

Precision Medicine with Imprecise Measurements: Exploring Measurement Error in Personalized Decision Making

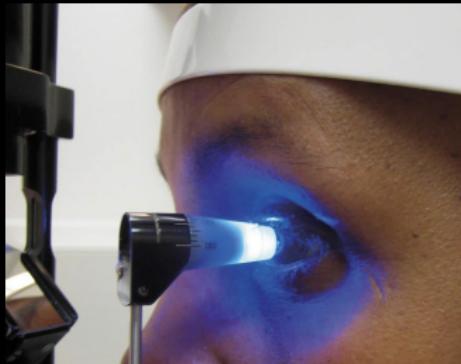
Michael Wallace, University of Waterloo

Slide deck and Shiny app links available at:
mpwallace.github.io

Glaucoma: One Disease, Many Treatments

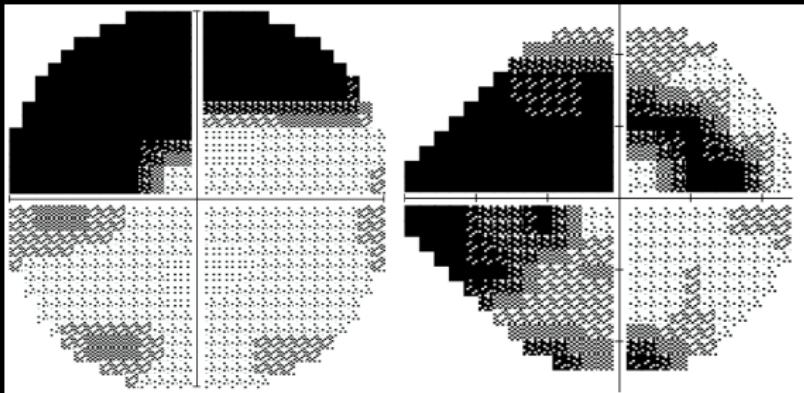
Glaucoma: group of eye diseases associated with elevated intraocular pressure (IOP).

IOP can be measured in various ways.



Glaucoma: One Disease, Many Treatments

Elevated IOP can cause vision loss, which can be measured through visual field tests.



Glaucoma: One Disease, Many Treatments

Treatment options attempt to lower IOP (and by extension preserve visual field), 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).



Glaucoma: One Disease, Many Treatments

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- Broader risk factors.
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Precision Medicine: Tailoring treatment decisions to patient-level characteristics.

Example: Patient is currently taking Azarga eye drops. A personalized treatment rule could be:

*"If current IOP is 15 or higher, add Alphagan eye drops,
otherwise continue with only Azarga."*

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(These decision rules can expand to include patient history, other variates, and longitudinal data.)

- Question: How do we choose the best decision rule?
Should our IOP cut-off be 13, 15, 20?

The Data

We typically work with data from observational studies.

Patient	Observed IOP	Drop added?	VF% at 3 months
1	16	No	73
2	20	Yes	55
3	21	Yes	50
4	16	Yes	61
5	15	No	42
...

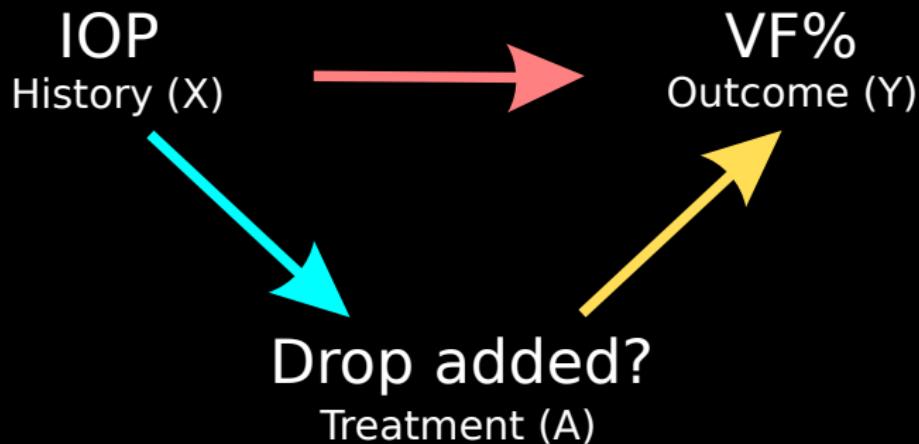
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VF% = Visual Field Percentage

Question: How do these variates relate?



Goal: Identify treatment A that optimizes $E[Y|X, A]$

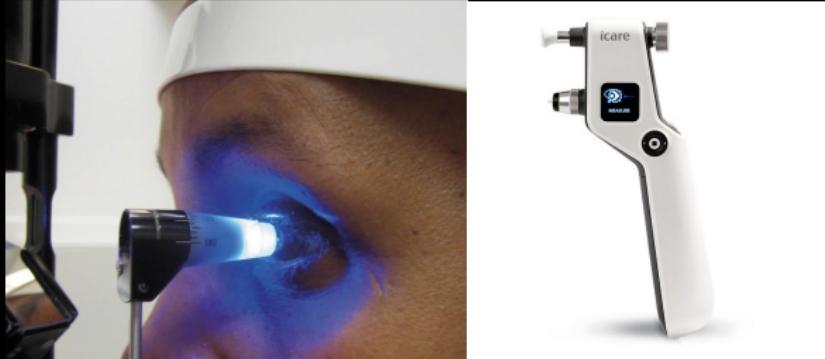
Measurement error: History

History

Target measurement: average IOP since last check-up.

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

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



Measurement error: Treatment

Treatment

Target measurement: adherence with prescribed dosing regimen.

Observed measurement: prescribed treatment or patient-reported adherence.

Full adherence with therapies reported in 10% of patients.

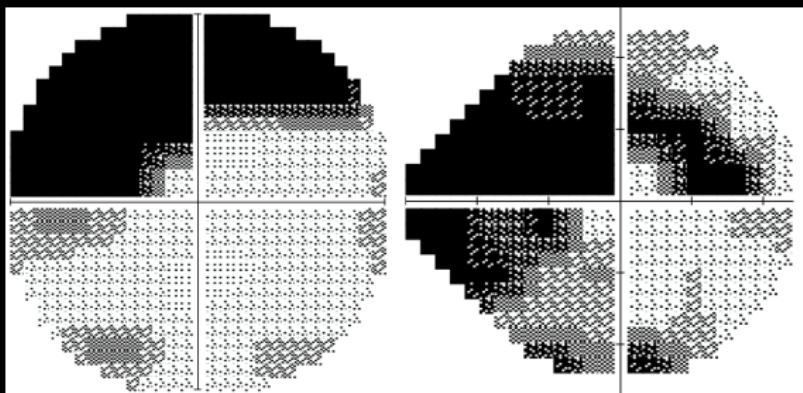


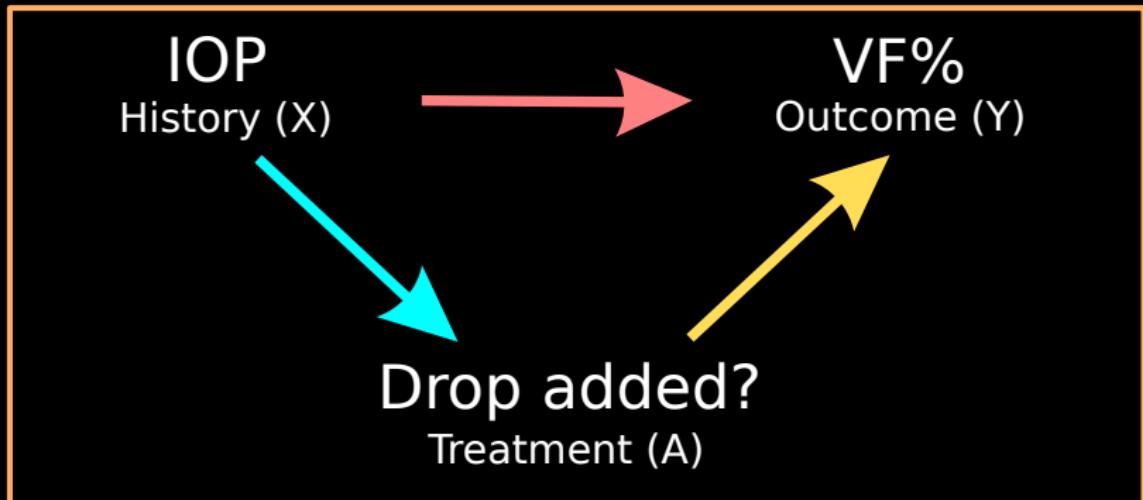
Measurement error: Outcome

Outcome

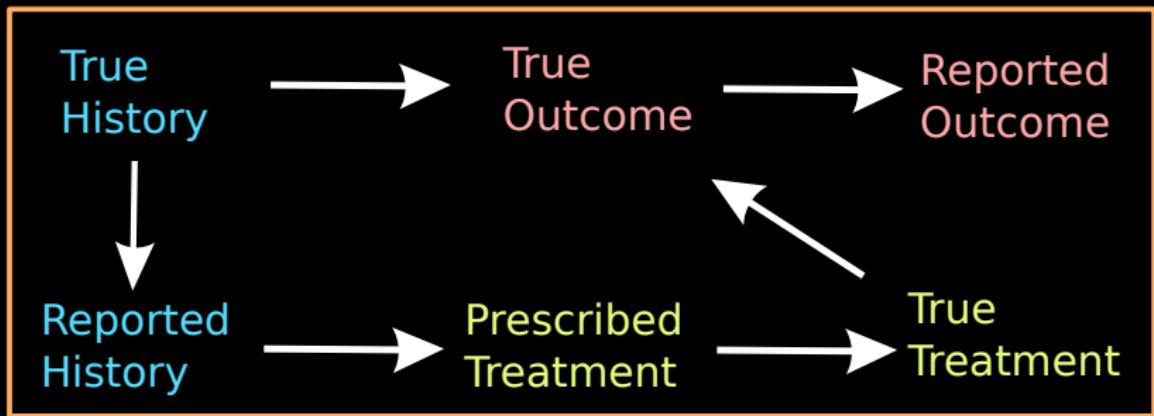
Target measurement: % of remaining vision.

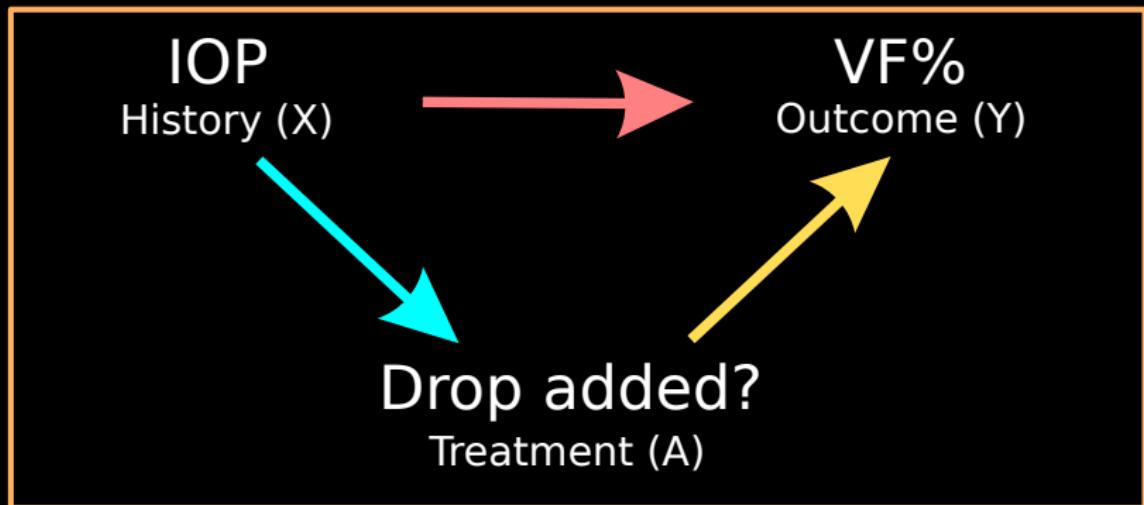
Observed measurement: visual field test.





Measurement error





Goal: Identify treatment A that optimizes $E[Y|X, A]$

Q-learning

G-estimation

OWL

IPTW

MSMs

A-learning

etc. etc. etc.

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dWOLS

Identifying the best treatment regime

$$\underbrace{E[Y|X, A]}_{\text{Expected outcome} \\ (\text{to be maximized})} \quad A \in \{0, 1\}$$

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

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- More generally:

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

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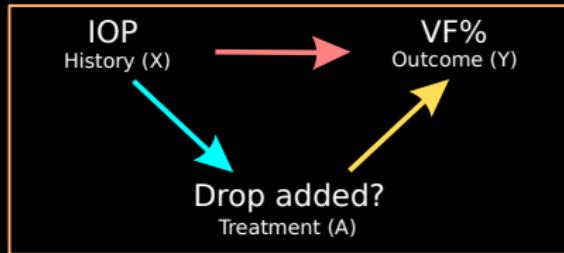
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- Simplifies focus: choose A that maximizes $\gamma(X, A; \psi)$.

Identifying the best treatment regime

- Suppose the true outcome model is:

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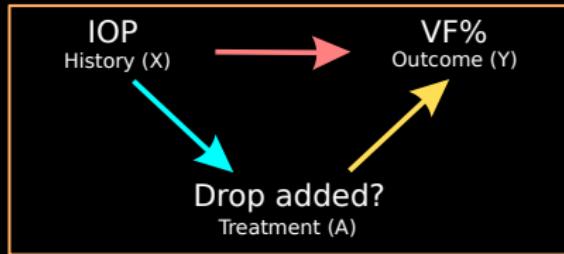
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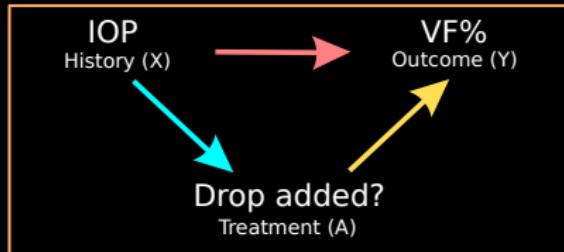
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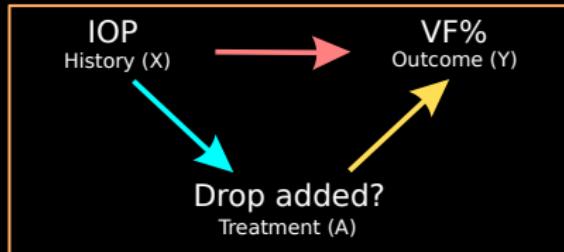
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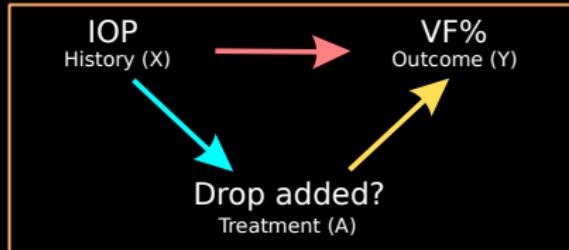
- Problem: A depends on IOP $\implies \psi_0, \psi_1$ mis-estimated.
- Solution: Account for this dependency.



Dynamic WOLS (dWOLS)

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

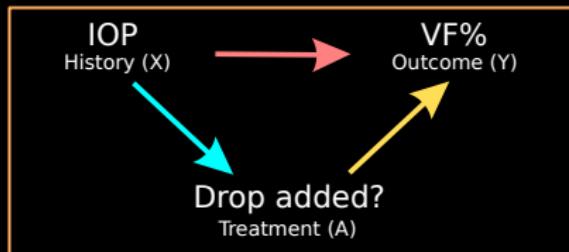
- Three models to specify:
 1. Treatment-free model: $G(X; \beta)$.
 2. Blip model: $\gamma(X, A; \psi)$.
 3. Treatment model: $P(A = 1|X; \alpha)$.



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



Identifying the best treatment regime

- Suppose the true outcome model is:

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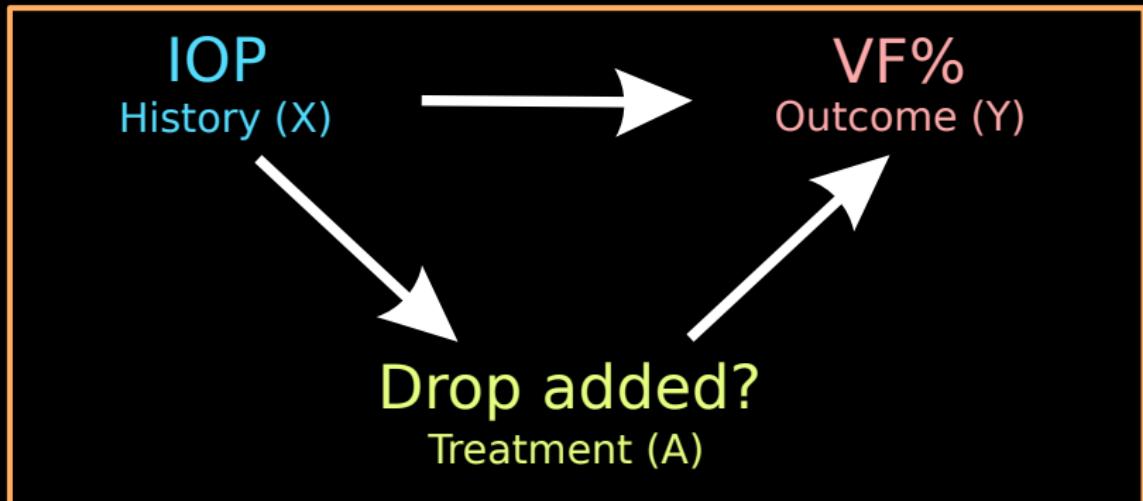
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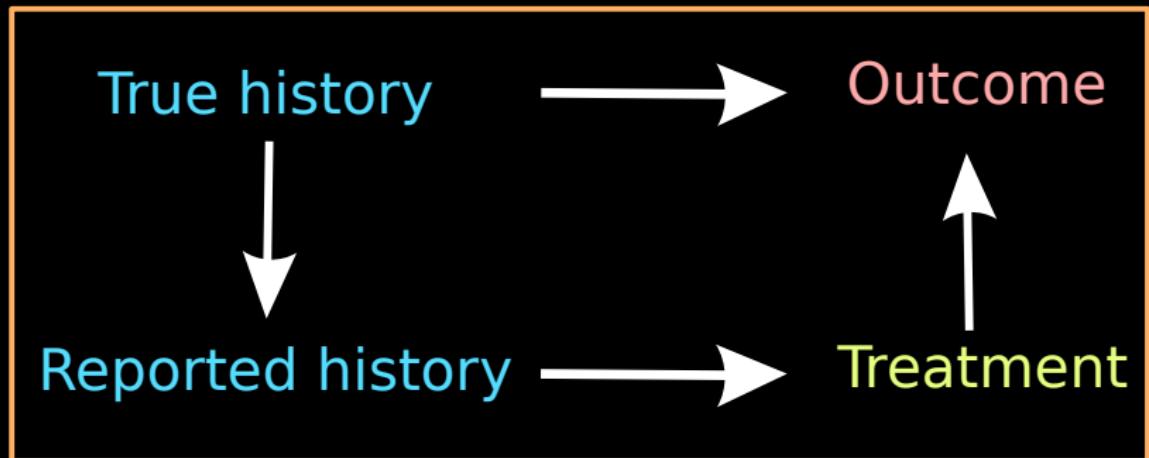
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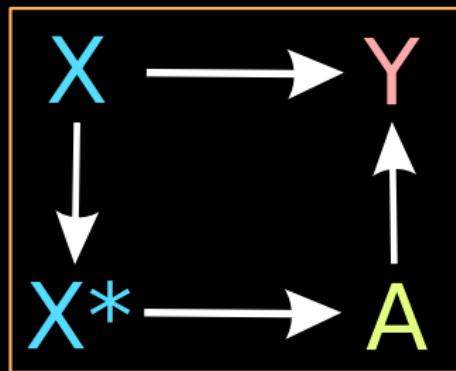
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- WOLS with weights $w = |A - P(A = 1|X; \hat{\alpha})|$ will still yield consistent estimators of ψ_0, ψ_1 .
- Estimators are “doubly robust”: consistent if at least one of treatment-free or treatment components correctly specified.
- The blip must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







Estimation: suppose the true outcome model is:

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

but we only observe

$$X^* = X + U \quad U \sim N(\mu_{ux}, \sigma_{ux}^2)$$

← → C shiny.math.uwaterloo.ca/sas/mwallace/ME/dwols/

Measurement Error and dWOLS

Explore the impact of measurement error on treatment decision rule estimation. Specify which variates are measured with error then click 'Simulate' to generate results. See 'Manual' tab for full details of simulations and input settings. For help or feedback, please contact Michael Wallace at the University of Waterloo through their [webpage](#) or Twitter.

Error in pre-treatment information (X)?
 Error in treatment (A)?
 Error in outcome (Y)?

Simulate

Show advanced options?

Summary Table Plot Manual

Is there measurement error in:

- Pre-treatment information? **YES** (error-prone)
- Treatment information? **NO** (error-free)
- Outcome? **NO** (error-free)

Across 100 simulated datasets of size n = 500, median (IQR) treatment accuracy:

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- Using error-prone data: **82.20%** (80.80-83.40%)

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Measurement Error

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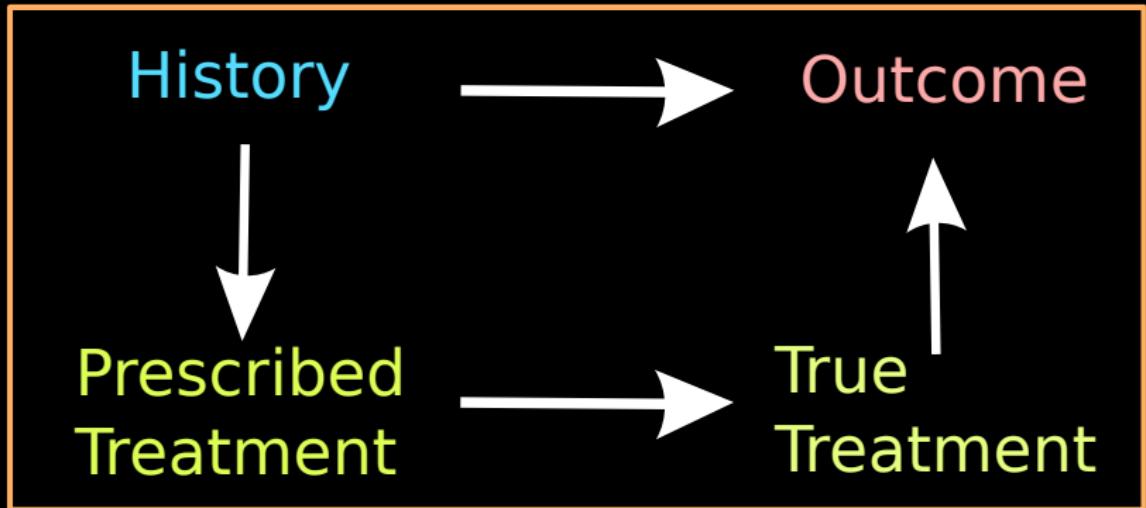
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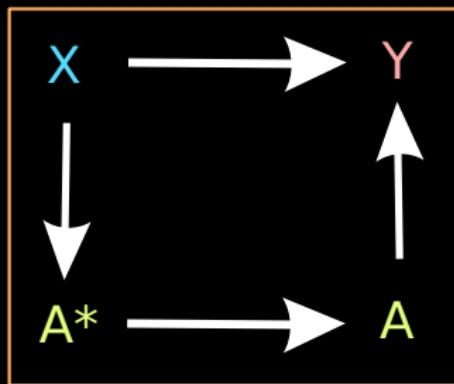
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- Because dWOLS grounded in standard regression theory, existing measurement error correction methods can be used.

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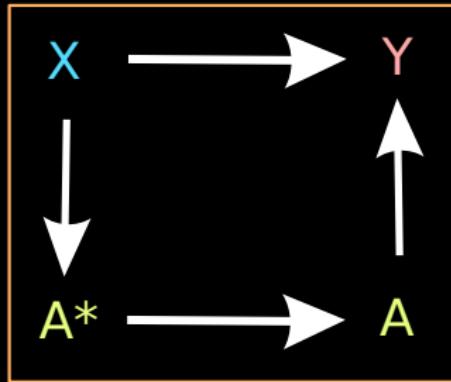
- Much established theory on errors in X in linear regression.
- Because dWOLS grounded in standard regression theory, existing measurement error correction methods can be used.
- Result: Regression Calibration can be used with dWOLS and maintain double robustness.





For binary A , misclassification can be characterized by the positive and negative predictive values:

$$PPV = P(A = 1 | A^* = 1) \quad NPV = P(A = 0 | A^* = 0)$$



Suppose the true outcome model is:

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

but we only observe A^* .

Key question: Do the misclassification probabilities depend on X ?

Shiny App: Error in A

shiny.math.uwaterloo.ca/sas/mwallace/ME/dwols/

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 Depends on X?
 Error in outcome (Y)?
 Show advanced options?

Simulate

Summary Table Plot Manual

Is there measurement error in:

- Pre-treatment information? **NO** (error-free)
- Treatment information? **YES** (independent of X)
- Outcome? **NO** (error-free)

Across 100 simulated datasets of size n = 500, median (IQR) treatment accuracy:

- Using error-free data: **88.70%** (84.60-92.30%)

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- Using error-prone data: **88.00%** (84.75-91.40%)

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Is there measurement error in:

- Pre-treatment information? **NO** (error-free)
- Treatment information? **YES** (not independent of X)
- Outcome? **NO** (error-free)

Across 100 simulated datasets of size n = 500, median (IQR) treatment accuracy:

- Using error-free data: **89.10%** (85.70-92.90%)
- Using error-prone data: **31.80%** (26.55-68.00%)

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

If misclassification does not depend on X , then our estimates of ψ_0, ψ_1 will be biased:

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$$\psi_0^* = (PPV + NPV - 1)\psi_0 \quad \psi_1^* = (PPV + NPV - 1)\psi_1$$

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However: our treatment rule is of the form

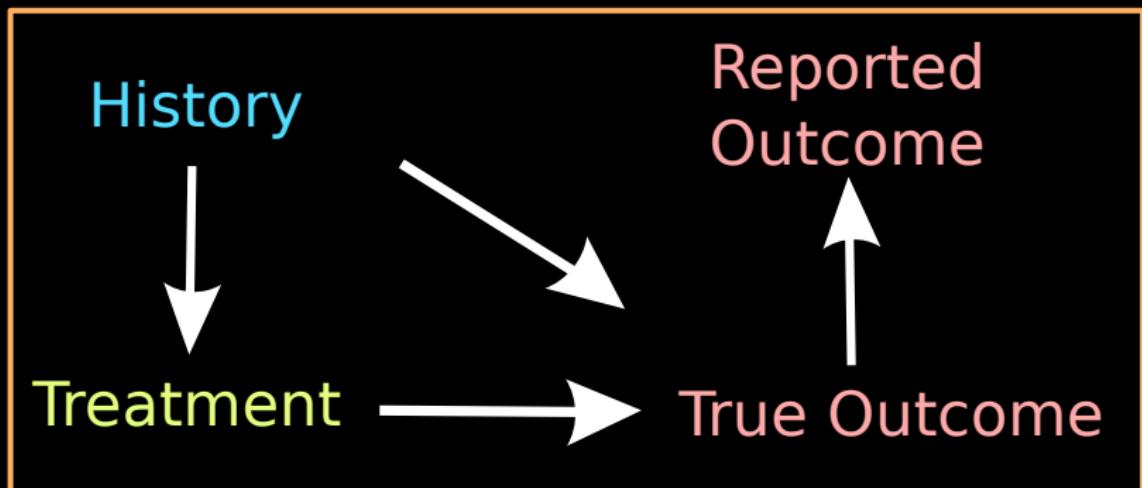
$$A = 1 \text{ if } \psi_0 + \psi_1 X > 0$$

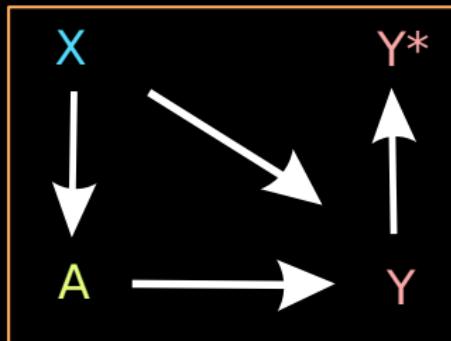
which is unaffected if ψ_0, ψ_1 are biased by the same factor.

If misclassification depends on X , then corrective action is required.

Upcoming work modifies G-estimation to account for treatment misclassification.

Further questions exist related to intention to treat analyses, and implications of (non-) adherence for identifying optimal treatment rules.





Suppose the true outcome model is:

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but we only observe

$$Y^* = Y + U \quad U \sim N(\mu_{uy}, \sigma_{uy}^2)$$

Shiny App: Error in Y

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

Depends on X? Depends on A?

Show advanced options?

Summary Table Plot Manual

Is there measurement error in:

- Pre-treatment information? **NO** (error-free)
- Treatment information? **NO** (error-free)
- Outcome? **YES** (independent of X, independent of A)

Across 100 simulated datasets of size n = 500, median (IQR) treatment accuracy:

- Using error-free data: **87.90%** (84.80-91.00%)

Shiny App: Error in Y

$$E[Y|X, A; \beta, \psi] = \beta_0 + \beta_1 X + \beta_2 X^2 + A(\psi_0 + \psi_1 X)$$
$$Y^* = Y + U \quad U \sim N(\mu_{uy}, \sigma_{uy}^2)$$

← → C shiny.math.uwaterloo.ca/sas/mwallace/ME/dwols/

Measurement Error and dWOLS

Explore the impact of measurement error on treatment decision rule estimation. Specify which variates are measured with error then click 'Simulate' to generate results. See 'Manual' tab for full details of simulations and input settings. For help or feedback, please contact Michael Wallace at the University of Waterloo through their [webpage](#) or Twitter.

- Error in pre-treatment information (X)?
 Error in treatment (A)?
 Error in outcome (Y)?
- Depends on X? Depends on A?

Simulate

- Show advanced options?

Summary Table Plot Manual

Is there measurement error in:

- Pre-treatment information? **NO** (error-free)
- Treatment information? **NO** (error-free)
- Outcome? **YES** (independent of X, independent of A)

Across 100 simulated datasets of size n = 500, median (IQR) treatment accuracy:

- Using error-free data: **87.90%** (84.80-91.00%)
- Using error-prone data: **87.70%** (84.40-90.85%)

Error independent of X, A : parameter estimates also unbiased.

Shiny App: Error in Y

$$E[Y|X, A; \beta, \psi] = \beta_0 + \beta_1 X + \beta_2 X^2 + A(\psi_0 + \psi_1 X)$$
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Error in pre-treatment information (X)?
 Error in treatment (A)?
 Error in outcome (Y)?

Depends on X? Depends on A?

Show advanced options?

Simulate

Summary Table Plot Manual

Is there measurement error in:

- Pre-treatment information? **NO** (error-free)
- Treatment information? **NO** (error-free)
- Outcome? **YES** (not independent of X, independent of A)

Across 100 simulated datasets of size n = 500, median (IQR) treatment accuracy:

- Using error-free data: **87.80%** (84.15-91.65%)
- Using error-prone data: **87.80%** (84.00-91.85%)

Error depends on X , not on A : ψ estimators still consistent.

Shiny App: Error in Y

$$E[Y|X, A; \beta, \psi] = \beta_0 + \beta_1 X + \beta_2 X^2 + A(\psi_0 + \psi_1 X)$$
$$Y^* = Y + U \quad U \sim N(\mu_{uy}, \sigma_{uy}^2)$$

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Measurement Error and dWOLS

Explore the impact of measurement error on treatment decision rule estimation. Specify which variates are measured with error then click 'Simulate' to generate results. See 'Manual' tab for full details of simulations and input settings. For help or feedback, please contact Michael Wallace at the University of Waterloo through their [webpage](#) or Twitter.

- Error in pre-treatment information (X)?
 Error in treatment (A)?
 Error in outcome (Y)?
- Depends on X? Depends on A?

Simulate

- Show advanced options?

Summary Table Plot Manual

Is there measurement error in:

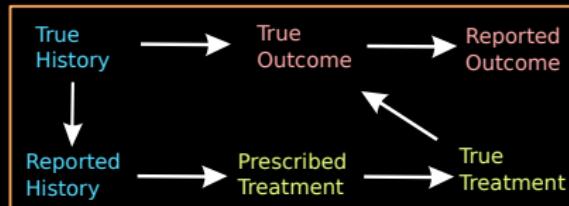
- Pre-treatment information? **NO** (error-free)
- Treatment information? **NO** (error-free)
- Outcome? **YES** (not independent of X, not independent of A)

Across 100 simulated datasets of size n = 500, median (IQR) treatment accuracy:

- Using error-free data: **87.90%** (84.40-91.40%)
- Using error-prone data: **56.20%** (45.75-67.80%)

Error not independent of X or A : ψ estimators no longer reliable.

- Personalized treatment decisions are an (increasingly) important element of healthcare delivery.
- Principles can be applied to any setting where decisions are tailored to individual-level data.
- Measurement error an important consideration in all elements of these problems.
- There are some special cases where errors have limited impact, or may be corrected for with standard theory.
- But: many more cases to explore.



Looking Ahead: Future Treatment

Suppose we conclude that our treatment rule should be:

“If 3-month average IOP ≥ 15 add secondary drop, otherwise, maintain current treatment regime.”

Looking Ahead: Future Treatment

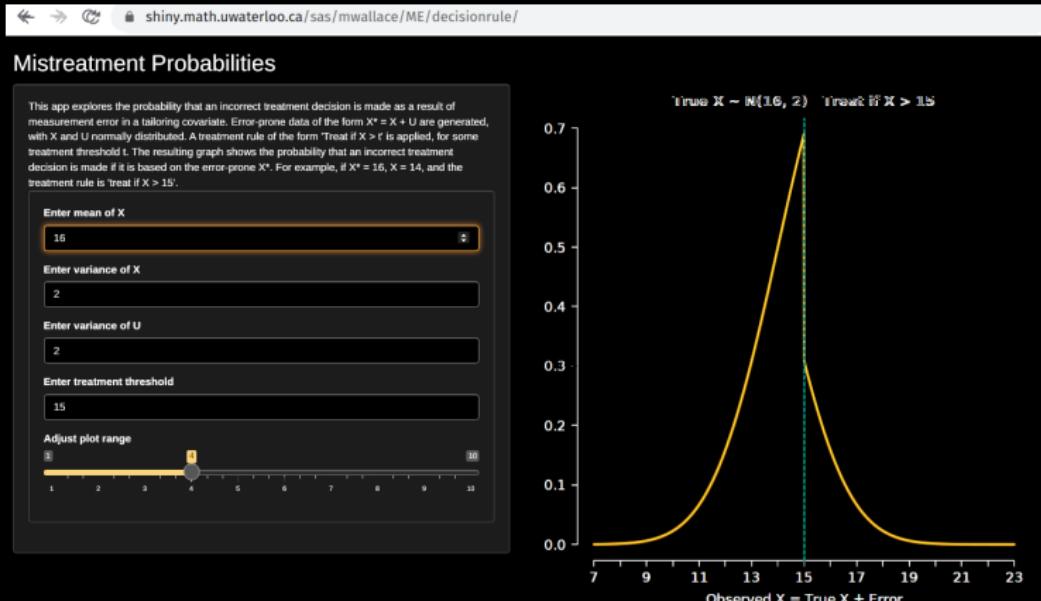
Suppose we conclude that our treatment rule should be:

“If 3-month average IOP ≥ 15 add secondary drop, otherwise, maintain current treatment regime.”

I go to the clinic and my IOP measurement is 16. Then what?

Looking Ahead: Future Treatment

Exploring these probabilities through a Shiny app:



All links available at <https://mpwallace.github.io/>

Acknowledgments



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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 in Tailoring Variates**: 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)
- **R Package DTRreg**: Available on CRAN.
- **Precision Medicine and Measurement Error More Broadly**: M. P. Wallace. Measurement error and precision medicine. In Cai T., Chakraborty B., Laber E., Moodie E. and van der Laan M. (Eds), *Handbook of Statistical Methods for Precision Medicine*. Chapman & Hall/CRC Handbooks of Modern Statistical Methods. Expected publication 2023.



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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*

“Isn’t this just a prediction problem?”

Only Scenario 4 is well-studied.

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*
4: “We always observe the truth.”	X	X