Ranking-based Data Integration for Robust Outcomes Prediction and Biomarker Detection

Statistical Analyses of Multi-Outcome data (June 30, 2026)

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Multi-Study Data Integration

- Many studies focus on refining the clinical utility of newer biomarkers.
  - Such studies often have modest sample sizes.
- While limited information may be available about these biomarkers, there is usually **substantial information** available about outcomes in the same disease context.
  - Published and validated risk models.
  - Large disease registries.
  - Artificial Intelligence (AI) **"foundation models"**

Aim 1: Borrowing External Information to Improve Risk Model Estimation

- **Leverage external sources** to improve the performance of a risk prediction model for a smaller study of interest.
- Inferences in **a study of interest** can be improved by leveraging existing information that is **"external"** to the study.
- **Directly combining** these sources can be challenging due to inherent differences in study designs and patient populations

Borrowing External Information in the Age of AI

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Prostate Cancer

Artificial INtelligence to Support Informed DEcision-making (INSIDE) for Improved Literature Analysis in Oncology

Article

A pathology foundation model for cancer diagnosis and prognosis prediction

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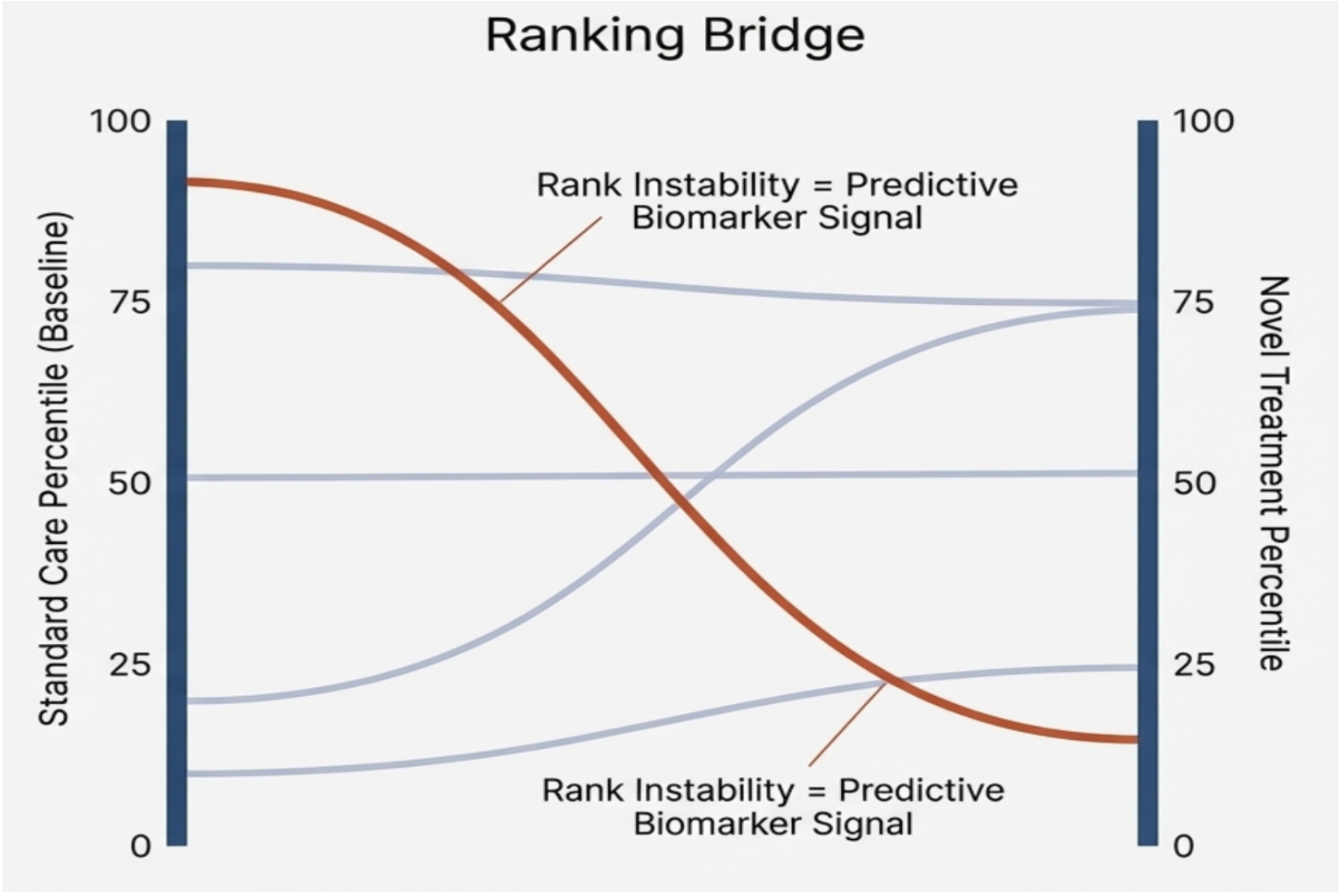
Histopathology image evaluation is indispensable for cancer diagnoses and subtype classification. Standard artificial intelligence methods for histopathology image

Aim 2: Precision Medicine and Contrasting External Risk Models

- Evaluating **how** external risk models **differ** can also provide useful information.
- Compare risk models across different studies involving **more than one treatment**.
- Look at **changes in risk rankings** across different treatment contexts.
- Aim for greater robustness by mainly integrating the **risk ranking information** across studies.

Contrasting Risk Rankings



Aim 1: Borrowing External Information to Improve Risk Model Estimation

Challenges of Integrating External Evidence

- **Outcome Incompatibility**: External and internal risk models may utilize different primary outcomes
  - Continuous vs. Binary outcomes
  - Progression-free survival (PFS) vs. Overall survival
  - PFS vs. "real-world" PFS.
  - PSA progression vs. Overall survival
- **Study Heterogeneity**
  - Differences in patient populations
  - Differences in standard of care over time

Challenges of Integrating External Evidence

- Many established risk models are not **well-calibrated** to generating particular survival probabilities.
- **Motivation**: The way many established risk models **order patients** is informative and is **more stable** across contexts.
- For example, in advanced **prostate cancer**:
  - Gleason score, visceral metastasis, disease volume, PSA levels will be consistent risk factors.

Internal Study Data Structure

- We have individual-level observations from an "internal study"

$$D_I = \{(Y_i, \mathbf{x}_i); i = 1, \ldots n_I\}, \qquad \mathbf{x}_i = (\mathbf{z}_i, \mathbf{b}_i)$$

- $\mathbf{z}_i$ - "conventional" covariates
- $\mathbf{b}_i$ - "novel" covariates
- **Goal**: Build a risk model for outcomes Y_i using all covariate information $\mathbf{x}_i$.

External Prognostic Model(s)

- Assume an external prognostic model can compute a **risk score** using the conventional covariates $\mathbf{z}_i$.
- Denote the external risk score function with

$$f_E(\mathbf{z}_i)$$

- **Larger values** of $f_E(\mathbf{z}_i)$ are interpreted as predicting **larger values** of $E(Y_i)$.
- $f_E(\mathbf{z}_i)$ does not need to be well-calibrated to the distribution of internal-dataset outcomes.
  - OncotypeDX recurrence score
  - Nottingham prognostic index
  - Bellmunt risk score
  - An older, historical risk model

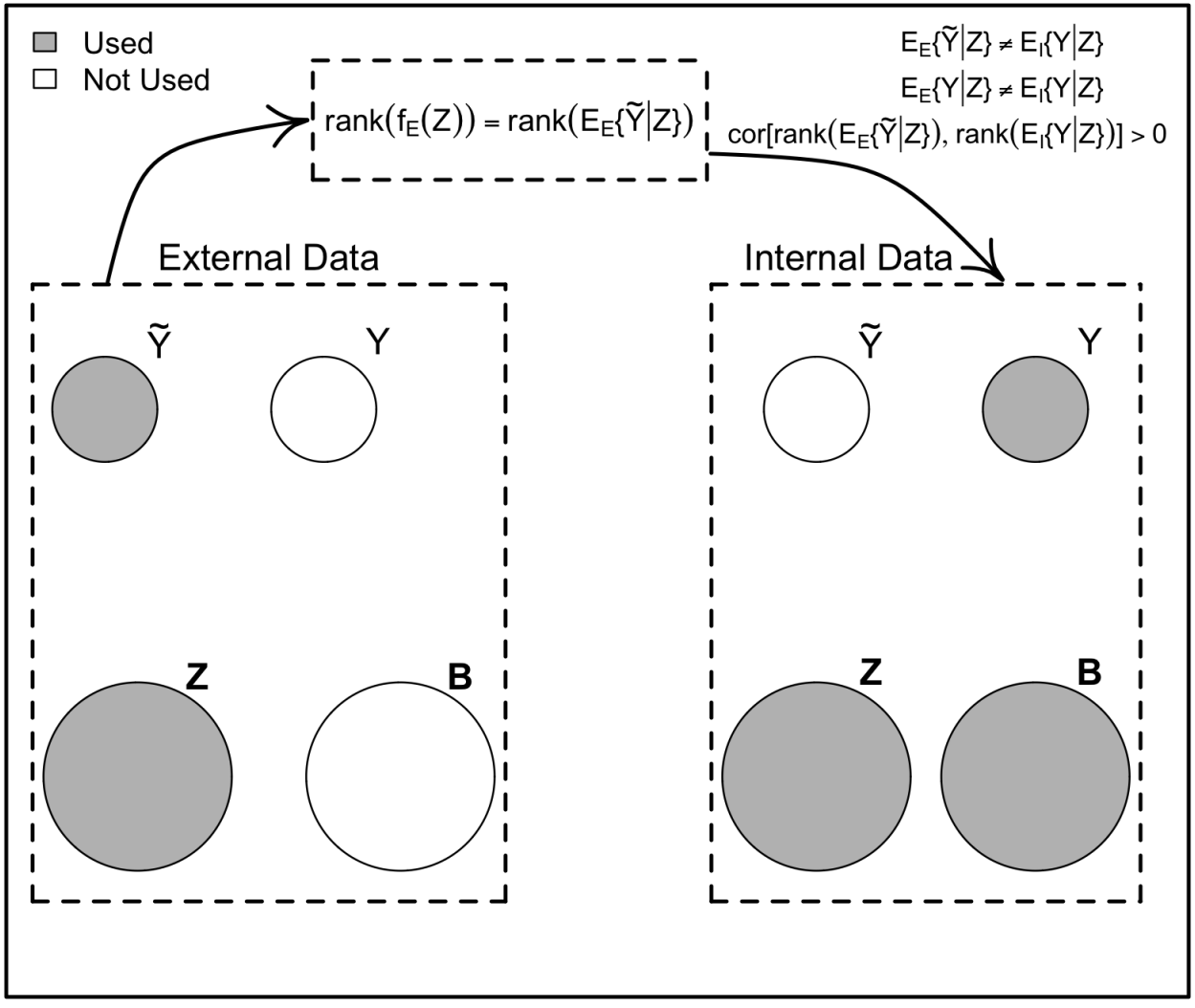
Transportability

- What are the relevant **"transportability assumptions"** for using $f_E(\mathbf{z}_i)$ in the context of the internal study?
- A risk score for the internal study would ideally use either

$$f_I(\mathbf{z}_i) = E_I(Y_i \mid \mathbf{z}_i) \quad \text{or} \quad g_I(\mathbf{x}_i) = E_I(Y_i \mid \mathbf{x}_i)$$

- We **will not** assume that $f_E(\mathbf{z}_i) = f_I(\mathbf{z}_i)$.
- Do assume that $f_E(\mathbf{z}_i)$ and $f_I(\mathbf{z}_i)$ (or $g_I(\mathbf{z}_i)$) have some degree of **nonparametric association**.

Transportability of Rankings



Transportability and External Risk Model Rankings

- How to harness nonparametric association between:
  - external risk scores
  - risk scores from internal model (for a fixed β)
- Start with the **rankings** from the external risk model:

$$\begin{aligned} r_i^E(\mathbf{z}_i) &= \text{rank}\{f_E(\mathbf{z}_i)\} \\ &= \sum_{j=1}^{n} I\Big(f_E(\mathbf{z}_i) \geq f_E(\mathbf{z}_j)\Big) \end{aligned}$$

Internal Risk Model

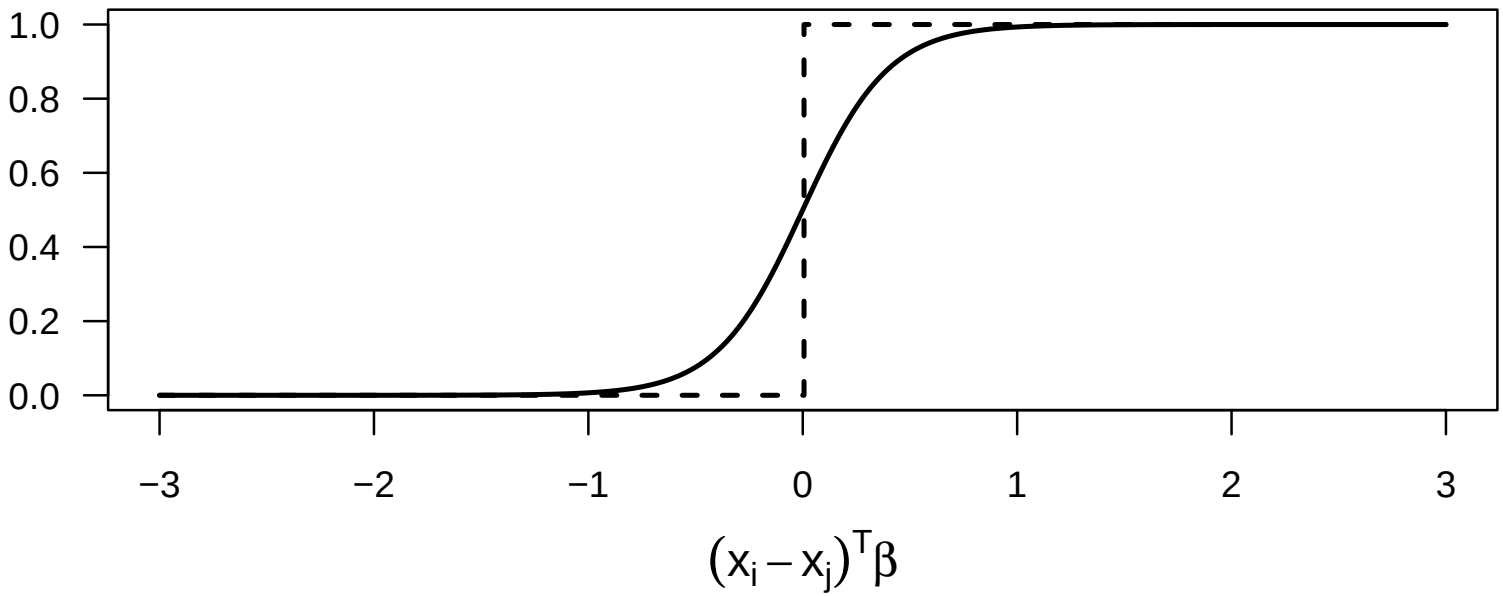
- For an internal risk regression model with parameters β, ranking according to risk is the same as ranking according to β.
  - These rankings can themselves be thought of as **model parameters**.
- Refer to these as **"ranking parameters"**:

$$\psi_i(\beta) = \text{rank}(\mathbf{x}_i^T \boldsymbol{\beta}) = \sum_{j=1}^{n} I\Big((\mathbf{x}_i - \mathbf{x}_j)^T \boldsymbol{\beta} \geq 0\Big)$$

- **Interpretation:** For a proposed β of the internal risk model, $\psi_i(\boldsymbol{\beta})$ is the ranking the internal risk model would assign to individual i.

Internal Risk Model

- **Strategy**: When estimating $\boldsymbol{\beta}$:
  - Compare $\psi_i(\boldsymbol{\beta})$ with the external rankings $r_i^E(\mathbf{z}_i)$.
  - Use smooth approximation: $\psi_i^\nu(\boldsymbol{\beta}) = \sum_{j=1}^n g_\nu\Big((\mathbf{x}_i - \mathbf{x}_j)^T\boldsymbol{\beta}\Big)$
  - $g_\nu(x) = 1/\{1+\exp(-x/\nu)\}$



Connecting Ranking Parameters with External Rankings

- Ranking parameters $\psi_i(\boldsymbol{\beta})$ represent rankings assigned by internal risk model.
- How to connect these with external ranking information?
- **Spearman's** (smooth) rank association:

$$D^{\nu}_{Sp,0}(\boldsymbol{\beta}; \mathbf{r}^E) = \frac{1}{4n^2} \sum_{i=1}^{n} \sum_{j=1}^{n} r_i^E(\mathbf{z}_i) g_\nu\Big((\mathbf{x}_i - \mathbf{x}_j)^T \boldsymbol{\beta}\Big)$$

- **Kendall's** (smooth) τ association

$$\frac{2}{n(n-1)} \sum_{i=1}^{n} \sum_{j=1}^{n} I\Big(r_i^E(\mathbf{z}_i) > r_j^E(\mathbf{z}_j)\Big) g_\nu\Big((\mathbf{x}_i - \mathbf{x}_j)^T \boldsymbol{\beta}\Big)$$

Estimating the Internal Risk Model

- Penalize the **negative rank association** between ranking parameters and external rankings and **minimize**

$$\ell_{\lambda,\alpha}(\beta_0, \boldsymbol{\beta}) = \frac{1}{2}\sum_{i=1}^{n}\left(Y_i - \beta_0 - \mathbf{x}_i^T\boldsymbol{\beta}\right)^2 + \frac{\alpha}{2}\underbrace{\sum_{j=1}^{p}\beta_j^2}_{L_2 \text{ penalty}} - \lambda \log \underbrace{D_\bullet^\nu(\boldsymbol{\beta}; \mathbf{r}^E)}_{\text{rank association}}$$

- Rank association can be expressed as:

$$D_\bullet^\nu(\boldsymbol{\beta}; \mathbf{r}^E) = \sum_{i=1}^{n}\sum_{j=1}^{n} w_{ij} g_\nu\left((\mathbf{x}_i - \mathbf{x}_j)^T\boldsymbol{\beta}\right)$$

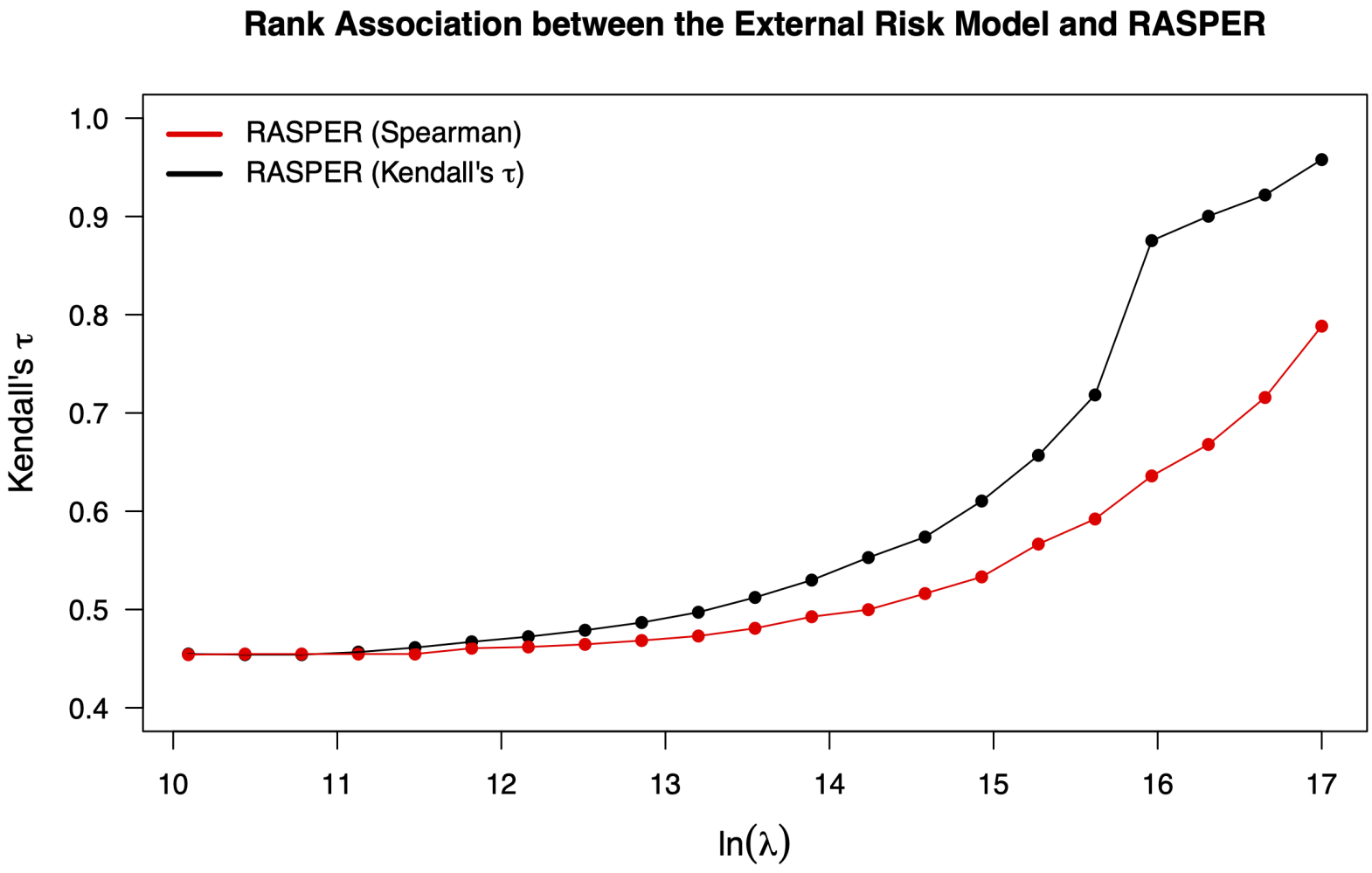
  - Spearman $w_{ij} = r_i^E(\mathbf{z}_i)/n^3$
  - Kendall's τ, $w_{ij} = 2I(r_i^E(\mathbf{z}_i) > r_j^E(\mathbf{z}_j))\big/(n(n-1))$

RASPER

- Refer to the vector of regression coefficients $\hat{\boldsymbol{\beta}}_{\lambda,\alpha}$ which minimize the ranking penalized objective function as:
- the **R**anking-**AS**sociated **PE**nalized **R**egression (RASPER) estimate

Varying the penalty term

- The rank association with the external model provides a natural range $\lambda_l \leq \lambda \leq \lambda_u$, for λ.



Hyperparameter Selection (LOO)

- The most effective approach is typically **leave-one-out** (LOO) cross-validation.
  - This is typically true for modest sample sizes (i.e., $n \leq 100$).

Simulation Studies

- RASPER performs well relative to more "direct borrowing" methods when:
  1. Distance between internal and external risk scores is large,
  2. **Rank correlation** between internal and external risk scores is **high**,
  3. The true internal model is **linear** and the external model is **nonlinear**.

Simulation Study

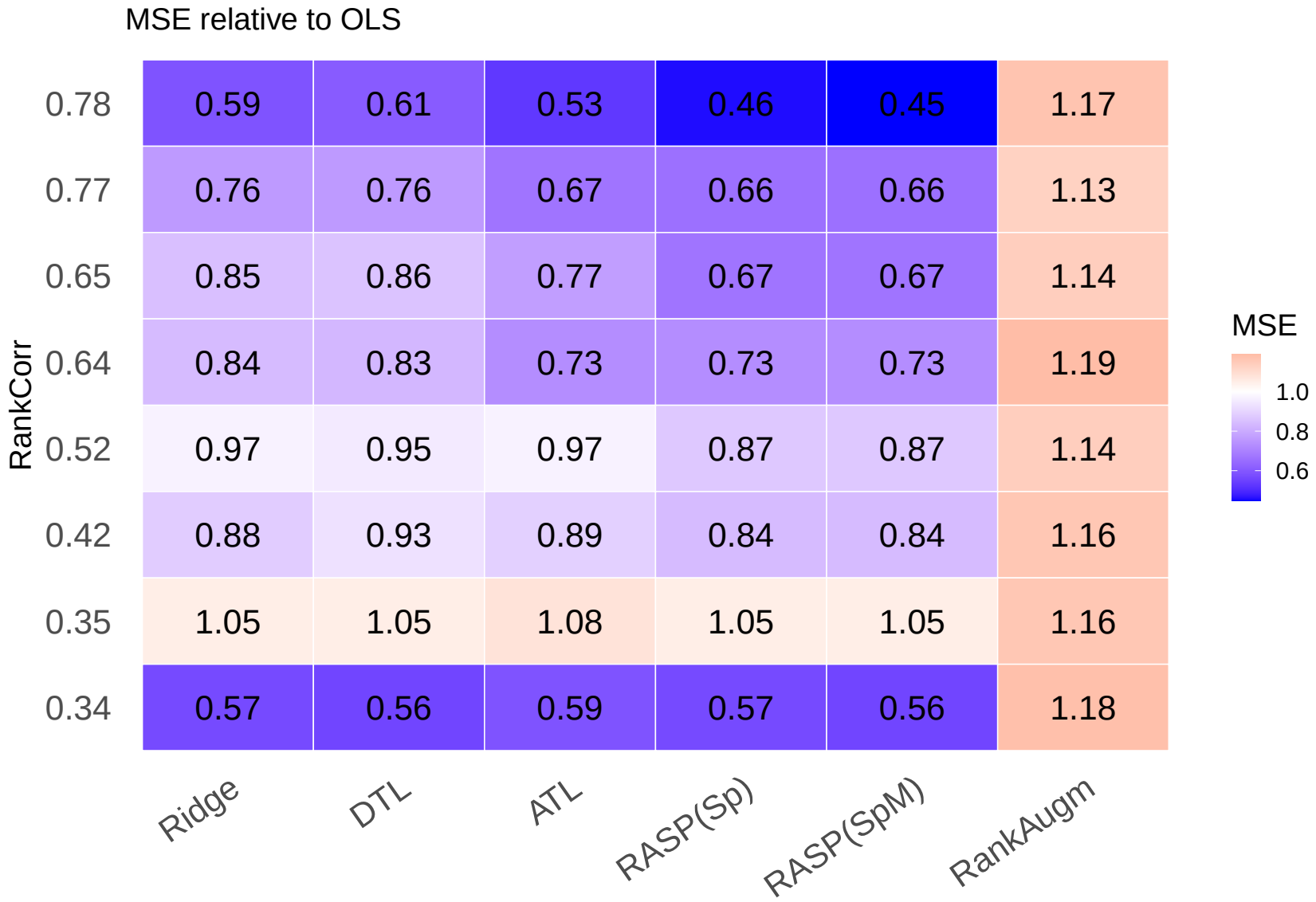
- True internal risk model is **linear**.
  - 4 conventional covariates
  - 2 novel covariates
- The mean of the external risk model is **nonlinear**

$$\mu_E(\mathbf{z}_i) = \Big(1 + f_1(z_{i1}) + \theta_2 f_2(z_{i2}) + \theta_3 f_1(z_{i1}) f_2(z_{i2})\Big) \times \exp\Big\{ -\theta_4 I(z_{i3} < 2) + 10\theta_4 I(z_{i3} \geq 2) - \theta_5 z_{i5} \Big\}$$

- For methods that require the external model to be linear, use an approximation of this nonlinear function

$$\tilde{\mu}_E(\mathbf{z}_i) = \sum_{j=1}^{p} \tilde{\beta}_{j,E} z_{ij}$$

Simulation Results (n=50)



Prognostic Model for ICI-treated Prostate Cancer Patients

- **Immune checkpoint inhibitors** (ICIs) have transformed cancer treatment in past 10-20 years.
- Use of ICI in treating **prostate cancer** has been more limited.
- Only patients with certain molecular signatures are treated with ICI
  - Mismatch Repair Deficiency (MMRd)
  - Microsatellite Instability (MSI)
  - Tumor Mutational Burder (TMB)

Prognostic Model for ICI-treated Prostate Cancer Patients

- To construct this prognostic model, we will use the **MSK-CHORD** data resource (Jee et al., 2024)
- Harmonized, real-world clinicogenomic data source
  - Large group of patients (n = 24,490)
  - Five cancer types
  - **Prostate cancer** (n = 3,211)
- Even though the number of prostate cancer is substantial, the number of **ICI-treated** patients is much smaller.
  - Only include ICI treatment for mCRPC patients.
  - Only include ICI treatment post chemotherapy

Prognostic Model for ICI-treated Prostate Cancer Patients

- After restricting the analysis to post-chemotherapy mCRPC patients with complete data
  - **n = 79** patients remaining for our analysis
- "Conventional" covariates to include:
  - **PSA** at start of ICI treatment
  - Presence of **visceral metastasis** at start of ICI treatment
  - **ECOG** performance status
  - **Time to progression** on chemotherapy prior to ICI

External Prognostic Model

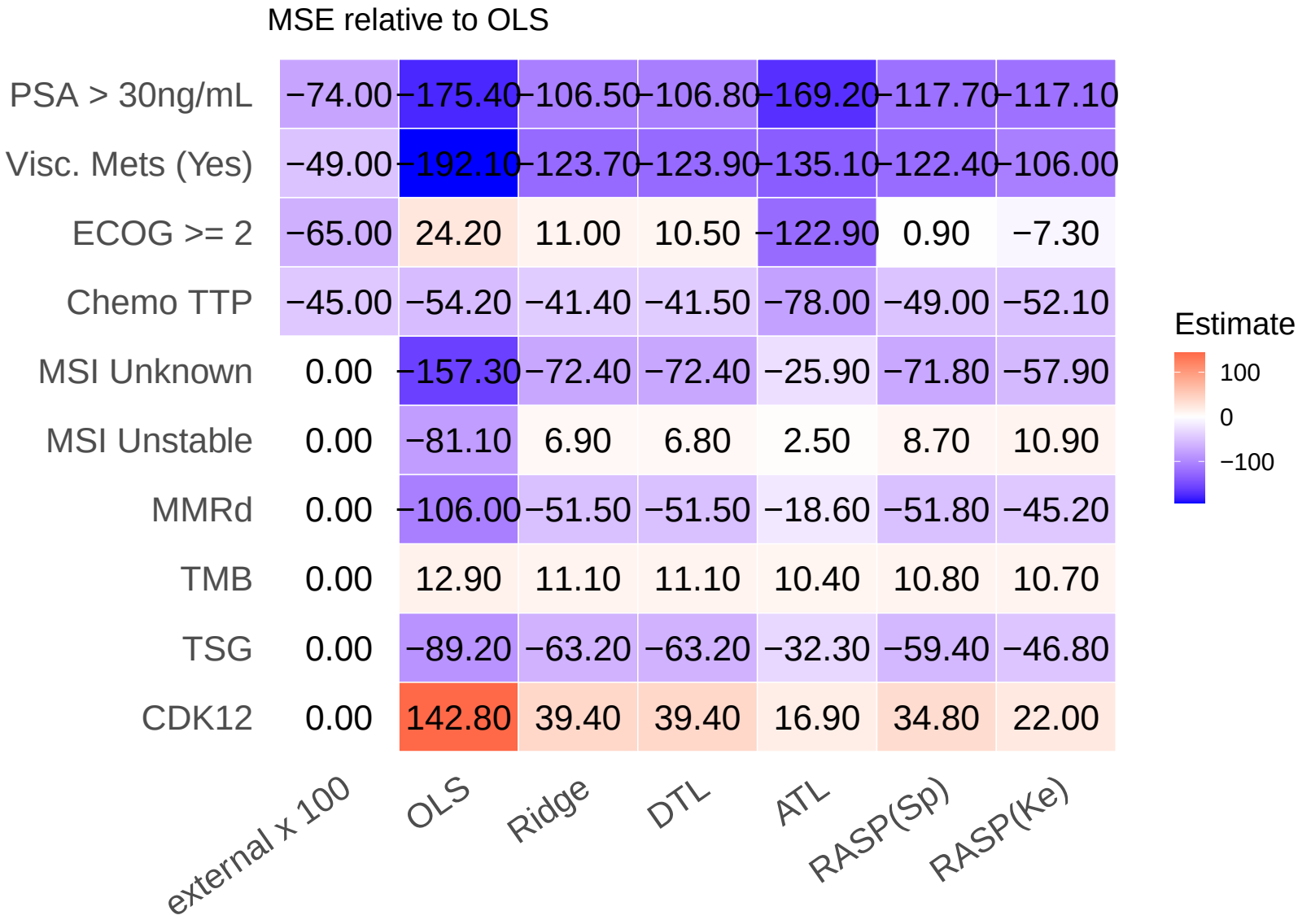
- Use a recently published nomogram (Suzuki et al. (2025)) designed to predict survival for (mCRPC) patients, **after** first-line chemotherapy.
- This risk score is:

$$
\begin{aligned}
f_E(\mathbf{z}_i) = 0.90 &+ 0.74 I(\mathrm{PSA}_i > 30 \tfrac{\mathrm{ng}}{\mathrm{ml}}) \\
&+ 0.49 I(\text{visceral metastasis}) \\
&+ 0.65 I(\mathrm{ECOG}_i \geq 2) \\
&- 0.45 \min\left\{2, \frac{\text{days to progression on prior chemo}}{180}\right\}.
\end{aligned}
$$

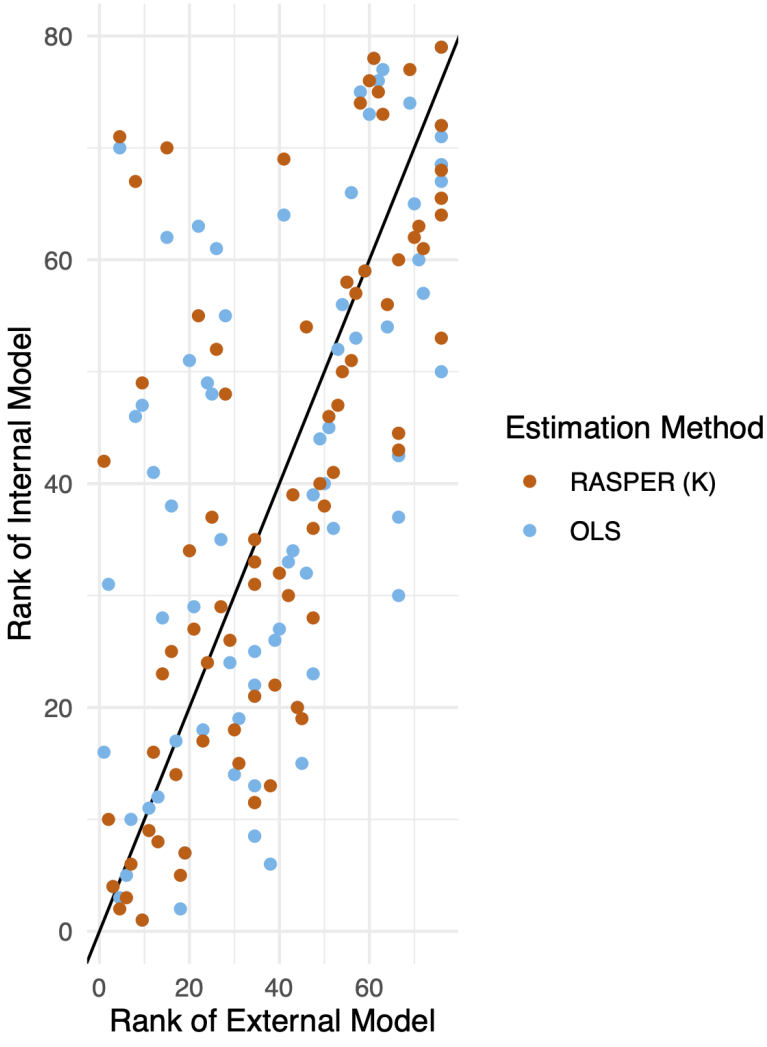
Novel Covariates

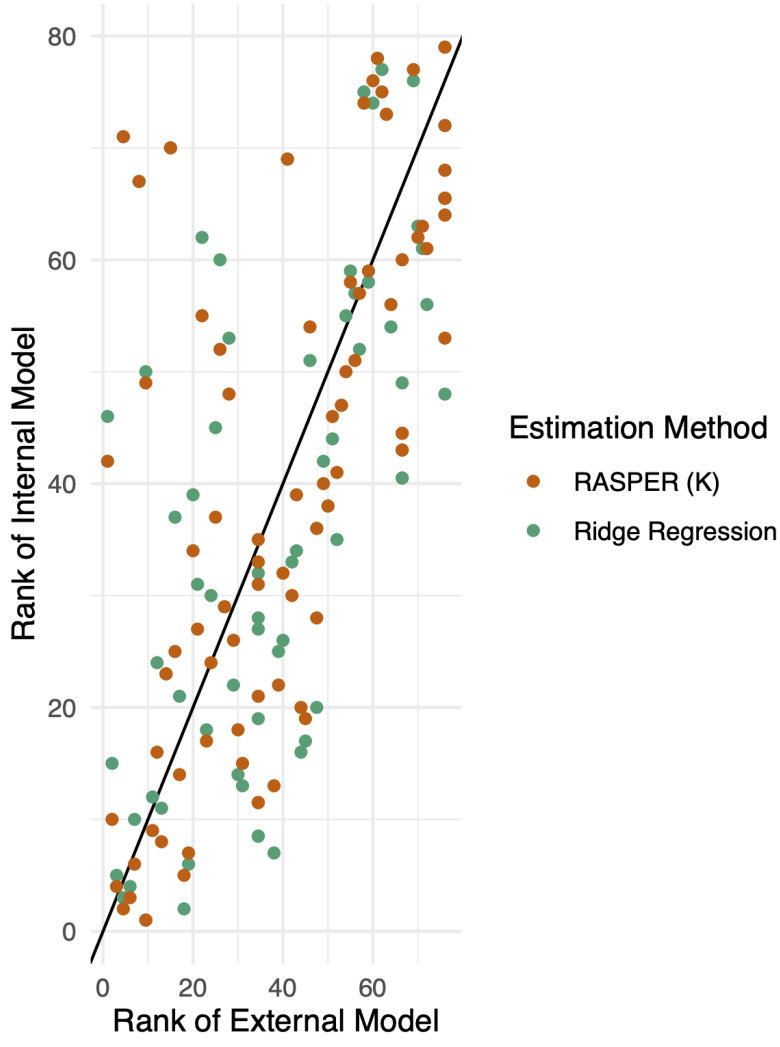
- **Goal**: Update the external model with the following **novel covariates**:
  1. **MMRd** (Yes/No)
  2. **MSI status** (stable, unstable, unknown)
  3. **Tumor mutational burden** (TMB)
  4. Alteration in a **tumor suppressor gene** (TSG) either *TP53*, *PTEN*, or *RB1*
  5. Alterations in the *CDK12* gene

Coefficient Estimates from an Internal 3-year RMST Model

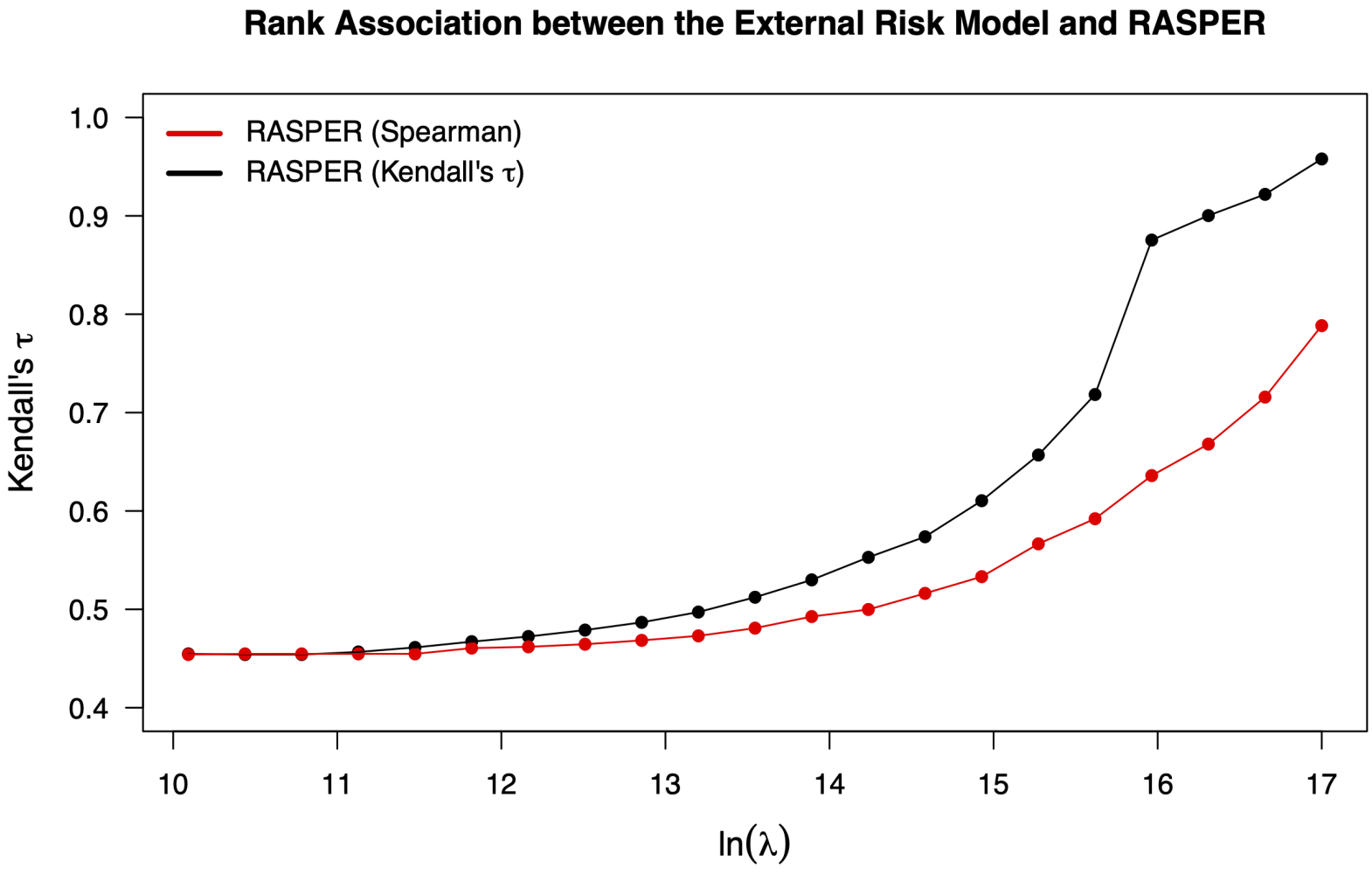


Ranking Comparisons





Rank Correlation with Suzuki (2025) model

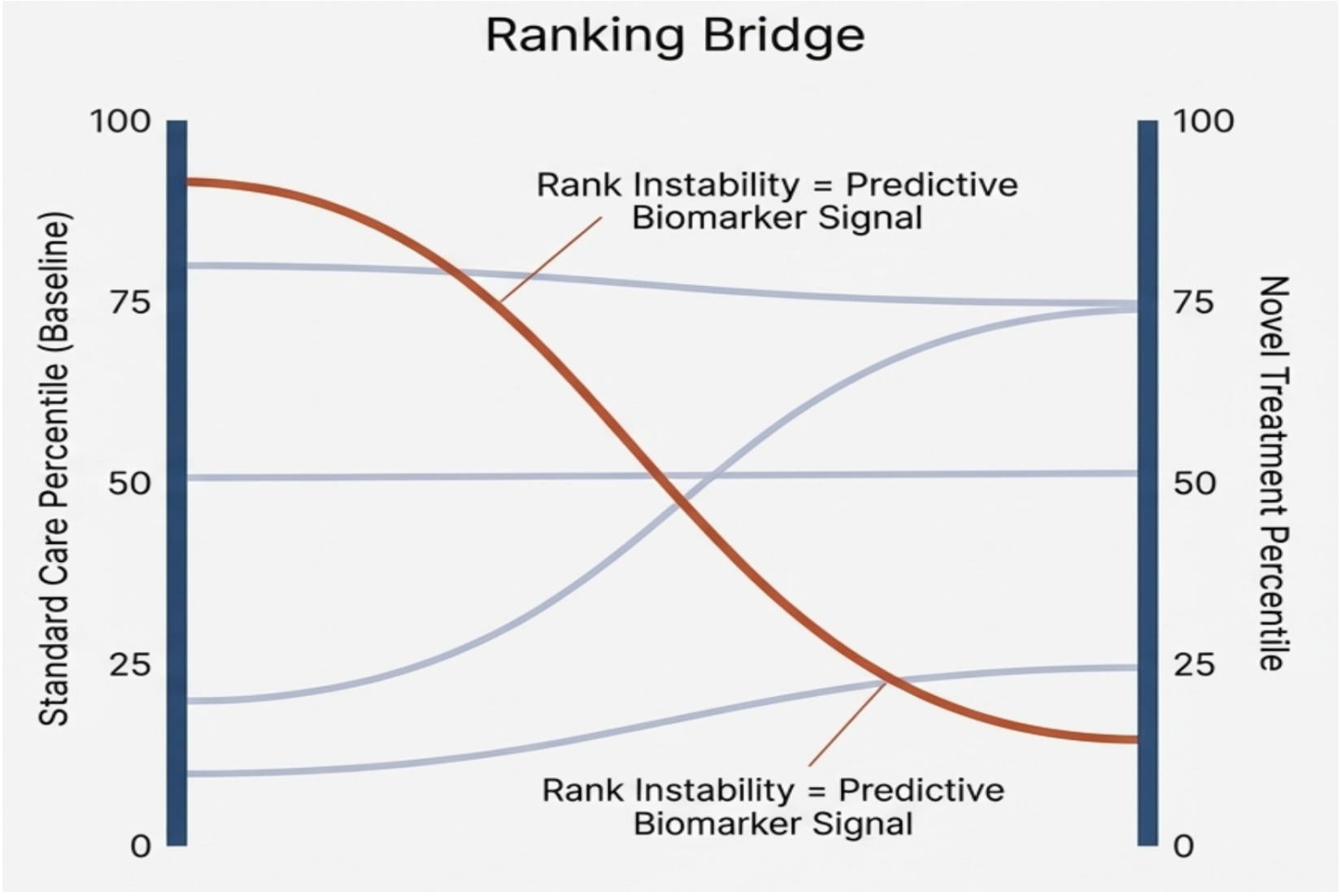


Aim 2: Precision Medicine and Contrasting External Risk Models

Precision Medicine and Real-World Evidence

- Major challenges when using **real-world evidence sources** to identify predictive biomarkers:
  - Observed treatments often under a **single standard of care**
  - Limited **direct comparisons** of two or more treatments.
- Comparing risk models across **different contexts** can be useful.
  - Look at changes in risk rankings across different treatment contexts.
  - Covariates associated with large changes in risk rankings: **potential predictive biomarkers**.

Ranking Discrepancies across contexts



Different Treatments across Different Contexts

- Consider **hypothetical outcomes** from the following four configurations

$$\text{Internal/Treatment: } Y_i = f(\mathbf{x}_i) + h(\mathbf{x}_i) + g(\mathbf{x}_i) + \varepsilon_i, \quad (1)$$
$$\text{Internal/Control: } Y_i = f(\mathbf{x}_i) + h(\mathbf{x}_i) + \varepsilon_i, \quad (2)$$
$$\text{External/Control: } Y_i = f(\mathbf{x}_i) + \varepsilon_i, \quad (3)$$
$$\text{External/Tretment: } Y_i = f(\mathbf{x}_i) + g(\mathbf{x}_i) + \varepsilon_i, \quad (4)$$

- Often **only observe** outcomes from settings (1) and (3)
- $g(\mathbf{x})$ **treatment effect variation** function
- $h(\mathbf{x})$ **context variation** function

Contrastive RASPER (CRASPER)

- Consider our **observed outcomes**

$$\begin{aligned} \text{Internal/Treatment: } Y_i &= f(\mathbf{x}_i) + h(\mathbf{x}_i) + g(\mathbf{x}_i) + \varepsilon_i, \\ \text{External/Control: } Y_i &= f(\mathbf{x}_i) + \varepsilon_i \end{aligned}$$

- We can directly estimate $f(\mathbf{x})$ from the **External/Control** context.
- Suppose $f(\mathbf{x})$ and $f(\mathbf{x}) + h(\mathbf{x})$ have high**rank association**.
- Then, we can use the approximation

$$f(\mathbf{x}_i) + h(\mathbf{x}_i) \approx c_0 \times \mathbf{x}_i^T \hat{\boldsymbol{\beta}}_r \tag{5}$$

where $\mathbf{x}^T \hat{\boldsymbol{\beta}}_r$ has very high **rank association** with $\hat{f}(\mathbf{x})$.

CRASPER

- Plug in $c_0 \times \mathbf{x}_i^T \hat{\boldsymbol{\beta}}_r$ for $f(\mathbf{x}_i) + h(\mathbf{x}_i)$.
- We then minimize:

$$\ell(\beta_0, c_0, \boldsymbol{\theta}) = \frac{1}{2n} \sum_{i=1}^{n} \left(Y_i - \beta_0 - \mathbf{x}_i^T \hat{\beta}_r - c_0 \mathbf{x}_i^T \theta \right)^2 + \alpha_1 \sum_{j=1}^{p} |\theta_j| + \frac{\alpha_2}{2} \sum_{j=1}^{p} \theta_j^2$$

- $\hat{\boldsymbol{\beta}}_r$ - Han's maximum rank correlation estimator for external risk scores $\hat{f}(\mathbf{x}_1), \ldots, \hat{f}(\mathbf{x}_n)$.
- **Parameter Constraint**: $c_0 \geq 0$.

CRASPER

- Generates an **interpretable, sparse model** for the **treatment effect variation** function $g(\mathbf{x})$
- Should primarily be used for **detecting** potential **predictive covariates**.
  - These covariates would need to be later validated.
- Relies strongly on the assumption of **ranking transportability** across study contexts.

RASPER Summary

- **Borrowing ranking information** has several advantages:
  - Rankings are often more transportable
  - Outcomes do not have to be "matched" across studies
- Borrowing is done by introducing the notion of **ranking parameters**.
- Penalization is done by looking at association between **ranking parameters** with **external ranks**.

Resources

- ArXiv paper describing RASPER in more detail:
  - **"Robust Updating of a Risk Prediction Model by Integrating External Ranking Information"**. https://arxiv.org/abs/2603.10389
- RASPER package https://github.com/nchenderson/rasper