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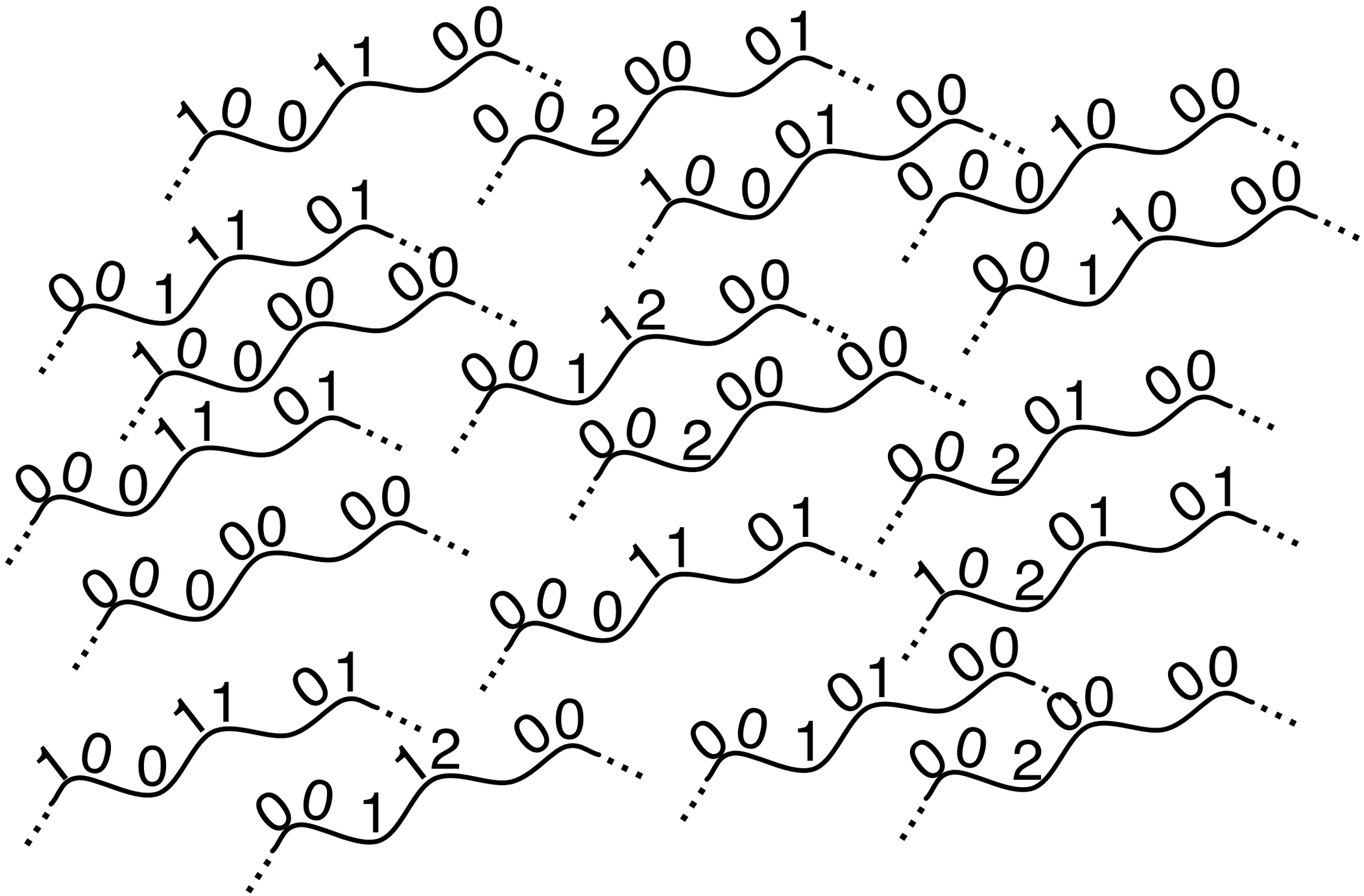
Single nucleotide polymorphisms (SNPs)



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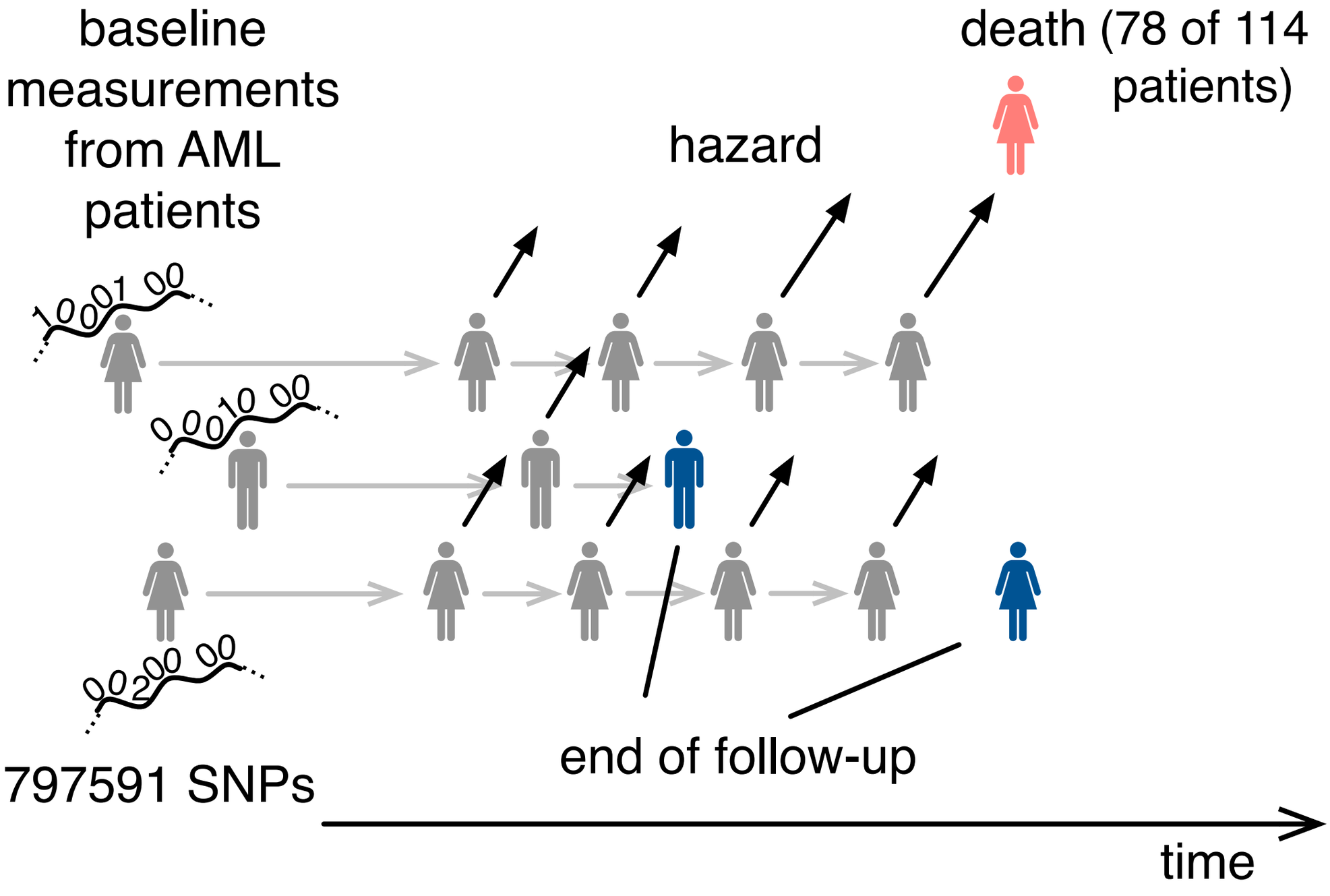
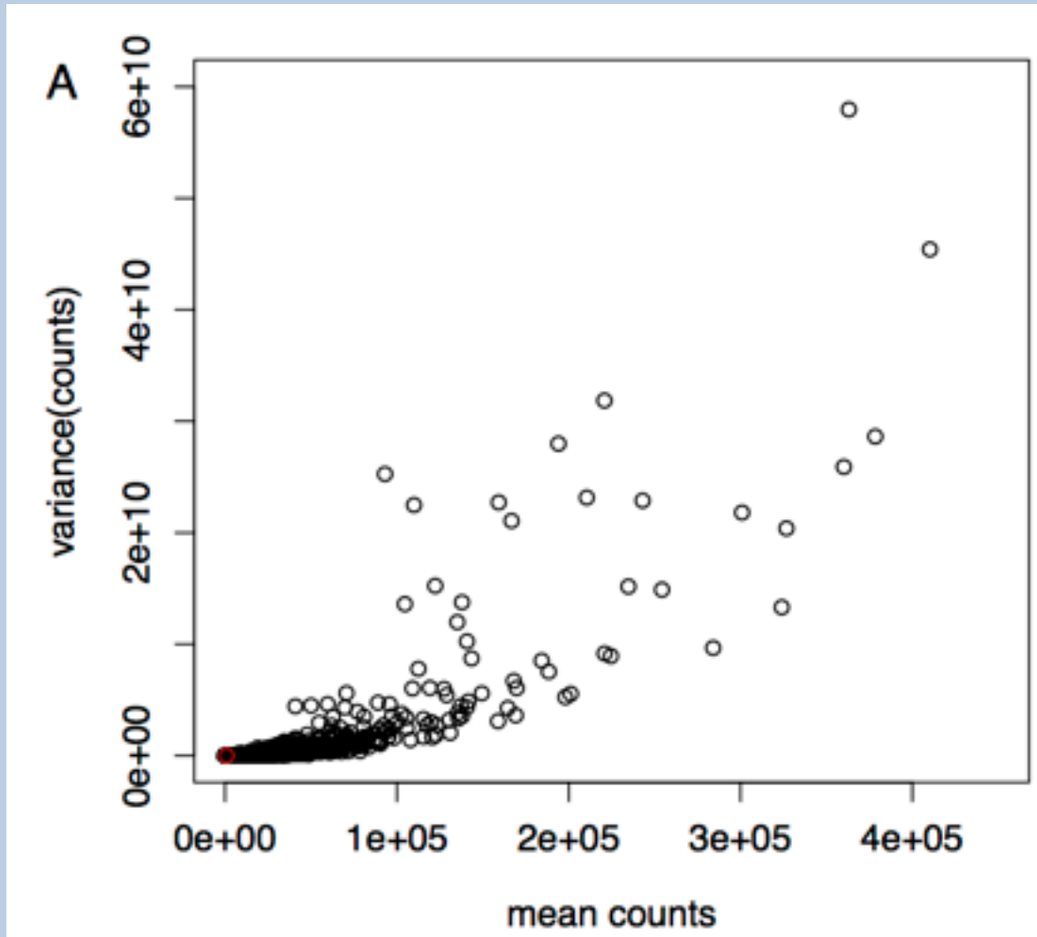
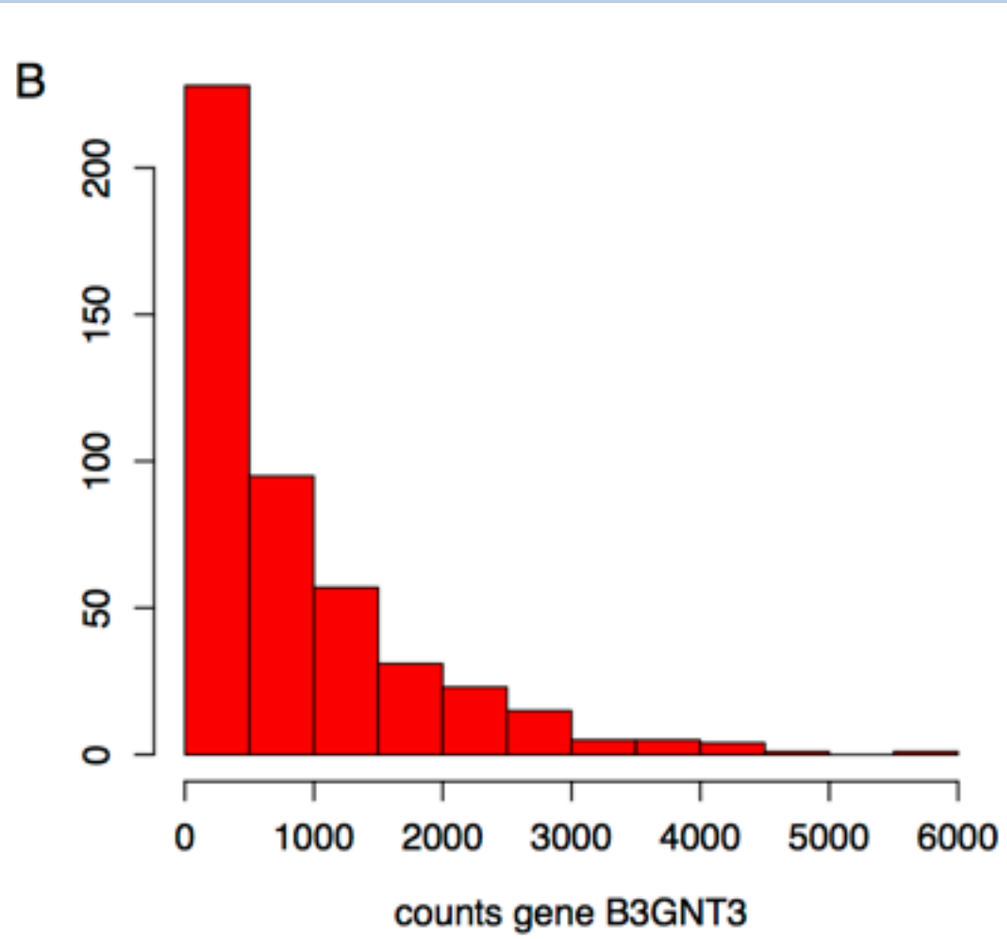
Prospective clinical cohort



RNA-Seq data

- 502 kidney renal clear cell carcinoma patients (from TCGA) with 160 deaths
- RNA-Seq measurements for 20,532 genes





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Risk prediction models

individual
risk

↗ $= \beta_1 \cdot 2 + \beta_2 \cdot 2 + \ldots + \beta_{797591} \cdot 0$

↗ $= \beta_1 \cdot 0 + \beta_2 \cdot 1 + \ldots + \beta_{797591} \cdot 1$

↗ $= \beta_1 \cdot 0 + \beta_2 \cdot 1 + \ldots + \beta_{797591} \cdot 0$

↗ $= \beta_1 \cdot 1 + \beta_2 \cdot 2 + \ldots + \beta_{797591} \cdot 2$

↗ $= \beta_1 \cdot 1 + \beta_2 \cdot 0 + \ldots + \beta_{797591} \cdot 0$

↗ $= \beta_1 \cdot 0 + \beta_2 \cdot 0 + \ldots + \beta_{797591} \cdot 2$

Risk prediction models

- Generalized linear models:
  - Observations (x_i, y_i), i=1,…,n, with response y_i and covariate vector $x_i = (x_{i1}, \ldots, x_{ip})'$
  - Model for an exponential family response with known response function g

$$E(y_i|x_i) = g(\eta_i) = g(x_i'\beta)$$

- Cox proportional hazards model
  - Observations (t_i, δ_i, x_i), i=1,…,n, with observed time t_i, and δ_i, taking value 1 if an event occurred and 0 in case of censoring
  - Model for the hazard, i.e., the instantaneous risk,

$$h(t|x_i) = h_0(t)\exp(x_i'\beta)$$

  with unspecified baseline hazard $h_0(t)$
- Estimation of parameter vector β by via (partial) log-likelihood $l(\beta)$

Componentwise likelihood-based boosting

- Cox model $h(t|x_i) = h_0(t)\exp(x_i'\beta)$ with partial log-likelihood $l(\beta)$
- Start with estimate $\hat{\beta}_0 = (0, \ldots, 0)'$ and offset $\hat{\eta}_{i,0} = 0$
- For k=1,…,M, boosting steps (selected by cross-validation),
  1. Determine best covariate j^*:
     - Candidate models with penalized likelihood estimates $\hat{\alpha}_{j,k}$
     - (Penalized) score statistic
  2. Perform updates

$$\hat{\beta}_{j,k} = \begin{cases} \hat{\beta}_{j,k-1} + \hat{\alpha}_{j,k} & \text{if } j = j^* \\ \hat{\beta}_{j,k-1} & \text{otherwise} \end{cases}$$

and

$$\hat{\eta}_{i,k} = x_i'\hat{\beta}_k$$

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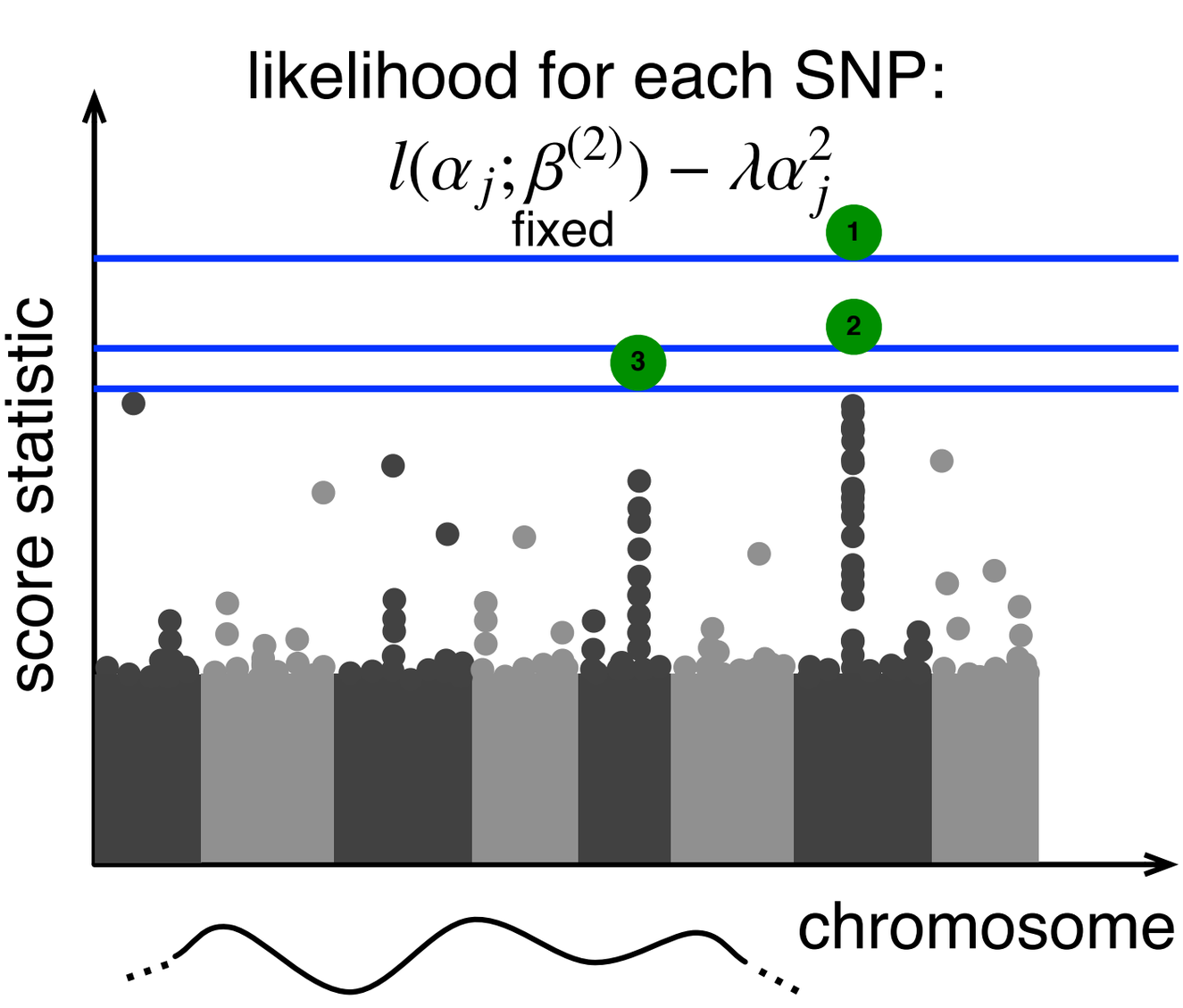
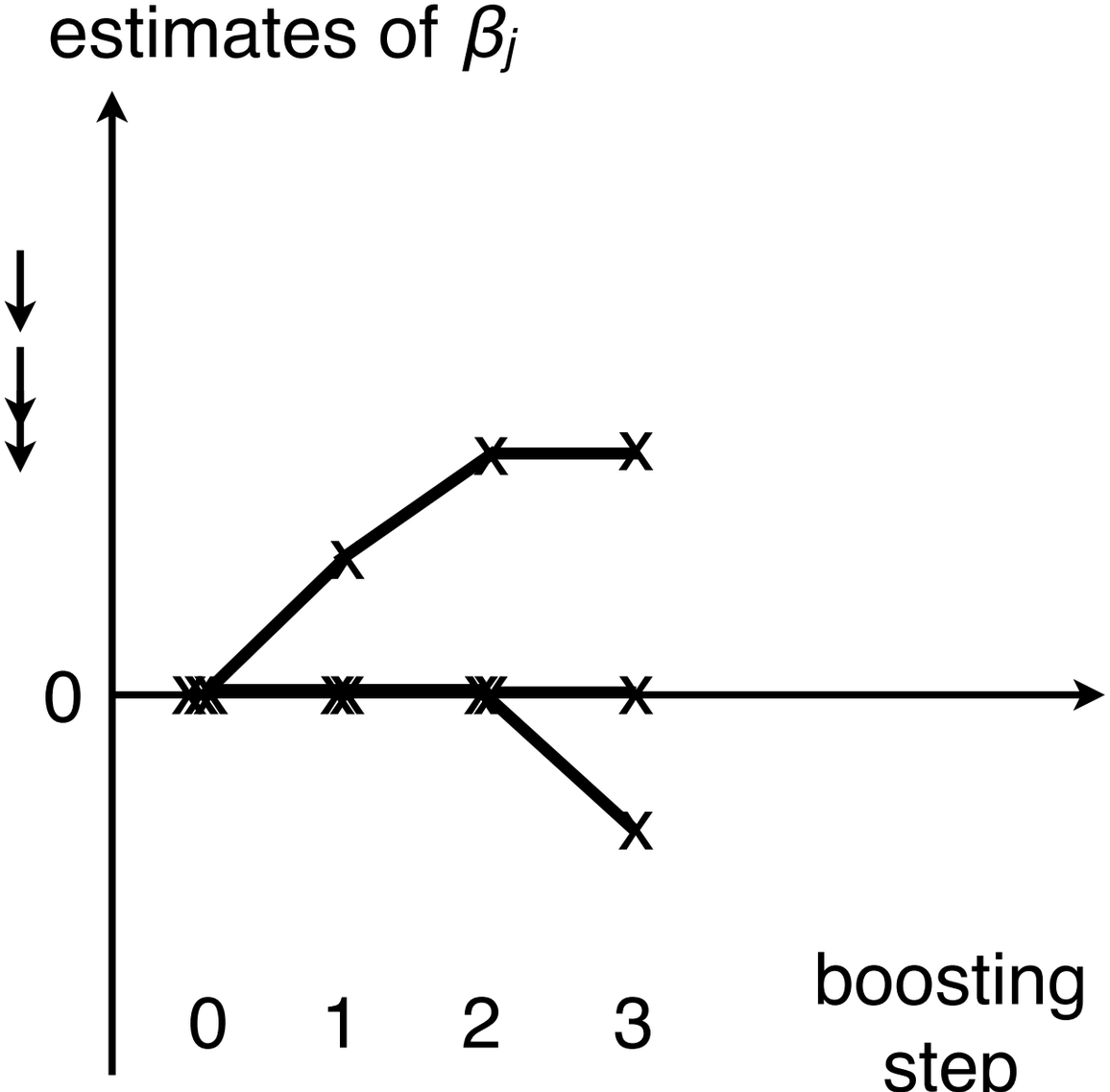
Componentwise likelihood-based boosting





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Adjusting for ...

established predictors

$$= \underbrace{\gamma_1 \cdot \text{age} + \gamma_2 \cdot \text{risk group} + \gamma_3 \cdot \text{treatment}}_{\textbf{un}\text{regularized}} + \underbrace{\beta_1 \cdot 2 + \beta_2 \cdot 2 + \ldots + \beta_{797591} \cdot 0}_{\text{regularized}}$$

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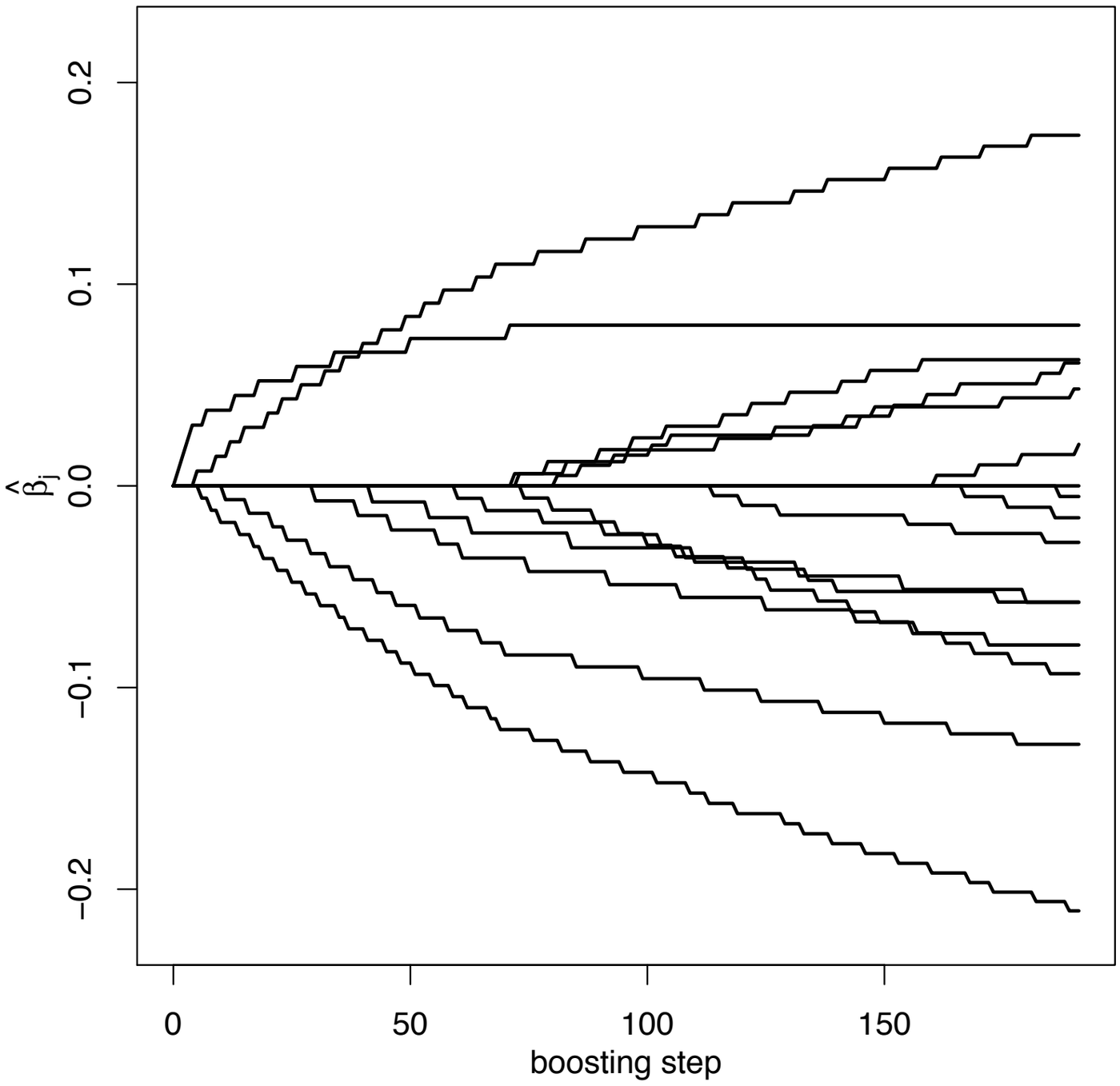
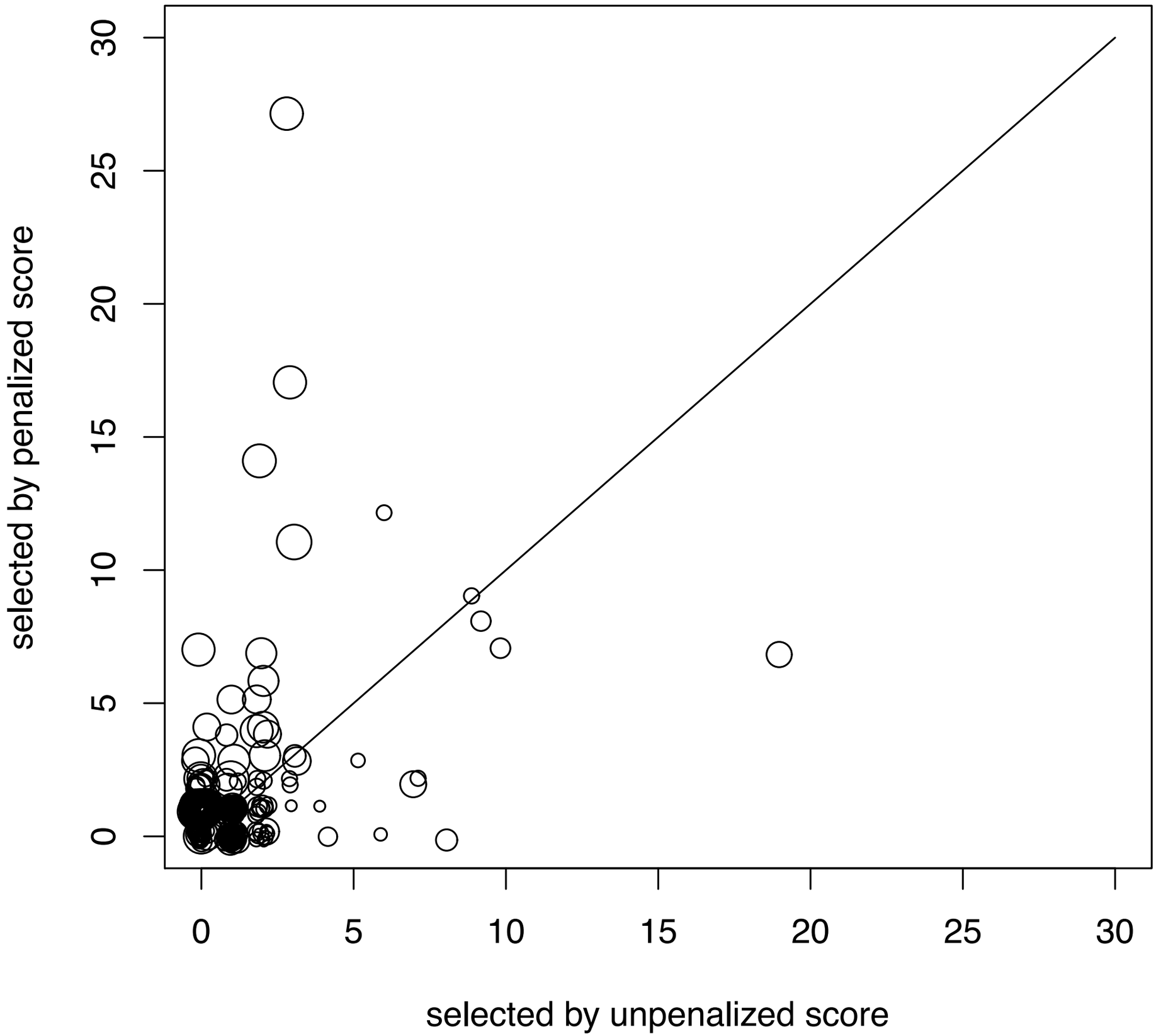
AML patients: coefficient paths



Choosing the score statistic ...

Penalized vs. Un-penalized

$$U_j^{(k)}(0)^2 / (I_j^{(k)}(0) + \lambda) \qquad U_j^{(k)}(0)^2 / I_j^{(k)}(0)$$


selected by penalized score
0
5
10
15
20
25
30
selected by unpenalized score

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Signature properties

	penalized	unpenalized
original signature	9	15
resampling Q50 / Q75	2 / 6	2 / 5
IF > 0 / > 10 / max	221 / 5 / 27	213 / 1 / 19

Bootstrap .632+ prediction error curves

- Apparent error

$$\overline{err}(t;\hat{r}) = \frac{1}{n}\sum_{i=1}^{n}(Y_i(t) - \hat{r}(t|x_i))^2 W(t;\hat{G})$$

  overestimates performance

- Bootstrap cross-validation estimate

$$\widehat{Err}_{B0}(t,\hat{r}) = \frac{1}{B}\sum_{b=1}^{B}\frac{1}{b_0}\sum_{i\notin\mathcal{J}_b}(Y_i(t) - \hat{r}_b(t|x_i))^2 W(t,\hat{G})$$

  underestimates performance

- Bootstrap .632+ estimate

$$\widehat{Err}_{.632+}(t,\hat{r}) = \left\{1-\omega(t)\right\}\overline{err}\,(t,\hat{r}) + \omega(t)\widehat{Err}_{B0}(t,\hat{r})$$

  adapts for overfitting potential

AML prediction error curves

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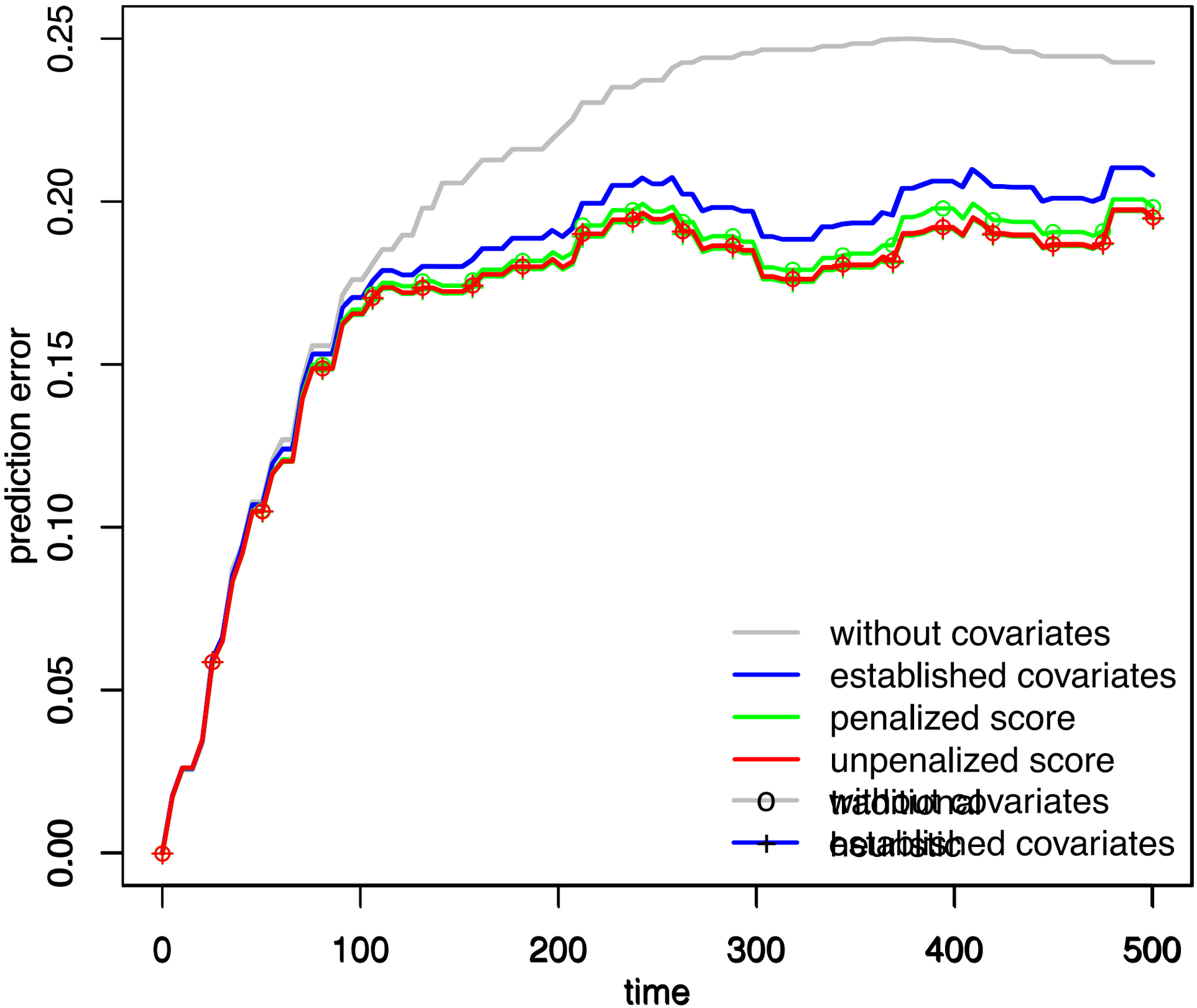

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Signature properties

SNP level:

	penalized	unpenalized
original signature	9	15
resampling Q50 / Q75	2 / 6	2 / 5
IF > 0 / > 10 / max	221 / 5 / 27	213 / 1 / 19

Gene level:

	penalized	unpenalized
original signature	17 (2/2)	19 (2/8)
resampling Q50 / Q75	4 / 9	3 / 7
IF > 0 / > 10 / max	249 / 11 / 43	252 / 4 / 29

SNPs: univariate test-based strategy

- One Cox proportional hazards model per SNP:
  Test statistic from comparing models “with vs. without SNP”
- Inclusion frequencies: select top SNPs (same number as boosting)
- Gene level summary:
  - Maximum value of test statistic per gene
  - Null distribution/p-value via permutation

	componentwise boosting		univariate test-based		
Gene/SNP	IF gene	IF SNP	IF gene	IF SNP	p-value
FSTL4	48		37		0.005
SNP_A-1925137		1		1	
SNP_A-1851005		1		0	
SNP_A-2065481		0		1	
SNP_A-1894802		0		1	
SNP_A-4217770		0		1	
SNP_A-4265215		37		13	
SNP_A-1983529		7		10	
SNP_A-1909042 u		0		8	
SNP_A-4254590		13		18	
SNP_A-2096046 u		1		12	
SNP_A-2310208 u		0		9	
SNP_A-1849858 u		1		20	
SNP_A-2084916		0		1	
SNP_A-2038408		0		3	
CYP24A1	8		3		0.065
SNP_A-2111160 b		8		3	
SNP_A-2041818 b		7		3	

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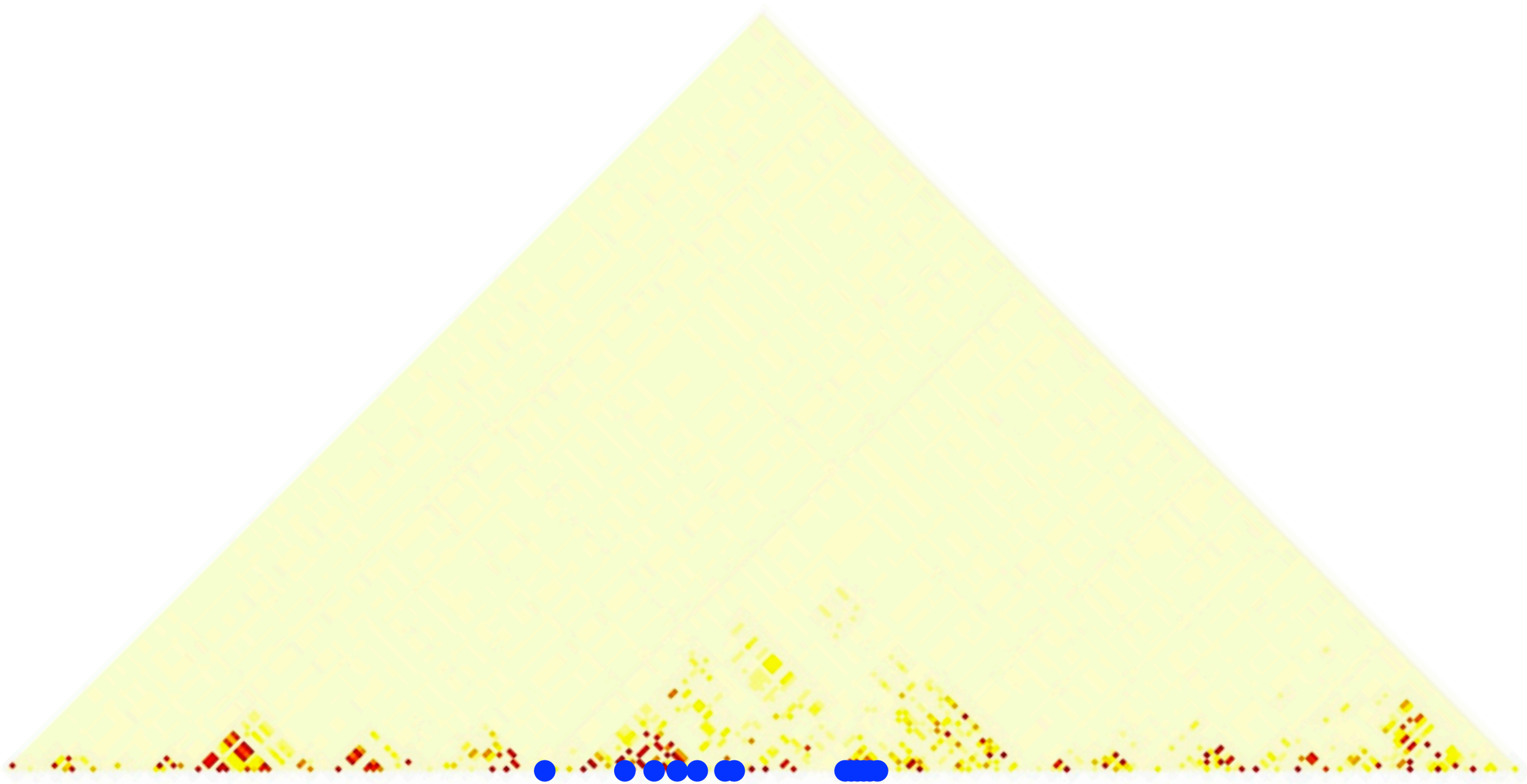
Linkage disequilibrium for gene *FSTL4*



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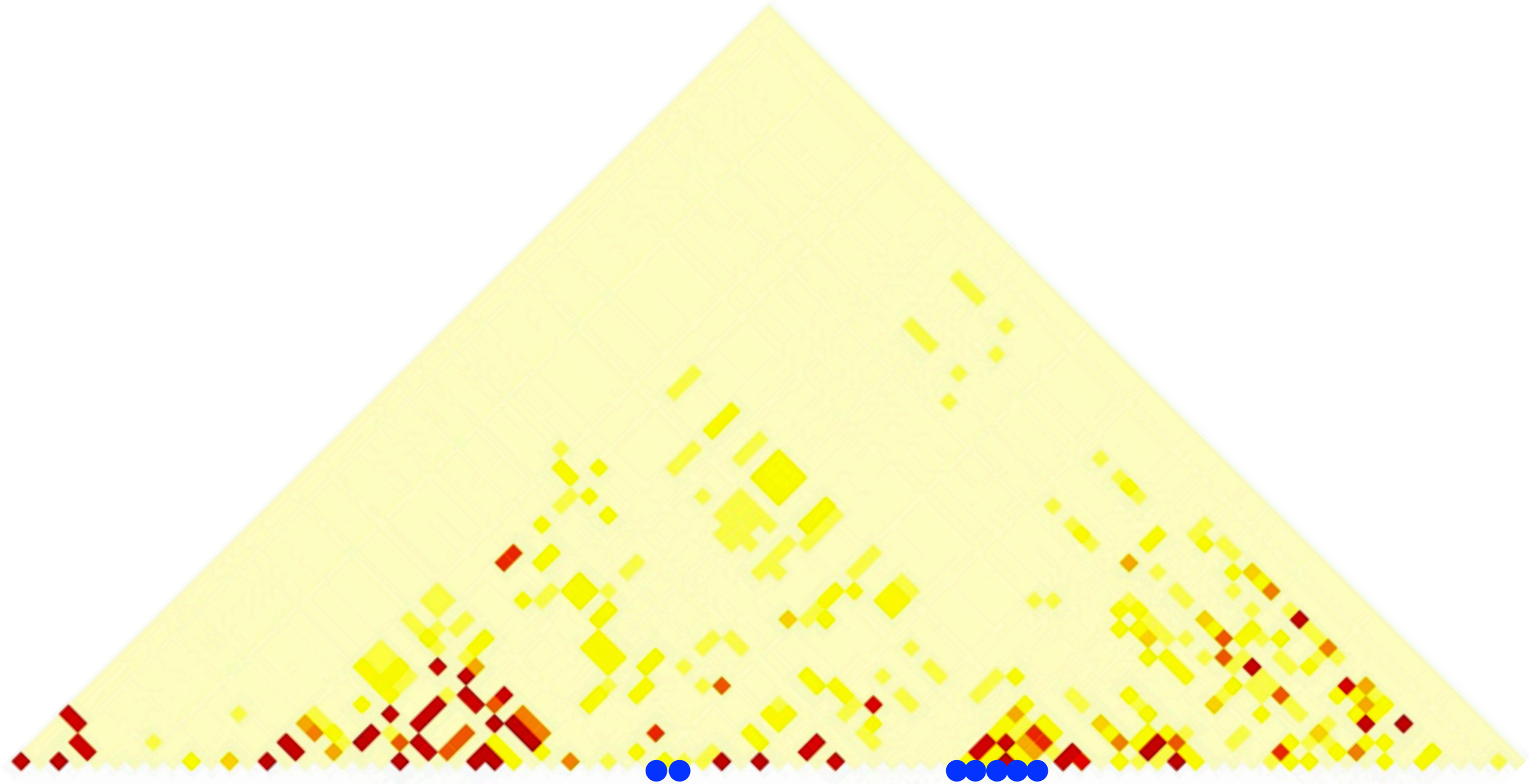
Linkage disequilibrium for gene *FSTL4*



Summing up

- SNP data in clinical cohort setting:
  - risk prediction models
  - (only) identify SNP signature
- RNA-Seq:
  - different way of measuring gene expression
  - distribution problematic compared to microarray data
- Componentwise boosting:
  - monotone coefficient paths, compared to lasso
  - different ways for dealing with variance, standardization
  - pre-transformation useful for RNA-Seq data
- Compared to univariate strategy:
  - find at least some SNPs
  - increased stability

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Thanks to ...

Methods

Isabella Zwiener
IMBEI Mainz, Germany

Martin Schumacher
IMBI Freiburg, Germany

Stefanie Hieke
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Axel Benner
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Modeling for the AML data

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