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A Bayesian model for surrogate endpoint evaluation in mixed biomarker populations

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What are surrogate endpoints?

Treatment → Final Clinical Outcome

Treatment effect on final clinical outcome

What are surrogate endpoints?

Treatment

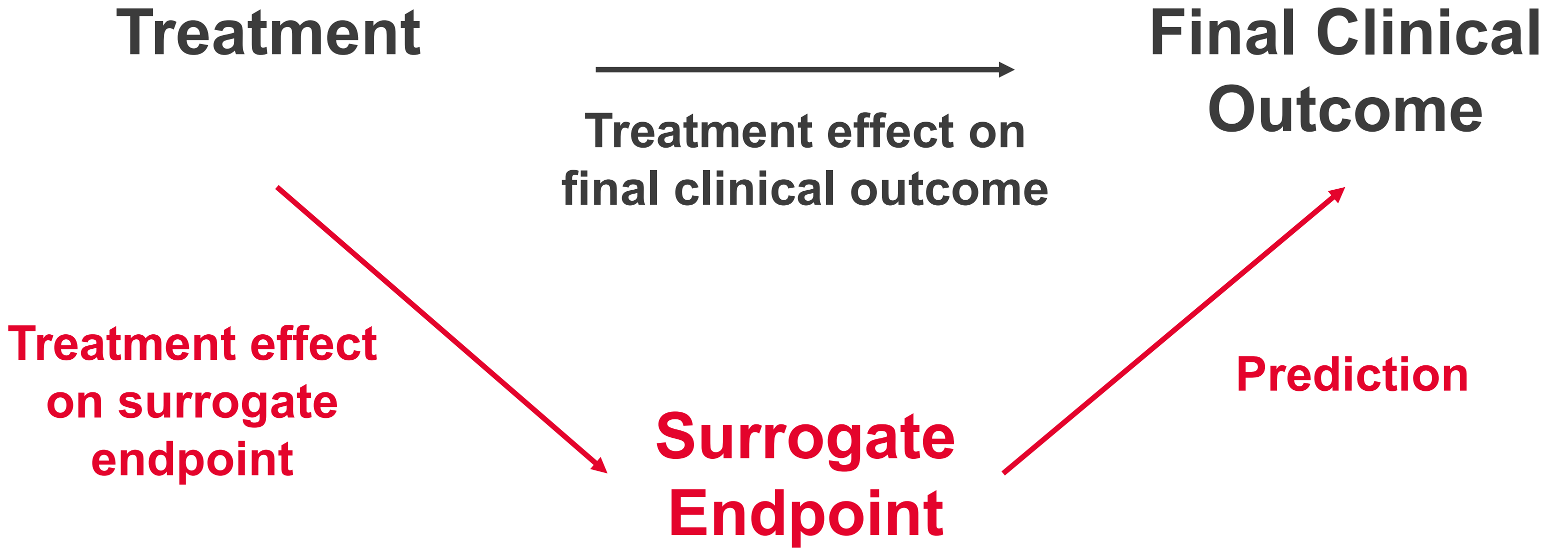
Treatment effect on final clinical outcome

Final Clinical Outcome

Treatment effect on surrogate endpoint

Surrogate Endpoint

What are surrogate endpoints?



Surrogate Endpoint Validation

Validation

- Trial-level
- Individual-level
- Biological Plausibility

The need for validation: failed surrogates

Disease	Treatment	Effect on surrogate	Effect on final
Post-MI	Anti-arrhythmic therapies	Reduced ventricular arrhythmia	Increased sudden death
Heart disease	Cholesterol lowering agents	Lowered cholesterol level	Increased mortality
Osteoporosis	Sodium fluoride	Increased bone mineral density	Increased fracture incidences

Bivariate random-effects meta-analysis

$$\begin{pmatrix} Y_{1i} \\ Y_{2i} \end{pmatrix} \sim N\left(\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix}, \Sigma_i = \begin{pmatrix} \sigma_{1i}^2 & \sigma_{1i}\sigma_{2i}\rho_{wi}^{12} \\ \sigma_{1i}\sigma_{2i}\rho_{wi}^{12} & \sigma_{2i}^2 \end{pmatrix} \right)$$

$$\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix} \sim N\left(\begin{pmatrix} d_1 \\ d_2 \end{pmatrix}, \begin{pmatrix} \tau_1^2 & \tau_1\tau_2\rho_b \\ \tau_1\tau_2\rho_b & \tau_2^2 \end{pmatrix} \right)$$

- Y_{1i}, Y_{2i} - observed treatment effects
- δ_{1i}, δ_{2i} - true treatment effects
- $\sigma_{1i}^2, \sigma_{2i}^2$ - within-study variances
- ρ_{wi}^{12} - within-study correlation

Bivariate random-effects meta-analysis

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- d_1, d_2 - pooled estimates
- τ_1^2, τ_2^2 - between-study variances
- ρ_b - between-study correlation

Bivariate random-effects meta-analysis

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$$\begin{cases} \delta_{1i} \sim N(\eta_1, \psi_1^2) \\ \delta_{2i} | \delta_{1i} \sim N(\eta_{2i}, \psi_2^2) \\ \boldsymbol{\eta_{2i} = \lambda_0 + \lambda_1 \delta_{1i}} \end{cases}$$

- λ_0 - intercept
- λ_1 - slope
- ψ_2^2 - conditional variance

Bivariate random-effects meta-analysis

$$\begin{pmatrix} Y_{1i} \\ Y_{2i} \end{pmatrix} \sim N\left(\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix}, \Sigma_i = \begin{pmatrix} \sigma_{1i}^2 & \sigma_{1i}\sigma_{2i}\rho_{wi}^{12} \\ \sigma_{1i}\sigma_{2i}\rho_{wi}^{12} & \sigma_{2i}^2 \end{pmatrix}\right)$$

$$\begin{cases} \delta_{1i} \sim N(\eta_1, \psi_1^2) \\ \delta_{2i} | \delta_{1i} \sim N(\eta_{2i}, \psi_2^2) \\ \boldsymbol{\eta_{2i} = \lambda_0 + \lambda_1 \delta_{1i}} \end{cases}$$

For a perfect surrogate relationship:

$$\lambda_0 = 0 \qquad \lambda_1 \neq 0 \qquad \psi_2^2 = 0$$

Priors

$$\begin{pmatrix} Y_{1i} \\ Y_{2i} \end{pmatrix} \sim N\left(\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix}, \Sigma_i = \begin{pmatrix} \sigma_{1i}^2 & \sigma_{1i}\sigma_{2i}\rho_{wi}^{12} \\ \sigma_{1i}\sigma_{2i}\rho_{wi}^{12} & \sigma_{2i}^2 \end{pmatrix}\right)$$

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Priors required which inform priors on surrogacy parameters

Priors

$$\begin{pmatrix} Y_{1i} \\ Y_{2i} \end{pmatrix} \sim N\left(\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix}, \Sigma_i = \begin{pmatrix} \sigma_{1i}^2 & \sigma_{1i}\sigma_{2i}\rho_{wi}^{12} \\ \sigma_{1i}\sigma_{2i}\rho_{wi}^{12} & \sigma_{2i}^2 \end{pmatrix} \right)$$

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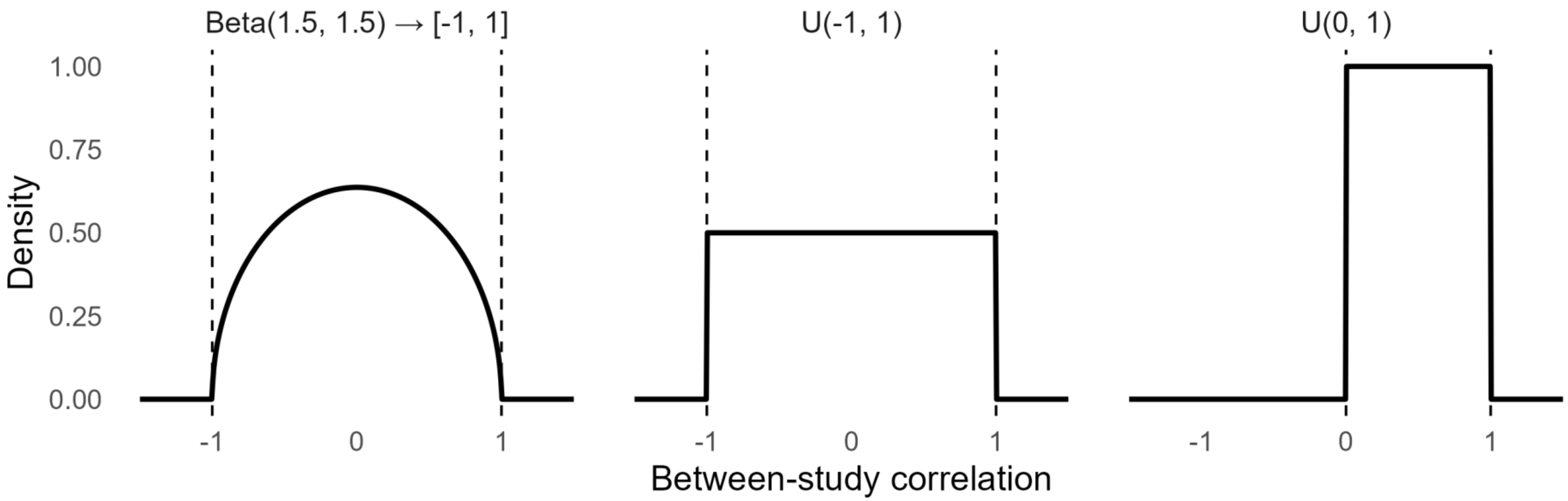
Prior for between-study correlation requires careful consideration

Priors

Prior for between-study correlation requires careful consideration



Priors

$$\begin{pmatrix} Y_{1i} \\ Y_{2i} \end{pmatrix} \sim N\left(\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix}, \Sigma_i = \begin{pmatrix} \sigma_{1i}^2 & \sigma_{1i}\sigma_{2i}\boldsymbol{\rho_{wi}^{12}} \\ \sigma_{1i}\sigma_{2i}\boldsymbol{\rho_{wi}^{12}} & \sigma_{2i}^2 \end{pmatrix}\right)$$

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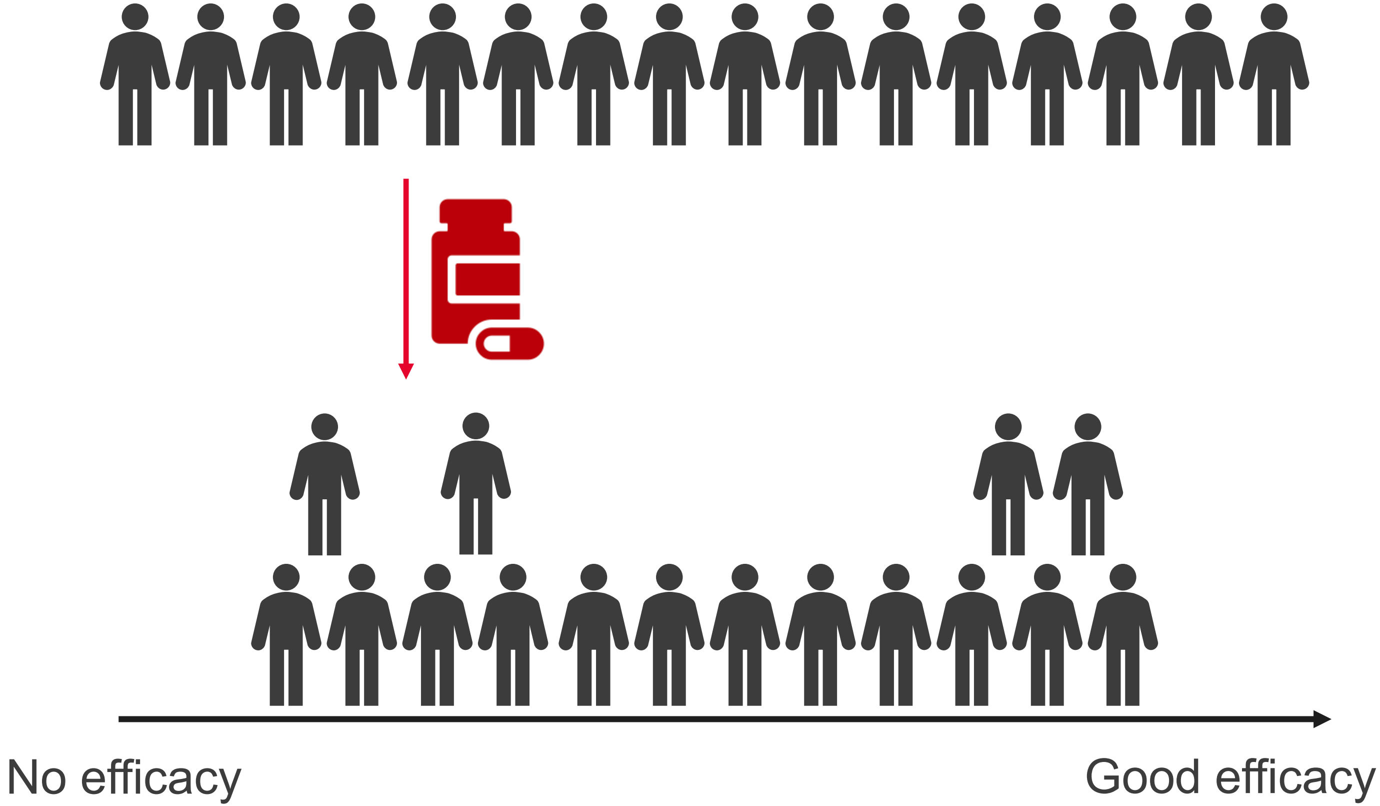
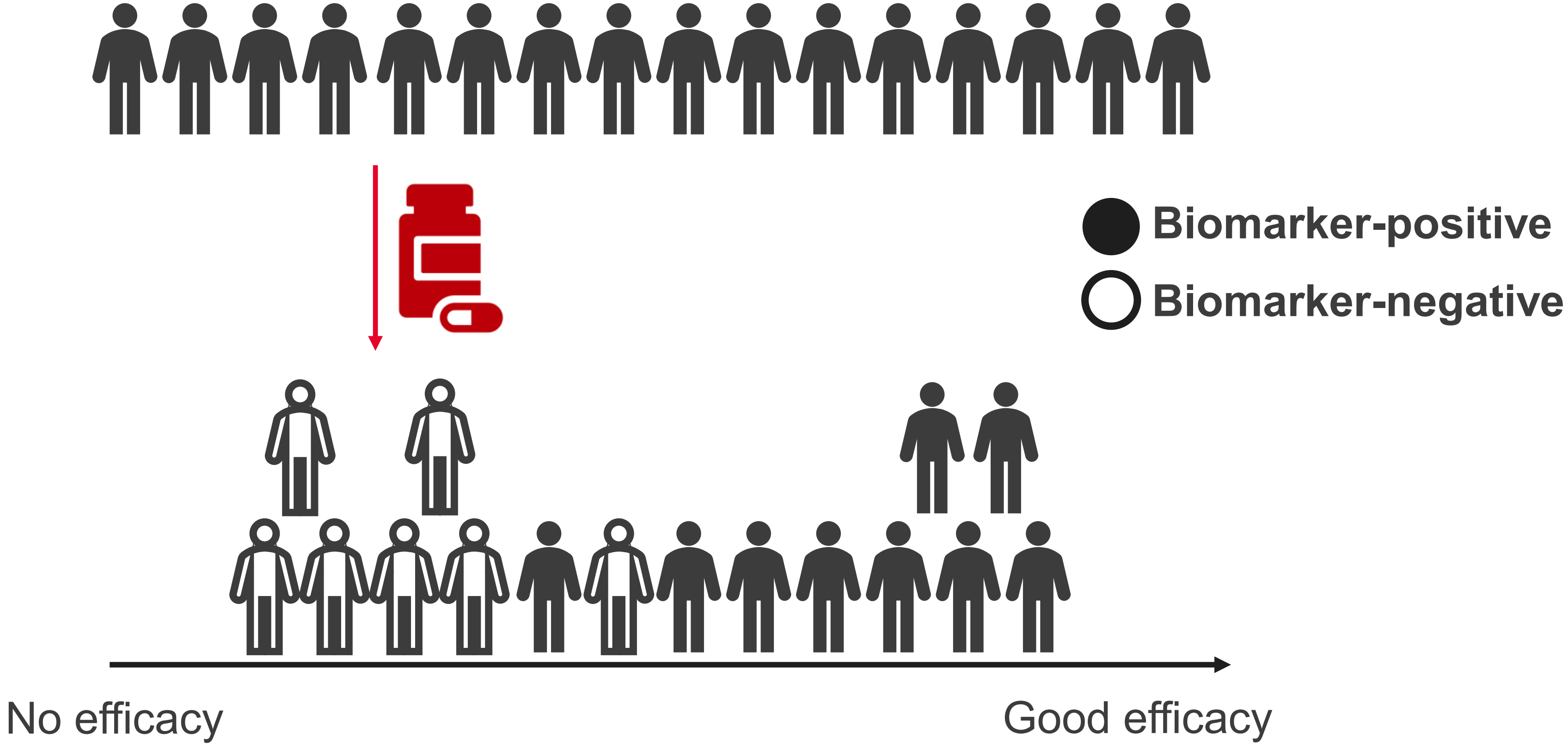
Specification of within-study correlation requires consideration

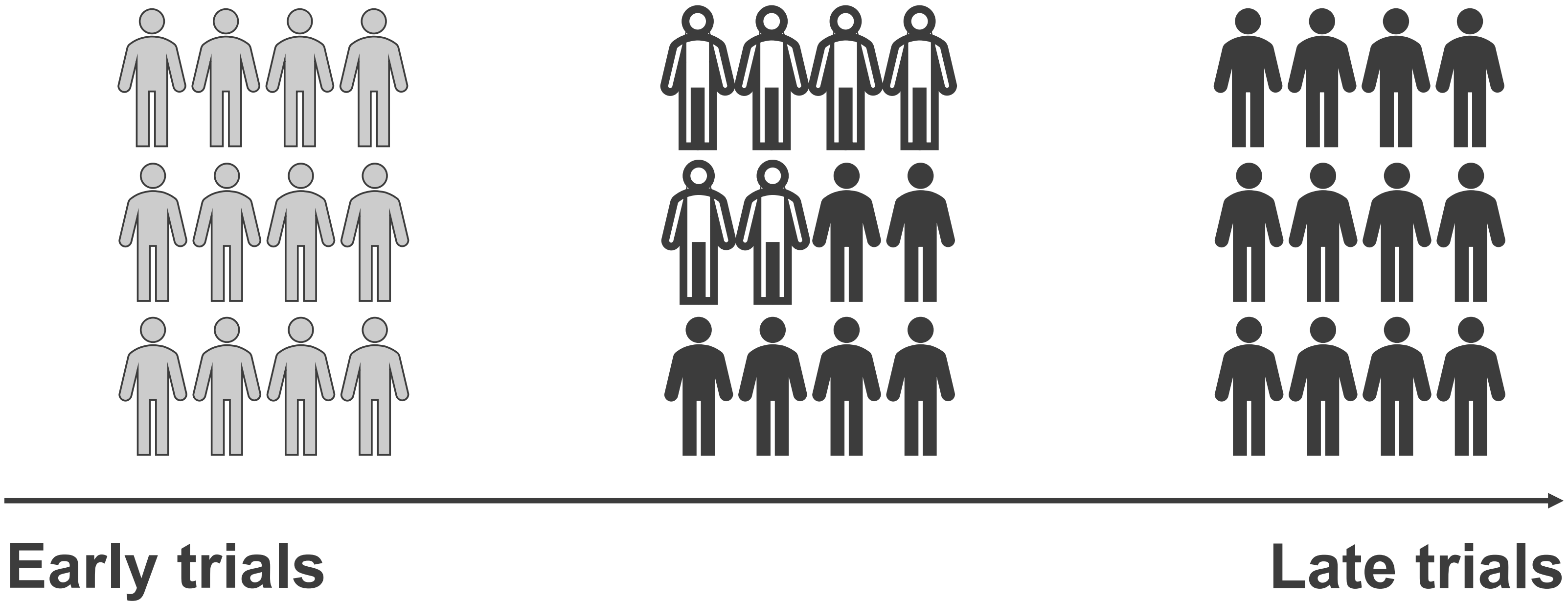
Predictive Biomarkers



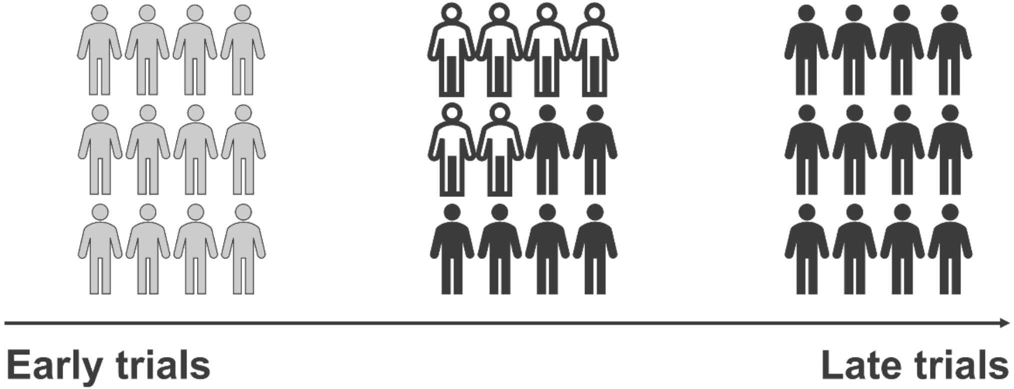
Predictive Biomarkers

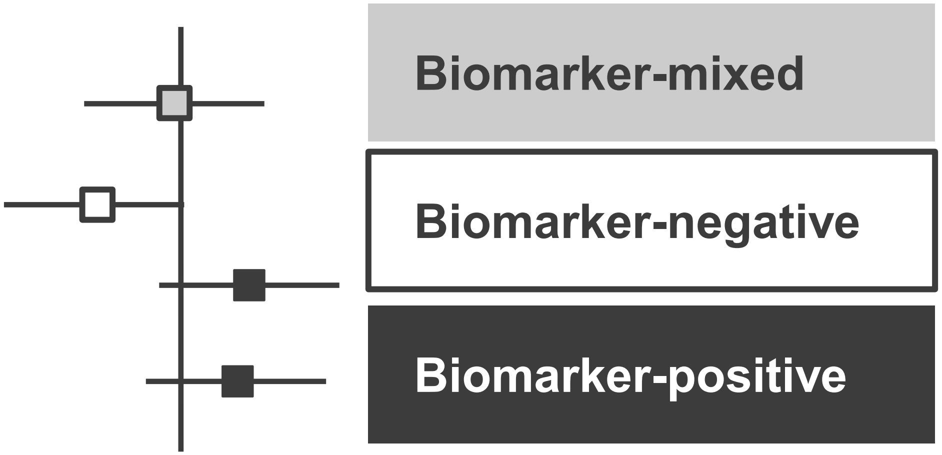


Mixed Biomarker Populations

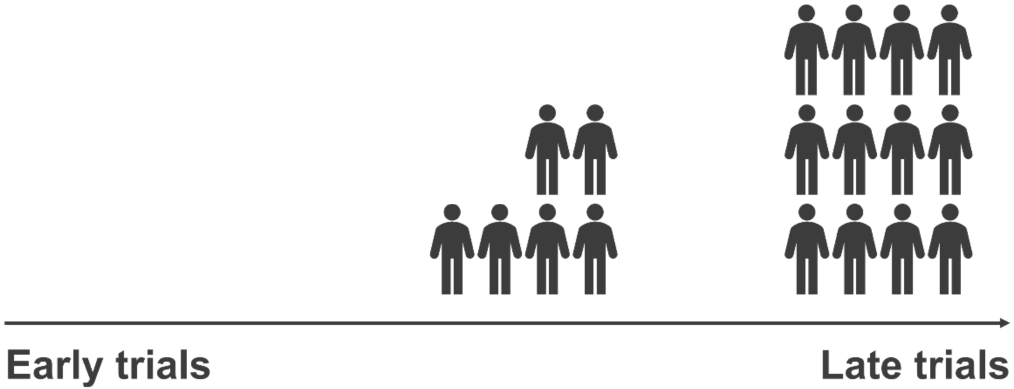


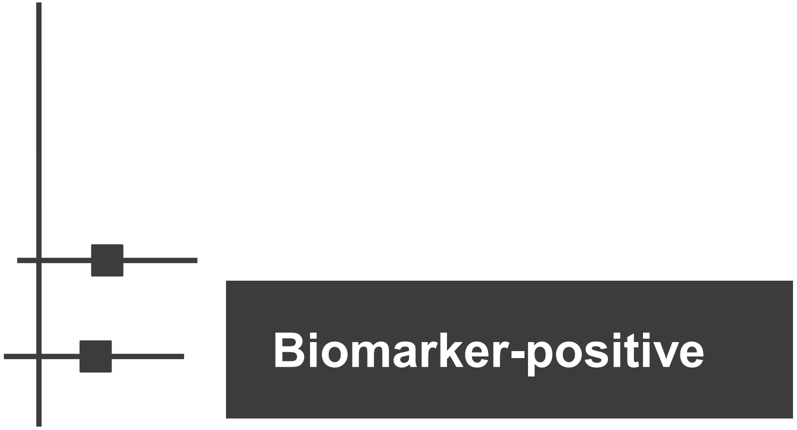
Mixed Biomarker Populations





Mixed Biomarker Populations





Objective

To extend bivariate random-effects meta-analysis to estimate trial-level surrogate relationships in a specified biomarker subgroup while incorporating data from trials conducted in alternative biomarker populations

Extended BRMA

$$\begin{pmatrix} Y_{1ij} \\ Y_{2ij} \end{pmatrix} \sim N\left(\begin{pmatrix} \delta_{1i+} + \boldsymbol{p_{ij}\beta_{1i}} \\ \delta_{2i+} + \boldsymbol{p_{ij}\beta_{2i}} \end{pmatrix}, \Sigma_{ij} = \begin{pmatrix} \sigma_{1ij}^2 & \sigma_{1ij}\sigma_{2ij}\rho_{wij}^{12} \\ \sigma_{1ij}\sigma_{2ij}\rho_{wij}^{12} & \sigma_{2ij}^2 \end{pmatrix}\right)$$

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Extended BRMA

For biomarker-positive group:

$$\begin{pmatrix} Y_{1i+} \\ Y_{2i+} \end{pmatrix} \sim N\left(\begin{pmatrix} \delta_{1i+} \\ \delta_{2i+} \end{pmatrix}, \Sigma_{i+} = \begin{pmatrix} \sigma_{1i+}^2 & \sigma_{1i+}\sigma_{2i+}\rho_{wi+}^{12} \\ \sigma_{1i+}\sigma_{2i+}\rho_{wi+}^{12} & \sigma_{2i+}^2 \end{pmatrix} \right)$$

Extended BRMA

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For biomarker-negative subgroup:

$$\begin{pmatrix} Y_{1i-} \\ Y_{2i-} \end{pmatrix} \sim N\left(\begin{pmatrix} \delta_{1i+} + \boldsymbol{\beta_{1i}} \\ \delta_{2i+} + \boldsymbol{\beta_{2i}} \end{pmatrix}, \Sigma_{i-} = \begin{pmatrix} \sigma_{1i-}^2 & \sigma_{1i-}\sigma_{2i-}\rho_{wi-}^{12} \\ \sigma_{1i-}\sigma_{2i-}\rho_{wi-}^{12} & \sigma_{2i-}^2 \end{pmatrix} \right)$$

Extended BRMA

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For biomarker-mixed populations:

$$\begin{pmatrix} Y_{1i\pm} \\ Y_{2i\pm} \end{pmatrix} \sim N\left(\begin{pmatrix} \delta_{1i+} + \boldsymbol{p_{i\pm}\beta_{1i}} \\ \delta_{2i+} + \boldsymbol{p_{i\pm}\beta_{2i}} \end{pmatrix}, \Sigma_{i\pm} = \begin{pmatrix} \sigma_{1i\pm}^2 & \sigma_{1i\pm}\sigma_{2i\pm}\rho_{wi\pm}^{12} \\ \sigma_{1i\pm}\sigma_{2i\pm}\rho_{wi\pm}^{12} & \sigma_{2i\pm}^2 \end{pmatrix}\right)$$

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For biomarker-negative subgroup:

$$\begin{pmatrix} Y_{1i-} \\ Y_{2i-} \end{pmatrix} \sim N \left(\begin{pmatrix} \boldsymbol{\delta_{1i+}} + \beta_{1i} \\ \boldsymbol{\delta_{2i+}} + \beta_{2i} \end{pmatrix}, \Sigma_{i-} = \begin{pmatrix} \sigma_{1i-}^2 & \sigma_{1i-}\sigma_{2i-}\rho_{wi-}^{12} \\ \sigma_{1i-}\sigma_{2i-}\rho_{wi-}^{12} & \sigma_{2i-}^2 \end{pmatrix} \right)$$

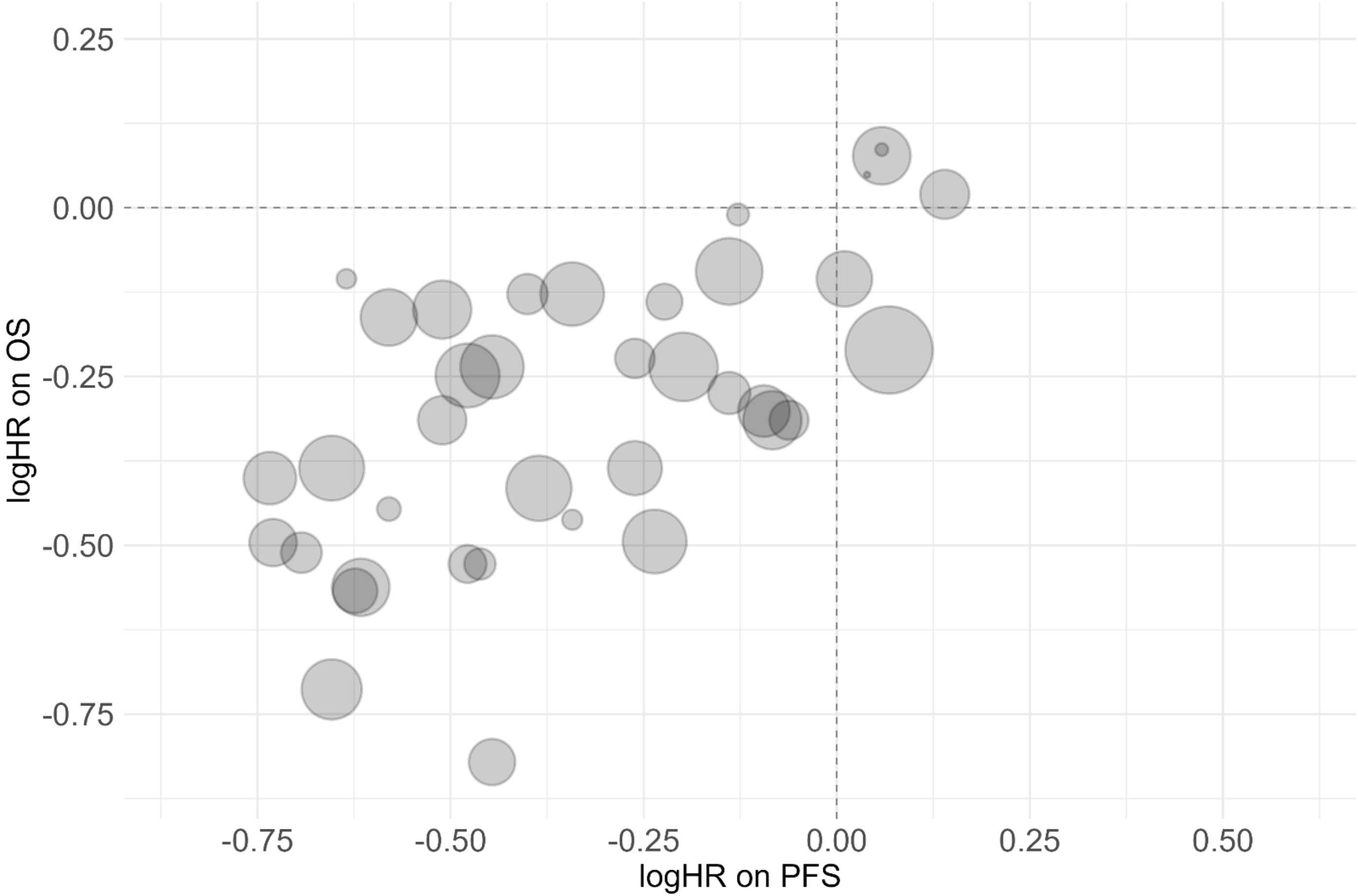
For biomarker-mixed populations:

$$\begin{pmatrix} Y_{1i\pm} \\ Y_{2i\pm} \end{pmatrix} \sim N \left(\begin{pmatrix} \boldsymbol{\delta_{1i+}} + p_{i\pm}\beta_{1i} \\ \boldsymbol{\delta_{2i+}} + p_{i\pm}\beta_{2i} \end{pmatrix}, \Sigma_{i\pm} = \begin{pmatrix} \sigma_{1i\pm}^2 & \sigma_{1i\pm}\sigma_{2i\pm}\rho_{wi\pm}^{12} \\ \sigma_{1i\pm}\sigma_{2i\pm}\rho_{wi\pm}^{12} & \sigma_{2i\pm}^2 \end{pmatrix} \right)$$

Between-study model for biomarker-positive group:

$$\begin{pmatrix} \boldsymbol{\delta_{1i+}} \\ \boldsymbol{\delta_{2i+}} \end{pmatrix} \sim N \left(\begin{pmatrix} d_{1+} \\ d_{2+} \end{pmatrix}, \begin{pmatrix} \tau_{1+}^2 & \tau_{1+}\tau_{2+}\rho_{b+} \\ \tau_{1+}\tau_{2+}\rho_{b+} & \tau_{2+}^2 \end{pmatrix} \right)$$

PFS as Surrogate for OS in Lung Cancer



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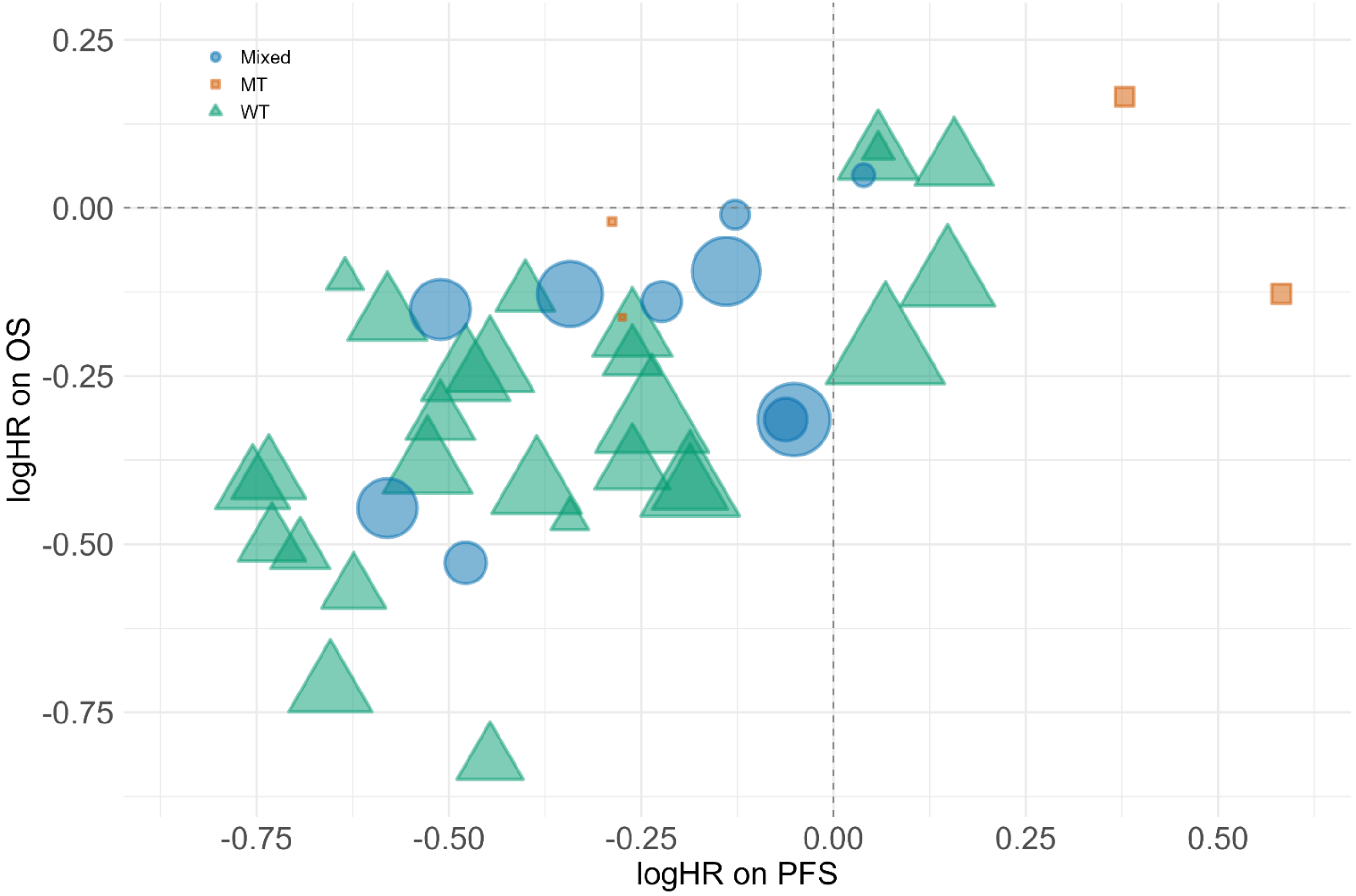
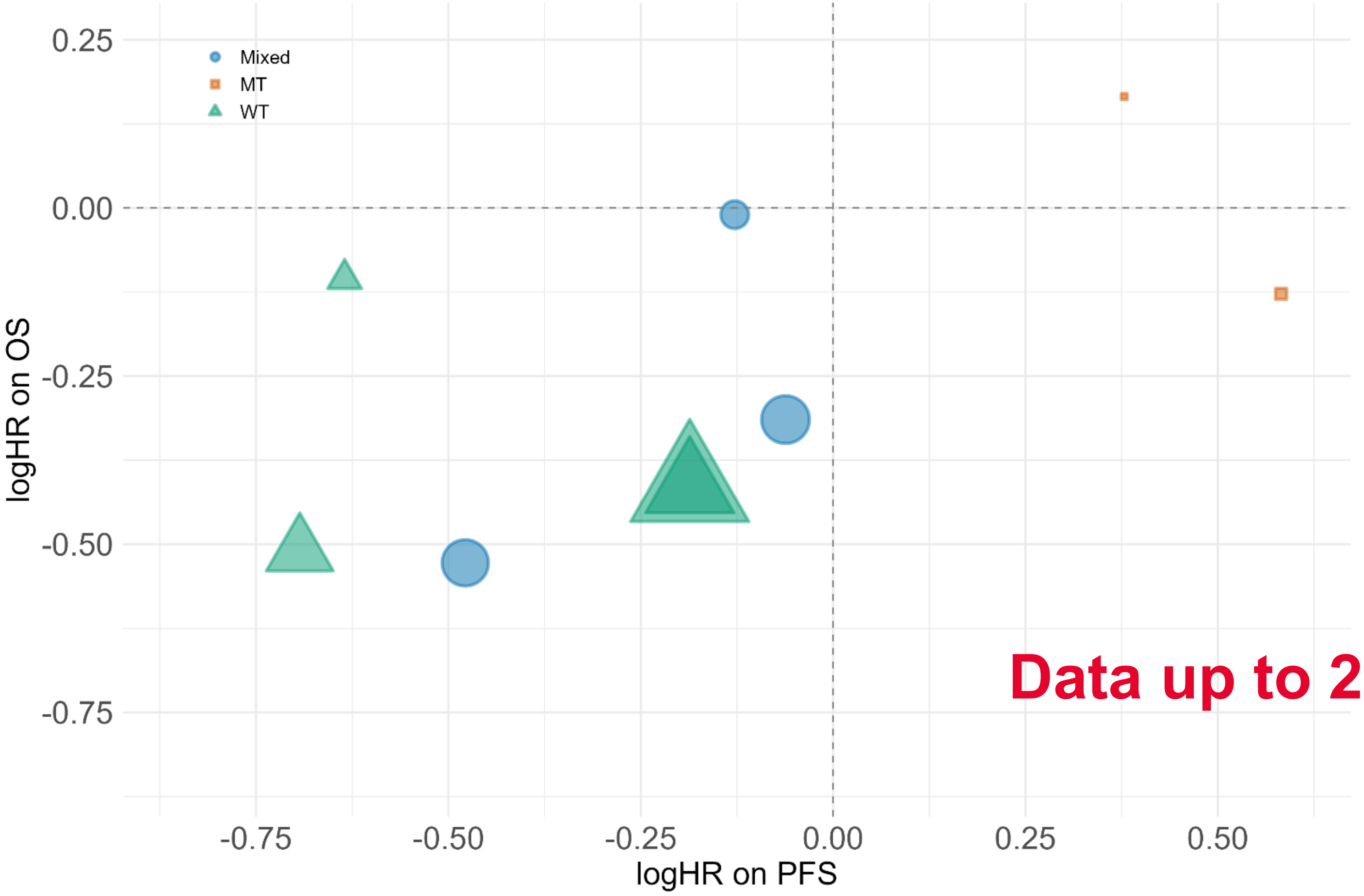
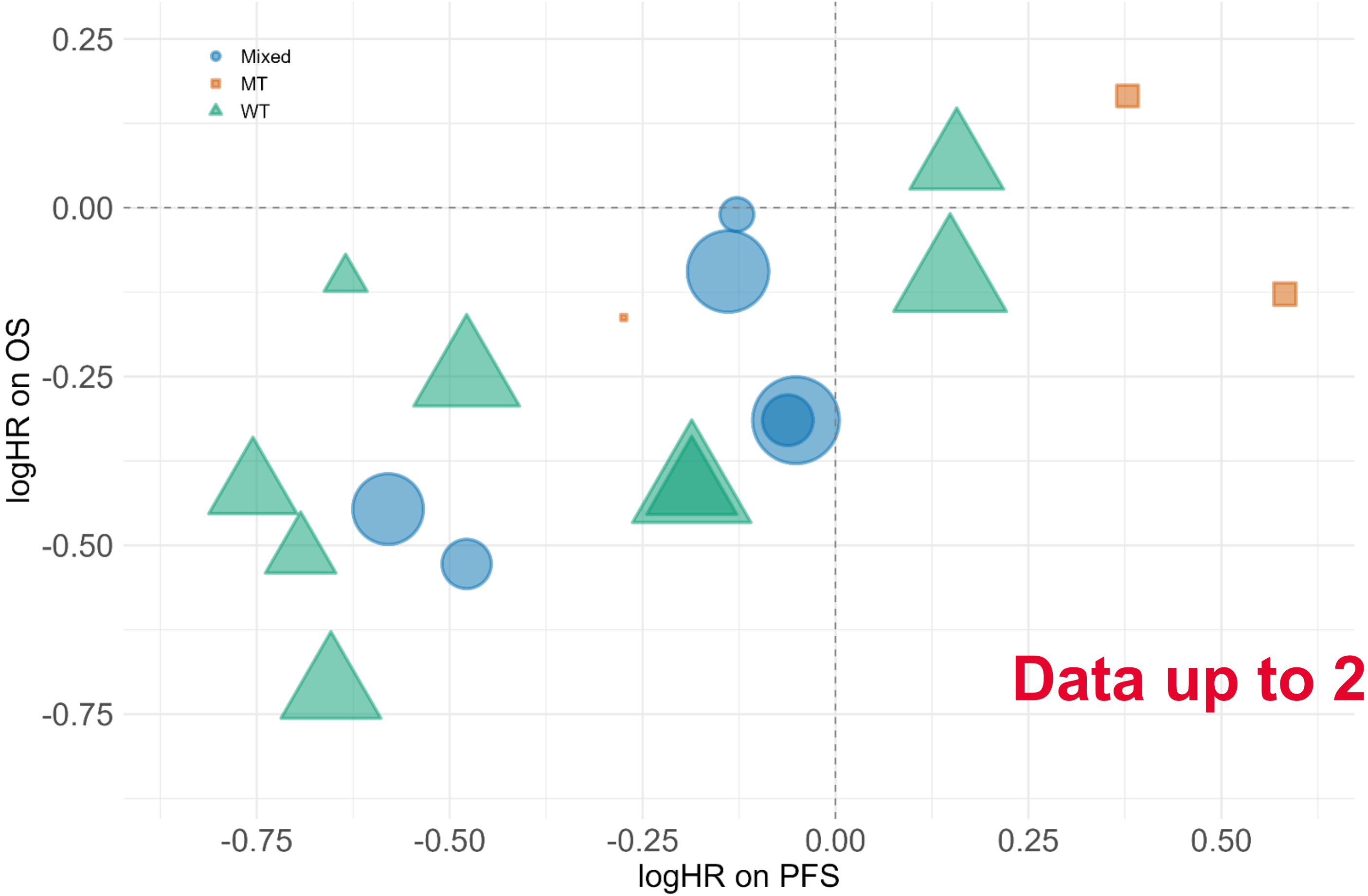


PFS as Surrogate for OS in Lung Cancer



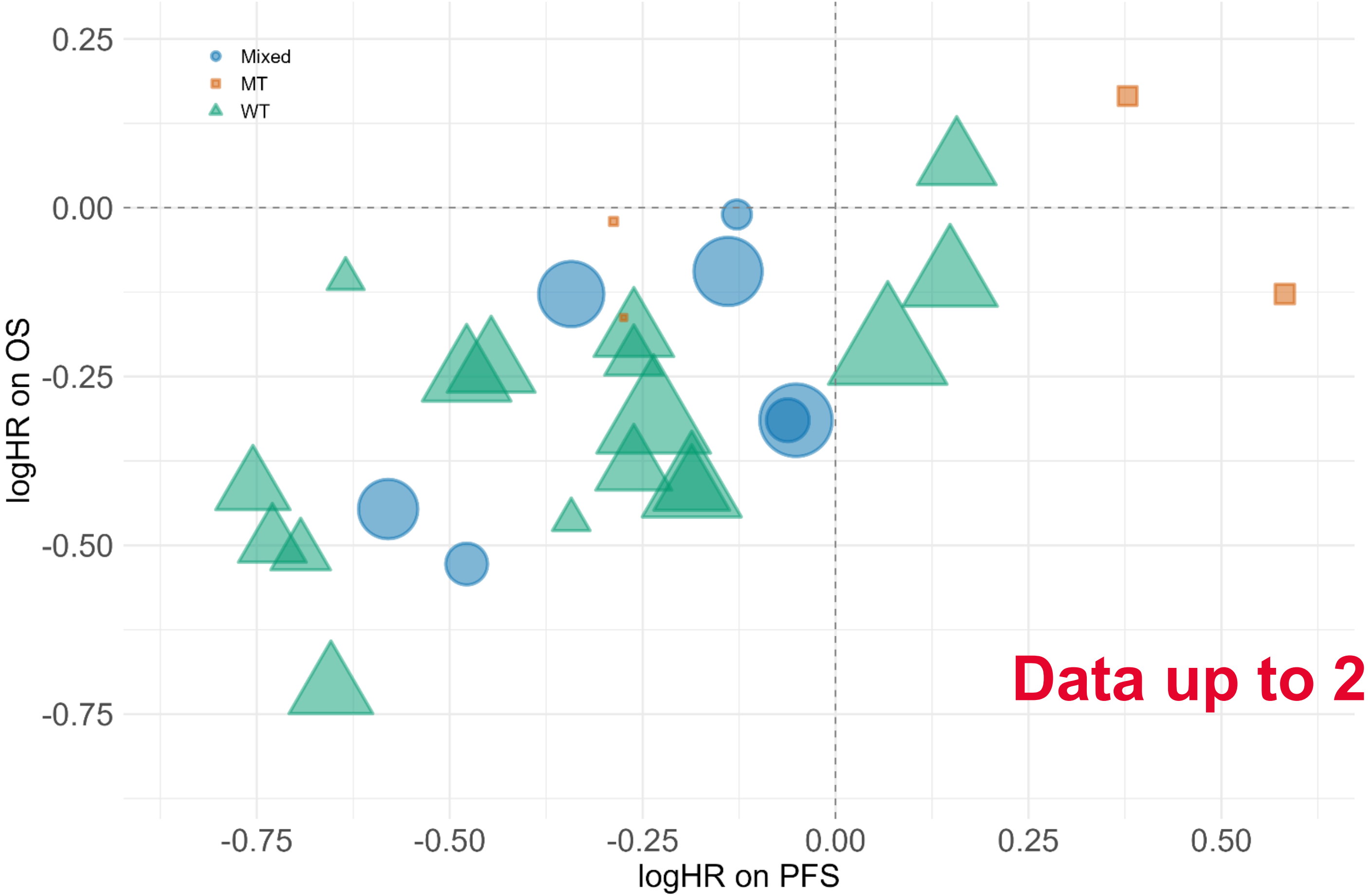
Data up to 2016

PFS as Surrogate for OS in Lung Cancer



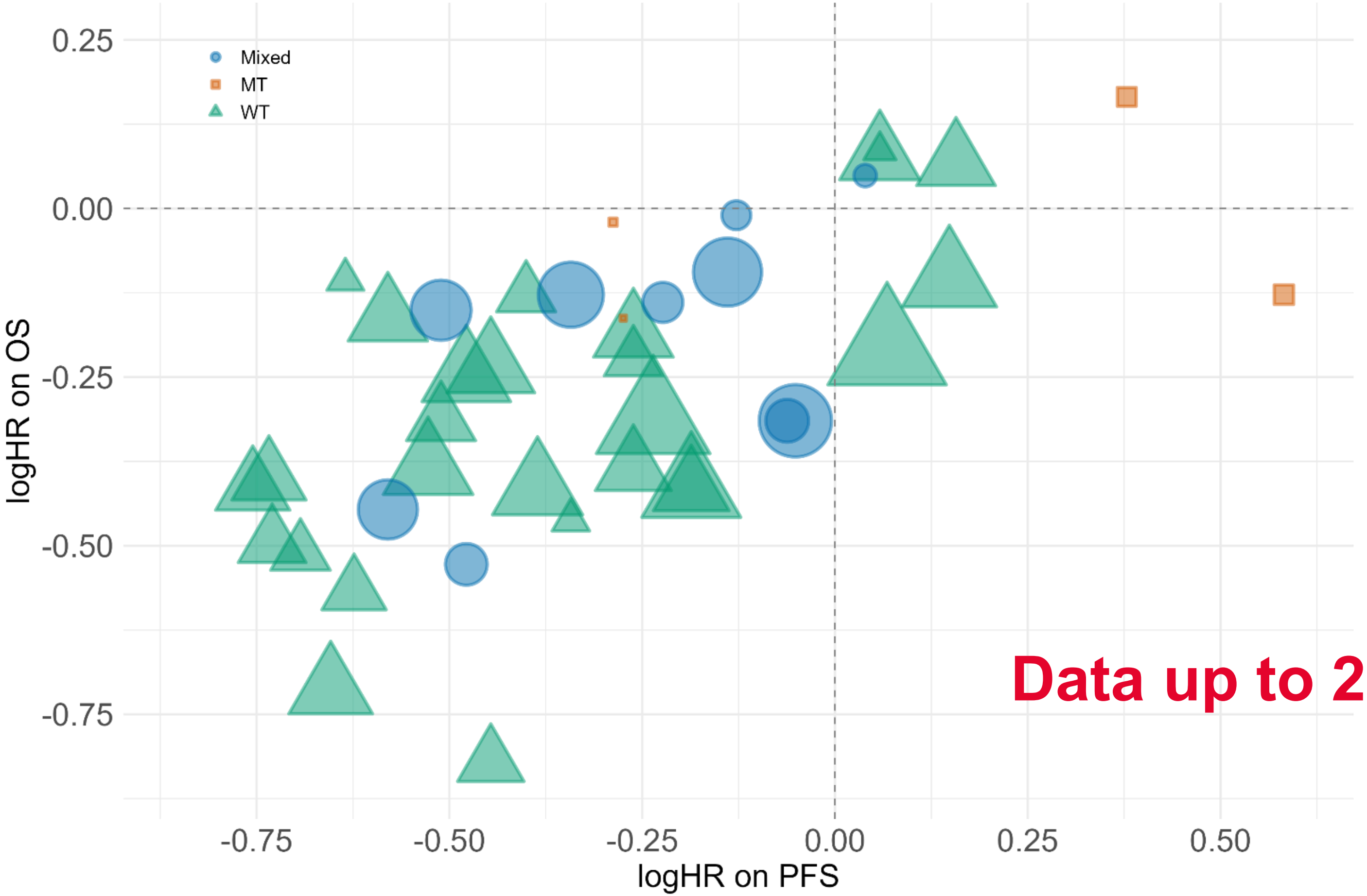
Data up to 2018

PFS as Surrogate for OS in Lung Cancer



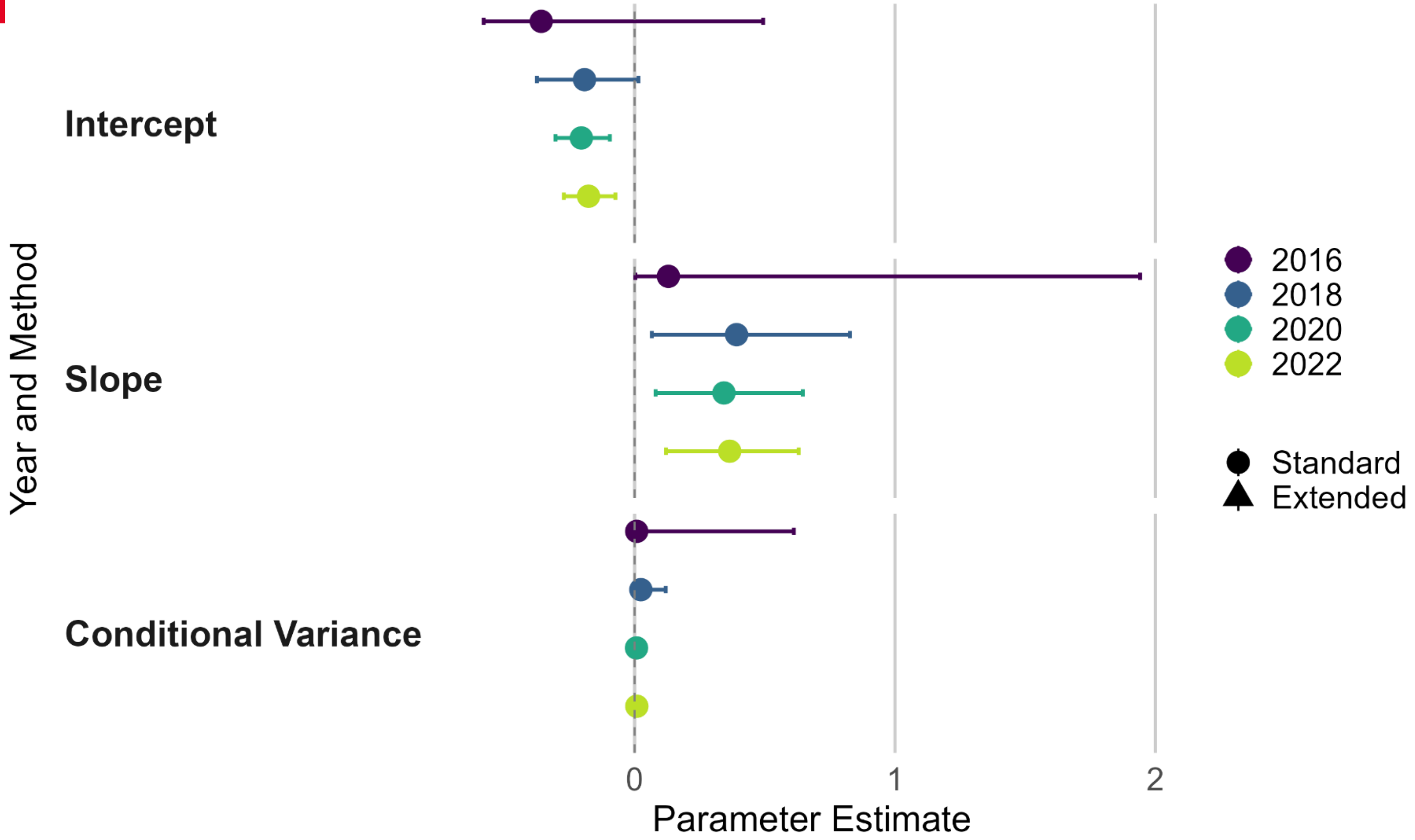
Data up to 2020

PFS as Surrogate for OS in Lung Cancer

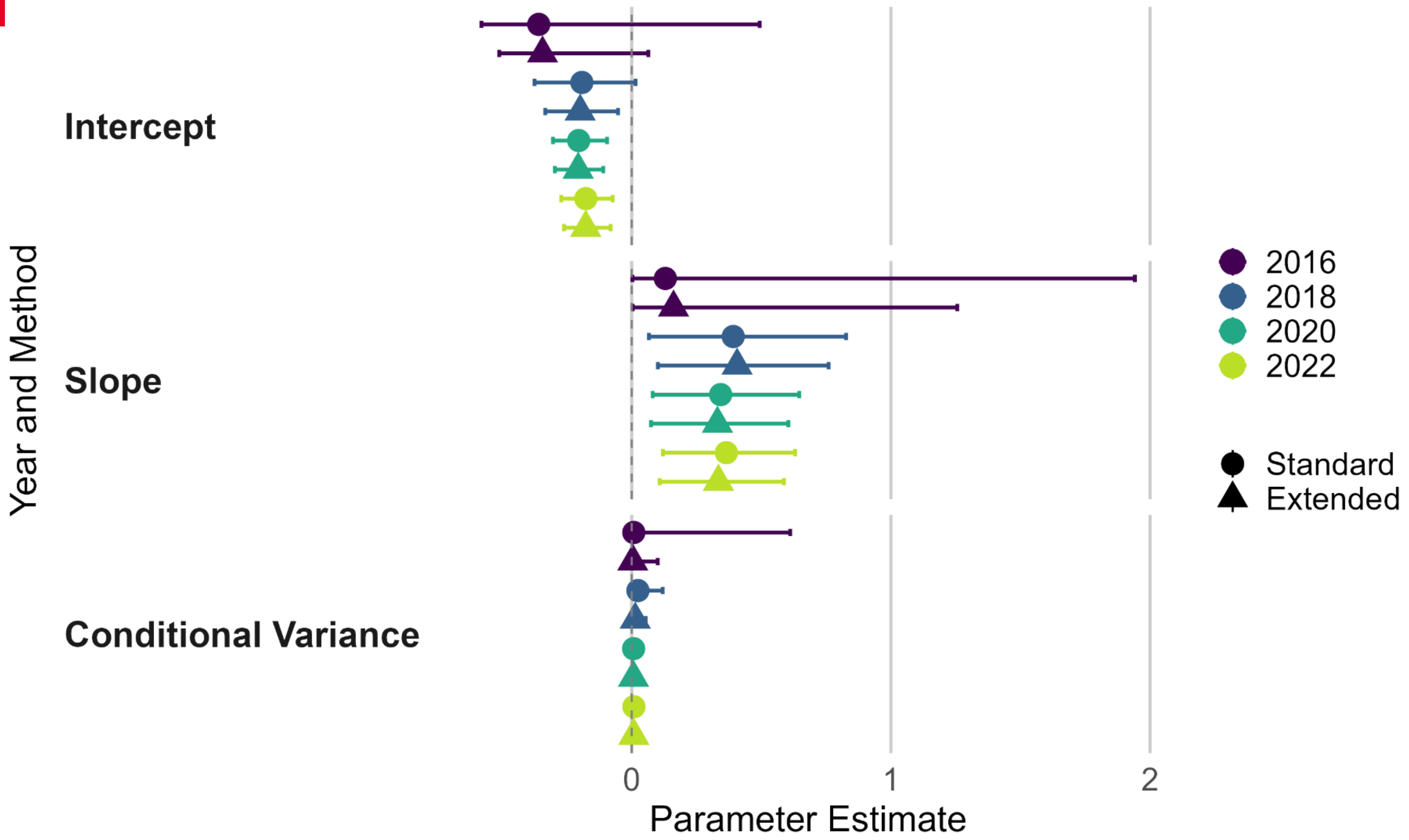


Data up to 2022

PFS as Surrogate for OS in Lung Cancer



PFS as Surrogate for OS in Lung Cancer



Discussion and Conclusions

- When conducting surrogacy analysis for regulatory approval or health technology assessment the patient population (specified by agency) may be limited to a biomarker subgroup.
- When trials are conducted in mixed populations, this can make it challenging to evaluate surrogacy relationships within biomarker sub-populations.
- The new method allows for utilising all available trial data to evaluate surrogacy within a biomarker group of interest.
- Simulation study confirmed improvement in precision of surrogacy parameters for extended model compared to standard model.
- Limitations:
  - Requires data from subgroup analysis for some studies
  - Simulation suggests increasing bias as systematic difference increases

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