A Novel Approach to Assess the Predictiveness of a Continuous Biomarker in Early Phases of Drug Development

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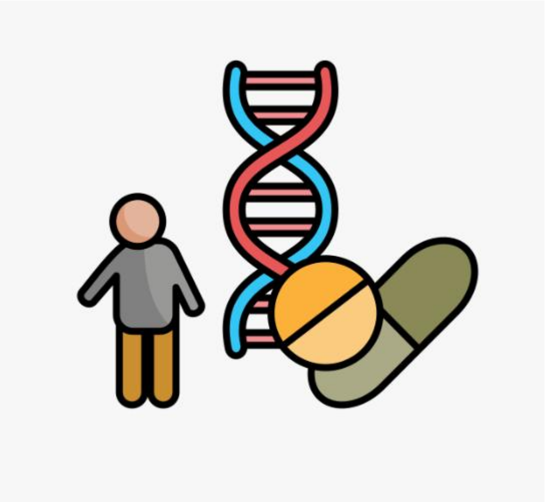
Biomarkers SIG and Treatment Effect Heterogeneity SIG

PSI 2026 CONFERENCE

Personalized medicine

- Development of personalized medicine
  - Adapt treatment to patient's characteristics
  - Especially in oncology but not exclusively



- Identify sub-populations that are likely to benefit from the drug

→ critical component of drug development and regulatory decision making

- Can help improve effectiveness/safety and success rates

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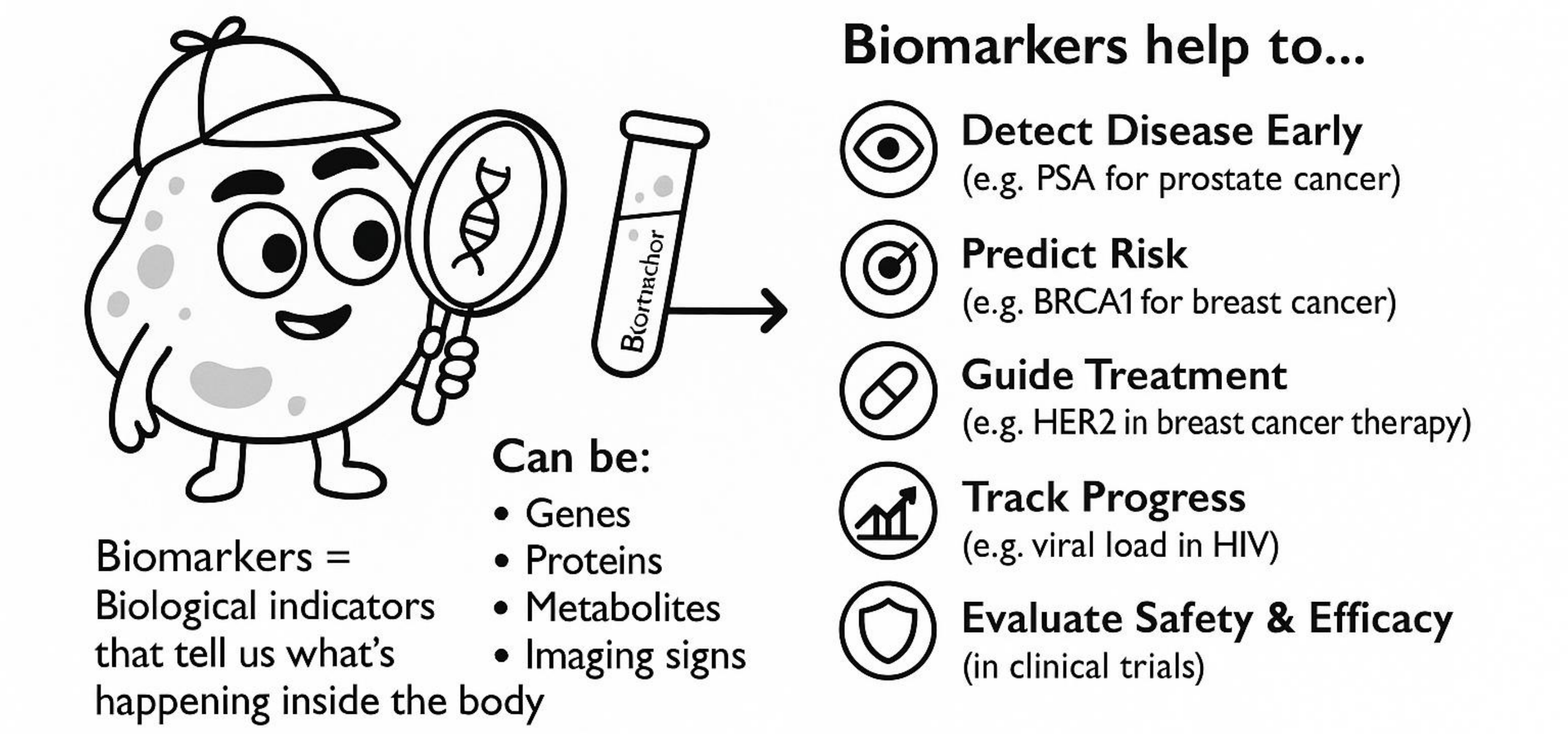
What is a biomarker?

- Some subgroups are known, others require empirical discovery
- Heterogeneity in response due to a wide variety of covariates: phenotypical, clinical, gene and protein expression markers, ... → biomarkers (but not only)



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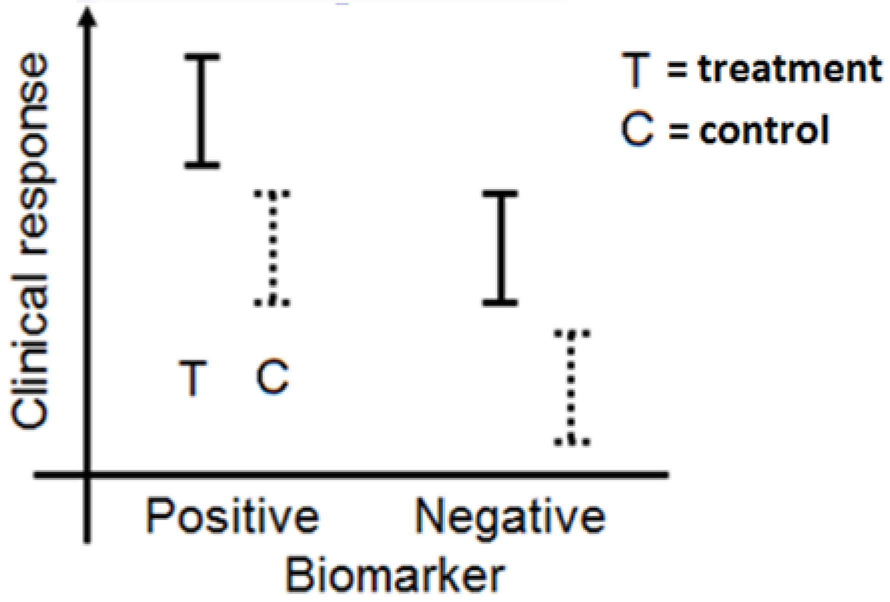
Prognostic vs predictive biomarker

- Small sample sizes in early-phase trials make it challenging to:
  - Validate biomarkers
  - Distinguish predictive from prognostic value

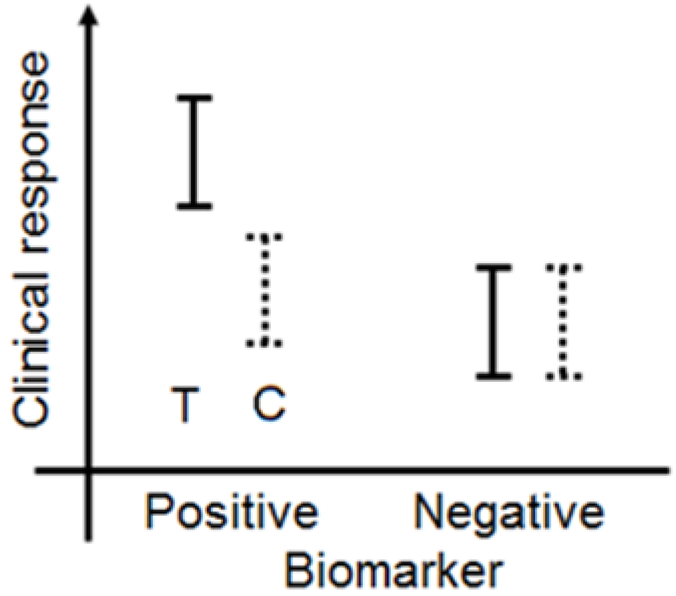
Prognostic biomarker

Response depends on patient's biomarker value and possibly on treatment, but $\perp\!\!\!\perp$ interaction biomarker $\times$ treatment



Predictive biomarker

Response depends on biomarker $\times$ treatment



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AKSA (Average Kolmogorov-Smirnov inspired Approach) - Serra et al. SIM 2025

Statistics in Medicine

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RESEARCH ARTICLE OPEN ACCESS

A Novel Approach to Assess the Predictiveness of a Continuous Biomarker in Early Phases of Drug Development

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AKSA

- General idea: estimate the “global trend” of the difference in responses between treatment and control over the range of biomarker values while accounting for uncertainty around this difference

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AKSA

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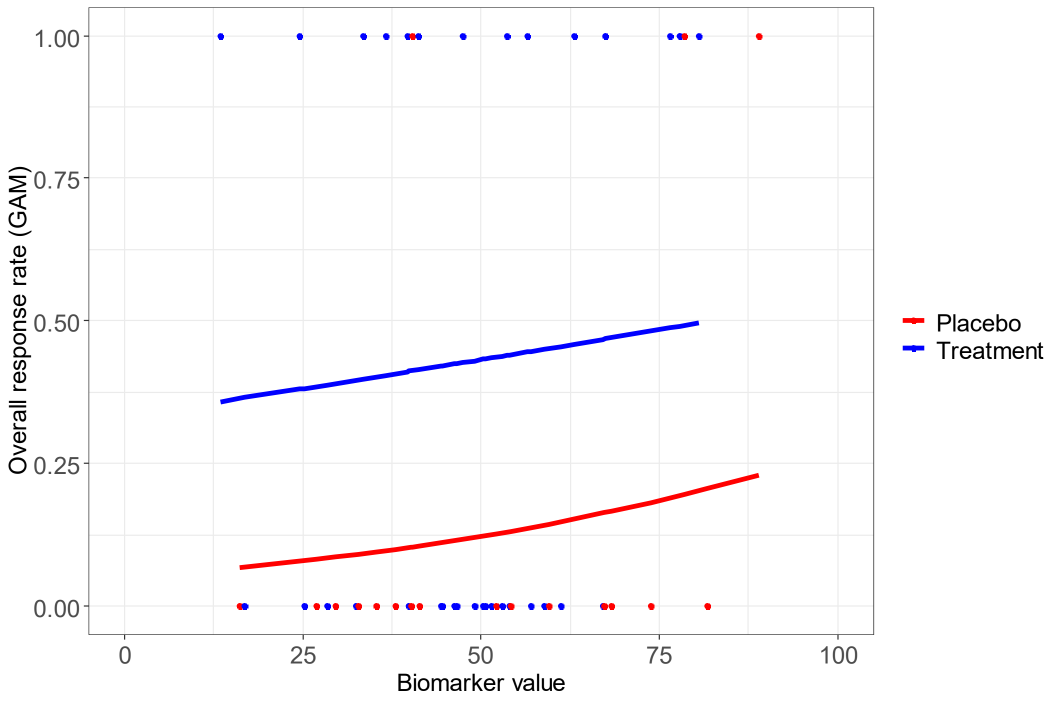
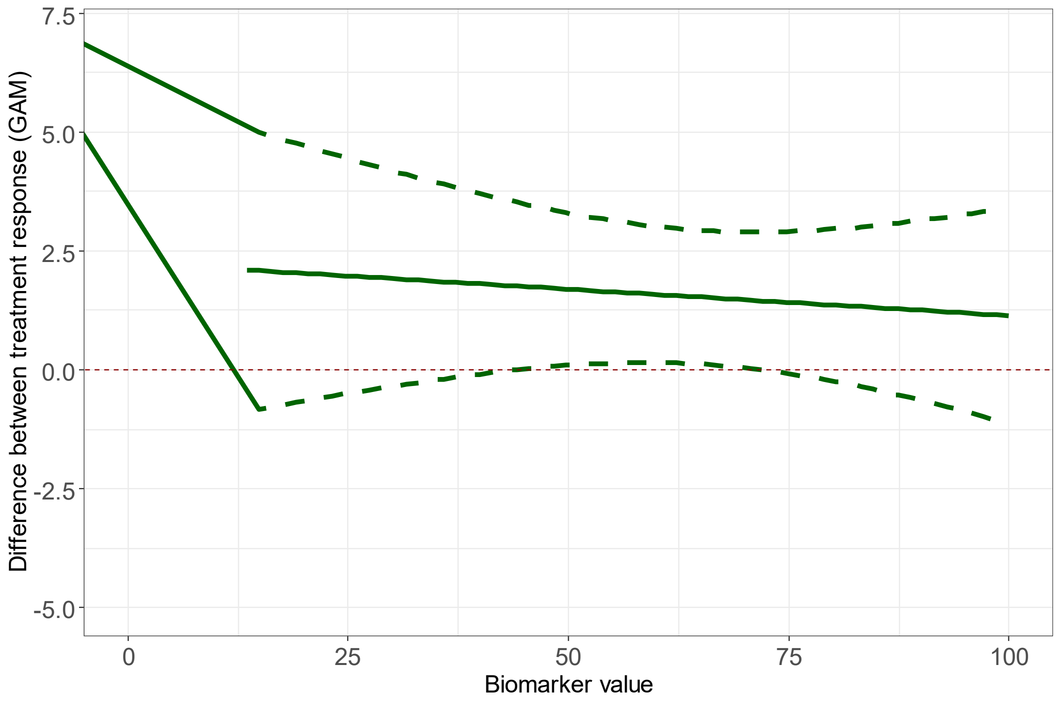
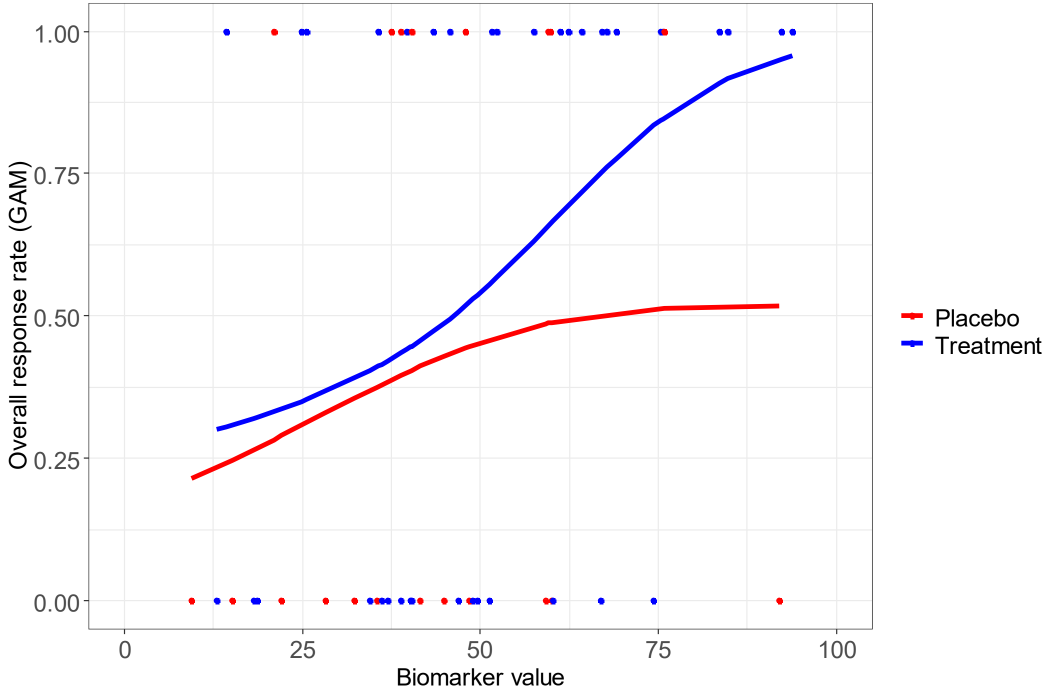


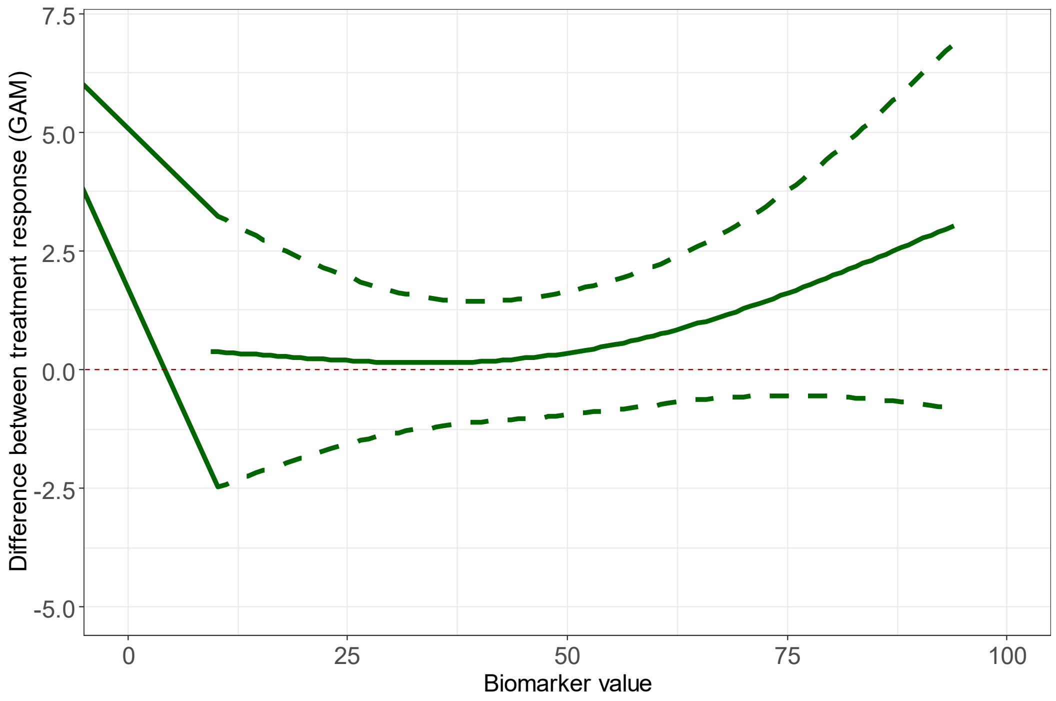


- **If no difference based on biomarker** (only potential treatment effect & prognostic effect) → flat trend / null slope

AKSA

- General idea: estimate the “global trend” of the difference in responses between treatment and control over the range of biomarker values while accounting for uncertainty around this difference





- **If positive difference based on biomarker**/covariate → positive trend / positive slope

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Estimated biomarker-response in each arm

1. Estimate the biomarker-response relationship $g(T, X, T \times X, C)$ as a function of:
   - Treatment group T
   - Biomarker value X
   - Interaction treatment x biomarker $T \times X$
   - Other prognostic variables C

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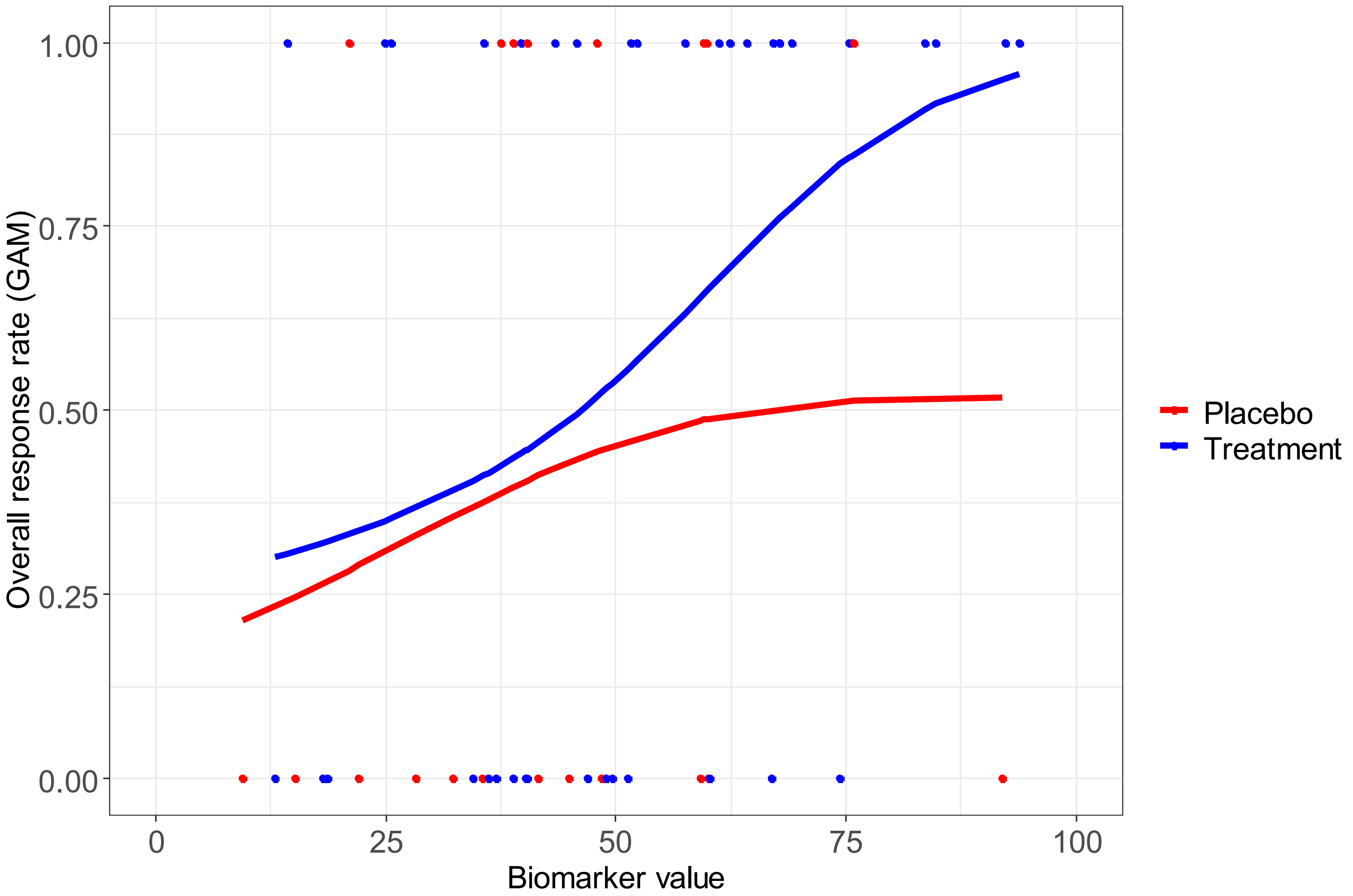
Estimated biomarker-response in each arm

Example:



Treatment effect and its standard error

2. Compute the difference between the estimated biomarker-response for treatment arm and control arm as a function of the biomarker value:

$$D(x) = g(T = 1, X, T = 1 \times x, C) - g(T = 0, x, T = 0 \times x, C)$$

and its standard error:

$$s(x) = \sqrt{se(g(T = 0, x, T = 0 \times x, C))^2 + se(g(T = 1, x, T = 1 \times x, C))^2}$$

→ This represents the treatment effect and its standard error given a biomarker value

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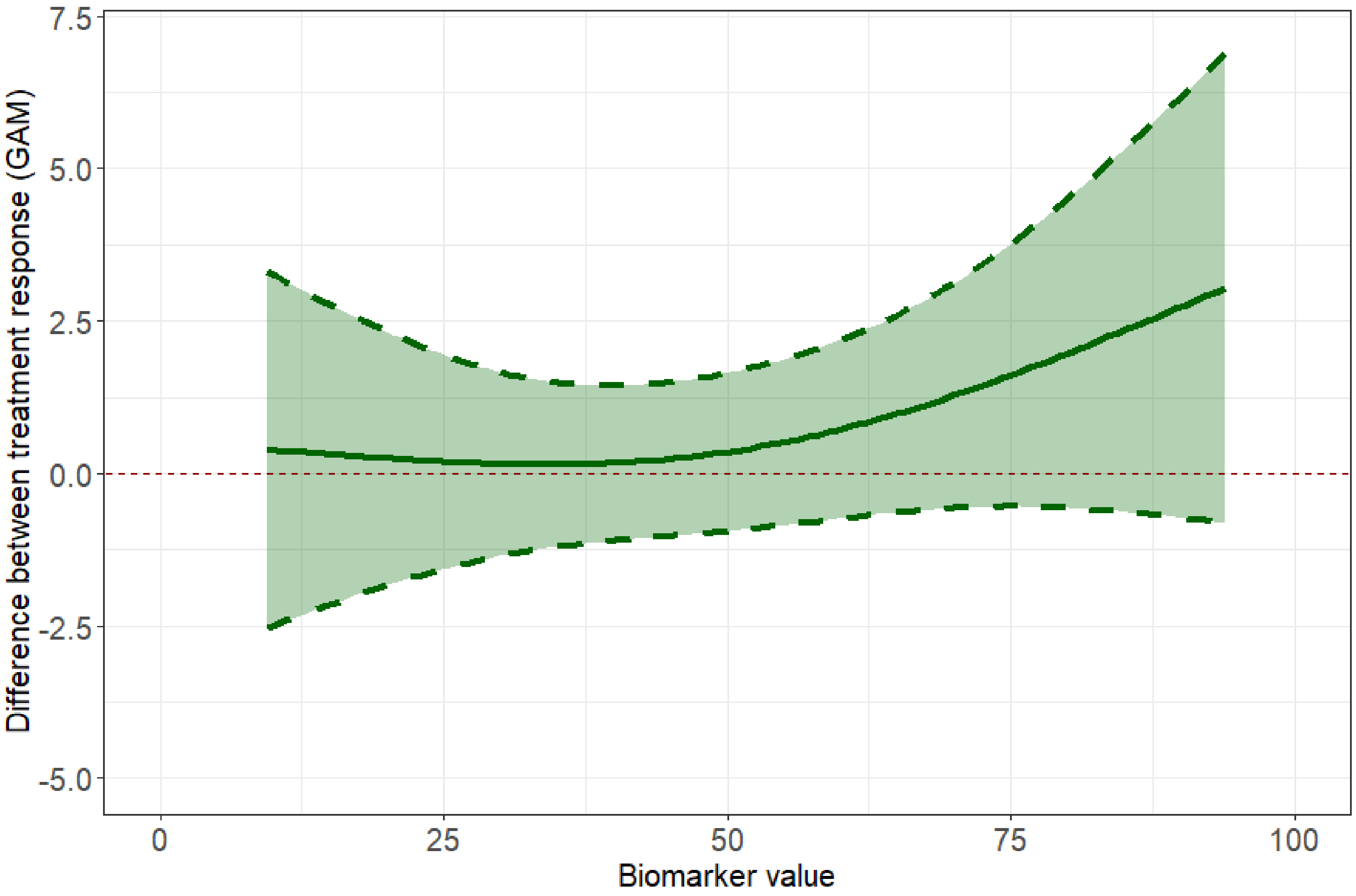
Treatment effect and its standard error

Example:



Difference in treatment effect for a couple of biomarker values

3. Consider a large number K of couples of biomarker values. For each couple (x_1, x_2) such as $x_1 \leq x_2$:
   - Determine the associated value on the y-axis, $D(x_1)$ and $D(x_2)$, and compute the difference $\mu = D(x_2) - D(x_1)$ and its standard error $\sigma = \sqrt{s(x_1)^2 + s(x_2)^2}$

   → This represents the difference of treatment effect between these two biomarker values and its associated standard error

   - Sample a difference of treatment effect: $\delta_k \sim N(\mu, \sigma^2)$

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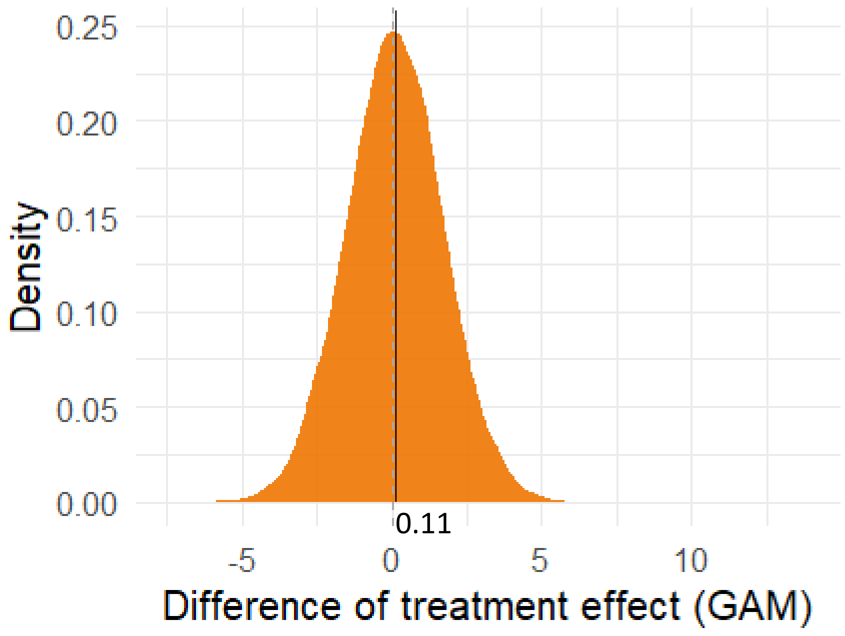
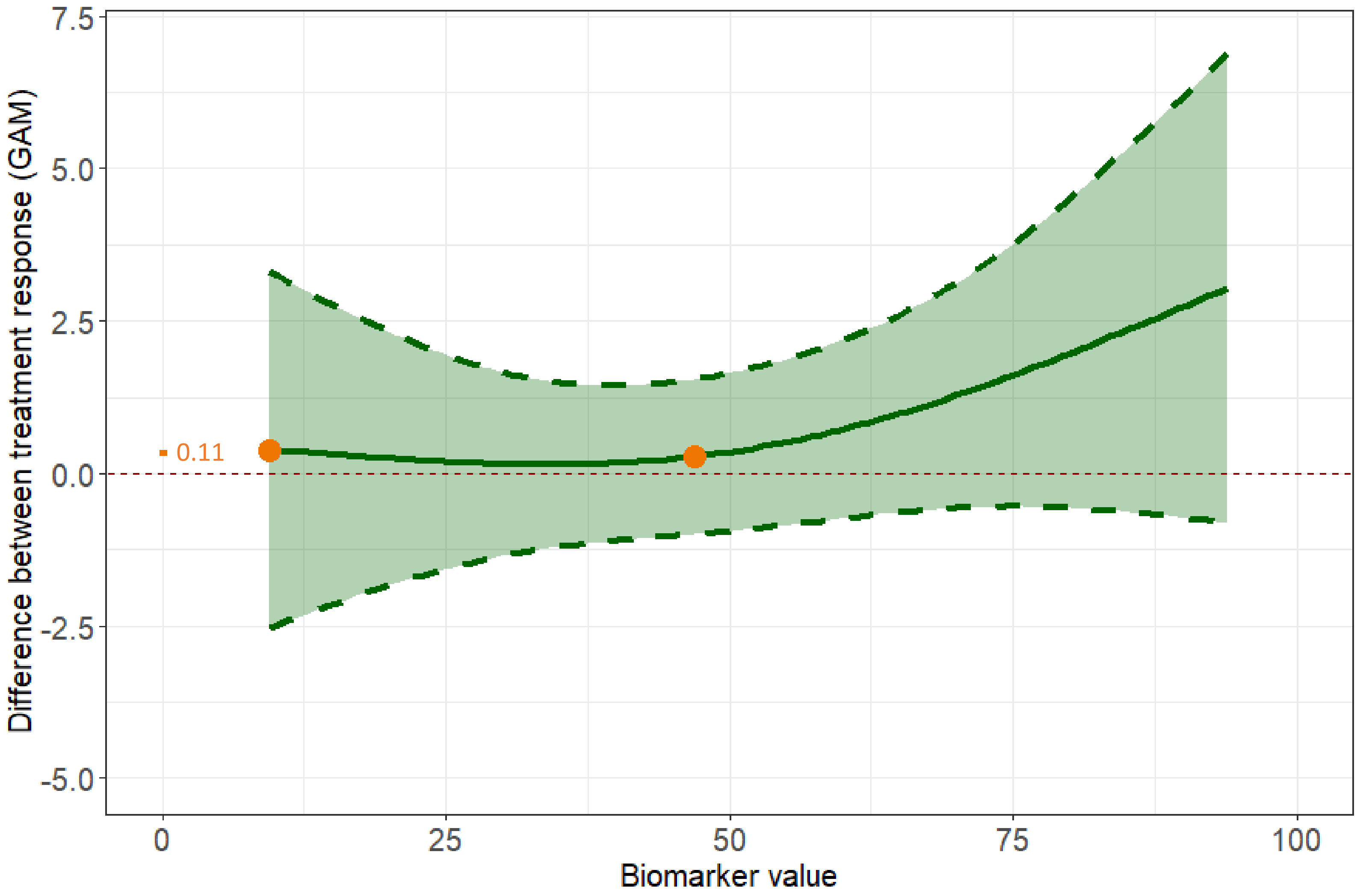
Difference in treatment effect for a couple of biomarker values

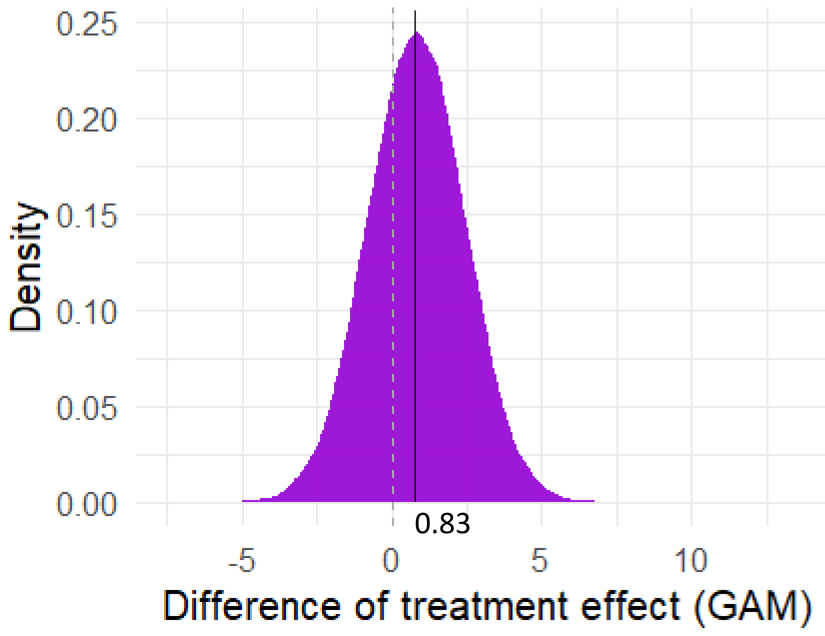
Example:

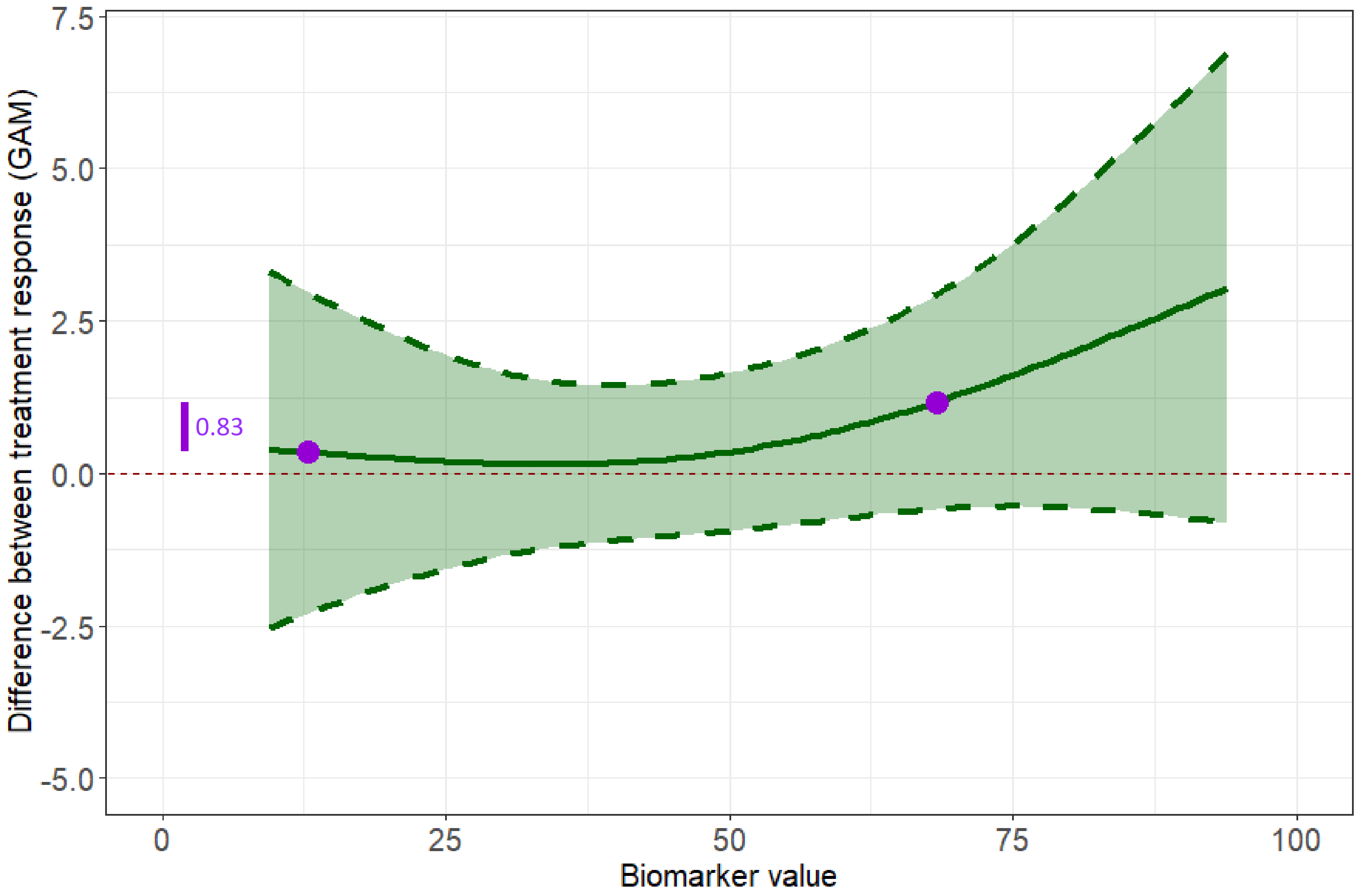




Difference in treatment effect for a couple of biomarker values

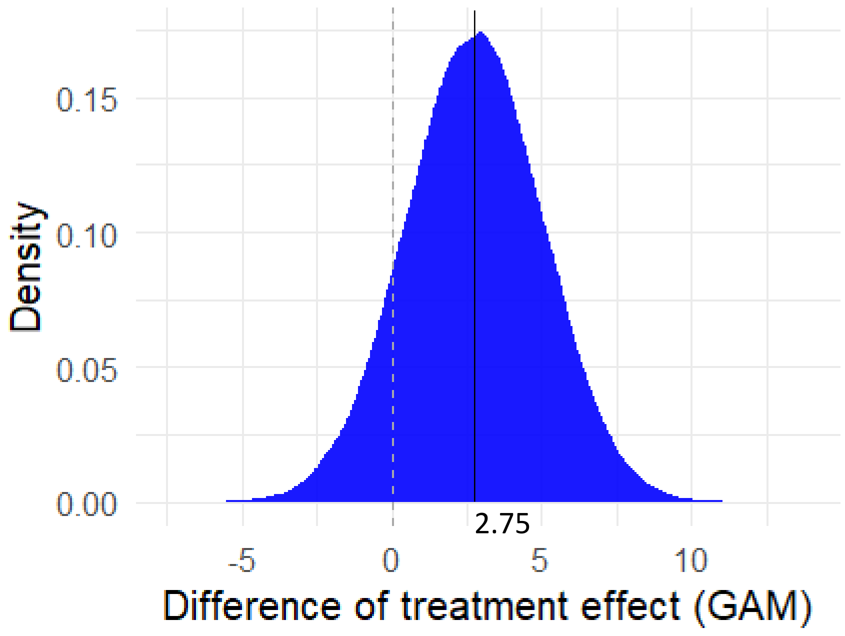
Example:

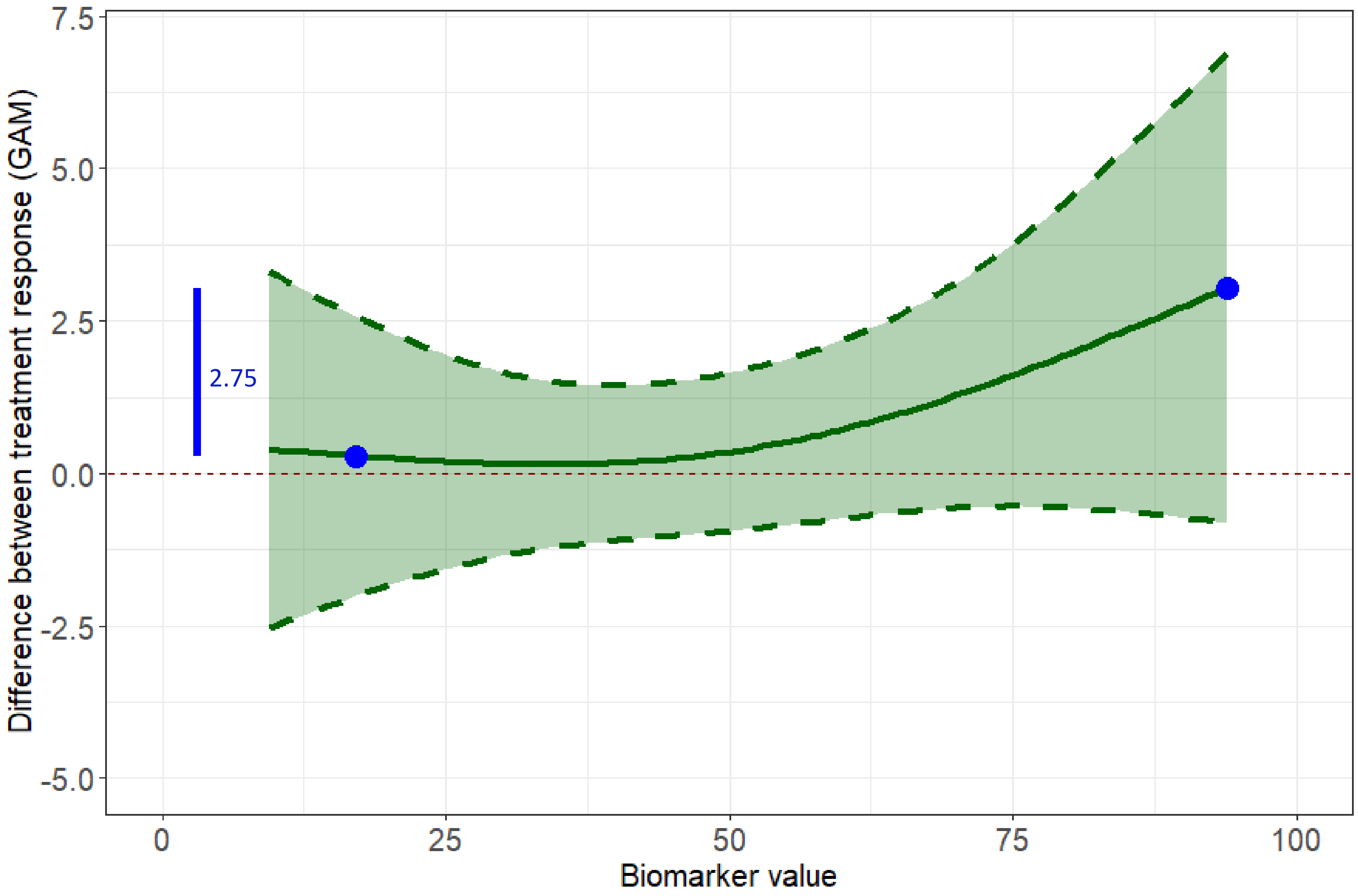




Difference in treatment effect for a couple of biomarker values

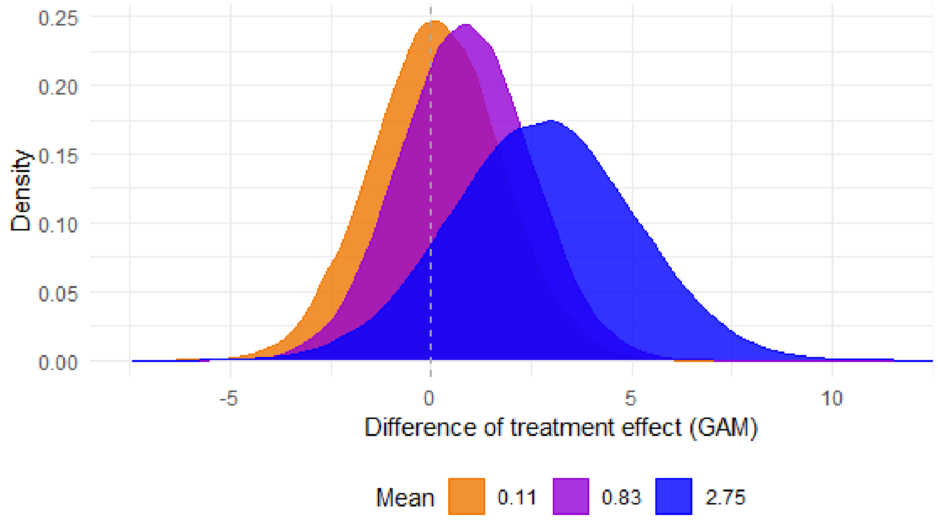
Example:

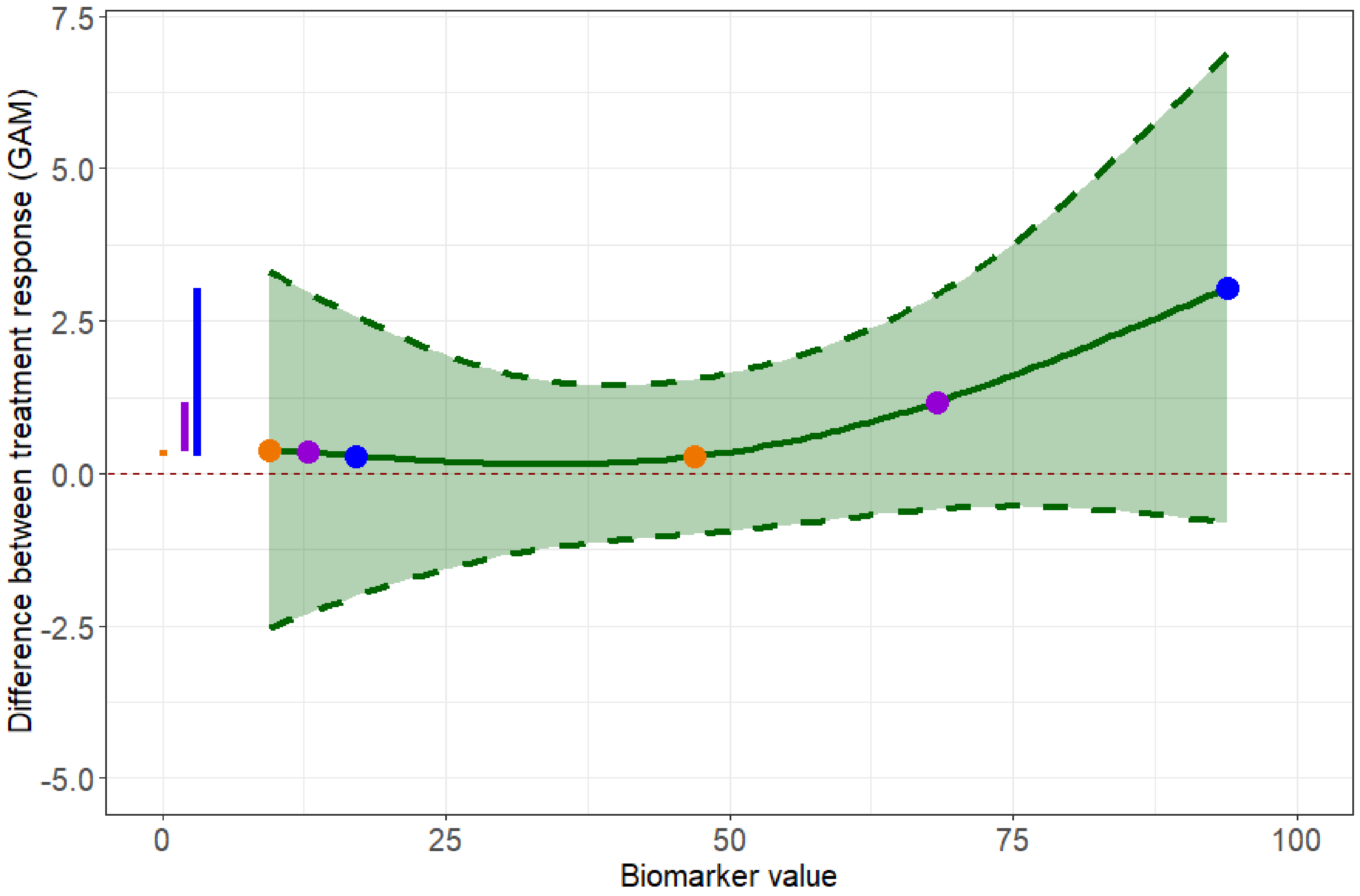




Difference in treatment effect for a couple of biomarker values

Example:





Average difference in treatment effect across all biomarker values

4. Estimate the probability that the average difference in treatment effect is positive across all biomarker values as the proportion of times the sampled value is positive:

$$P(\Delta > 0) = \frac{1}{K}\sum_{k=1}^{K} \mathbb{I}_{\delta_k > 0}$$

The biomarker is declared predictive if $P(\Delta > 0) > \alpha_{AKSA}$, where α_{AKSA} is defined to control the type I error at level α (under null scenario for all assumed biomarker distributions)

→ Assess the probability of a positive trend in the difference in treatment effect as a function of biomarker value / how confident we are in this trend

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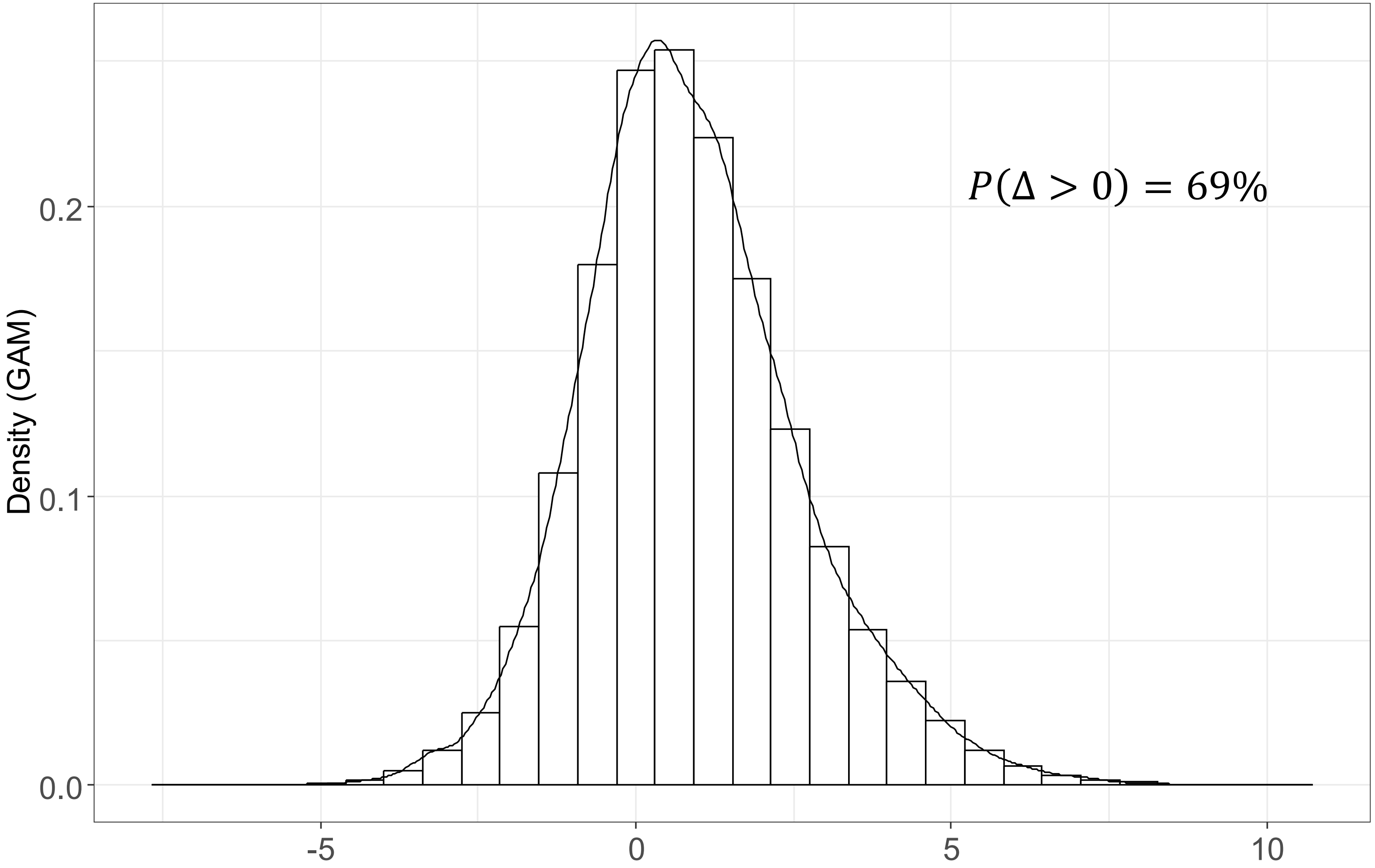
Average difference in treatment effect across all biomarker values

Example:



Comparison to other approaches

- Interaction Test Approach (IT): test for the interaction biomarker-by-treatment term in the generalized linear model (logit function), p-value compared to α_{IT} where α_{IT} is defined to control type I error at level α

- Interaction Test Approach With a Dichotomised Biomarker (ITD): use IT with $\mathbb{I}(X > c)$ instead of X in the logit model for a set of c values, minimum p-value (across c) compared to α_{ITD} to control type I error at level α

- Likelihood Ratio Test (LR): model with (T, X) vs model with $(T, X, T \times X)$, parameter associated to $T \times X$ tested equal to 0, p-value compared to α_{LR} defined to control type I error at level α

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Comparison to other approaches

- Subpopulation Treatment Effect Pattern Plot (STEPP): divide population on overlapping subgroups, test that treatment effects in all subgroups are the same (no sign of heterogeneity), p-value compared to α_{STEPP} defined to control type I error at level α

- Probability to Find a Cutoff (cutoff): declare biomarker predictive if a cut-off point is found by fitting two step functions with ordinary least squares considering treatment and control arms separately and:

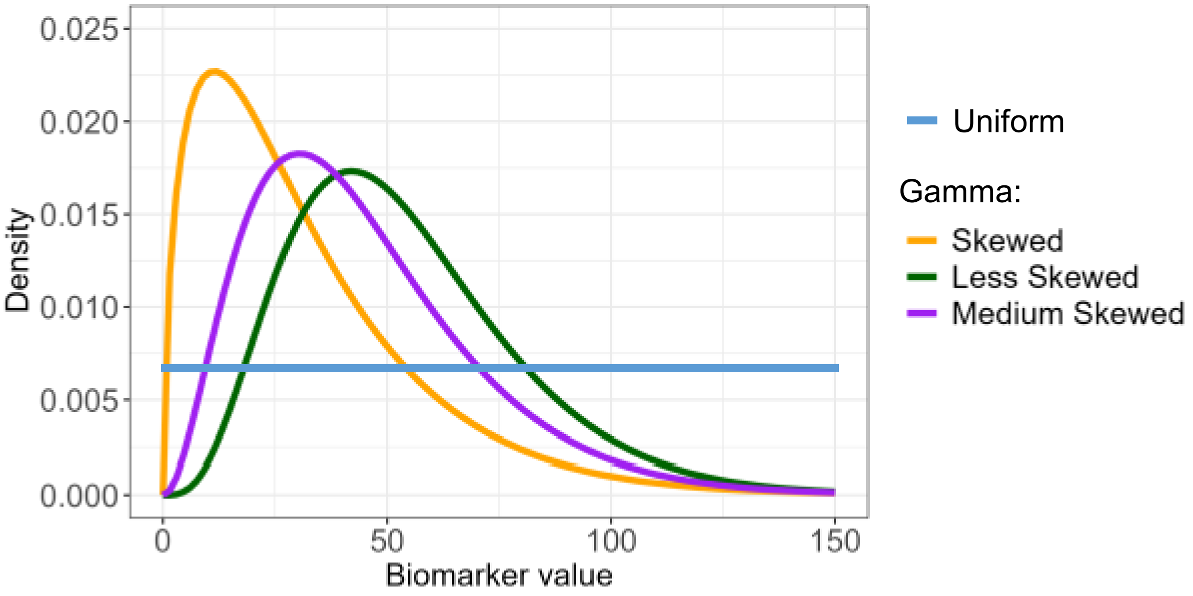
$$P(\text{mean difference trt}-\text{ctl above cut}-\text{off} > \text{mean difference below cut}-\text{off}) > \alpha_{cutoff}$$

and α_{cutoff} chosen to control type I error at level α

- Delong Test to Compare ROC Curves (Delong): compare the area under the empirical ROC curves (AUC) for treatment and control arms, test AUC are equals, p-value compared to α_{Delong} to control type I error at level α

Comparison to other approaches

- Biomarker distributions:



- Scenarios: with more or less prognostic effect and more or less predictive effect

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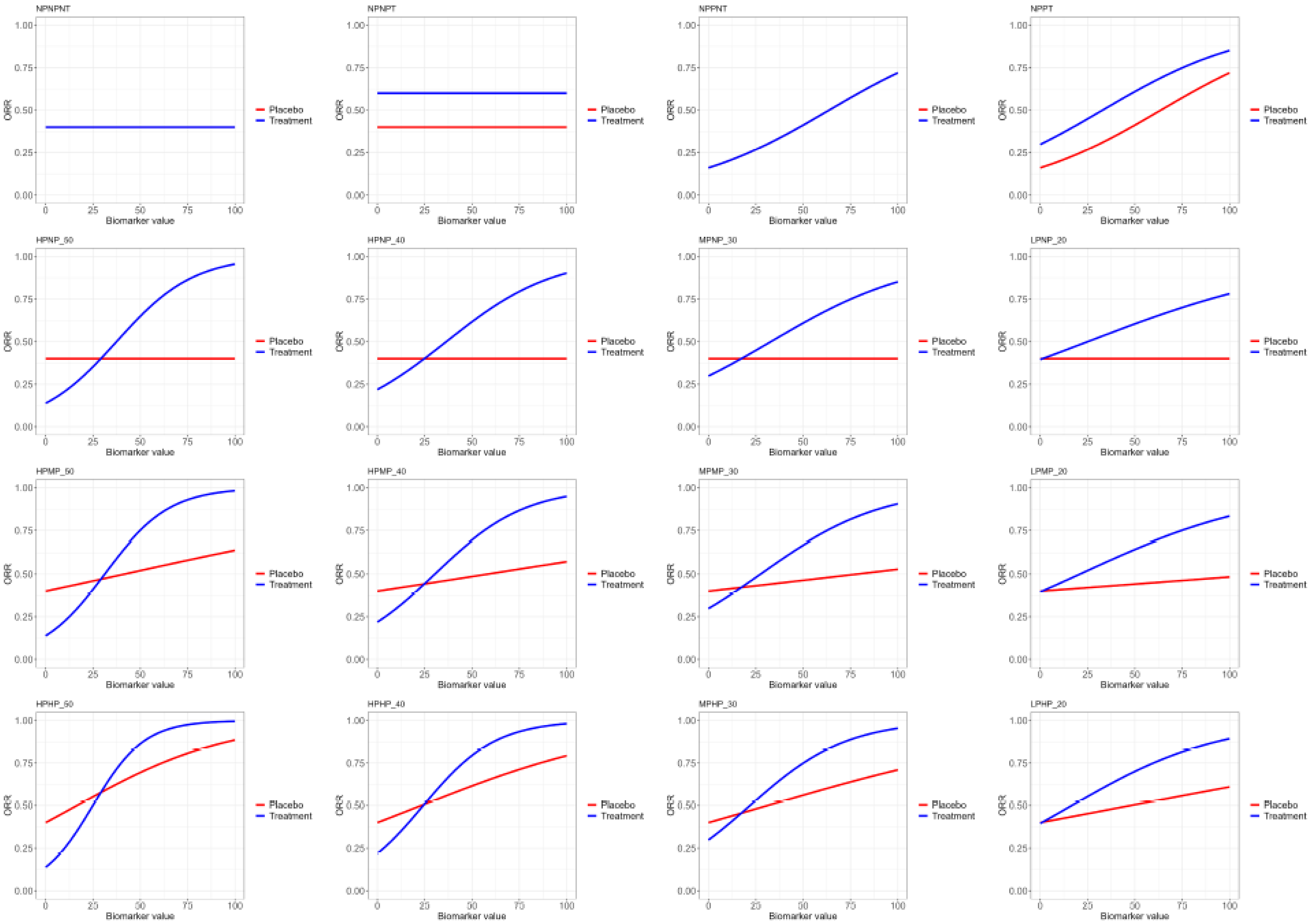

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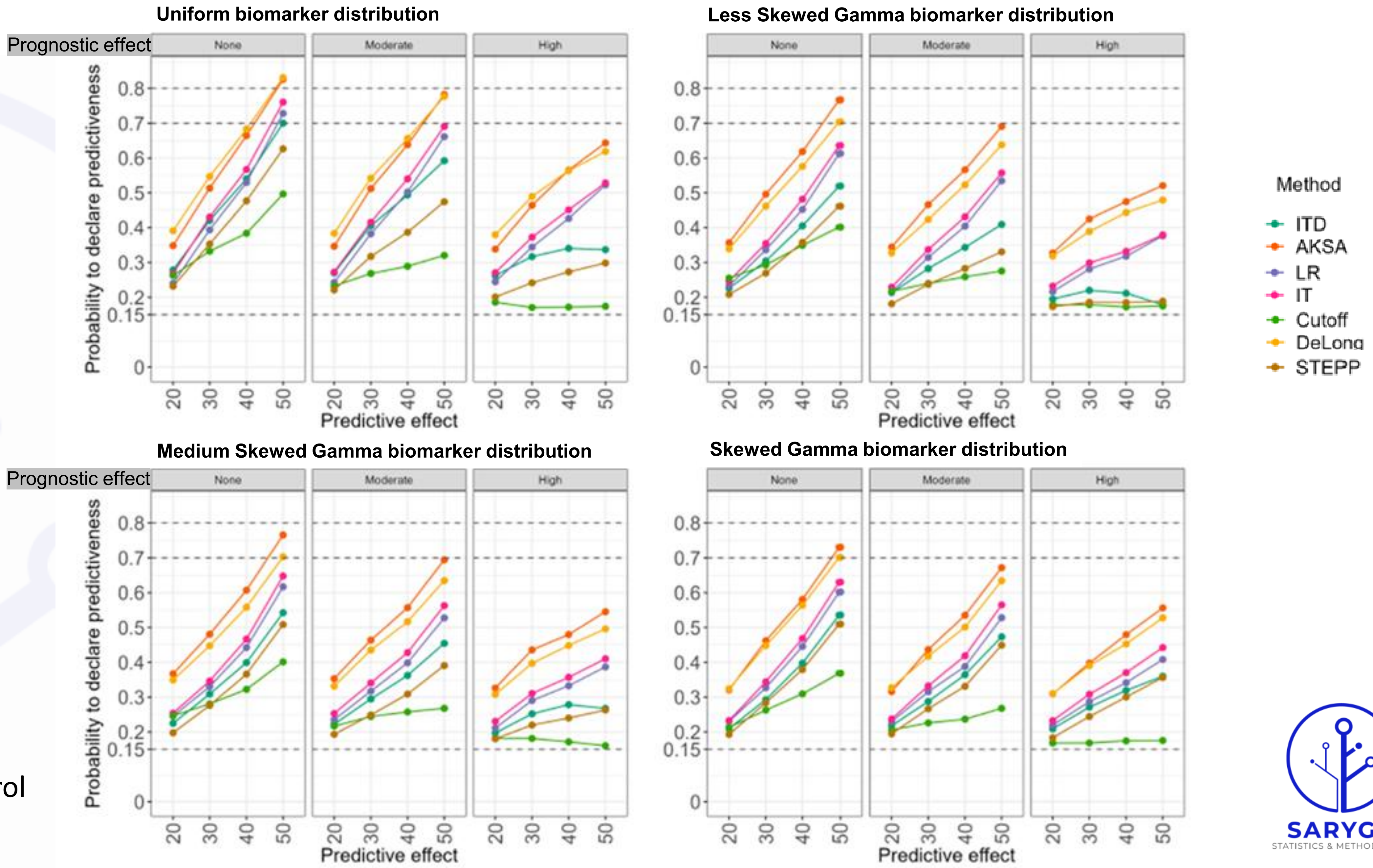
Simulation results



Sample size
treatment:control
= 40:20

Extension to multiple covariates of different types

- Extension to n multiple continuous covariates:
  - Same idea but instead of sampling two biomarker values x_1 and x_2 such as $x_1 \leq x_2$, sample two n-uples $(x_1^{(1)}, \ldots x_1^{(n)})$, and $(x_2^{(1)}, \ldots x_2^{(n)})$ such as $x_1^{(1)} \leq x_2^{(1)}, \ldots, x_1^{(n)} \leq x_2^{(n)}$

- Extension to categorical covariates:
  - If ordinal covariate → same as continuous
  - If nominal covariate → consider all possible orders ?

Approach to be evaluated through a simulation study to compare it with other approaches → extension paper

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Conclusion

- We introduced AKSA, a novel approach to assess predictiveness of a continuous biomarker
- Key advantages:
  - Captures global treatment effect trends
  - Accounts for uncertainty
  - Performs well in small sample settings
- Simulation results show:
  - Good power compared to existing methods
  - Controlled type I error

Practical relevance → particularly suited for early-phase clinical trials

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