A Nonparametric Framework for Treatment Effect Modifier Discovery in High Dimensions

Causal Inference in Randomized Studies - ACIC 2023

Philippe Boileau, UC Berkeley — May 2023

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Motivation

Metastatic Renal Cell Carcinoma

Finding biomarkers predictive of clinical benefit

(Previous) standard of care, tyrosine kinase inhibitors, are ineffective

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IMmotion 150
Phase 2

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vs
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Metastatic Renal Cell Carcinoma

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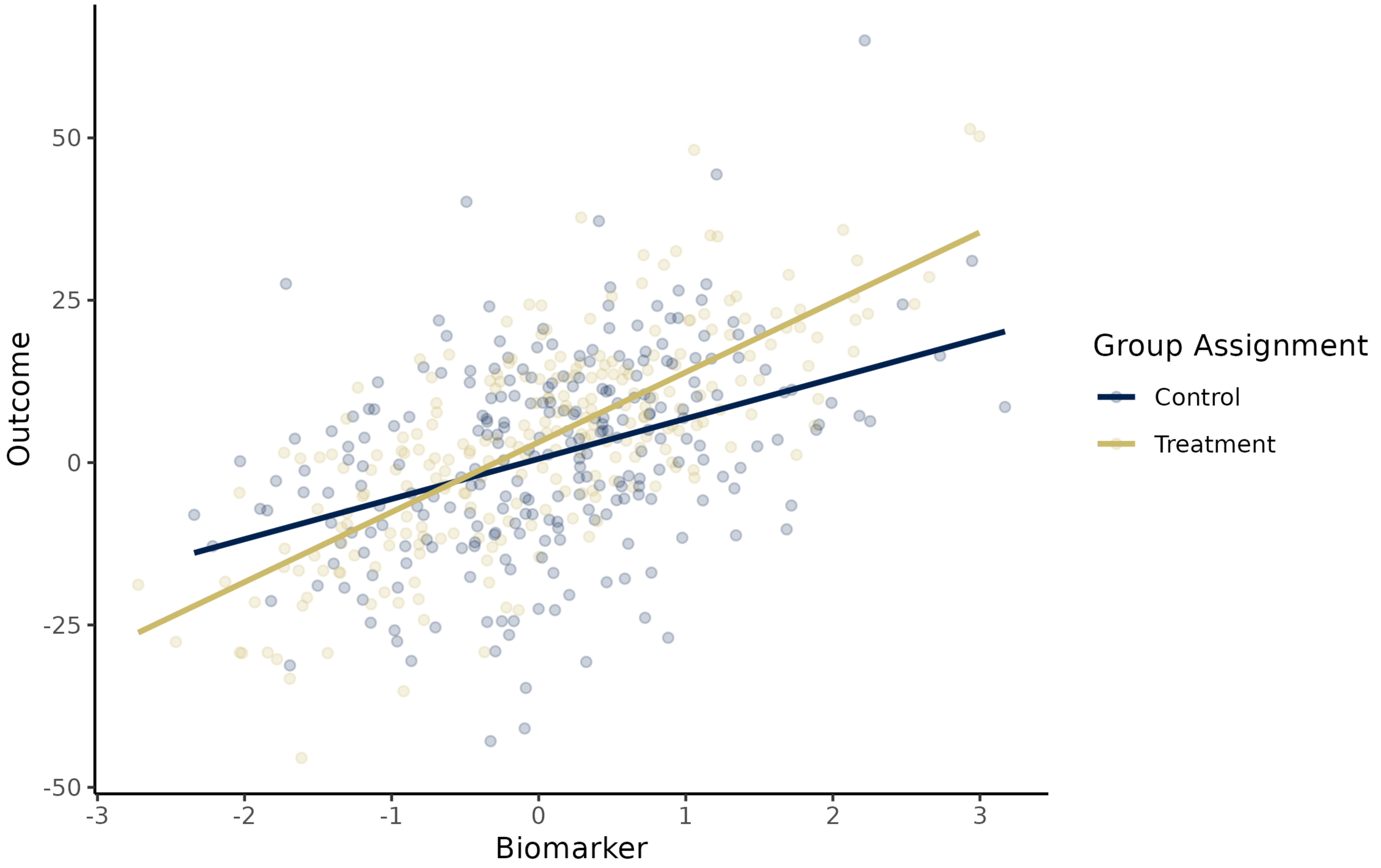
Predictive Biomarkers: Treatment Effect Modifiers



Predictive Biomarker Applications

Predictive biomarkers drive personalized medicine

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Predictive biomarkers drive personalized medicine

- **Diagnostic assay development:** Who benefits most from a therapy?
- **Targeted drug discovery**: What is the biological mechanism of a therapy?
- **Refined clinical trials**: Establish a subset of the patient population for which therapy is more efficacious?

Discovering Treatment Effect Modifiers

A variable selection problem

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  - Linear models with treatment-biomarker interaction terms
  - Conditional average treatment effect (CATE) estimation
- Harder when there are a large number of biomarkers: Penalized versions of the above methods are used.
- **Bottom line**: Discovery of predictive biomarkers is the byproduct of another inference procedure.

Example: Modified Covariates Approach

Tian et al. (2014): A Simple Method for Estimating Interactions between a Treatment and a Large Number of Covariates

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transformed outcome = treatment + treatment x biomarker 1 + … + treatment x biomarker p

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Predictive biomarkers have non-zero coefficients

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We need to consider alternative problem formulations.

Variable Importance Parameters

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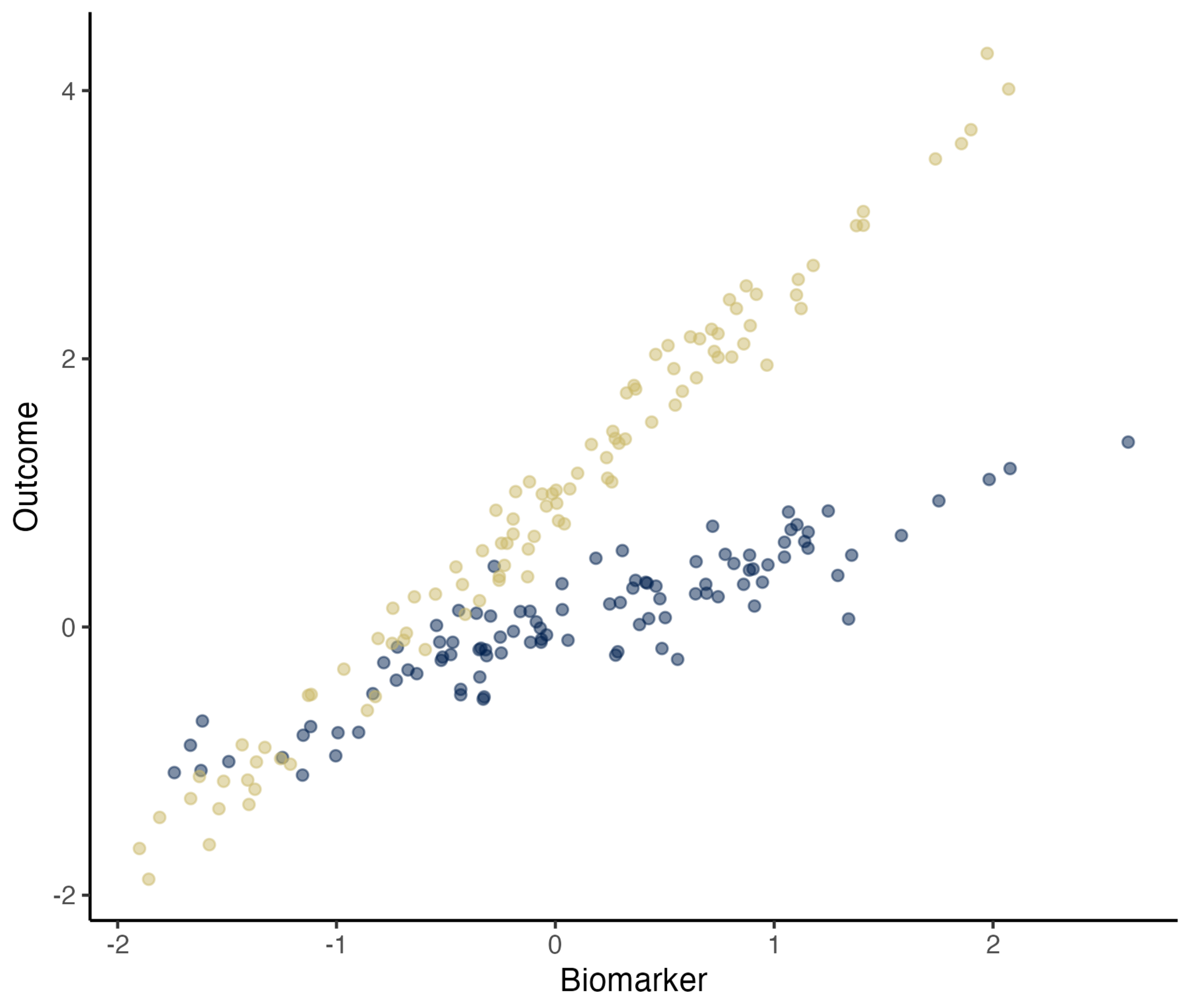

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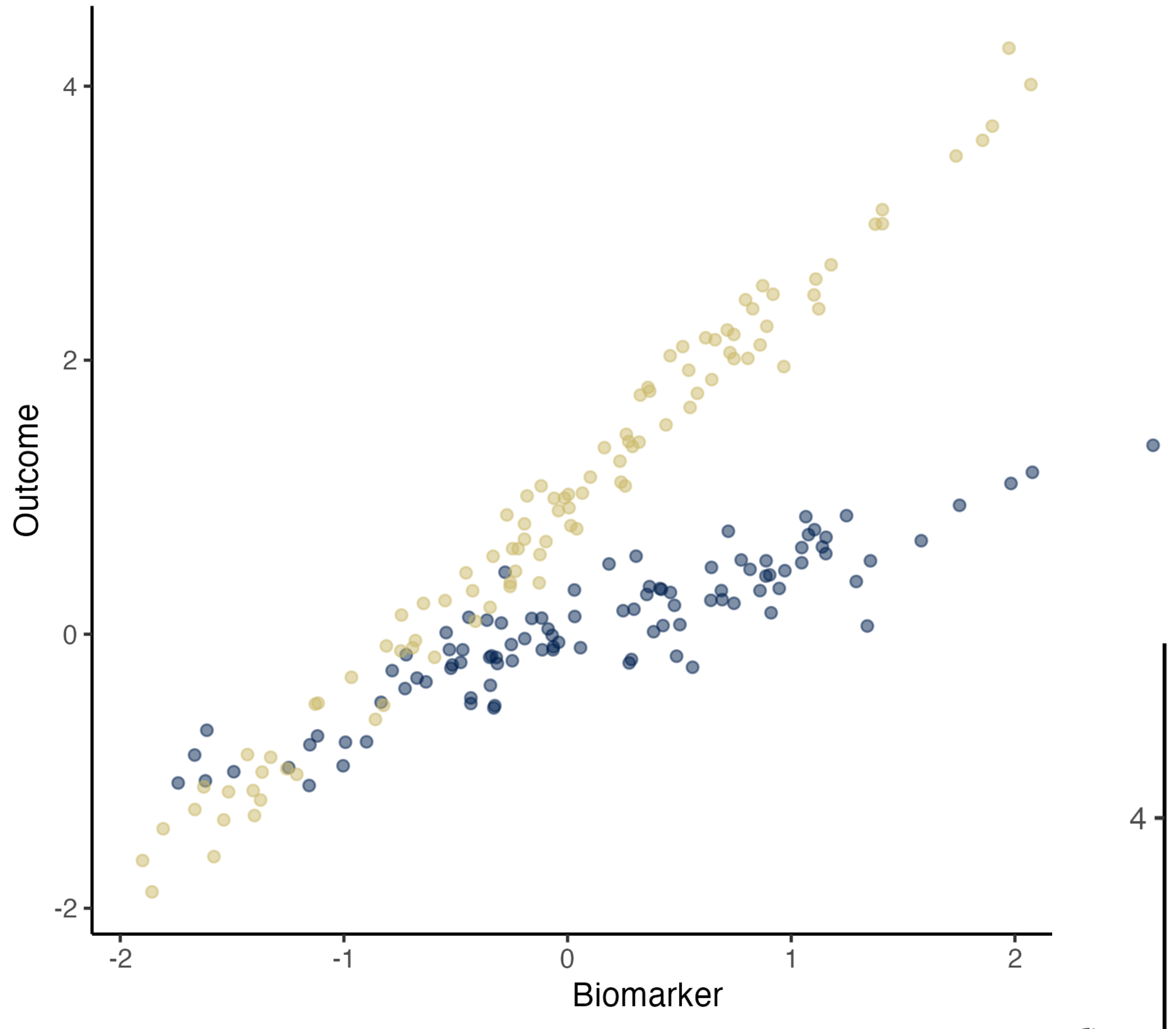

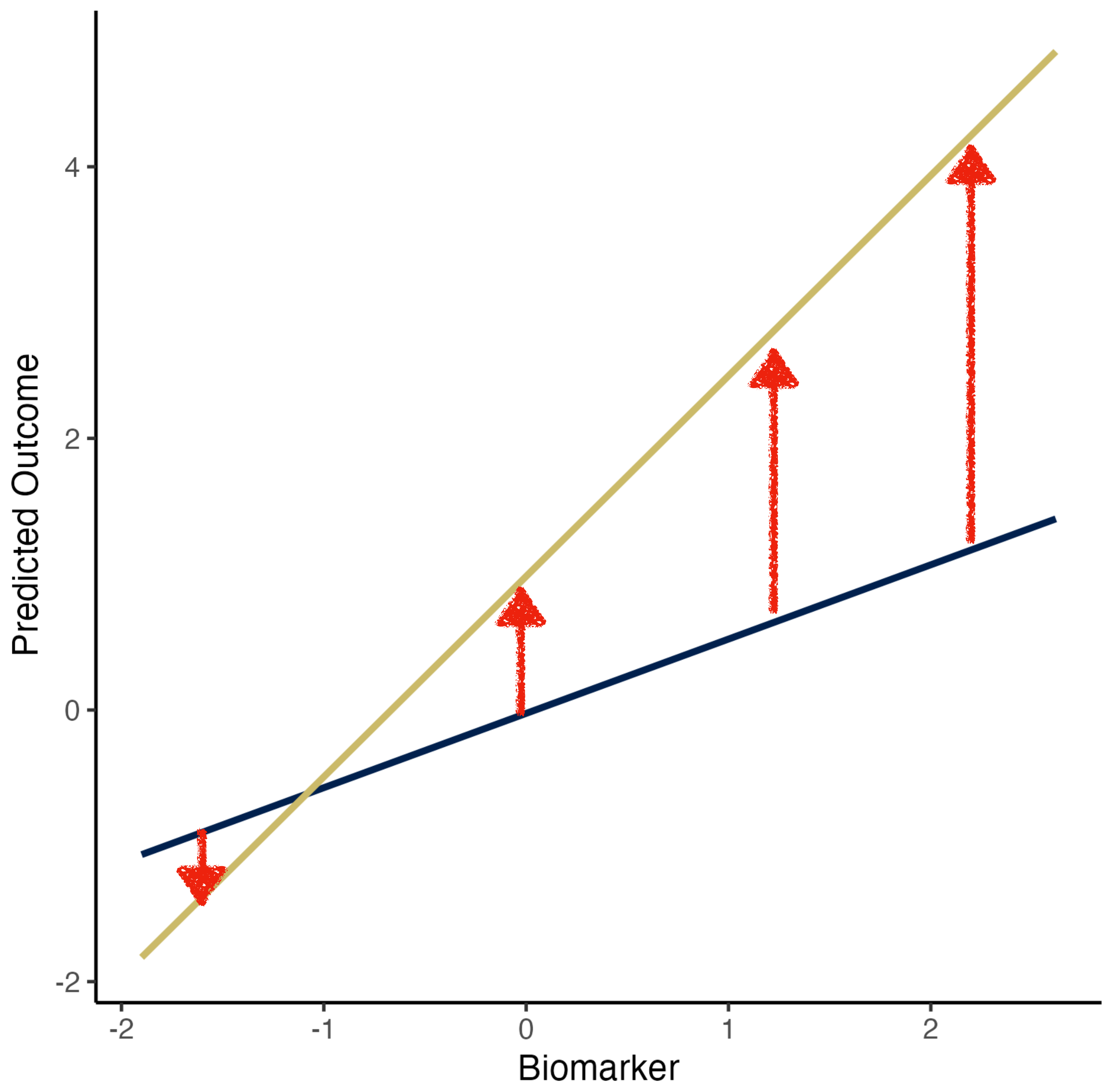

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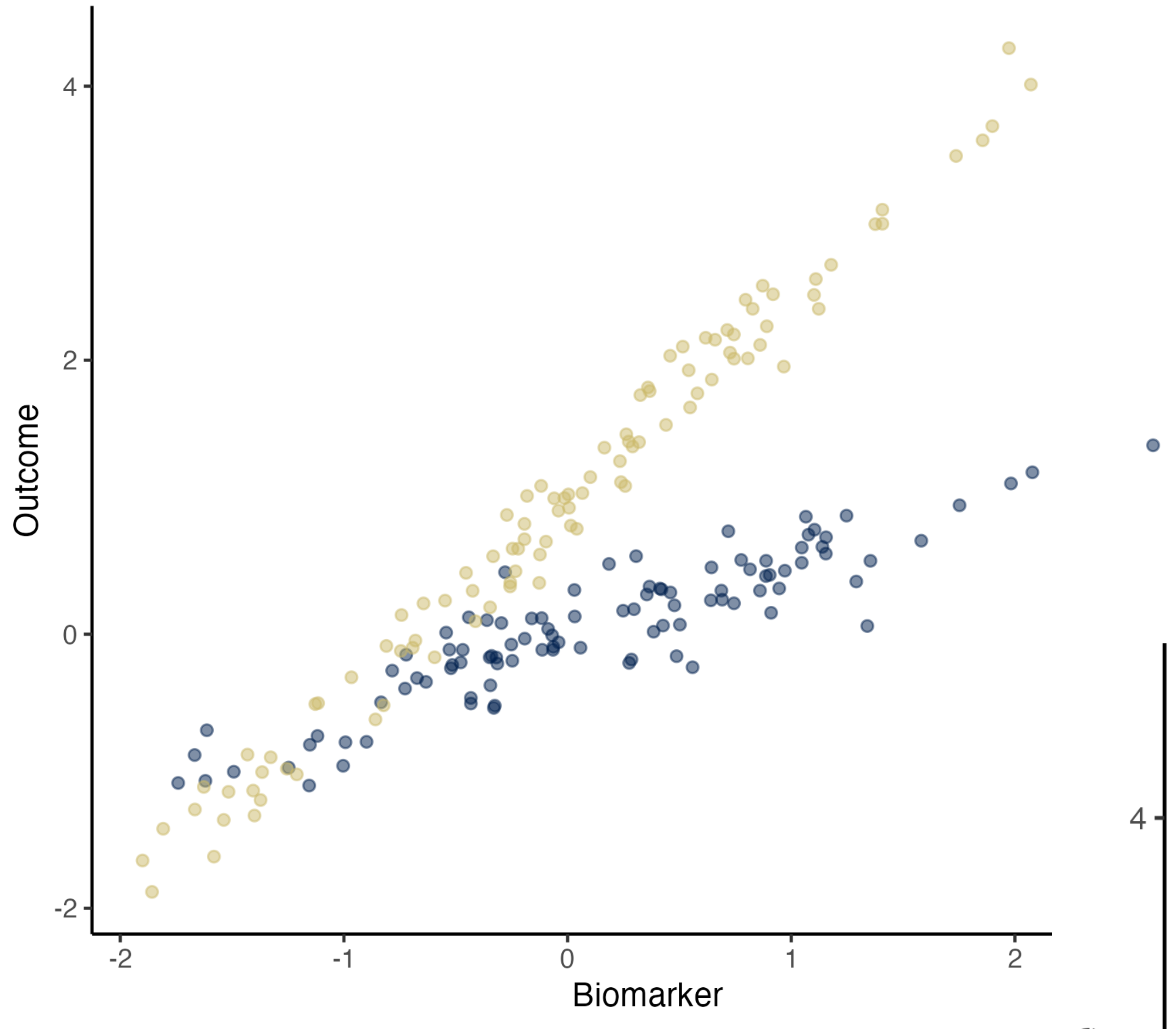

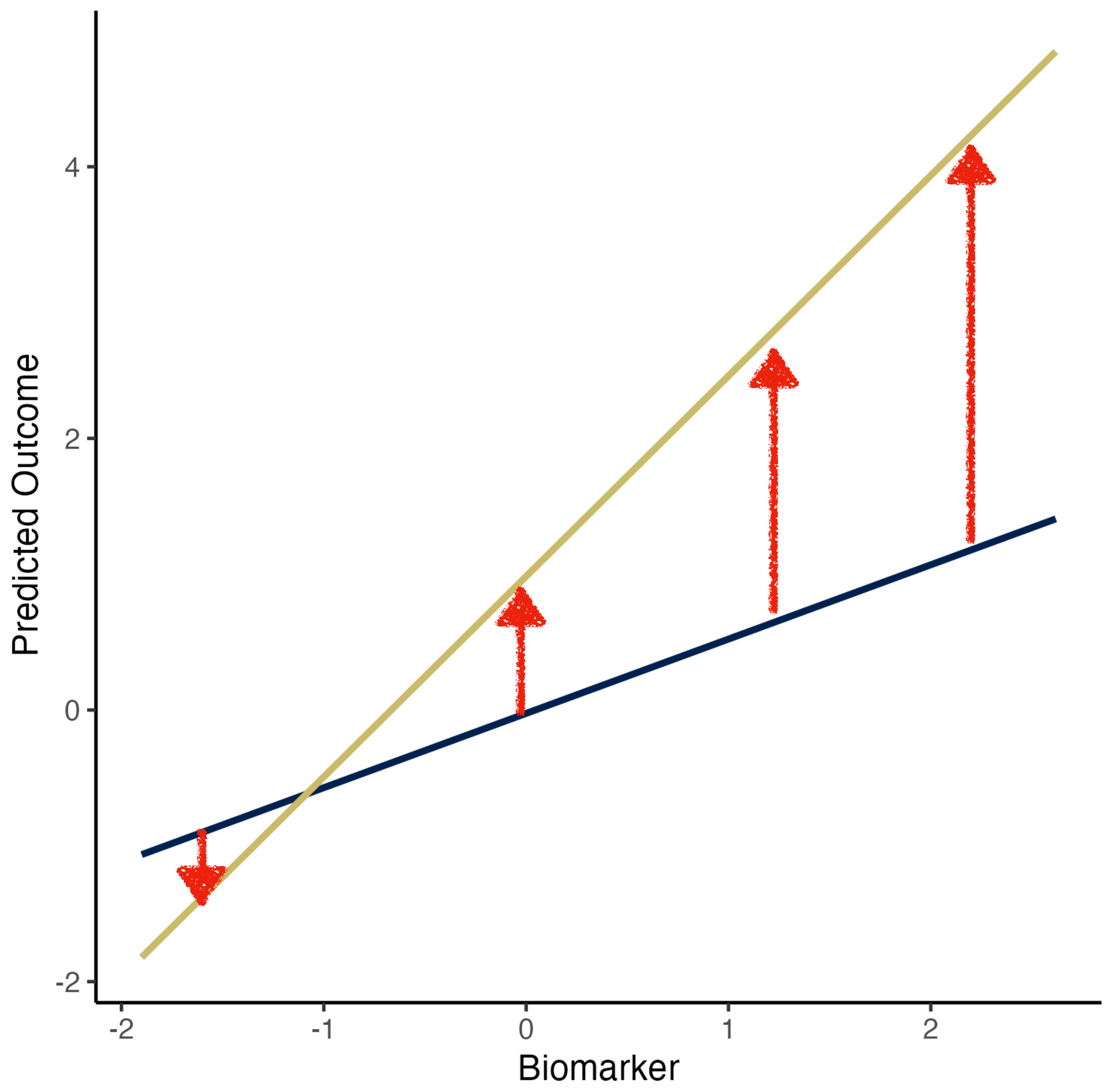

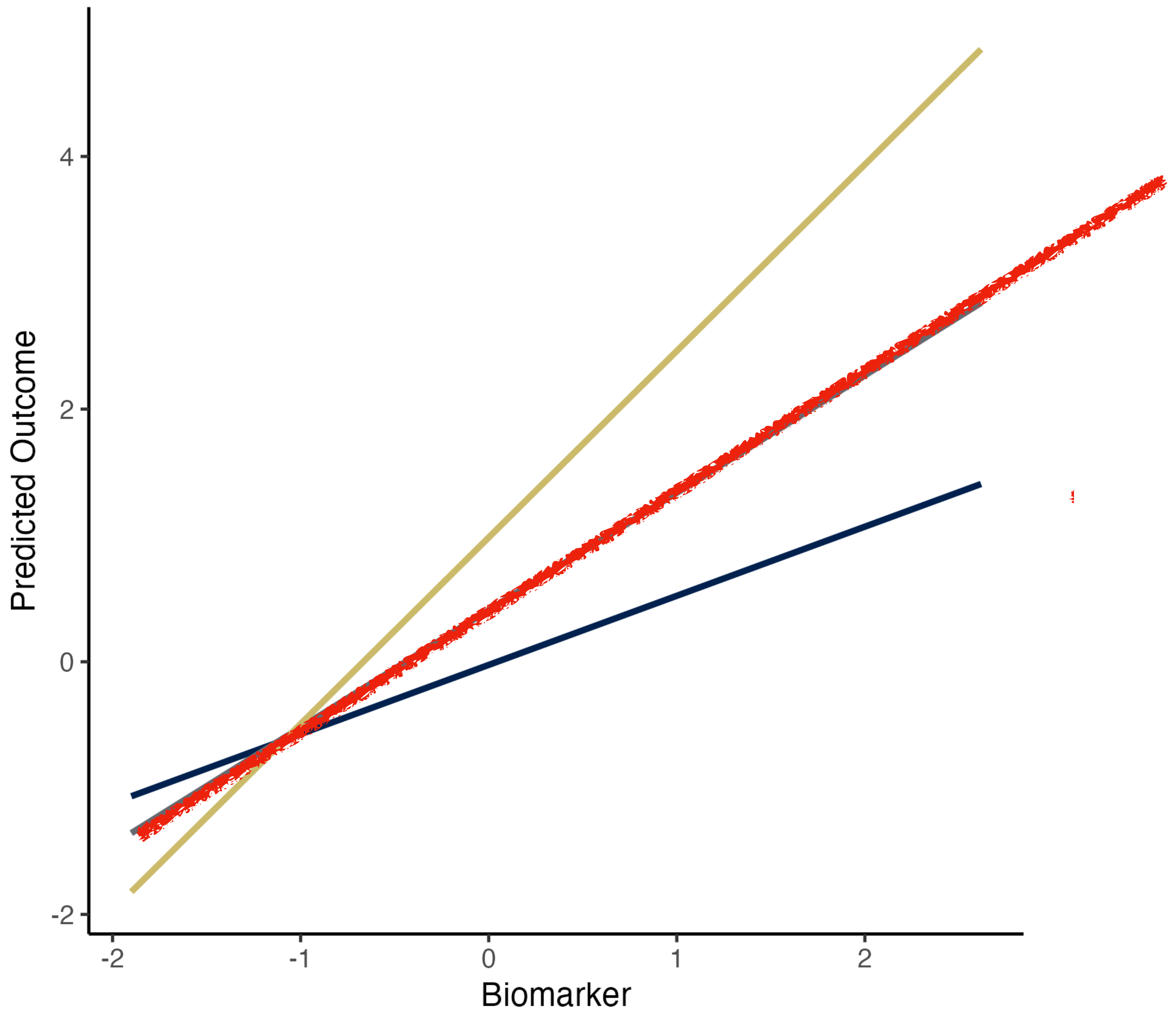

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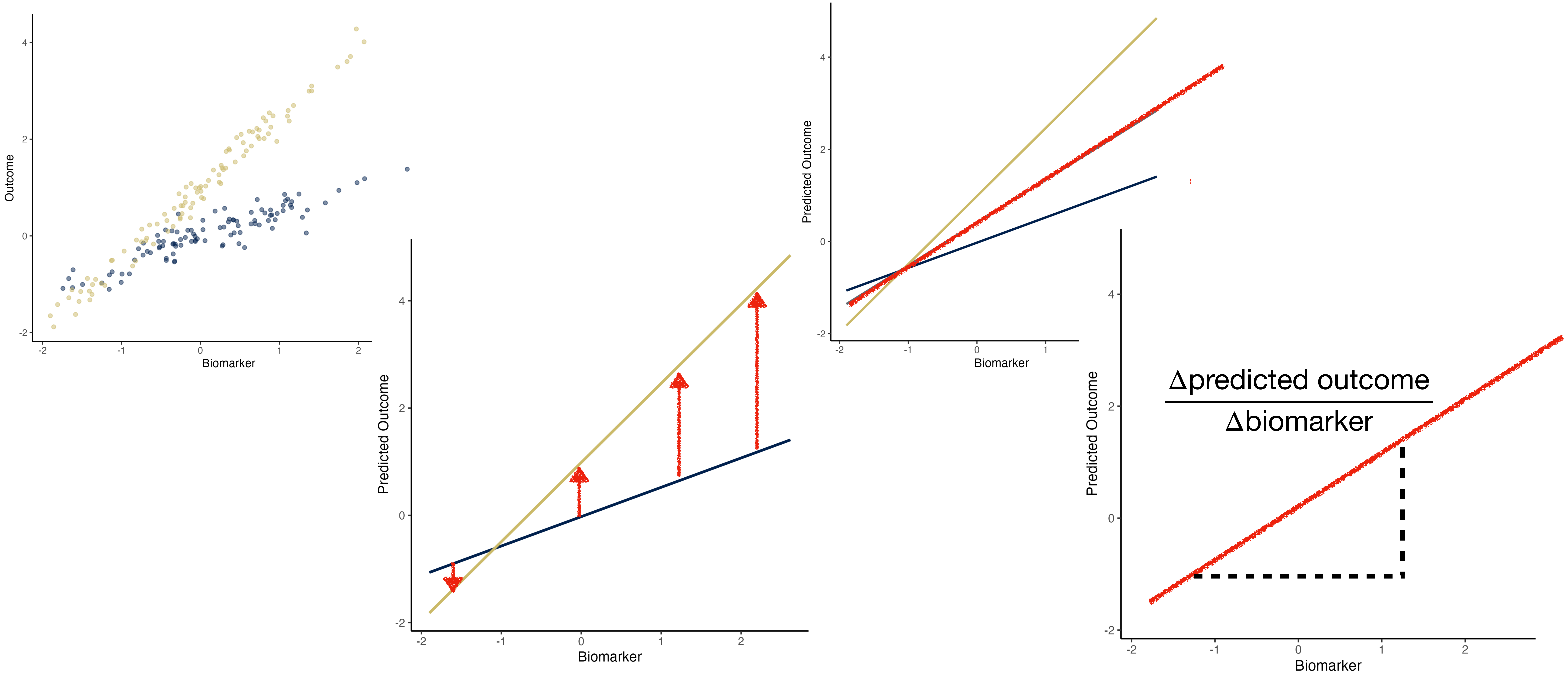

Treatment Effect Modifier Variable Importance Parameters

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Pathwise differentiable treatment effect parameter

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Define univariate conditional parameter

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TEM-VIP:
Projection of conditional parameter onto simple linear model

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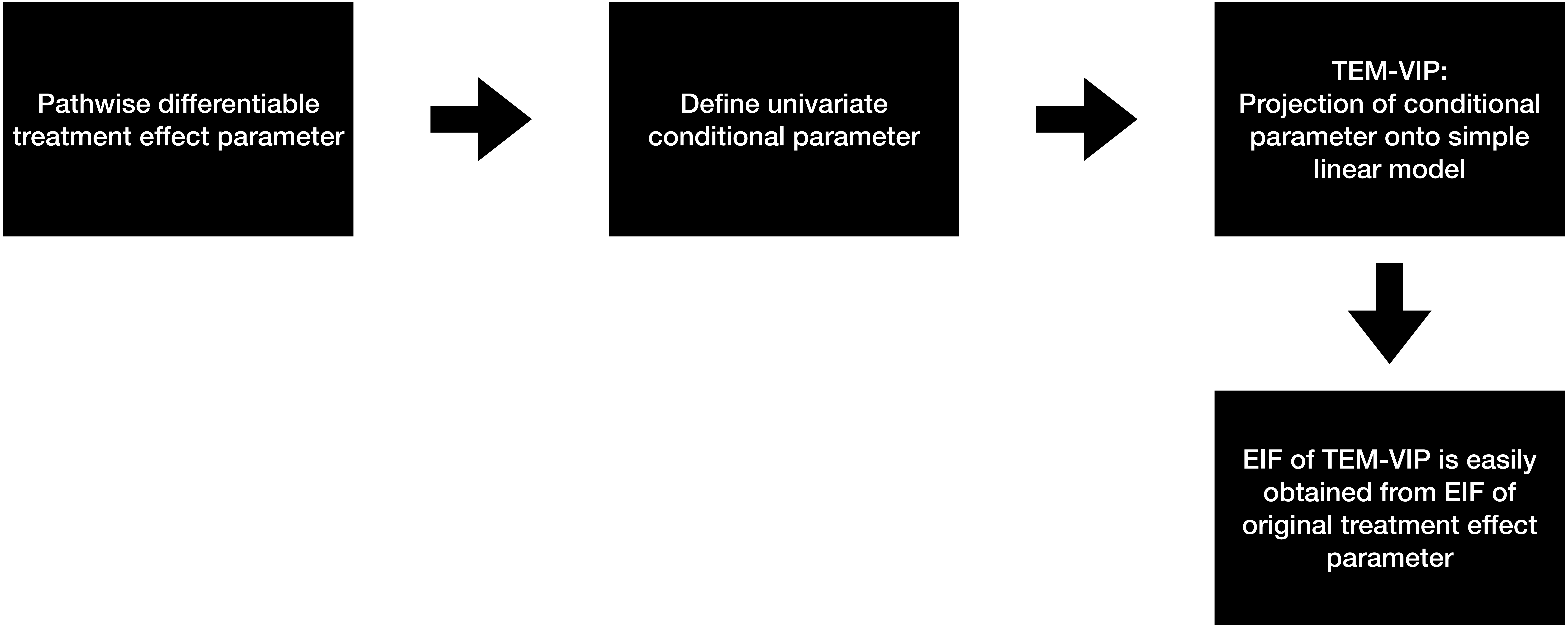

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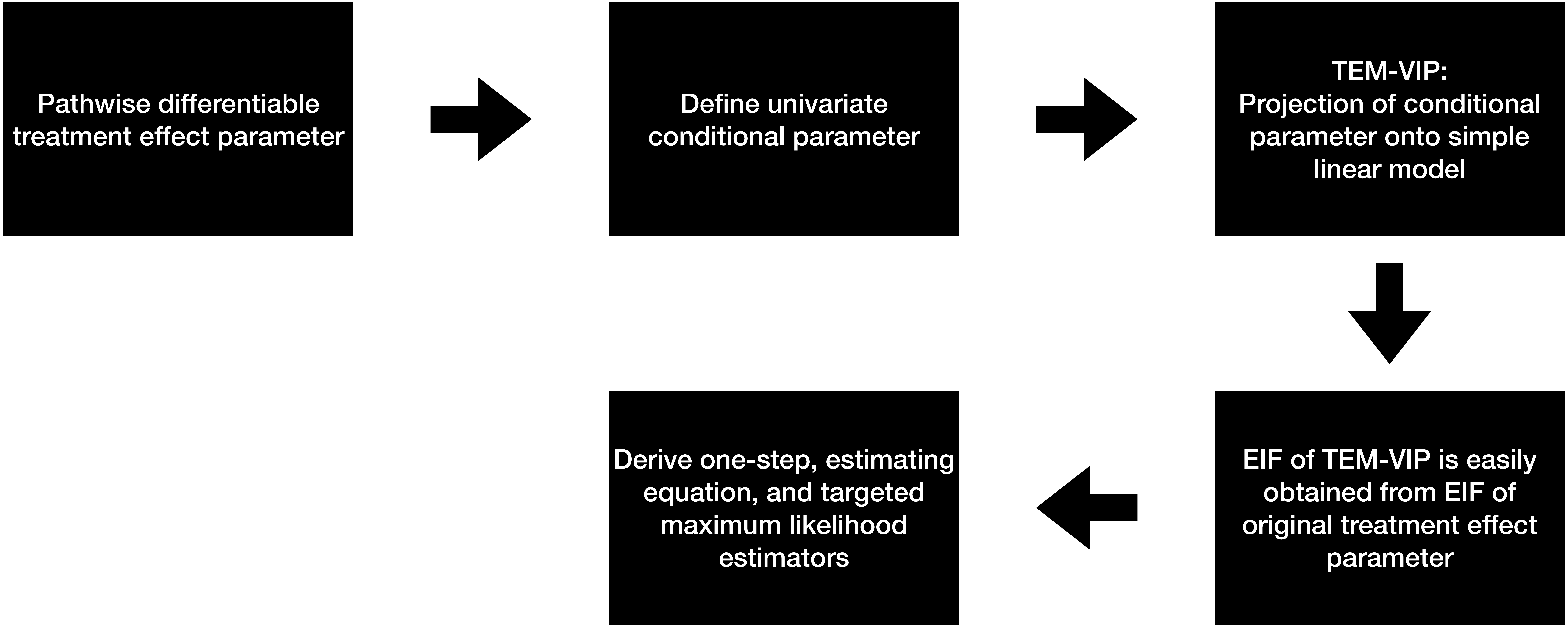

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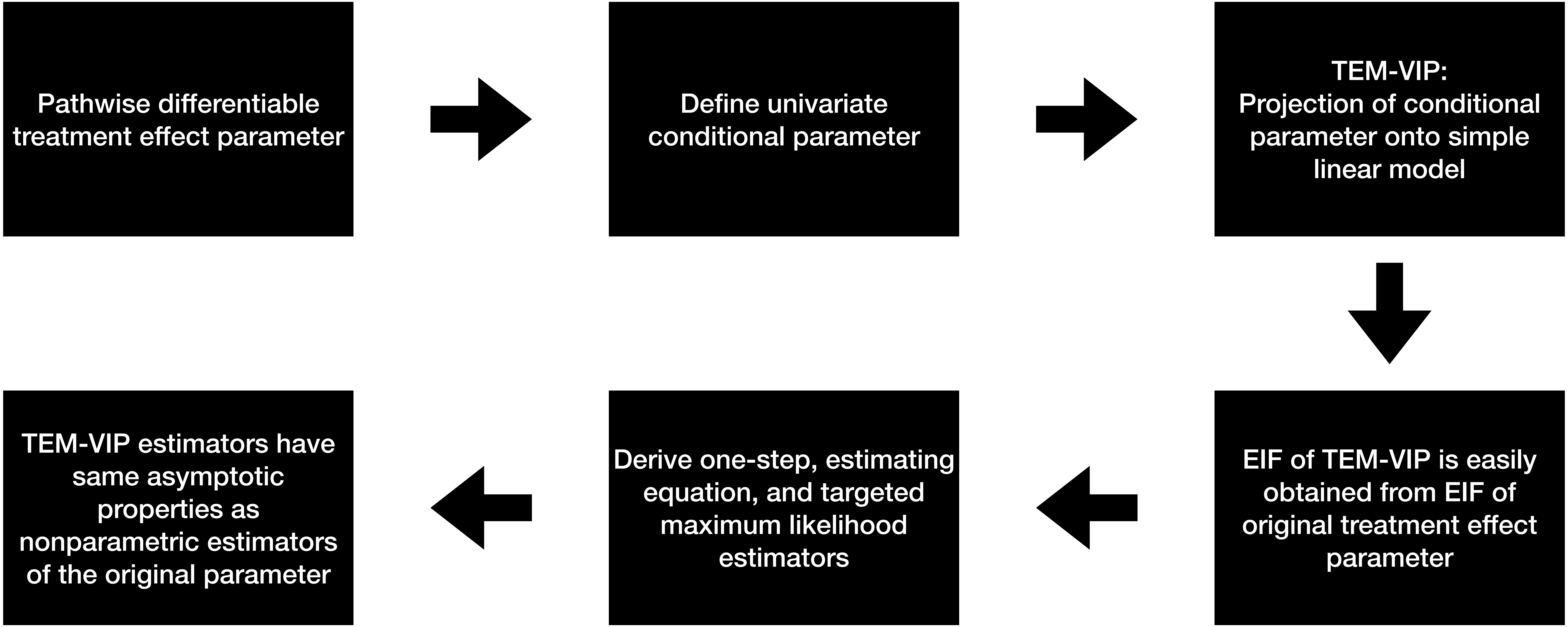

TEM-VIP Examples

Treatment Effect	Effect Type	Outcome Type
Average treatment effect	Absolute	Continuous
Average treatment effect	Absolute	Binary
Average treatment effect	Absolute	Count
Relative risk	Relative	Positive continuous
Relative risk	Relative	Count
Relative risk	Relative	Binary
Restricted mean survival time	Absolute	Right-censored time-to-event
Survival time ratio	Relative	Right-censored time-to-event

ATE-Based Absolute TEM-VIP in Action

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```
n ← 200
biomarker_1 ← rnorm(n, mean = 0, sd = 1)
biomarker_2 ← rnorm(n, mean = 0, sd = 1)
biomarker_3 ← rnorm(n, mean = 0, sd = 1)
biomarker_4 ← rnorm(n, mean = 0, sd = 1)
covariate ← rbinom(n, 1, 0.4)
treatment ← rbinom(n, 1, 0.5)
response ← covar + 1 * biomarker_1 * treatment
              + 2 * biomarker_2 * treatment
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	Est.	**SE**	**Z-score**	**P**	**P (BH)**
biomarker_2	1.90	0.0768	24.7	3.58E-13	1.43E-13
biomarker_1	0.820	0.129	6.38	1.75E-10	3.51E-10
biomarker_3	0.0482	0.145	0.333	7.39E-01	9.03E-01
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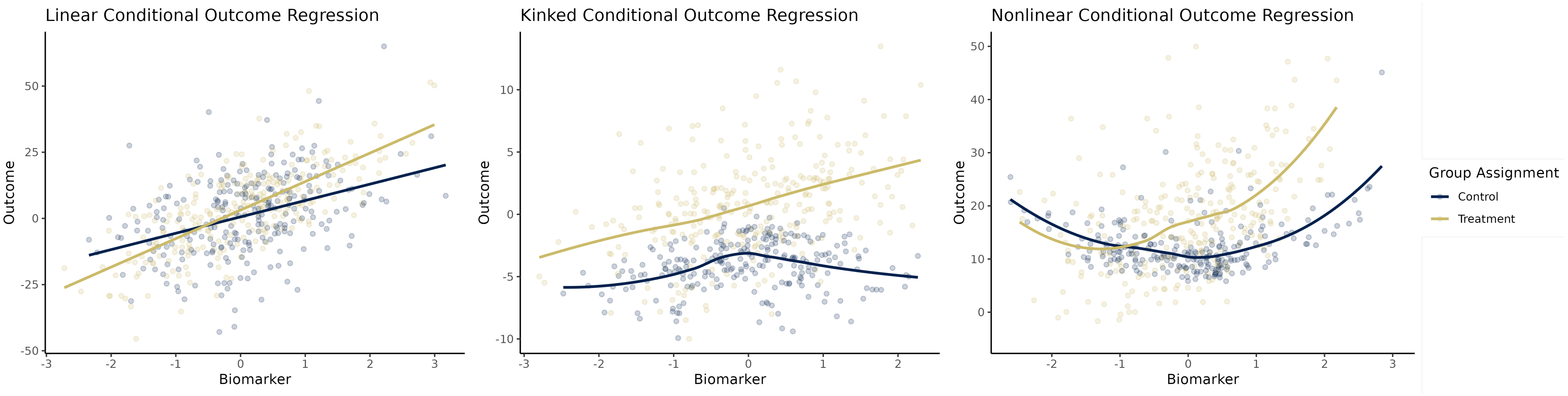
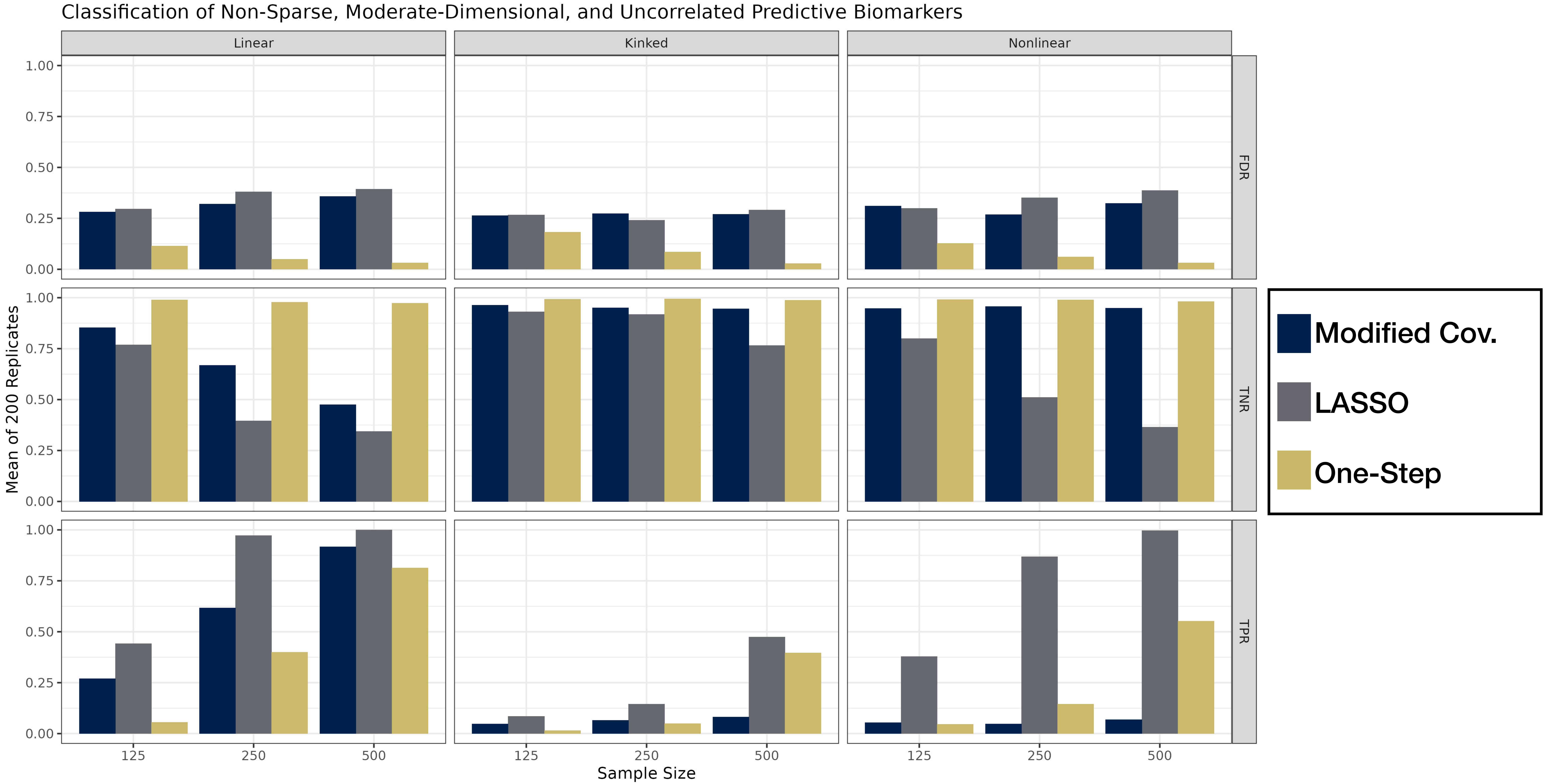
Simulation Study: ATE-Based Absolute TEM-VIP

Simulations: Assess Finite Sample Behaviour

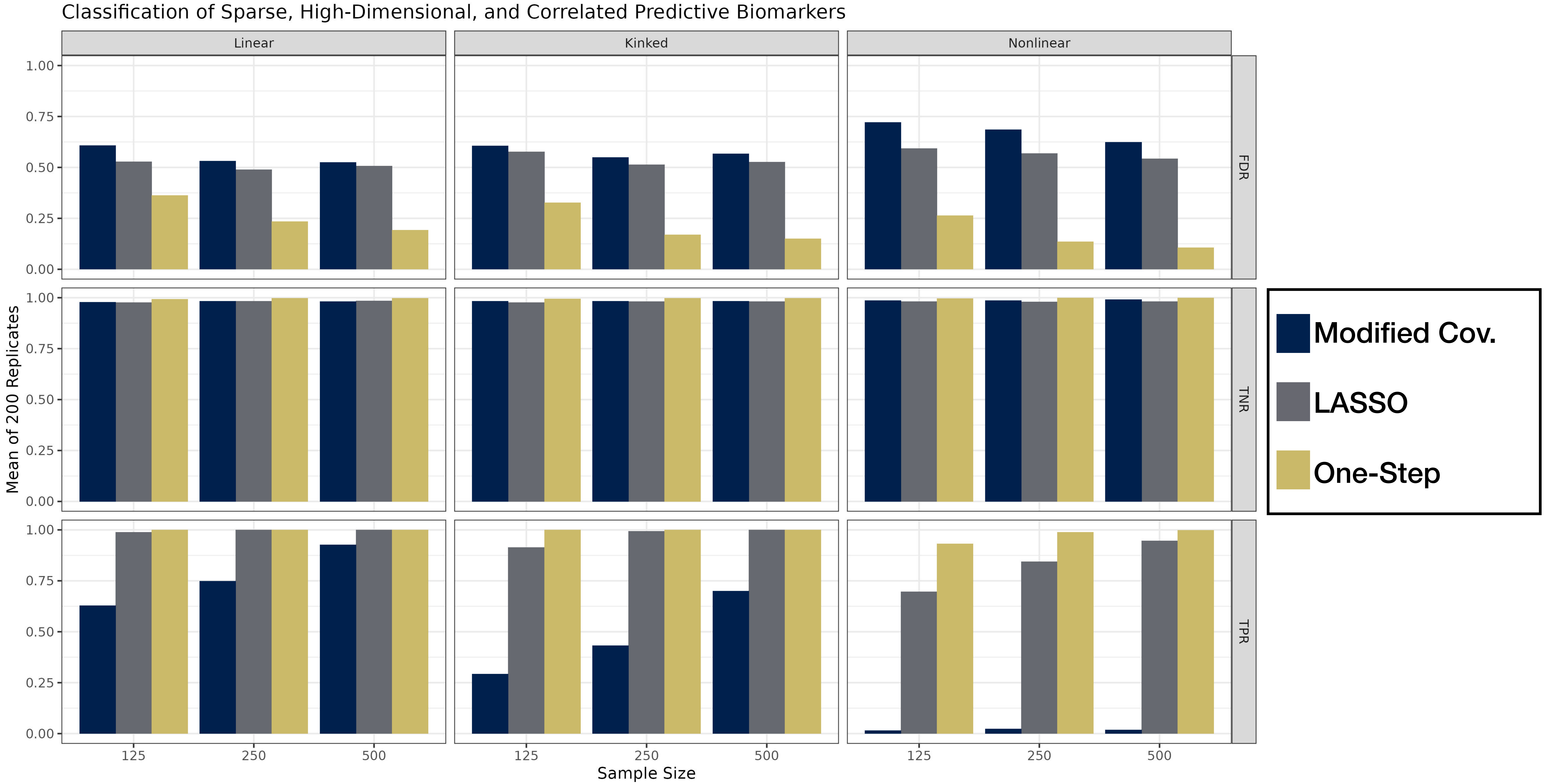


Difficulty

One-Step Controls False Positive Rates



One-Step *Still* Controls False Positive Rates



Application to IMmotion 150/151

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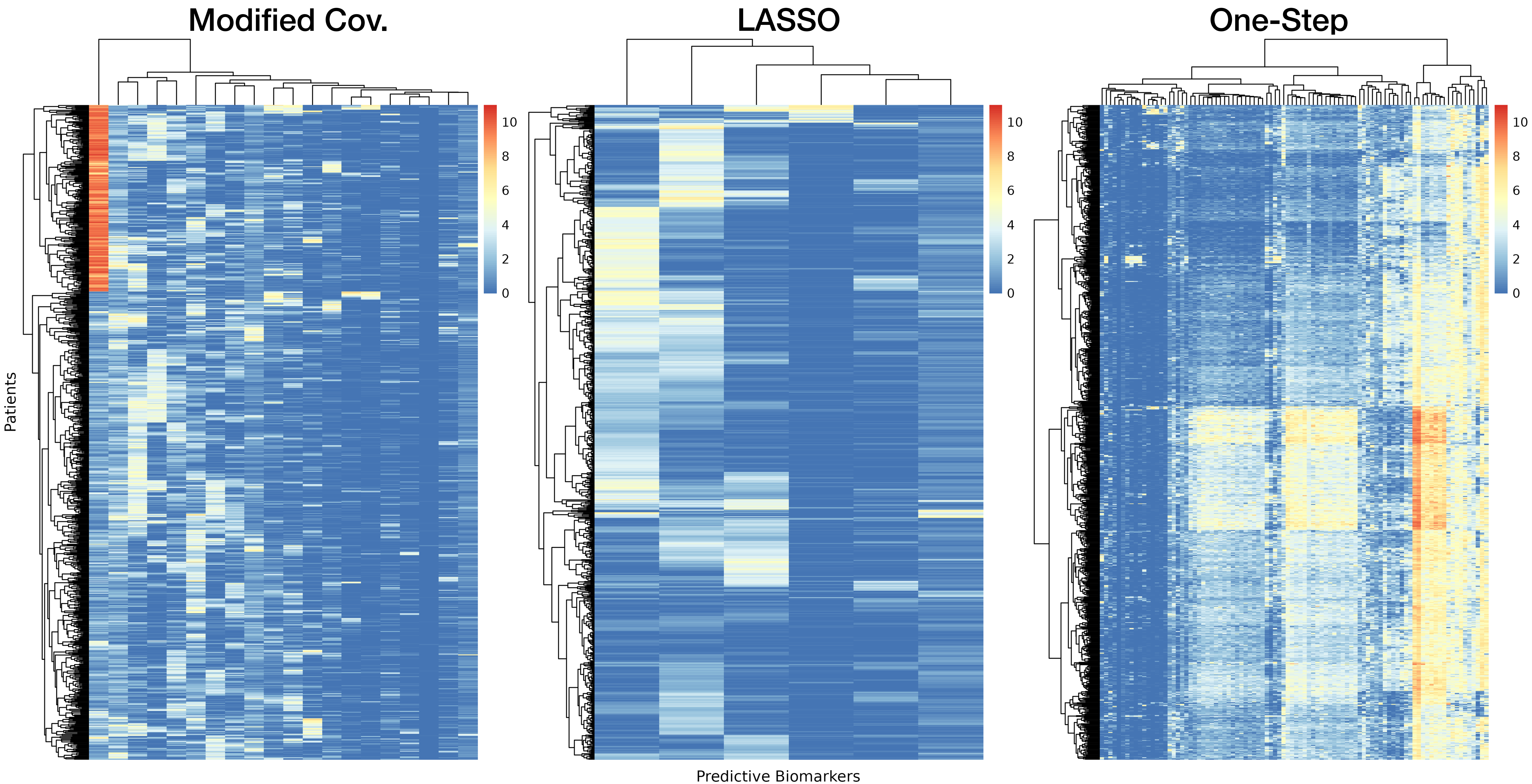
92 genes were identified as predictive using a 5% FDR cutoff. They are associated with immune responses, including those mediated by B cells and lymphocytes.

Validation on IMmotion 151

One-step identifies meaningful predictive biomarkers



Papers, software and contact info at **pboileau.ca**