RISE-Meta: Meta-analytic Evaluation of High-Dimensional Trial-Level Surrogates Applied to Vaccinology

Biostatistics Seminar, March 2026

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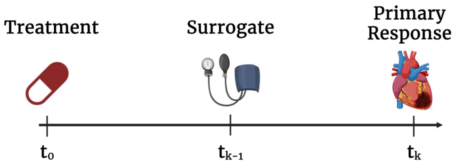
Surrogate Markers

What is a surrogate marker?

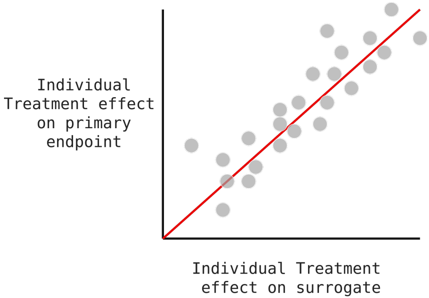
- **Intermediate endpoint**
- Treatment effect on surrogate **predicts treatment effect(s) on primary endpoint**



Treatment	**Primary endpoint**	**Surrogate**	**Advantage**
Antiretroviral therapy	Progression to AIDS	Plasma HIV-1 viral load	Observed sooner
Statin therapy	Major cardiovascular events	Reduction in LDL cholesterol	Easy to measure, observed sooner
Yellow fever vaccination	Yellow fever infection	Neutralising antibody titre	Measuring vaccine response when disease is not endemic

Individual versus trial-level surrogates

Individual-Level Surrogate



- Evaluated with correlation, association, cross-validation... (Gabriel, 2017)

Individual versus trial-level surrogates

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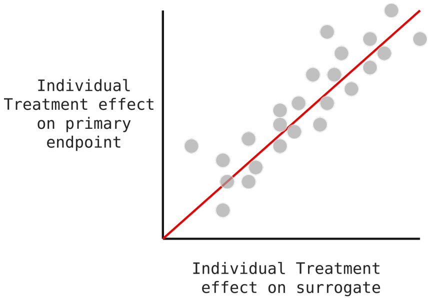

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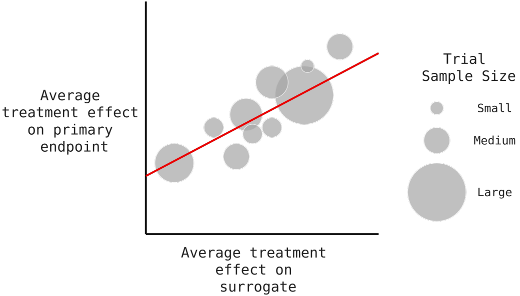
Trial-Level Surrogate

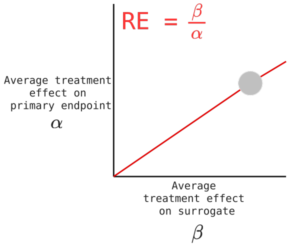


- Evaluated in *single-trial* or *multi-trial framework*

Evaluation of Trial-Level Surrogacy

Single-Trial Framework

- Proportion of treatment effect explained (Freedman, 1992), relative effect (Buyse, 2000), nonparametric approaches (Parast, 2024; Hughes, 2025)
- **Implicit assumption about portability**



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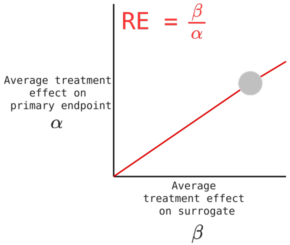
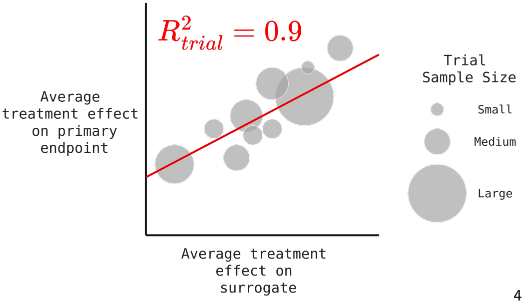


Multi-Trial Framework

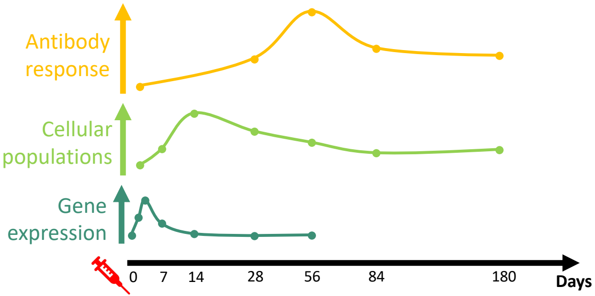
- Targets **generalisability** of surrogate across clinical settings
- Evaluated with meta-analysis (Molenberghs, 2002)



High-Dimensional Surrogates

High-dimensional data in biomedical research

- High-throughput technologies: **thousands of variables per sample**
  - e.g. transcriptomics, proteomics, metabolomics
- Potential as **biomarkers** of downstream endpoints
- Literature focused on differential analysis and individual prediction, **surrogates previously unexplored**



Credit: Boris Hejblum

Surrogate evaluation is challenging in high-dimension

Previously existing methods

- Restrictive assumptions
- Large sample sizes
- Low-dimensional

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Rank-based Identifiation of high-dimensional SurrogatE markers (RISE) (Hughes, 2025)

- Nonparametric evaluation of high-dimensional surrogates in small sample setting
- Single-trial framework

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Goal: Extend RISE to meta-analytic setting

Identify **generalisable high-dimensional surrogates**

RISE

Notation

Data structure

- $m = 1, \ldots, M$: trials
- $i = 1, \ldots, N_m$: individuals in trial m
- $j = 1, \ldots, J$: candidate surrogate markers

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Variables

- Binary treatment $A_{i,m} \in \{0, 1\}$
- Primary endpoint $Y^a_{i,m}$
- Surrogate vector $\boldsymbol{S}^a_{i,m} = (S^a_{i,1,m}, \ldots, S^a_{i,J,m})$

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- Primary endpoint $Y_{i,m}^a$
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Observed data

- $\left(A_{i,m}, Y_{i,m}^{A_{i,m}}, \boldsymbol{S}_{i,m}^{A_{i,m}}\right) \; \forall i$
- independent, i.i.d. within trial m

Within-trial effect measures

Treatment effects with U-statistics (Parast, 2024; Hughes, 2025)

$$U_{Y,m} = \mathbb{P}(Y^1_{i,m} > Y^0_{l,m}) + \tfrac{1}{2}\mathbb{P}(Y^1_{i,m} = Y^0_{l,m})$$

$$U_{S,m} = \mathbb{P}(S^1_{i,m} > S^0_{l,m}) + \tfrac{1}{2}\mathbb{P}(S^1_{i,m} = S^0_{l,m})$$

- **Probability** that treated individual has *greater* response than control
  - $\Rightarrow$ > 0.5: positive effect $= 0.5$: no effect < 0.5: negative effect

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Within-trial surrogacy

- $\delta_m = U_{Y,m} - U_{S,m}$
  - **bias in estimating effect** on Y observing only S
- **Quantity of interest for meta-analysis!**

Within-Trial Estimation

$$G(x,y) = \begin{cases} 1, & x > y \\ \frac{1}{2}, & x = y \\ 0, & x < y \end{cases}$$

Active treatment vs control

$$\widehat{U}_{Y,m} = \frac{1}{N_m^1 N_m^0} \sum_{i=1}^{N_m^1} \sum_{l=1}^{N_m^0} G(Y_{i,m}^1, Y_{l,m}^0), \quad \widehat{U}_{S,m} = \frac{1}{N_m^1 N_m^0} \sum_{i=1}^{N_m^1} \sum_{l=1}^{N_m^0} G(S_{i,m}^1, S_{l,m}^0)$$

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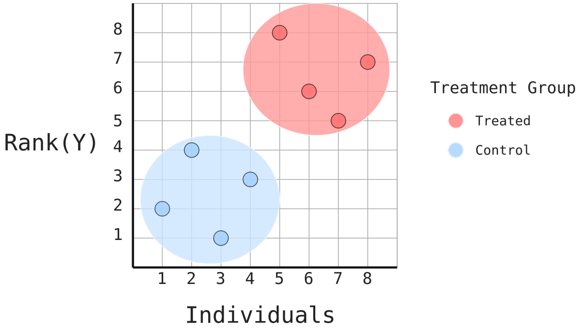
Paired setting

$$\widehat{U}_{Y,m} = \frac{1}{N_m} \sum_{i=1}^{N_m} G(Y_{i,m}^1, Y_{i,m}^0), \quad \widehat{U}_{S,m} = \frac{1}{N_m} \sum_{i=1}^{N_m} G(S_{i,m}^1, S_{i,m}^0)$$

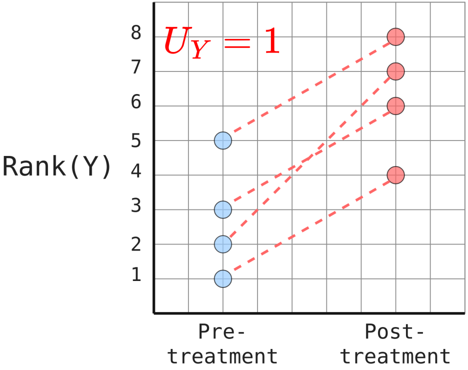
Intuition for estimation - Active versus control

$U_Y = 1$



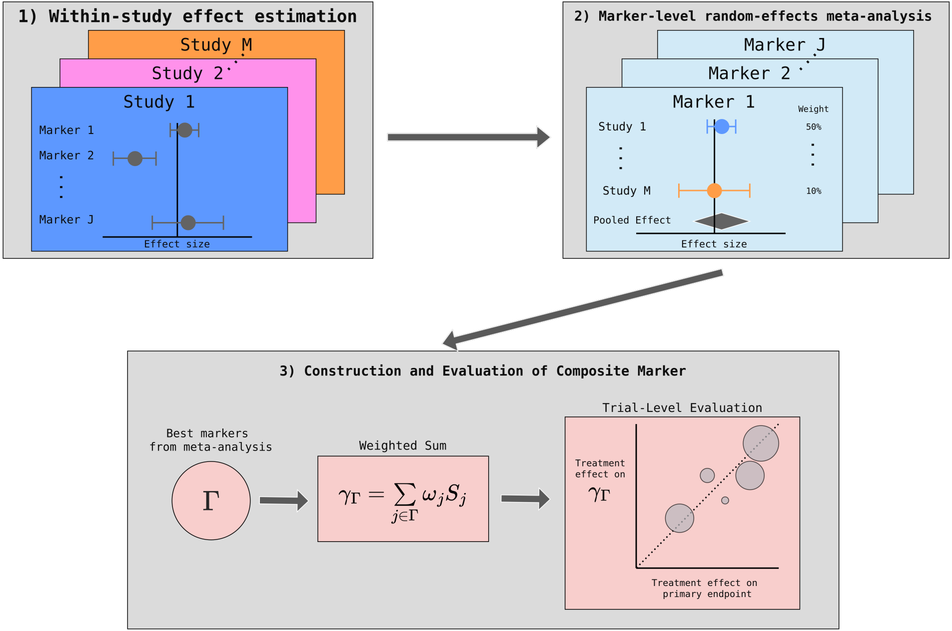
$\widehat{U}_{Y,m} = 1 \implies$ **perfect group separation by Y in trial m**

Intuition for estimation - paired case



$\widehat{U}_{Y,m} = 1 \implies$ **response improves with treatment for every individual in trial** m

RISE-Meta


1) Within-study effect estimation
Study M
Study 2
Study 1
Marker 1
Marker 2
Marker J
Effect size
2) Marker-level random-effects meta-analysis
Marker J
Marker 2
Marker 1
Weight
Study 1
50%
Study M
10%
Pooled Effect
Effect size
3) Construction and Evaluation of Composite Marker
Best markers
from meta-analysis
Γ
Weighted Sum
$\gamma_\Gamma = \sum_{j \in \Gamma} \omega_j S_j$
Trial-Level Evaluation
Treatment
effect on
γ_Γ
Treatment effect on
primary endpoint

Random effects meta-analysis model

Assume within-trial effects $\delta_m = U_{Y,m} - U_{S,m}$ are gaussian (DerSimonian, 1986)

$$\delta_m \sim N(\mu_\delta,\ \sigma^2_{\delta,m} + \tau^2_\delta)$$

where

- μ_δ: common mean effect
- $\sigma^2_{\delta,m}$: study-specific variance in trial m
- τ^2_δ: common between-study variance
  - Estimated with REML

Estimating the mean effect

Estimate **pooled effect as weighted sum of within-trial estimates**

$$\widehat{\mu_\delta} = \frac{\sum_{m=1}^{M} \widehat{w_{\delta,m}} \, \widehat{\delta}_m}{\sum_{m=1}^{M} \widehat{w_{\delta,m}}}$$

weights are **inverse variances**

$$\widehat{w_{\delta,m}} = \frac{1}{\widehat{\sigma_{\delta,m}}^2 + \widehat{\tau_\delta}^2}$$

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- Recommend variance estimated with Hartung-Knapp estimator $\widehat{\mathrm{Var}}_{\mathsf{HK}}$ (Hartung, 2001)
- $(1-\alpha) \times 100\%$ C.I. : $\widehat{\mu_\delta} \pm q_{t_{M-1},1-\alpha/2} \sqrt{\widehat{\mathrm{Var}}_{\mathsf{HK}}(\widehat{\mu_\delta})}$

Hypothesis testing on pooled effect

Goal: test surrogacy with $\mu_\delta \in [-\varepsilon, \varepsilon]$

Propose a *two one-sided test* (TOST) procedure to test (Schuirmann, 1987)

$$H_{0L}^{\text{TOST}} : \mu_\delta \leq -\varepsilon, \quad H_{0U}^{\text{TOST}} : \mu_\delta \geq \varepsilon$$

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$\Rightarrow$ two sets of test statistics and p-values

$$T_L = \frac{\widehat{\mu}_\delta + \varepsilon}{\widehat{\text{SE}}_{HK}}, \quad p_L = 1 - F_{t,M-1}(T_L),$$

$$T_U = \frac{\widehat{\mu}_\delta + \varepsilon}{\widehat{\text{SE}}_{HK}}, \quad p_U = 1 - F_{t,M-1}(T_U),$$

$F_{t,M-1}$ is c.d.f. of t-distribution with $M-1$ degrees of freedom. Combined p-value is

$$p_{\text{TOST}} = \max(p_L, p_U)$$

Deriving a signature of promising markers

- p_j = p-value for jth marker testing $\widehat{\mu}_{\delta_j} \in [-\varepsilon, \varepsilon]$
- Apply correction to control for false discovery rate (Benjamini, 1995)
- $p_{adj,j}$ = adjusted p-value for jth marker

Define a signature set

$$\Gamma = \{j : p_{adj,j} \leq \alpha\}$$

Constructing a composite surrogate signature

Goal: combine markers $S_j : j \in \Gamma$ into a univariate signature

- **Surrogacy strength component:** $\widehat{a}_j = \dfrac{\varepsilon - |\widehat{\mu}_{\delta,j}|}{\varepsilon}$

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Composite signature:

$$\widehat{\gamma}_\Gamma = \sum_{j\in\Gamma} \widehat{\omega}_j\,\bar{S}_j$$

Prediction intervals

- **Confidence intervals misleading** in presence of between-trial **heterogeneity** (IntHout, 2016)
  - Good trial-level surrogate must have $\mu_\delta \approx 0$ **and consistent estimation** across trials

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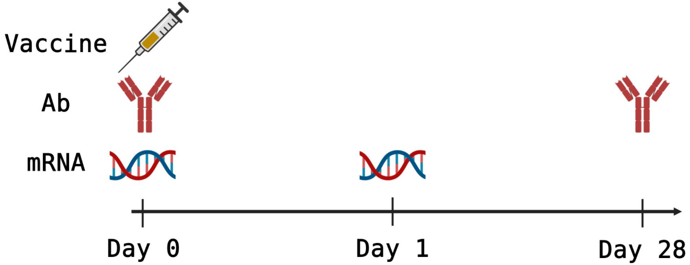
- **Confidence intervals misleading** in presence of between-trial **heterogeneity** (IntHout, 2016)
  - Good trial-level surrogate must have $\mu_\delta \approx 0$ **and consistent estimation** across trials
- **Prediction interval**: likely range of effect estimates in **new trials**
- $(1-\alpha) \times 100\%$ P.I. given by

$$\widehat{\mu_\delta} \pm q_{t_{M-1},\,1-\alpha/2} \sqrt{\widehat{\mathrm{Var}}_{HK}(\widehat{\mu_\delta}) + \widehat{\tau}_\delta^2}$$

Application

Application to inactivated influenza vaccine

- **Open data** from **4 trials** in Human Immune Project Consortium on inactivated flu vaccine (Diray-Arce, 2022)
- **Primary endpoint:** Day 28 antibody response (nAb/HAI)
- **Surrogate candidates :** gene expression of $\approx 10,000$ genes
- **Paired setting** (each individual pre- & post-vaccination Ab and GE)



Can we use RISE-Meta to derive a **generalisable signature** of **gene expression**, measured at 1 day after vaccination, which is **predictive of the vaccine effect** on the **antibodies**, measured at 28 days post-vaccination?

Analysis Details

- **Transform data gene-level $\Rightarrow$ geneset-level**
  - Transformation = within-geneset mean expression
  - $\Rightarrow$ **reduce dimension**, improve interpretability
  - Genesets: blood transcriptional modules ($J = 174$ after removing untitled) (Li, 2013)

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- **Sample splitting to mitigate overfitting** (Ball, 2020)
  - Marker-level meta-analyses on training data ($\frac{2}{3}$ within each trial)
  - Evaluate composite marker on test data

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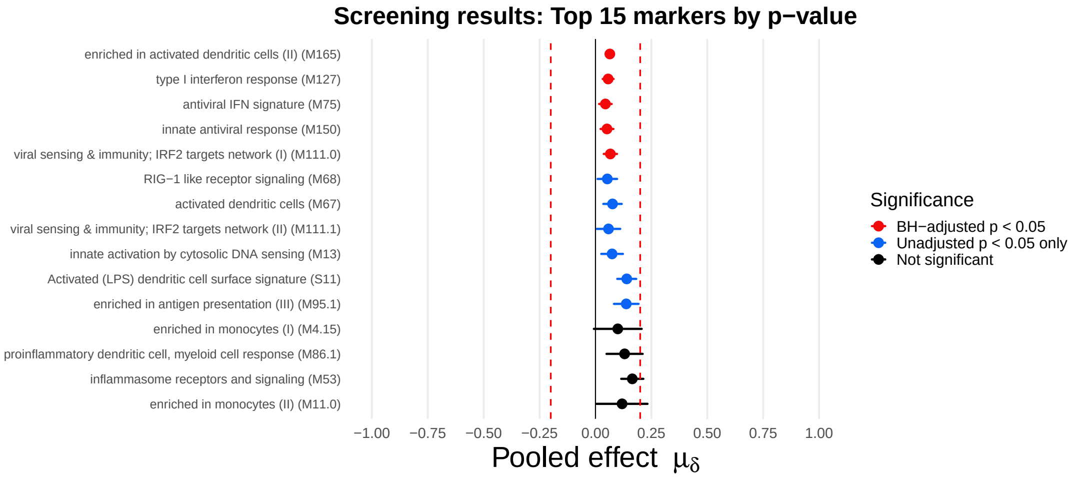
  - Evaluate composite marker on test data
- Hyperparameters : $\varepsilon = 0.2$, $\alpha = 0.05$, Benjamini-Hochberg correction

Interferon and dendritic cell signals dominate the signature



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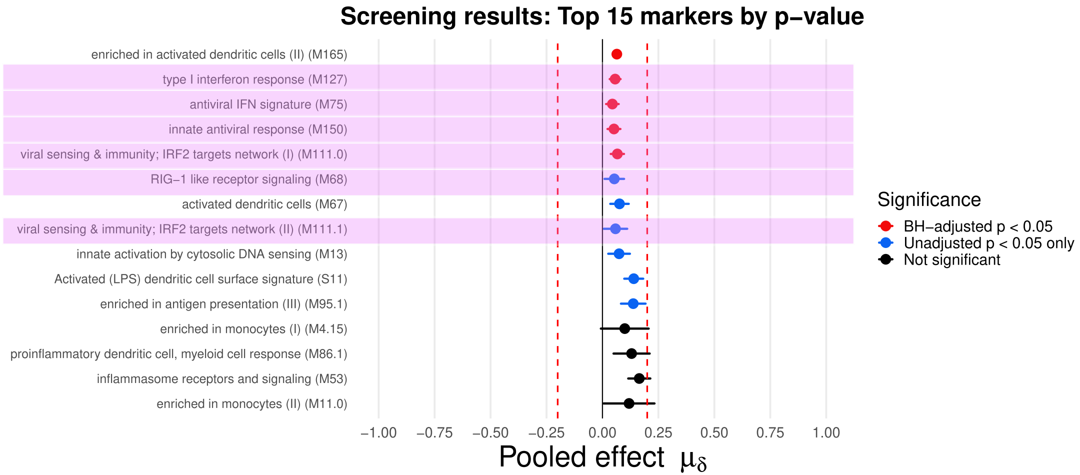

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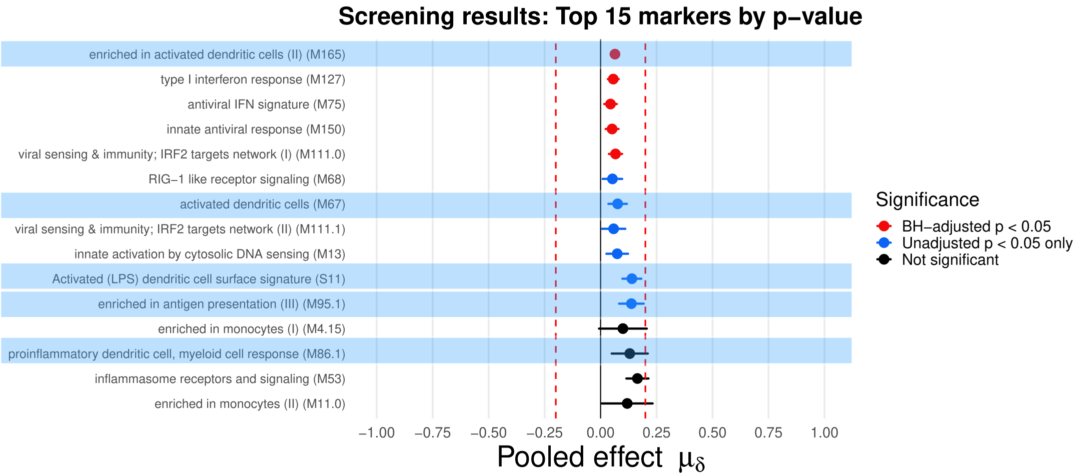
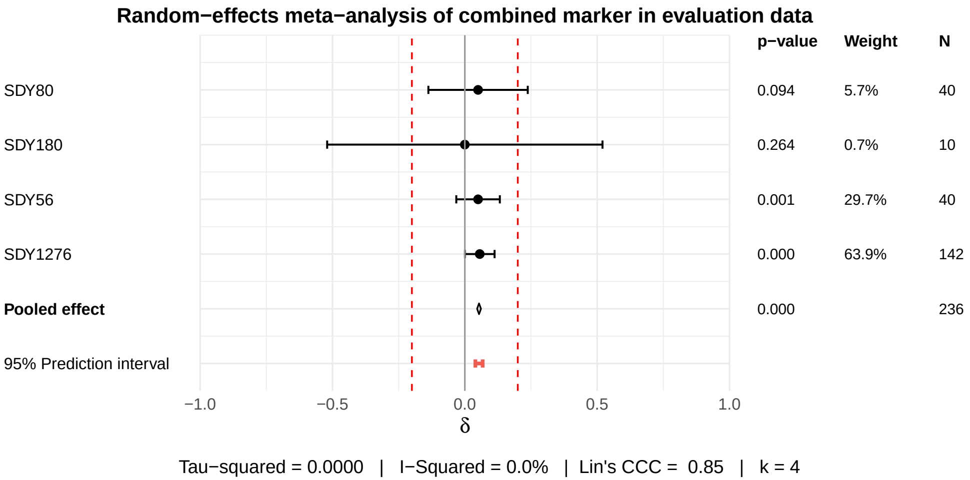


Evaluation of composite signature on independent data



Discussion

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- RISE: statistical framework for high-dimensional surrogate evaluation in a **single-trial**
- **Meta-analysis: gold-standard** for evaluation of surrogacy considering **between-study heterogeneity**
- Application: **promising signature** of biologically relevant genes **predictive of flu vaccine effect** on the later antibody response

RISE-Meta is a novel statistical framework for the **meta-analysis of high-dimensional trial-level surrogate markers**

Discussion

- RISE: statistical framework for high-dimensional surrogate evaluation in a **single-trial**
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> **RISE-Meta** is a novel statistical framework for the **meta-analysis of high-dimensional trial-level surrogate markers**

Perspectives

$\Rightarrow$ Extension to other outcome types (binary, survival)

$\Rightarrow$ Simulations to explore limits (number of studies, study size)

$\Rightarrow$ Bayesian meta-analysis when number of trials is small?

Thank you!

RISE Available in the **R package** `SurrogateRank`

RISE-Meta available soon

Hughes A, Parast L, Thiébaut R & Hejblum BP. RISE: Two-stage rank-based identification of high-dimensional surrogate markers applied to vaccinology. *Statistics in Medicine* 44(20-22):e70241, 2025.
DOI: 10.1002/sim.70241

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Data Description

Available studies

Study	Year	Study Description
SDY61	2008	Systems Biology of 2007 Influenza Vaccination in Humans
SDY269	2009	Systems Biology of 2008 Influenza Vaccination in Humans
SDY270	2009	Systems Biology of 2009 Influenza Vaccination in Humans
SDY180	2010	Systems scale interactive exploration reveals quantitative and qualitative differences in response to 2009-2010 Fluzone influenza vaccine and pneumococcal vaccine
SDY56	2010	Systems Biology of 2010 trivalent Influenza vaccine (TIV) in young and elderly
SDY67	2010	Bioinformatics Approach to 2010-2011 TIV Influenza A/H1N1 Vaccine Immune Profiling
SDY1119	2011	Systems Biology of 2011 trivalent Influenza vaccine (TIV) in young and elderly individuals, healthy or with T2D
SDY224	2011	Immune Responses to Seasonal TIV 2010-2011 Influenza Vaccination in Humans
SDY404	2011	Immunologic and genomic signatures of influenza vaccine response - 2011
SDY63	2011	Immunologic and genomic signatures of influenza vaccine response - 2010
SDY400	2012	Immunologic and genomic signatures of influenza vaccine response - 2012
SDY1276	2013	Time series of global gene expression after trivalent influenza vaccination in humans
SDY520	2013	Immunologic and genomic signatures of influenza vaccine response - 2013
SDY80	2014	Cellular and molecular characterization of the immune response in healthy NIH employees at baseline, and after immunization with the H1N1 or seasonal influenza vaccines
SDY640	2014	Immunologic and genomic signatures of influenza vaccine response - 2014

Inclusion/Exclusion Criteria

Study	Inclusion	Exclusion
SDY61	Healthy adults	
SDY269	Healthy adults	
SDY270	Healthy adults	
SDY180	Healthy adults (18-64)	Pregnancy, allergies, vaccines within 2 months
SDY56	Healthy adults (18-40 or ≥ 65)	Recent infections/vaccines, chronic illnesses, pregnancy
SDY67	Healthy adults (50-74)	
SDY1119	Healthy or type 2 diabetic adults, immunocompetent	Other illnesses, pregnancy, drug intake
SDY224	Healthy adults (18-69)	Other illnesses, pregnancy, drug intake
SDY404	Healthy adults (21-30 or ≥ 65)	
SDY63	Healthy adults (21-30 or ≥ 65)	
SDY400	Healthy adults (21-30 or ≥ 65)	
SDY1276	Healthy adults (18-40), white	Influenza infection or vaccine within 3 years
SDY520	Healthy adults (21-30 or ≥ 65)	
SDY80	Healthy adults, NIH employee	
SDY640	Healthy adults (21-30 or ≥ 65)	

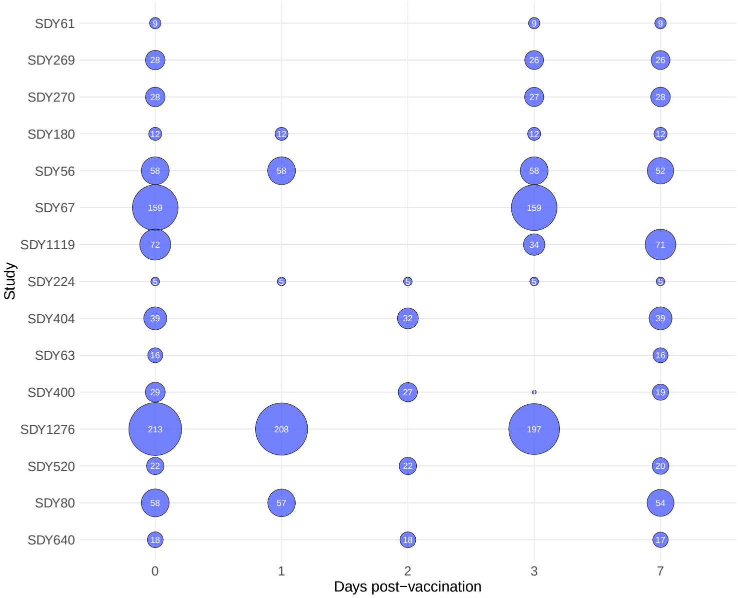
Inclusion criteria for surrogate analysis

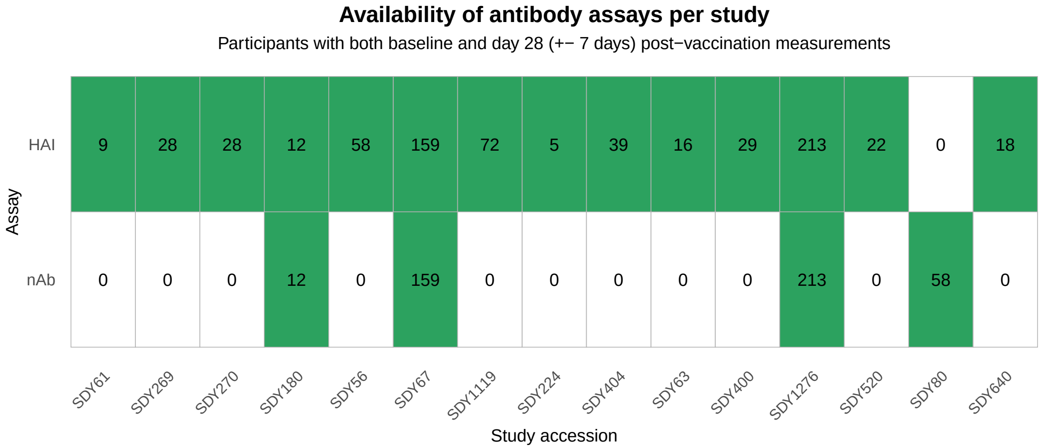
Participants must:

- be healthy adults (18+),
- receive inactivated influenza vaccine,
- have at least one immune response assay measurement (nAb, HAI) at baseline AND day 28 (+-7 days)
- have gene expression measured both at baseline AND post-vaccination

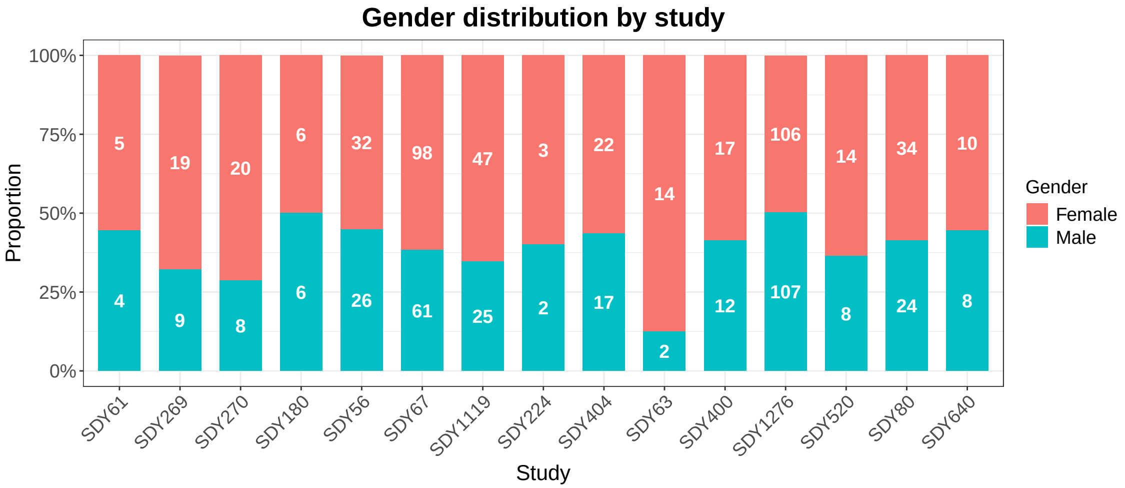
Number of transcriptomic observations across time per study

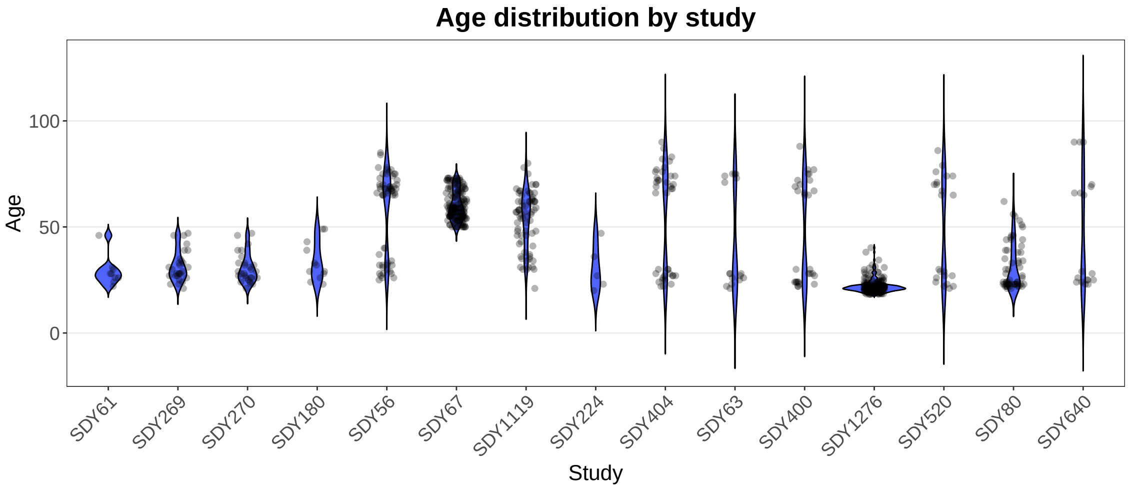
Selected timepoints, healthy adults with baseline and post−vaccination data





- Use nAb if available, otherwise HAI


Gender distribution by study
Proportion
100%
75%
50%
25%
0%
5
4
19
9
20
8
6
6
32
26
98
61
47
25
3
2
22
17
14
2
17
12
106
107
14
8
34
24
10
8
SDY61
SDY269
SDY270
SDY180
SDY56
SDY67
SDY1119
SDY224
SDY404
SDY63
SDY400
SDY1276
SDY520
SDY80
SDY640
Study
Gender
Female
Male



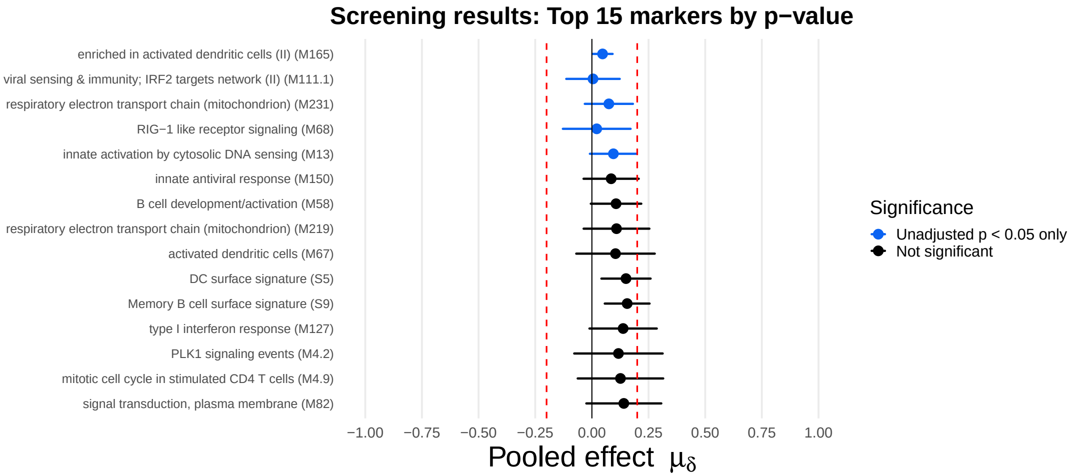
Age distribution by study
Age
100
50
0
SDY61
SDY269
SDY270
SDY180
SDY56
SDY67
SDY1119
SDY224
SDY404
SDY63
SDY400
SDY1276
SDY520
SDY80
SDY640
Study

Supplementary Analyses

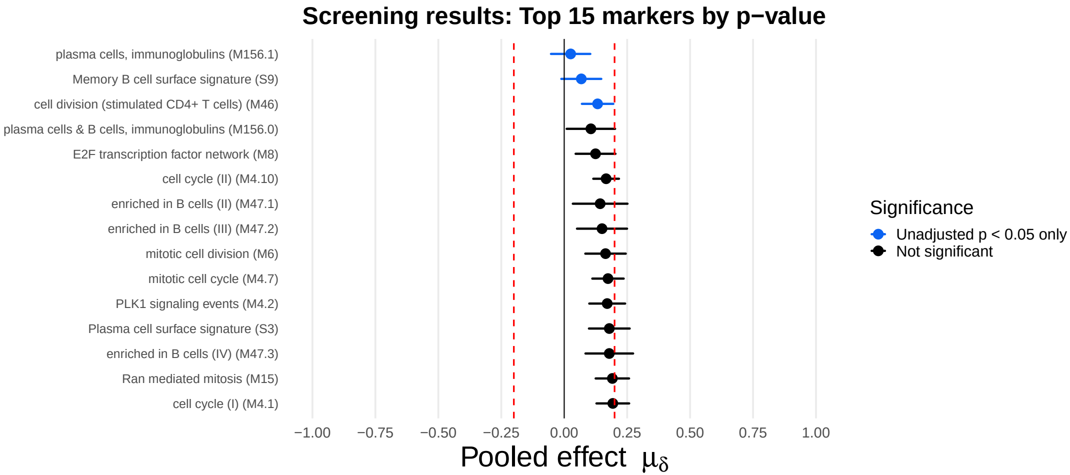
Supplementary analyses

- Day 1, 2, 3, 7 post-vaccination
- Genewise analyses

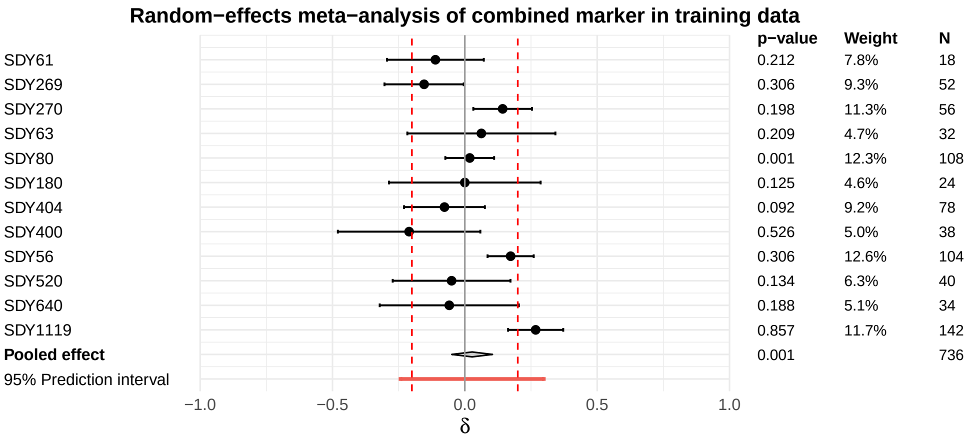
Day 2 screening results



Day 7 screening results

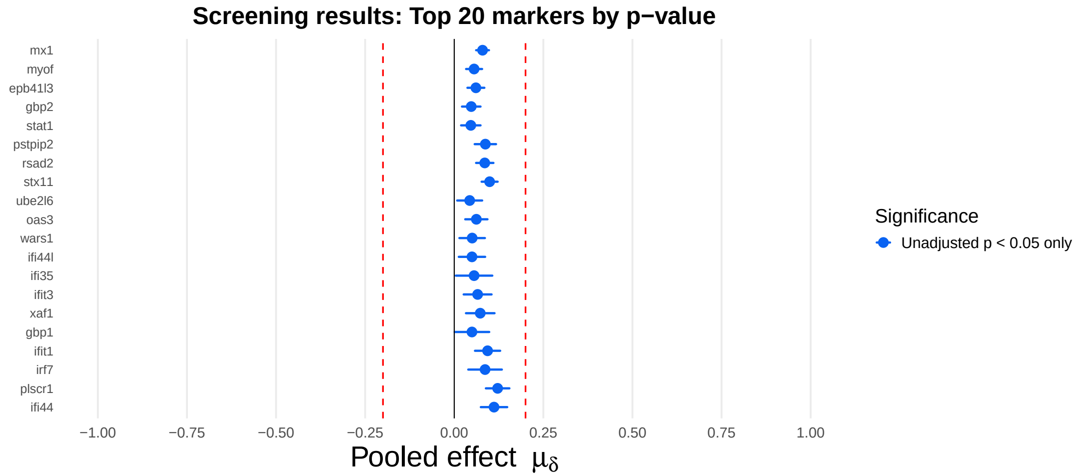


Day 7 evaluation results

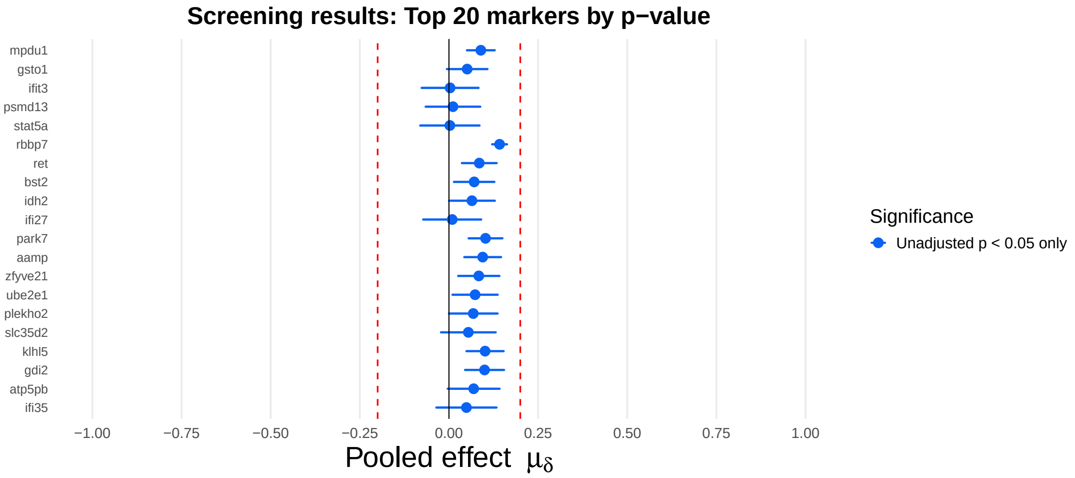


Tau−squared = 0.0129 | I−Squared = 64.8% | Lin's CCC = 0.21 | k = 12

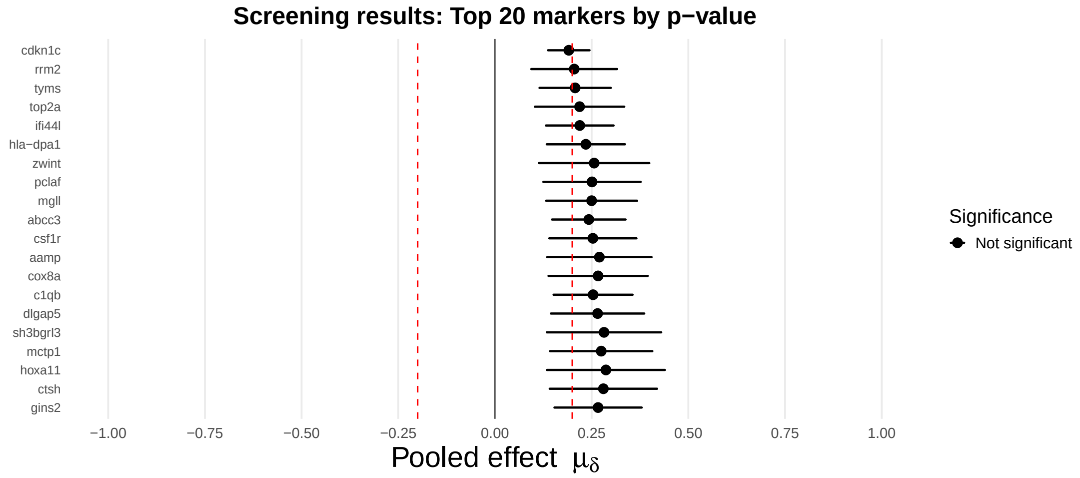
Day 1 Genewise Analysis



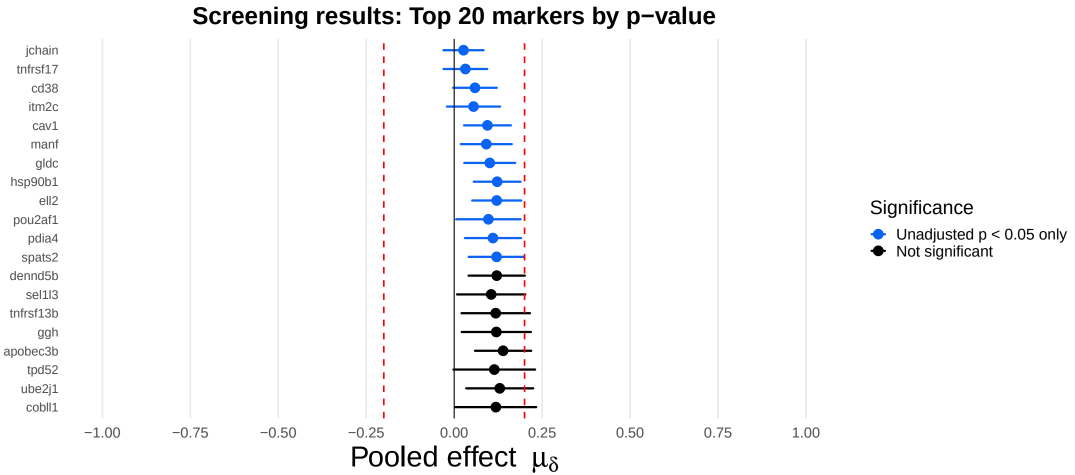
Day 2 Genewise Analysis



Day 3 Genewise Analysis



Day 7 Genewise Analysis



Simulation

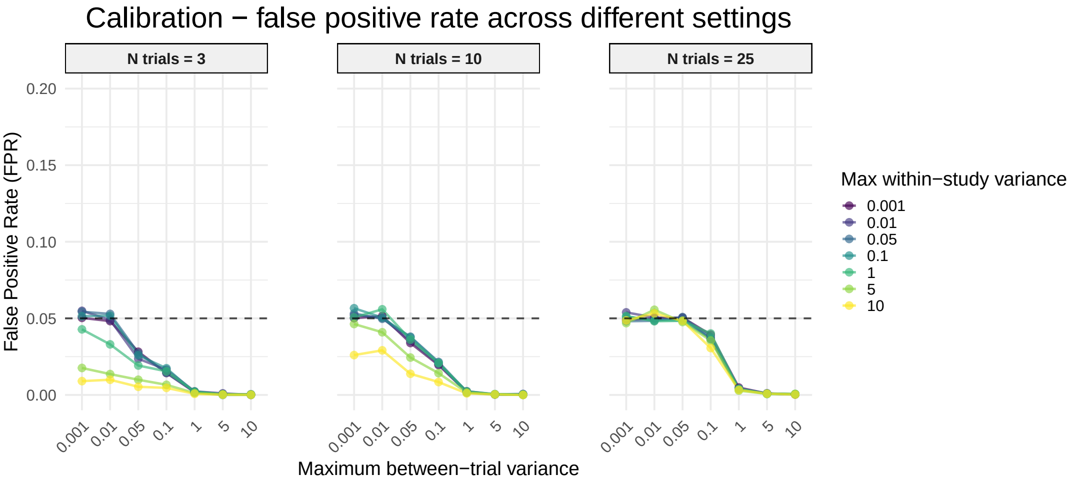
Gaussian simulation

- Simulate true deltas: $\delta_{m,j}^{\text{true}} \sim \mathcal{N}(\mu_{\delta,j}, \tau_{\delta,j}^2)$
  - allow heterogeneity to vary across markers :
    $\tau_{\delta,j}^2 \sim \mathcal{U}(u_{\tau,min}, u_{\tau,max}), \qquad 0 \leq u_{\tau,min} \leq u_{\tau,max}$
- add sampling error : $\widehat{\delta}_{m,j} \sim \mathcal{N}(\delta_{m,j}^{\text{true}}, \sigma_{m,j}^2)$
  - where $\sigma_{m,j}^2 = \frac{\nu_j}{n_m}$ has trial-specific component $n_m > 0$ and marker-specific component $\nu_j \sim \mathcal{U}(u_{\nu,min}, u_{\nu,max}), \qquad 0 < u_{\nu,min} \leq u_{\nu,max}$

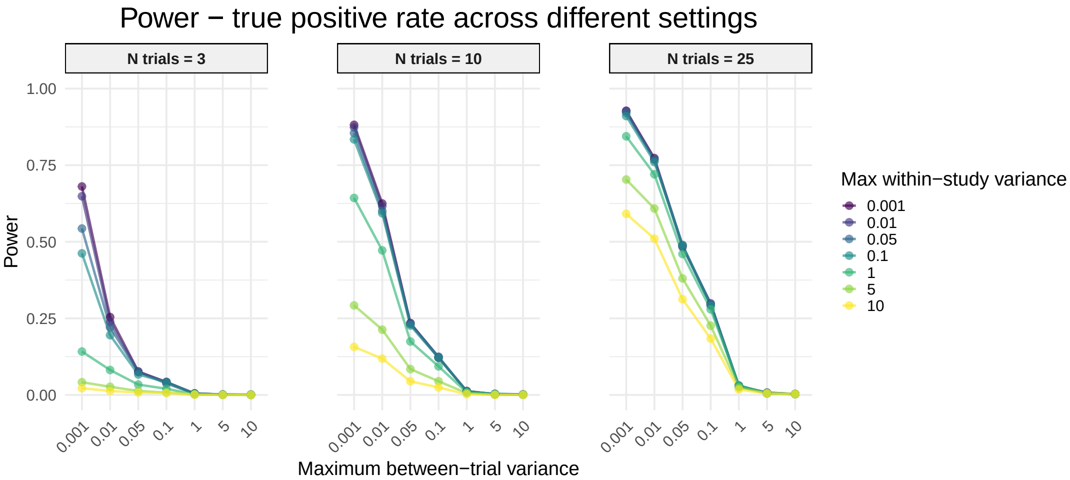
Definition of surrogate validity

- S_j valid if $\mu_{\delta,j} \in (-\varepsilon, \varepsilon)$
- S_j invalid if : $\mu_{\delta,j} \in [-1, -\varepsilon] \bigcup [\varepsilon, 1]$
- To examine calibration, generate invalid surrogates in "worst-case" (i.e. on boundary defined by ε)
  - Better case scenarios will be at least as well calibrated

Calibration



Power


Power − true positive rate across different settings
N trials = 3
N trials = 10
N trials = 25
Power
1.00
0.75
0.50
0.25
0.00
0.001
0.01
0.05
0.1
1
5
10
Maximum between−trial variance
Max within−study variance
0.001
0.01
0.05
0.1
1
5
10