Beyond Estimation: Next Steps for Precision Medicine

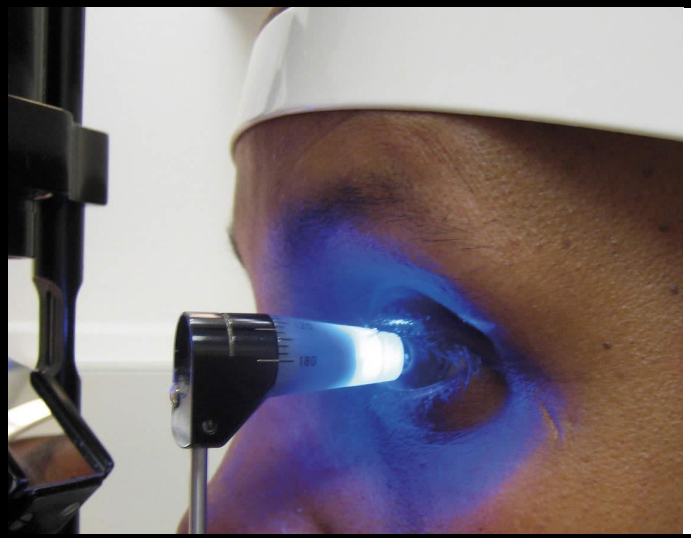
Michael Wallace, University of Waterloo

Slides available at: `mpwallace.github.io`

Glaucoma: One Disease, Many Treatments

Glaucoma: group of eye diseases associated with elevated intraocular pressure (IOP).

IOP can be measured in various ways.



Glaucoma: One Disease, Many Treatments

Treatment options attempt to lower IOP, they include:

- Lifestyle changes.
- Eye drops (numerous options).
- Surgery.

Glaucoma: One Disease, Many Treatments

Treatment decisions are made based on various factors:

- Current and past IOP.
- Current and past treatments.
- Concerns over side effects.
- Broader risk factors.
- Other characteristics (such as age).

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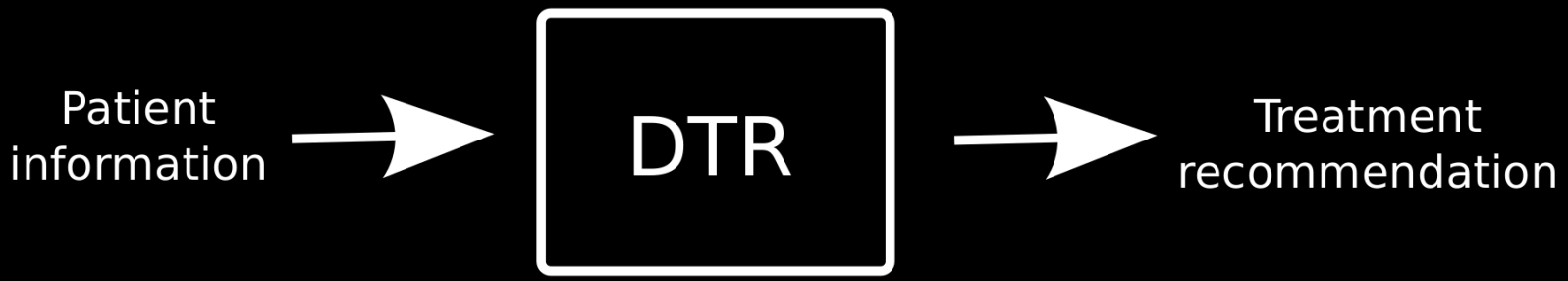
Precision Medicine: tailoring treatment decisions to patient-level characteristics.

Dynamic treatment regimes

- Dynamic treatment regimes (DTRs) 'formalize' personalized treatment:

  "*Patient presents with historic IOP of 13 and is taking Azarga. If current IOP is 15 or higher, add Alphagan, otherwise continue with only Azarga.*"



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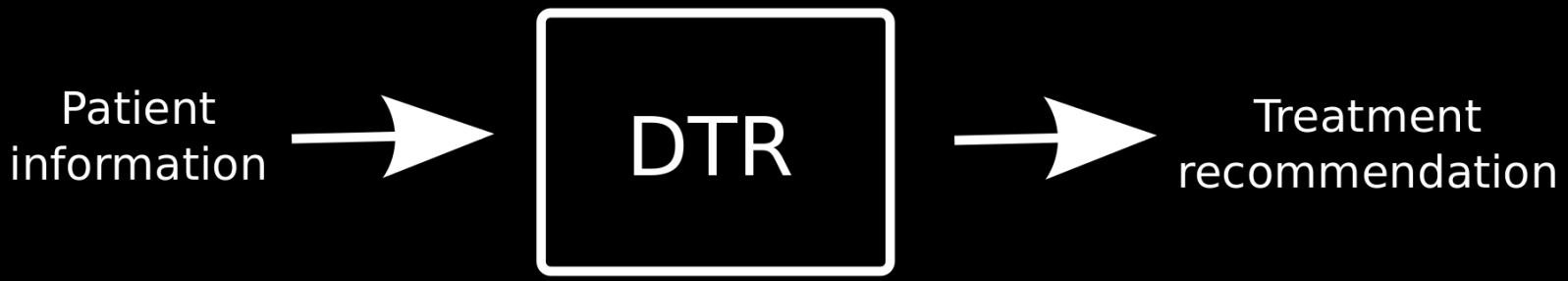

- How do we choose the best DTR?

  Should our IOP cut-off be 13, 15, 20?

- What makes this difficult?

The Data

We typically work with data from observational studies.

Patient	Observed IOP	Drop added?	IOP at 3 months
1	16	No	15
2	20	Yes	16
3	21	Yes	17
4	16	Yes	16
5	15	No	18
...	...	...	...

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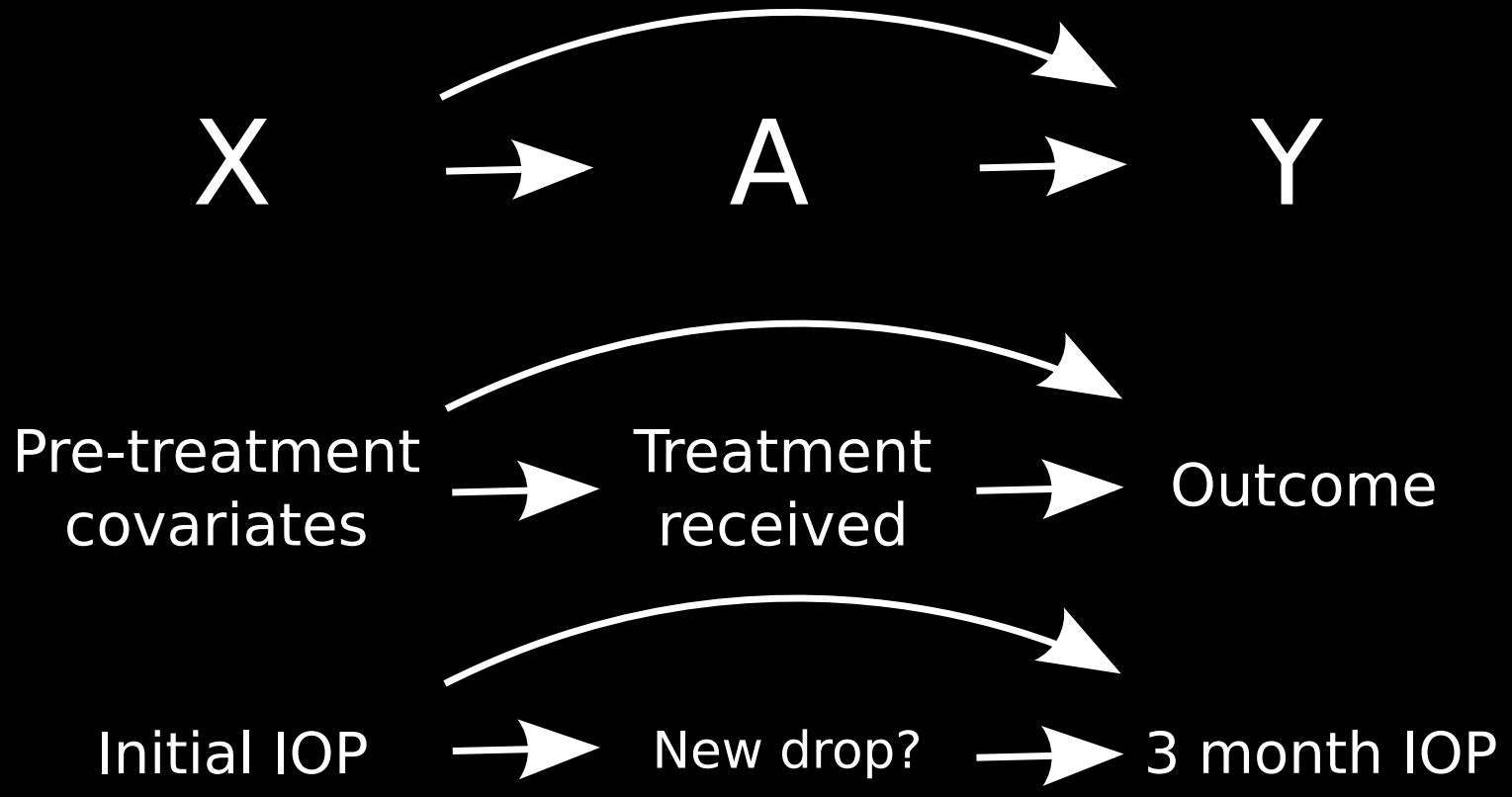
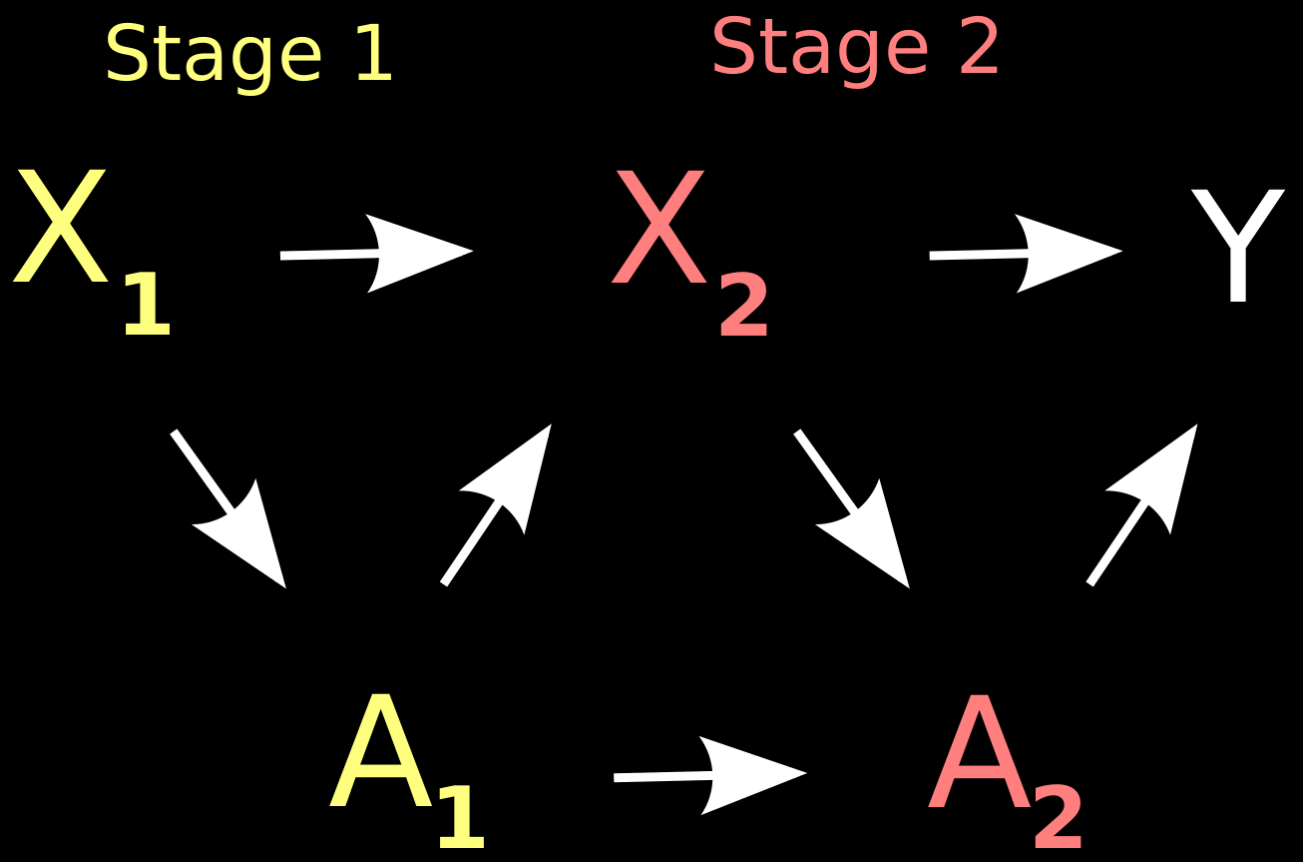
Notation



DTR: treatment A^{opt} that optimizes $E[Y|X, A^{opt}]$

Identifying the best treatment regime: multi-stage



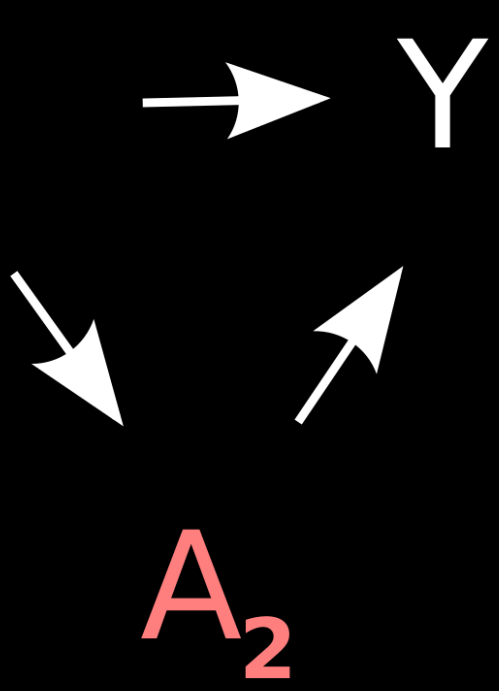
More often, we work in stages.

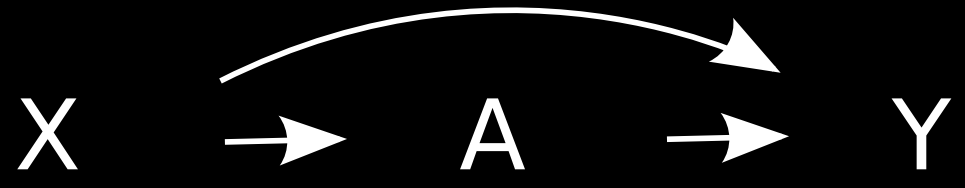
DTR: treatment sequence A_1^{opt}, A_2^{opt}

Identifying the best treatment regime: multi-stage

Stage 2

$H_2 = (X_1, A_1, X_2)$





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Lots of methods available:

Q-learning

MSMs

G-estimation

IPTW

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OWL

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- We might propose the following model

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"Treat $(A = 1)$ if $\psi_0 + \psi_1 \text{IOP} > 0$"

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- More generally, split outcome into two components:

$$\underbrace{E[Y|X,A;\beta,\psi]}_{\text{Expected outcome (to be maximized)}} = \overbrace{G(X;\beta)}^{\text{Impact of patient history in the absence of treatment}} + \underbrace{\gamma(X,A;\psi)}_{\text{Impact of treatment on outcome}}$$

- Simplifies focus: find A^{opt} that maximizes $\gamma(X,A;\psi)$.

Identifying the best treatment regime

- Suppose the true outcome model is:

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$$E[Y|X, A; \beta, \psi] = G(X; \beta) + \gamma(X, A; \psi)$$

- Three models to specify:
  1. Blip model: $\gamma(X, A; \psi)$.
  2. Treatment-free model: $G(X; \beta)$.
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- Estimate ψ via WOLS of Y on covariates in blip and treatment-free models, with weights $w = |A - P(A = 1|X; \hat{\alpha})|$.

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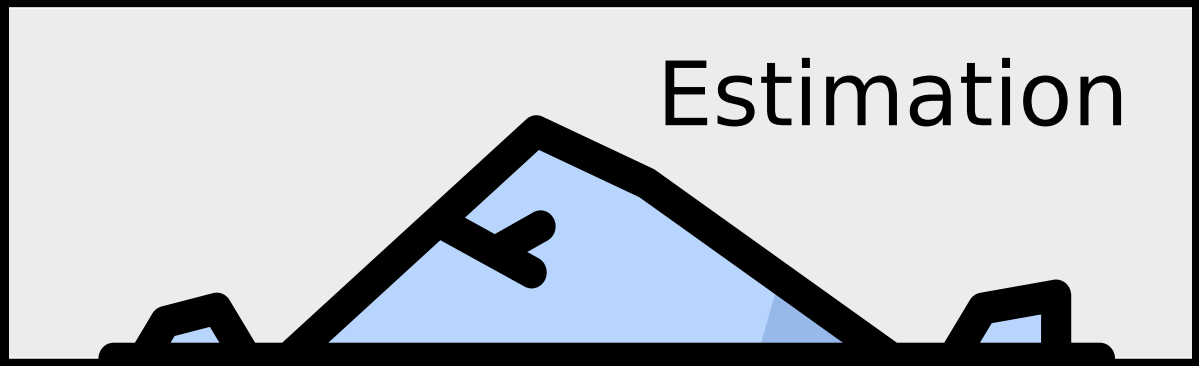
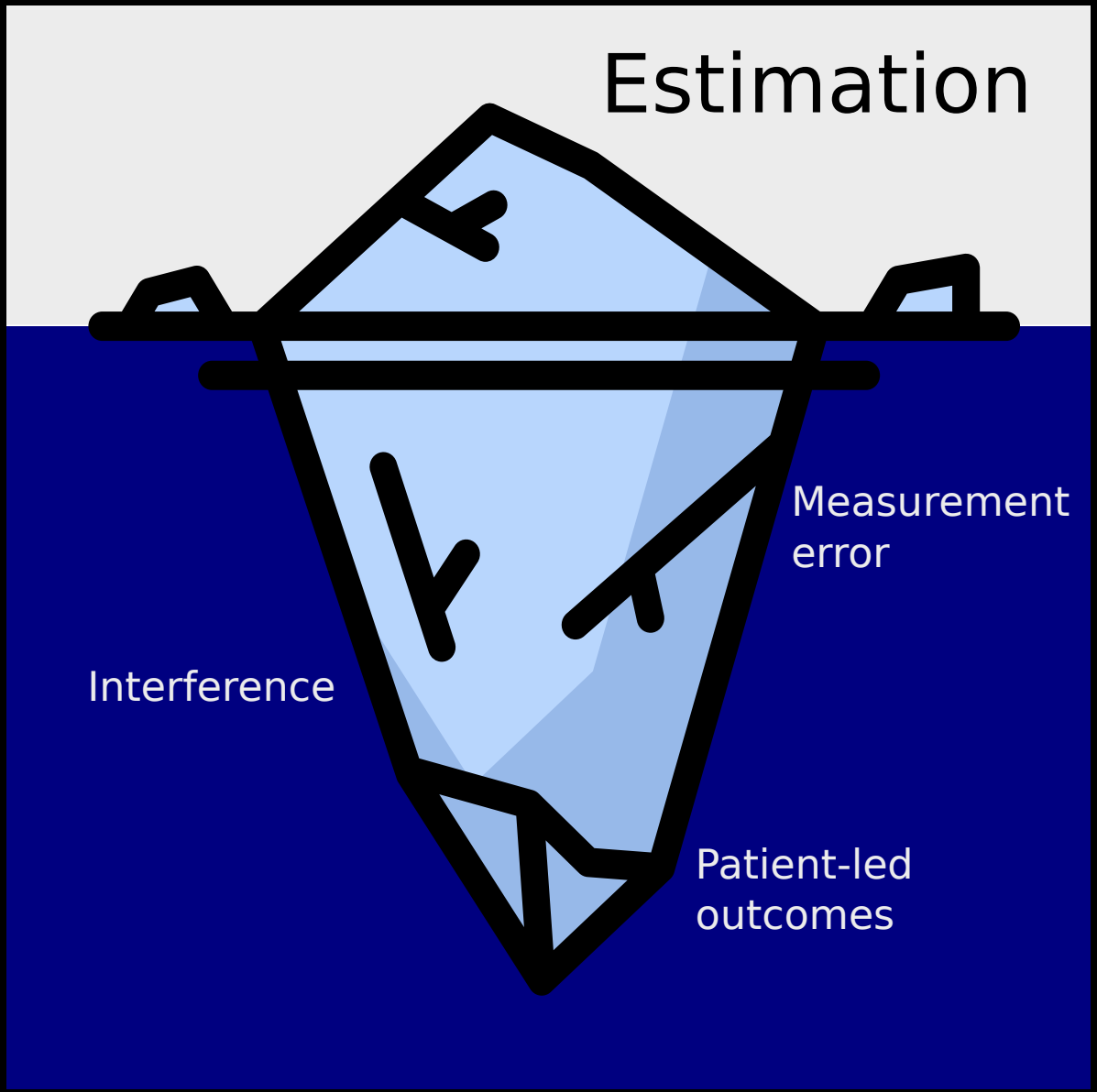
- A weighted regression with weights $w = |A - P(A = 1|X; \hat{\alpha})|$ will still yield consistent estimators of ψ_0, ψ_1.
- The estimators are "doubly robust": consistent if at least one of the treatment-free or treatment components is correctly specified.
- The blip must always be correct.



So all we have to do is specify some models, estimate the model parameters, then choose the treatment that maximizes the expected outcome - easy!

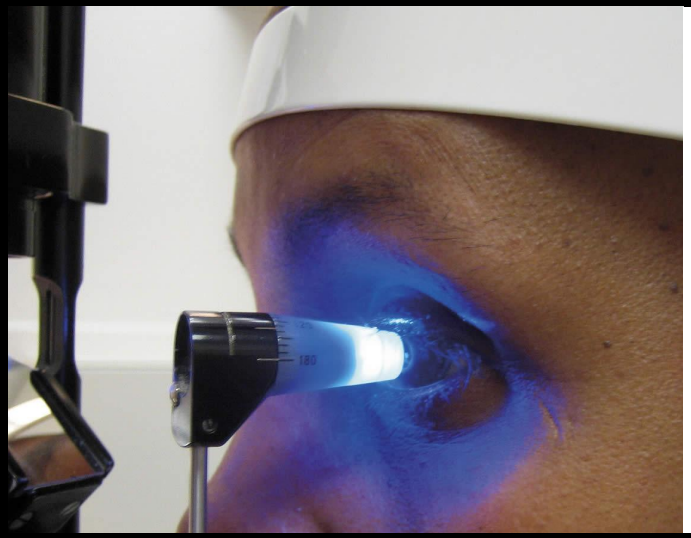
Estimation

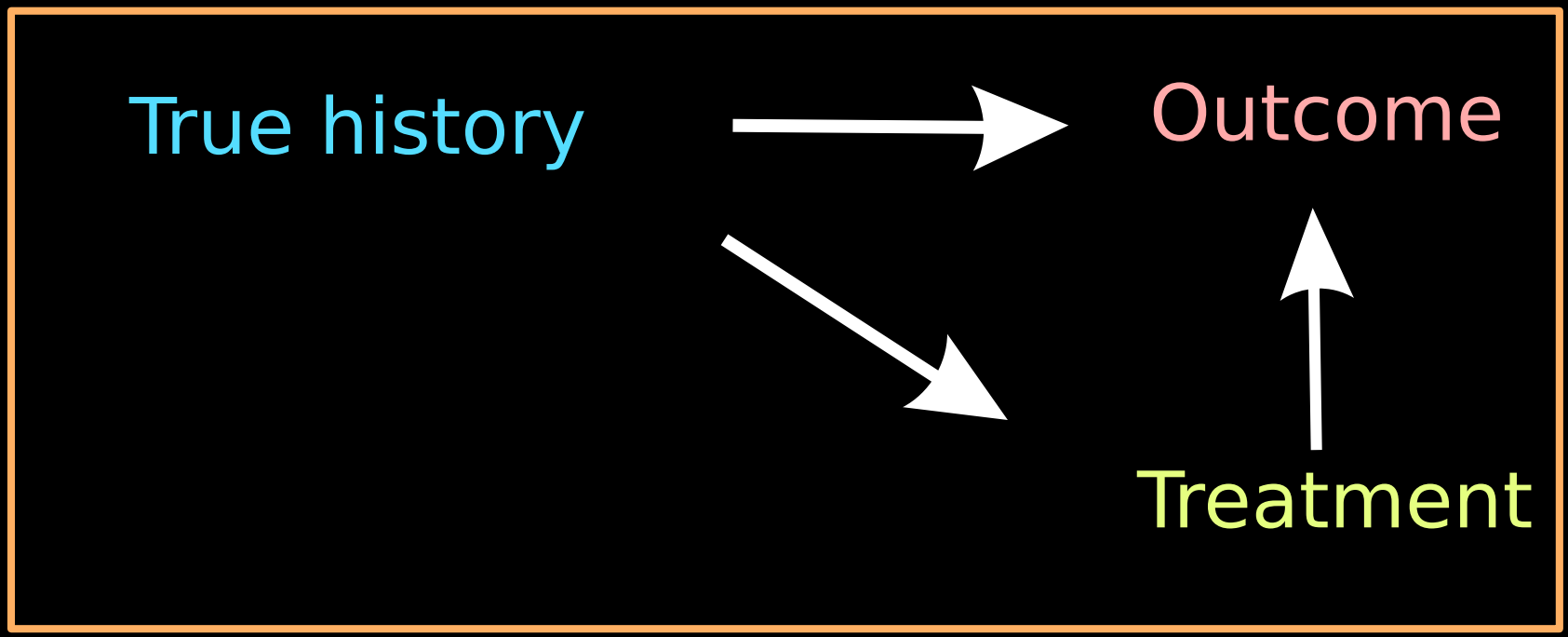


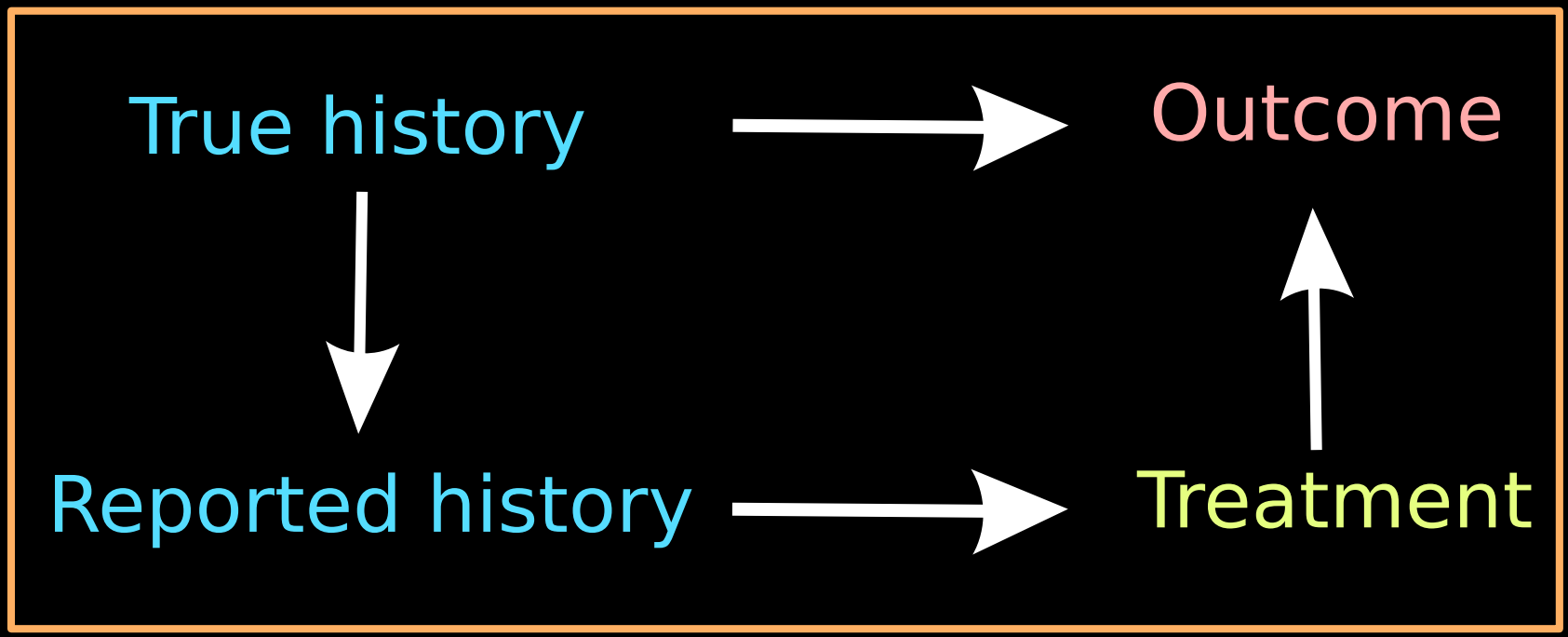
Target measurement: 'average' IOP.

Observed measurement: 1-3 in-clinic readings within < 5 minutes.

Some patients have access to more regular at-home tonometry.




True history
Outcome
Treatment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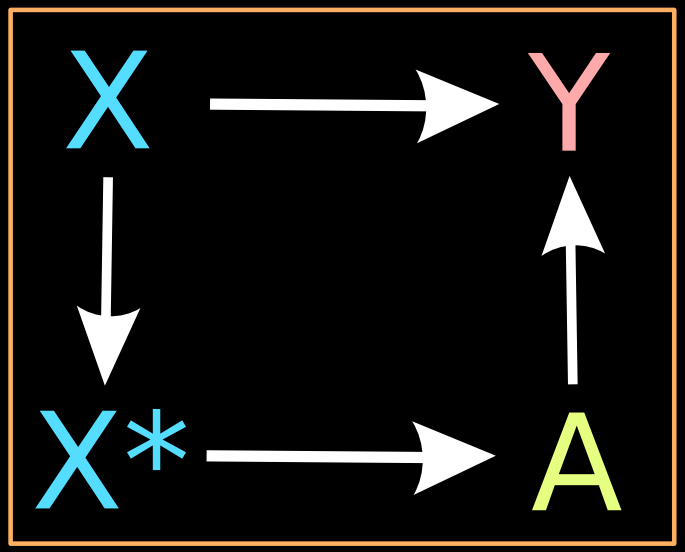
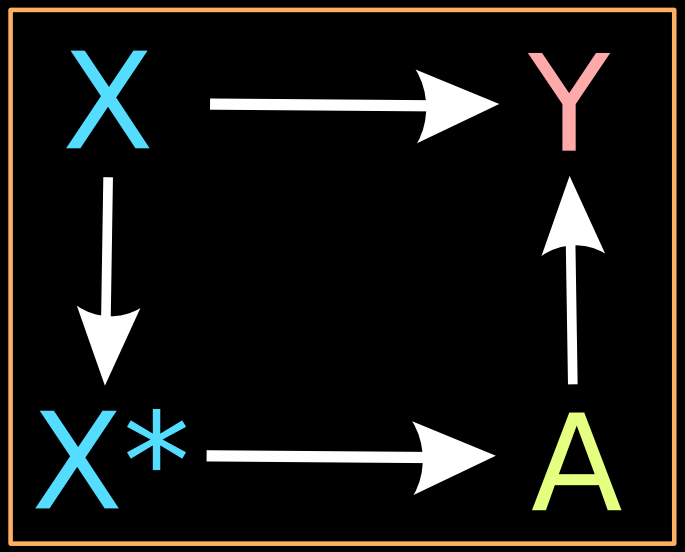


Estimation: suppose the true outcome model is:

$$E[Y|X, A; \beta, \psi] = \beta_0 + \beta_1 X + \beta_2 X^2 + A(\psi_0 + \psi_1 X)$$

If we only observe X^*. What happens? What can we do about it?



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If we only observe X^*. What happens? What can we do about it?

Solution: 'correct' for the measurement error using additional data.

Assume: classical additive measurement error:

$$\text{Observed} = \text{True} + \text{Error}$$
$$X^* = X + U$$

$U \sim N(0, \sigma_u^2)$; $Y \perp X^* | X$

Assume: replicate measurements available on at least some patients.

Patient	First IOP measurement	Second IOP measurement
1	16	15
2	20	16
3	21	17
4	16	16
5	15	18
...	...	...

Simple correction method: Regression Calibration.

Principle:

1. Use additional data to estimate $E[X|X^*, A] = X_{rc}$.
2. Replace X with X_{rc} and carry out a standard analysis.
3. Adjust the resulting standard errors to account for the estimation in step 1.

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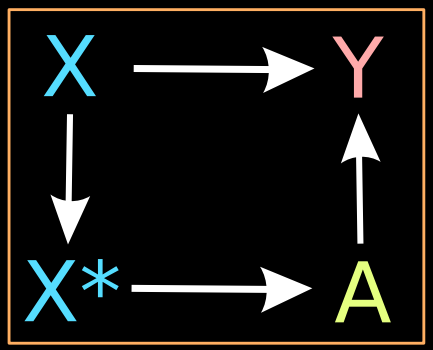

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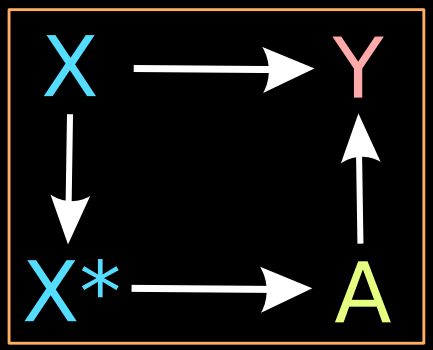

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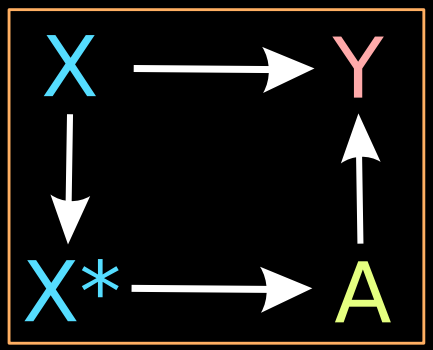

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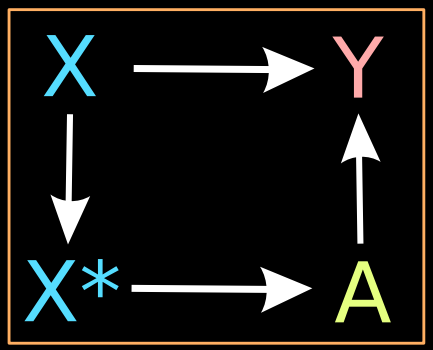
where A depends on X^*.
- Establish (approximate) covariate balance in X_{rc} by regressing A on X_{rc}.



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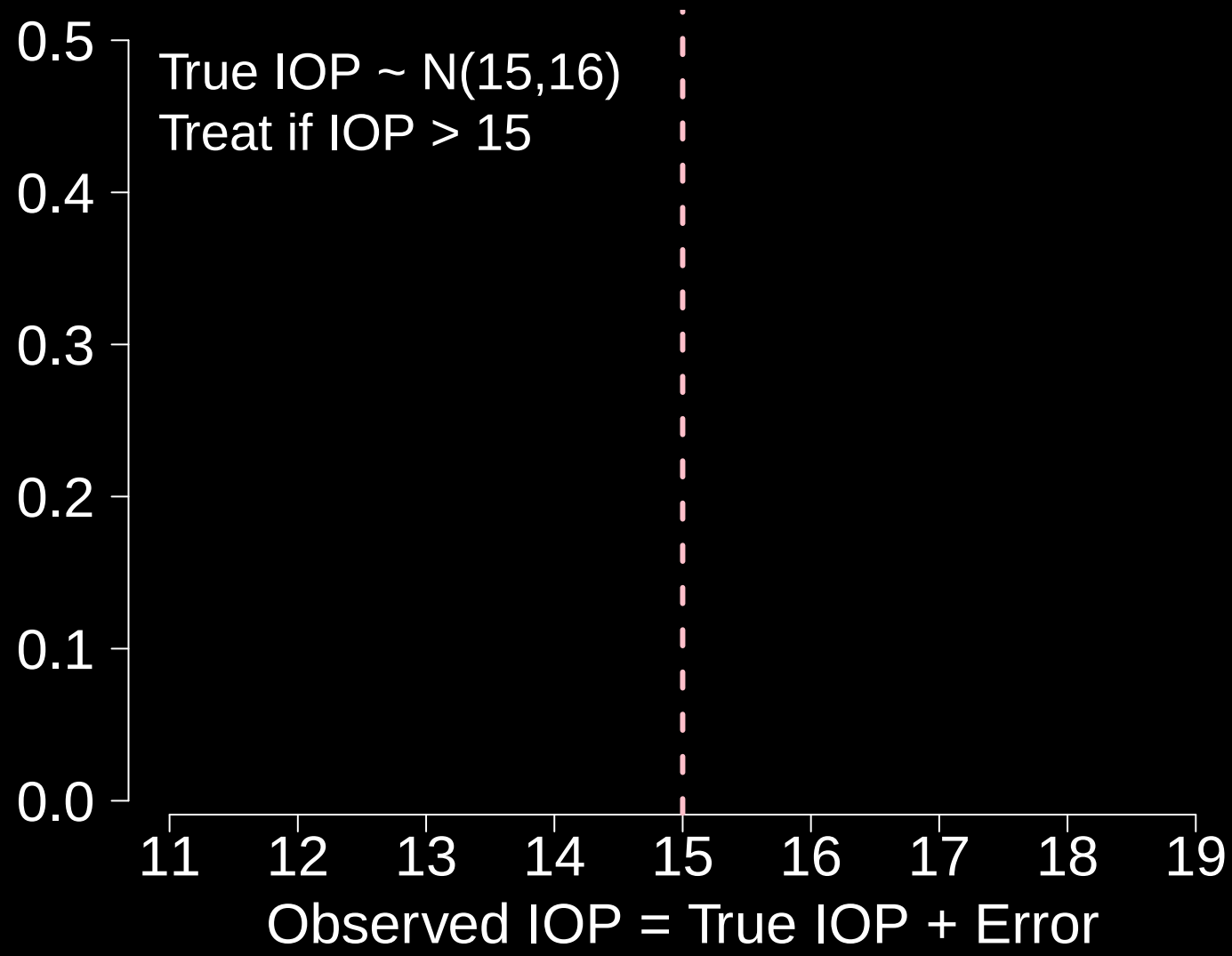
What is $P(X \leq 15 | X^* = 16)$?

In some settings, results fairly intuitive:



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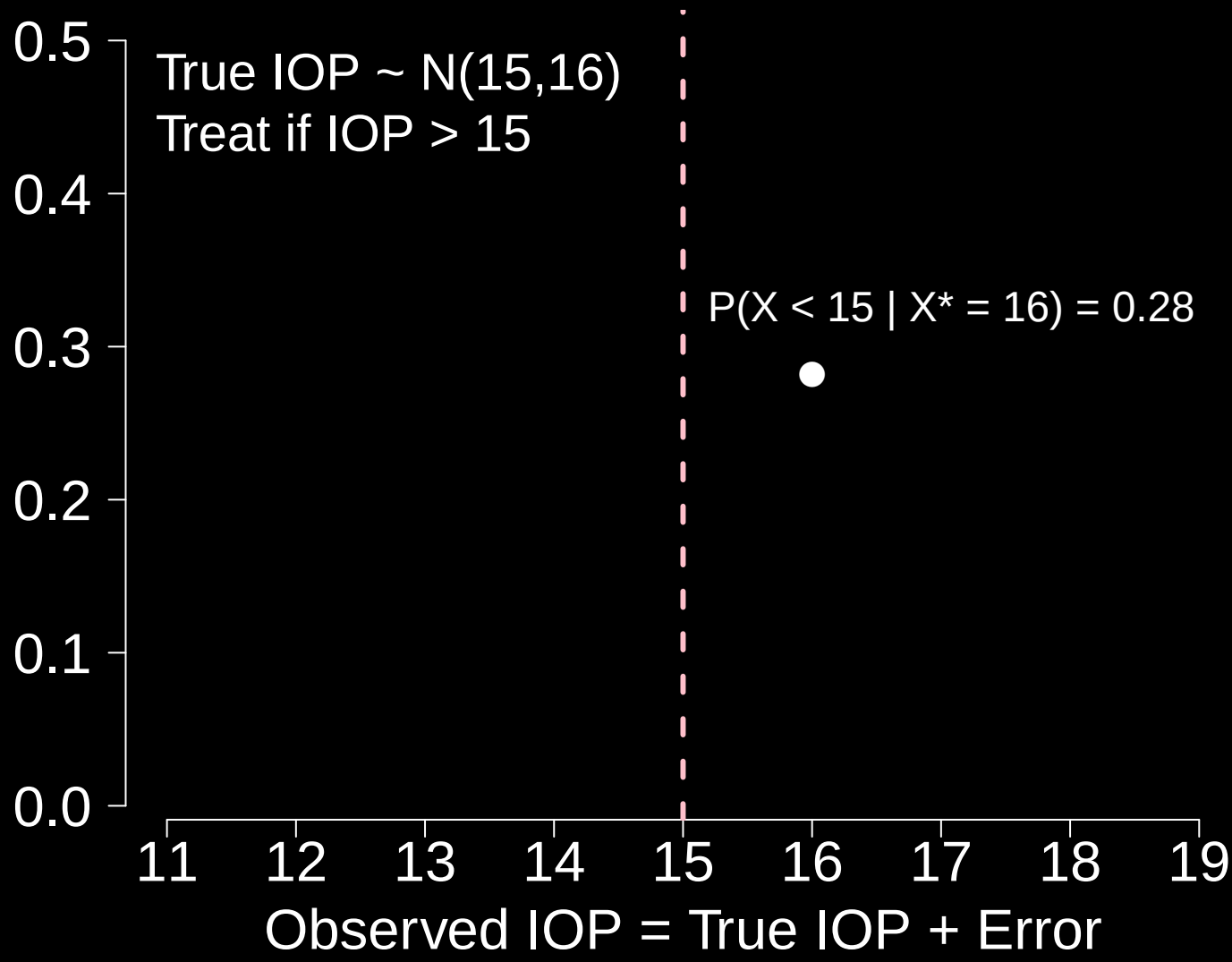

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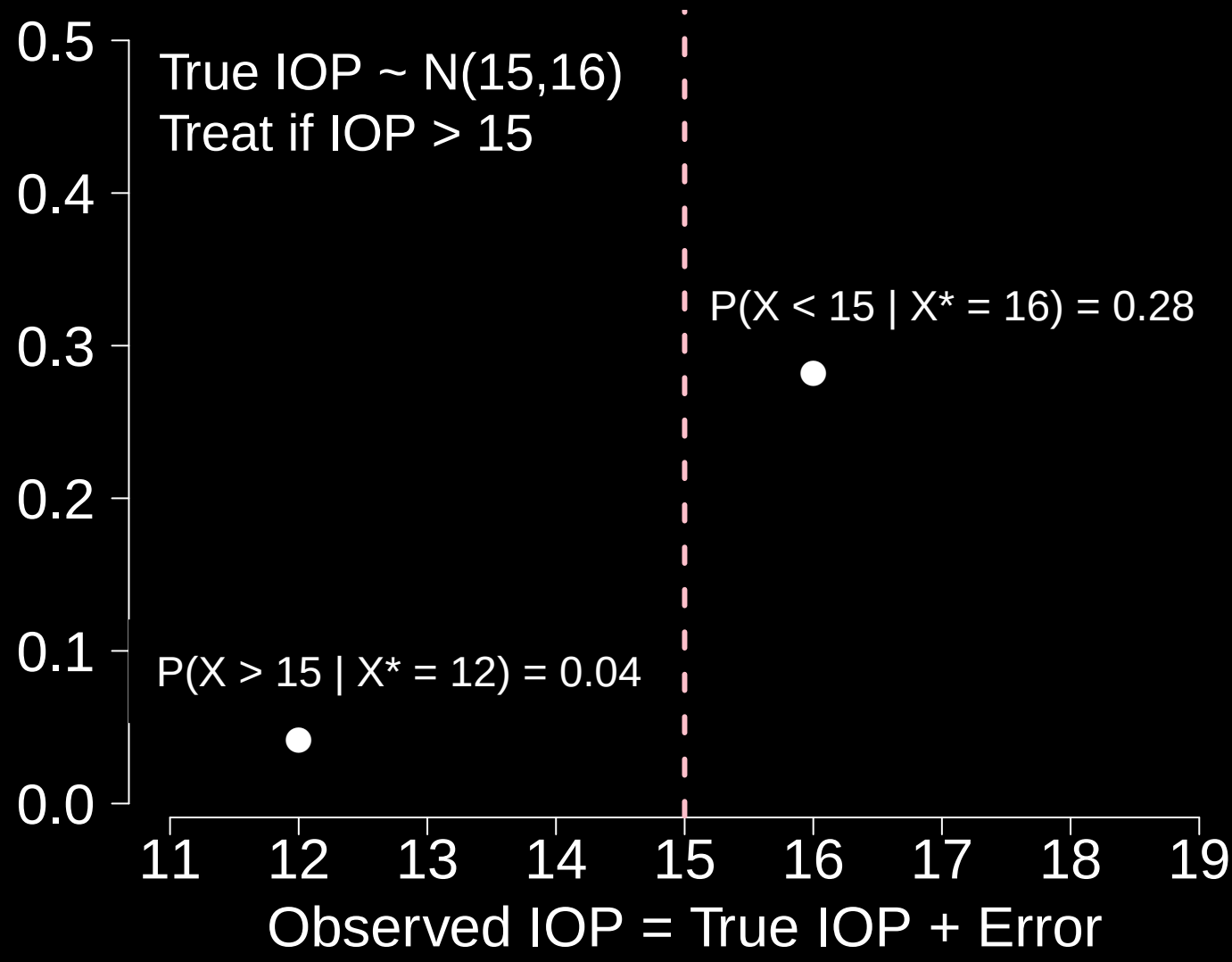

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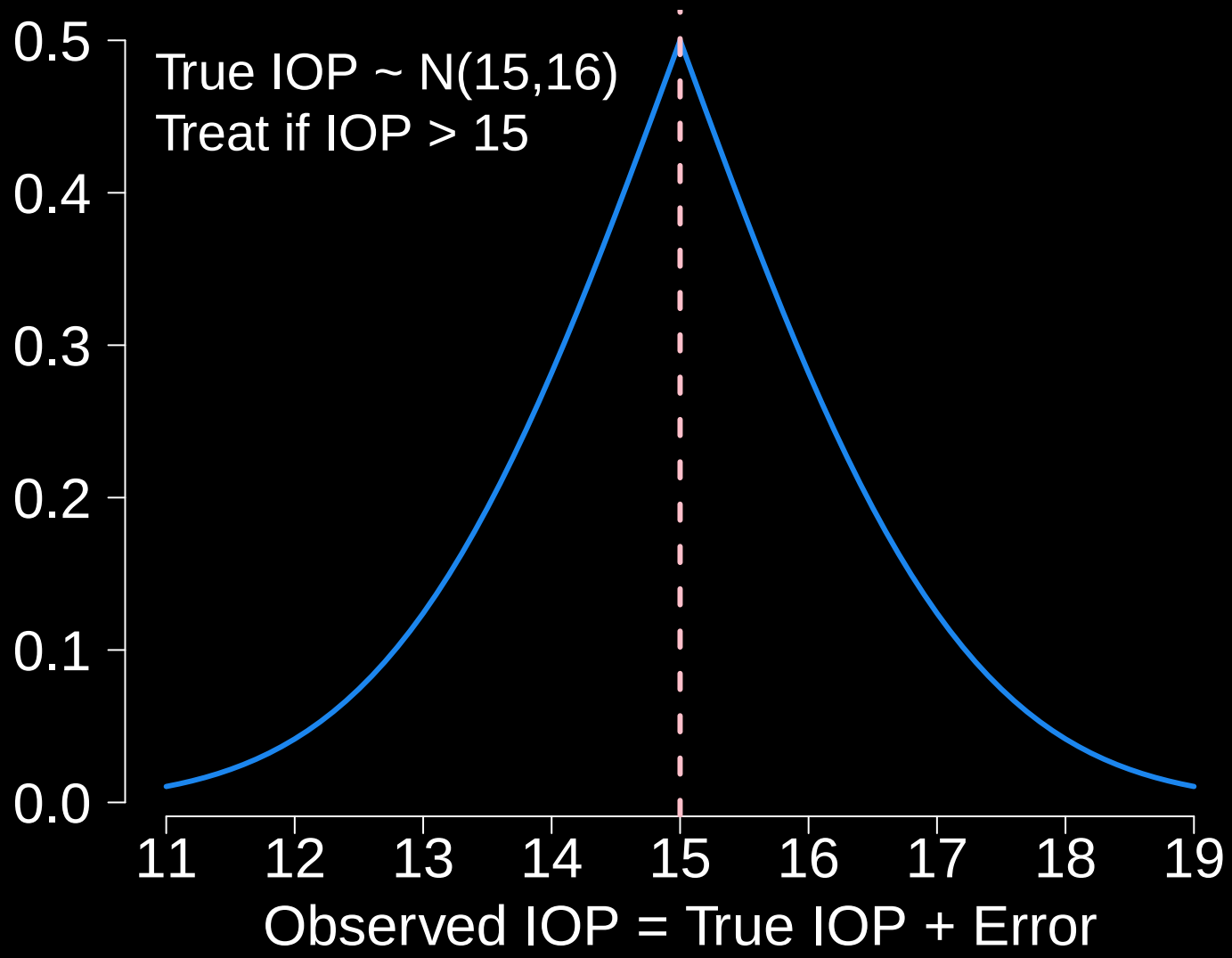

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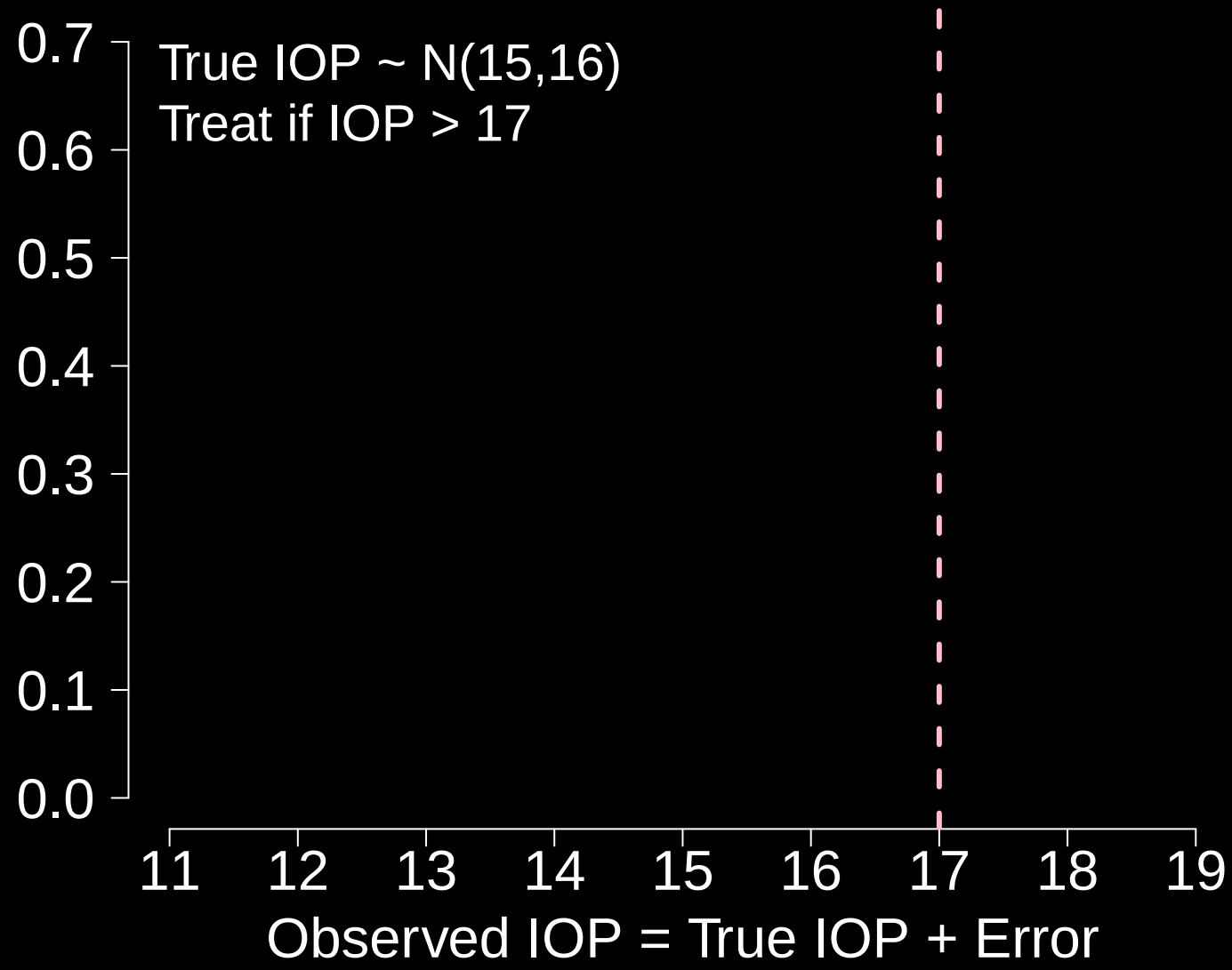

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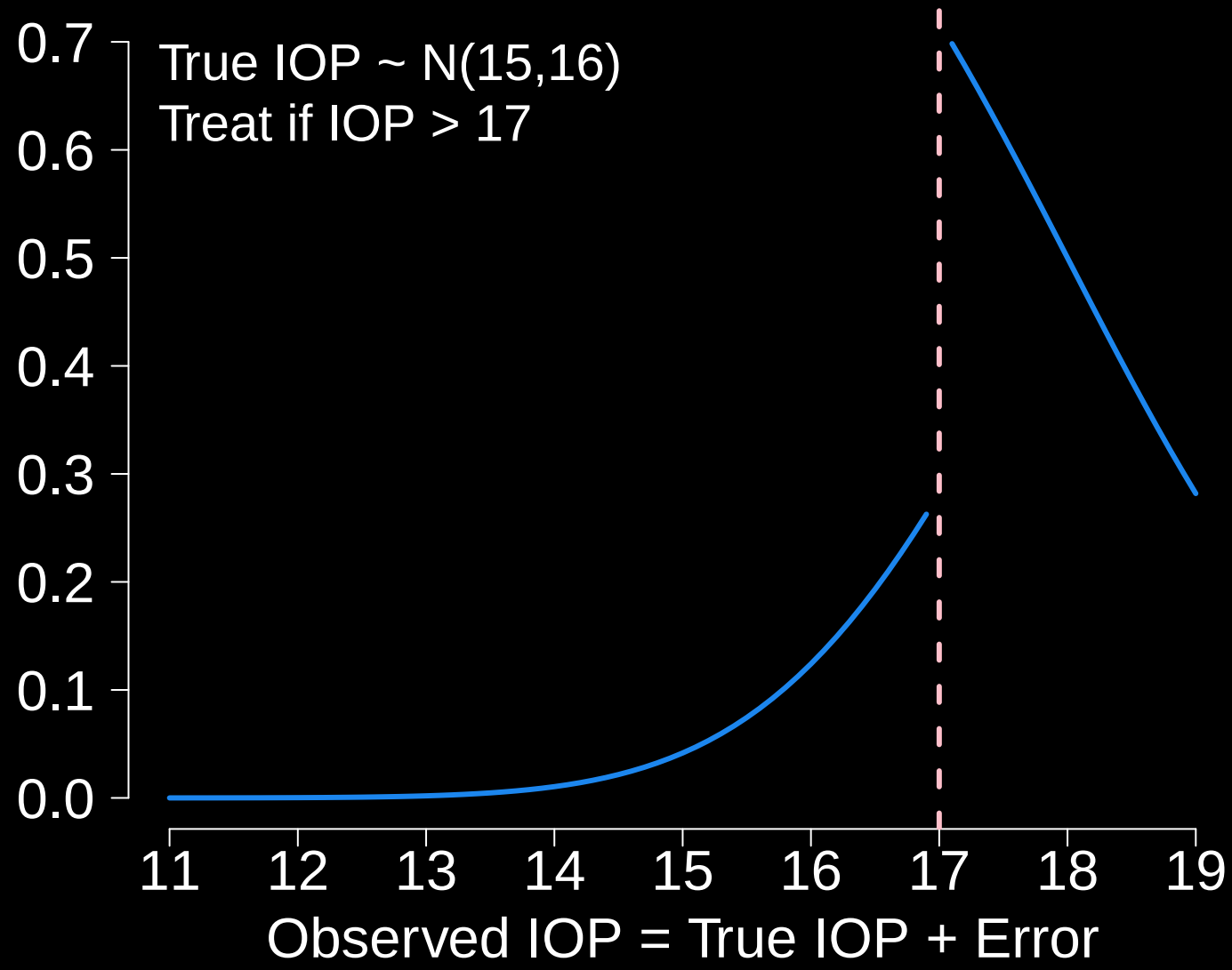

"Isn't this just a prediction problem?"

Data availability will vary by study and by variable:

Scenario	Analysis	Application
1: "We never observe the truth."	X^*	X^*

"Isn't this just a prediction problem?"

What if error-free data are possible, but expensive?

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2: "Past data are error-prone, but future data may not be."	X^*	X
3: "Past data are not error-prone, but future data may be."	X	X^*

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Only Scenario 4 is well-studied.

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Correcting for measurement error is at worst competitive with an analysis that ignores it completely.

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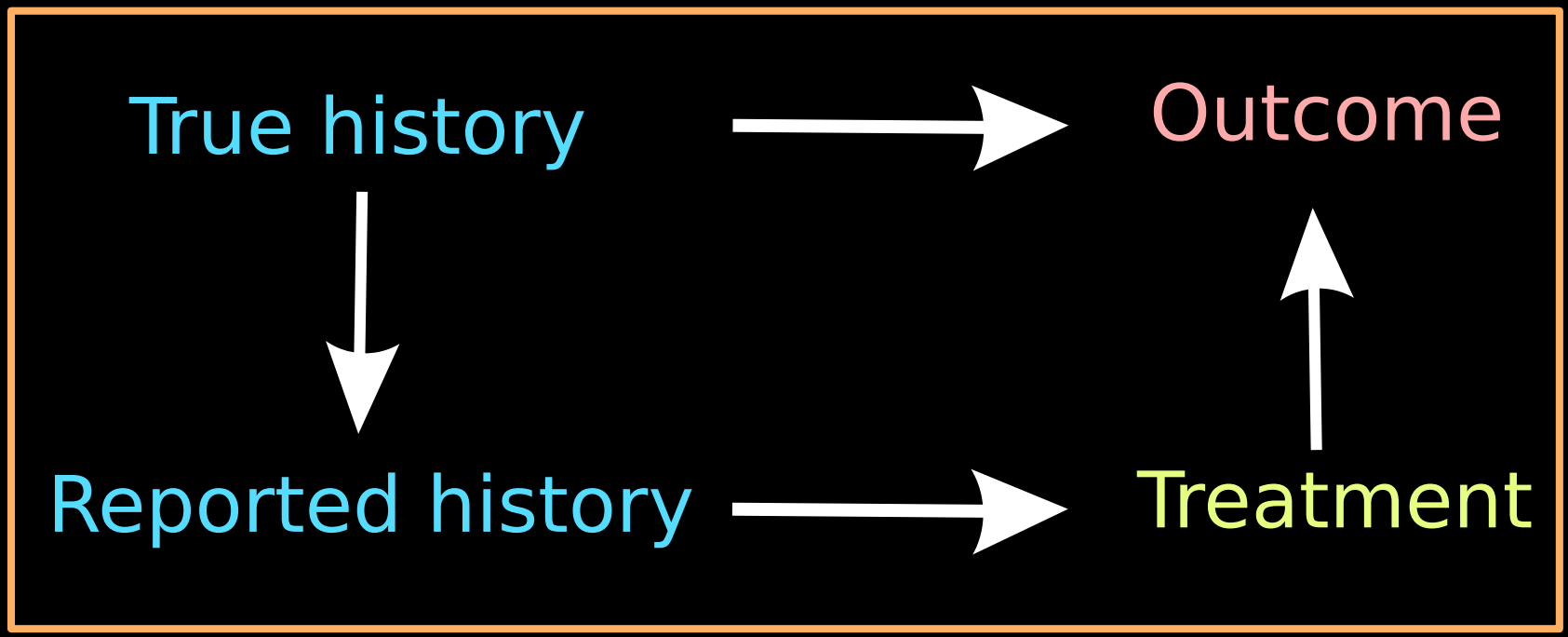
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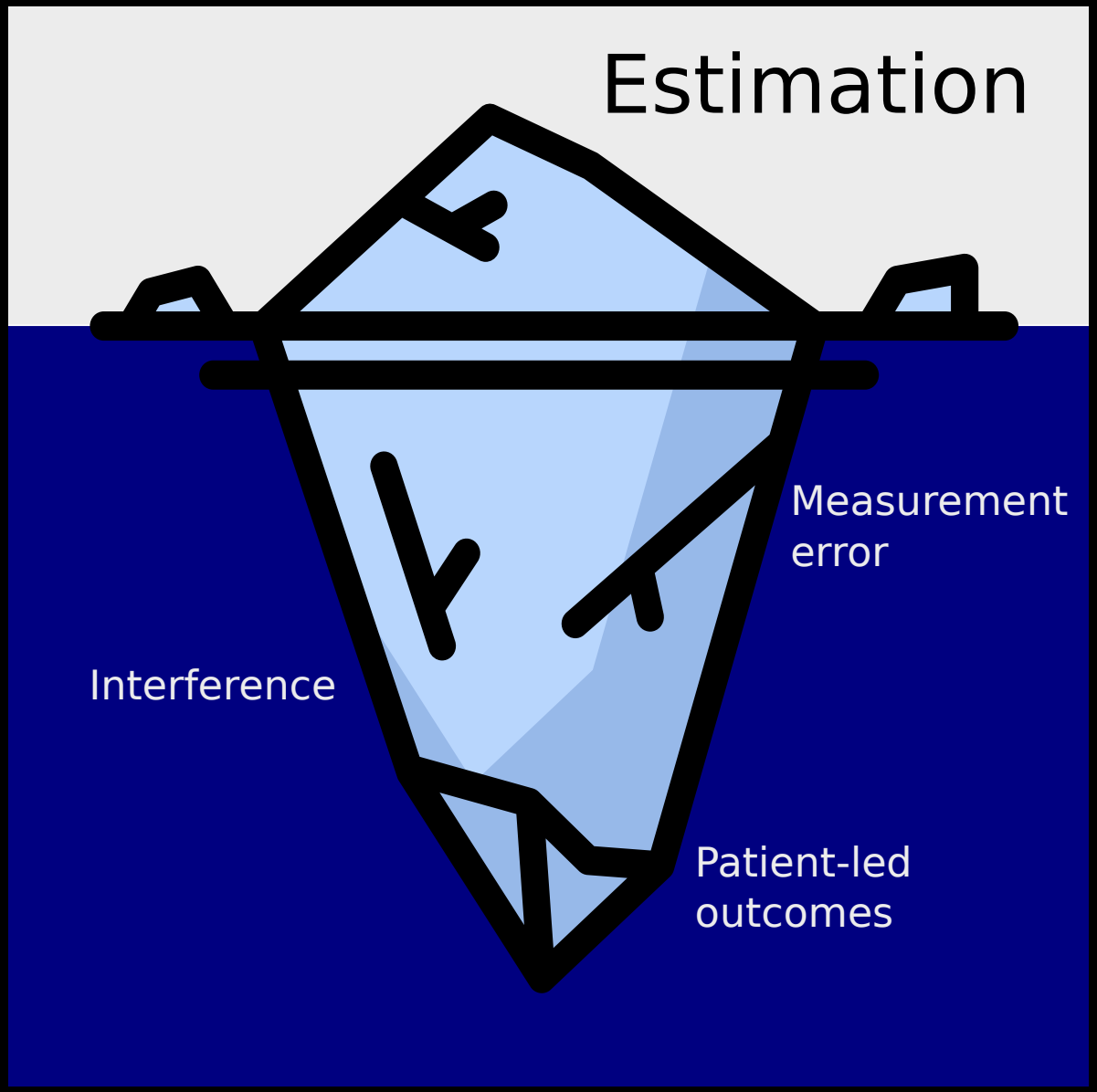
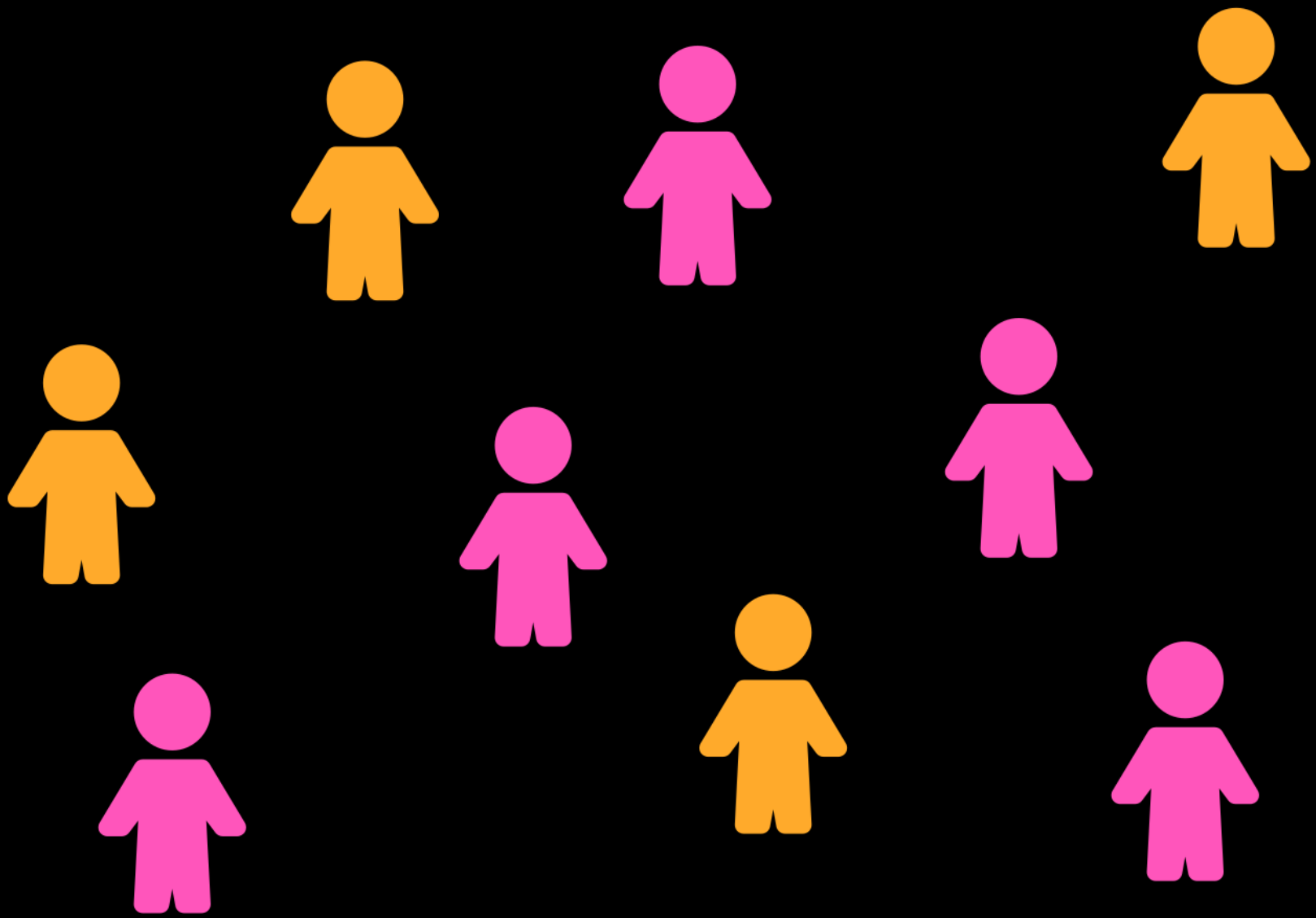

Estimation
Measurement error
Interference
Patient-led outcomes

No man is an Island, entire of itself; every man is a piece of the Continent, a part of the main; if a clod be washed away by the sea, Europe is the less, as well as if a promontory were, as well as if a manor of thy friends or of thine own were; any man's death diminishes me, because I am involved in Mankind; And therefore never send to know for whom the bell tolls; It tolls for thee.

(John Donne)

Interference: another patient's treatment doesn't affect my outcome.

Common assumption: no interference (or ‘spillover’):



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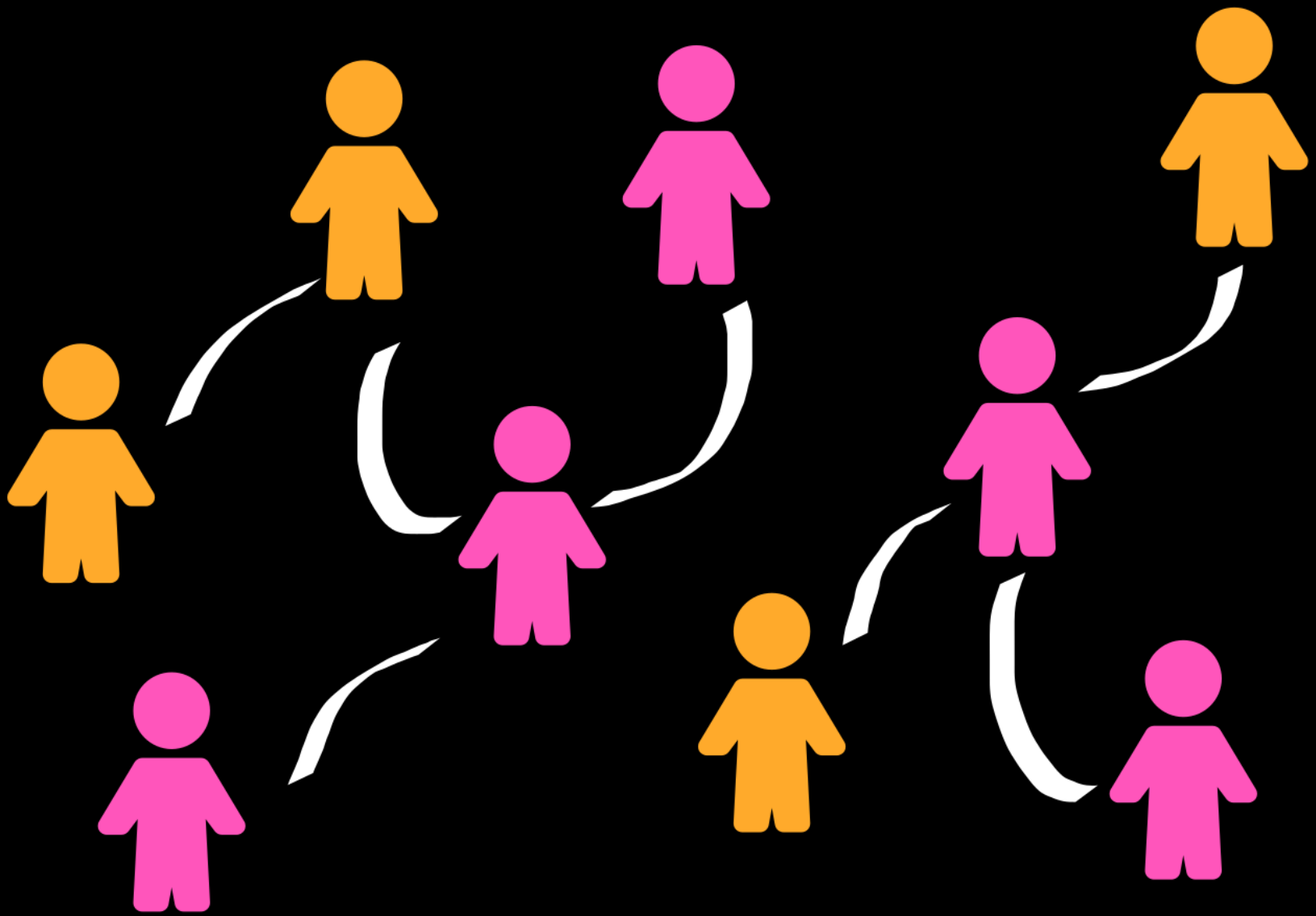
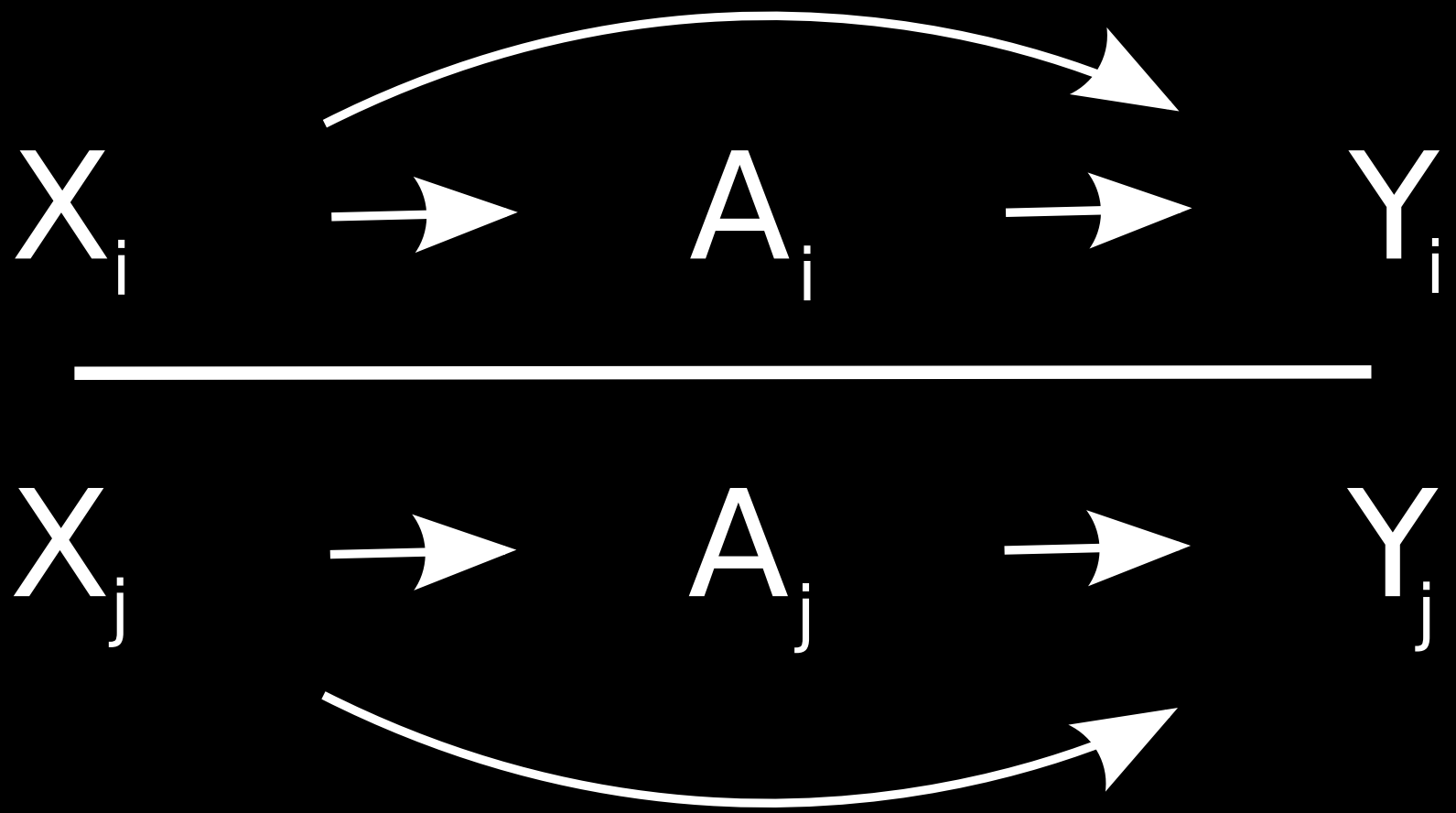
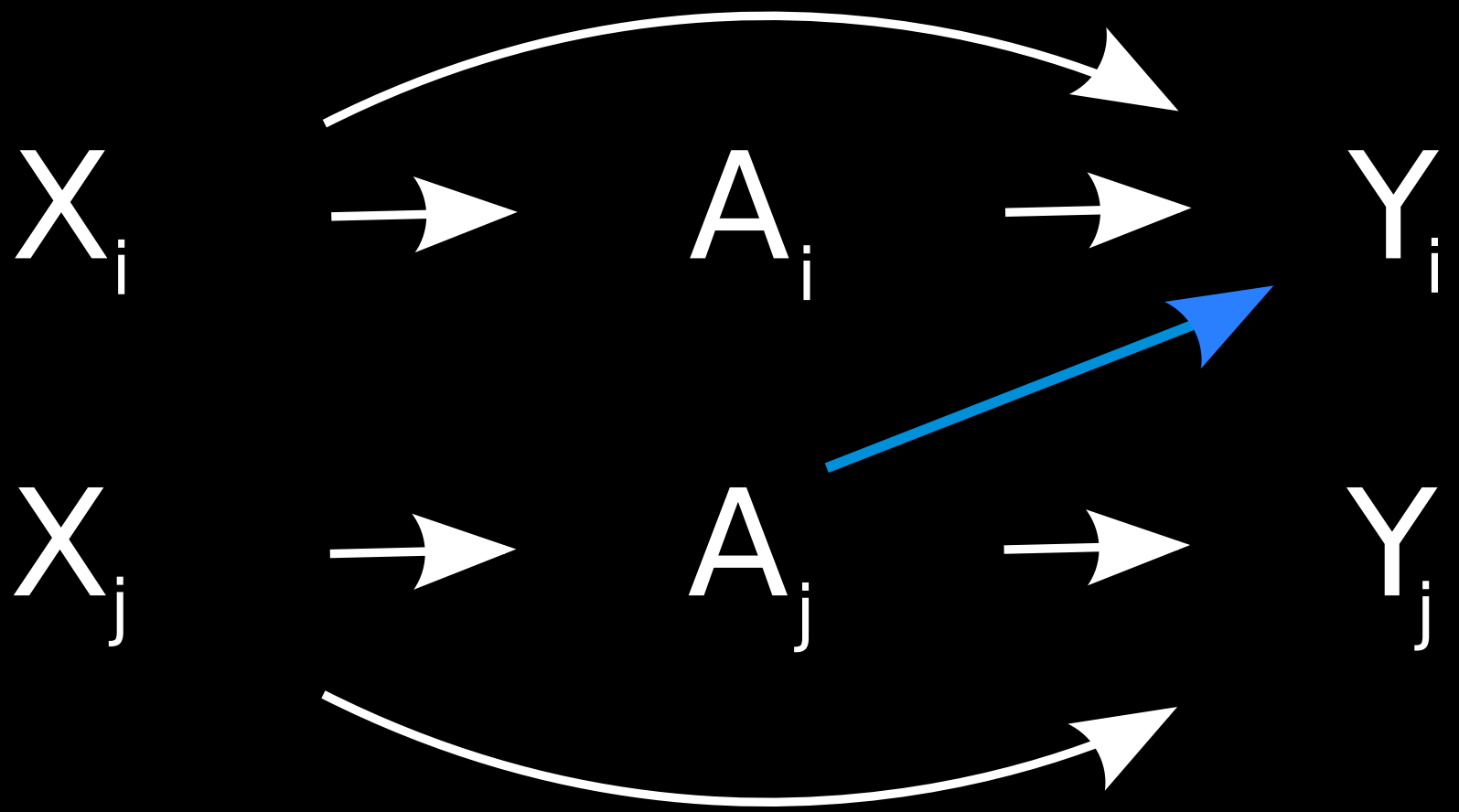



X_i
A_i
Y_i
X_j
A_j
Y_j


X_i
A_i
Y_i
X_j
A_j
Y_j

Identifying the best treatment regime

- No interference:

$$\underbrace{E[Y|X, A]}_{\text{Expected outcome (to be maximized)}}$$

- We might propose the following model

$$E[Y_i|X_i, A_i; \beta, \psi] = \beta_0 + \beta_1 X_i + A_i(\psi_0 + \psi_1 X_i)$$

"Treat $(A_i = 1)$ if $\psi_0 + \psi_1 X_i > 0$"

With interference: two ideas:

- (1) Add interaction terms:
  $E[Y|X, A; \beta, \psi] = \beta_0 + \beta_1 X_i + \beta_2 X_j + A_i(\psi_0 + \psi_1 X_i + \psi_2 A_j)$
- Then dWOLS proceeds as usual: "Treat ($A_i = 1$) if $\psi_0 + \psi_1 X_i + \psi_2 A_j > 0$"

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- Then dWOLS proceeds as usual: "Treat ($A_i = 1$) if $\psi_0 + \psi_1 X_i + \psi_2 A_j > 0$"
- (2) Use 'network propensity weights': for each individual i, apply weights based on the probability their neighbour is treated.

Estimation is only half the battle.

Example: Alex and Blake share a household. The following table summarizes the ranking of the four possible combinations of a binary treatment:

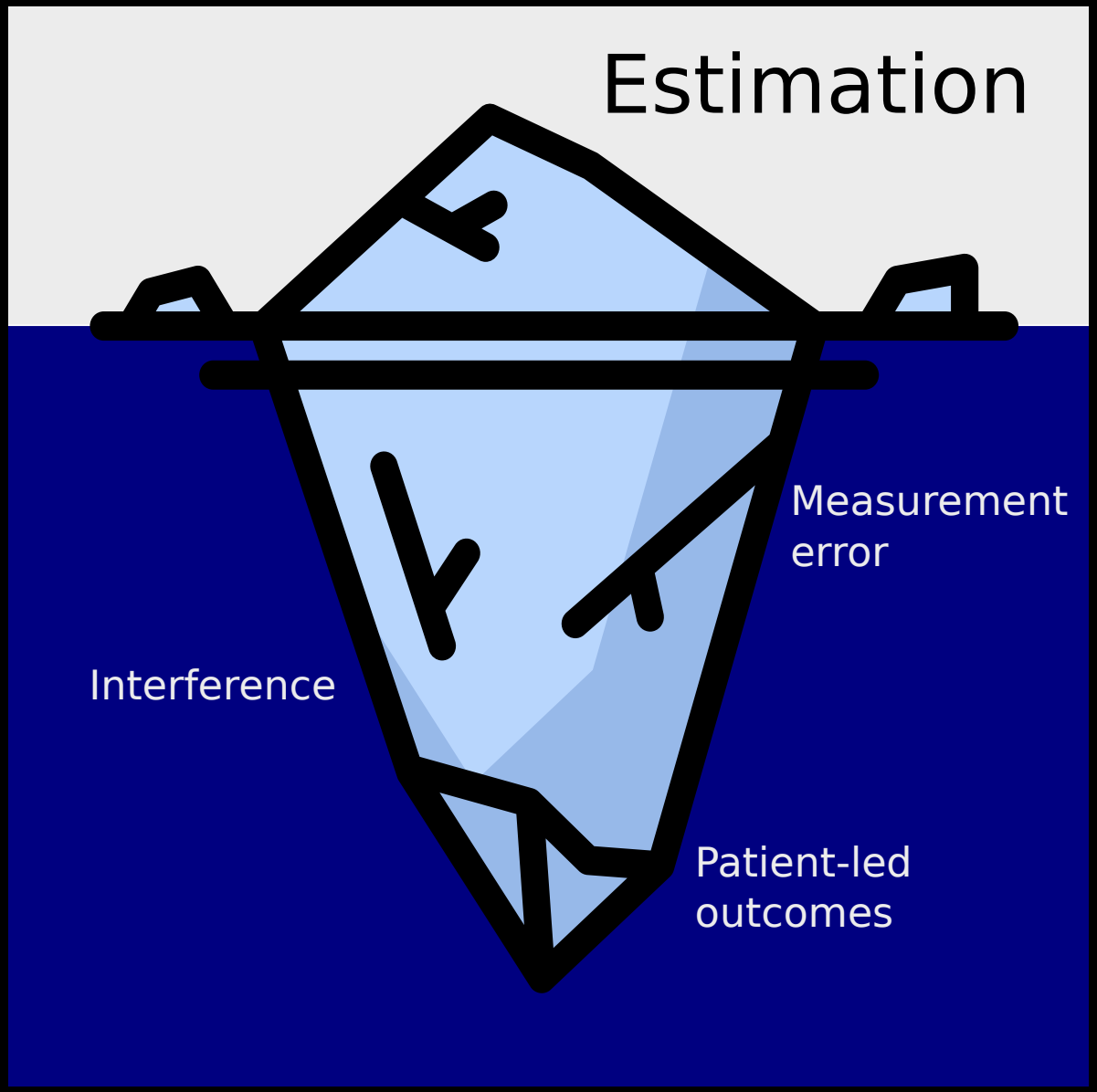
Rank	Alex	Blake
1	o	-
2	-	o
3	o	o
4	-	-

Treatment: o
No treatment: -

- In what order do we prescribe treatments to patients?
- What if resources are limited?
- How do we balance the needs of the individual against the needs of the population?

Rank	Alex	Blake
1	o	-
2	-	o
3	o	o
4	-	-

Treatment: o
No treatment: -


Estimation
Measurement error
Interference
Patient-led outcomes

Patient-led outcomes

Recall the treatment options for glaucoma:

- Lifestyle changes.
- Eye drops (numerous options).
- Surgery.

Treatments have various side effects, including:

- ‘Minor’: eyelash growth, iris discoloration.
- ‘Major’: additional vision loss.

Prior research tells us the probability of side effects, and the 'average' IOP decrease following each treatment.

Suppose you had the swallowing predicted effects:

Treatment	Iris discoloration	Eyelash growth	Vision loss	E[IOP change]
Drop A	80%	40%	1%	2
Drop B	90%	30%	1%	2

Which treatment do you choose? What influences your decision?

How do we elicit this information from patients?

Prior research tells us the probability of side effects, and the 'average' IOP decrease following each treatment.

Suppose you had the swallowing predicted effects:

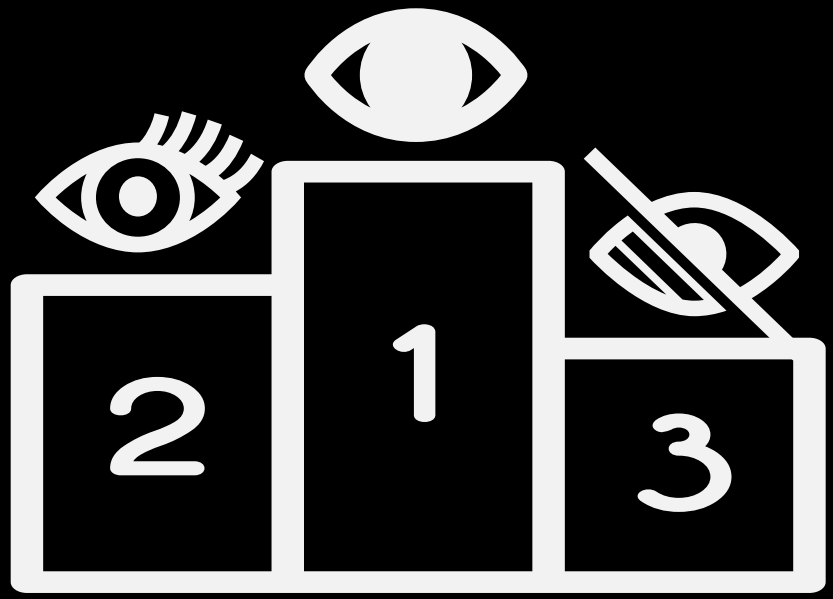
Treatment	Iris discoloration	Eyelash growth	Vision loss	E[IOP change]
Drop A	80%	40%	1%	2
Drop B	90%	30%	1%	2
Surgery	1%	0%	5%	3

Which treatment do you choose? What influences your decision?

How do we elicit this information from patients?

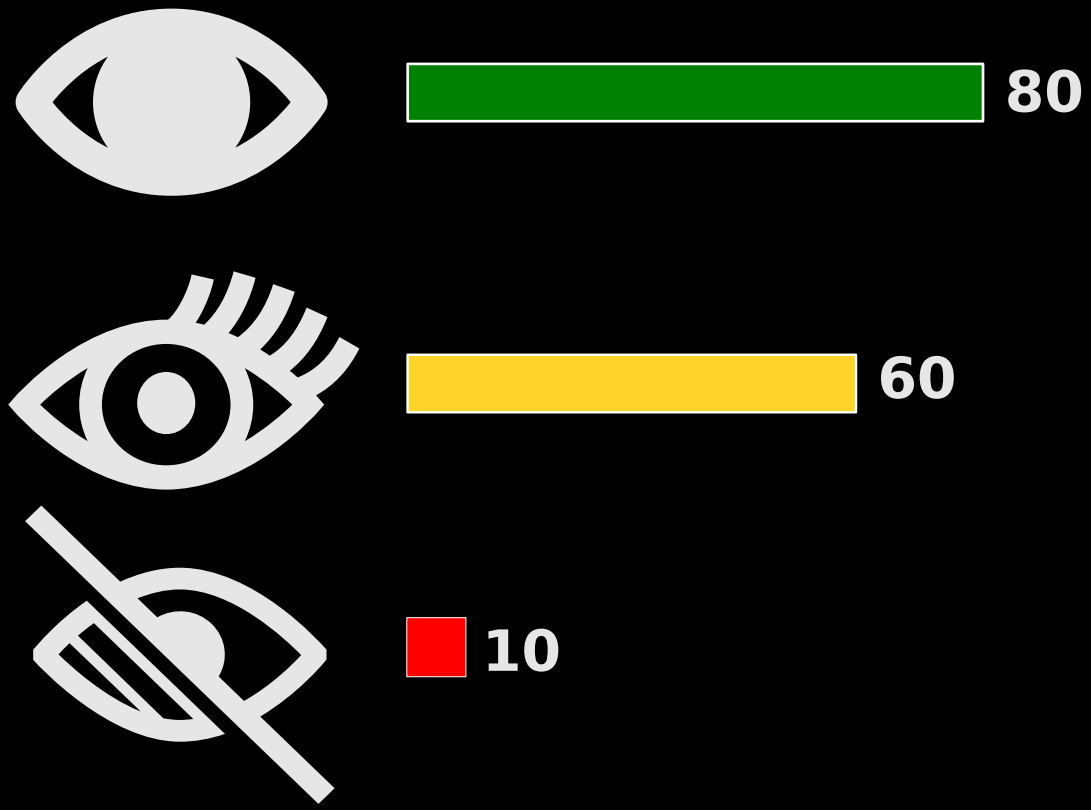
Patients can provide information to varying degrees:

- Ranking: "I would prefer iris discoloration to eyelash growth, and prefer both to additional vision loss."



Patients can provide information to varying degrees:

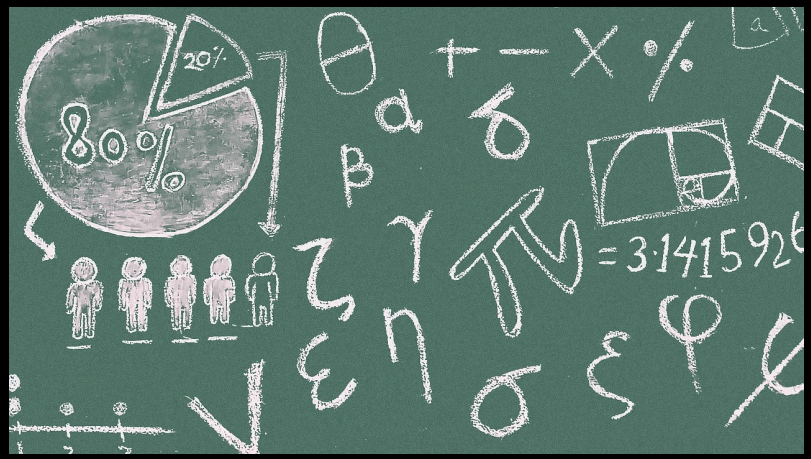
- Weighting: “I would slightly prefer iris discoloration to eyelash growth, and greatly prefer both to vision loss.”



Patient-led outcomes

Patients can provide information to varying degrees:

- Utility functions: "I want to maximize this complicated function of all the possible outcomes."



Patient-led outcomes

Patients can provide information to varying degrees:

- Ranking: "I would prefer iris discoloration to eyelash growth, and prefer both to additional vision loss."
- Weighting: "I would prefer iris discoloration twice as much as eyelash growth, and ten times as much as additional vision loss."
- Utility functions: "I want to maximize this function of the possible outcomes."

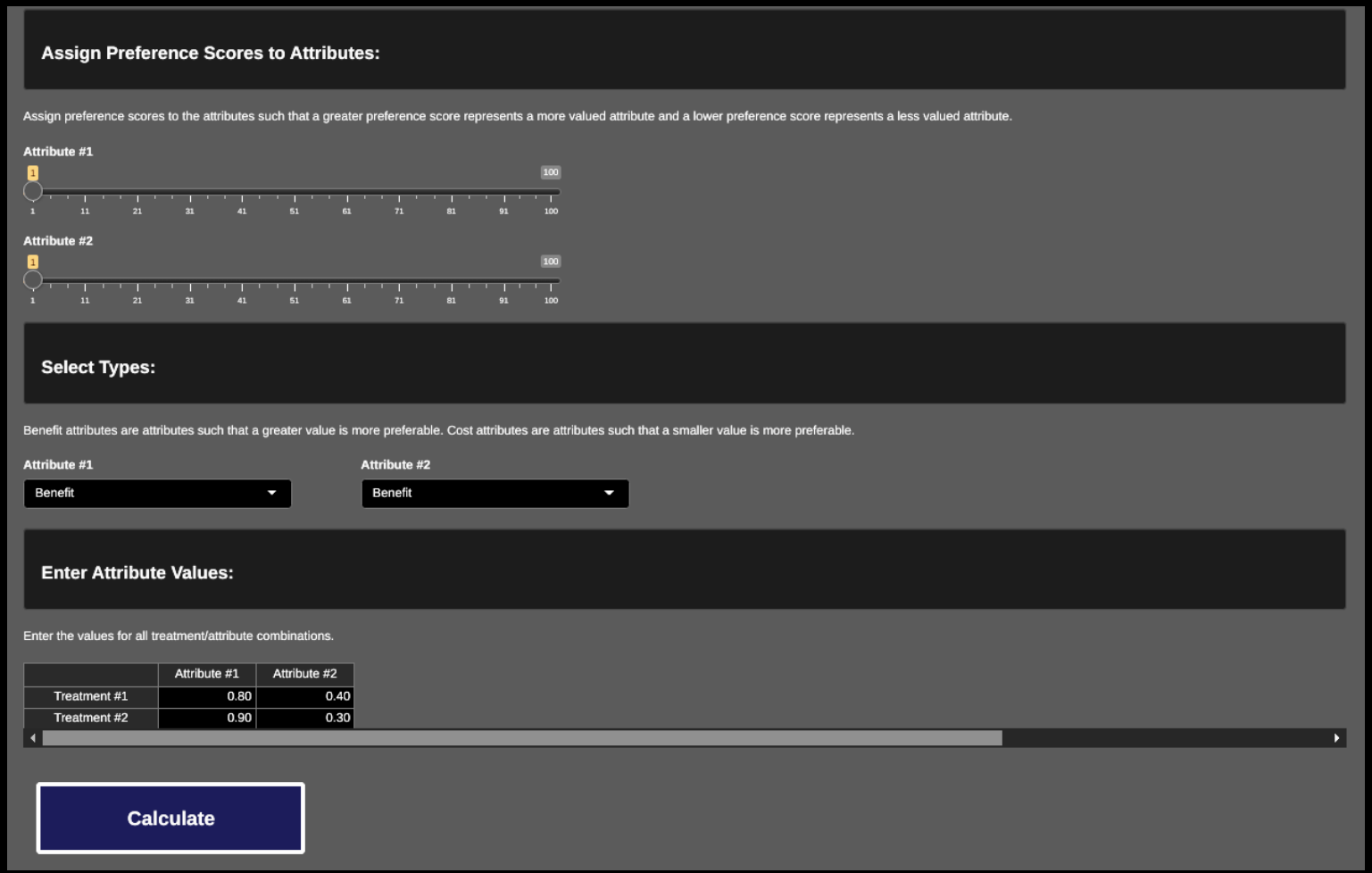
Methods from *multi-attribute decision making* can be applied to recommend treatment options.

We can also consider non-probabilistic properties of treatments, such as their cost.

Treatment	Cost	Iris discoloration	Eyelash growth	Vision loss	IOP change
Drop A	$	80%	40%	1%	2
Drop B	$$	90%	30%	1%	2
Surgery	$$$	1%	0%	5%	3

Such methods can be implemented via web-based applications:

`https://shiny.math.uwaterloo.ca/sas/mwallace/mapp/madm/`



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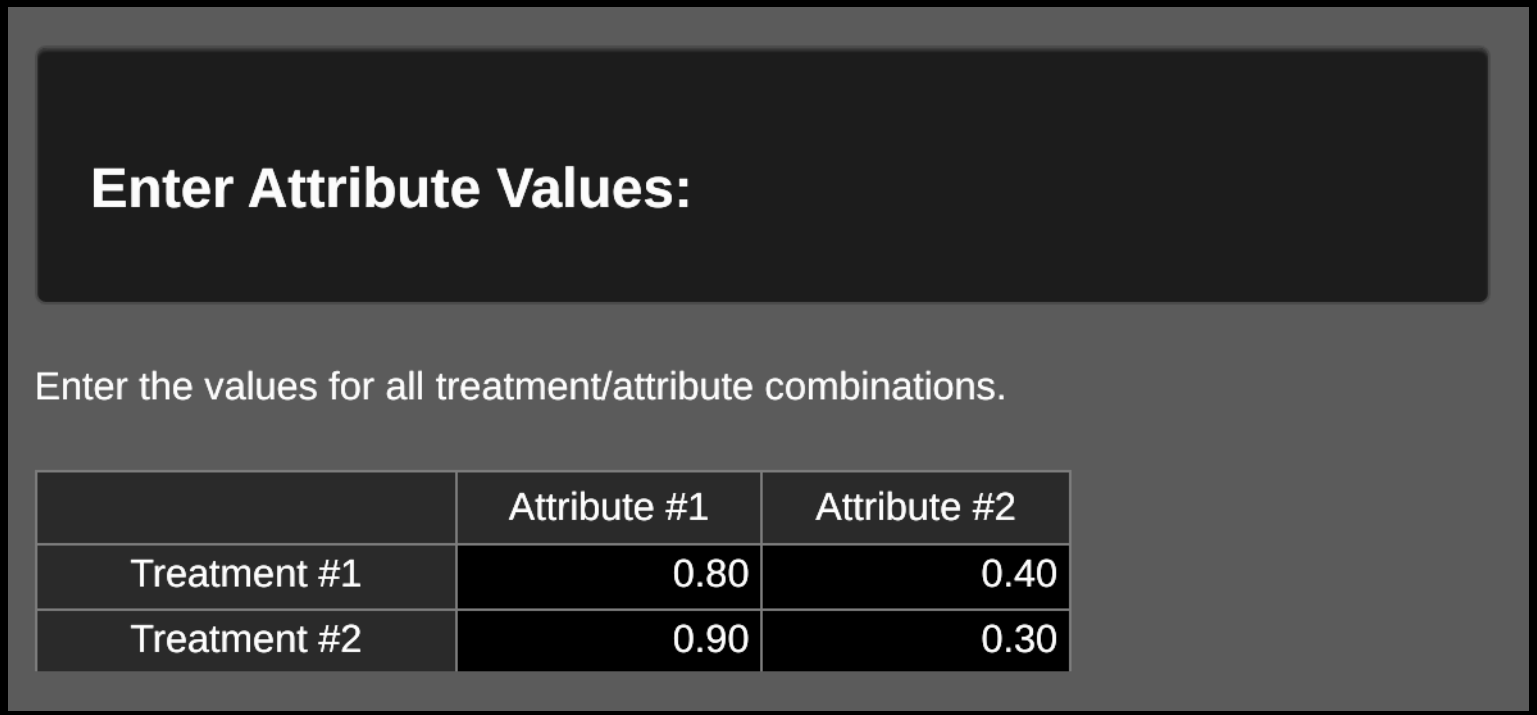

Enter Attribute Values:

Enter the values for all treatment/attribute combinations.

	Attribute #1	Attribute #2
Treatment #1	0.80	0.40
Treatment #2	0.90	0.30

Such methods can be implemented via web-based applications:

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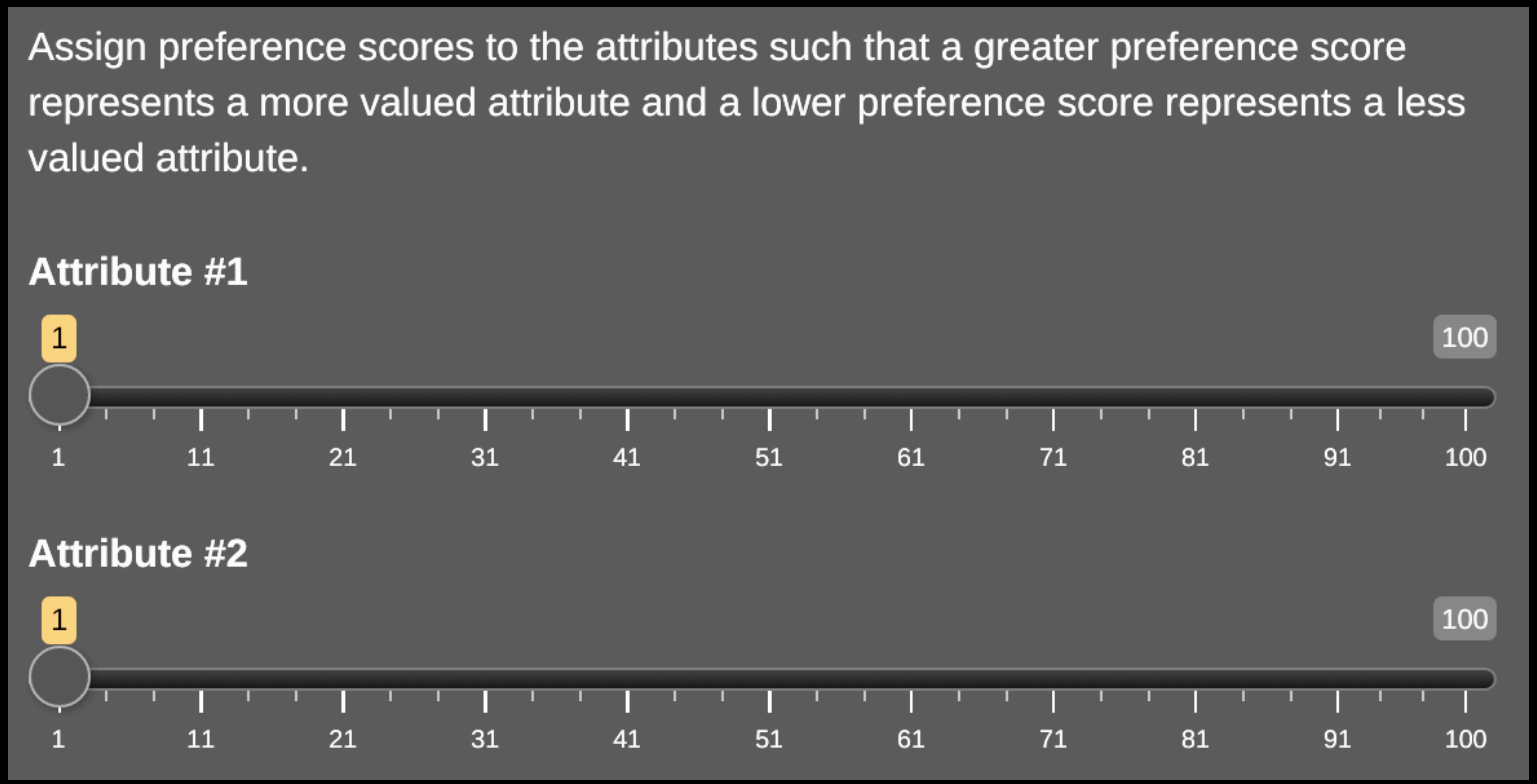
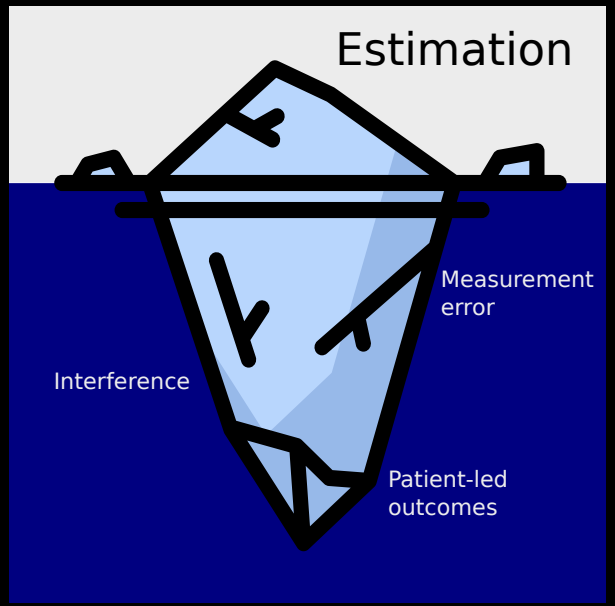


So where are we now?

- DTRs an important tool in precision medicine.
- Lots of estimation methods available, ease of implementation, and avoiding 'black boxes' a big challenge.
- Beyond estimation: lots of interesting, open, practical problems to work on.
  - Measurement error.
  - Interference.
  - Patient-led outcomes.
  - Model assessment.
  - Treatment quality.
  - etc. etc. etc.



Acknowledgments

Dylan Spicker: Measurement Error

Cong Jiang: Interference and Networks

Grace Tompkins: Patient-Led Outcomes

Marzieh Rizi: Interference and Networks

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- **dWOLS**: M. P. Wallace and E. E. M. Moodie (2015). Doubly-robust dynamic treatment regimen estimation via weighted least squares. *Biometrics* **71(3)** 636-644.

- **Precision Medicine and Measurement Error**: D. Spicker and M. P. Wallace (2020). Measurement error and precision medicine: error-prone tailoring covariates in dynamic treatment regimes. *Statistics in Medicine* **39(26)** https://doi.org/10.1002/sim.8690

- **Precision Medicine and Interference**: C. Jiang, M. E. Thompson, M. P. Wallace (2022). Dynamic treatment regimes with interference. *Canadian Journal of Statistics. In press*

✉ michael.wallace@uwaterloo.ca @statacake

mpwallace.github.io