From prediction to treatment decision: aligning development, evaluation and monitoring

ISCB session ‘Prediction modelling meets causal inference for clinical decision making’

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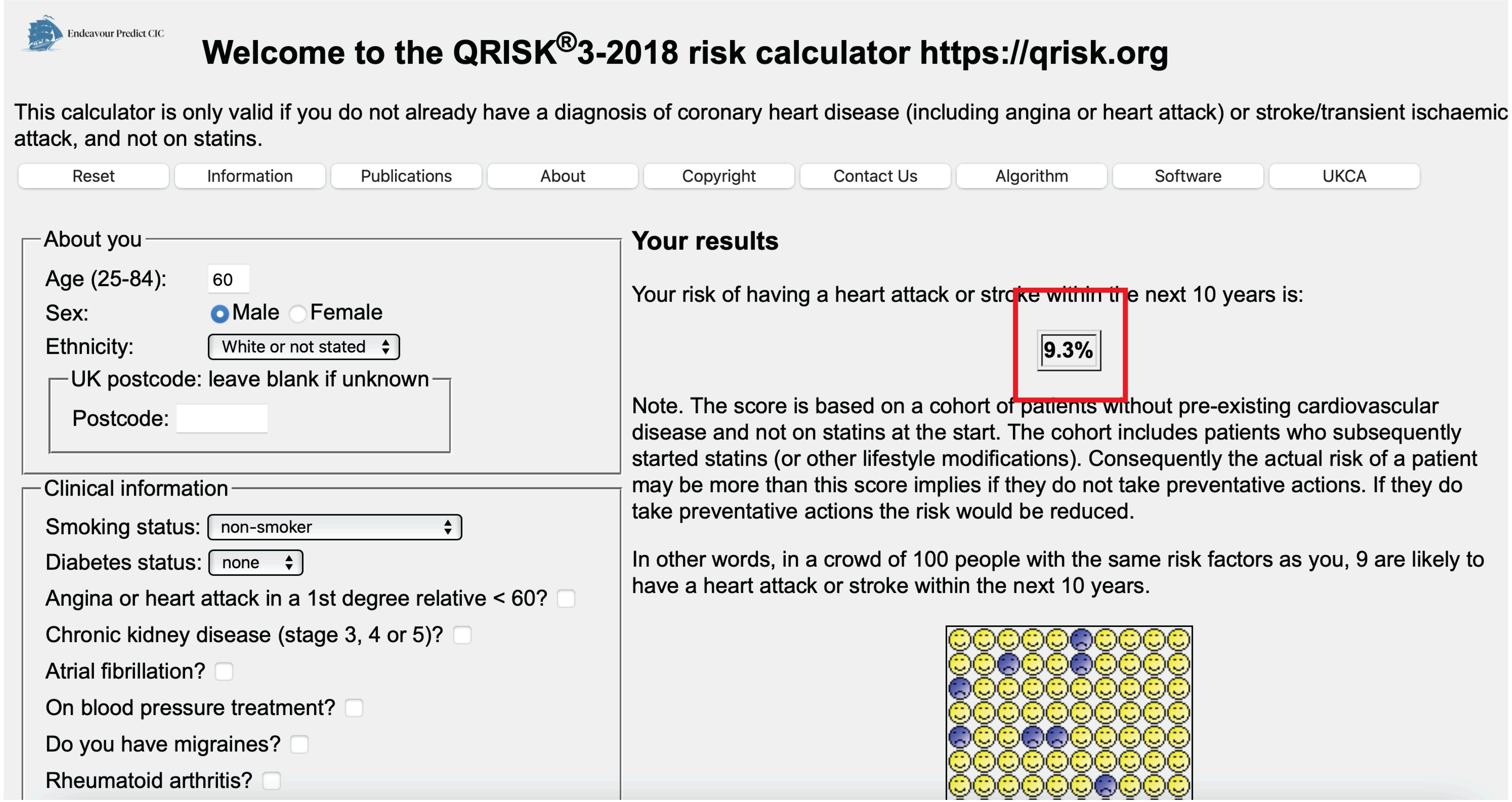
Much of biostatistics, data-science and AI is ‘predict, predict, predict!’

Using medical information, predict 10-year heart attack risk



Welcome to the QRISK®3-2018 risk calculator https://qrisk.org

This calculator is only valid if you do not already have a diagnosis of coronary heart disease (including angina or heart attack) or stroke/transient ischaemic attack, and not on statins.

About you

Age (25-84): 60

Sex: ● Male ○ Female

Ethnicity: White or not stated

UK postcode: leave blank if unknown

Postcode:

Clinical information

Smoking status: non-smoker

Diabetes status: none

Angina or heart attack in a 1st degree relative < 60? □

Chronic kidney disease (stage 3, 4 or 5)? □

Atrial fibrillation? □

On blood pressure treatment? □

Do you have migraines? □

Rheumatoid arthritis? □

Your results

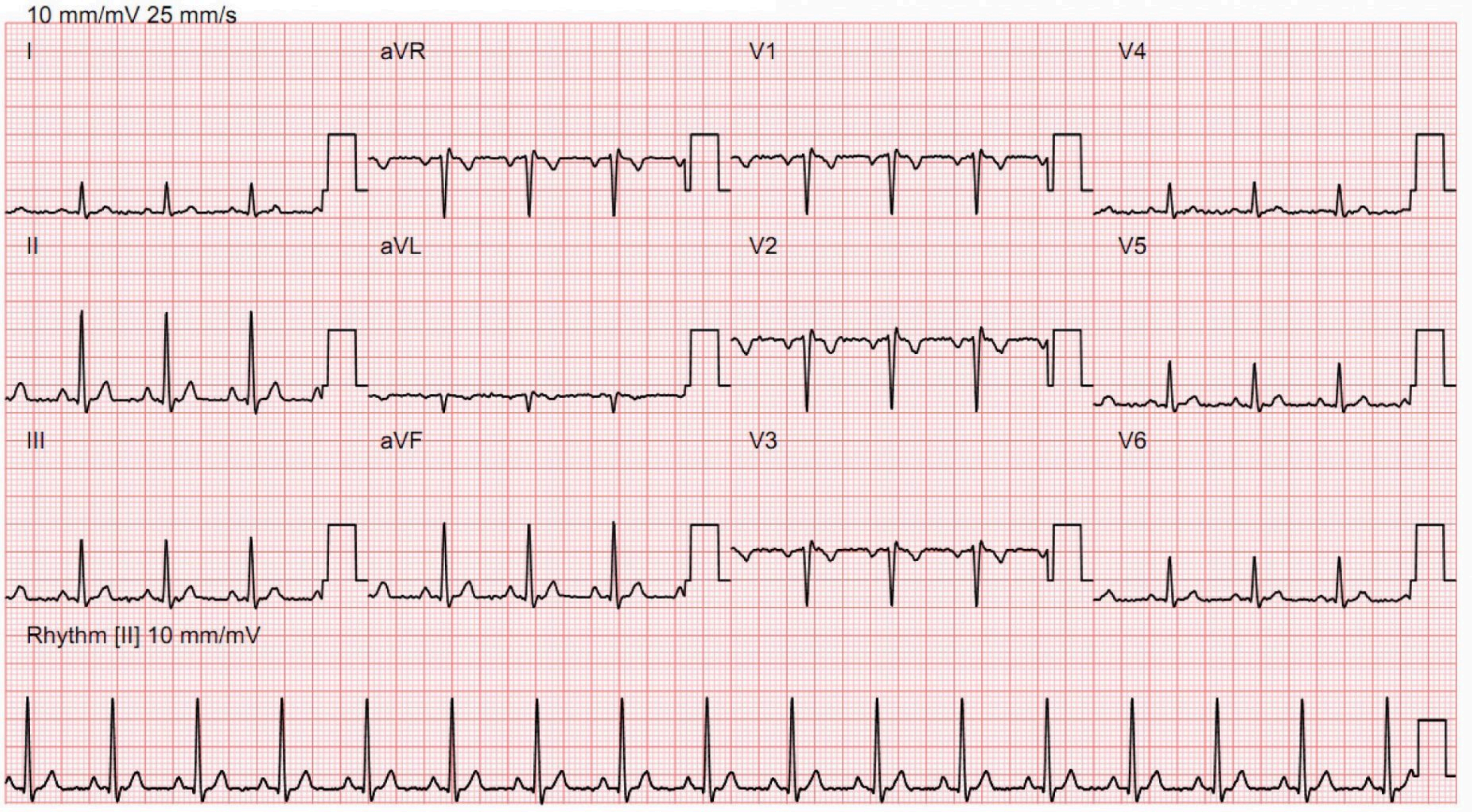
Your risk of having a heart attack or stroke within the next 10 years is:

9.3%

Note. The score is based on a cohort of patients without pre-existing cardiovascular disease and not on statins at the start. The cohort includes patients who subsequently started statins (or other lifestyle modifications). Consequently the actual risk of a patient may be more than this score implies if they do not take preventative actions. If they do take preventative actions the risk would be reduced.

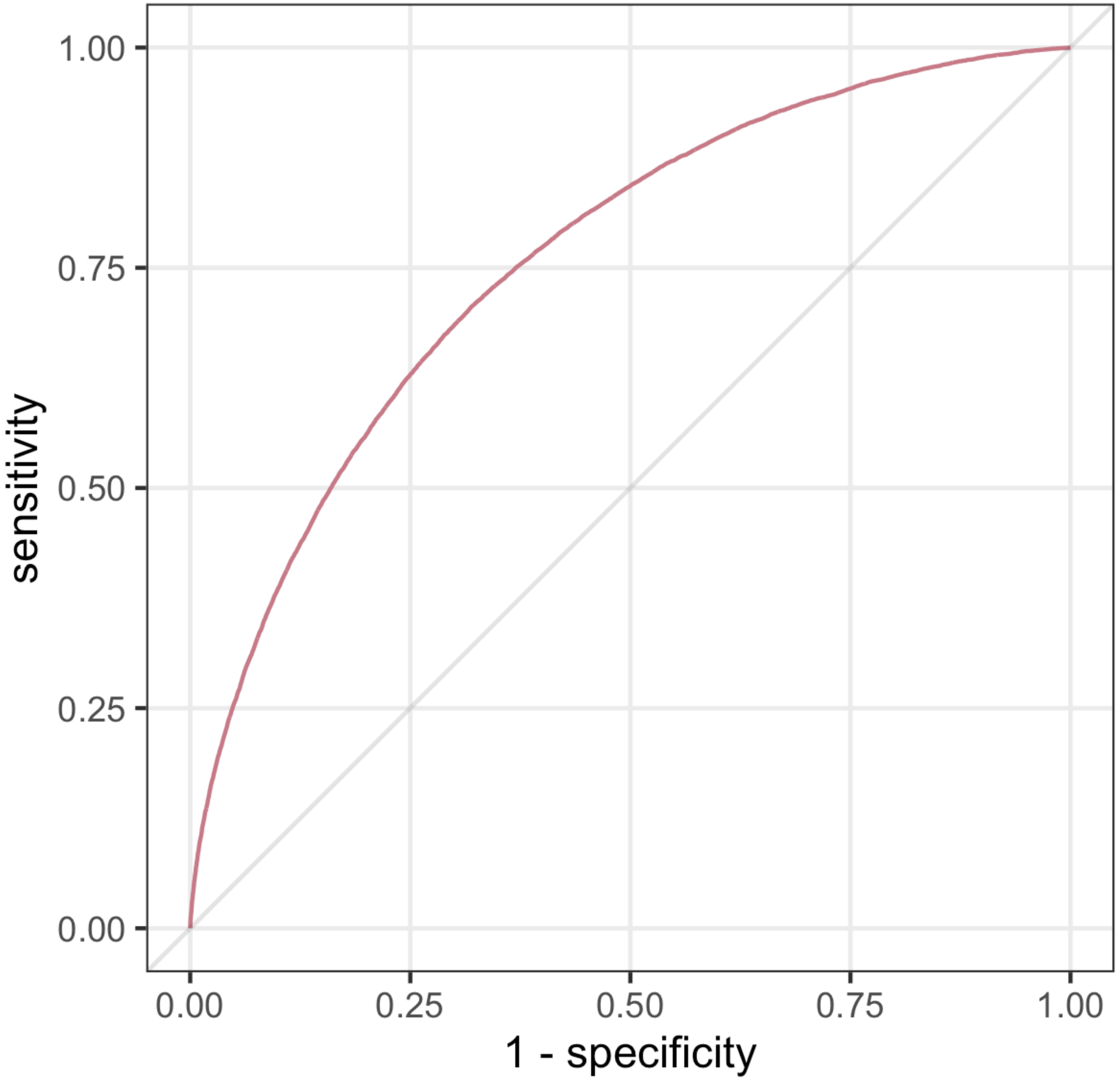
In other words, in a crowd of 100 people with the same risk factors as you, 9 are likely to have a heart attack or stroke within the next 10 years.

from an ECG, predict presence of heart failure (typically diagnosed with cardiac echo)



Predictive performance measures

- sensitivity, specificity
- AUC
- accuracy
- calibration



10 year heart attack risk (Hippisley-Cox et al. 2024)

- prediction: heart attack in 10 years
- intervention: prescribe cholesterol lowering medication
- outcome: heart attack
- outcome (impact): reduce heart attacks

Predict presence of heart failure from ECG (Yao et al. 2021)

- prediction: heart failure
- intervention: refer patient for cardiac echo
- outcome: diagnosis of heart failure on echo
- outcome (impact): reduce preventable early cardiac death / morbidity

Predictive performance vs impact

predictive performance

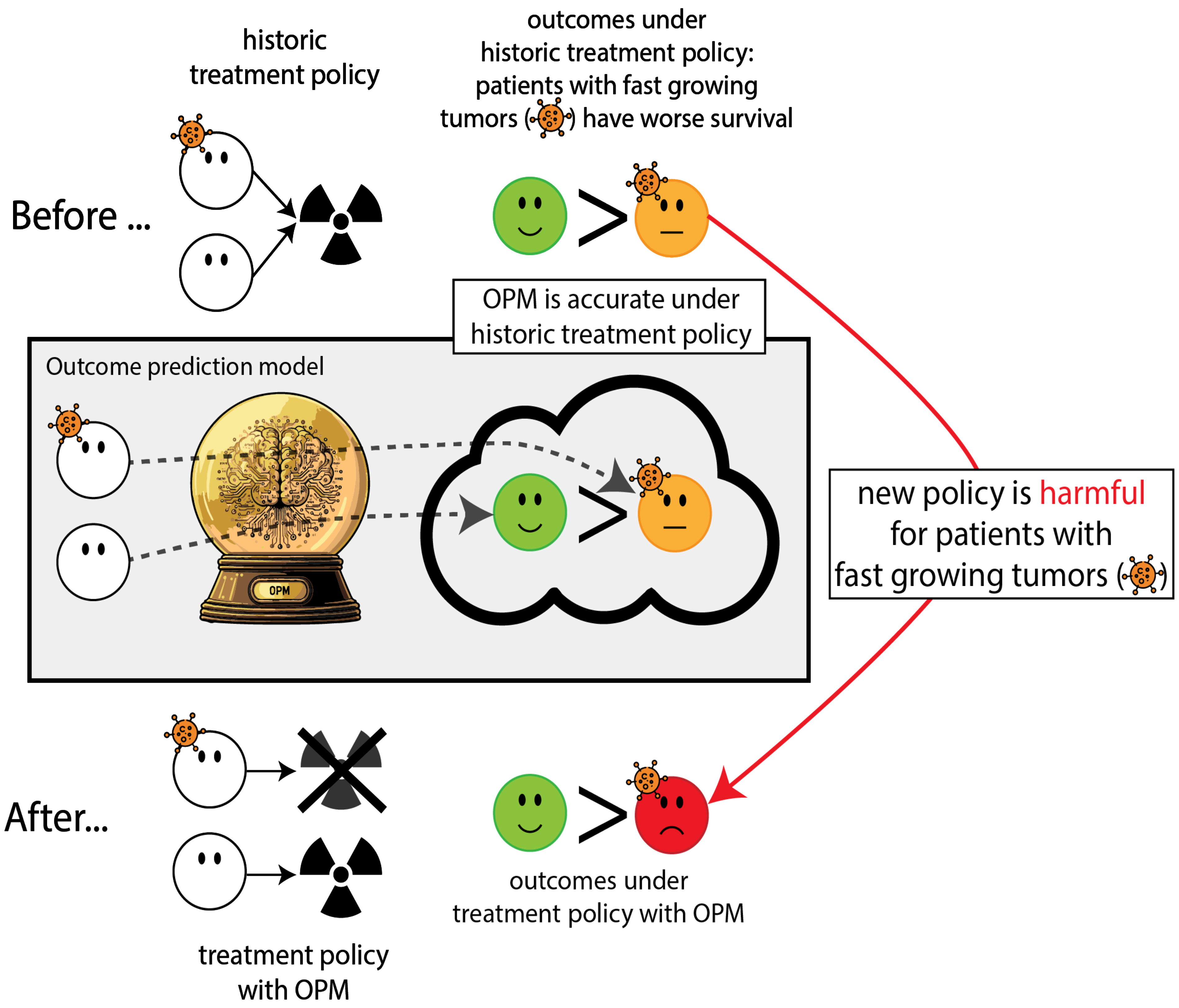
- sensitivity, specificity
- AUC
- accuracy
- calibration

healthcare impact

- interventions (medical decisions)
- patient outcomes

- the hope is: better predictive performance $\implies$ better impact
- unfortunately, this is not automatically the case

When accurate prediction models yield harmful self-fulfilling prophecies (Van Amsterdam et al. 2025)



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

new policy is harmful for patients with fast growing tumors (🦠)

After...

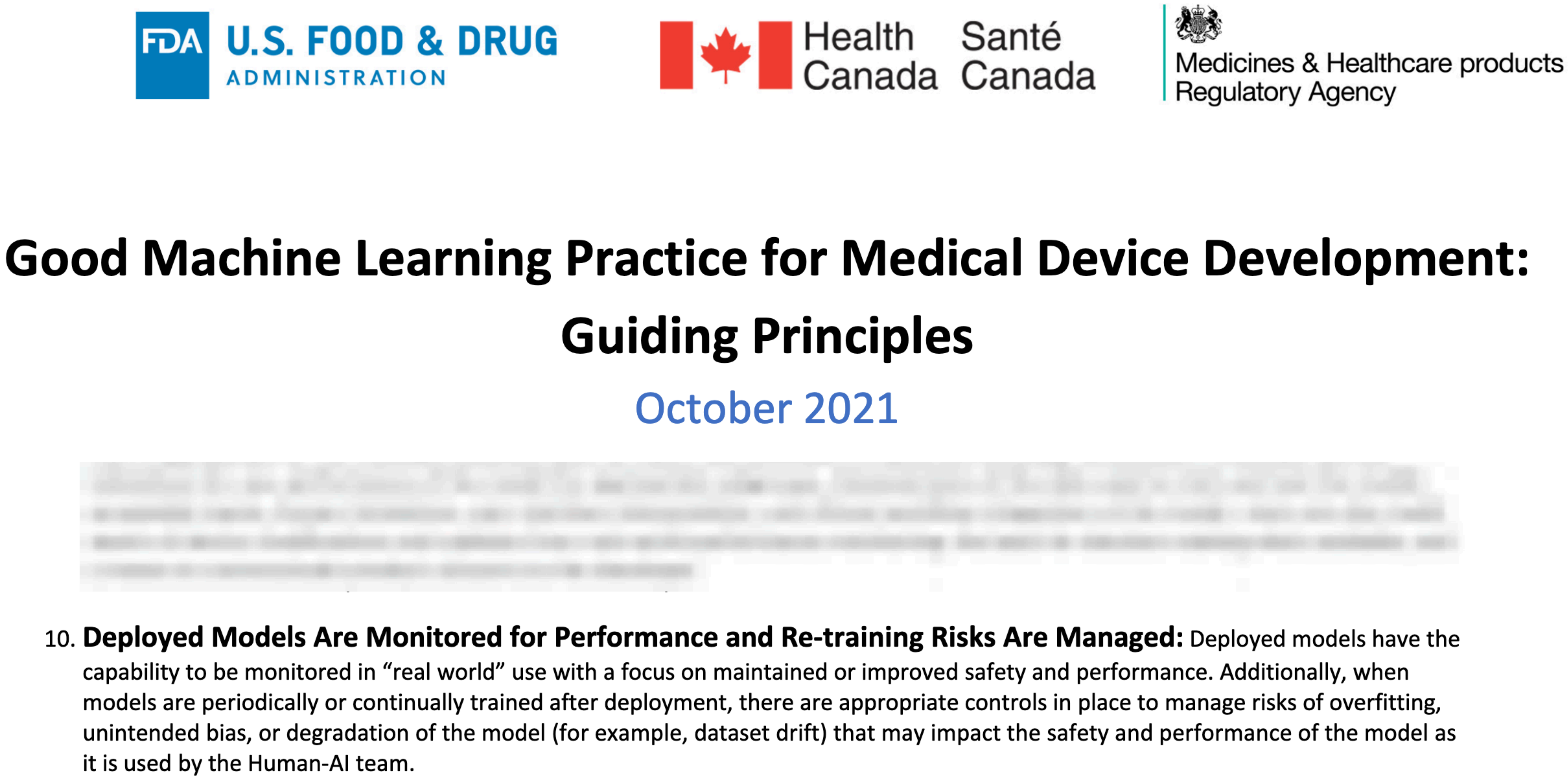
outcomes under treatment policy with OPM

treatment policy with OPM

What happened here?

- had a ‘good’ model, got a bad policy
- model predicted outcome (survival) *under historic treatment policy* (always radiation)
- did not predict what outcomes would be under *alternative policy* (no radiation)
- in this case, unmodeled *treatment effect heterogeneity* (aka treatment effect modification, interation, differing conditional average treatment effects)

Regulation to the rescue: we need to monitor (AI) models



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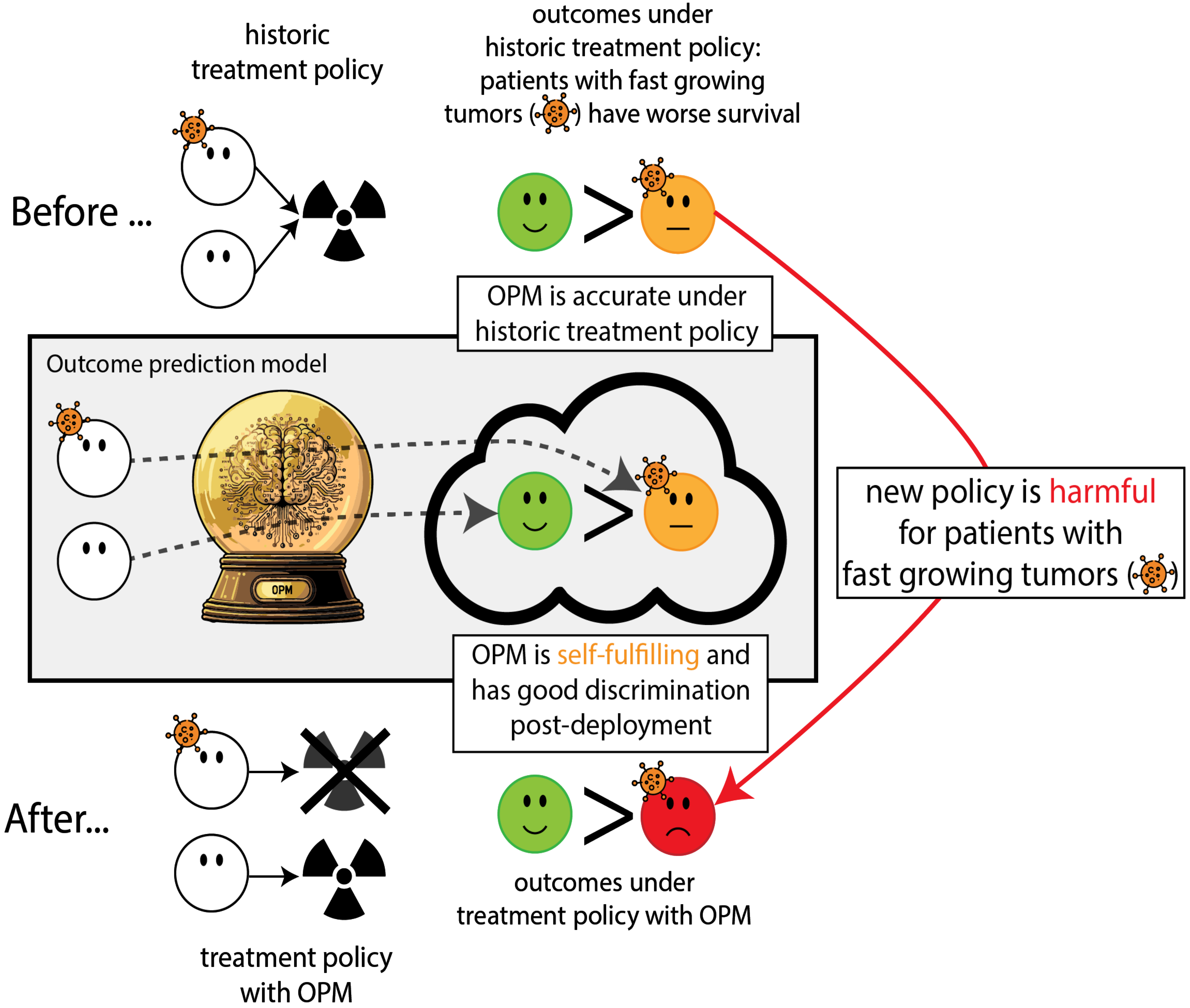
Good Machine Learning Practice for Medical Device Development: Guiding Principles

October 2021

[illegible]

10. **Deployed Models Are Monitored for Performance and Re-training Risks Are Managed:** Deployed models have the capability to be monitored in “real world” use with a focus on maintained or improved safety and performance. Additionally, when models are periodically or continually trained after deployment, there are appropriate controls in place to manage risks of overfitting, unintended bias, or degradation of the model (for example, dataset drift) that may impact the safety and performance of the model as it is used by the Human-AI team.

Let’s monitor the model performance over time



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

new policy is harmful for patients with fast growing tumors (🦠)

OPM is self-fulfilling and has good discrimination post-deployment

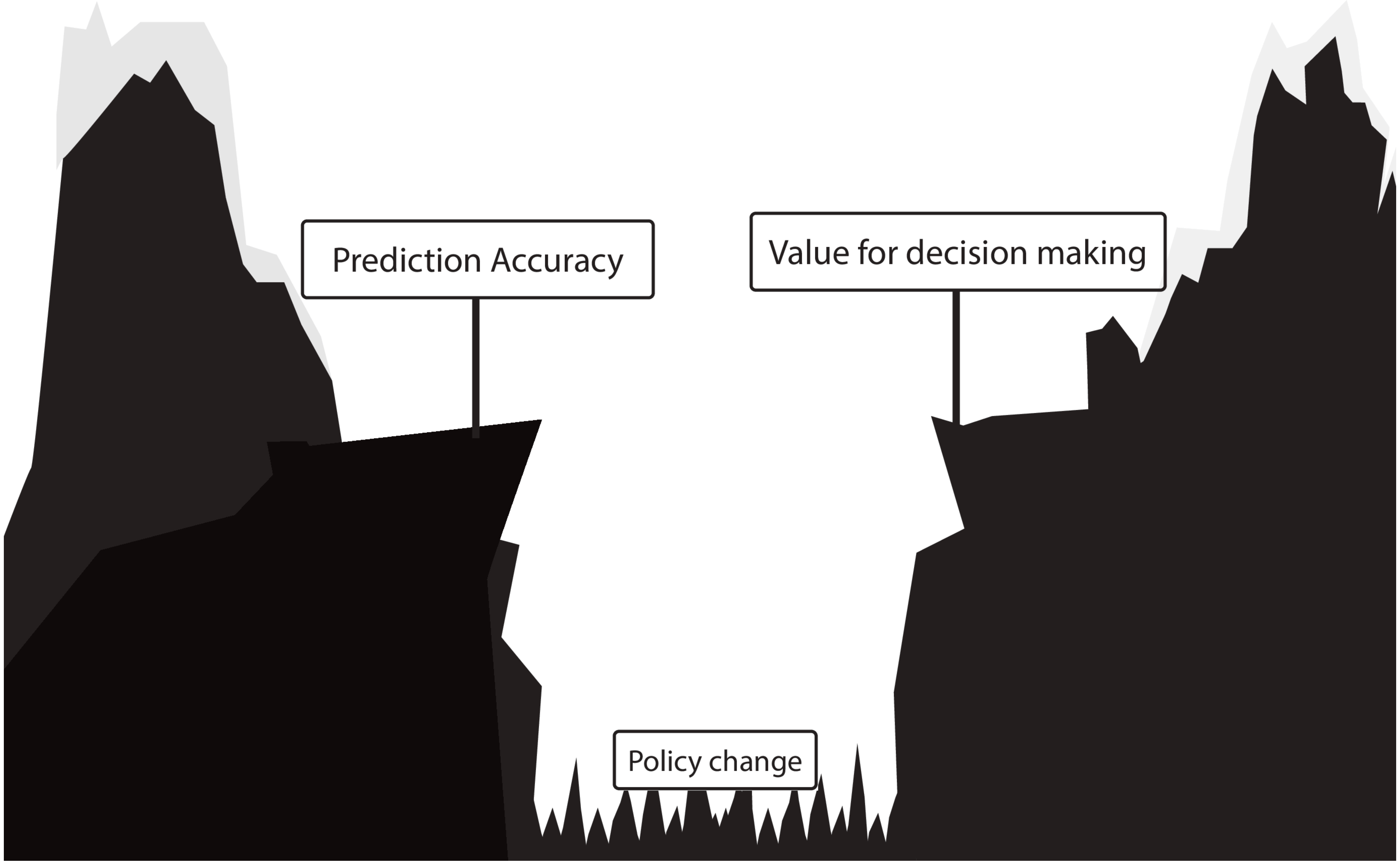
After...

outcomes under treatment policy with OPM

treatment policy with OPM

What happened in monitoring?

- the model re-inforced its own predictions (self-fulfilling prophecy)
- took a measure of predictive performance (AUC)
- mistook it for a measure of (good) impact
- many potential examples (e.g. ICU stop treatment (Balcarcel et al. 2025), others (Center n.d.))


Prediction Accuracy
Value for decision making
Policy change

Another way: prediction under intervention

When predicting an outcome to support decisions regarding an intervention,

this prediction needs a clear relationship with the targeted intervention (van Amsterdam et al. 2024)

> **Hilden and Habbema on prognosis** (Hilden and Habbema 1987)
>
> “Prognosis cannot be divorced from contemplated medical action, nor from action to be taken by the patient in response to prognostication.”

- not: what’s risk of heart attack given age and cholesterol,
- but: what’s risk of heart attack given age and cholesterol, **if we were not to give cholesterol lowering medication** (vs. if we would)
- may sound like $1 + 1 = 2$ but often not done; e.g. in the development data of Qrisk3, many patients already underwent cholesterol lowering medication (Peek, Sperrin, and van Staa 2017)

Prediction under hypothetical intervention incorporates effects of treatment in its predictions

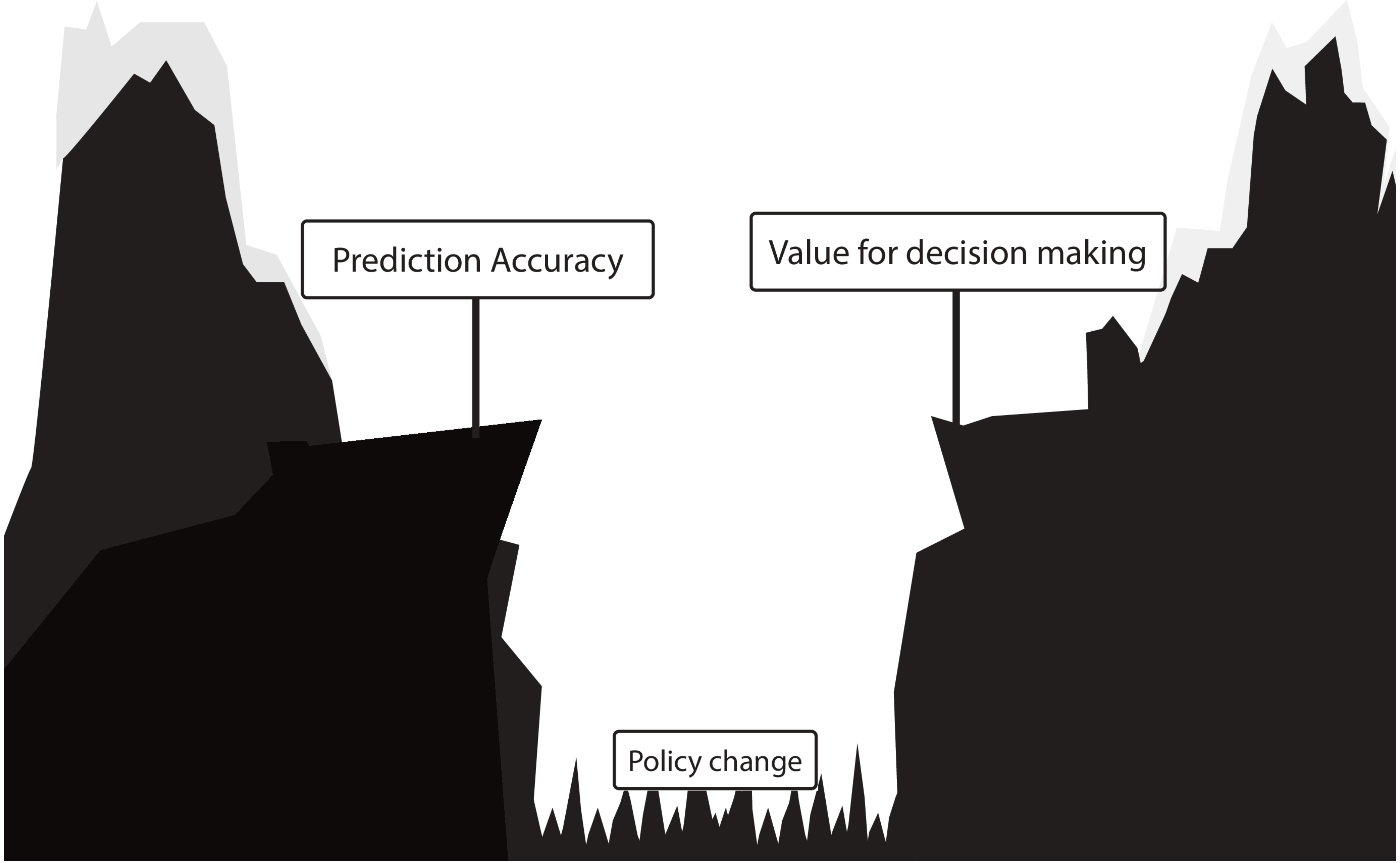
- estimates the expected outcome Y
  - **if we were to give treatment** T to patient with features X
- a.k.a. ‘counterfactual prediction’
- can predict outcomes under multiple treatments, where one treatment may be ‘no (additional) treatment / standard treatment’

How to build prediction under intervention models?

- in its simplest form, can be just like fitting any other predictive model, as long as **causal identifyability assumptions** are fulfilled:
  - unconfoundedness (no hidden variables causing both the intervention and the outcome)
  - positivity, consistency
- these hold by design in Randomized Controlled Trials (RCT)
- RCTs are in that sense ideal (e.g. Kent et al. 2020), but:
  - typically limited sample size
  - may not have measured right information (e.g. imaging markers, new biomarkers, full-EHR)
  - trial participants may not be representative of the target population of use (e.g. Lewis et al. 2003)
- can *emulate* RCTs with non-experimental (*observational*) data using a causal inference framework, e.g. using target trial emulation

Benefits of prediction under intervention

- policy rule: if expected outcome under treatment A is better than under treatment B (potentially by a certain margin), give treatment A, otherwise B
- as opposed to other prediction models, this policy has foreseeable positive impact on health outcomes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Benefits of prediction under intervention

- policy rule: if expected outcome under treatment A is better than under treatment B (potentially by a certain margin), give treatment A, otherwise B
- as opposed to other prediction models, this policy has foreseable positive impact on health outcomes
- as a ‘bonus’, these models have stable calibration under shifts in policy that depend on the models’ features (e.g. Feng et al. 2024)

Measuring pre- and post-deployment

		pre-deploy	deployment study
	metric		
model	discrimination (AUC)	✅	
	calibration	✅	
health system	interventions	✅	
	patient outcomes	✅	

Legend

🔁 changes ✅ stable 🔻 worsens

Measuring pre- and post-deployment

		pre-deploy	post-deploy
	metric		
model	discrimination (AUC)	✅	🔁
	calibration	✅	🔻
health system	interventions	✅	🔁
	patient outcomes	✅	🔁

Legend

🔁 changes ✅ stable 🔻 worsens

- for ‘non-causal’ prognosis prediction models that don’t factor in treatment decisions:
  - AUC will change, calibration will worsen as distribution changes
  - interventions and patient outcomes may change in unforeseen ways

Measuring pre- and post-deployment

		pre-deploy	‘non-causal’	‘causal’
	metric			
model	discrimination (AUC)	✅	🔁	🔁
	calibration	✅	🔻	✅
health system	interventions	✅	🔁	📈
	patient outcomes	✅	🔁	📈

Legend

🔁 changes ✅ stable 🔻 worsens 📈 changes in expected way

- for prediction under intervention model
  - calibration preserved under shifts in policy conditional on the model’s features
  - interventions and outcomes change in foreseeable ways (under assumption on policy)

Current status

- reporting guidelines (e.g. TRIPOD+AI / PROBAST+AI (Collins et al. 2024; Moons et al. 2025)) do not require a clear enoough description of relation between prediction and treatment ("Prognostic Models for Decision Support Need to Report Their Targeted Treatments and the Expected Changes in Treatment Decisions" 2024)
- some acceptance criteria lists (AJCC) even allow for harmful self-fulfilling prophecies (Kattan et al. 2016)
- EMA and FDA are developing monitoring guidelines, mostly emphasis on **predictive performance**, but **good performance ≠ postive impact**

Takeaways

- when predicting prognosis, need well defined relation between prediction and potential treatment decisions
- in particular, *prediction under intervention* has the advantages of:
  1. clear relationship between model performance and value for decision making
  2. stable calibration under shifts in treatment policy, conditional on the model's features
- these models need unconfoundedness, so either
  - develop using RCT data
  - use observational causal inference
- evaluate and monitor prediction models based on what we care about: impact on healthcare

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