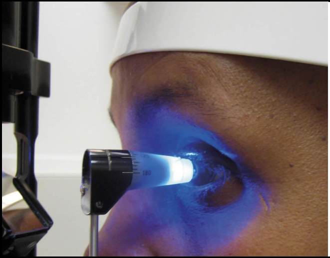
Beyond Estimation: Next Steps for Precision Medicine

Michael Wallace, University of Waterloo

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 (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?

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
...	...	...	...

We typically work with data from observational studies.

Patient	Observed IOP X	Drop added? A	IOP at 3 months Y
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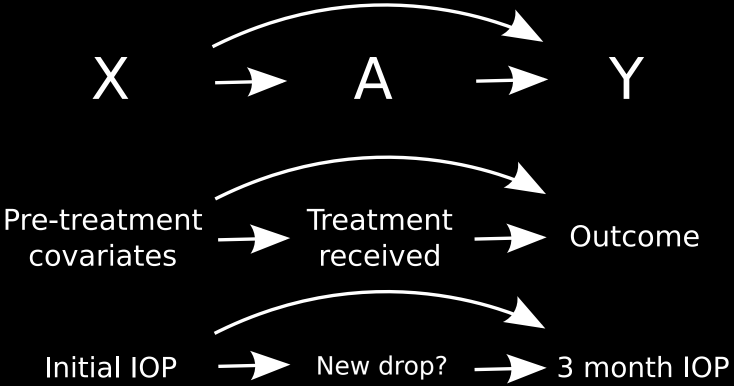
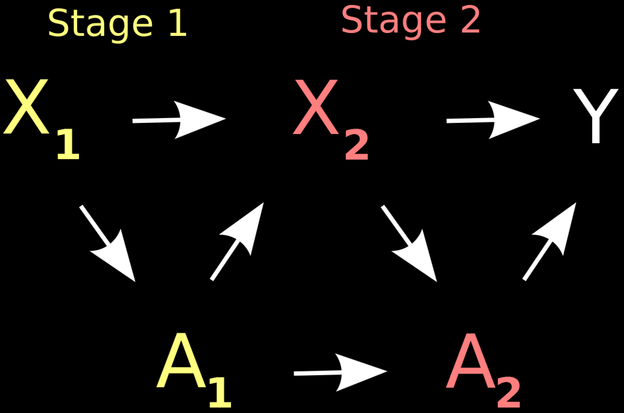


DTR: treatment A^{opt} that optimizes $E[Y|X, A^{opt}]$



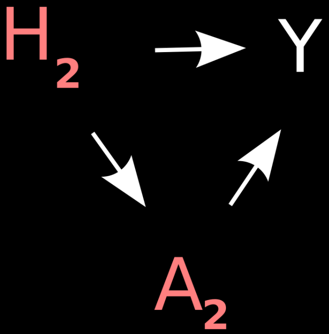
More often,
we work
in stages.

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

Identifying the best treatment regime: multi-stage

$$H_2 = (X_1, A_1, X_2)$$

Stage 2



Single Stage Analysis

$$\begin{tikzcd} X \arrow[r] \arrow[rr, bend left] & A \arrow[r] & Y \end{tikzcd}$$

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1	16	No	15
2	20	Yes	16
3	21	Yes	17
4	16	Yes	16
5	15	No	18
...	...	...	...

Lots of methods available:

Q-learning

MSMs

G-estimation

IPTW

dWOLS

OWL

A-learning

etc...

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- We might propose the following model

$$E[Y|X, A; \beta, \psi] = \beta_0 + \beta_1 \text{IOP} + A(\psi_0 + \psi_1 \text{IOP})$$

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

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- More generally, split outcome into two components:

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

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

- Suppose the true outcome model is:

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- But we propose:

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- Three models to specify:
  1. Blip model: $\gamma(X, A; \psi)$.
  2. Treatment-free model: $G(X; \beta)$.
  3. Treatment model: $P(A = 1|X; \alpha)$.

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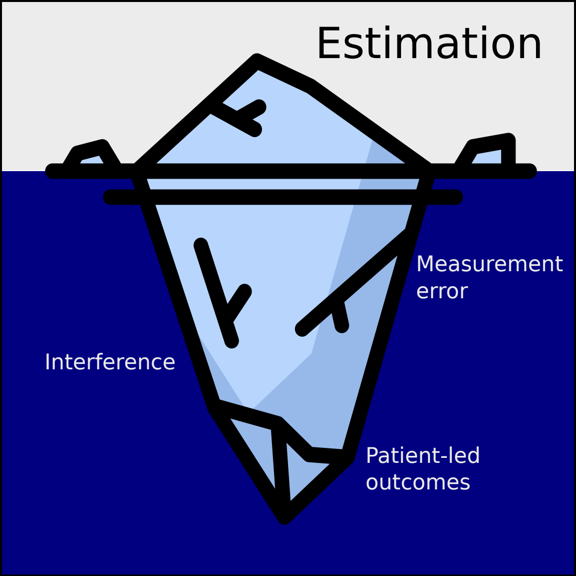
- A weighted regression with weights $w = |A - P(A = 1|X; \hat{\alpha})|$ will still yield consistent estimators of ψ_0, ψ_1.
- The estimators are "doubly robust": consistent if at least one of the treatment-free or treatment components is correctly specified.
- The blip must always be correct.

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

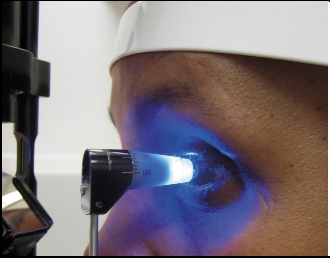

Estimation
Measurement error
Interference
Patient-led outcomes

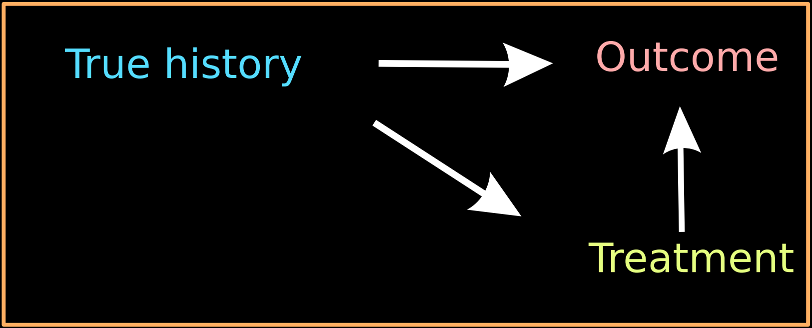
Measurement error

Target measurement: ‘average’ IOP.

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

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

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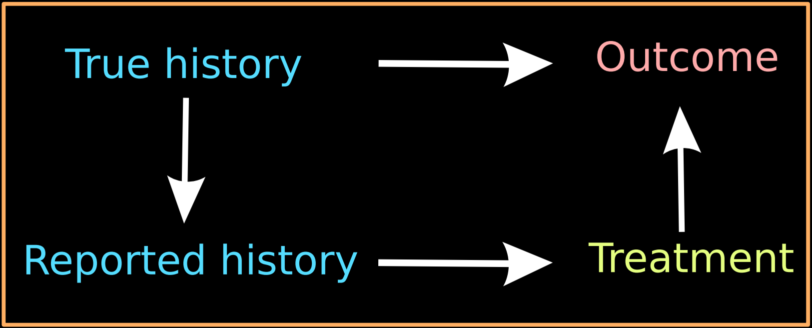
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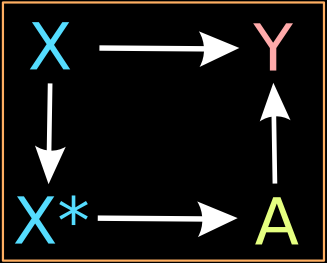
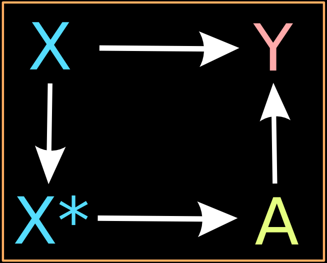


Estimation: suppose the true outcome model is:

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

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



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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
...	...	...

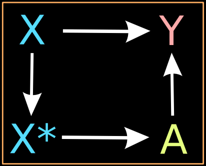
Simple correction method: Regression Calibration.

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.

- Suppose the true outcome model is:

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



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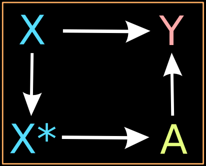

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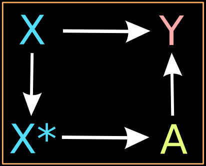

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where A depends on X^*.
- Establish (approximate) covariate balance in X_{rc} by regressing A on X_{rc}.

$$\begin{array}{ccc} X & \longrightarrow & Y \\ \downarrow & & \uparrow \\ X^* & \longrightarrow & A \end{array}$$

Suppose we conclude that our treatment rule should be:

"If 3-month average IOP > 15 add secondary drop, otherwise, maintain current treatment regime."

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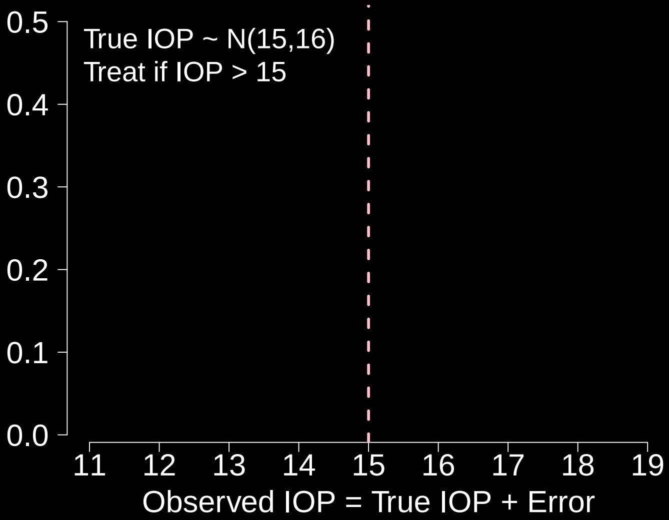
What is $P(X \leq 15 | X^* = 16)$?

In some settings, results fairly intuitive:



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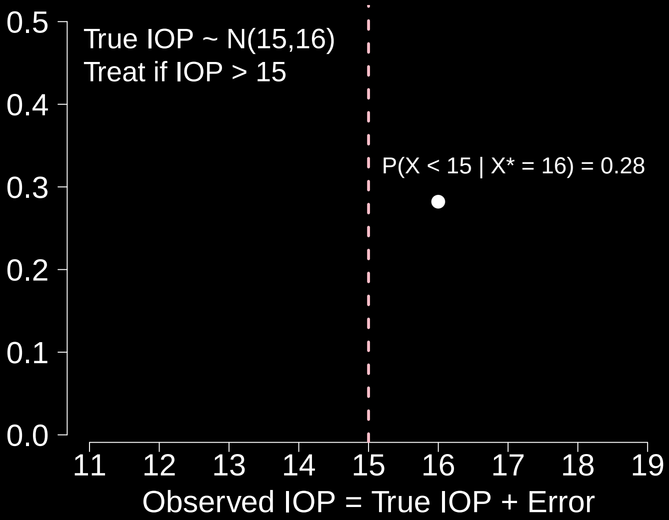

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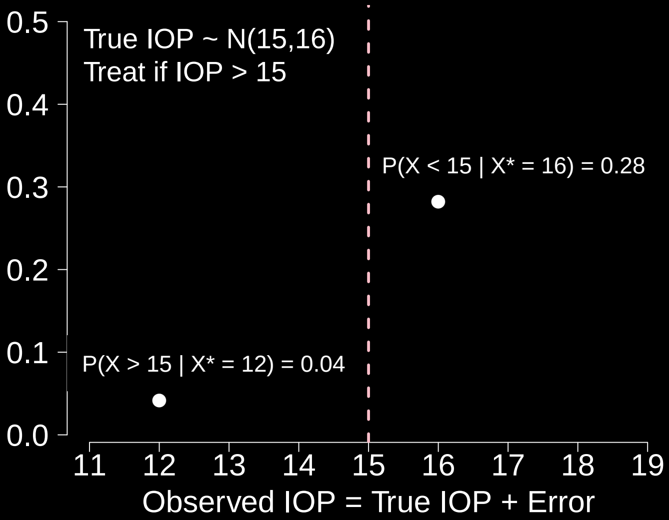

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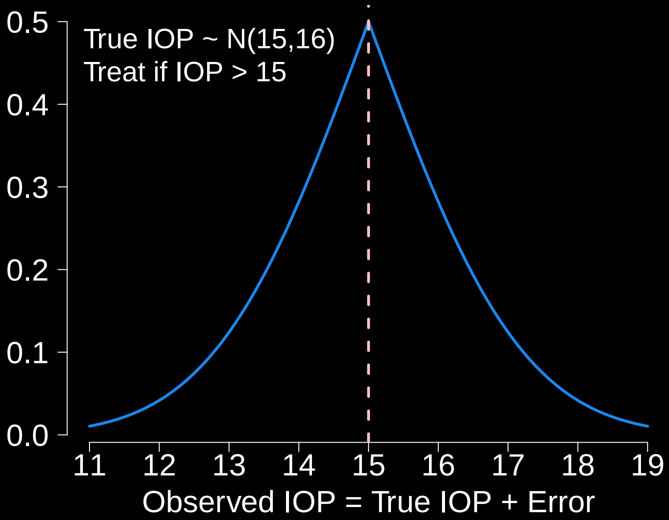

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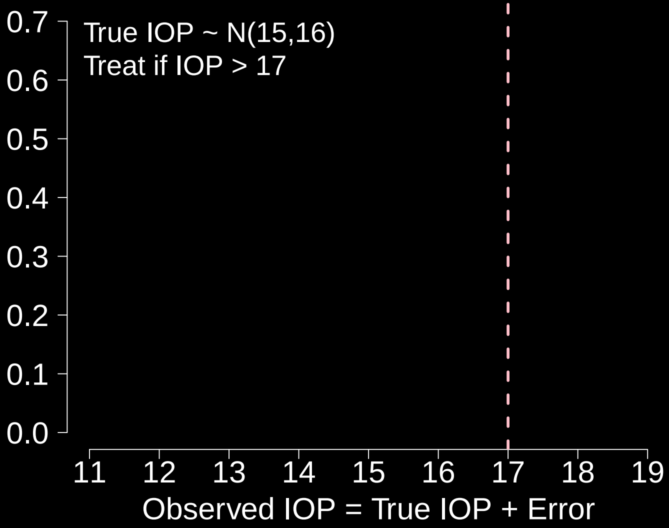

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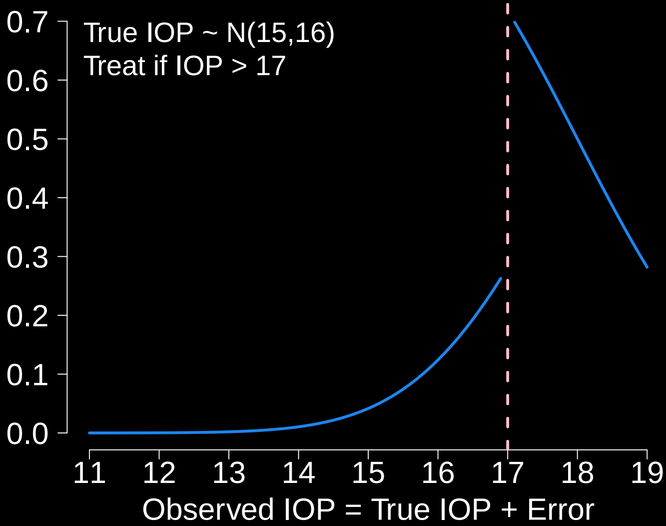

“Isn’t this just a prediction problem?”

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?

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

Only Scenario 4 is well-studied.

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"Isn't this just a prediction problem?"

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

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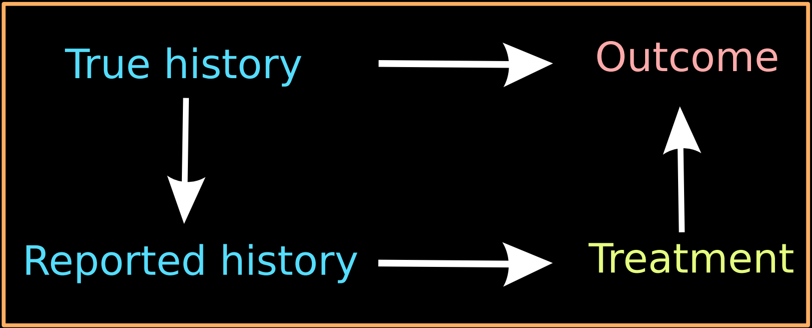
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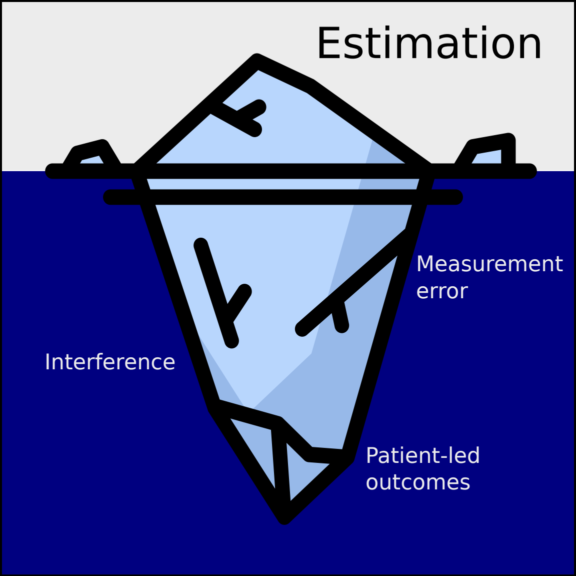
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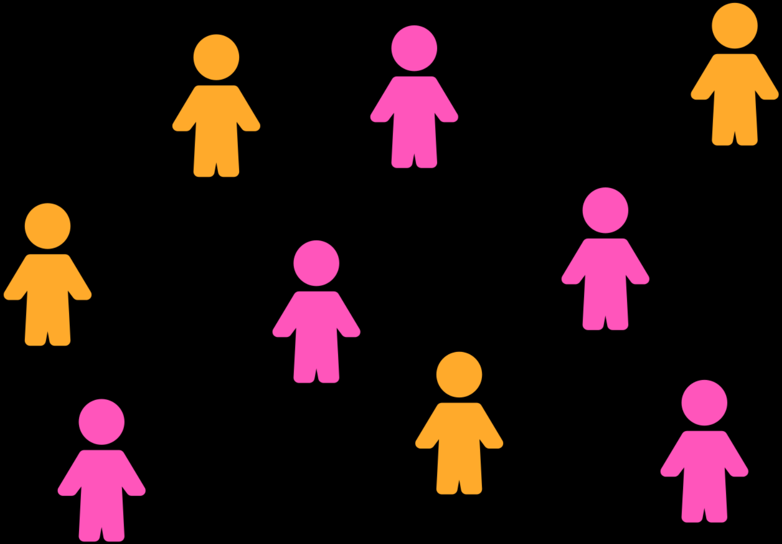
No man is an Island, entire of itself; every man is a piece of the Continent, a part of the main; if a clod be washed away by the sea, Europe is the less, as well as if a promontory were, as well as if a manor of thy friends or of thine own were; any man's death diminishes me, because I am involved in 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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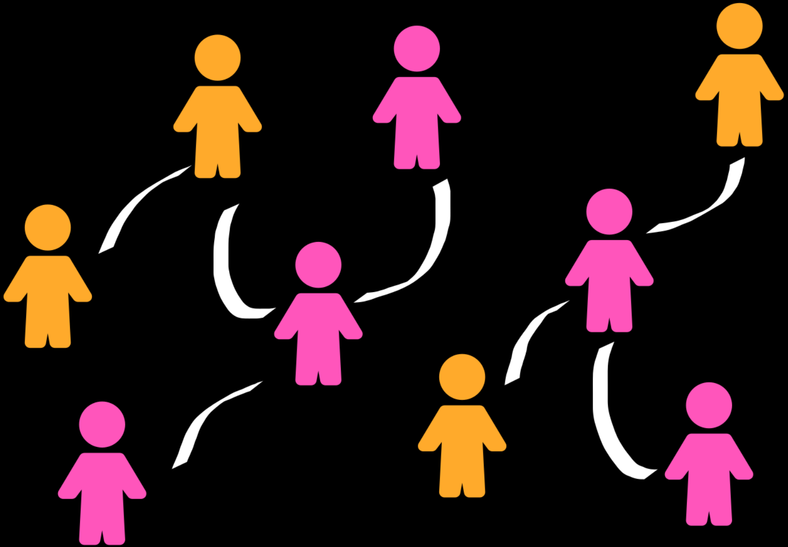
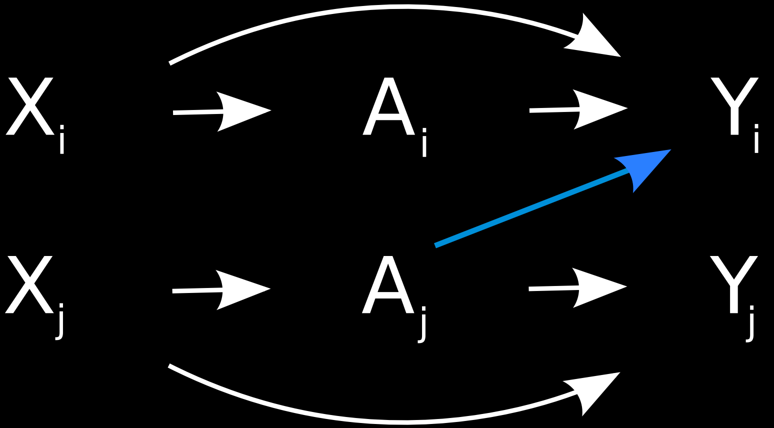


Interference

$$\begin{tikzcd}
X_i \arrow[r] \arrow[rr, bend left] & A_i \arrow[r] & Y_i \\
X_j \arrow[r] \arrow[rr, bend right] & A_j \arrow[r] & Y_j
\end{tikzcd}$$


X_i
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- No interference:

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

With interference: two ideas:

- (1) Add interaction terms:
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- (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	-
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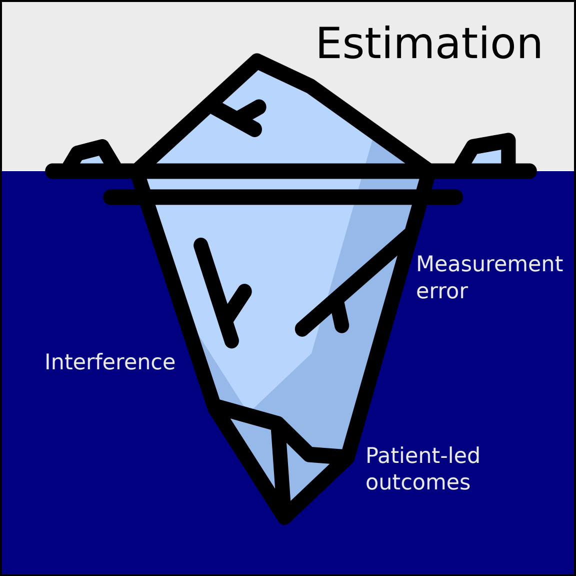
3	o	o
4	-	-

Treatment: o
No treatment: -


Estimation
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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?

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Surgery	1%	0%	5%	3

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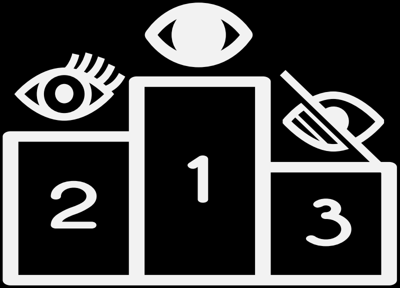
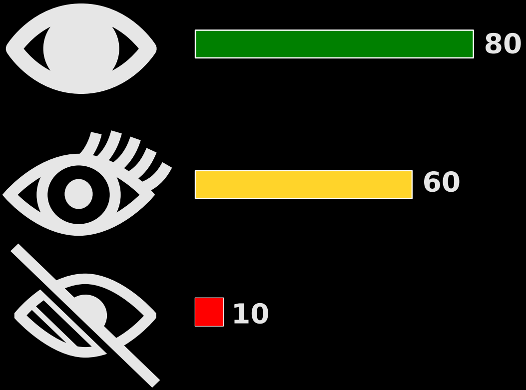
Patients can provide information to varying degrees:

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



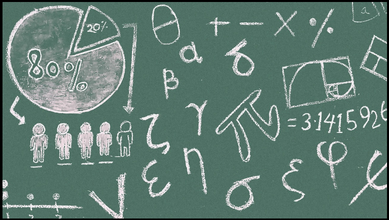
Patients can provide information to varying degrees:

- Weighting: "I would prefer iris discoloration twice as much as eyelash growth, and ten times as much as additional vision loss."



Patients can provide information to varying degrees:

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

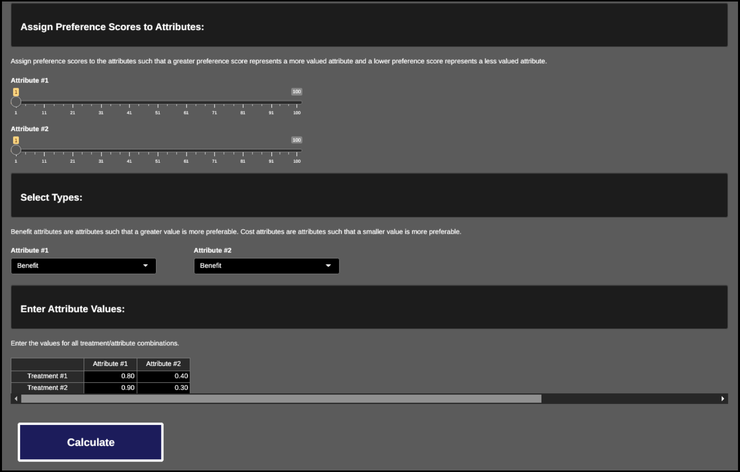
Methods from *multi-attribute decision making* can be applied to recommend treatment options.

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/



Such methods can be implemented via web-based applications:

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

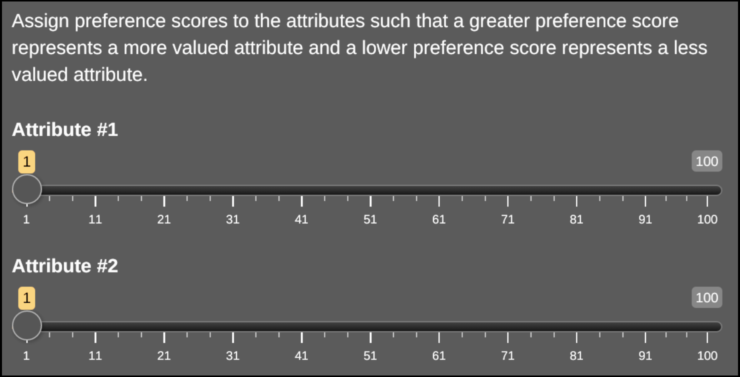
Enter Attribute Values:

Enter the values for all treatment/attribute combinations.

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

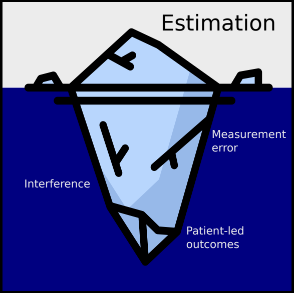
Such methods can be implemented via web-based applications:

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



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

NSERC CRSNG

CIHR IRSC Canadian Institutes of Health Research Instituts de recherche en santé du Canada

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

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