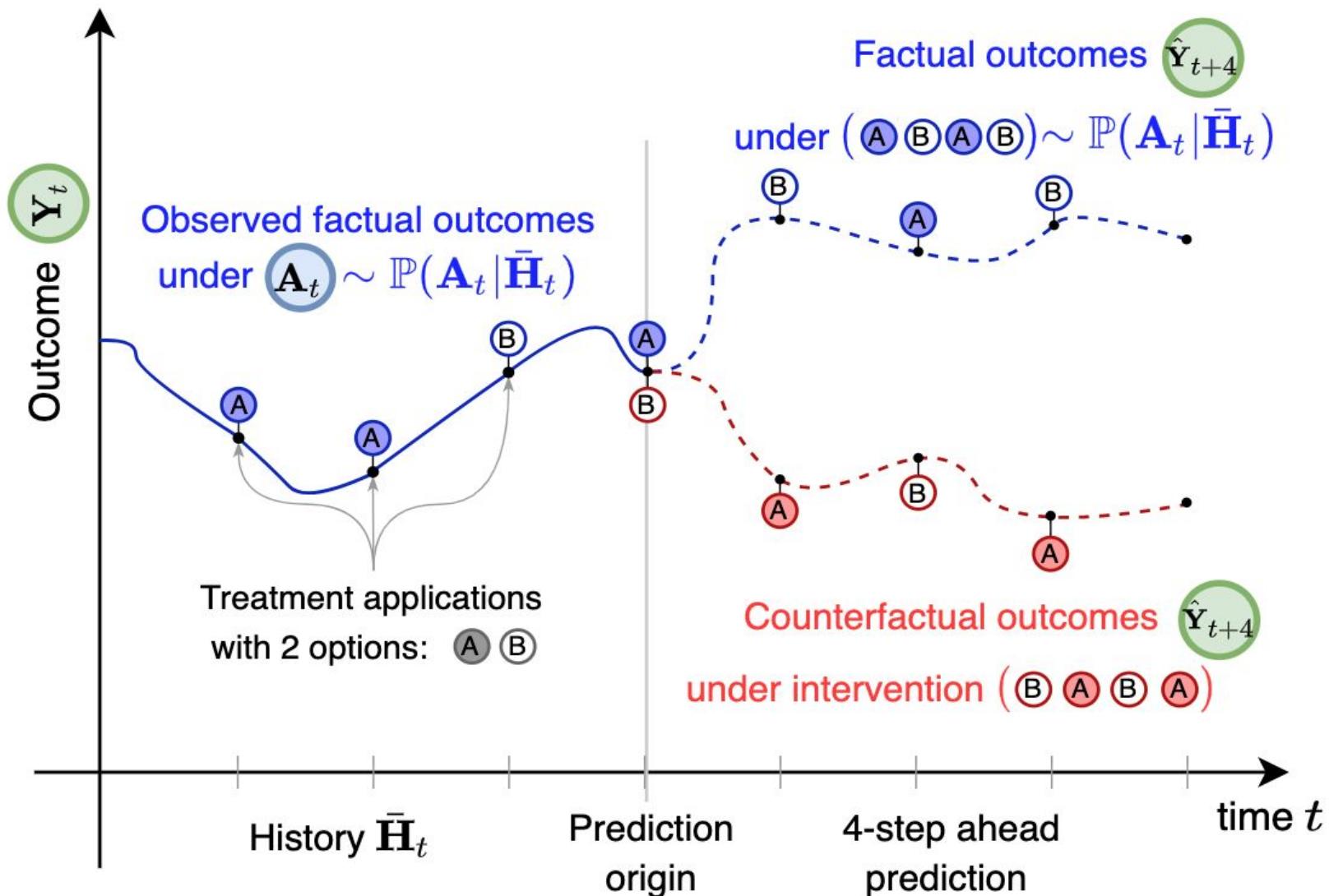


Model validity: Robustness checks wrt. violation of assumptions



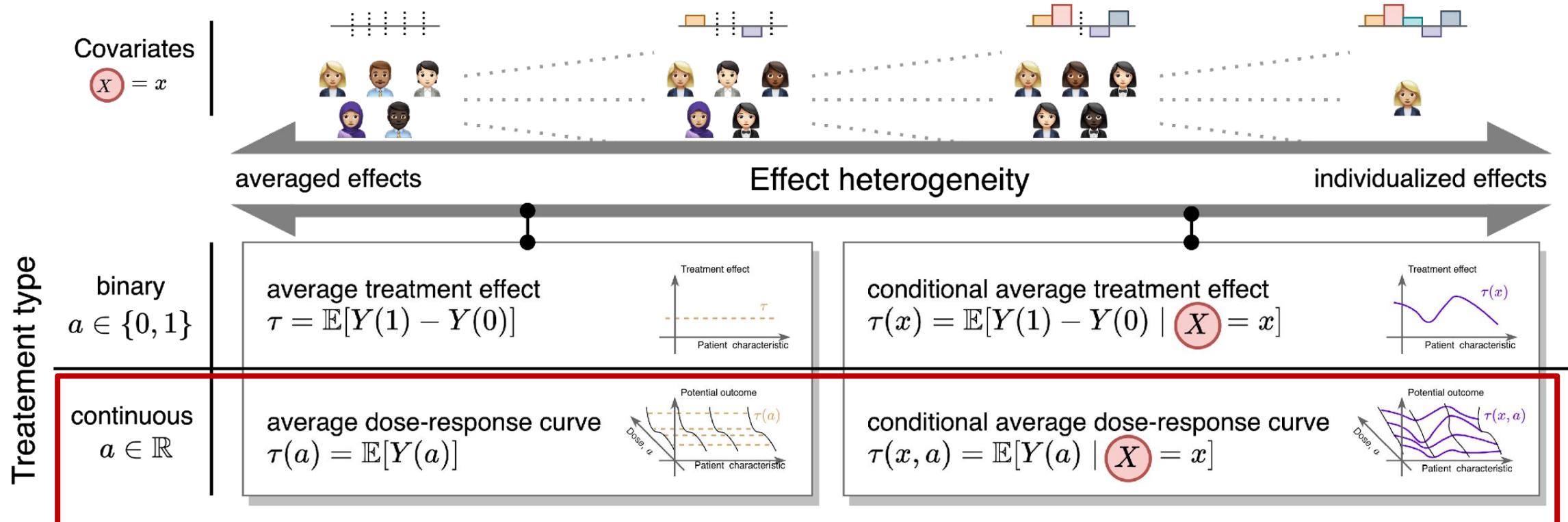
EXTENSIONS & OPEN RESEARCH QUESTIONS

Flexibility: Causal ML for predicting outcomes over time

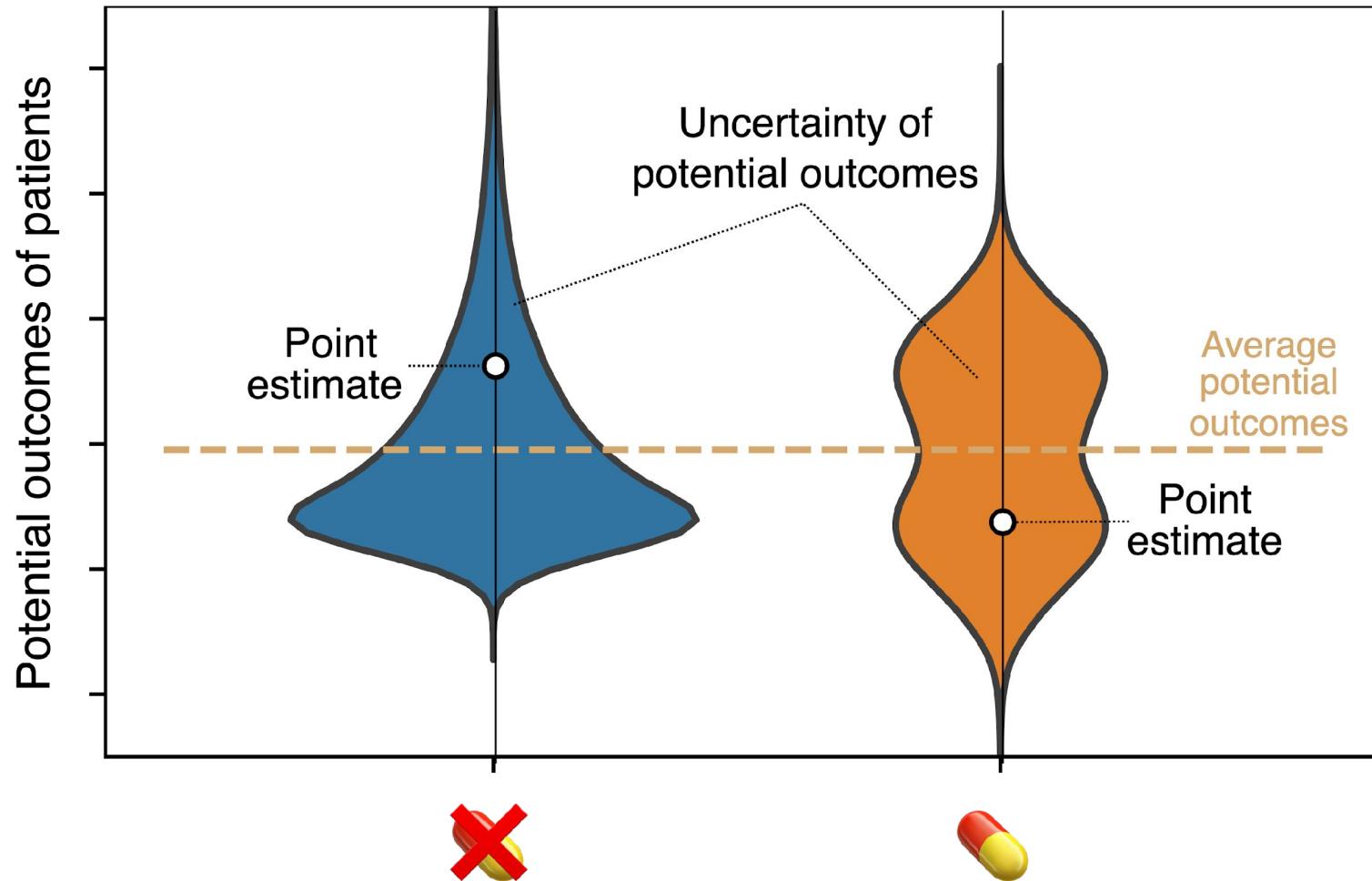


EXTENSIONS & OPEN RESEARCH QUESTIONS

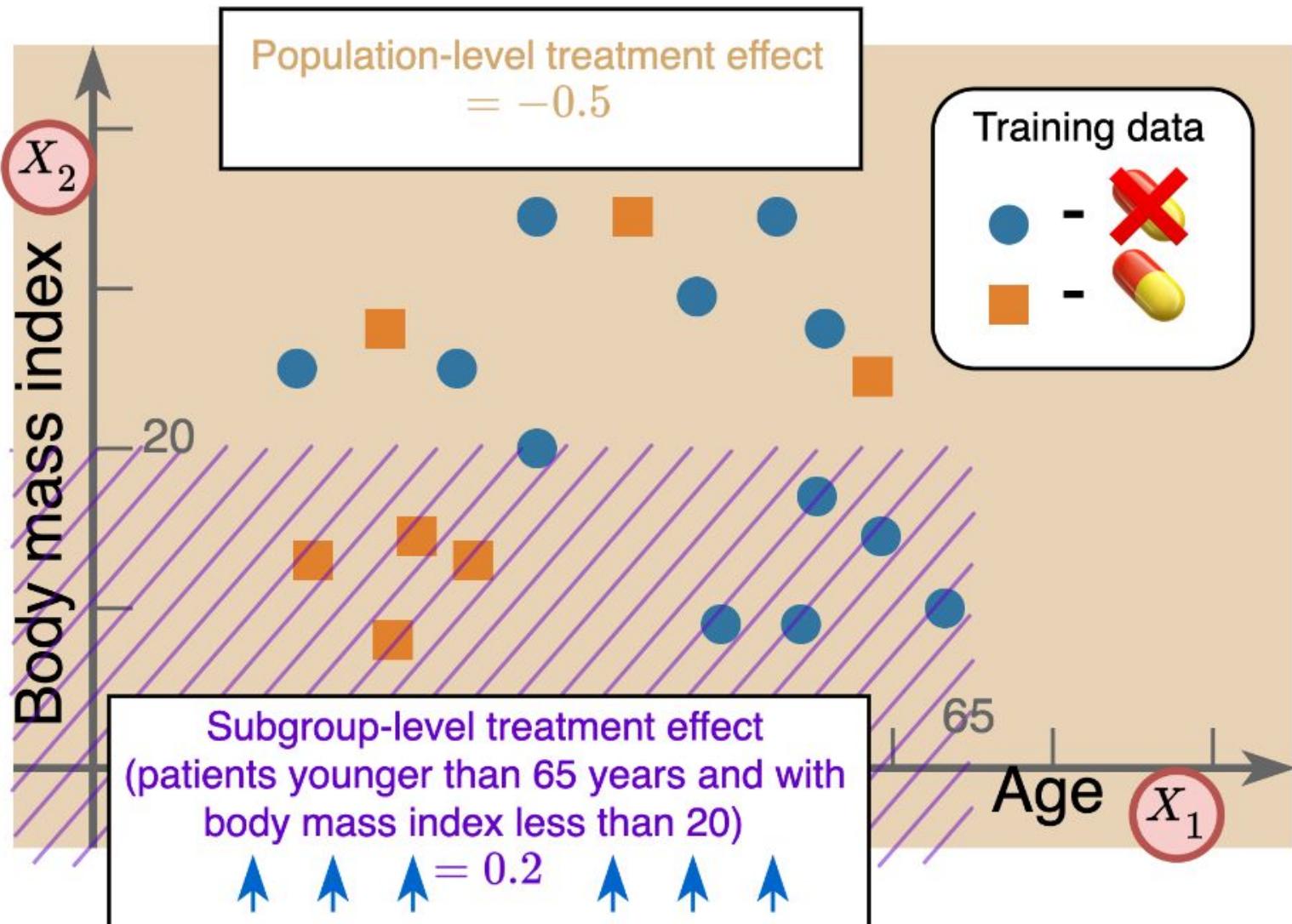
Flexibility: Continuous / high-dimensional treatments



Uncertainty quantification

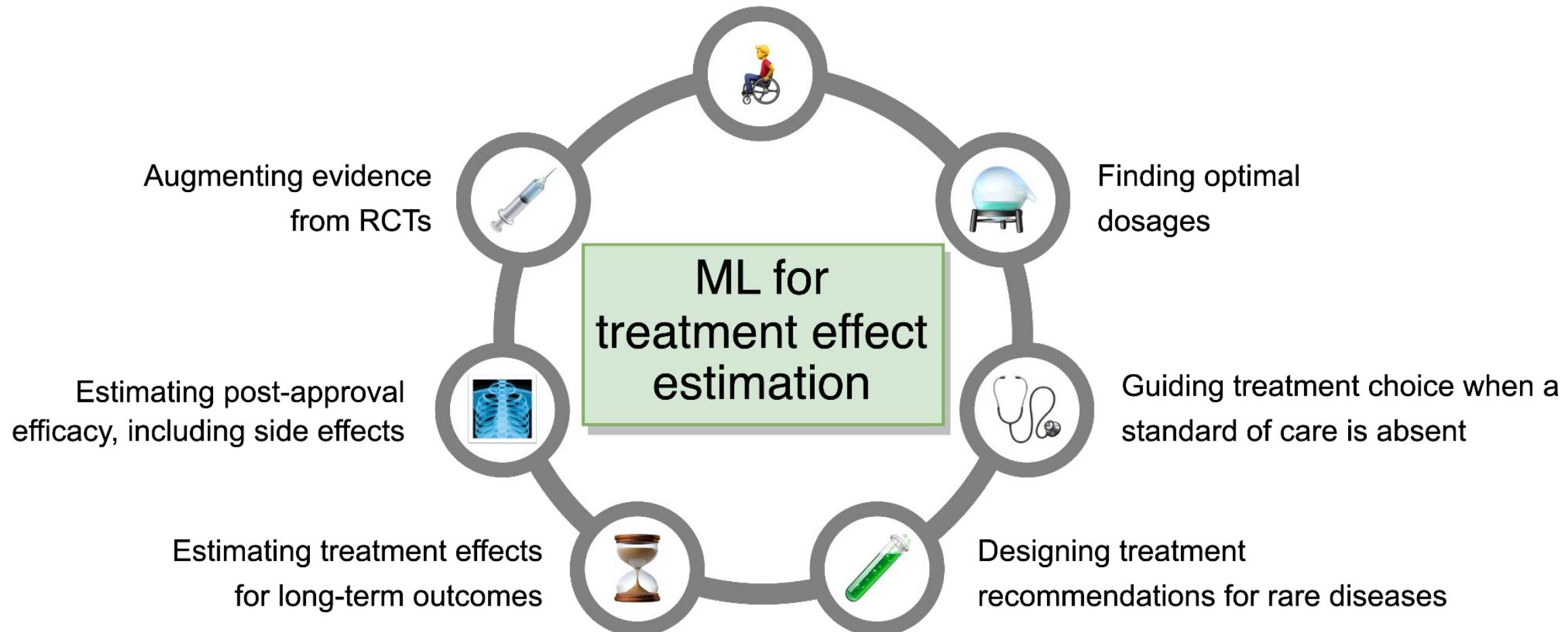


Identifying predictive biomarkers (=treatment responders)



Promises of Causal ML

Estimating treatment effects for vulnerable groups





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