RISE: rank-based identification of high-dimensional surrogate markers applied to vaccinology

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Inserm La science pour la santé From science to health

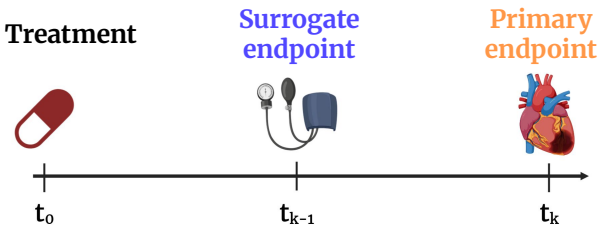
Inria

I have no current or past relationships with commercial entities.

Introduction

What is a surrogate marker?

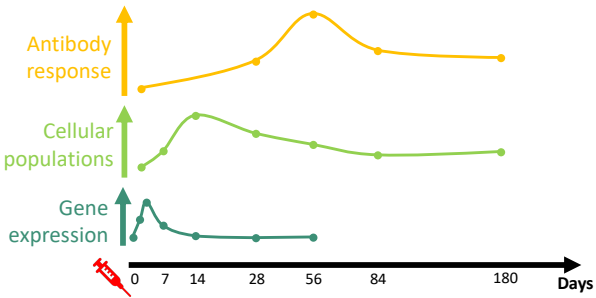
- **Replacement** for a clinically relevant primary endpoint
  - measured cheaper, faster, less invasively...
- Treatment effects on surrogate **predict treatment effects** on primary endpoint



Example of an intermediate variable as a surrogate marker for a primary endpoint.

High-dimensional data in biomedical research

- $p >> n$
- **Biomarkers** of downstream endpoints
- **High-dim surrogates unexplored** in literature



Example of longitudinal data collected in a modern vaccine experiment.

Challenges of surrogate evaluation in high dimensions

Challenges in high-dimensional data

- Low signal-to-noise ratio
- Study heterogeneity
- Large dynamic range

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Limitations of existing methods

- Restrictive assumptions
- Require large sample sizes
- Limited to low-dimensional settings

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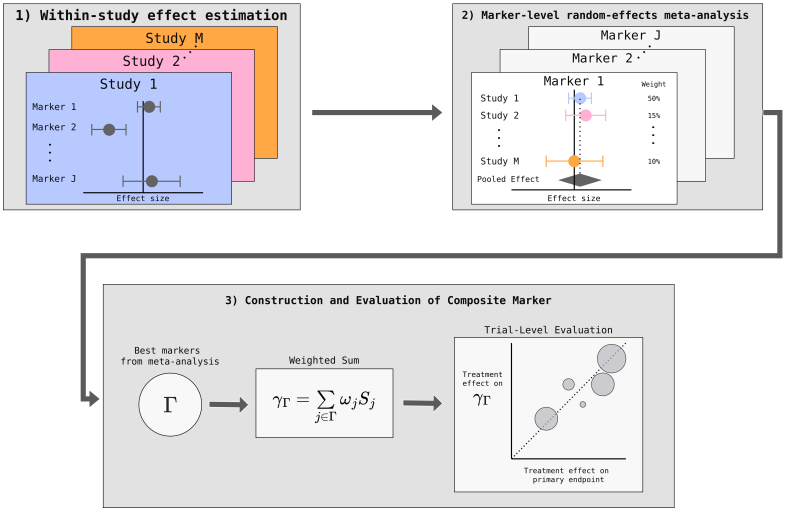
Limitations of existing methods

- Restrictive assumptions
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Need new methods to evaluate high-dimensional surrogates in small samples

Methods

Overview of RISE-Meta



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 ${Y_{i,m}}^a$
- Surrogates $\boldsymbol{S}_{i,m}{}^a = ({S_{i,1,m}}^a, \ldots, {S_{i,J,m}}^a)$

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i.i.d. within trial m, trials independent

Within-trial effect measures

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

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

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

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

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

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

Within-trial surrogacy

- $\delta_{m,j} = U_{Y,m} - U_{S,j,m}$
- **Quantity of interest for meta-analysis**

Random effects meta-analysis model

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

$$\delta_{m,j} \sim N(\mu_j, \sigma^2_{m,j} + \tau^2_j)$$

where

- μ_j: common mean effect
- $\sigma^2_{m,j}$: study-specific variance in trial m
- τ^2_j: common between-study variance

Hypothesis testing on pooled effect

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

Two one-sided test for (Schuirmann, 1987)

$$H_{0L,j} : \mu_j \leq -\varepsilon, \quad H_{0U,j} : \mu_j \geq \varepsilon$$

Hypothesis testing on pooled effect

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Two one-sided test for (Schuirmann, 1987)

$$H_{0L,j} : \mu_j \leq -\varepsilon, \quad H_{0U,j} : \mu_j \geq \varepsilon$$

- Apply multiplicity correction (Benjamini, 1995) $\rightarrow q_j =$ adjusted p-value for jth marker

Surrogate signature set

$$\Gamma = \{j : q_j \leq \alpha\}$$

Constructing a composite surrogate signature

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

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

Constructing a composite surrogate signature

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

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- **Combined standardised weight:** $\widehat{\lambda}_j = \dfrac{\widehat{a}_j \widehat{b}_j}{\max_{j \in \Gamma} \widehat{a}_j \widehat{b}_j}$

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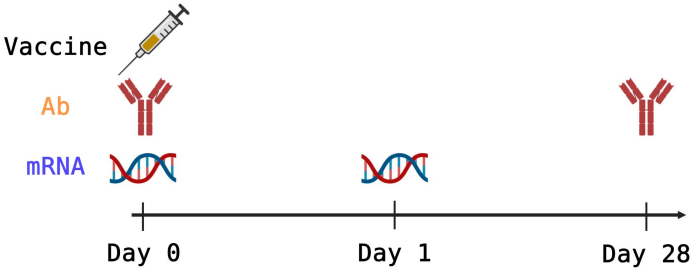
Composite signature:

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

Application

Application to inactivated influenza vaccine

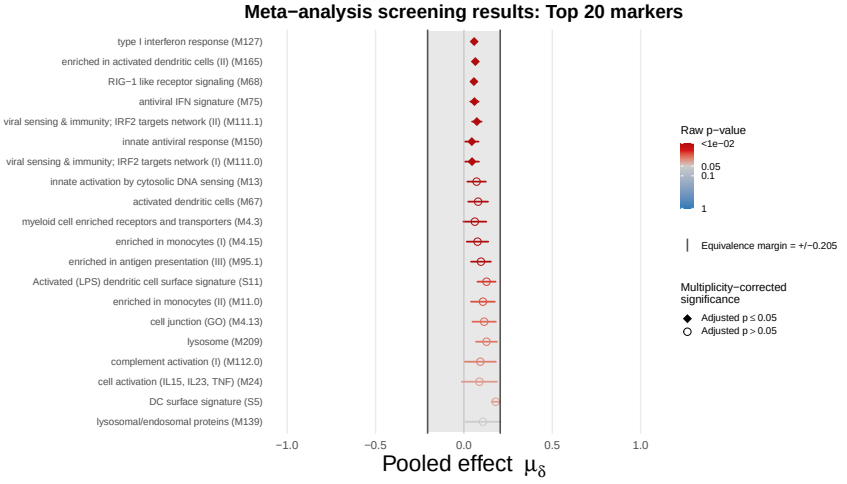
- **Open data** from **4 trials** on inactivated flu vaccine (Diray-Arce, 2022)
- Primary endpoint: day 28 antibody response (nAb/HAI assays)
- Surrogate candidates: day 1 expression of 258 *gene sets* (Li, 2013)
- **Paired setting**: each individual measured pre- & post-vaccination



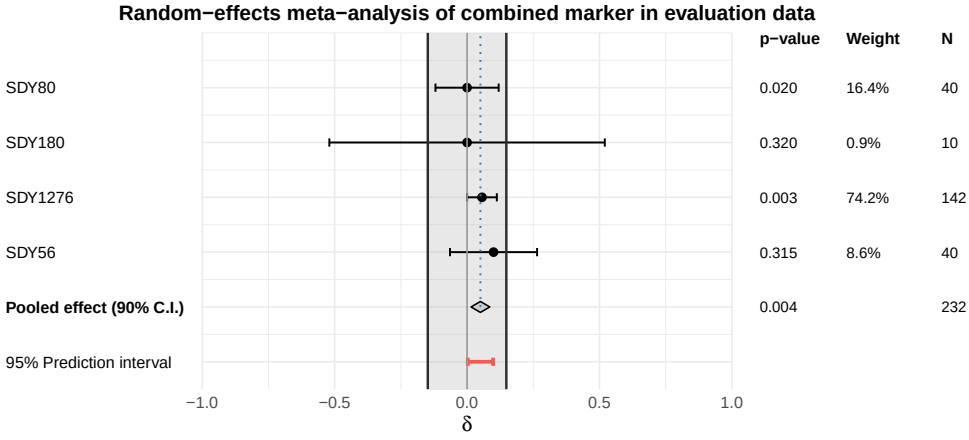
Graphical description of the data on inactivated flu vaccination.

Can RISE-Meta derive a **generalisable signature** of gene expression which **predicts the treatment effect** on the antibodies 27 days later?

Screening finds a biologically relevant signature



Evaluation of composite signature on independent data



Tau−squared = 6e−11 | I−Squared = 0.0 % | CCC = 0.94 | $\varepsilon = 0.148$

Discussion

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- **RISE-Meta:** evaluates **high-dimensional surrogates** in the **multi-trial** setting
- Application: **promising signature** of biologically relevant genes **predictive of flu vaccine effect** on the later antibody response

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- **RISE-Meta:** evaluates **high-dimensional surrogates** in the **multi-trial** setting
- Application: **promising signature** of biologically relevant genes **predictive of flu vaccine effect** on the later antibody response

Perspectives

⇒ Extension to other outcome types (binary, survival)

⇒ Bayesian meta-analysis when number of trials is small?

Thank you!



SurrogateRank R package, CRAN



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



Hughes A, Thiébaut R, Parast L & Hejblum BP.
Meta-Analysis of High-Dimensional Surrogate Markers.
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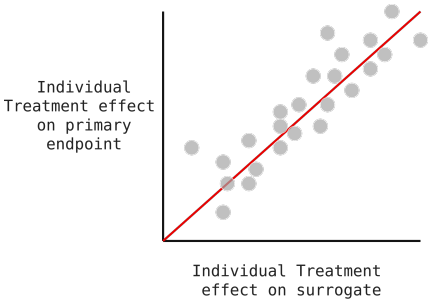
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Introduction

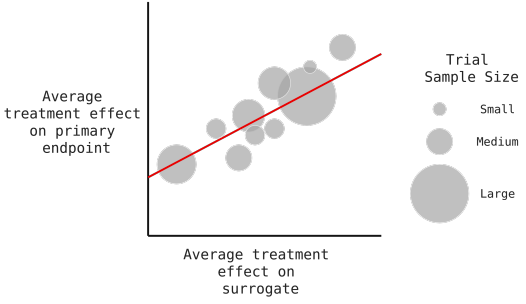
Individual versus trial-level surrogates

Individual-Level Surrogate



- Evaluated with correlation, cross-validation, individual causal association... (Gabriel, 2017; Alonso, 2016)

Trial-Level Surrogate

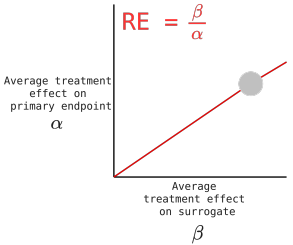


- Evaluated in *single-trial* or *multi-trial framework* (Buyse, 2000)

Evaluation of Trial-Level Surrogacy

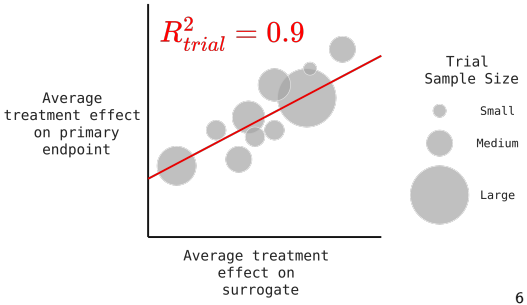
Single-Trial Framework

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



Multi-Trial Framework

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



Methods

Within-Trial Estimation

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

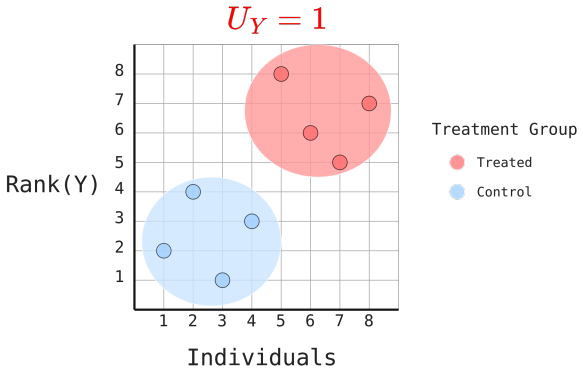
Active treatment vs control

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

Paired setting

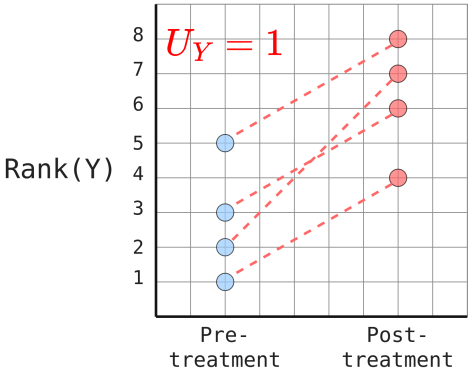
$$\widehat{U}_{Y,m} = \frac{1}{N_m} \sum_{i=1}^{N_m} G({Y_{i,m}}^1, {Y_{i,m}}^0), \quad \widehat{U}_{S,j,m} = \frac{1}{N_m} \sum_{i=1}^{N_m} G({S_{i,j,m}}^1, {S_{i,j,m}}^0)$$

Intuition for estimation - Active versus control



$\widehat{U}_{Y,m} = 1 \implies$ **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

Estimating the mean effect

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

$$\widehat{\mu}_j = \frac{\sum_{m=1}^{M} \widehat{w}_{m,j}\, \widehat{\delta}_{m,j}}{\sum_{m=1}^{M} \widehat{w}_{m,j}}$$

weights are **inverse variances**

$$\widehat{w}_{m,j} = \frac{1}{\widehat{\sigma}^2_{m,j} + \widehat{\tau}_j^{\,2}}$$

- Hartung-Knapp variance estimator (Hartung, 2001)
- $(1-\alpha) \times 100\%$ C.I. : $\widehat{\mu}_j \;\pm\; q_{M-1,\,1-\alpha/2}\, \sqrt{\widehat{\mathrm{Var}}(\widehat{\mu}_j)}$

Prediction intervals

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

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

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

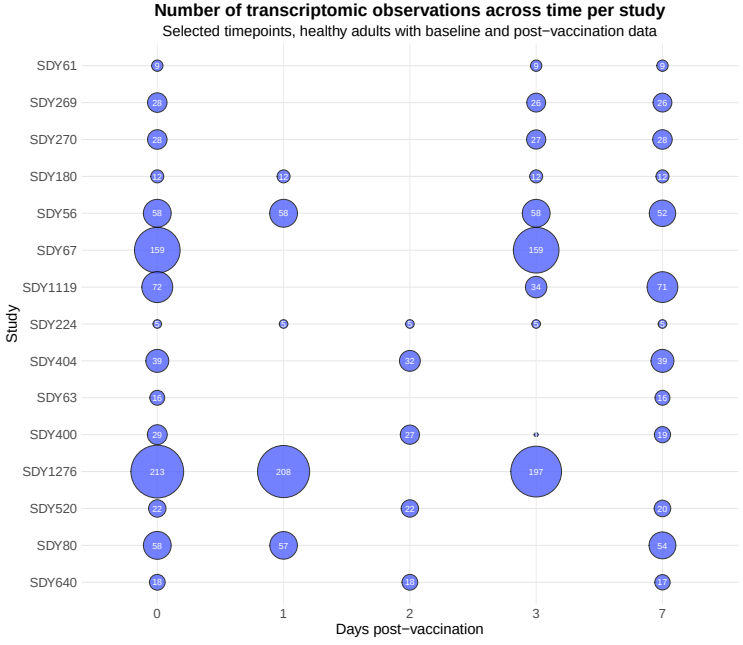
Inclusion/Exclusion Criteria

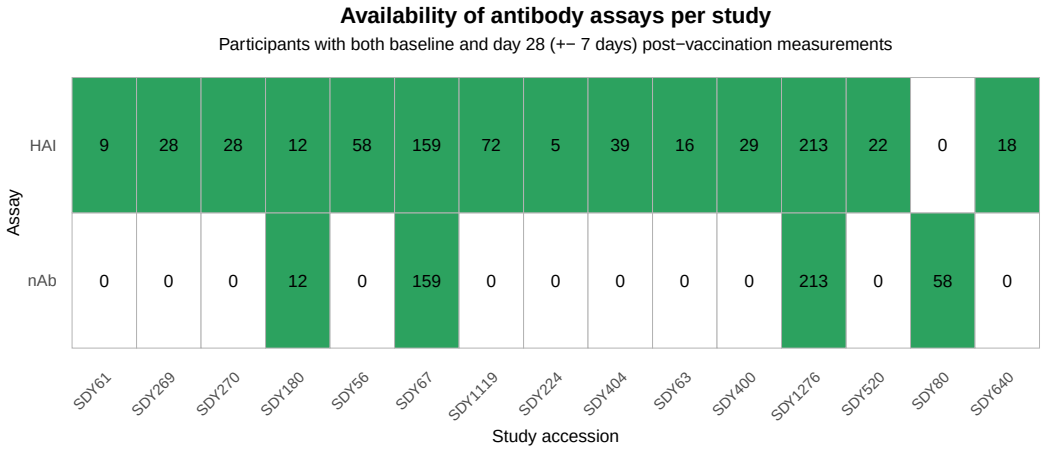
Study	Inclusion	Exclusion
SDY61	Healthy adults	
SDY269	Healthy adults	
SDY270	Healthy adults	
SDY180	Healthy adults (18-64)	Pregnancy, allergies, vaccines within 2 months
SDY56	Healthy adults (18-40 or ≥ 65)	Recent infections/vaccines, chronic illnesses, pregnancy
SDY67	Healthy adults (50-74)	
SDY1119	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

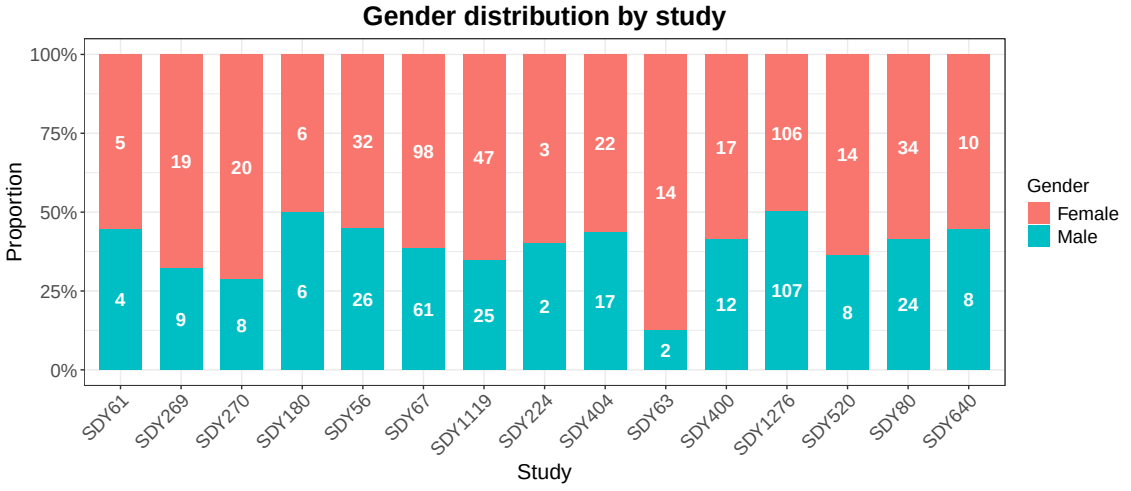
Participants must:

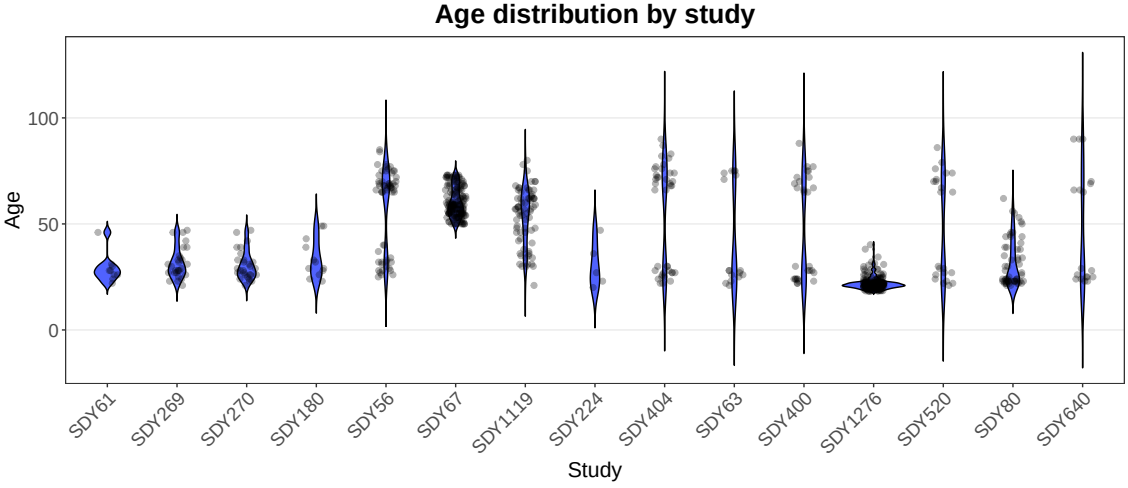
- be healthy adults (18+),
- receive inactivated influenza vaccine,
- have at least one immune response assay measurement (nAb, HAI) at baseline AND day 28 (+-7 days)
- have gene expression measured both at baseline AND post-vaccination


Number of transcriptomic observations across time per study
Selected timepoints, healthy adults with baseline and post−vaccination data
Study
SDY61
SDY269
SDY270
SDY180
SDY56
SDY67
SDY1119
SDY224
SDY404
SDY63
SDY400
SDY1276
SDY520
SDY80
SDY640
0
28
29
19
58
159
72
0
39
16
29
213
22
58
18
0
58
19
58
159
34
0
32
0
27
208
22
57
18
0
58
19
58
159
34
0
32
0
27
197
22
57
18
0
52
19
71
0
39
16
19
0
20
54
17
0
1
2
3
7
Days post−vaccination



- Use nAb if available, otherwise HAI


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

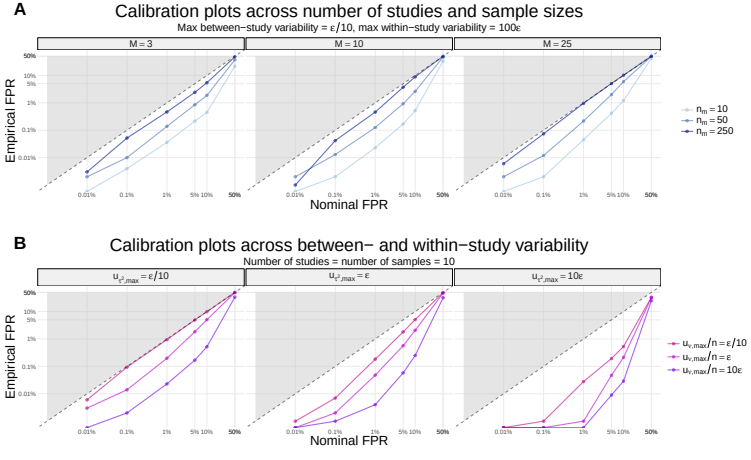

Age distribution by study
Age
100
50
0
SDY61
SDY269
SDY270
SDY180
SDY56
SDY67
SDY1119
SDY224
SDY404
SDY63
SDY400
SDY1276
SDY520
SDY80
SDY640
Study

Simulation

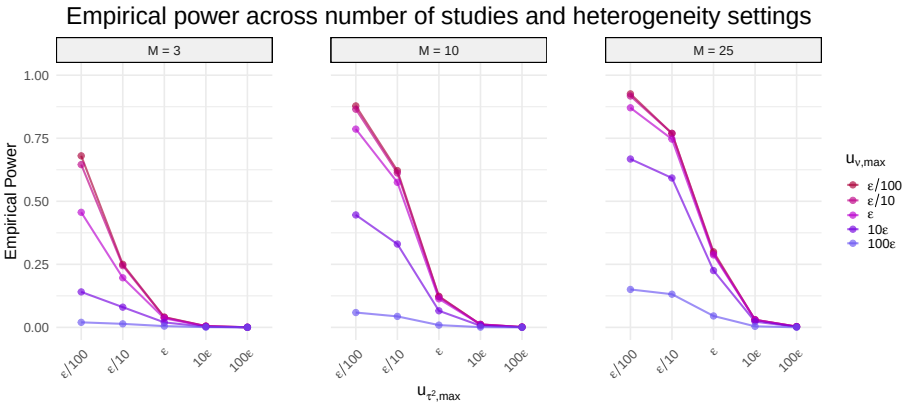
Simulation setup

- **Scenario 1 (calibration / FPR):** simulate only *invalid* surrogates, $\mu_j \in \{-\varepsilon, \varepsilon\}$
- **Scenario 2 (power):** simulate only *valid* surrogates, $\mu_j \sim \mathcal{U}(-\varepsilon, \varepsilon)$.

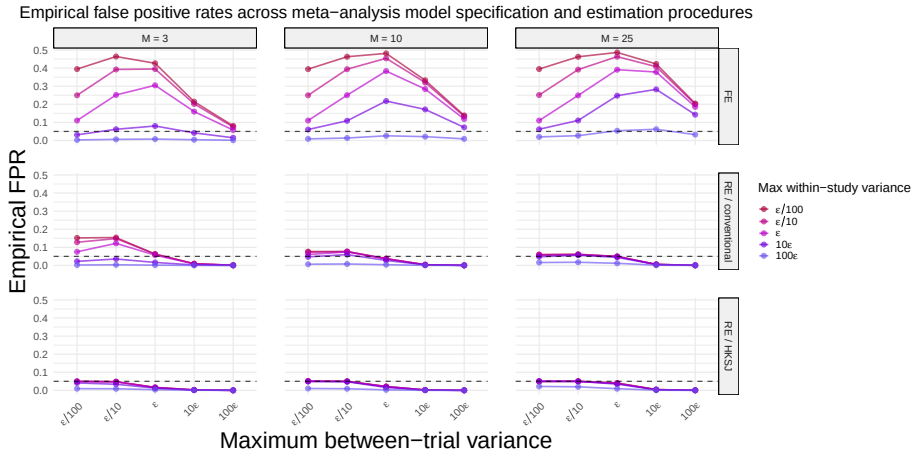
Sencario 1: calibration



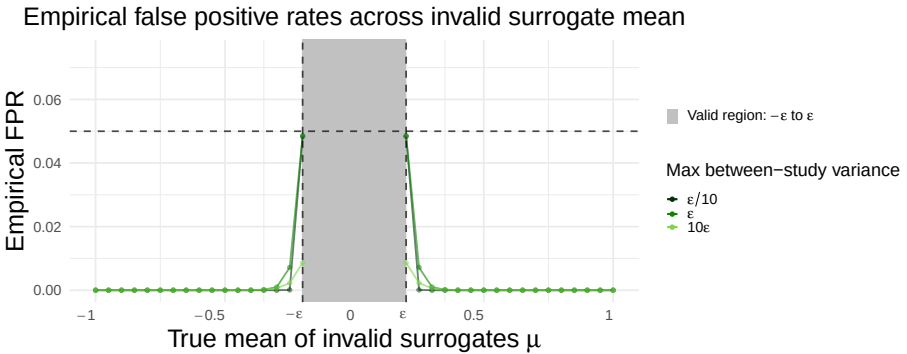
Scenario 2: power



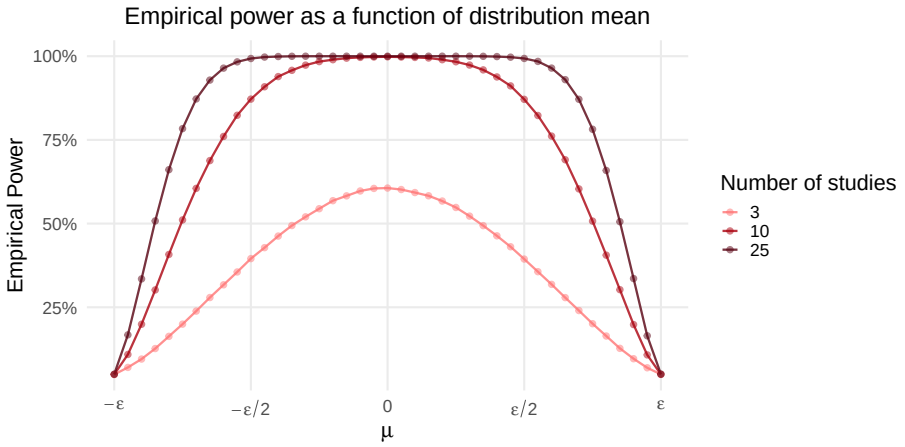
Scenario 1: estimation procedures



Scenario 1: proximity of mean to equivalence bound



Scenario 2: power and distance within equivalence bound



Application

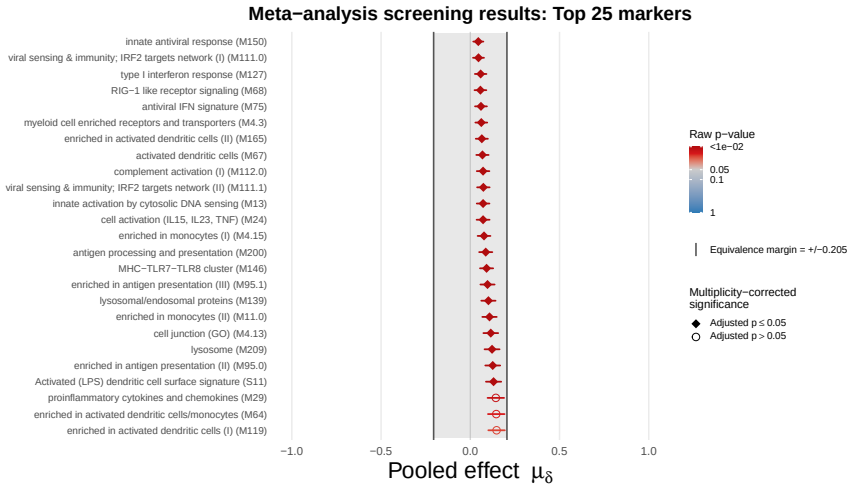
Analysis Details

- **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)

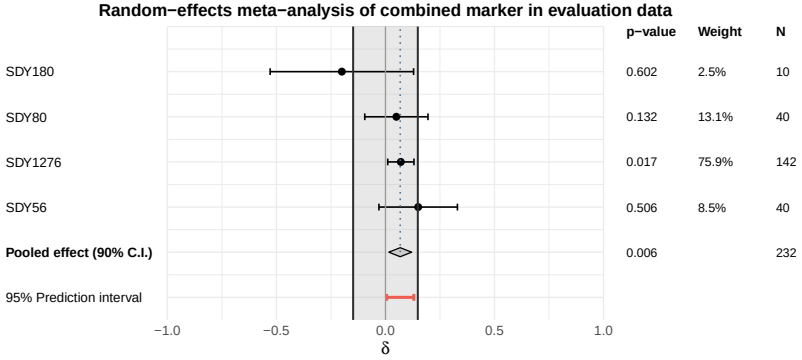
- **Sample splitting to mitigate overfitting** (Ball, 2020)
  - Marker-level meta-analyses on training data ($\frac{2}{3}$ within each trial)
  - Evaluate composite marker on test data

- Hyperparameters : $\varepsilon = 0.2$, $\alpha = 0.05$, Benjamini-Hochberg correction

Screening: fixed effect model

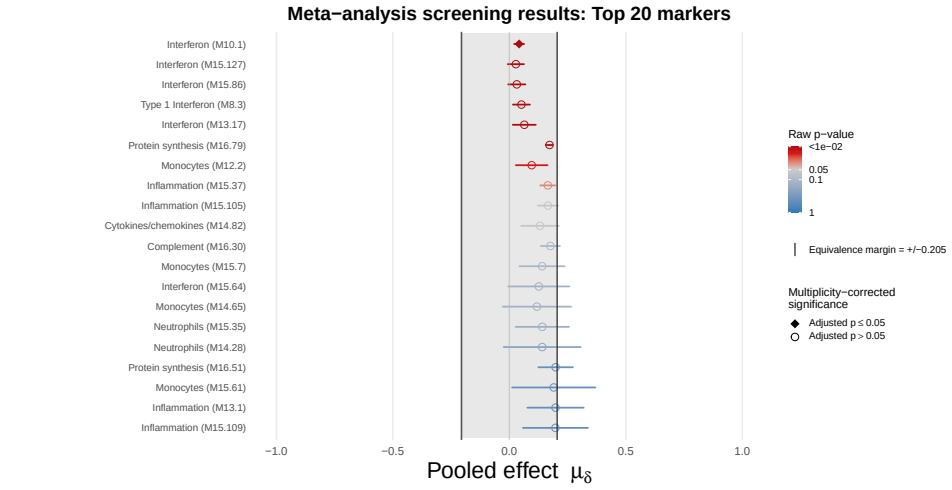


Evaluation: fixed effect model

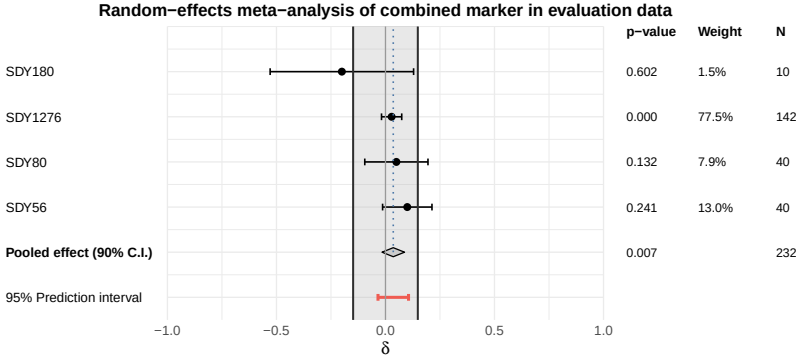


Tau−squared = 0e+00 | I−Squared = 0.0 % | CCC = 0.38 | $\varepsilon = 0.148$

Screening: Blood Gen 3 modules

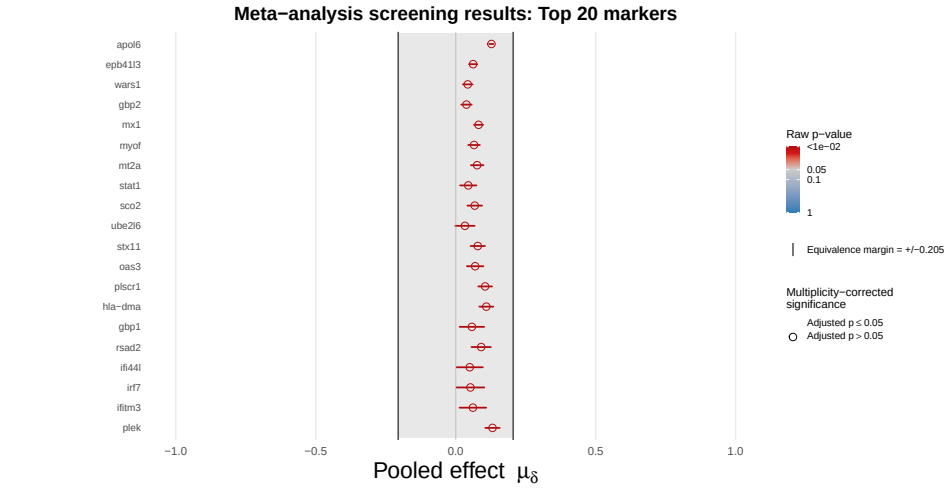


Evaluation: Blood Gen 3 modules



Tau−squared = 6e−11 | I−Squared = 0.0 % | CCC = 0.53 | $\varepsilon = 0.148$

Screening: genewise approach

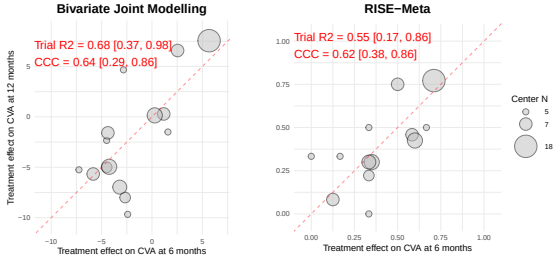


Method comparison

Comparison with classical surrogate meta-evaluation

- **Goal**: compare RISE-Meta with classical *bivariate joint modelling* approach (Buyse, 2000) on low-dimensional examples
- **ARMD dataset:** age-related macular degeneration trial (interferon-α vs placebo).
  - Primary endpoint: 12-month change in visual acuity
  - Surrogate candidate: 6-month change in visual acuity
  - 109 patients, 15 centers
- **Ovarian dataset:**
  - Primary endpoint: overall survival time
  - Surrogate candidate: progression-free survival time
  - 1,168 patients, 42 centers

A) Age−related macular degeneration dataset



B) Ovarian cancer dataset

