Causal perspectives on prediction modeling

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Recap: causal questions

- questions of *association* are of the kind:
  - what is the probability of Y (potentially: after observing X)?, e.g.:
    - what is the chance of rain tomorrow given that is was dry today?
    - what is the chance a patient with lung cancer lives more than 10% after diagnosis?
  - these *hands behind your back and passively observe the world*-questions
- *causal* questions are of the kind:
  - how would Y change when we intervene on T?, e.g.:
    - if we would send all pregant women to the hospital for delivery, what would happen with neonatal outcomes?
    - if we start a marketing campain, by how much would our revenue increase?
  - these tell us what would happen if we changed something

What is prediction?

Examples of prediction tasks

observe an X, want to know what to expect for Y

1. X = patient caughs, Y = patient has lung cancer
2. X = ECG, Y = patient has heart attack
3. X = CT-scan, Y = patient dies within 2 years

Prediction: typical approach

1. define population, find a cohort
2. measure X at *prediction baseline*
3. measure Y
    a. cross-sectional (e.g. diagnosis)
    b. longitudinal follow-up (e.g. survival)
4. use a statistical learning technique (e.g. regression, machine learning)

- fit model f to observed $\{x_i, y_i\}$ with a criterion / loss function

5. evaluate prediction performance with e.g. discrimination, calibration, R^2

Prediction: typical estimand

Let f depend on parameter θ, prediction typically aims for:

$$f_\theta(x) \to E[Y|X = x]$$

- when Y is binary:
  - probability of a heart attack in 10 years, given age and cholesterol
  - probability of lung cancer, given symptoms and CT-scan
  - typical evaluation metrics:
    - discrimination: sensitivity, specificity, AUC
    - calibration

Causal inference: typical approach

1. define target population and targeted treatment comparison
2. run randomized controlled trial, randomizing treatment allocation (when possible)
3. measure patient outcomes
4. estimate parameter that summarizes *average treatment effect* (ATE)

typical estimand:

$$E[Y|\text{do}(T = 1)] - E[Y|\text{do}(T = 0)]$$

Causal inference versus prediction

prediction

- typical estimand $E[Y|X]$
- typical study: longitudinal cohort
- typical interpretation: X predicts Y
- primary use: know what Y to expect when observing a new X *assuming no change in joint distribution*

causal inference

- typical estimand $E[Y|\text{do}(T = 1)] - E[Y|\text{do}(T = 0)]$
- typical study: RCT (or observational causal inference study)
- typical interpretation: *causal effect* of T on Y
- primary use: know what change in Y to expect when *changing the treatment policy*

What do we mean with treatment policy?

A treatment policy π is a procedure for determining the treatment

Assuming T is binary, π can be:

- $\pi = 0.5$ (a 1/1 RCT)
- give blood pressure pill to patients with hypertension:

$$\pi(blood\,pressure) = \begin{cases} 1, & blood\,pressure > 140 mmHg \\ 0, & \text{otherwise} \end{cases}$$

- give statins to patients with more than 10% predicted risk of heart attack:

$$\pi(X) = \begin{cases} 1, & f(X) > 0.1 \\ 0, & \text{otherwise} \end{cases}$$

- the propensity score can be seen as a (non-deterministic) treatment policy

Where can prediction and causality meet?

1. prediction has a causal interpretation
2. prediction does not have a causal interpretation:
   a. but is used for a causal task (e.g. treatment decision making)
   b. but predictions can be improved with causal thinking in terms of e.g.:
   - interpretability, robustness, ‘spurious correlations’, generalization, fairness, selection bias

2a. Prediction model used for a causal task


TREATMENT DECISION
DECISION SUPPORT
What the hell is this?
PREDICTION MODEL
imgflip.com

Using prediction models for decision making is often thought of as a good idea

For example:

1. give chemotherapy to cancer patients with high predicted risk of recurrence
2. give statins to patients with a high risk of a heart attack

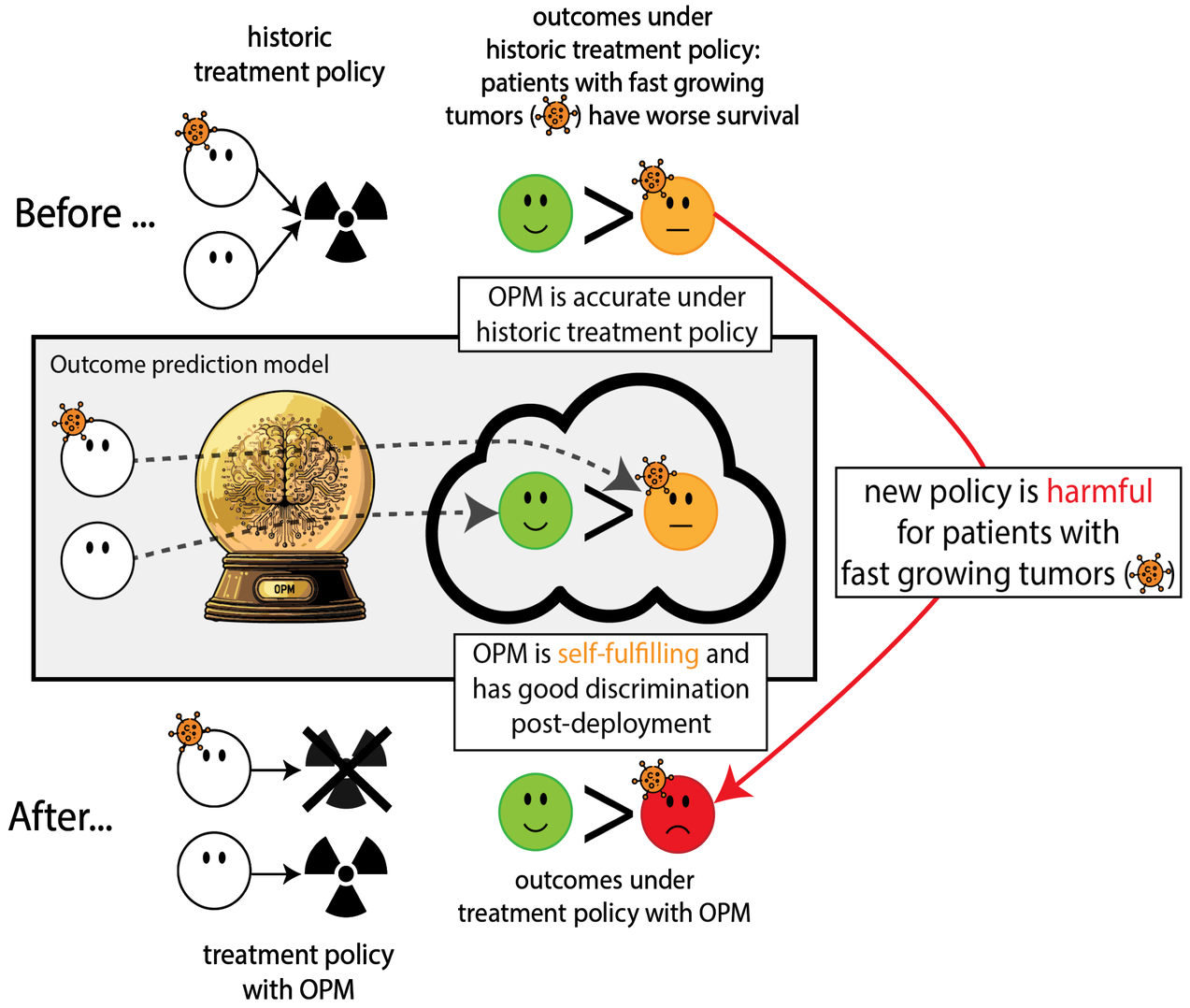
TRIPOD+AI on prediction models (Collins et al. 2024)

"Their primary use is to support clinical decision making, such as … **initiate treatment or lifestyle changes.**"

⚠ **This may lead to bad situations when:**

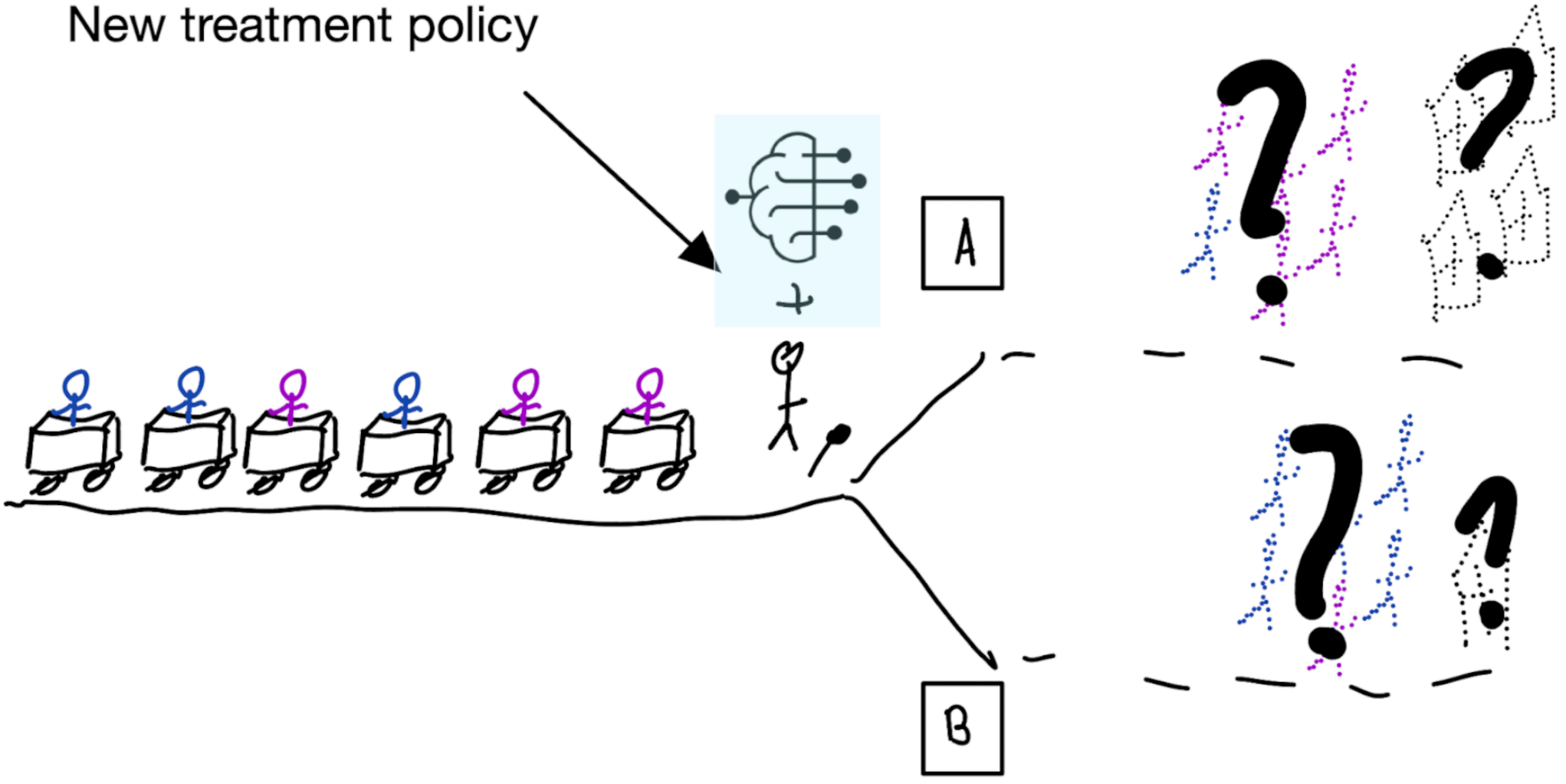
1. ignoring the treatments patients may have had during training / validation of prediction model
2. only considering measures of predictive accuracy as sufficient evidence for safe deployment

When accurate prediction models yield harmful self-fulfilling prophecies


historic
treatment policy
outcomes under
historic treatment policy:
patients with fast growing
tumors ( ) have worse survival
Before ...
OPM is accurate under
historic treatment policy
Outcome prediction model
OPM
new policy is harmful
for patients with
fast growing tumors ( )
OPM is self-fulfilling and
has good discrimination
post-deployment
After...
outcomes under
treatment policy with OPM
treatment policy
with OPM

Building models for decision support without regards for the historic treatment policy is a bad idea

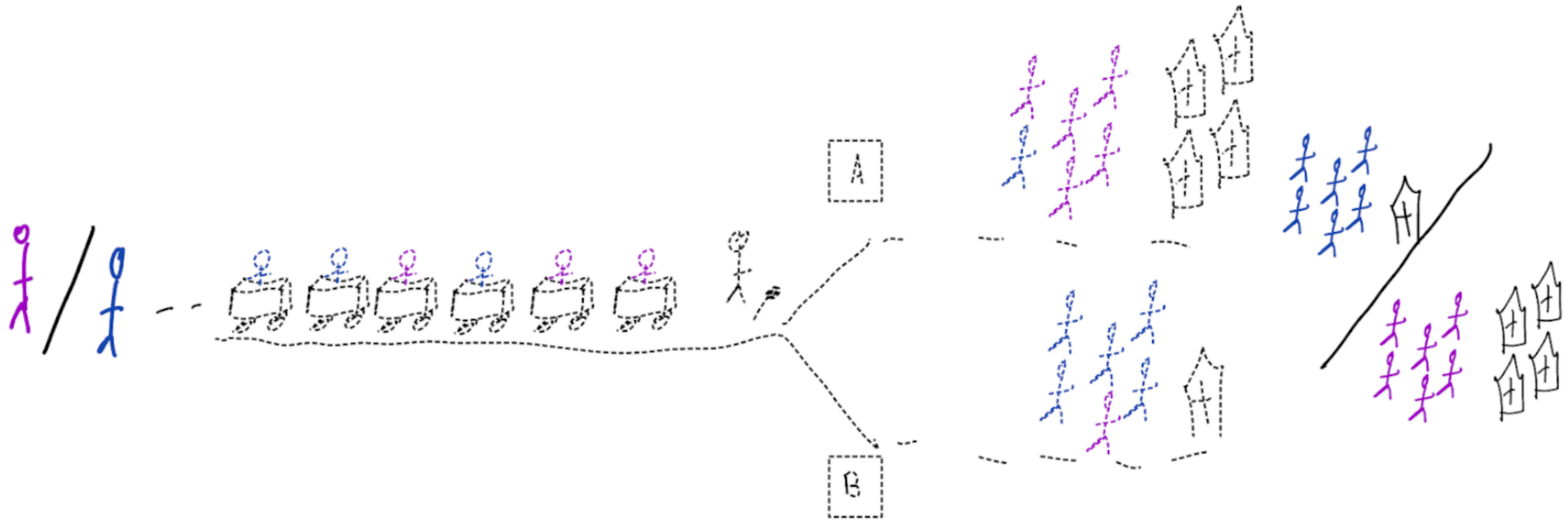
New treatment policy



The question is not “is my model accurate before / after deployment”,

but did deploying the model improve patient outcomes?

Treatment-naive prediction models



$$E[Y|X] = E[E_{t \sim \pi_0(X)}[Y|X,t]]$$

Is this obvious?

Prediction modeling is very popular in medical research

Landscape of clinical prediction models

- 1382 models for cardiovascular disease (Wessler, 2021)
- 731 models related to COVID-19 (Wynants, 2020)
- 408 models for COPD prognosis (Bellou, 2019)
- 363 models for cardiovascular disease general population (Damen, 2016)
- 327 models for toxicity prediction after radiotherapy (Takada, 2022)
- 263 prognosis models in obstetrics (Kleinrouweler, 2016)
- 258 models mortality after general trauma (Munter, 2017)
- 160 female-specific models for cardiovascular disease (Baart, 2019)
- 142 models for mortality prediction in preterm infants (van Beek, 2021)
- 119 models for critical care prognosis in LMIC (Haniffa, 2018)
- 101 models for primary gastric cancer prognosis (Feng, 2019)
- 99 models for neck pain (Wingbermühle, 2018)
- 81 models for sudden cardiac arrest (Carrick, 2020)
- 74 models for contrast-induced acute kidney injury (Allen, 2017)
- 73 models for 28/30 day hospital readmission (Zhou, 2016)
- 68 models for preeclampsia (De Kat, 2019)
- 68 models for living donor kidney/iver transplant counselling (Haller, 2022)
- 67 models for traumatic brain injury prognosis (Dijkland, 2019)
- 64 models for suicide / suicide attempt (Belsher, 2019)
- 61 models for dementia (Hou, 2019)
- 58 models for breast cancer prognosis (Phung, 2019)
- 52 models for pre-eclampsia (Townsend, 2019)
- 52 models for colorectal cancer risk (Usher-Smith, 2016)
- 48 models for incident hypertension (Sun, 2017)
- 46 models for melanoma (Kaiser, 2020)
- 46 models for prognosis after carotid revascularisation (Volkers, 2017)
- 43 models for mortality in critically ill (Keuning, 2019)
- 42 models for kidney failure in chronic kidney disease (Ramspek, 2019)
- 40 models for incident heart failure (Sahle, 2017)
- 37 models for treatment response in pulmonary TB (Peetluk, 2021)
- 35 models for in vitro fertilisation (Ratna, 2020)
- 34 models for stroke in type-2 diabetes (Chowdhury, 2019)
- 34 models for graft failure in kidney transplantation (Kabore, 2017)
- 31 models for length of stay in ICU (Verburg, 2016)
- 30 models for low back pain (Haskins, 2015)
- 27 models for pediatric early warning systems (Trubey, 2019)
- 27 models for malaria prognosis (Njim, 2019)
- 26 models for postoperative outcomes colorectal cancer (Souwer, 2020)
- 26 models for childhood asthma (Kothalawa, 2020)
- 25 models for lung cancer risk (Gray, 2016)
- 25 models for re-admission after admitted for heart failure (Mahajan, 2018)
- 23 models for recovery after ischemic stroke (Jampathong, 2018)
- 23 models for delirium in older adults (Lindroth, 2018)
- 21 models for atrial fibrillation detection in community (Himmelreich, 2020)
- 19 models for survival after resectable pancreatic cancer (Stijker, 2019)
- 18 models for recurrence hep. carc. after liver transplant (Al-Ameri, 2020)
- 18 models for future hypertension in children (Hamoen, 2018)
- 18 models for risk of falls after stroke (Walsh, 2016)
- 18 models for mortality in acute pancreatitis (Di, 2016)
- 17 models for bacterial meningitis (van Zeggeren, 2019)
- 17 models for cardiovascular disease in hypertensive population (Cai, 2020)
- 14 models for ICU delirium risk (Chen, 2020)
- 14 models for diabetic retinopathy progression (Haider, 2019)

UMC Utrecht

Recommended validation practices and reporting guidelines do not protect against harm

because they do not evaluate the policy change

CA Cancer J Clin. 2016 Sep;66(5):370-4. doi: 10.3322/caac.21339. Epub 2016 Jan 19.

American Joint Committee on Cancer acceptance criteria for inclusion of risk models for individualized prognosis in the practice of precision medicine

Michael W Kattan [1], Kenneth R Hess [2], Mahul B Amin [3], Ying Lu [4], Karl G M Moons [5], Jeffrey E Gershenwald [6], Phyllis A Gimotty [7], Justin H Guinney [8], Susan Halabi [9], Alexander J Lazar [10], Alyson L Mahar [11], Tushar Patel [12], Daniel J Sargent [13], Martin R Weiser [14], Carolyn Compton [15]; members of the AJCC Precision Medicine Core

Affiliations + expand

PMID: 26784705 PMCID: PMC4955656 DOI: 10.3322/caac.21339

BMJ. 2024 Apr 16:385:e078378. doi: 10.1136/bmj-2023-078378.

TRIPOD+AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods

Gary S Collins [1], Karel G M Moons [2], Paula Dhiman [1], Richard D Riley [3 4], Andrew L Beam [5], Ben Van Calster [6 7], Marzyeh Ghassemi [8], Xiaoxuan Liu [9 10], Johannes B Reitsma [2], Maarten van Smeden [2], Anne-Laure Boulesteix [11], Jennifer Catherine Camaradou [12 13], Leo Anthony Celi [14 15 16], Spiros Denaxas [17 18], Alastair K Denniston [4 9], Ben Glocker [19], Robert M Golub [20], Hugh Harvey [21], Georg Heinze [22], Michael M Hoffman [23 24 25 26], André Pascal Kengne [27], Emily Lam [12], Naomi Lee [28], Elizabeth W Loder [29 30], Lena Maier-Hein [31], Bilal A Mateen [17 32 33], Melissa D McCradden [34 35], Lauren Oakden-Rayner [36], Johan Ordish [37], Richard Parnell [12], Sherri Rose [36], Karandeep Singh [38], Laure Wynants [39], Patricia Logullo [1]

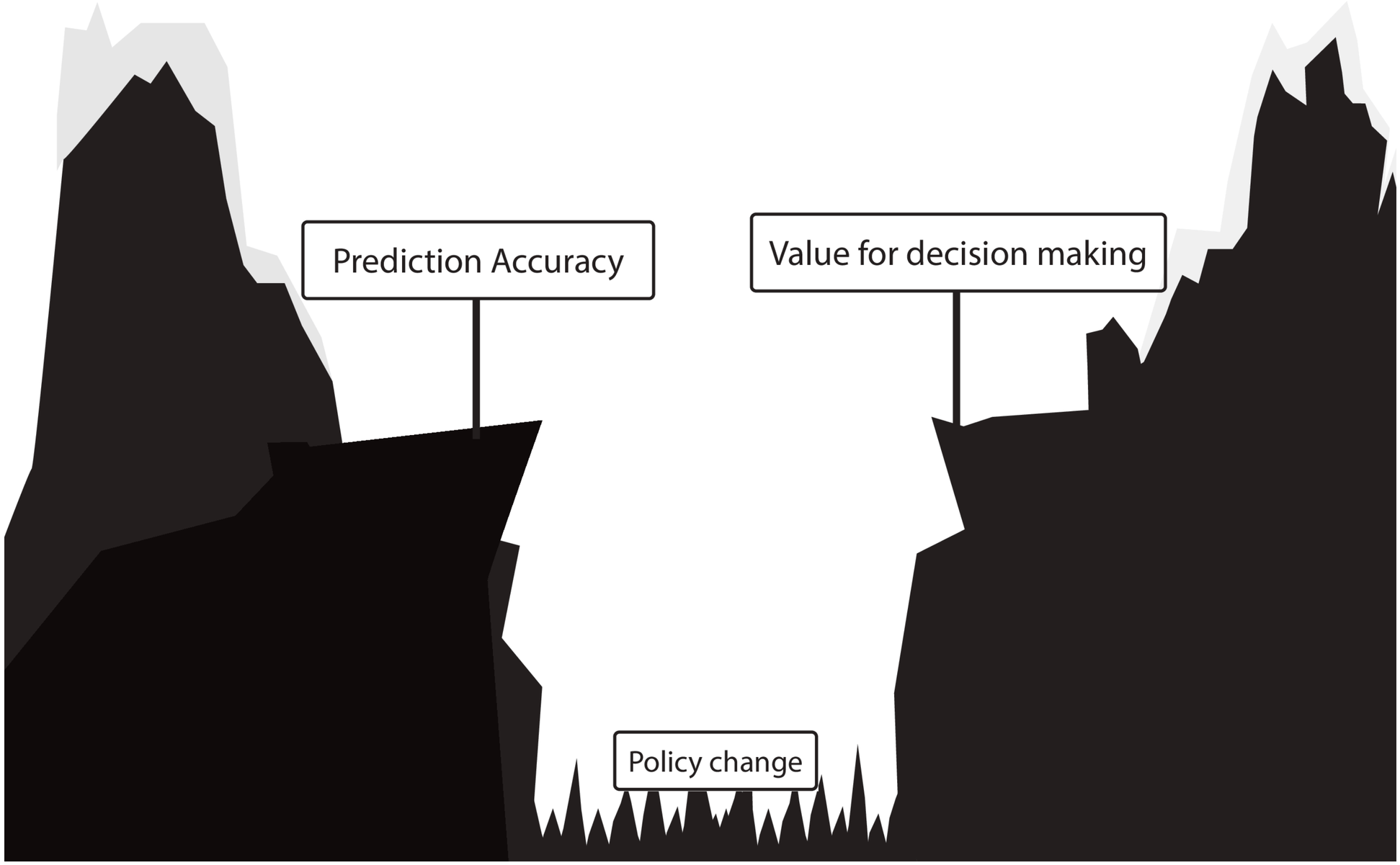
Affiliations + expand

PMID: 38626948 DOI: 10.1136/bmj-2023-078378

BMJ (Clinical r

Bigger data does not protect against harmful prediction models

More flexible models do not protect against harmful prediction models


Prediction Accuracy
Value for decision making
Policy change

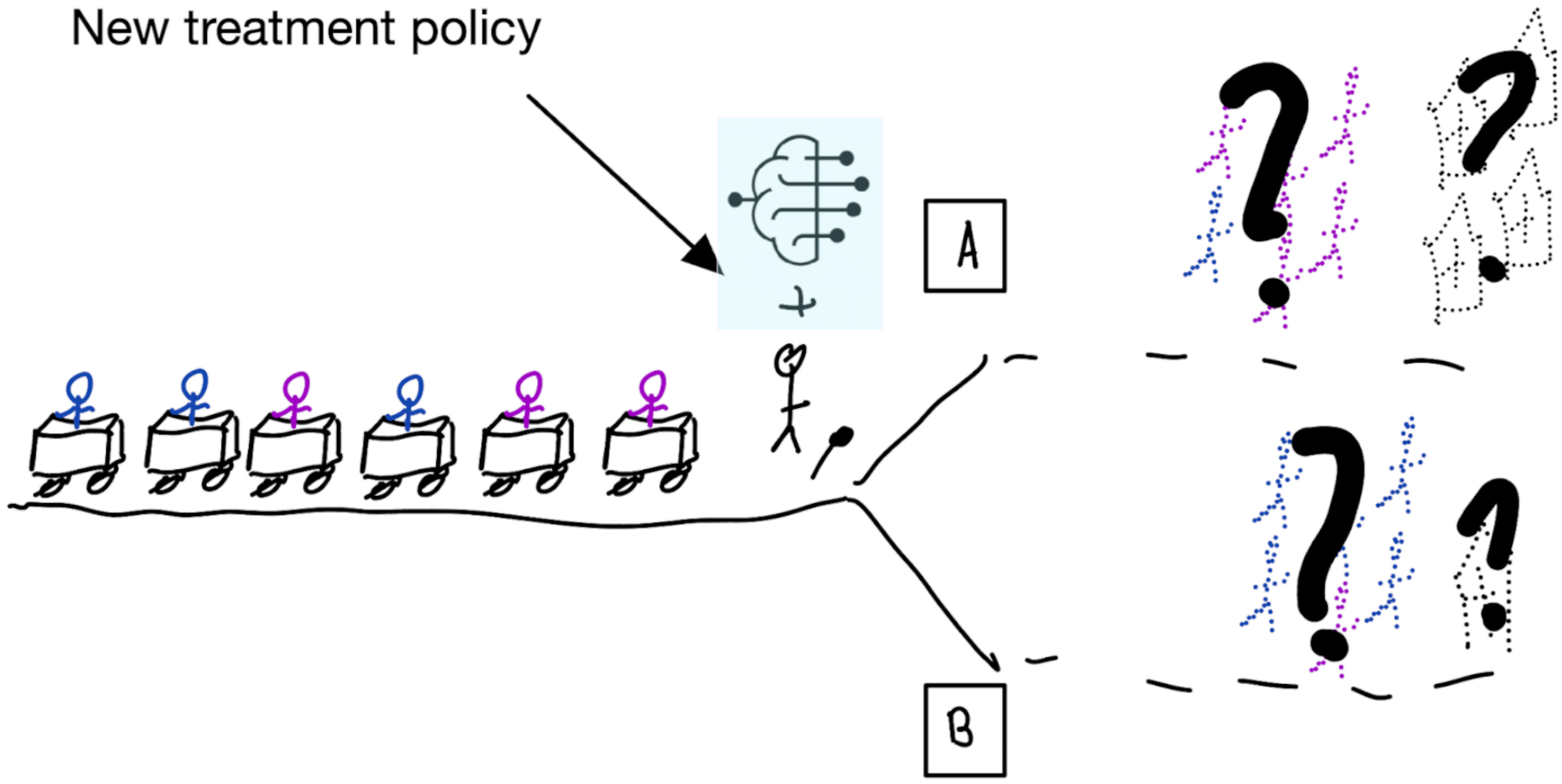
What to do?

What to do?

1. Evaluate policy change (cluster randomized controlled trial)
2. Build models that are likely to have value for decision making

How to evaluate the effect of a new treatment policy?

Deploying a model is an intervention that changes the way treatment decisions are made



How do we learn about the effect of an intervention?

With causal inference!

- for using a decision support model, the unit of intervention is usually *the doctor*
- randomly assign *doctors* to have access to the model or not
- measure differences in **treatment decisions** and **patient outcomes**
- this called a cluster RCT
- if using model improves outcomes, use that one

Using cluster RCTs to evaluated models for decision making is not a new idea (Cooper et al. 1997)

"As one possibility, suppose that a trial is performed in which clinicians are randomized either to have or not to have access to such a decision aid in making decisions about where to treat patients who present with pneumonia."

⚠ **What we don't learn**

was the model predicting anything sensible?

What if we cannot do this (cluster randomized) trial?

Off-policy evaluation

1. have historic RCT data, want to evaluate new policy π_1
   - target distribution $p(t|x) = \pi_1(x)$
   - observed distribution $q(t|x) = 0.5$
   - note: when $\pi_1(x)$ is deterministic (e.g. give the treatment when $f(x) > 0.1$), we get the following:
     a. when randomized treatment is concordant with π_1, keep the patient (weight = 1), otherwise, remove from the data (weight = 0)
     b. calculate average outcomes in the kept patients
   - this way, multiple alternative policies may be evaluated
2. have historic observational data, want to evaluate new policy π_1:
   - target distribution $p(t|x) = \pi_1(x)$
   - observed distribution $q(t|x) = \pi_0(x)$
   - we need to estimate q (i.e. the propensity score), this procedure relies on the standard causal inference assumptions (no confounding, positivity)
   - use importance sampling to estimate the expected value of Y under π_1 from the observed data

How to build prediction models for decision support?

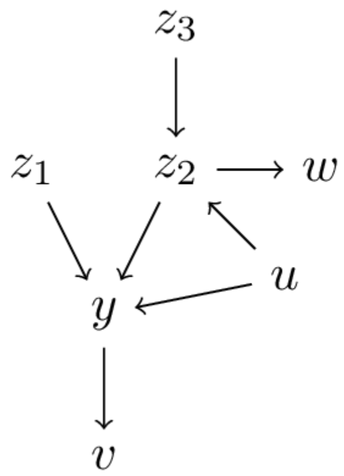
1. Prediction has a causal interpretation

What can we mean with predictions having a causal interpretation?

Let $f : \mathbb{X} \rightarrow \mathbb{Y}$ be a prediction model for outcome Y using features X

1. X is an ancestor of Y ($X = \{z_1, z_2, z_3\}$)
2. X is a direct cause of Y ($X = \{z_1, z_2\}$)
3. $f : \mathbb{X} \rightarrow \mathbb{Y}$ describes the causal effect of X on Y ($X = \{z_1\}$), i.e.:

$$f(x) = E[Y|\text{do}(X = x)]$$



4. $f : \mathbb{T} \times \mathbb{X} \rightarrow \mathbb{Y}$ describes the causal effect of T on Y conditional on X ($T = \{z_1\}, X = \{z_2, z_3, w\}$:

$$f(t, x) = E[Y|\text{do}(T = t), X = x]$$

interpretation 3. all covariates are *causal*

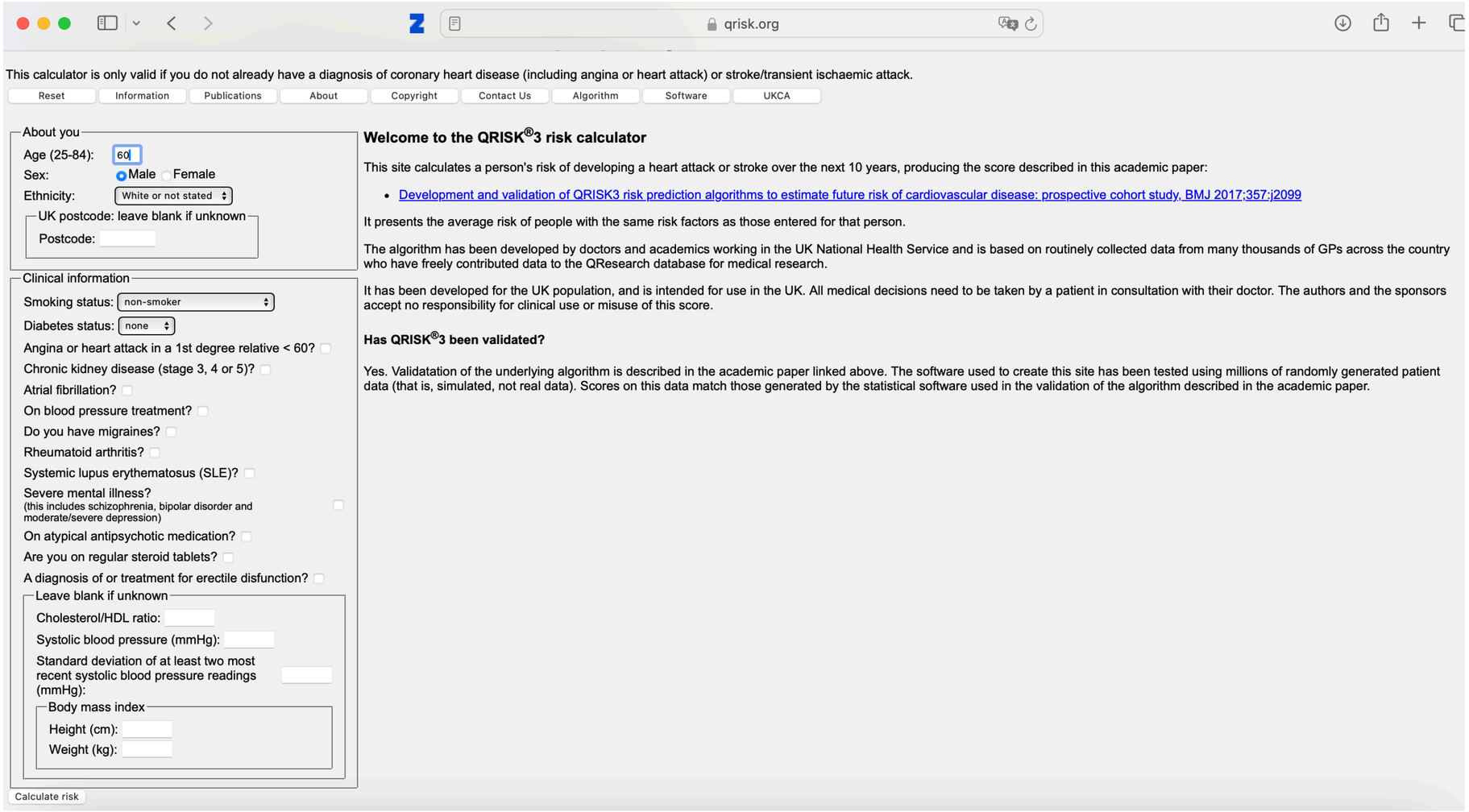
Let $f : \mathbb{X} \rightarrow \mathbb{Y}$ be a prediction model for outcome Y using features X

$$f(x) = E[Y|\text{do}(X = x)]$$

- this is almost never true (i.e. back-door rule holds for **all** variables)
- too often this is assumed / interpreted this way (*table 2 fallacy* in health care literature)

Example of table 2 fallacy when mis-using Qrisk

Qrisk3: a risk prediction model for cardiovascular events in the coming 10-years. Widely used in the United Kingdom for deciding which patients should get statins



Qrisk3 - risks:

can go wrong when:

- e.g. fill in current length and weight
  - reduce weight by 5 kgs
  - interpret difference as ‘effect of weight loss’
- check or un-check blood pressure medication
  - observe that with blood pressure medication, risk is higher

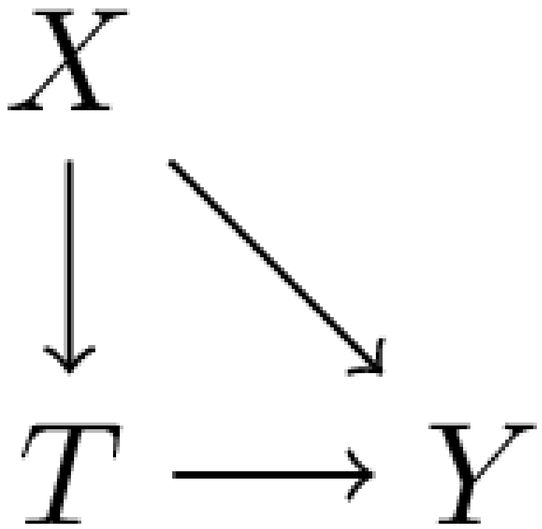
What else could go wrong?

- Qrisk3 states it is validated, but validated for what?
- Qrisk3 is validated for non-use!

interpretation 4. some covariates are *causal*

or: prediction-under-intervention

$$f(t,x) = E[Y|\text{do}(T = t), X = x]$$



- interpretation: *what is the expected value of Y if we were to assign treatment t by intervention, given that we know $X = x$ in this patient*

using *treatment naive* prediction models for decision support

prediction-under-intervention

Estimand for prediction-under-intervention models

What is the estimand?

- prediction: $E[Y|X]$
- average treatment effect: $E[Y|\text{do}(T = 1)] - E[Y|\text{do}(T = 0)]$
- conditional average treatment effect: $E[Y|\text{do}(T = 1), X] - E[Y|\text{do}(T = 0), X]$
- prediction-under-intervention: $E[Y|\text{do}(T = t), X]$

note:

- from prediction-under-intervention models, the CATE can be derived
- in these models and the CATE: T has a causal interpretation, X does not!
  - i.e. X does not *cause* the effect of treatment to be different

Developing prediction-under-intervention models

- requires causal inference assumptions or RCTs
- single RCTs often not big enough, or did not measure the right Xs
- when X is not a sufficient adjustment set, but $X + L$ is, can use e.g. propensity score methods
- assumption of no unobserved confounding often hard to justify in observational data
- but there's more between heaven (RCT) and earth (confounder adjustment)
  - proxy-variable methods (e.g. Miao, Geng, and Tchetgen Tchetgen 2018; van Amsterdam et al. 2022)
  - constant relative treatment effect assumption (e.g. Alaa et al. 2021; van Amsterdam and Ranganath 2023; Candido dos Reis et al. 2017)
  - diff-in-diff
  - instrumental variable analysis (Wald 1940; Puli and Ranganath 2021; Hartford et al. 2017)
  - front-door analysis
- not covered now: formulating correct estimands (and getting the right data) becomes much more complicated when considering dynamic treatment decision processes (e.g. blood pressure control with multiple follow-up visits)

Evaluation of prediction-under-intervention models

- prediction accuracy can be tested in RCTs, or in observational data with specialized methods accounting for confounding (e.g. Keogh and van Geloven 2024)
- in confounded observational data, typical metrics (e.g. AUC or calibration) are not sufficient as we want to predict well in data from *other distribution than observed data* (i.e. other treatment decisions)
- a new *policy* can be evaluated in historic RCTs (e.g. Karmali et al. 2018)
- ultimate test is cluster RCT
- if not perfect, likely a better recipe than *treatment-naive* models

2b. improving non-causal prediction models with causality

- interpretability
- robustness / ‘spurious correlations’ / generalization
- fairness
- selection bias

Interpretability

- end-users (e.g. doctors) often want to understand *why* a prediction model returns a certain prediction
- this has two possible interpretations:

  a. explain the model (i.e. the computations)

  b. explain the world (i.e. why is this patient at high risk of a certain outcome)
- b. often has a causal connotation, though achieving this is may be unfeasible as you need causal assumptions on all covariates (rember table 2 fallacy)

Robustness / spurious correlations / generalization

- prediction models are developed in some data, but are intended to be used elsewhere (in location, time, other)
- in causal language, shifts in distributions can be denoted as interventions on specific nodes
- prediction models that include (direct) causes may be more robust to changes as the chain between X and Y is shorter
- some machine learning algorithms like deep learning are very good at detecting ‘background’ signals, e.g.:
  - detect the scanner type from a CT-scanner
    - if hospital A has scanner type 1 and hospital B has scanner type 2
    - and the outcome rates differ between the hospitals, models may (mis)use the scanner type to predict the outcome
    - what will the model predict in hospital C? or when A or B buy a scanner of different type?
  - may be preventable with causality

Fairness

- in the historic distribution, outcomes may be affected by unequal treatment of certain demographic groups
- instead of perpetuating inequities, we may want to design models that diminish them
- this means intervening in the distribution (= a causal task)
- causality has a strong vocabulary for formalizing fairness
- actually achieving fairness is highly non-trivial, not in the least part due to unclear definitions
- chosing to not include sensitive attributes in a prediction model is often not gauranteed to improve fairness

Selection bias

- have samples from some selected subpopulation
  - university hospital
  - older men
- want to generalize to another subpopulation
  - general practitioner
  - younger women
- use DAGs to express the difference between source and target population
- calculate e.g. expected performance on target population with techniques like importance sampling

Wrap-up

- predictions can have causal interpretations
- prediction-under-intervention: causal with respect to treatment (not covariates)
- mis-use of non-causal models for causal tasks (e.g. prediction model for treatment decisions) is perilous
  - always think about the policy change and its effect on outcomes
- evaluate policy changes with cluster RCTs, or historic RCTs and importance sampling
- causal thinking may improve other aspects of non-causal prediction models such as robustness, fairness, generalization

Proof of importance sampling unbiasedness

assuming x is discrete, otherwise replace sums with integrals for continuous x

want to compute the expected value of $g(x)$ over distribution p, but we have samples from another distribution $x \sim q$

$$E_{x\sim q}\left[\frac{p(x)}{q(x)}g(x)\right] = \sum_x q(x)\left(\frac{p(x)}{q(x)}g(x)\right) = \sum_x p(x)g(x) = E_{x\sim p}\left[g(x)\right]$$

this assumes $q(x) > 0$ whenever $p(x) > 0$ for the ratio p/q to be defined

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