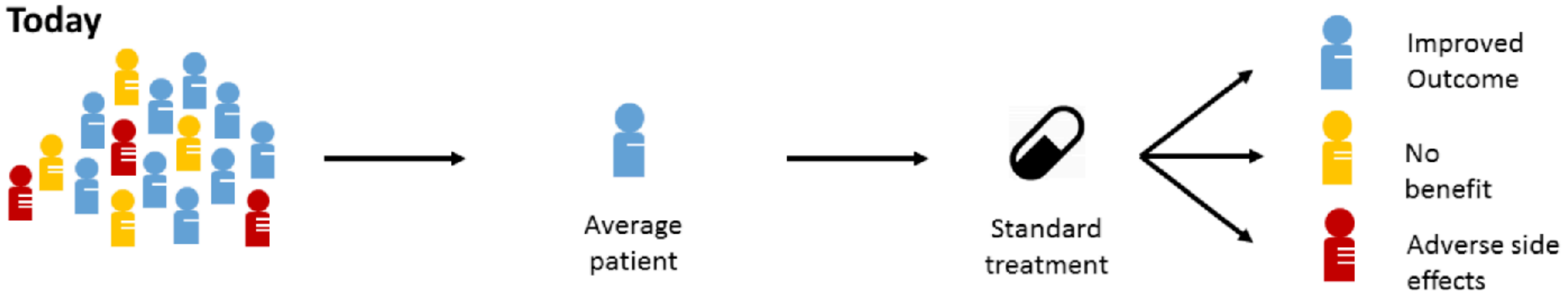
Kevin Wang

From linear regression to precision medicine

Precision medicine: predicting best cause of action using omics data



https://www.chiefscientist.gov.au/wp-content/uploads/Precision-medicine-final.pdf

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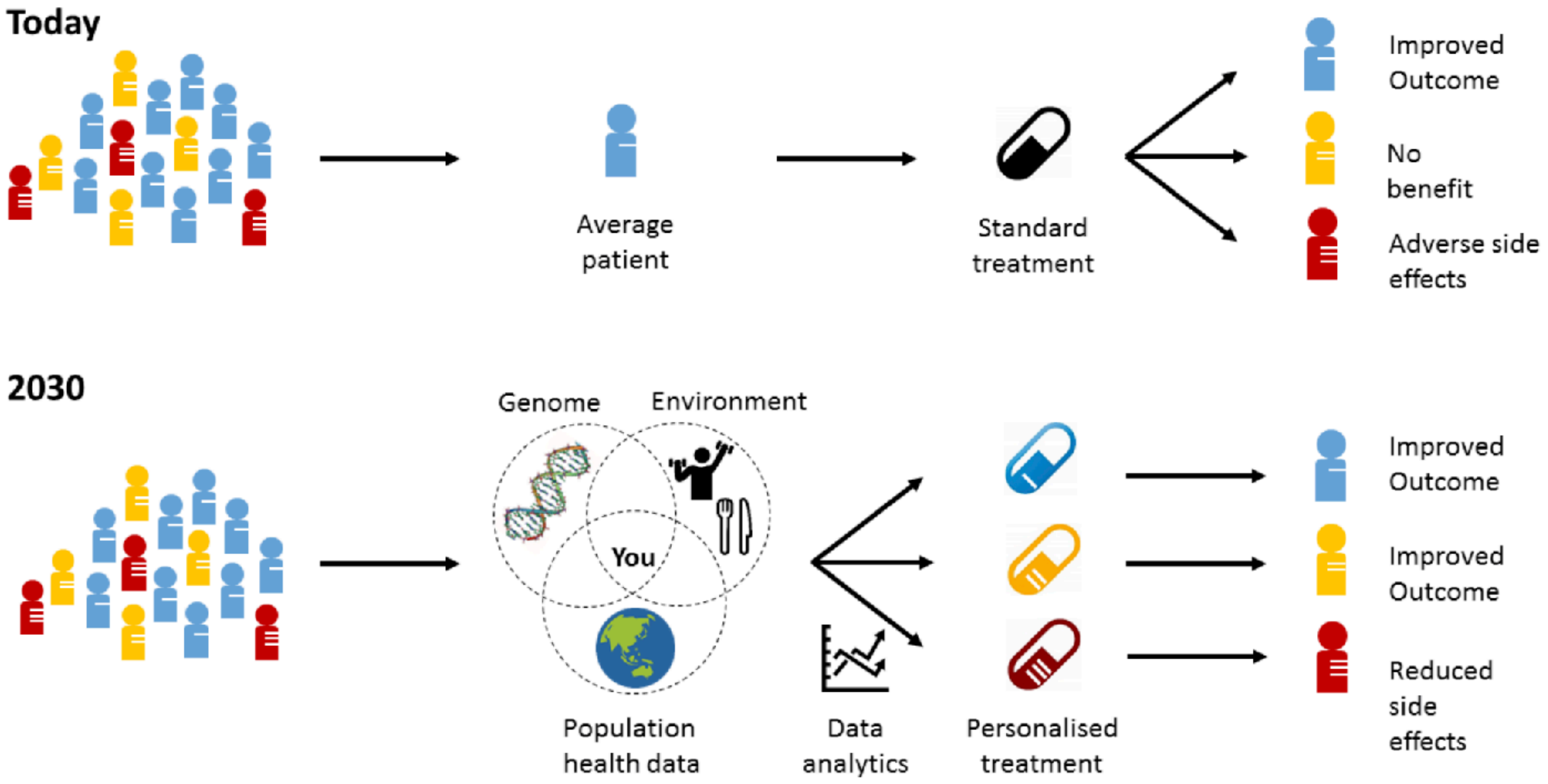


https://www.chiefscientist.gov.au/wp-content/uploads/Precision-medicine-final.pdf

HOW DID WE GET HERE?

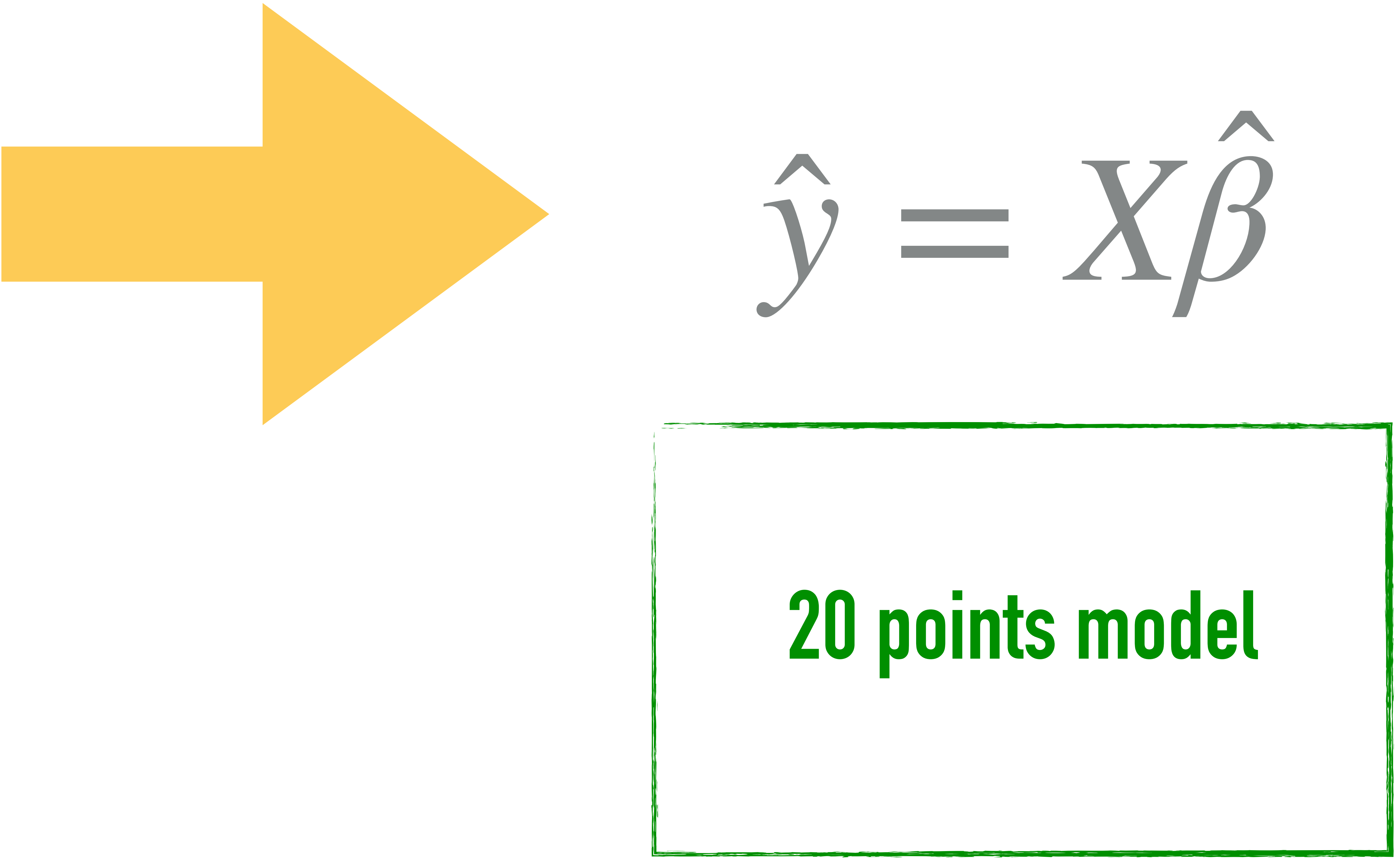
REGRESSION ANALYSIS BEFORE THE 1950’S

Linear regression

- A response variable often captures some complicated physical mechanism
- Predictor variables are usually quantities that are more manageable

Cox Proportional Hazard model

- Framingham heart disease risk score:
  - Age (Years)
  - Cholesterol (mg/dL)
  - If smoker (Yes/No)
  - HDL cholesterol (mg/dL)
  - Systolic blood pressure (mm Hg)



$$\hat{y} = X\hat{\beta}$$

20 points model

Least square regression is a projection

- A linear regression aims to explain as much complications in the response variable using the predictors as possible.
- L2 projection of y upon a subspace spanned by the column vectors of the predictor matrix.

Linear regression as minimisation problem

- A well studied problem

When the least squares solution fails

- When $n < p$, we have more parameters to be estimated (p) than observations we have collected (n). An overdetermined linear system.
- A simulation shows that the beta vector blows up!

CONSTRAINED REGRESSION ANALYSIS

When the beta blows up, we put a lid on it

- Ridge regression came around1945.

The same simulation, but with Ridge

REGRESSION OF THE 21ST CENTURY

Least Absolute Shrinkage and Selection Operator

- There are “only” three norms: L1, L2 and L-inf
- Tibshirani 1996 replaced L2 penalty with the L1.
- The original paper is now cited about 30,000 times.

Why variable selection

- Every variable you put into your model introduces variations into your estimation and prediction.
- For the informative variables, this is fine! In fact, you should be happy because it tells you a broad range of what to expect.
- But for non-informative variables, this variation is a nuisance, a noise that undermines your model.
- Variable selection aims to keep the informative ones and kill the latter.

Various wonderful properties of Lasso

Visualisation of the Lasso and the simulation

Robert Tibshirani

A GALLERY DEDICATED TO THE LASSO

Whenever Lasso fails, a small modification of the optimisation equation fixes it

- Highly correlated features
- Stability in selection
- Group structures
- Fused Lasso
-

CPOP: CROSS PLATFORM OMICS PREDICTION

Statistics is not invincible

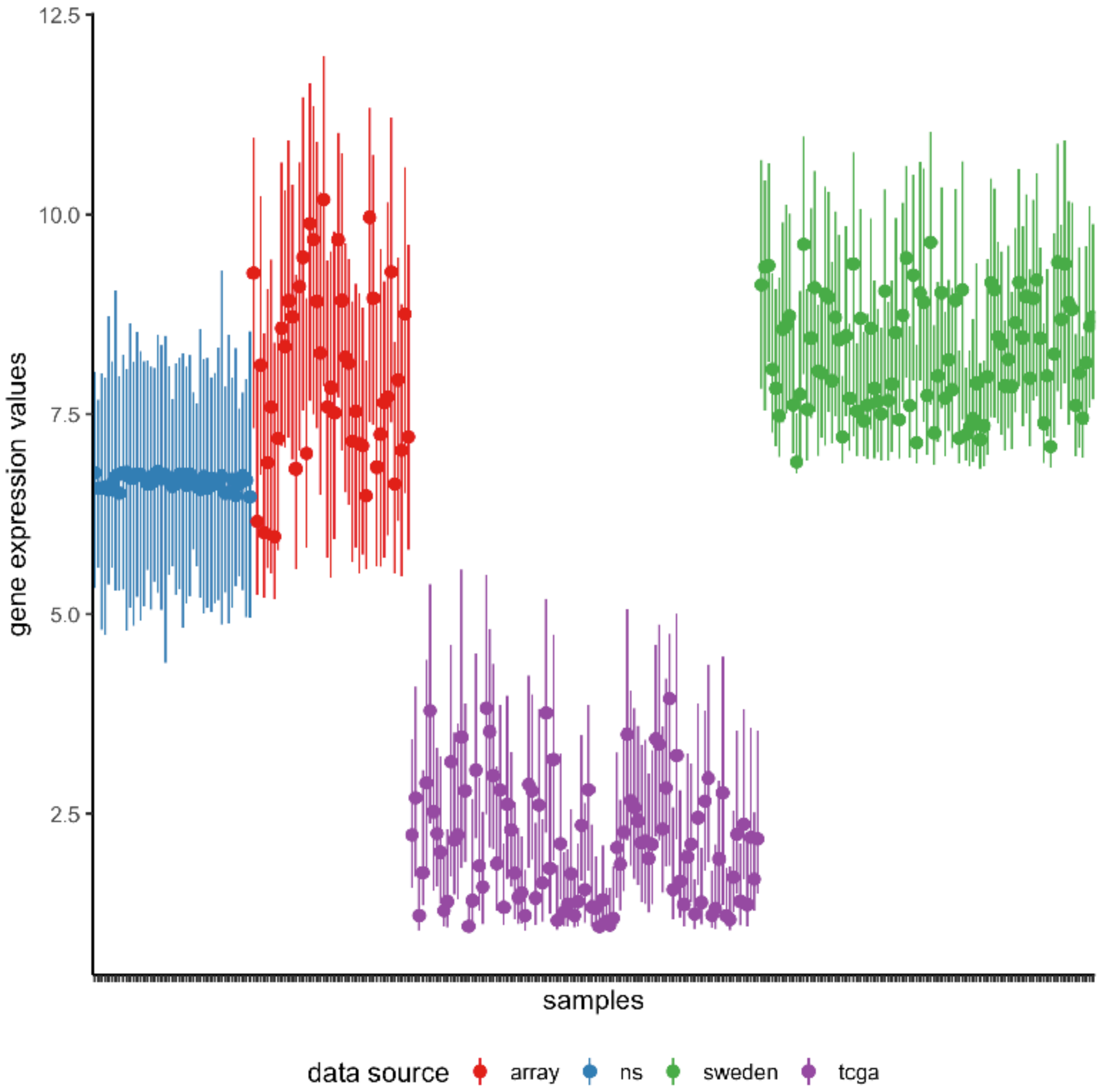
- When your training data and validation data are not of the same statistical properties, any model would do miserably.

Omics-based clinical risk score: what is so difficult?

Omics features are typically on a relative scale and unitless

$$\hat{y}_1 = X_1\hat{\beta}_1$$

$$\hat{y}_2 = X_2\hat{\beta}_1 = (X_1 + \mathbf{1})\hat{\beta}_1$$

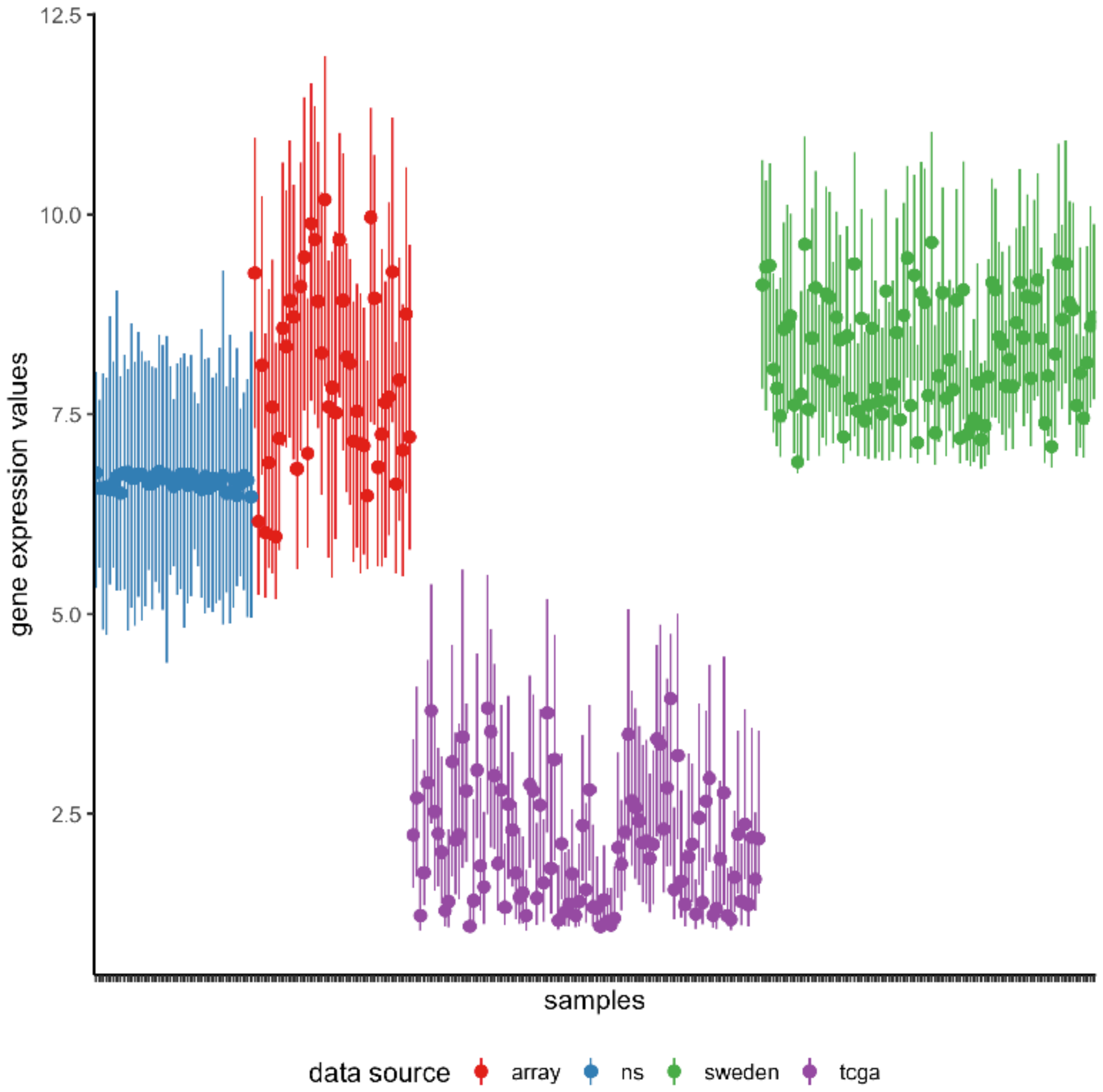


Omics-based clinical risk score: what is so difficult?

1. Practical: we cannot renormalise data in a clinical setting

	Sample 1	Sample 2	Sample 3
Gene 1	1.2	2.1	1.5
Gene 2	5.6	4.6	7.1
Gene 3	9.2	10.1	6.9
Gene 4	4.1	3.6	2.7

Sample 4
1.2
1.4
8.6
7.1



The flowchart of a clinical risk score

Data

Model

Prediction

(X_1, y_1)

(X_2, y_2)

$\hat{\beta}_1$

$\hat{y}_1 = X_1\hat{\beta}_1$

$\hat{y}_2 = X_2\hat{\beta}_1$

The flowchart of a clinical risk score

Data

$$(X_1, y_1)$$

$$(X_2, y_2)$$

No renormalisation

Model

$$\hat{\beta}_1$$

No model retraining

Prediction

$$\hat{y}_1 = X_1\hat{\beta}_1$$

$$\hat{y}_2 = X_2\hat{\beta}_1$$

Scale-equivalent prediction

Statistical challenges

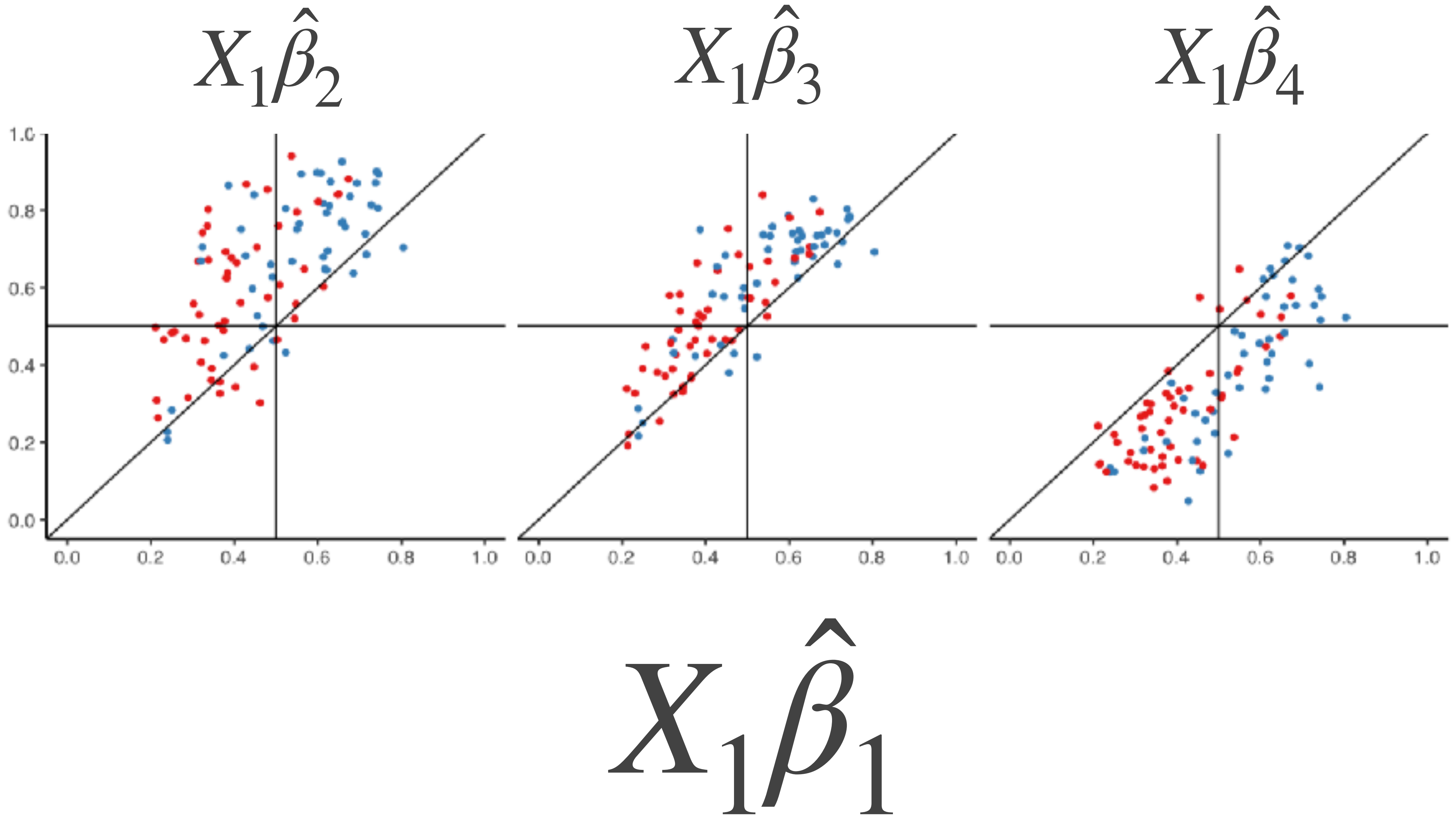
1. Concordance in gene features scaling across platforms

2. Concordance in feature selection and coefficient estimates

3. Single-patient prediction

Transferability

For the same samples,
the prediction from one gene expression platform
should be equivalent to another platform



First component of CPOP: feature engineering

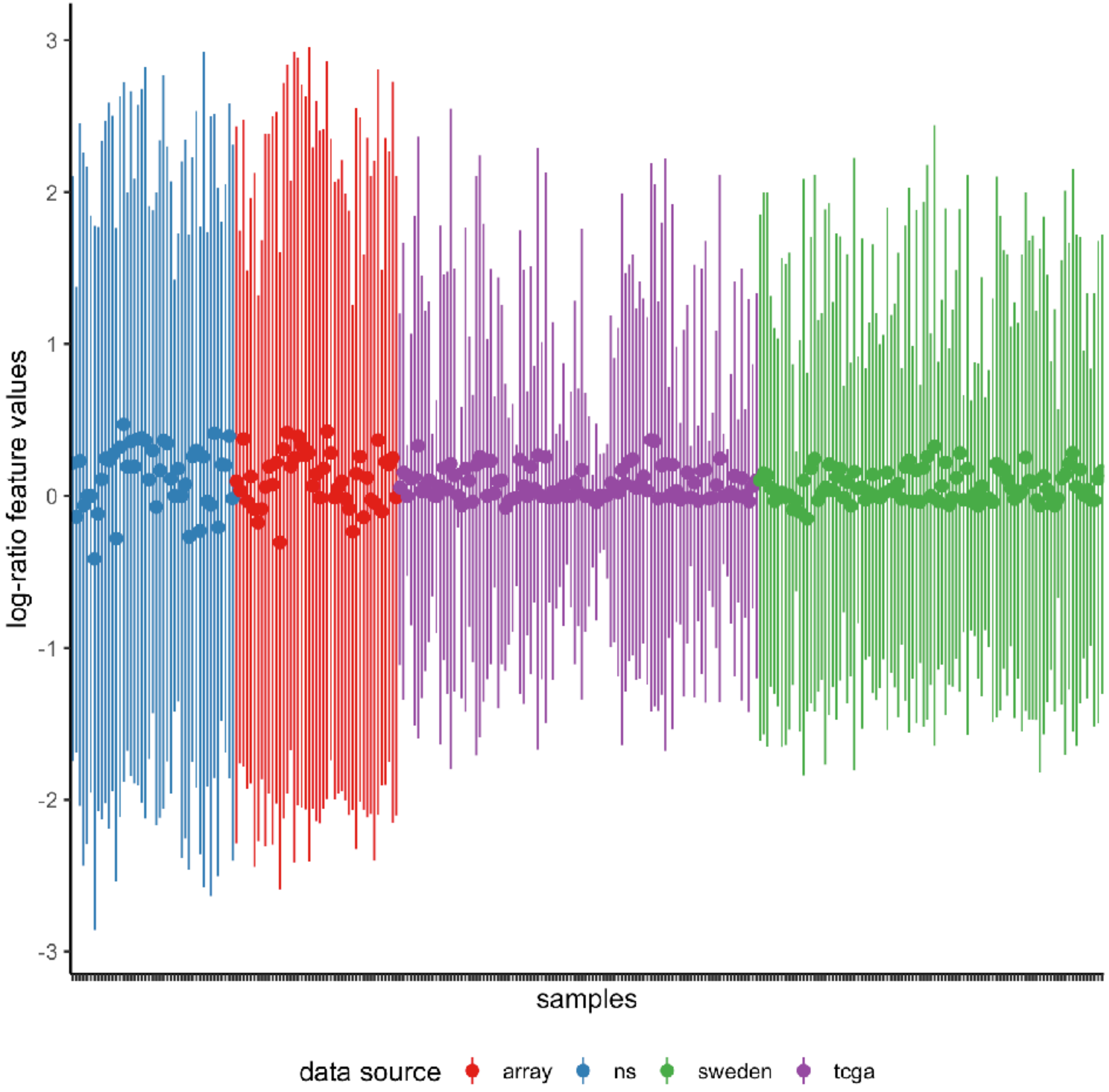
就让我 来次透彻心扉的痛
都拿走 让我再次两手空空
只有奄奄一息过
那个真正的我
他才能够诞生

Within-sample feature standardisation

Single-patient prediction prevents us from calculating any cross-sample statistics, so the natural solution is within-sample standardisation

Log-ratio

log(gene A) – log(gene B)



The solution is trivial?

1. Concordance in gene features scaling across platforms
2. Concordance in feature selection and coefficient estimates
3. Single-patient prediction

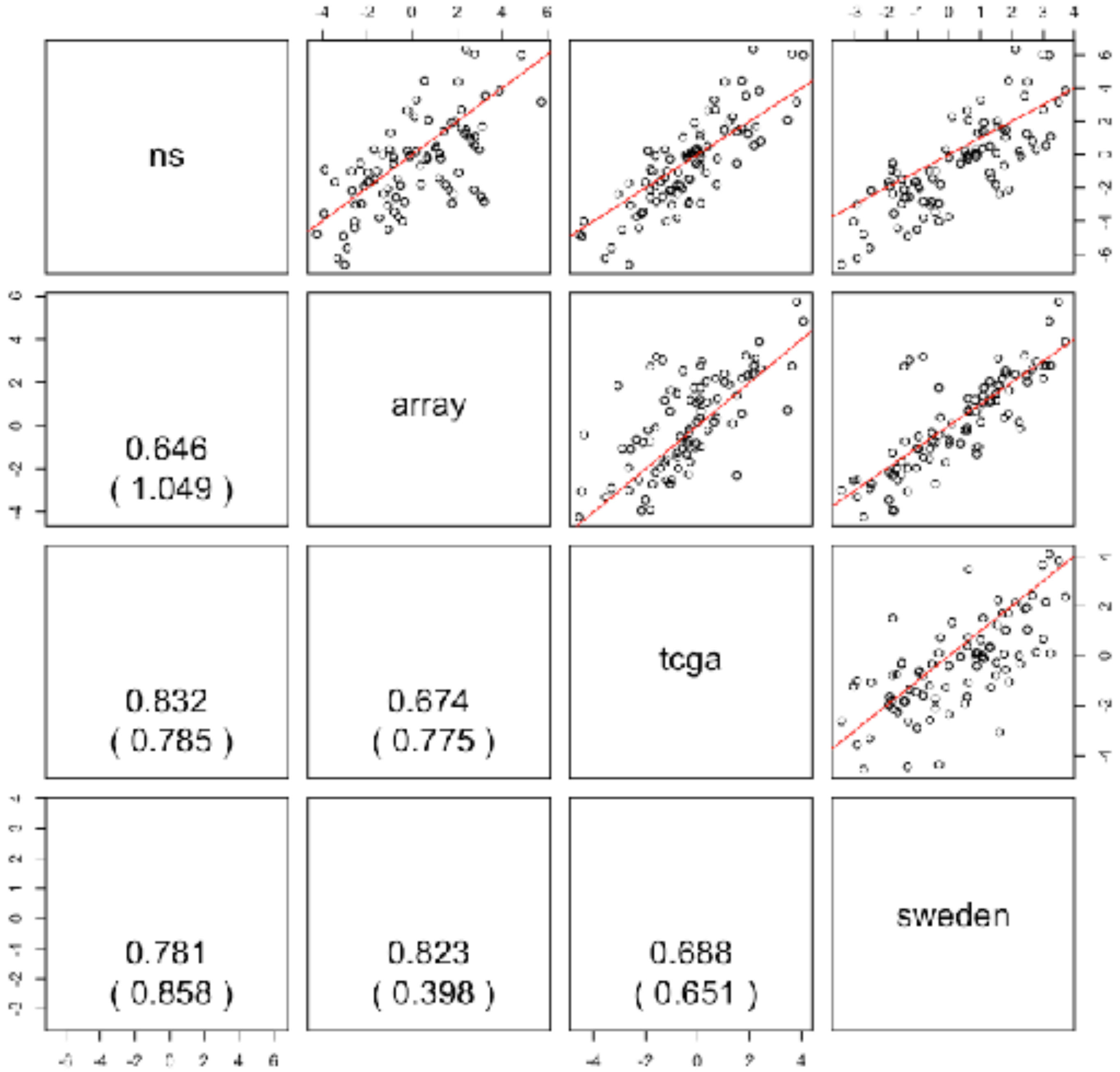
The solution is trivial?

1. Concordance in log-ratio features scaling across platforms

2. Concordance in feature selection and coefficient estimates

3. ~~Single-patient prediction~~

Concordance of log-ratios after Lasso selection



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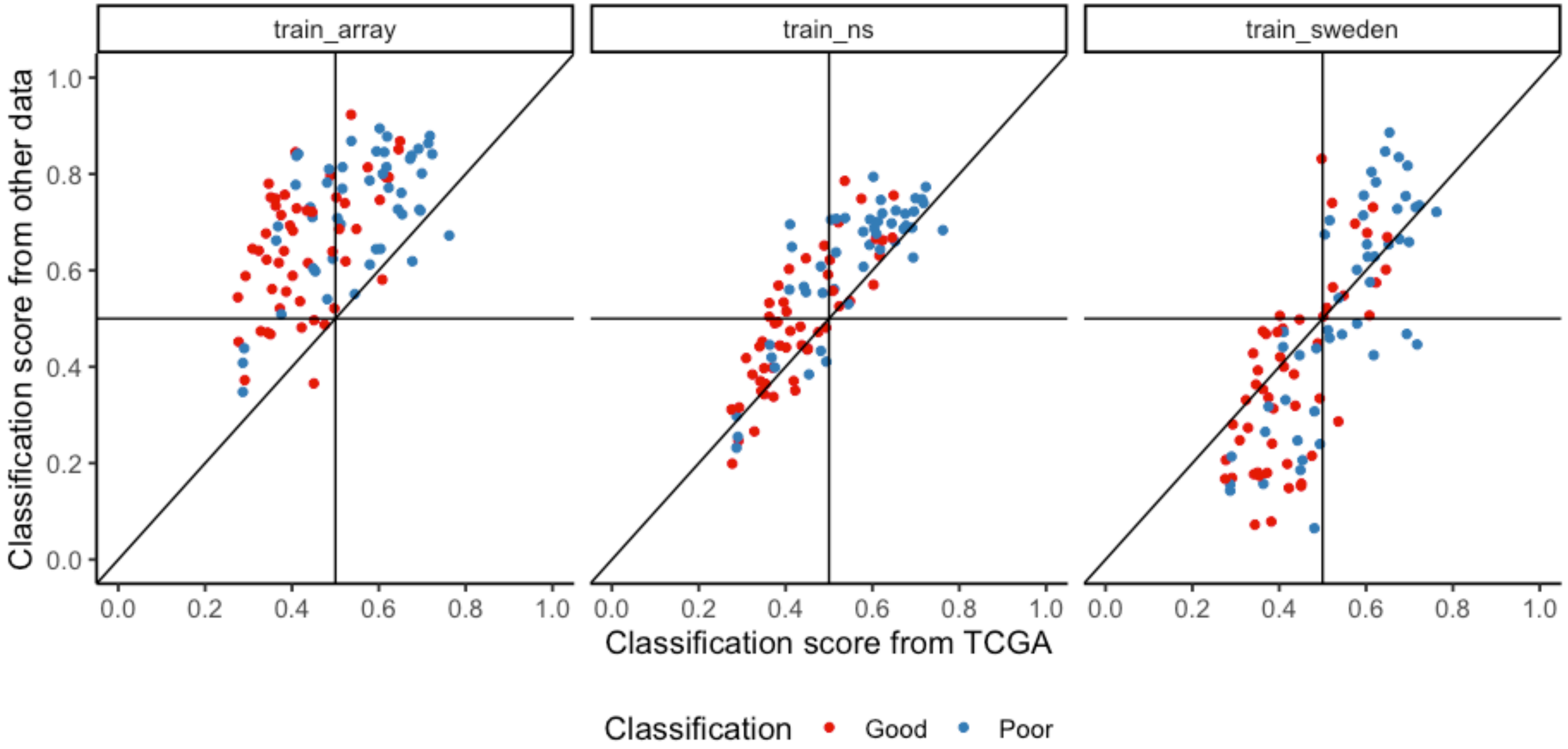
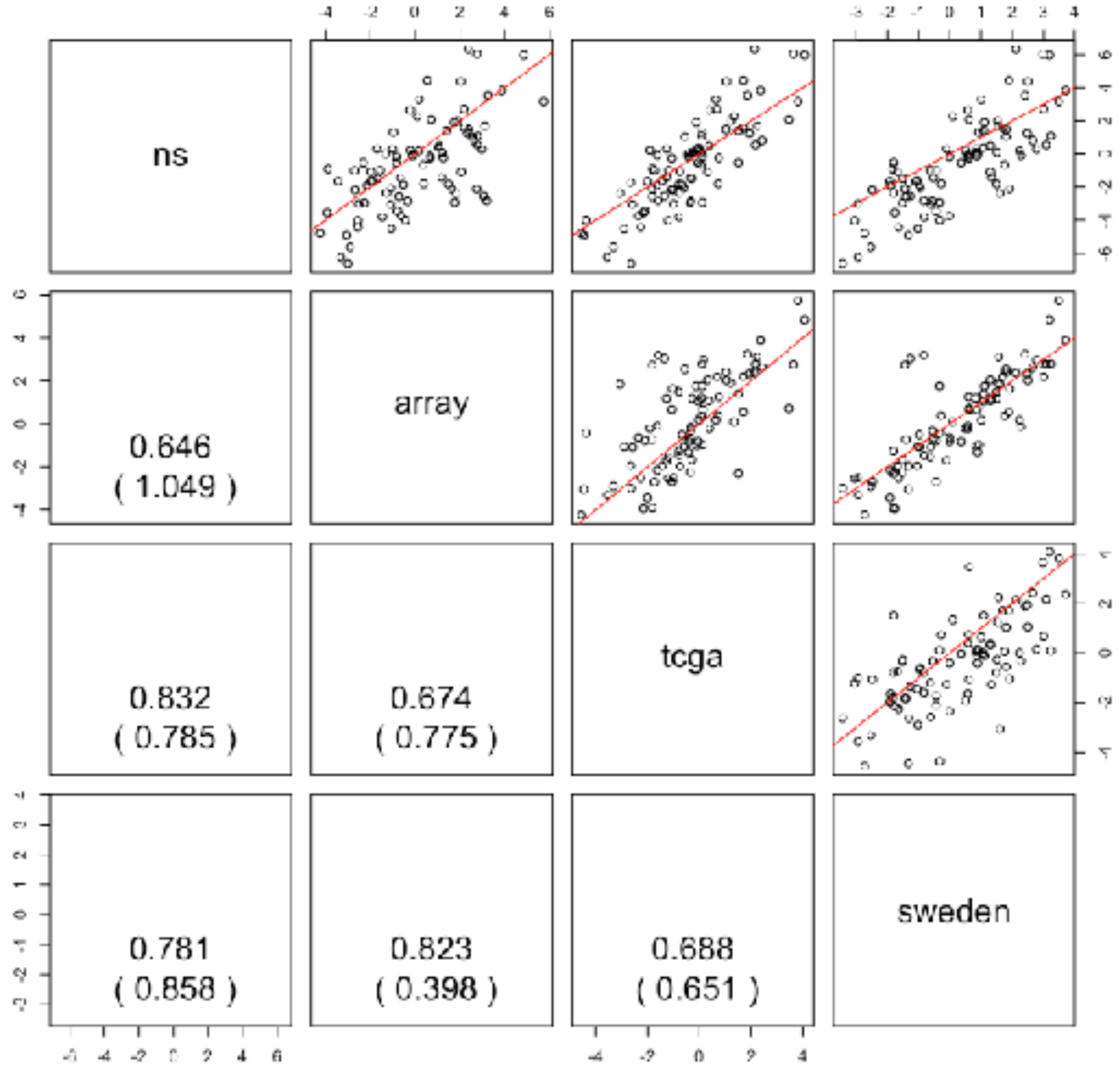


Concordance of log-ratios after Lasso selection



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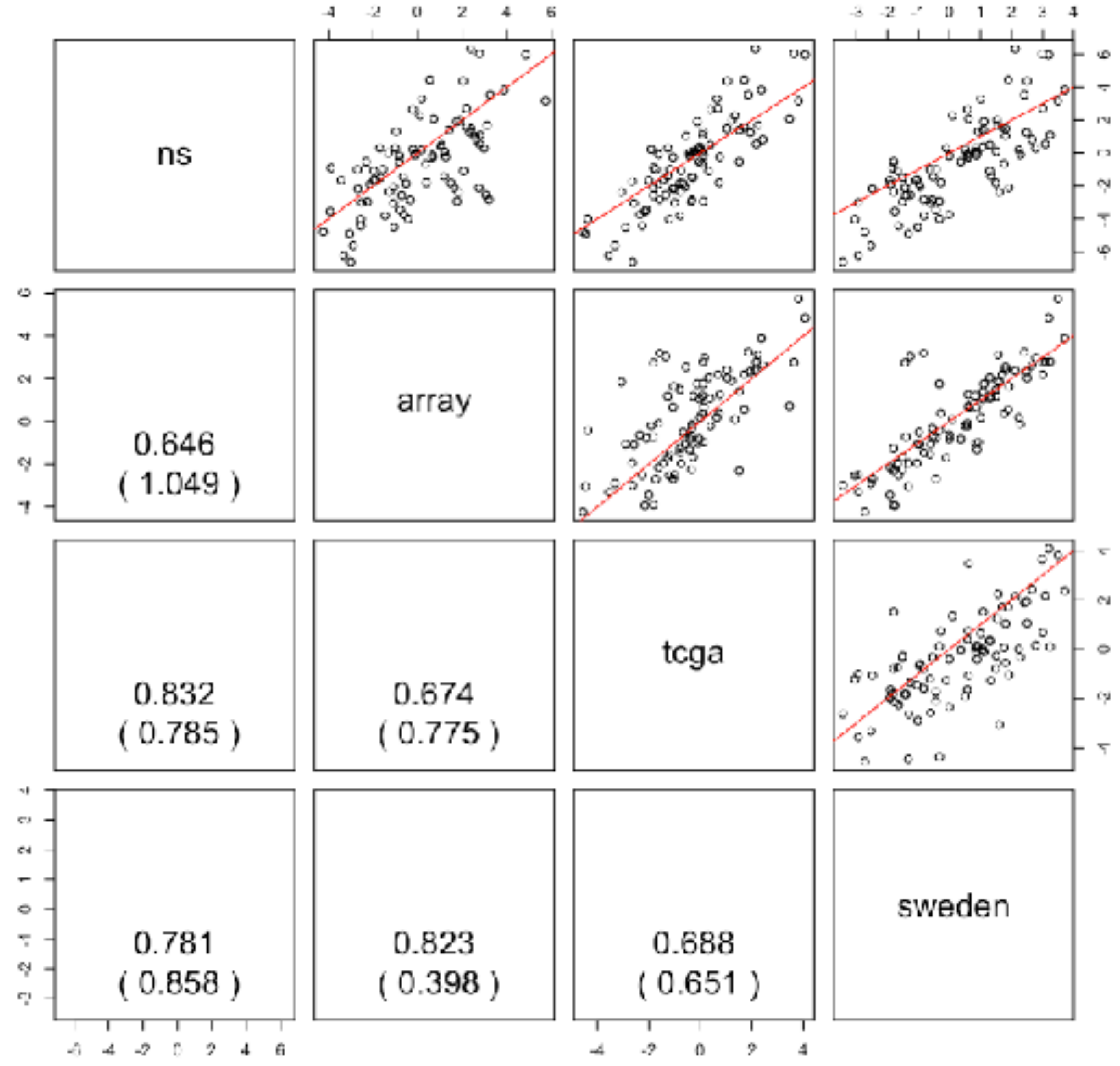
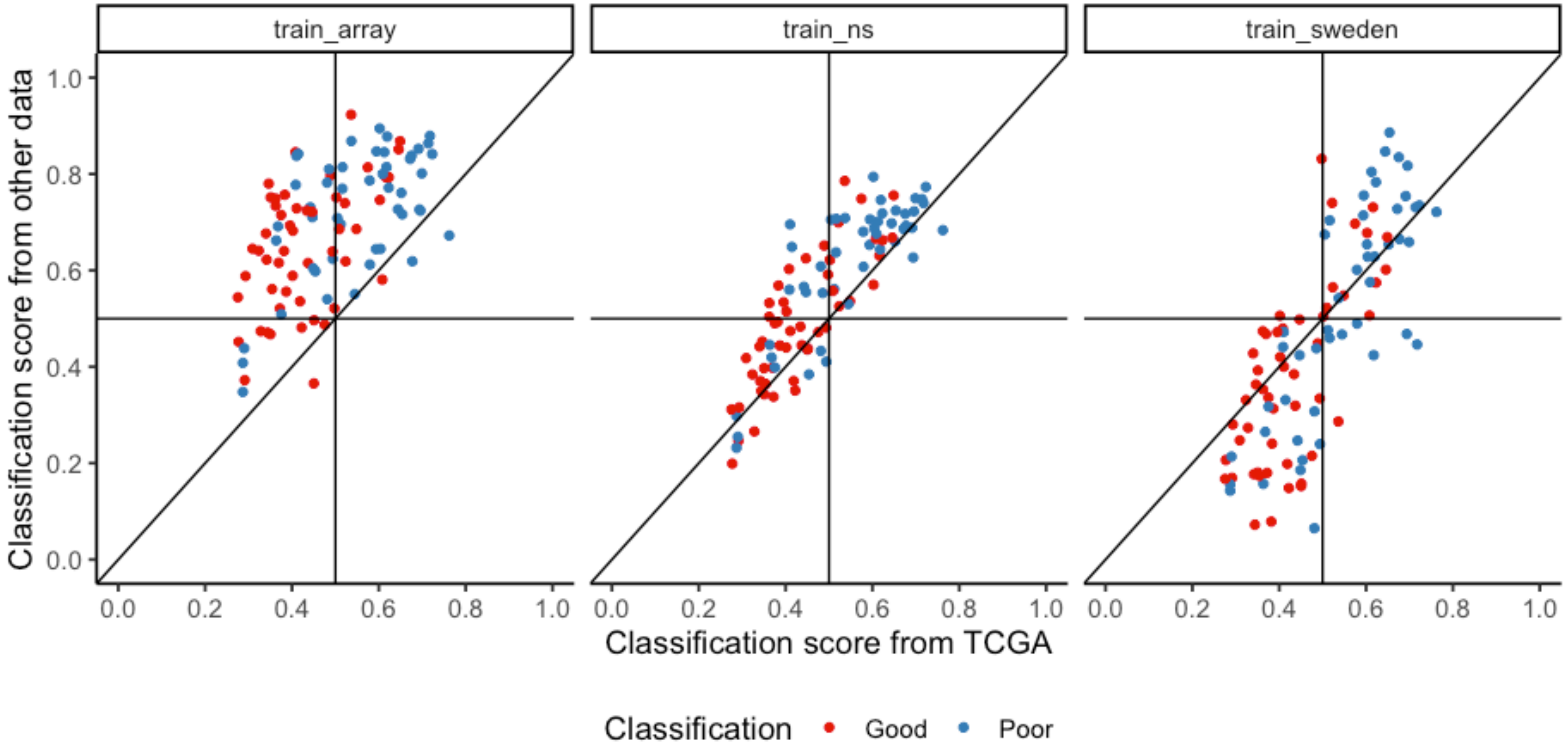




Lasso variable selection is NOT stable

The solution is not so trivial

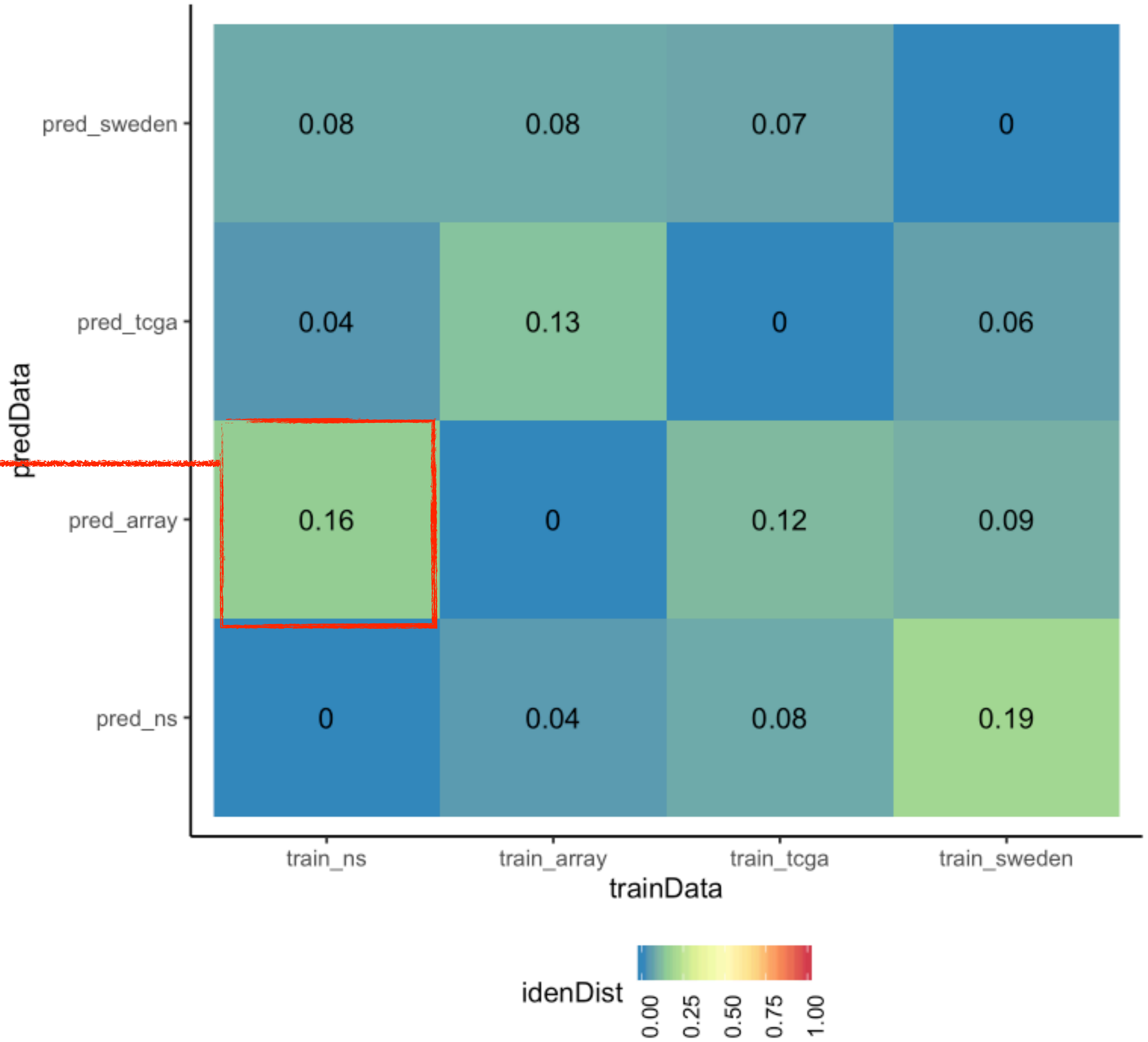
Estimated prognosis probabilities from

training data

vs

validation data

differ by 0.16 on average



Second component of CPOP:
feature selection and estimation stability

我曾经毁了我的一切
只想永远地离开
我曾经堕入无边黑暗
想挣扎无法自拔
我曾经 像你 像他 像那野草 野花
绝望着 也渴望着
也哭 也笑 也平凡着

Motivation for CPOP: one patient cohort, two gene expression data

$$Z_1\hat{\beta}_1 \approx Z_2\hat{\beta}_2$$

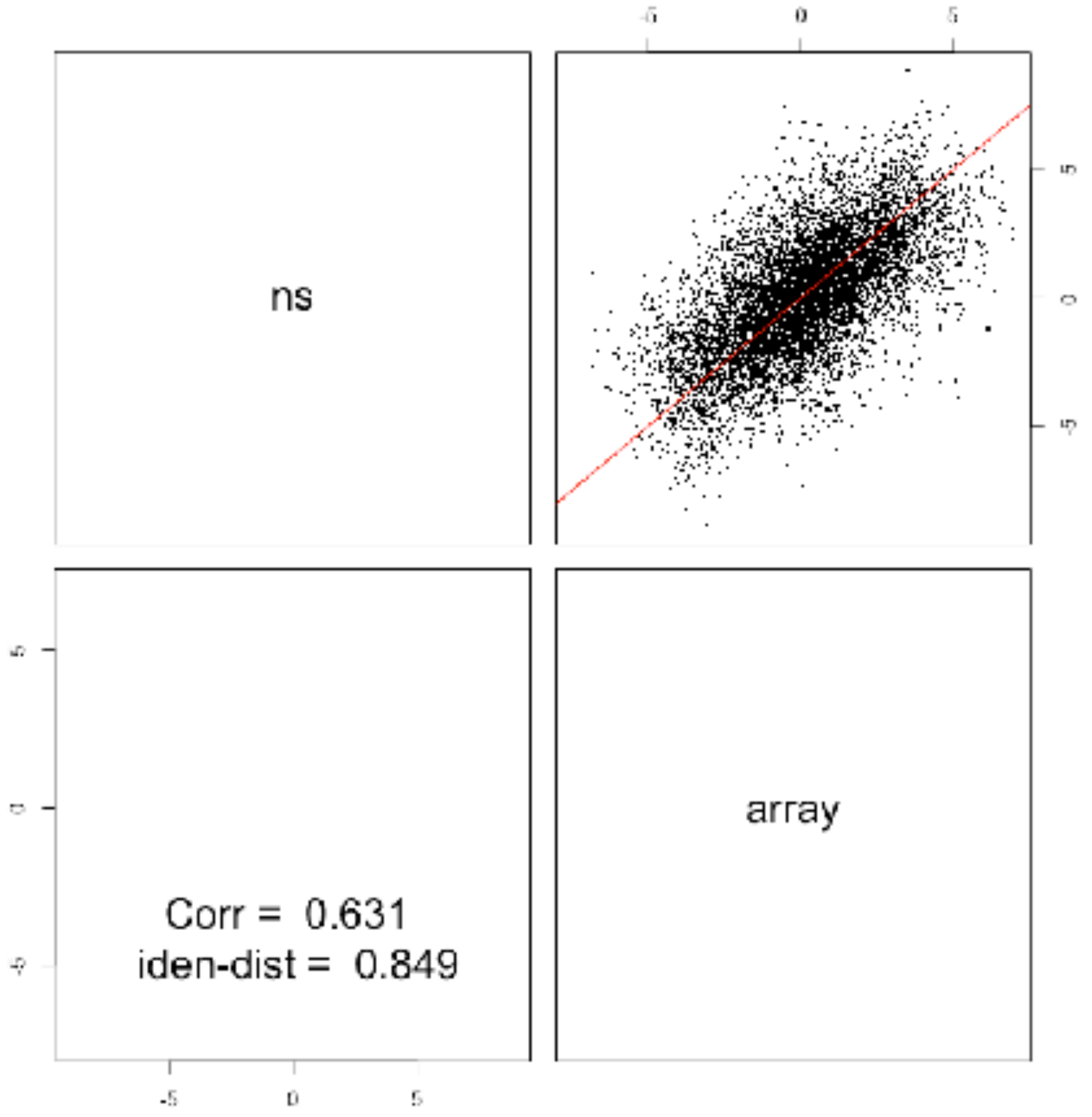
loosely translate to

$$Z_1 \approx Z_2$$ column-wise

$$\hat{\beta}_1 \approx \hat{\beta}_2$$ element-wise

CPOP weighted variable selection

1. Perform a **weighted Lasso** by placing higher weights on features closer to the identity line



$$Z_1 \approx Z_2$$

CPOP weighted variable selection

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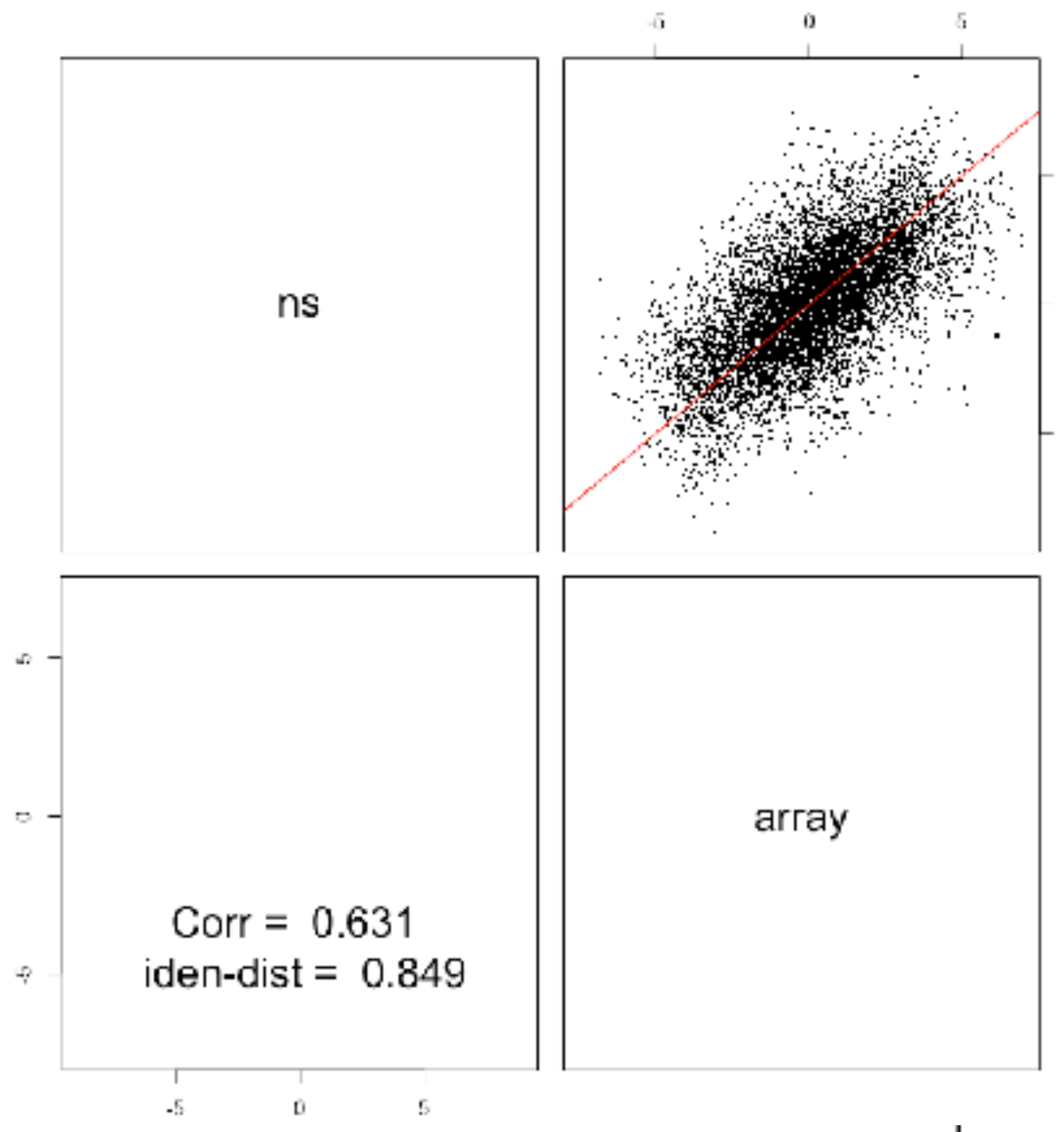
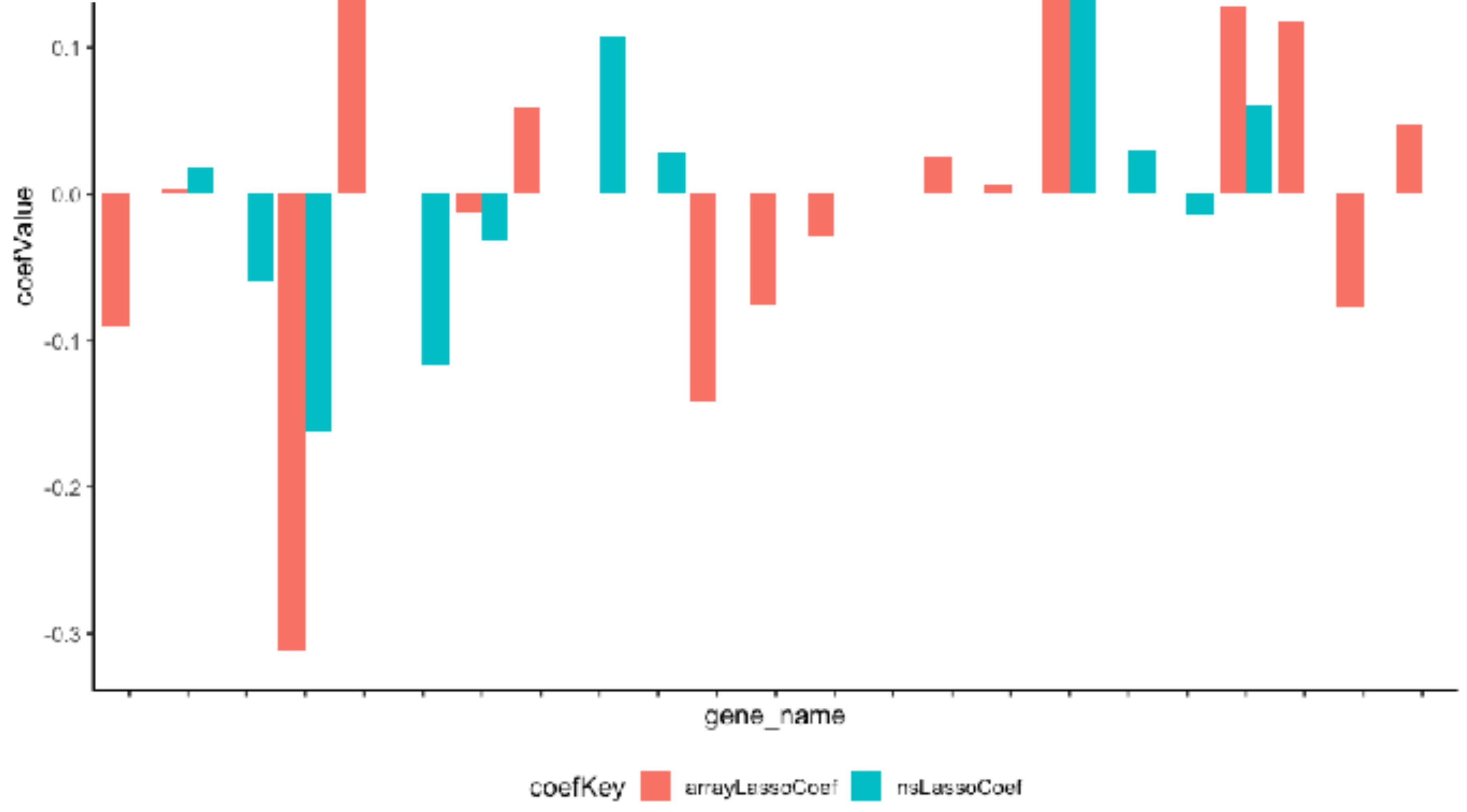


$$Z_1 \approx Z_2$$

2. Perform a **Ridge regression** and only retain those features with coefficients similar to each other

$$\hat{\beta}_1 \approx \hat{\beta}_2$$



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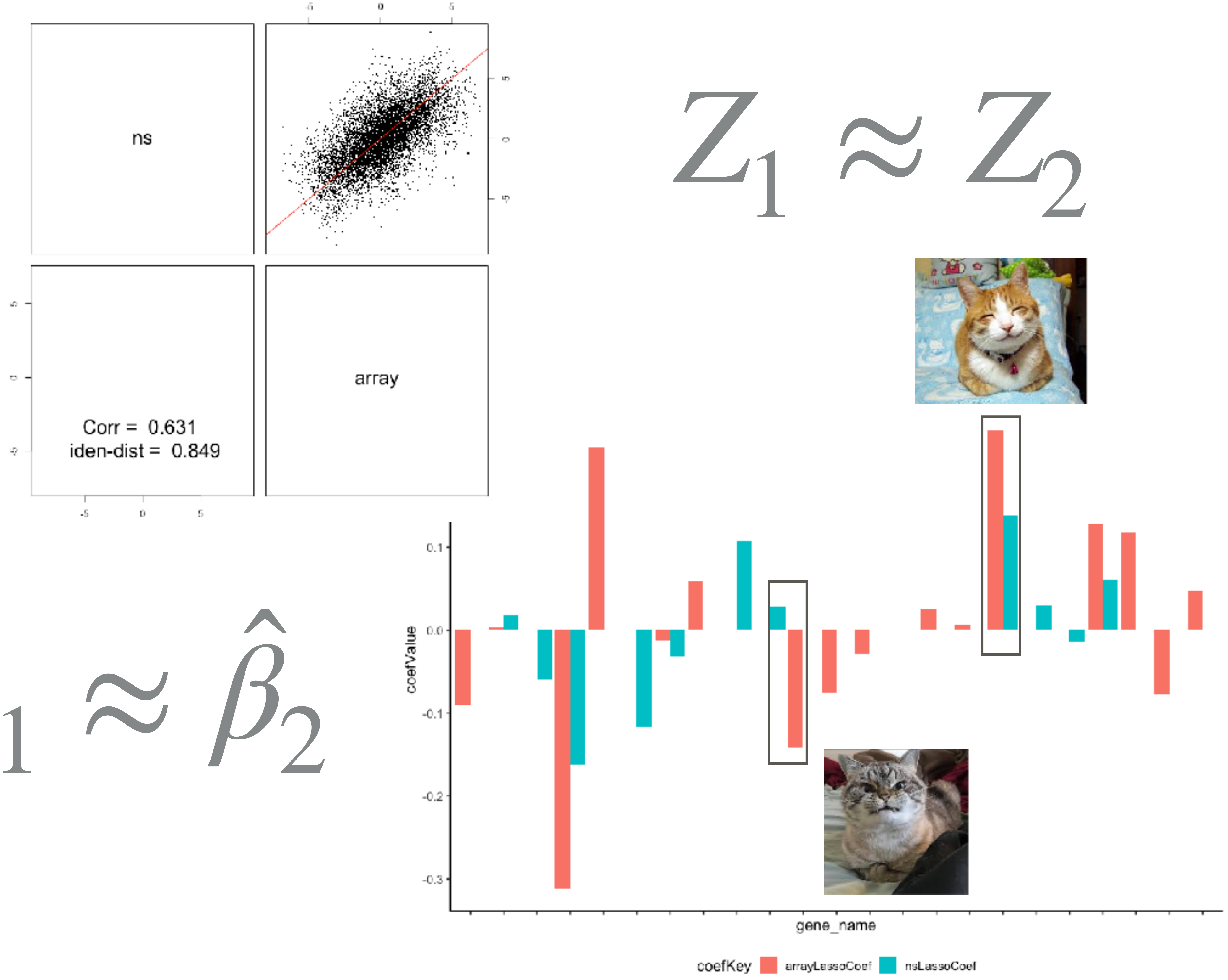


$$Z_1 \approx Z_2$$

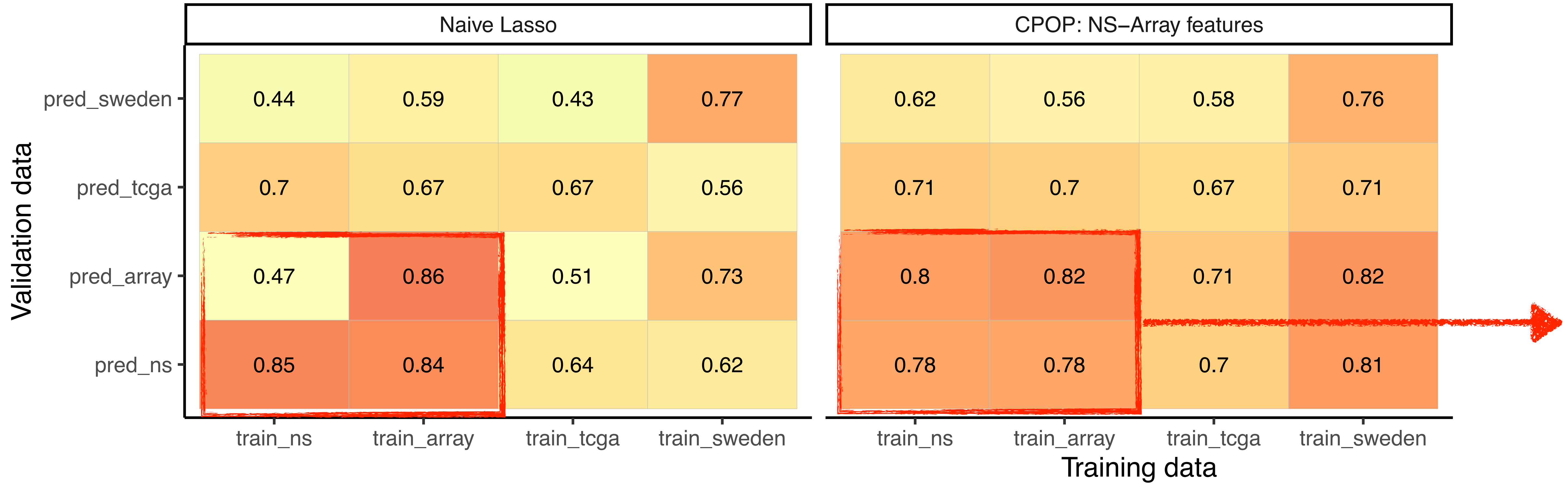
$$\hat{\beta}_1 \approx \hat{\beta}_2$$

CPOP results 1: four melanoma data

1. Predictive performance of CPOP matches that of re-substitution

2. Smaller identity distance between predicted values

F1 classification statistic under various models



Naive Lasso

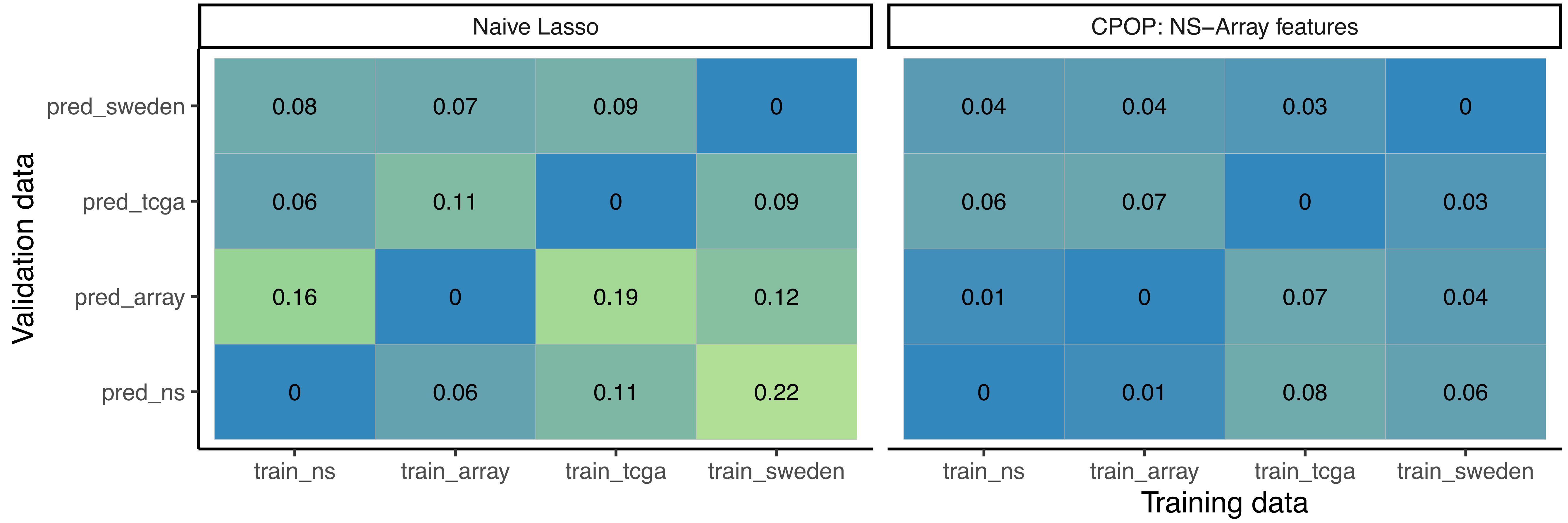
Validation data	train_ns	train_array	train_tcga	train_sweden
pred_sweden	0.44	0.59	0.43	0.77
pred_tcga	0.7	0.67	0.67	0.56
pred_array	0.47	0.86	0.51	0.73
pred_ns	0.85	0.84	0.64	0.62

CPOP: NS–Array features

Validation data	train_ns	train_array	train_tcga	train_sweden
pred_sweden	0.62	0.56	0.58	0.76
pred_tcga	0.71	0.7	0.67	0.71
pred_array	0.8	0.82	0.71	0.82
pred_ns	0.78	0.78	0.7	0.81

Datasets for feature selection

Identity distance between predicted values under various models



Naive Lasso

Validation data	train_ns	train_array	train_tcga	train_sweden
pred_sweden	0.08	0.07	0.09	0
pred_tcga	0.06	0.11	0	0.09
pred_array	0.16	0	0.19	0.12
pred_ns	0	0.06	0.11	0.22

CPOP: NS–Array features

Validation data	train_ns	train_array	train_tcga	train_sweden
pred_sweden	0.04	0.04	0.03	0
pred_tcga	0.06	0.07	0	0.03
pred_array	0.01	0	0.07	0.04
pred_ns	0	0.01	0.08	0.06

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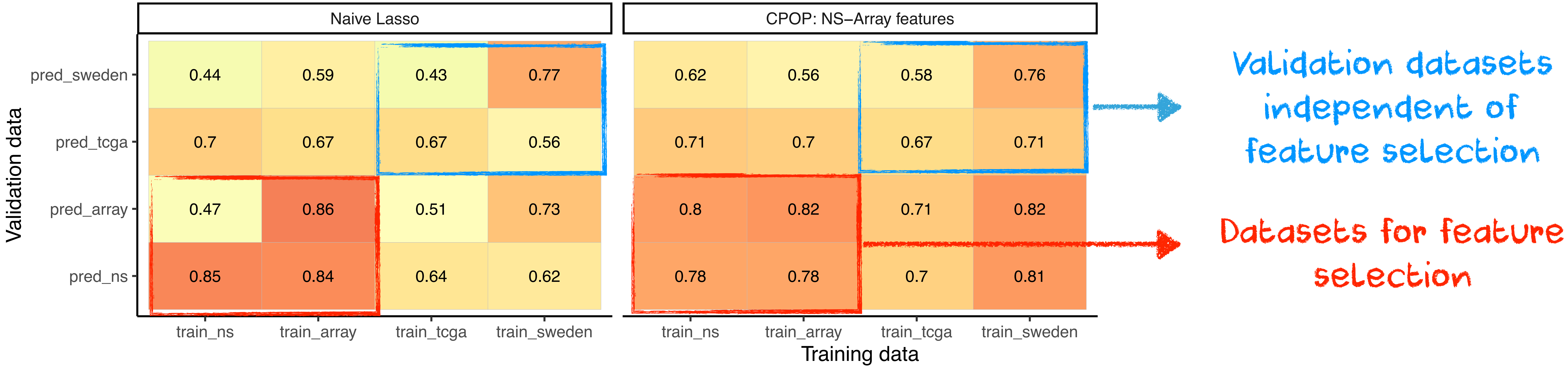

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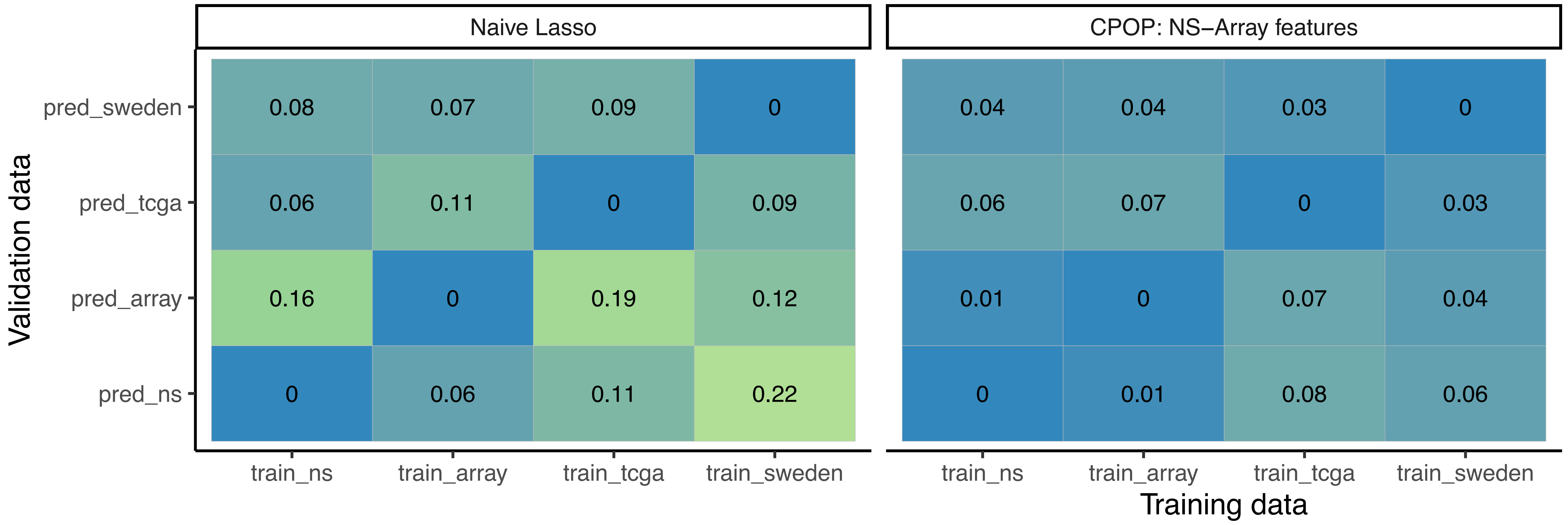
Validation datasets independent of feature selection

Datasets for feature selection

Identity distance between predicted values under various models



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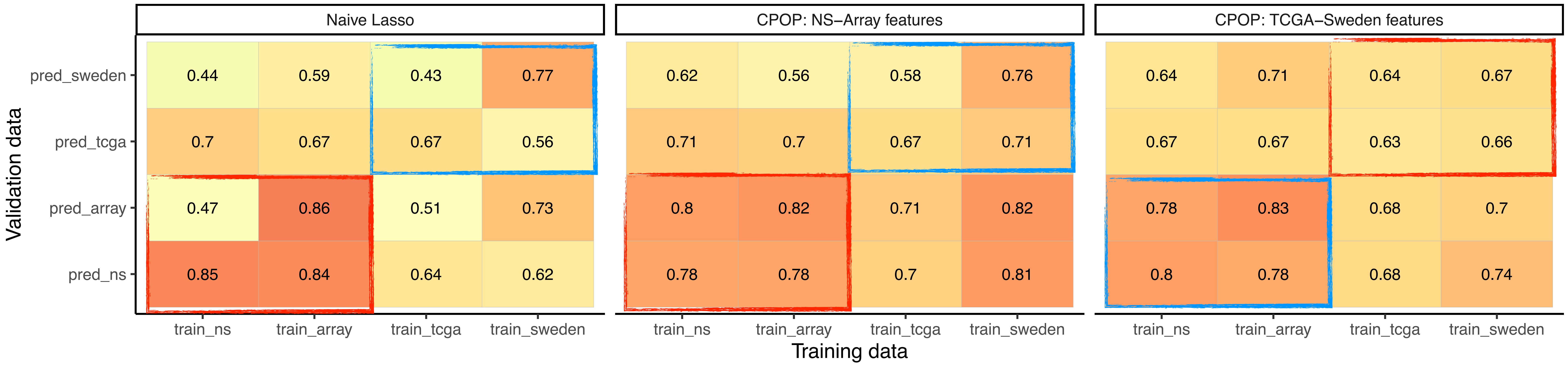

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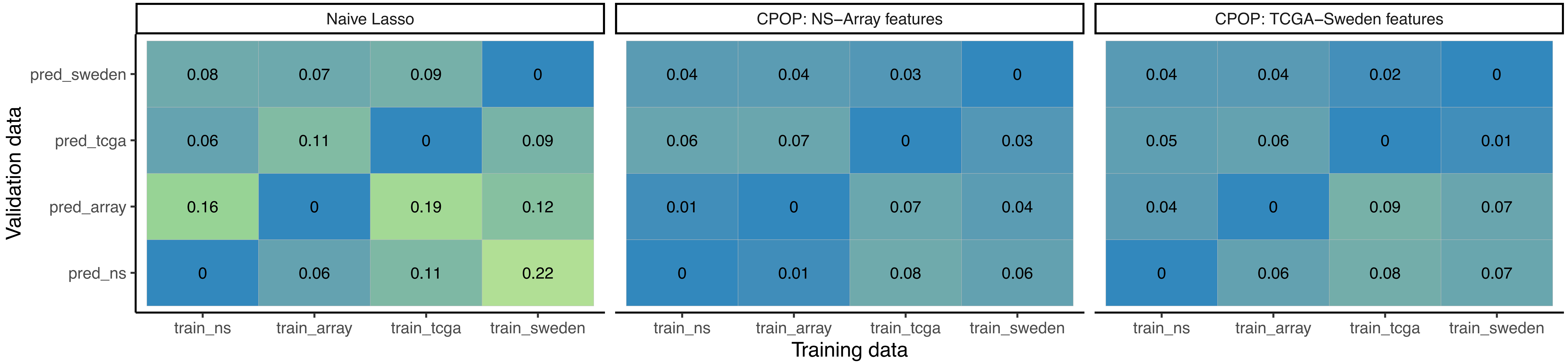
pred_ns	0.78	0.78	0.7	0.81

CPOP: TCGA–Sweden features

	train_ns	train_array	train_tcga	train_sweden
pred_sweden	0.64	0.71	0.64	0.67
pred_tcga	0.67	0.67	0.63	0.66
pred_array	0.78	0.83	0.68	0.7
pred_ns	0.8	0.78	0.68	0.74

Identity distance between predicted values under various models



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pred_array	0.01	0	0.07	0.04
pred_ns	0	0.01	0.08	0.06

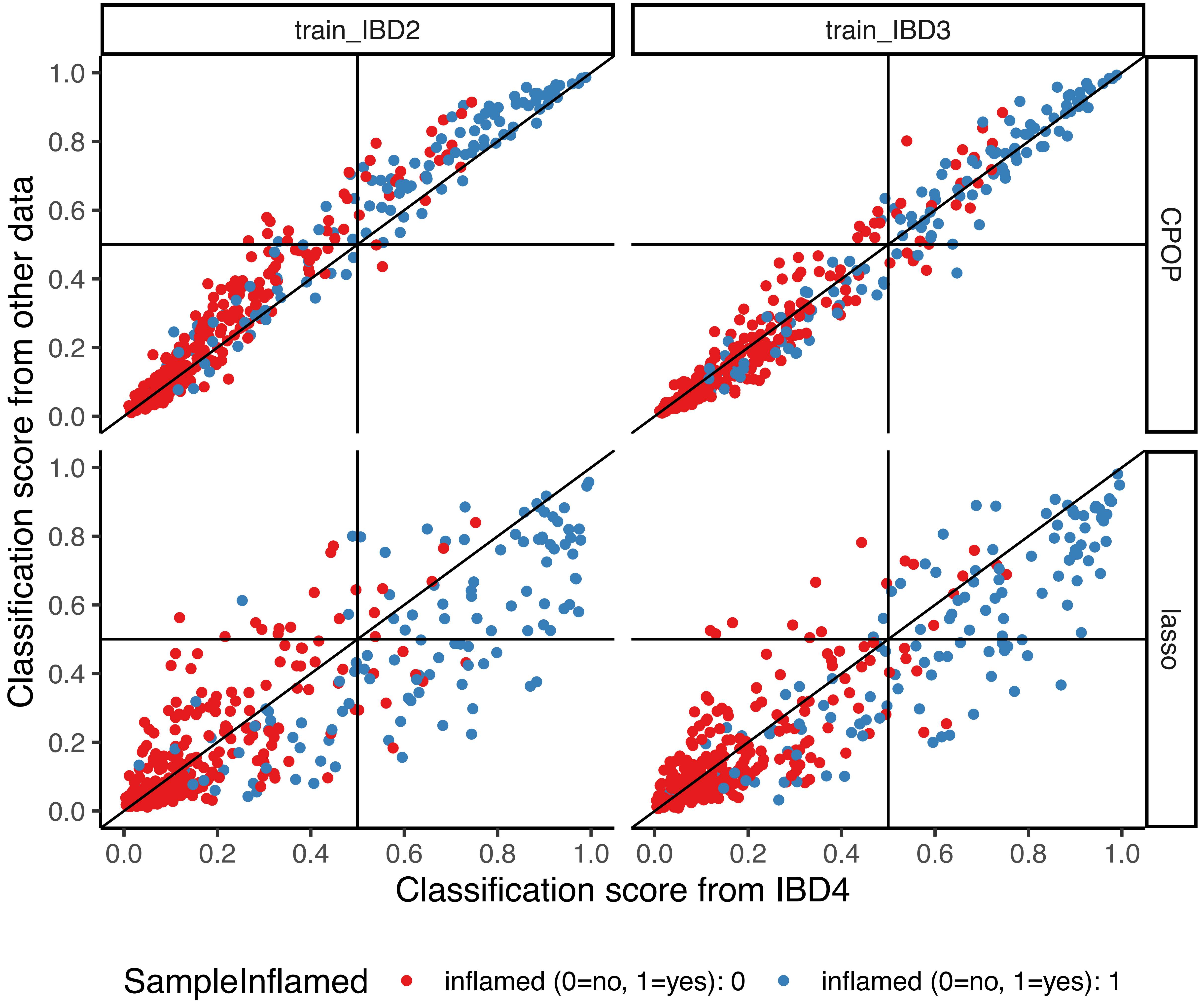
CPOP: TCGA–Sweden features

	train_ns	train_array	train_tcga	train_sweden
pred_sweden	0.04	0.04	0.02	0
pred_tcga	0.05	0.06	0	0.01
pred_array	0.04	0	0.09	0.07
pred_ns	0	0.06	0.08	0.07

CPOP results 2: prospective prediction

- CPOP on IBD NanoString data demonstrated improvements on stability

- We are planning to exploring other data of higher relevance to precision medicine (e.g. drug sensitivity)


train_IBD2
train_IBD3
CPOP
lasso
Classification score from other data
Classification score from IBD4
SampleInflamed
● inflamed (0=no, 1=yes): 0
● inflamed (0=no, 1=yes): 1