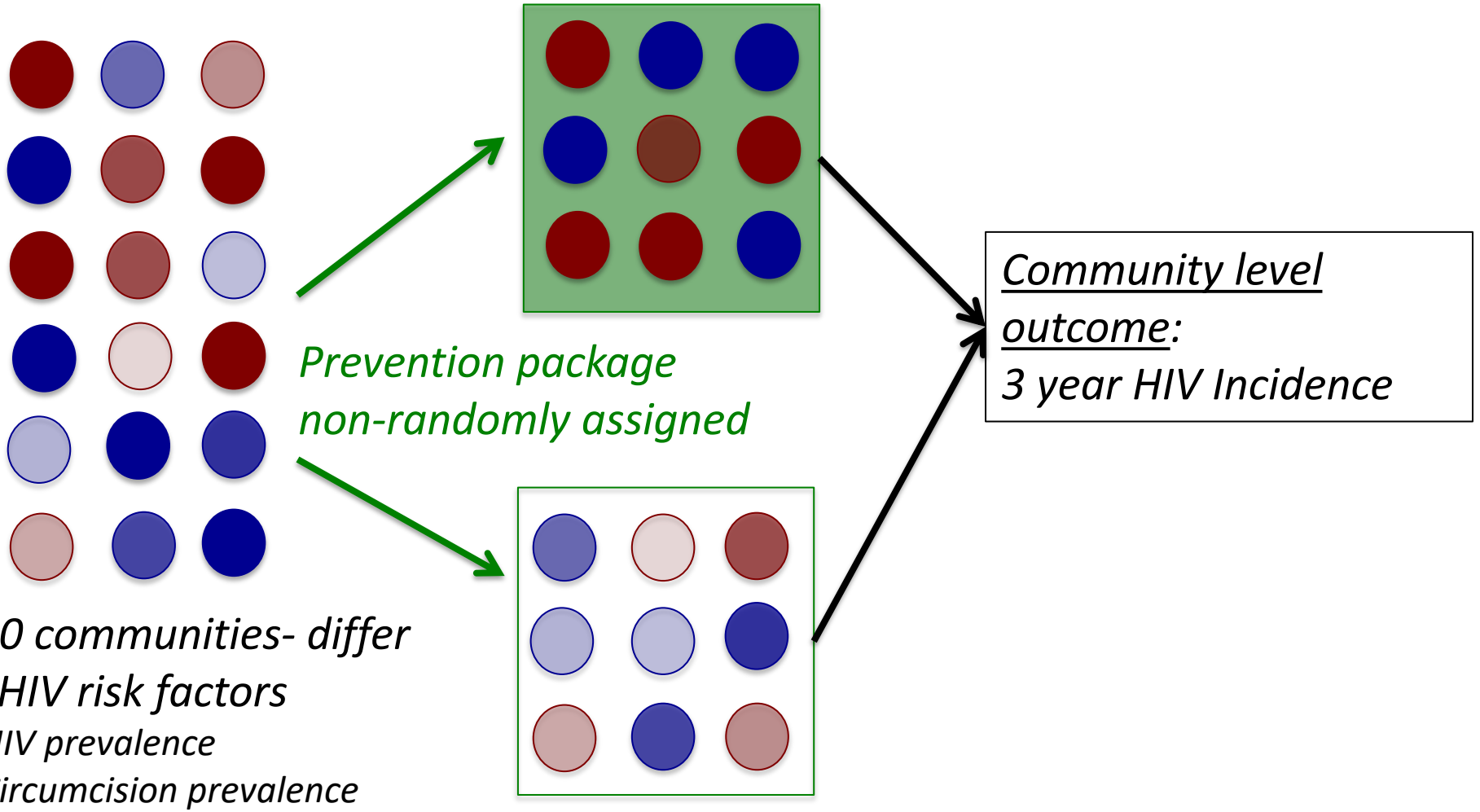
Lecture 12

TMLE Examples, Interpretation, Wrap-up

Outline

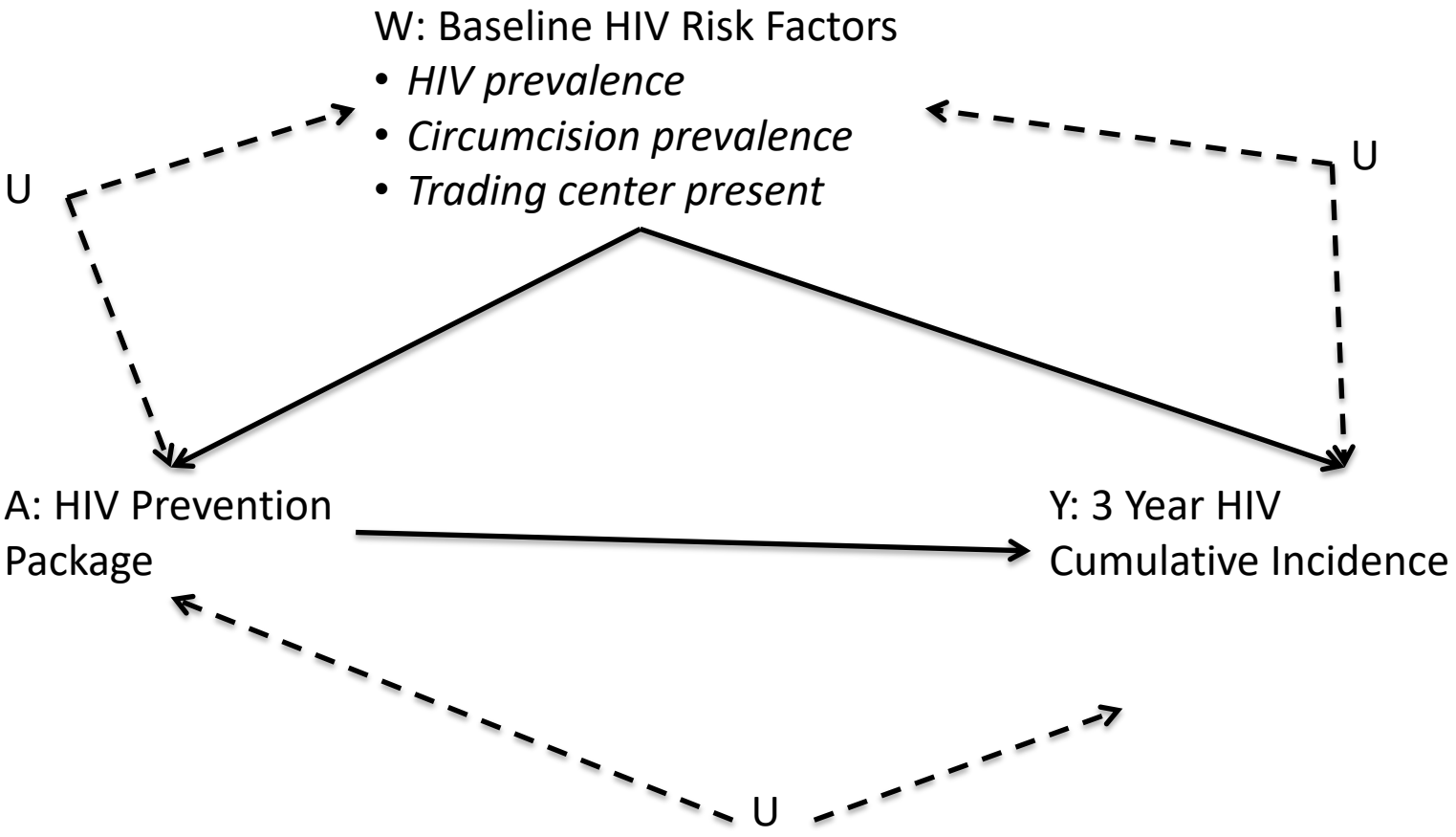
1. TMLE: Some examples
   - Simulated HIV data
   - Real Observational data
   - Real data from RCTs
2. Various approaches to interpreting results
3. Wrap up and frontiers

Ex: Impact of a Prevention Intervention on HIV Incidence (Simulated Data)



The Roadmap in Action

1. Causal model



The Roadmap in Action

2. Causal Question

- **Target Causal Parameter**: **Average treatment effect**
- Difference between average counterfactual 3 year HIV incidence if all communities had received the prevention package *versus* all communities had not received the prevention package
- $E(Y_1)-E(Y_0)$

The Roadmap in Action

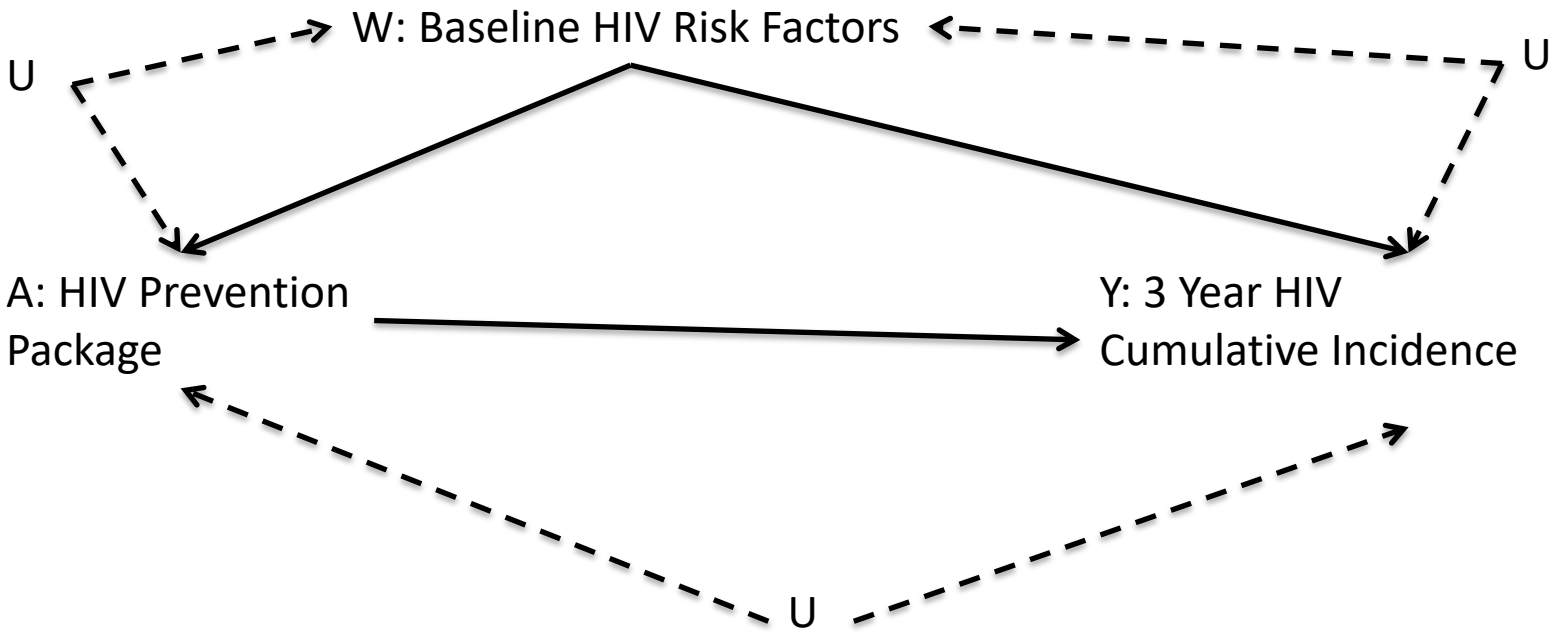
3. Observed Data

- 100 randomly sampled communities
- On each we measure:
  - W: Baseline confounders
  - A: receipt of the prevention package
  - Y: 3 year cumulative incidence
- Observe 100 independent and identically distributed copies of O=(W,A,Y)

The Roadmap in Action

4. Identification

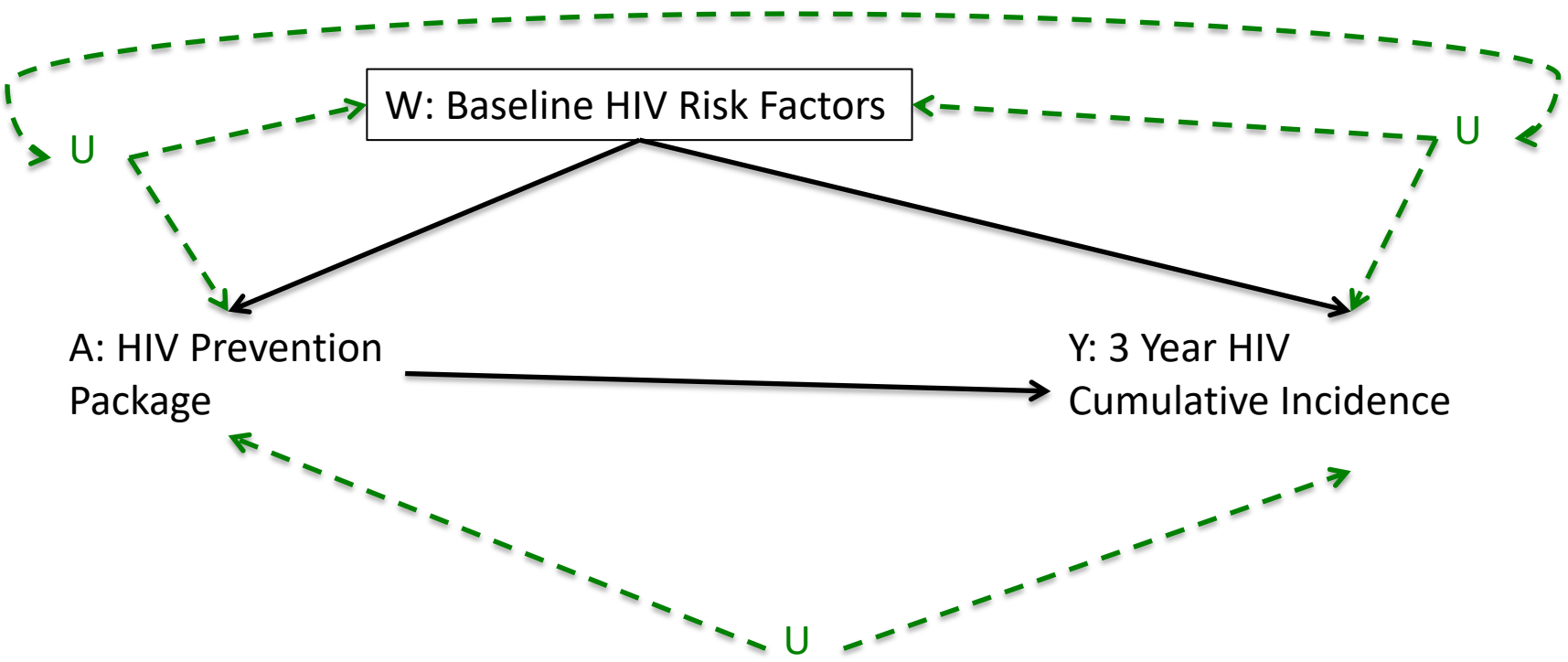
- Do we know enough to translate our causal question to a statistical question?



The Roadmap in Action

4. Identification

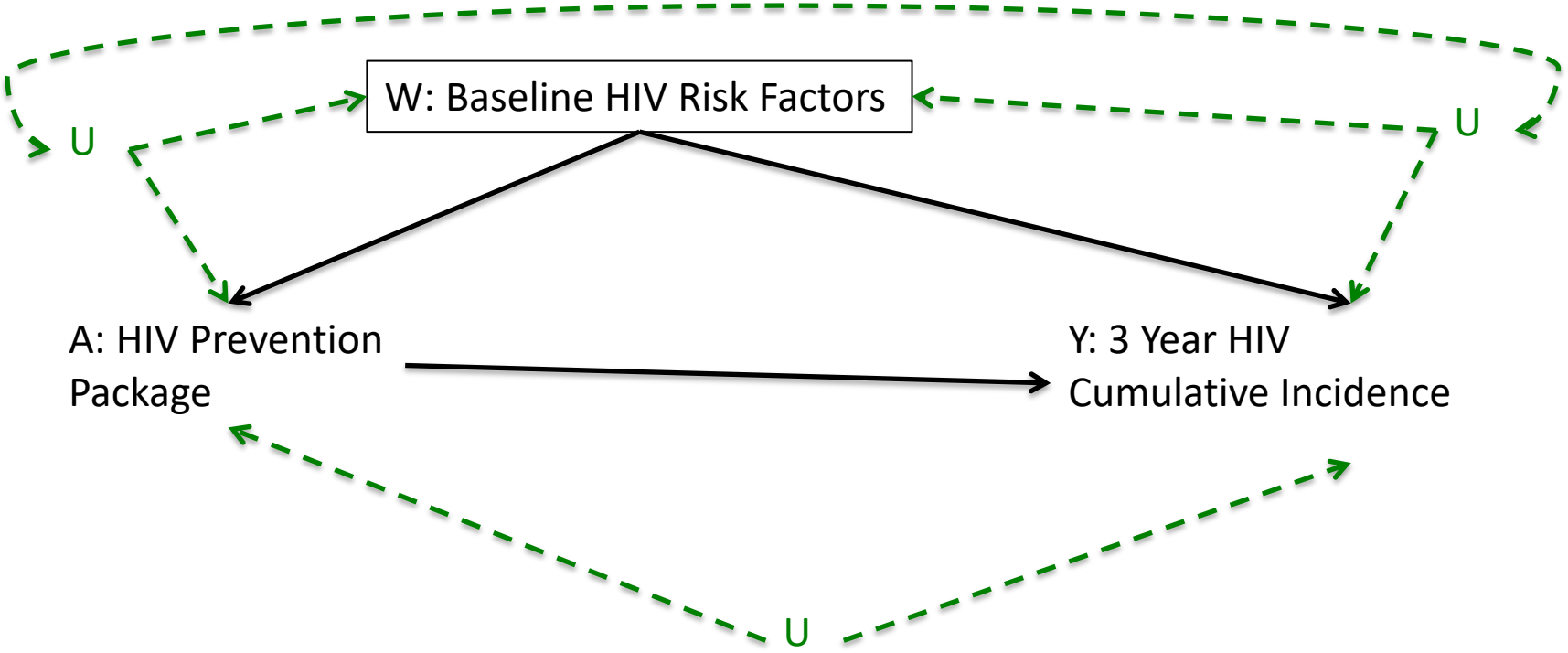
- Do we know enough to translate our causal question to a statistical question? **NO**



The Roadmap in Action

4. Identification: Convenience Assumptions

- Under what additional assumptions can we translate our causal question to a statistical question? *No unmeasured confounding*



The Roadmap in Action

5. Statistical Model and Estimand

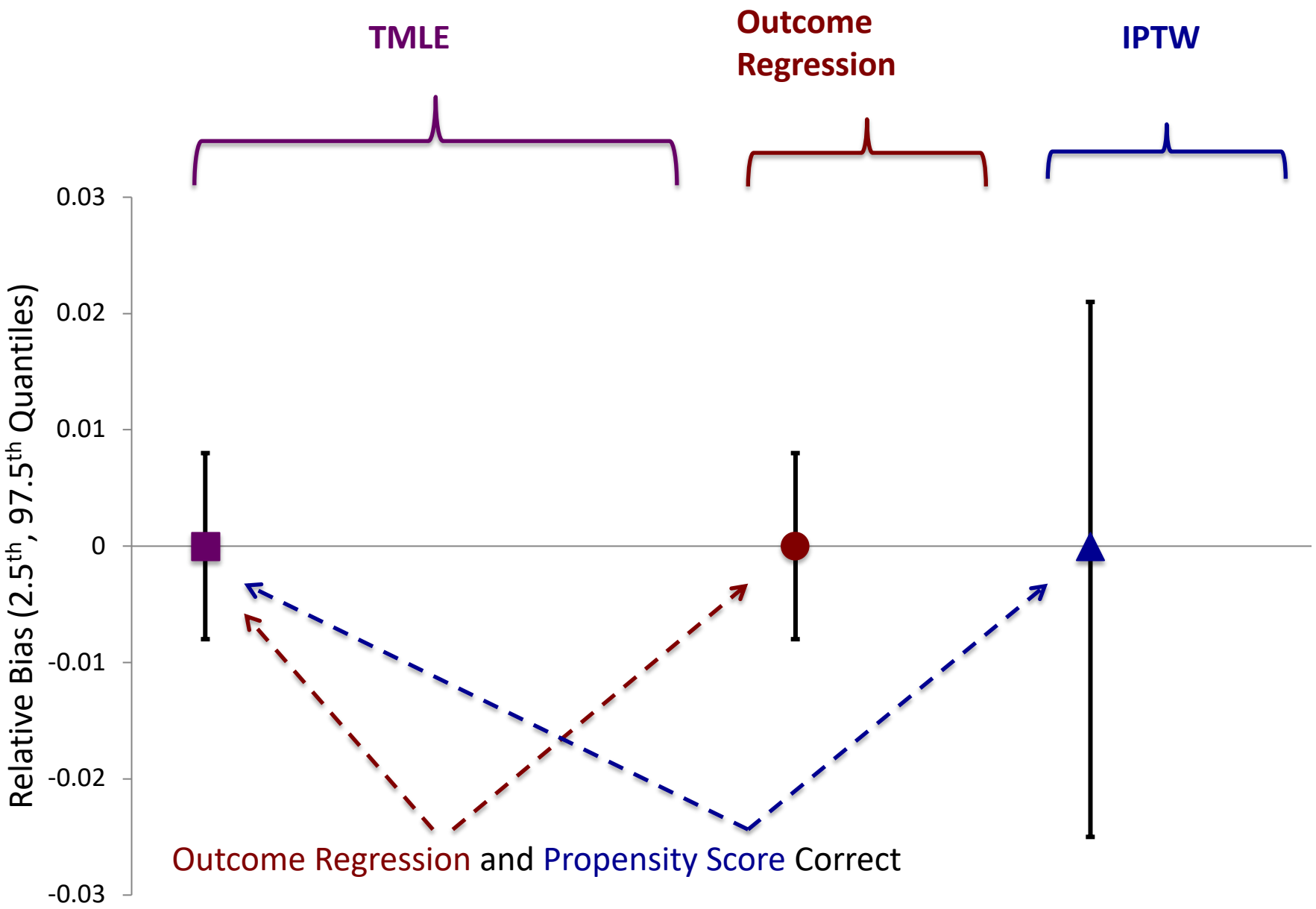
1. Statistical model
   - Absent any other knowledge, observed data O=(W,A,Y) might have any distribution
   - Non-parametric statistical model
2. Statistical quantity to estimate (estimand)
   - Under our causal model + assumptions, **average treatment effect** = observed difference in mean outcome within confounder strata, standardized to distribution of confounders

$$E(Y_1 - Y_0) = \sum_w E(Y \mid A=1, W=w) - E(Y \mid A=0, W=w) P(W=w)$$

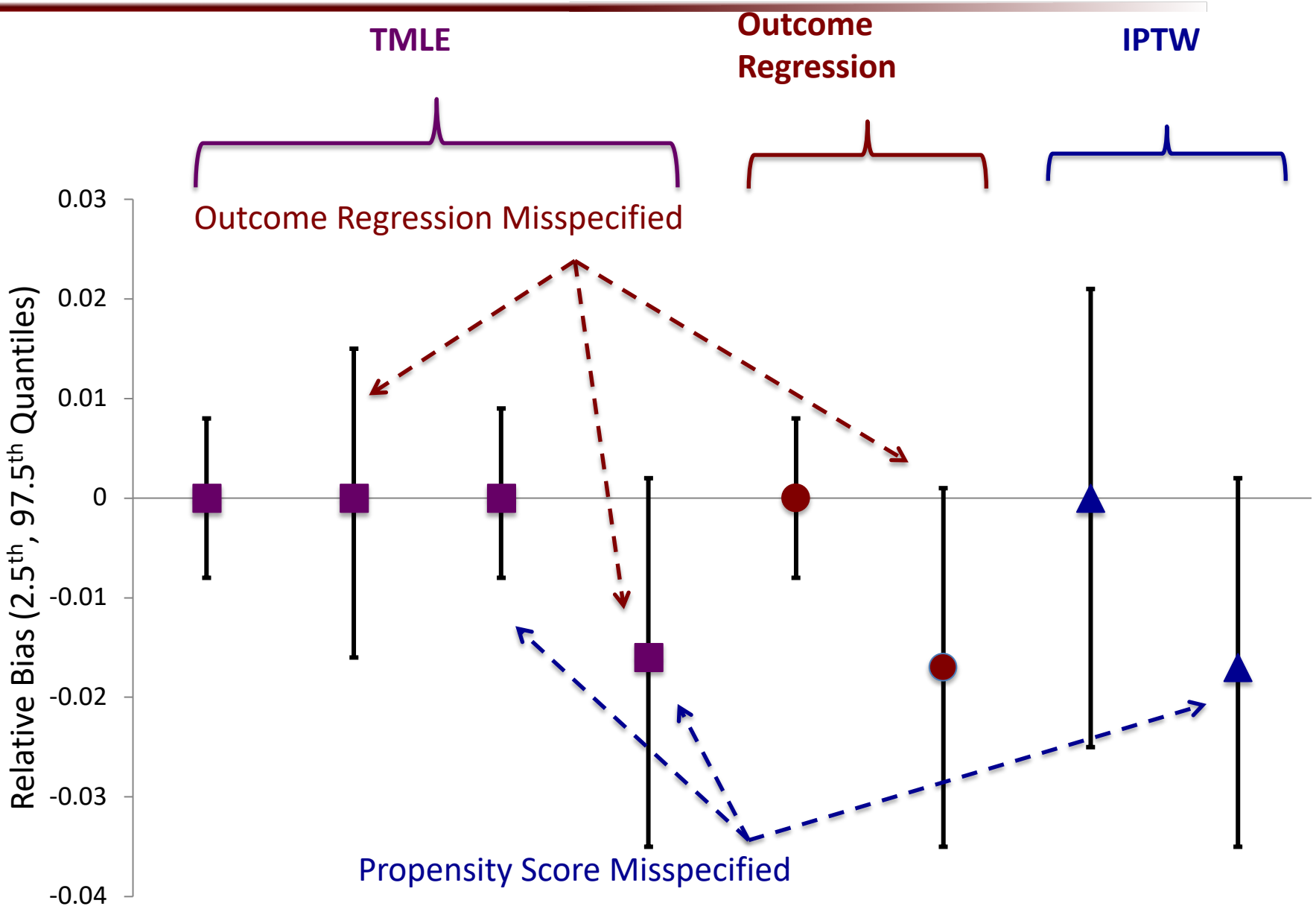
The Roadmap in Action

- **6. Estimation**
- Choosing an estimator is a **statistical problem**
  - For a given model and estimand, many choices
  - One estimator is not "more causal" than another
- Estimators **do have important differences** in their **statistical properties**
  - Even for point treatment settings

Double Robustness: Simulated Example



Double Robustness: Simulated Example



A hybrid mobile approach for population-wide HIV testing in rural east Africa: an observational study

Gabriel Chamie, Tamara D Clark, Jane Kabami, Kevin Kadede, Emmanuel Ssemmondo, Rachel Steinfeld, Geoff Lavoy, Dalsone Kwarisiima, Norton Sang, Vivek Jain, Harsha Thirumurthy, Teri Liegler, Laura B Balzer, Maya L Petersen, Craig R Cohen, Elizabeth A Bukusi, Moses R Kamya, Diane V Havlir, Edwin D Charlebois

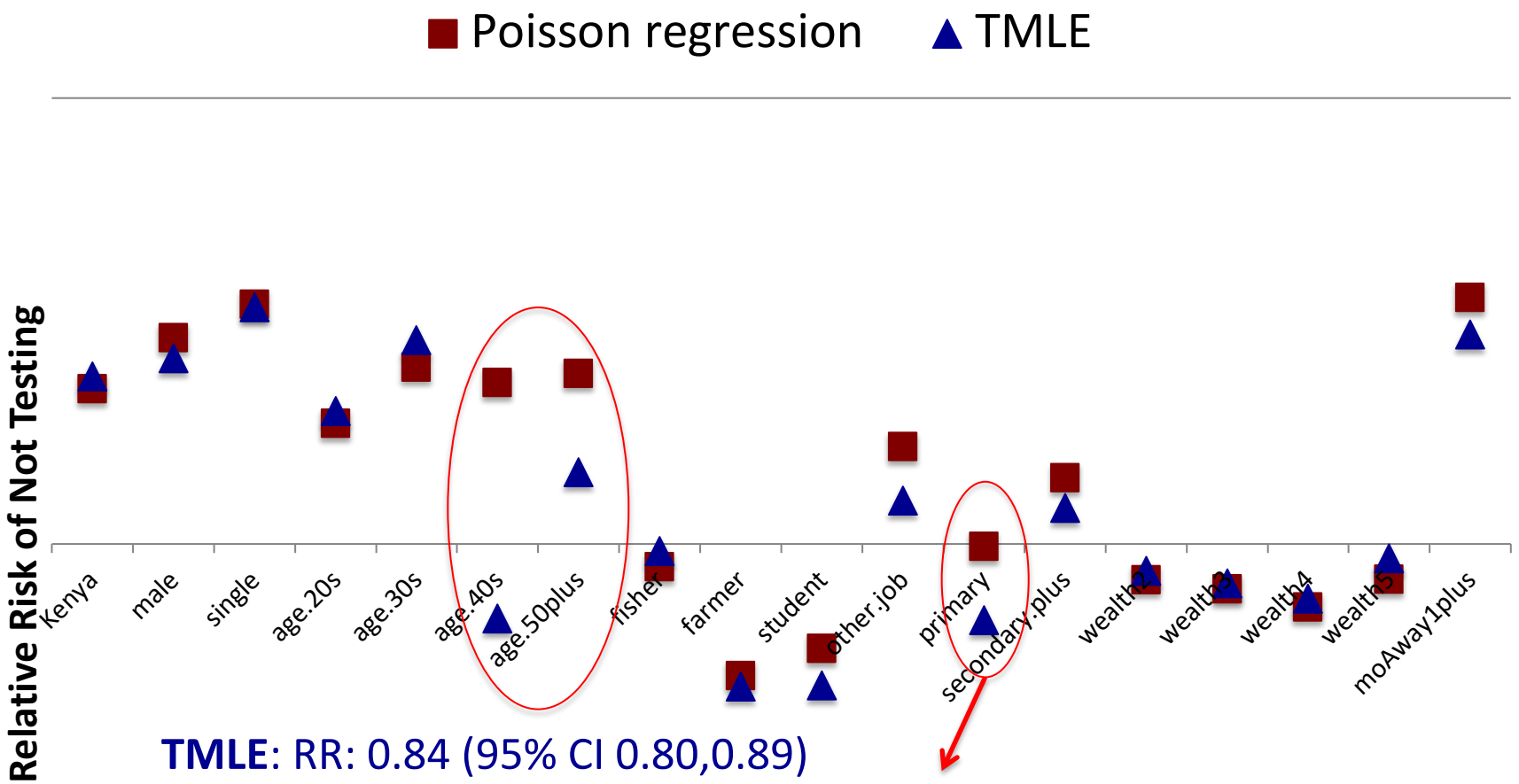
- SEARCH HIV Prevention Trial
  - www.searchendaids.com
  - 89% baseline population testing coverage
- **Determinants of baseline HIV testing uptake?**
  - Without causal assumptions: adjusted predictors
- **Many covariates**: Region, age, gender, occupation, marital, education, wealth, mobility
- **Parametric regression… how to specify?**
  - Logistic? Poisson? Which variables? Which interactions?

Chamie et al, *Lancet HIV*, 2016

Does it matter in practice?

- Not always, but sometimes
  - Estimates from standard approach and TMLE sometimes very similar
  - But sometimes, estimates and inference can change
- Example: HIV testing uptake in SEARCH Trial
  - Goal: estimate the relative risk of not testing, adjusting for other covariates
  1. Poisson regression
  2. TMLE

Ex. HIV Testing Uptake in SEARCH



TMLE: RR: 0.84 (95% CI 0.80,0.89)

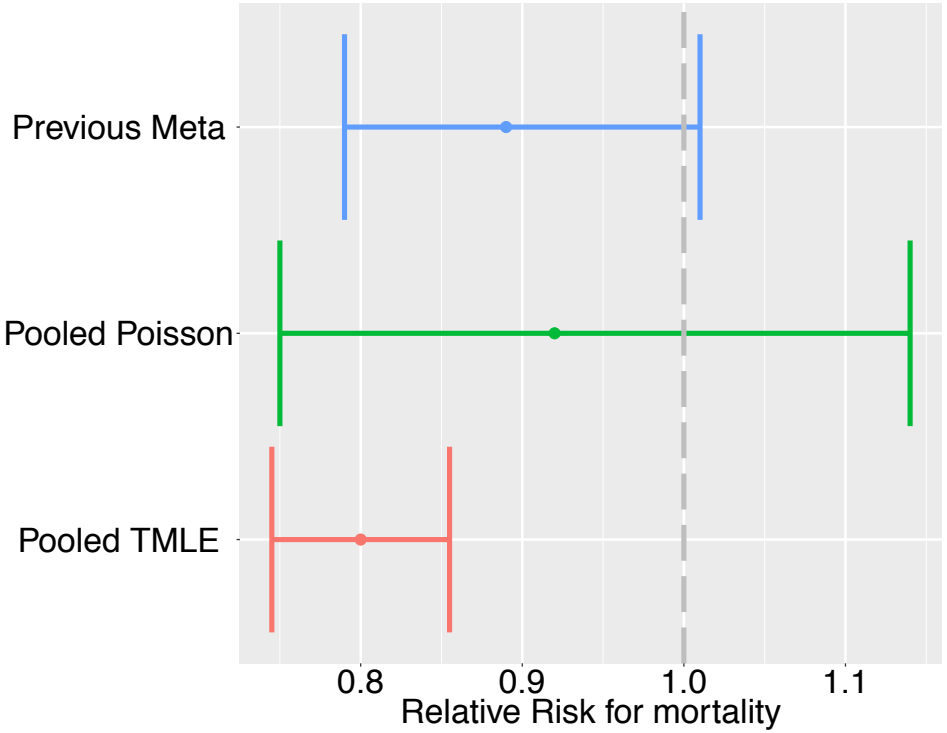
- *Adults with a primary education more likely to test than those with less than a primary education*

Poisson: RR: 0.99 (95% CI 0.94, 1.05)

- *No difference*

TMLE for RCTs

- Do corticosteroids reduce mortality for adults with septic shock?
  - 35 randomized trials, ~5000 patients: still no answer



Previous Meta-Analysis of 35 trials: **No significant benefit**

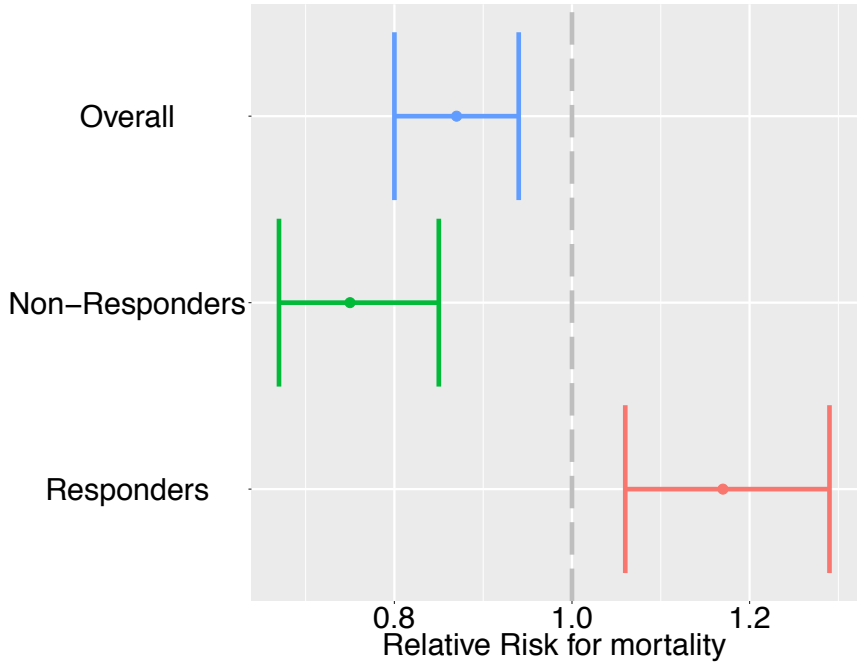
Pooled analysis of 3 major RCTs (1300 patients) with standard methods: **No significant benefit**

Pooled analysis of 3 major RCTs using **Targeted Learning**: **Significant reduction in mortality**

Pirracchio 2016

Not just is there an effect, but for whom?

- In Sepsis re-analysis: Targeted Learning showed **all benefit** occurred in a key subgroup
  - Heterogeneity in patient populations one cause of inconsistent results



Effect Heterogeneity by Response to ACTH Stimulation

Pirracchio 2016

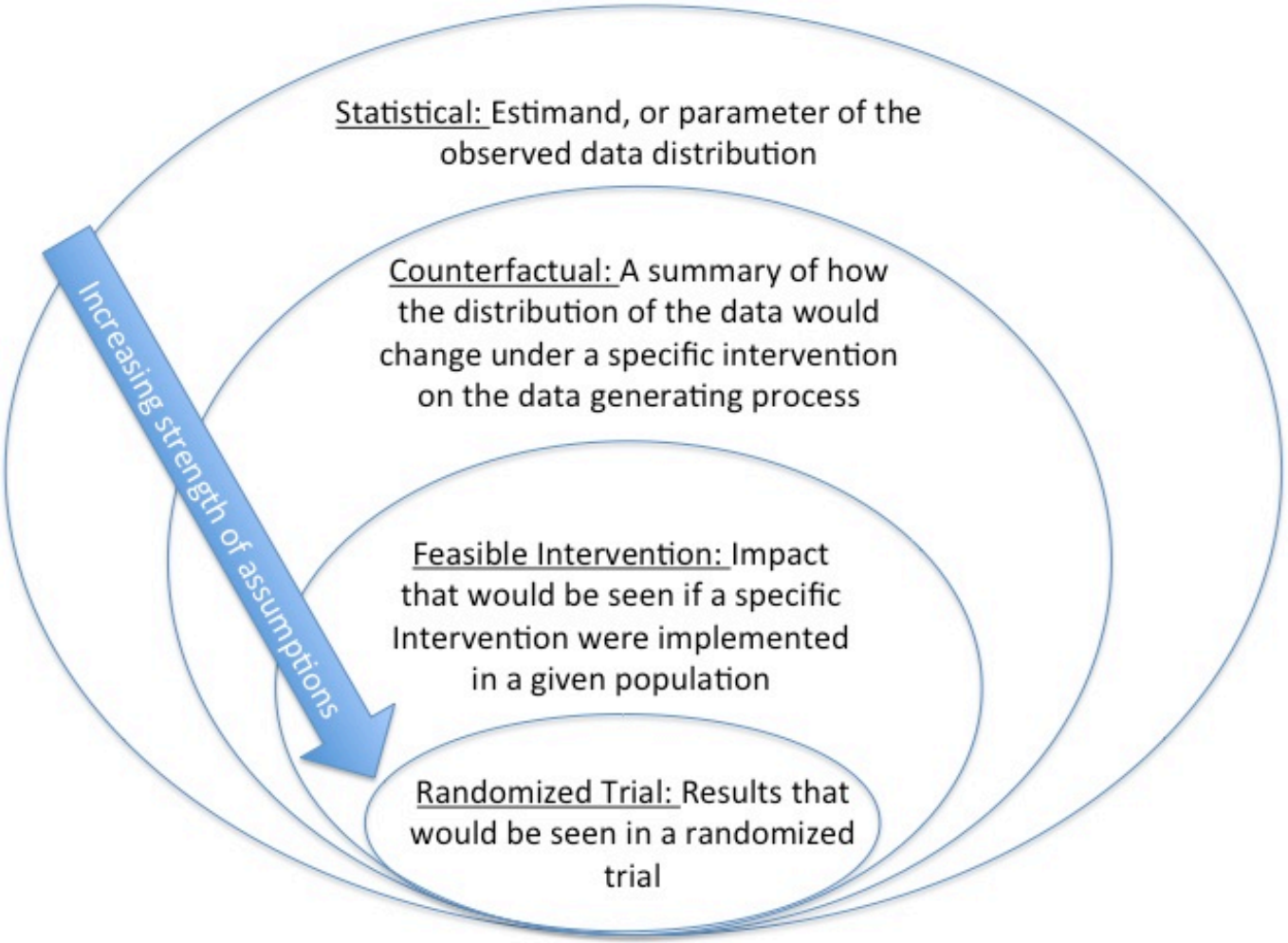
Interpretation

1. Various approaches to interpreting results
2. Wrap up and frontiers

Back to the Roadmap

1. Specify **Causal Model** representing real background knowledge
2. Specify **Causal Question**
3. Specify **Observed Data** and link to causal model
4. **Identify** : Knowledge + data sufficient?
5. Commit to an **estimand** as close to question as possible, and a **statistical model** representing real knowledge.
6. **Estimate**
7. **Interpret** Results

A Hierarchy of Interpretations



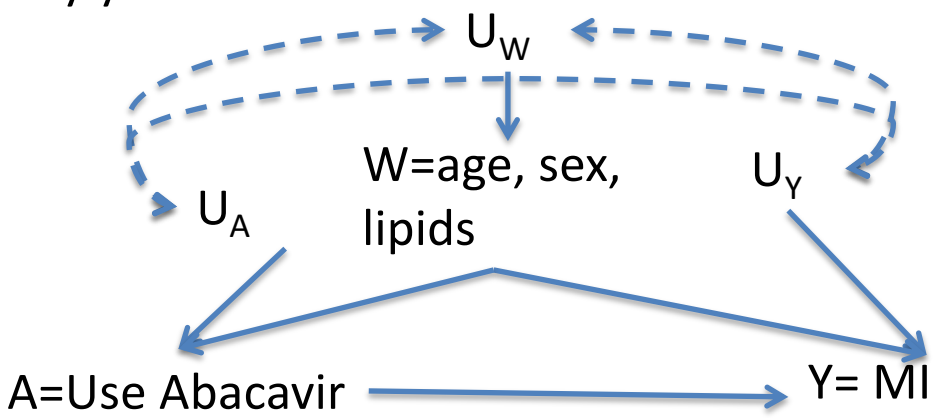
Petersen and van der Laan, *Epidemiology* 2014

Example: Abacavir and Cardiovascular Disease

- Analysis of observational data from several cohorts suggested abacavir use associated with increased risk of myocardial infarction among treated HIV-infected population
  - Other analyses found no evidence of such an association….
- Example of a causal question: Does use of abacavir (ABC) increase risk of myocardial infarction (MI)?

Example: Abacavir and Cardiovascular Disease, point treatment version

- X=O=(W,A,Y)
  - W= baseline covariates (age, sex, lipid profile) measured at start of ART
  - A= Indicator First ART Regimen contains Abacavir
  - Y= Myocardial Infarction by year 5



- Target Causal Parameter: $E_{U,X}(Y_1-Y_0)$

$$\Psi(P_0) = \sum_w E_0(Y \mid A=1, W=w) - E_0(Y \mid A=0, W=w) P_0(W=w)$$

$$\hat{\Psi}(P_n) = 0.02 \ (95\% \text{ CI: } 0.01, 0.03)$$

Statistical Interpretation

- An estimate of our statistical target parameter
  - Ex: Difference in probability of developing MI by year 5 among subjects with identical age, sex, and lipids who started ART with vs. without Abacavir, standardized to the age, sex and lipid distribution of the whole population
- Quality of the estimate depends on
  - Whether statistical model contains the truth
  - Sample size/ data support for the estimand
  - Estimator

Counterfactual Interpretation

- Change in (some aspect of) the outcome distribution under hypothetical modification to conditions under which data were generated
  - Ex. Difference in counterfactual probability of MI by year 5 under under hypothetical intervention in which whole population started an ART regimen with abacavir versus if no one did
- Moving from statistical to counterfactual interpretation requires that untestable identifiability assumptions hold
  - Ex. Under the assumption that age, sex, and lipids satisfy the backdoor criteria (ie are sufficient to adjust for confounding)

Real World Interpretation

- What would we see if an intervention were implemented in the real world?
- Moving from counterfactual to real world interpretation requires
  - Same intervention
    - or “Treatment variation irrelevance” (eg vanderWeele)
  - Same data generating process
    - Relaxing this: Transportability (eg Pearl, Bareinboim)
  - Ex: Same use of other drugs in the regimen, how the assignment occurs (ie. via a policy vs. patient/provider preference) doesn’t change the effect…

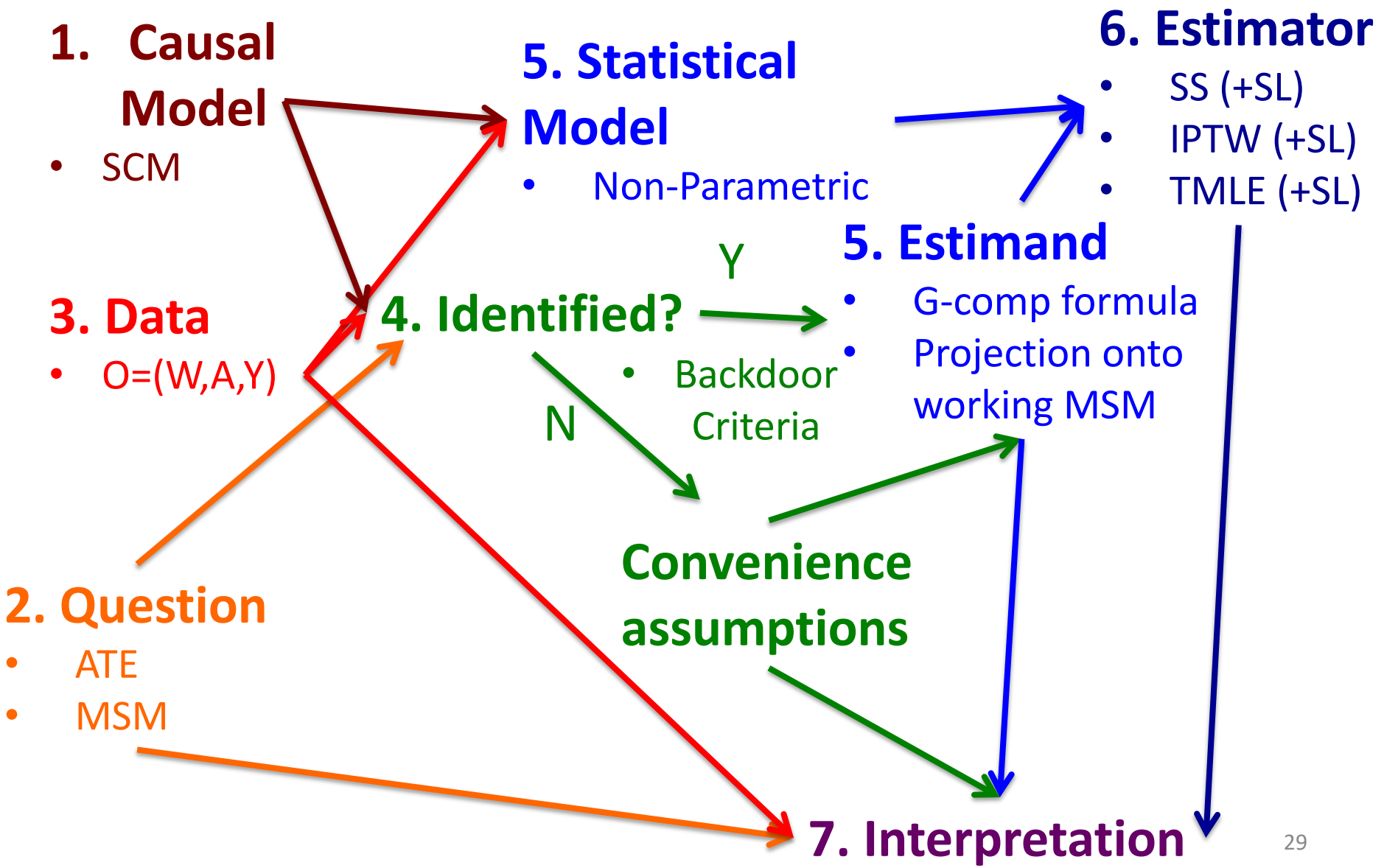
RCT Interpretation

- What would we see if an intervention were evaluated in a randomized trial
  - Ex: Subjects starting ART were randomly assigned to regimen with versus without abacavir
- Moving from real world to RCT interpretation requires
  - Effective randomization
  - Perfect compliance
  - Perfect follow up

Interpreting Results: Take Home Points

- Always have a statistical interpretation
  - If your statistical model contains the truth, you have enough support in your data, and you choose a good estimator
- How far to go beyond this is up to you/reader/policy maker
- Should be based on a frank evaluation of the plausibility of the assumptions required

What have we accomplished?



This is just the beginning…

1. Specify a Casual Model

- We have focused on SCM of Pearl
- Other formal Casual frameworks
  - "Neyman-Rubin" Potential Outcome
  - Dawid: Decision Theoretic
  - Robins & Richardson: Minimal Causal Model
  - Etc…
  - Differ in extent and type of non testable assumptions, assumptions about the nature of causality, etc…

2. Specify Causal Question

- We have focused on using counterfactuals to define
  1. "Point treatment effects": Static intervention on a single variable
  2. ATE and parameters defined using a (working) MSM
- LOTS more options
  - Interventions on multiple nodes
  - Dynamic (ie personalized or adaptive) interventions
  - Mediation
  - Etc…
  - Review: Petersen & van der Laan *Epidemiology* 2014

3. Specify observed data and its link to the casual model

- We have focused on independent random samples: n i.i.d. copies of $O=(W,A,Y)\sim P_0$
- Lots of more complex data structures and links
  - Hierarchical data
  - Longitudinal data, Missingness
  - Case control sampling
  - “Adaptive randomization”
  - Etc…

4. Identify

- We have focused on the Back-door criteria/ Randomization assumption
- Many more identifiability results
  - Ex. Front door criteria, Instrumental variables
  - Ex. Sequential back door criteria for multiple intervention nodes
  - Etc.
- Causal frameworks provide a tool for developing these-> new statistical estimand that under specific assumptions give us a wished for causal quantity

5. Commit to a Statistical Model and Estimand (Target parameter of the observed data distribution)

- We have focused on a non-parametric statistical model for P_0
- If your have real model knowledge, by all means use it
  - Straightforward to incorporate in SCM
  - Ex: You know something about how the exposure was assigned
- Statistical model should contain the truth

6. Estimate

- We have focused on three estimators
  - Simple (or non-targeted) substitution estimator
  - Inverse probability of treatment weighted estimator
  - TMLE
  - Inference based on NP- bootstrap or IC
- Each of these requires doing a good job estimating some part of the observed data distribution well
  - $E_0(Y|A,W)$, $g_0(A|W)$, or both
  - We focused on data adaptive methods (and in particular Super Learning) to help ensure this
- Other estimators for same quantity exist
  - Ex. Propensity score matching, using the estimated propensity score as a dimension reduction…

7. Interpret.

- My perspective: A target causal parameter need not correspond to feasible randomized experiment, or hypothetical intervention in order to be of interest
- There is lots of debate on this topic! Decide for yourself….
  - See Petersen & van der Laan *Epidemiology* 2014 for a brief review and some key references to get started

Formal Causal Frameworks provide a very general toolbox to…

1. Represent background knowledge and uncertainty more accurately
2. Frame sharper questions
3. Evaluate/improve plausibility of assumptions
4. Optimize analysis to give best possible answer to motivating question
5. More accurately evaluate uncertainty/make better inferences

Use your tools well!