Predicting time-to-event outcomes based on high-dimensional multivariate longitudinal information

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Motivating example: Renal graft failure

- Patients with kidney transplant between 1983 and 2000 at U.H.Leuven
- Clinical interest:

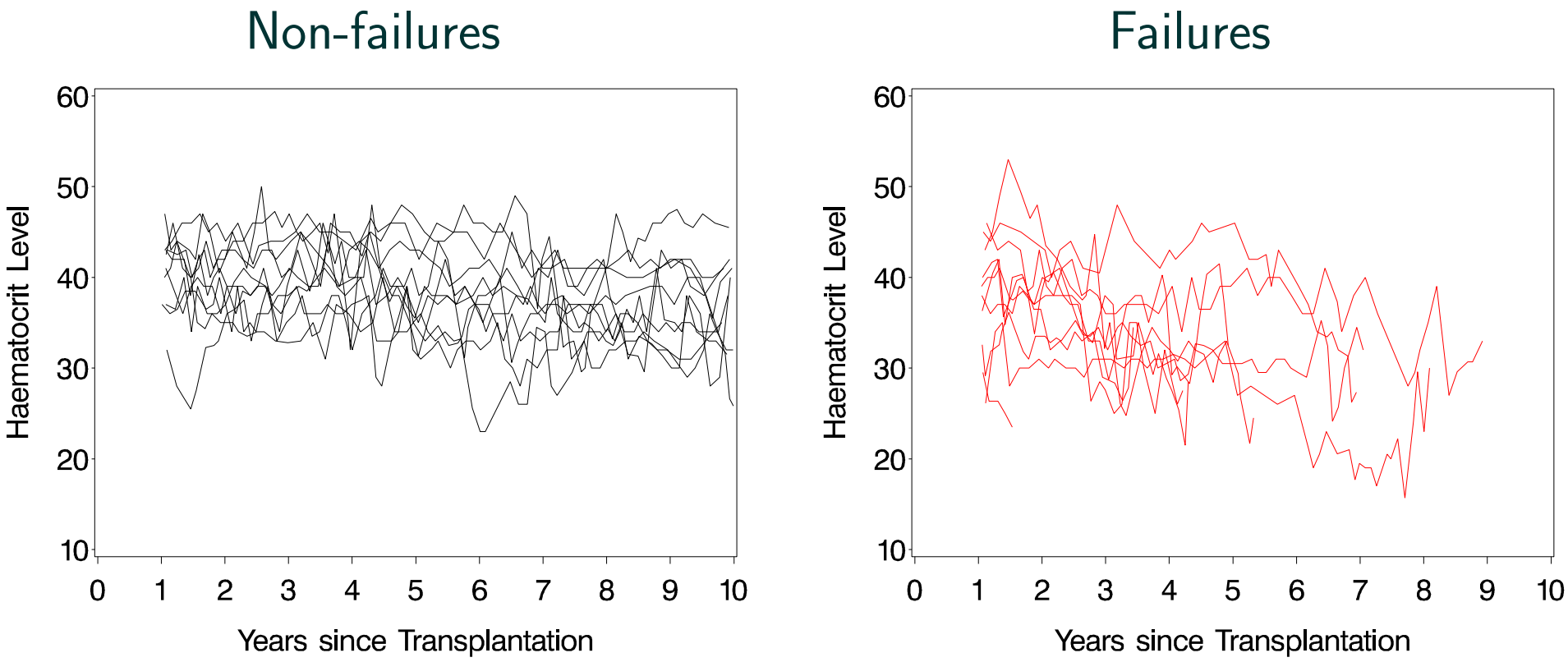
Continuous prediction of long-term success of graft ($>$ 10 years)

- Conditional on:
  - ▷ not losing graft during first year
  - ▷ not dying in the first 10 years for reasons not related to transplantation.

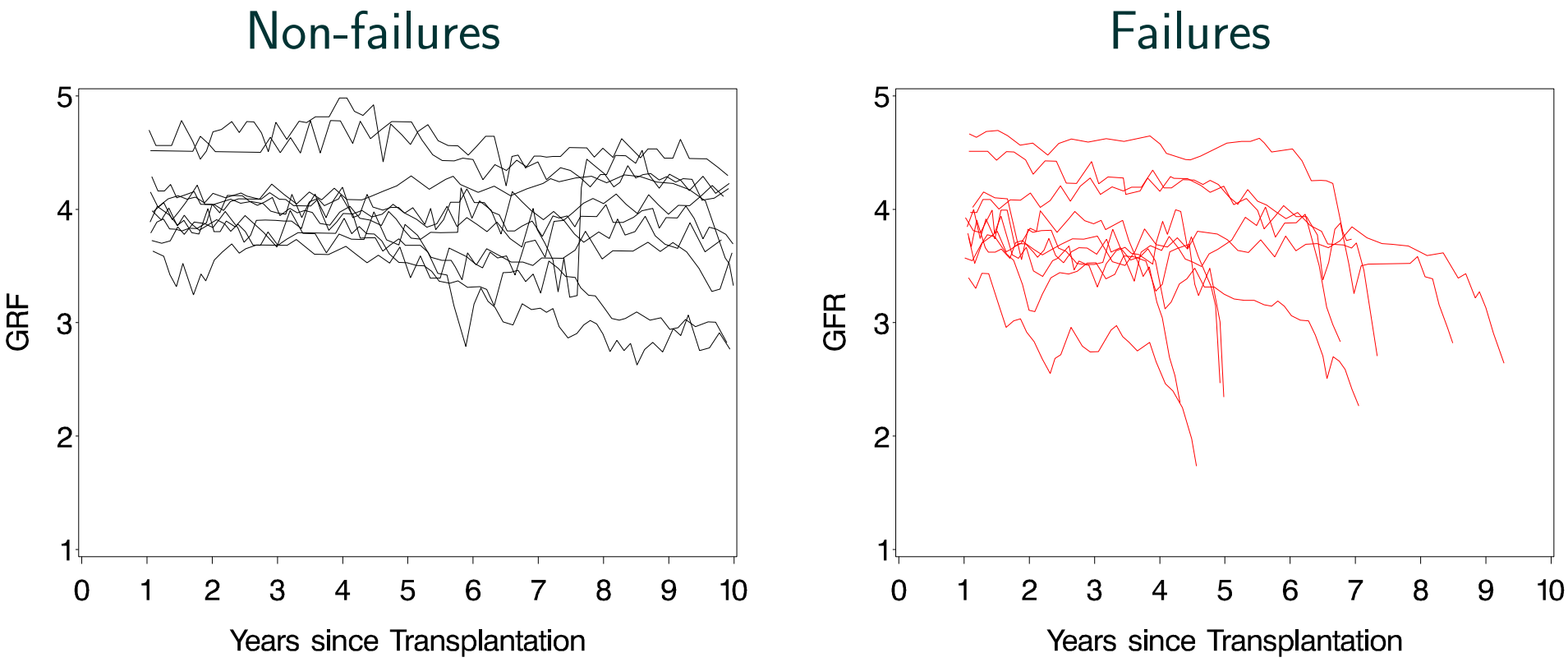
Motivating example (cont'd)

- Information: 949 patients, with 1-78 visits per patient
  - ▷ 341 patients with functioning graft after 10 years
  - ▷ 91 patients with a graft failure before 10 years
  - ▷ 517 patients with functioning graft, but FU $<$ 10 yrs
- Prediction based on longitudinal measurements of:
  - ▷ Haematocrit Level
  - ▷ Filtration Rate
  - ▷ Proteinuria
  - ▷ Blood Pressure

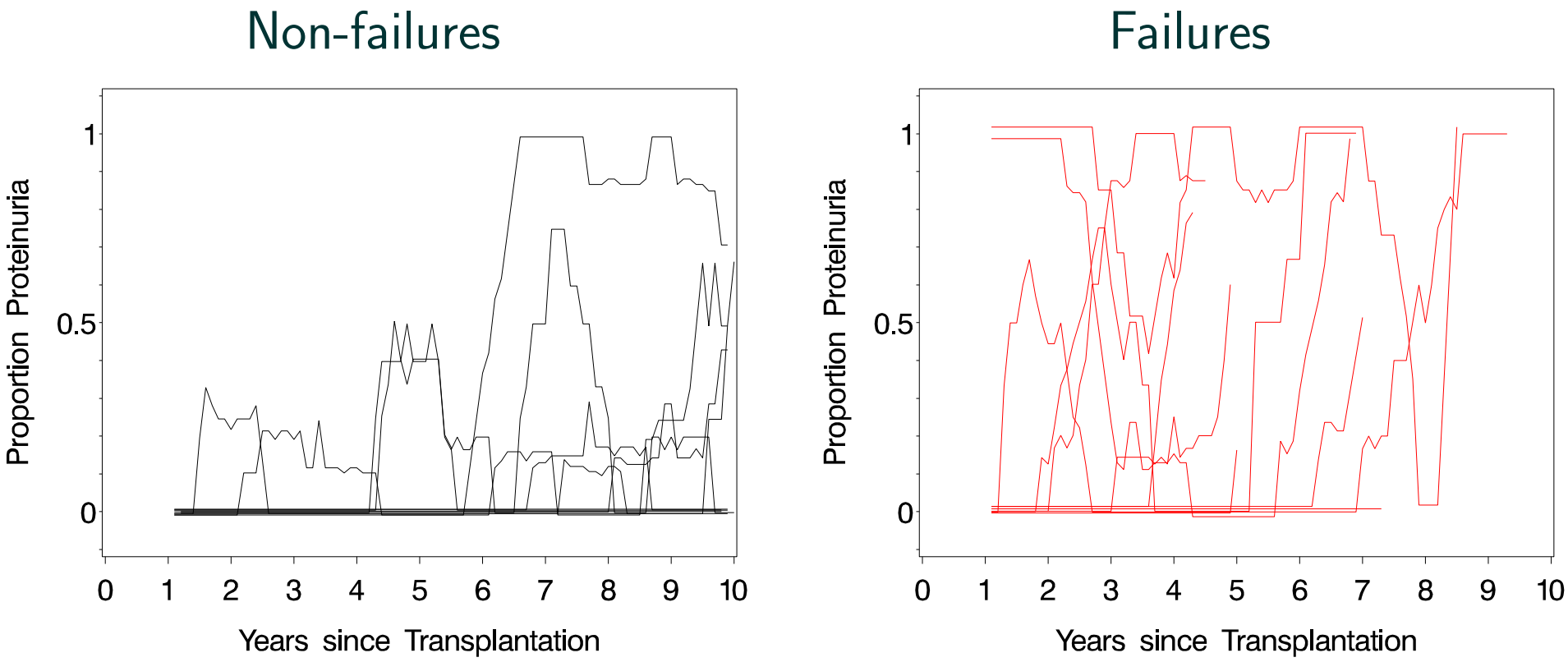
Haematocrit level



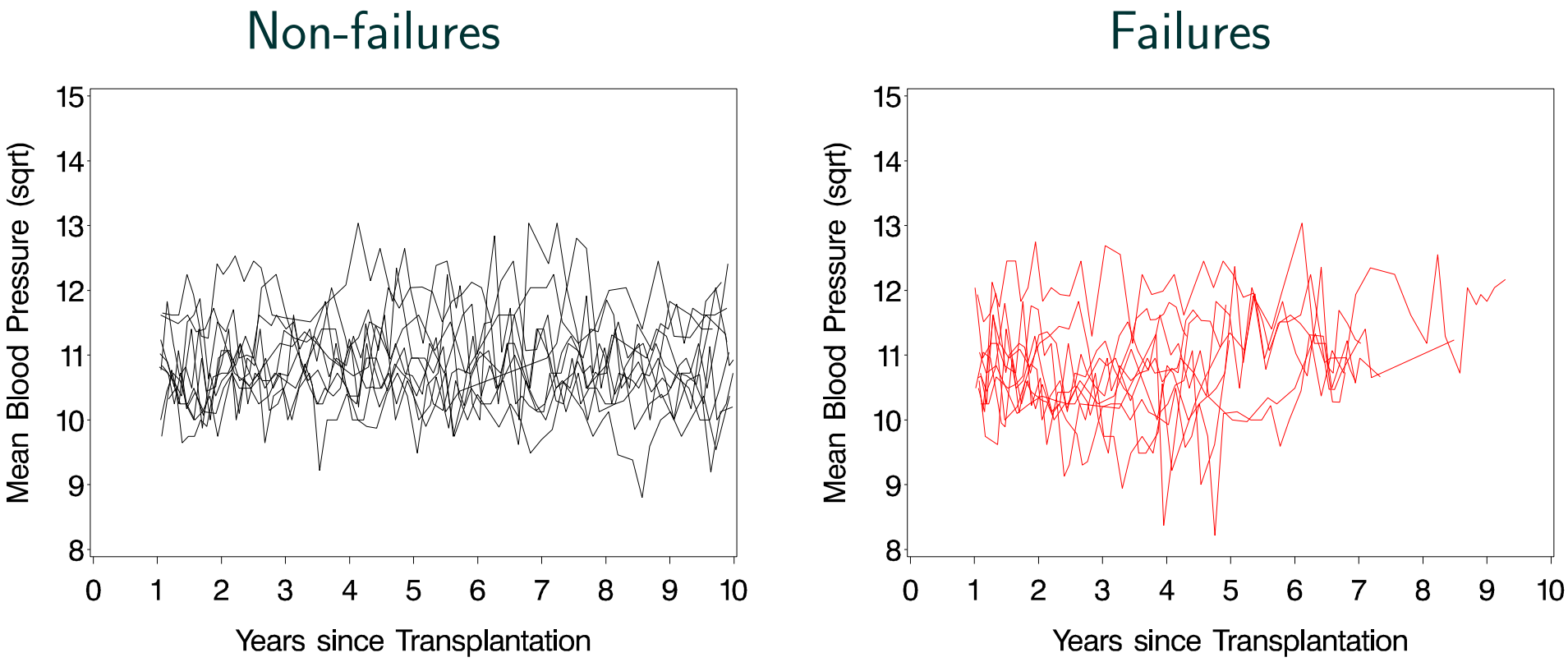
Glomerular filtration rate (GFR)



Presence of proteinuria



Mean blood pressure



Aim of the analysis

$$H_i(t) = P_i(t \leq F_i \leq 120 \mid \boldsymbol{y}_i^{\leq t}), \quad \forall t$$

Specification of conditional distribution for $(F_i \mid \boldsymbol{Y}_i^{\leq t})$ problematic due to:

- ▷ Unbalanced nature of the longitudinal data
- ▷ The different outcome types in $\boldsymbol{Y}_i$
- ▷ The running time t

A pattern-mixture approach

$$f(F_i, \boldsymbol{Y}_i) = f(\boldsymbol{Y}_i | F_i) f(F_i)$$

$$\Downarrow$$

$$f(F_i, \boldsymbol{Y}_i^{\leq t}) = f(\boldsymbol{Y}_i^{\leq t} | F_i) f(F_i)$$

$$\Downarrow + \text{Bayes rule}$$

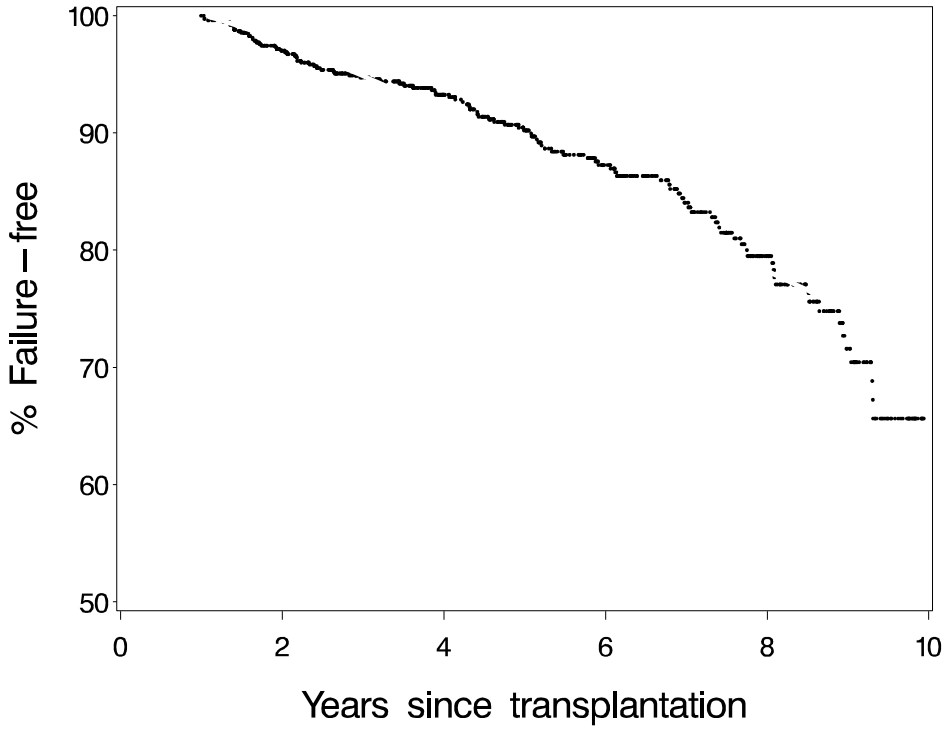
$$H_i(t) = P_i(t \leq F_i \leq 120 \mid \boldsymbol{y}_i^{\leq t})$$

$$= \frac{f_i(\boldsymbol{y}_i^{\leq t} \mid t \leq F_i \leq 120) P(F_i \leq 120 | F_i \geq t)}{f_i(\boldsymbol{y}_i^{\leq t} \mid t \leq F_i \leq 120) P(F_i \leq 120 | F_i \geq t) + f_i(\boldsymbol{y}_i^{\leq t} \mid F_i > 120) P(F_i > 120 | F_i \geq t)}$$

Prior probabilities

$$H_i(t) = \frac{f_i(\boldsymbol{y}_i^{\leq t} | t \leq F_i \leq 120) P(F_i \leq 120 | F_i \geq t)}{f_i(\boldsymbol{y}_i^{\leq t} | t \leq F_i \leq 120) P(F_i \leq 120 | F_i \geq t) + f_i(\boldsymbol{y}_i^{\leq t} | F_i > 120) P(F_i > 120 | F_i \geq t)}$$

Time-specific prior probabilities from Kaplan-Meier estimate:



Models for longitudinal outcomes

$$H_i(t) = \frac{f_i(\boldsymbol{y}_i^{\leq t}|t \leq F_i \leq 120)P(F_i \leq 120|F_i \geq t)}{f_i(\boldsymbol{y}_i^{\leq t}|t \leq F_i \leq 120)P(F_i \leq 120|F_i \geq t) + f_i(\boldsymbol{y}_i^{\leq t}|F_i > 120)P(F_i > 120|F_i \geq t)}$$

- Mixed model for each outcome separately:

$$\boldsymbol{Y_{1i}}|\boldsymbol{b_{1i}} \sim G_{1i}(\boldsymbol{\psi}_1, \boldsymbol{b_{1i}}), \quad \ldots, \quad \boldsymbol{Y_{4i}}|\boldsymbol{b_{4i}} \sim G_{4i}(\boldsymbol{\psi}_4, \boldsymbol{b_{4i}})$$

- Linear, generalized linear, and non-linear mixed models possible

- Joint model through joint distribution for all random effects:

$$(\boldsymbol{b'_{1i}}, \ldots, \boldsymbol{b'_{4i}})' \sim N(\boldsymbol{0}, D)$$

- Advantage: Model building for each outcome separately

Description of non-failures

$$H_i(t) = \frac{f_i(\boldsymbol{y}_i^{\leq t}|t \leq F_i \leq 120)P(F_i \leq 120|F_i \geq t)}{f_i(\boldsymbol{y}_i^{\leq t}|t \leq F_i \leq 120)P(F_i \leq 120|F_i \geq t) + f_i(\boldsymbol{y}_i^{\leq t}|F_i > 120)P(F_i > 120|F_i \geq t)}$$

- Outcomes measured during first 10 yrs.
- If failure, then only after 10 yrs.
- Assumption: Models do not depend on F_i

Mixed models for non-failures

- Haematocrit:

$$Y_{1i}(t) = \beta_{01} + b_{01i} + (\beta_{11} + b_{11i})t + \varepsilon_{1i}(t)$$

- GFR:

$$Y_{2i}(t) = \beta_{02} + b_{02i} + (\beta_{12} + b_{12i})t + \varepsilon_{2i}(t)$$

- Proteinuria:

$$\text{logit}\{P(Y_{3i}(t))\} = \beta_{03} + b_{03i} + \beta_{13}t$$

- Mean Blood Pressure:

$$Y_{4i}(t) = \beta_{04} + b_{04i} + (\beta_{14} + b_{14i})t + \varepsilon_{4i}(t)$$

Description of failures

$$H_i(t) = \frac{f_i(\boldsymbol{y}_i^{\leq t} | t \leq F_i \leq 120) P(F_i \leq 120 | F_i \geq t)}{f_i(\boldsymbol{y}_i^{\leq t} | t \leq F_i \leq 120) P(F_i \leq 120 | F_i \geq t) + f_i(\boldsymbol{y}_i^{\leq t} | F_i > 120) P(F_i > 120 | F_i \geq t)}$$

- Outcomes measured until moment of failure

- Implication: Models depend on F_i:

$$f_i(\boldsymbol{y}_i^{\leq t} \mid t \leq F_i \leq 120)$$
$$= \sum_{k=t}^{119} f_i(\boldsymbol{y}_i^{\leq t} \mid k \leq F_i \leq k+1) P(k \leq F_i \leq k+1) / P(t \leq F_i \leq 120)$$
$$\approx \sum_{k=t}^{119} f_i(\boldsymbol{y}_i^{\leq t} \mid F_i = k + \frac{1}{2}) P(k \leq F_i \leq k+1) / P(t \leq F_i \leq 120)$$

Mixed models for failures

- Haematocrit:

$$Y_{1i}(t) = \beta_{01} + \gamma_{01}F_i + b_{01i} + (\beta_{11} + \gamma_{11}F_i + b_{11i})t + \varepsilon_{1i}(t)$$

- GFR:

$$Y_{2i}(t) = \begin{cases} \phi_0 + b_{02i} + \beta_{12}[t - \phi_2] + \varepsilon_{2i}(t) & \text{if } t \leq \phi_2 \\ \phi_0 + b_{02i} + \beta_{32}[t - \phi_2] + \varepsilon_{2i}(t) & \text{if } t > \phi_2 \end{cases}$$

with $\phi_0 = \beta_{02} + \gamma_{02}F_i$ and $\phi_2 = \beta_{22} + \gamma_{22}F_i$

- Proteinuria:

$$\text{logit}\{P(Y_{3i}(t))\} = \beta_{03} + \gamma_{03}F_i + b_{03i} + (\beta_{13} + \gamma_{13}F_i)t$$

- Mean Blood Pressure:

$$Y_{4i}(t) = \beta_{04} + \gamma_{04}F_i + b_{04i} + (\beta_{14} + \gamma_{14}F_i + b_{14i})t + \varepsilon_{4i}(t)$$

Mixed models: Summary

	Non-Failures	Failures
Haematocrit:	LMM (2)	LMM (2)
GFR:	LMM (2)	NLMM (1)
Proteinuria:	GLMM (1)	GLMM (1)
Mean Blood Pressure:	LMM (2)	LMM (2)

$\Longrightarrow$ 2 mixed models with many random effects (7 & 6)

$\Longrightarrow$ computational difficulties

Joint mixed model: Pairwise approach

- Fit all 6 bivariate models using (RE)ML:

$$(\boldsymbol{Y}_1, \boldsymbol{Y}_2), (\boldsymbol{Y}_1, \boldsymbol{Y}_3), (\boldsymbol{Y}_1, \boldsymbol{Y}_4), (\boldsymbol{Y}_2, \boldsymbol{Y}_3), (\boldsymbol{Y}_2, \boldsymbol{Y}_4), (\boldsymbol{Y}_3, \boldsymbol{Y}_4)$$

- Equivalent to maximizing pseudo likelihood:

$$p\ell(\boldsymbol{\Theta}) = \ell(\boldsymbol{\Theta}_{1,2}|\boldsymbol{Y}_1, \boldsymbol{Y}_2) + \ell(\boldsymbol{\Theta}_{1,3}|\boldsymbol{Y}_1, \boldsymbol{Y}_3) + \ldots + \ell(\boldsymbol{\Theta}_{3,4}|\boldsymbol{Y}_3, \boldsymbol{Y}_4)$$

- Asymptotic properties (from pseudo likelihood theory):

$$\sqrt{N}(\widehat{\boldsymbol{\Theta}} - \boldsymbol{\Theta}) \sim MVN(\mathbf{0}, J^{-1}KJ^{-1})$$

  J and K consist of first and second-order derivatives of $p\ell$.

- Multiple estimates for same parameters are averaged

Fieuws & Verbeke, Biometrics (2006)

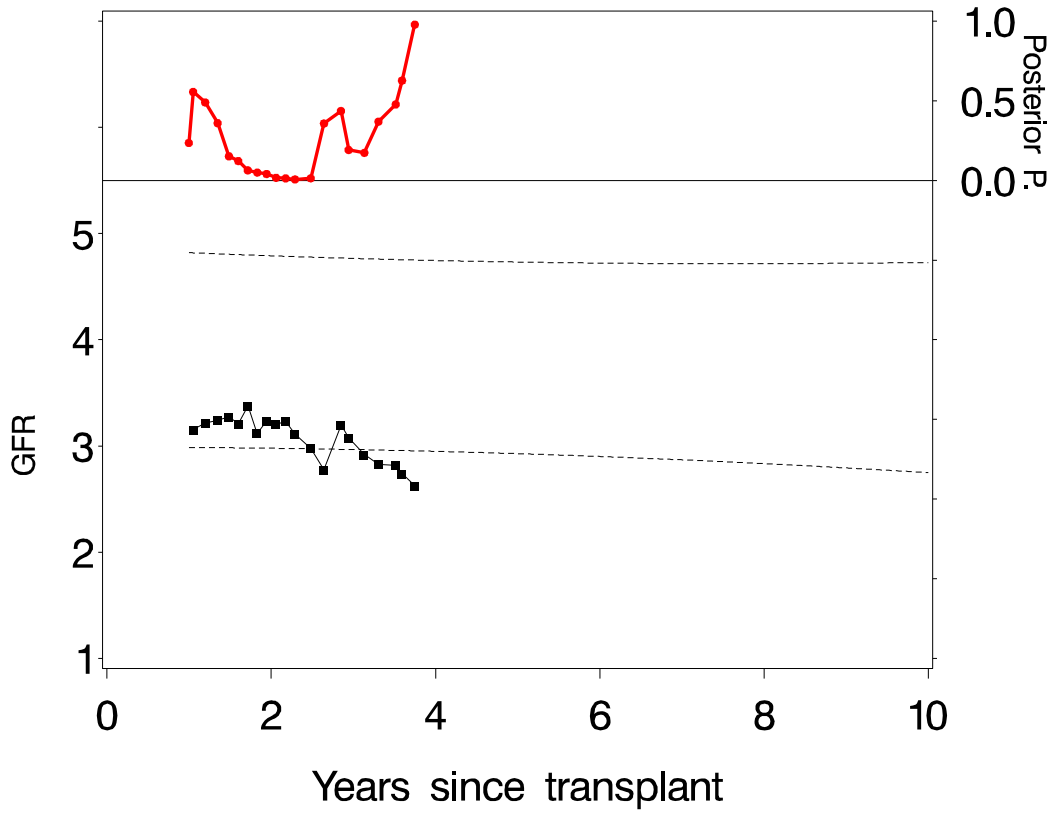
Association between markers ?

L.R. test for no association in each pairwise model:

	Non-failures			Failures		
Markers	Δ dev.	#	p	Δ dev.	#	p
1,2:	82.8	4	< 0.0001	18.9	2	< 0.0001
1,3:	18	2	0.0001	7.2	2	0.027
1,4:	6.4	4	0.17	2.6	4	0.63
2,3:	22.4	2	< 0.0001	0.3	1	0.58
2,4:	8.1	4	0.09	0.1	2	0.95
3,4:	7.4	2	0.025	6.1	2	0.047

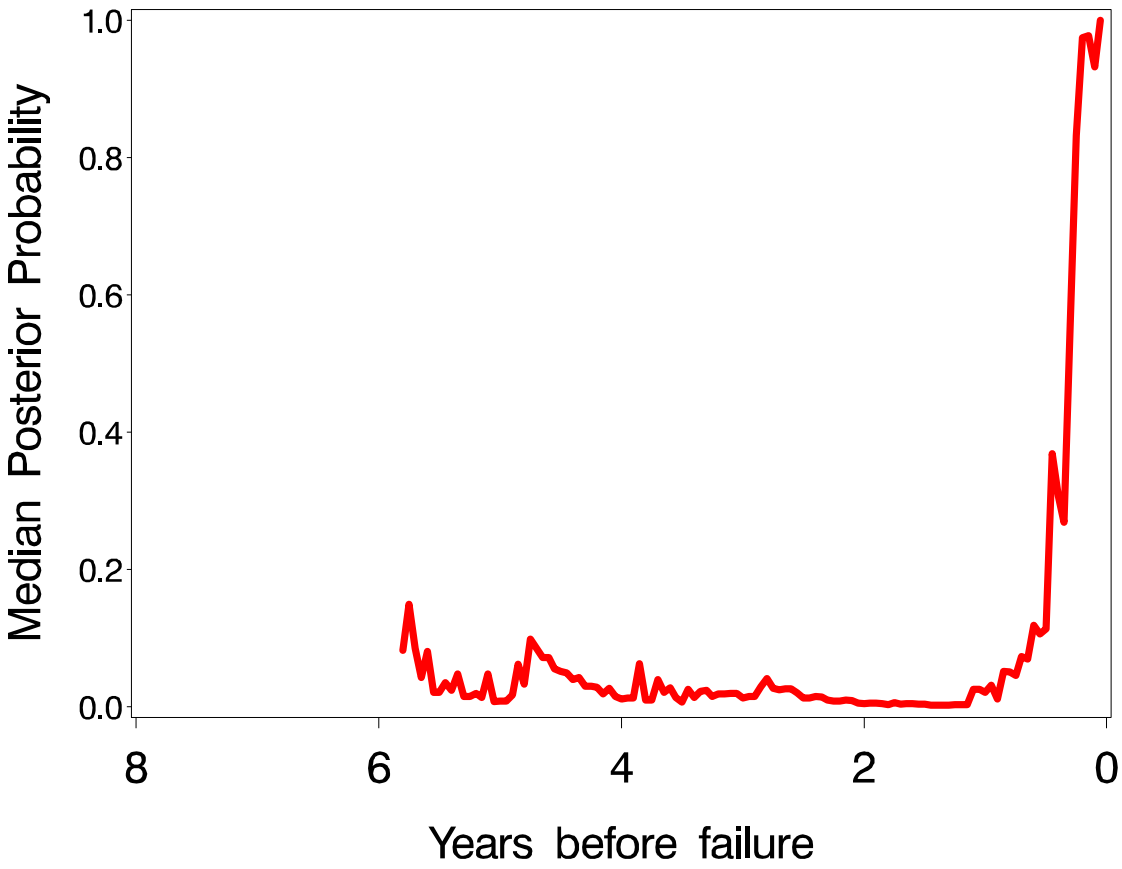
Posterior probabilities based on GFR only

- Training and validation dataset (50% of patients)
- Example for 1 failure from validation dataset:



Median posterior probability, GFR only

- All failures in validation dataset:



Discriminant analysis using 4 markers

Strategies:

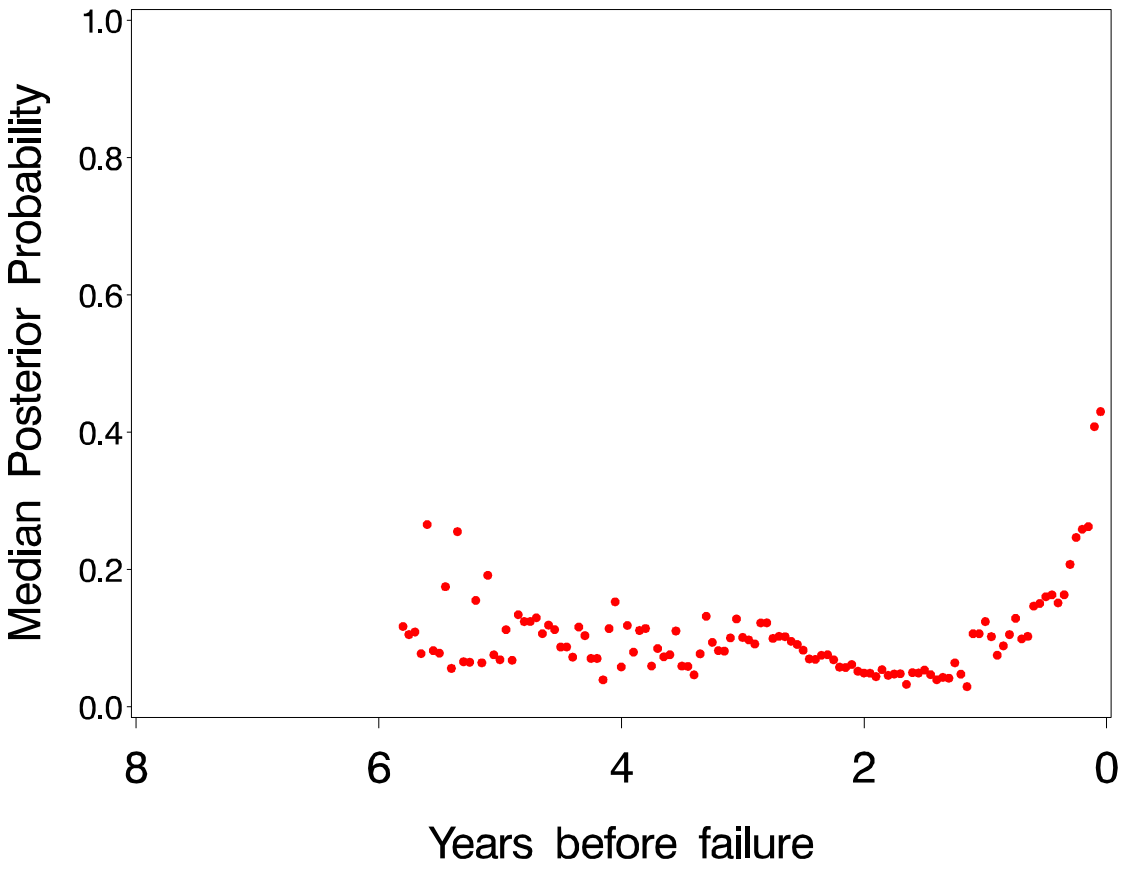
- Decision based on highest posterior probability
- Joint model assuming uncorrelated markers
- Joint model allowing markers to be correlated

Median posterior probability: Failures

- 46 patients in validation set who fail
- Median posterior probabilities to fail within the remaining period
- As a function of time: years before failure

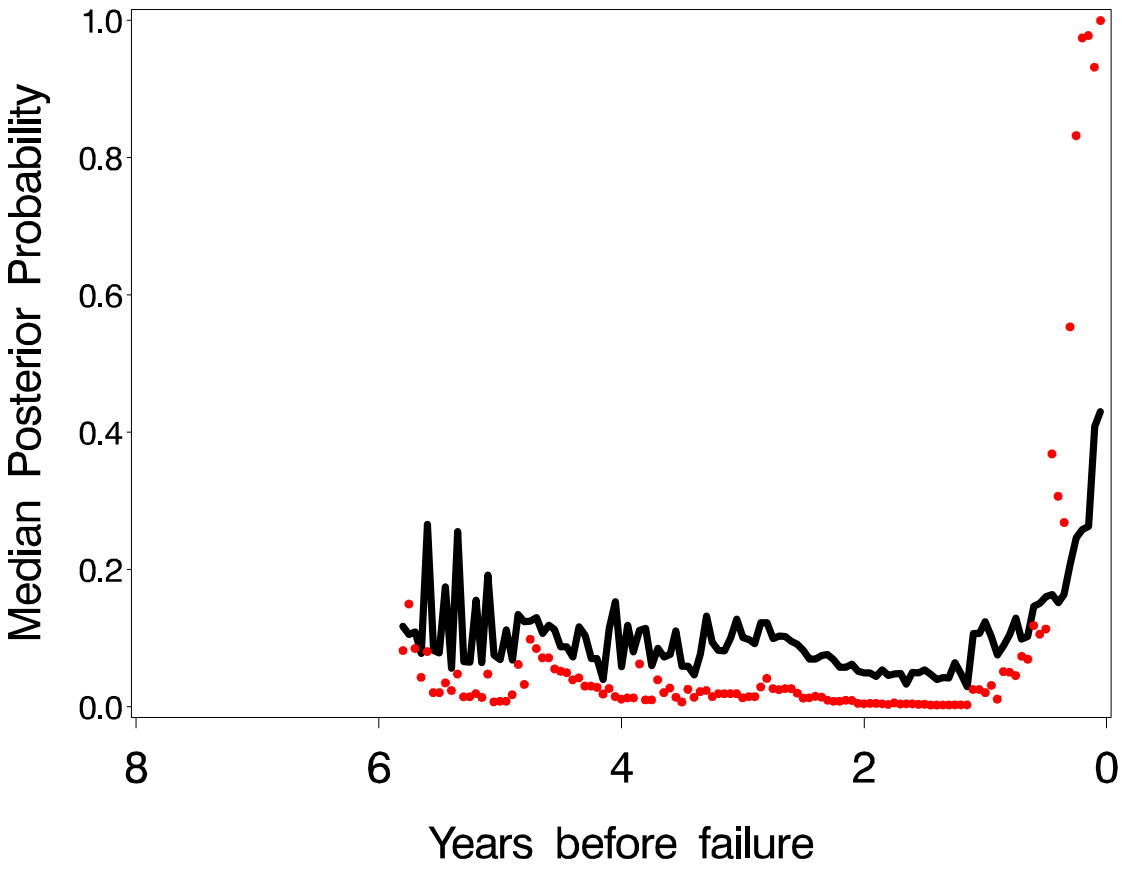
Median posterior probability: Failures

- Only Haematocrit:



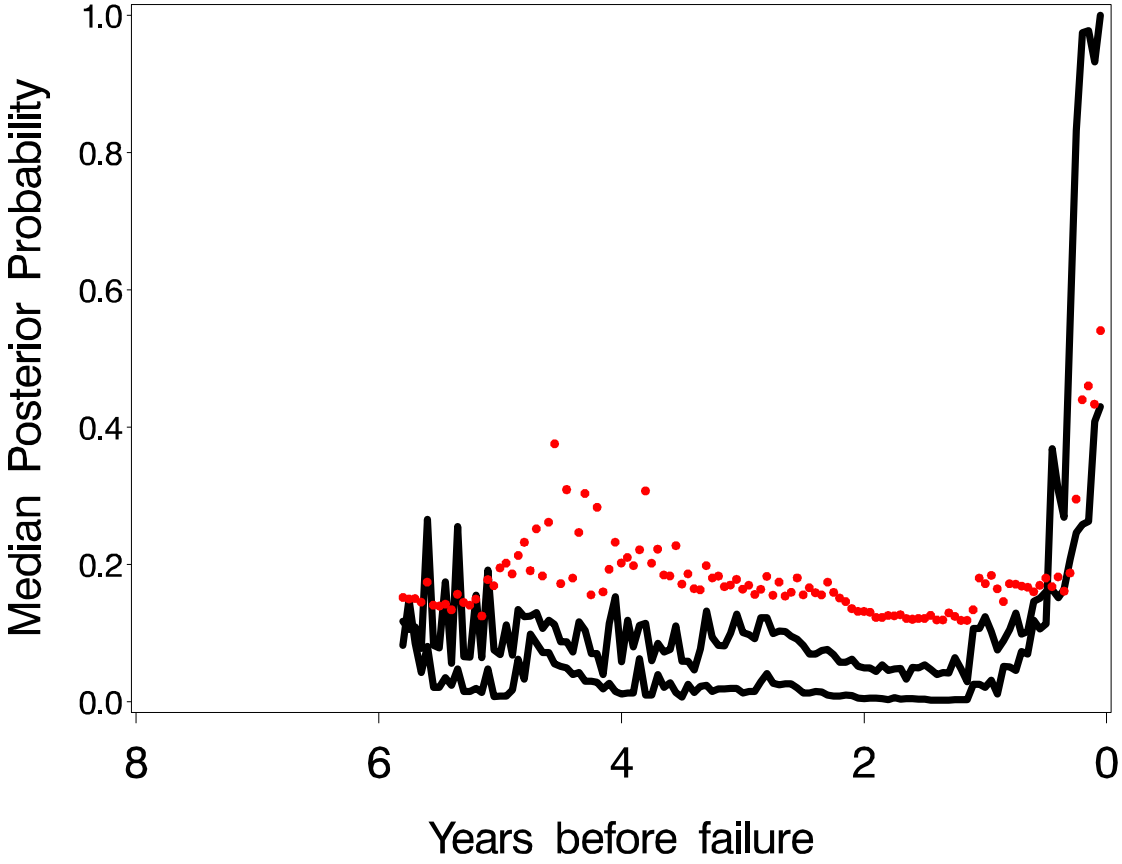
Median posterior probability: Failures

- Only GFR:



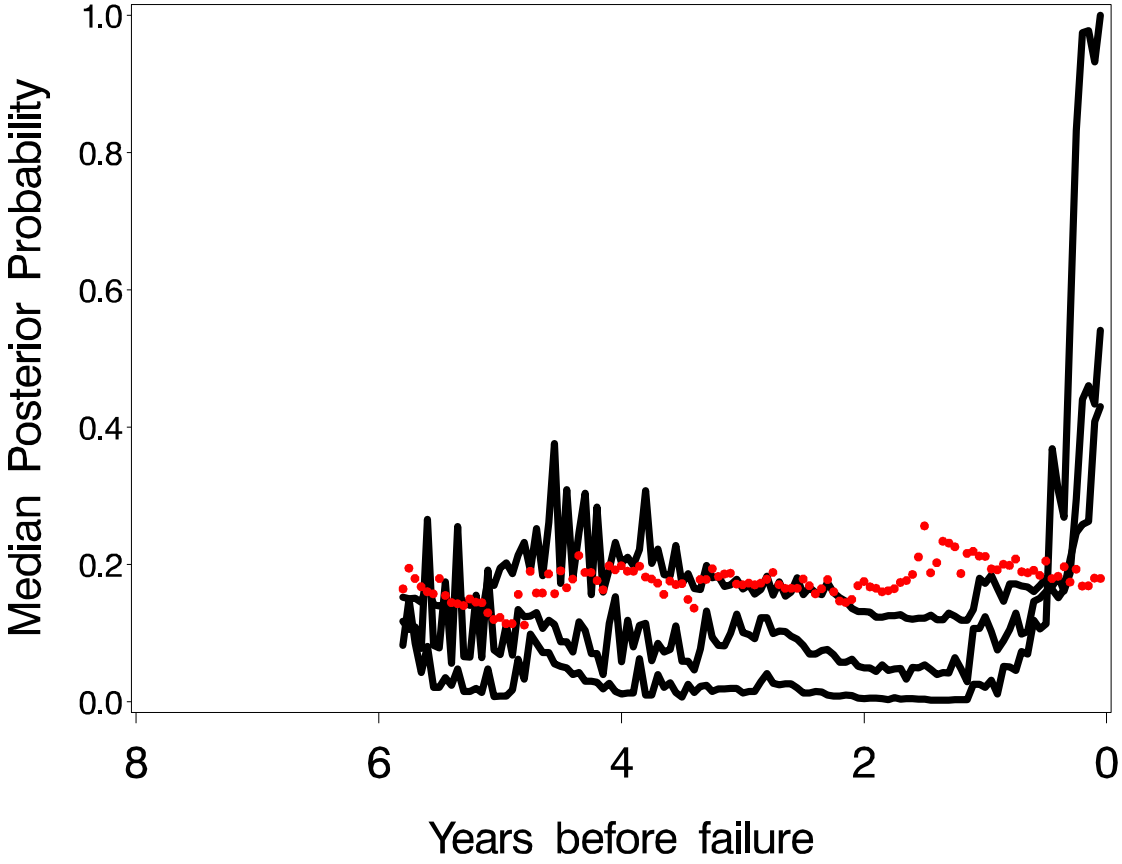
Median posterior probability: Failures

- Only Proteinuria:



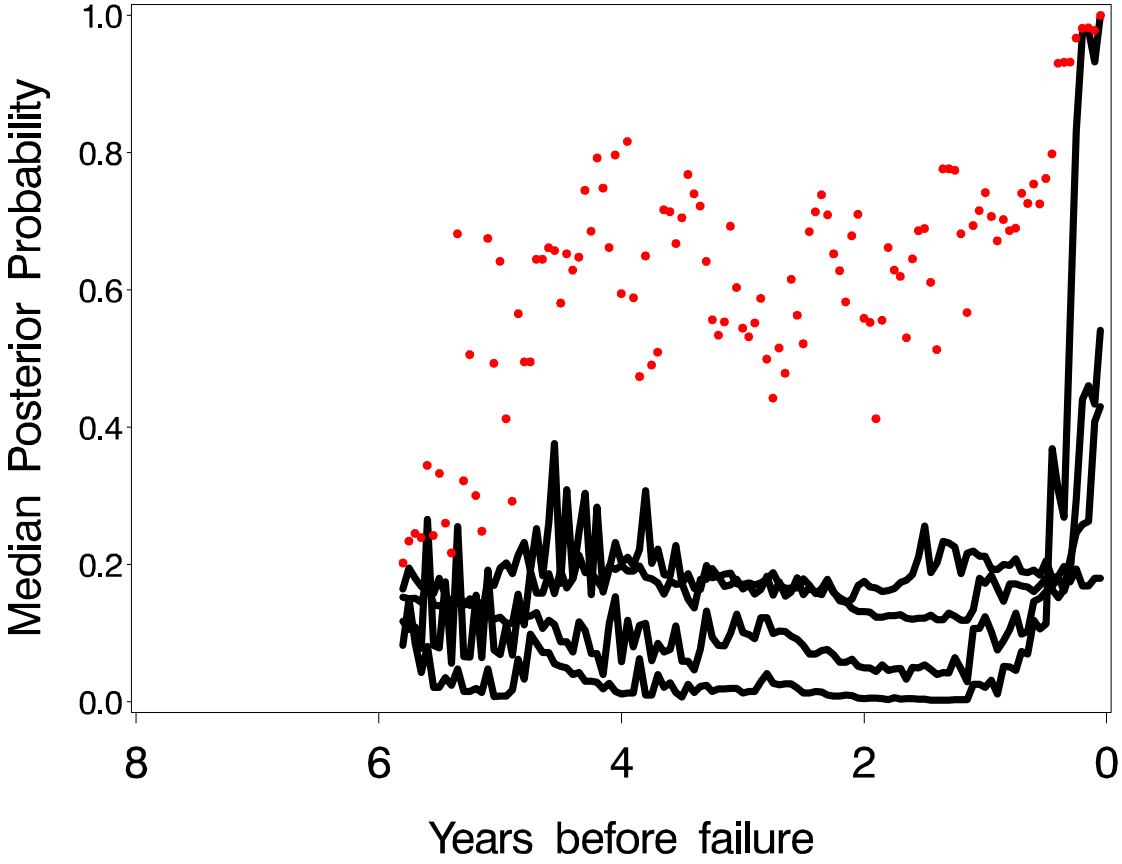
Median posterior probability: Failures

- Only Mean Blood Pressure:



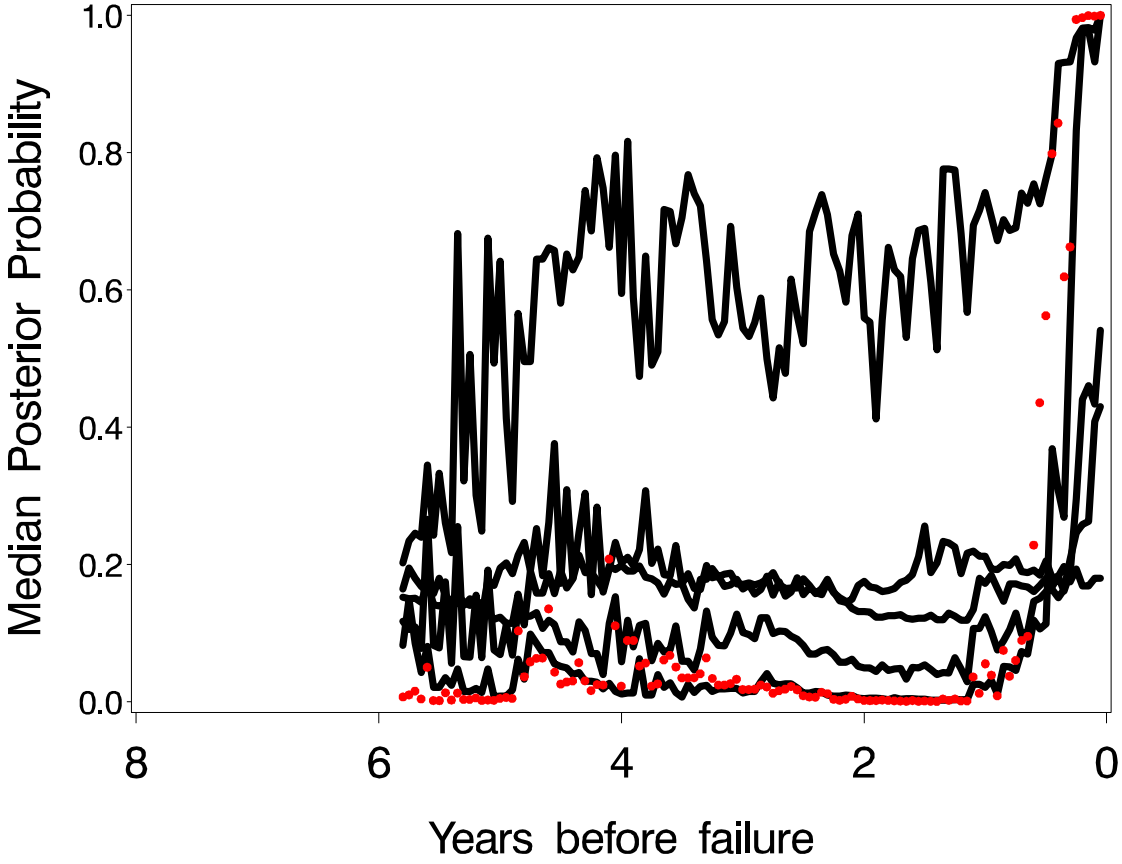
Median posterior probability: Failures

- Highest posterior probability over all four markers:



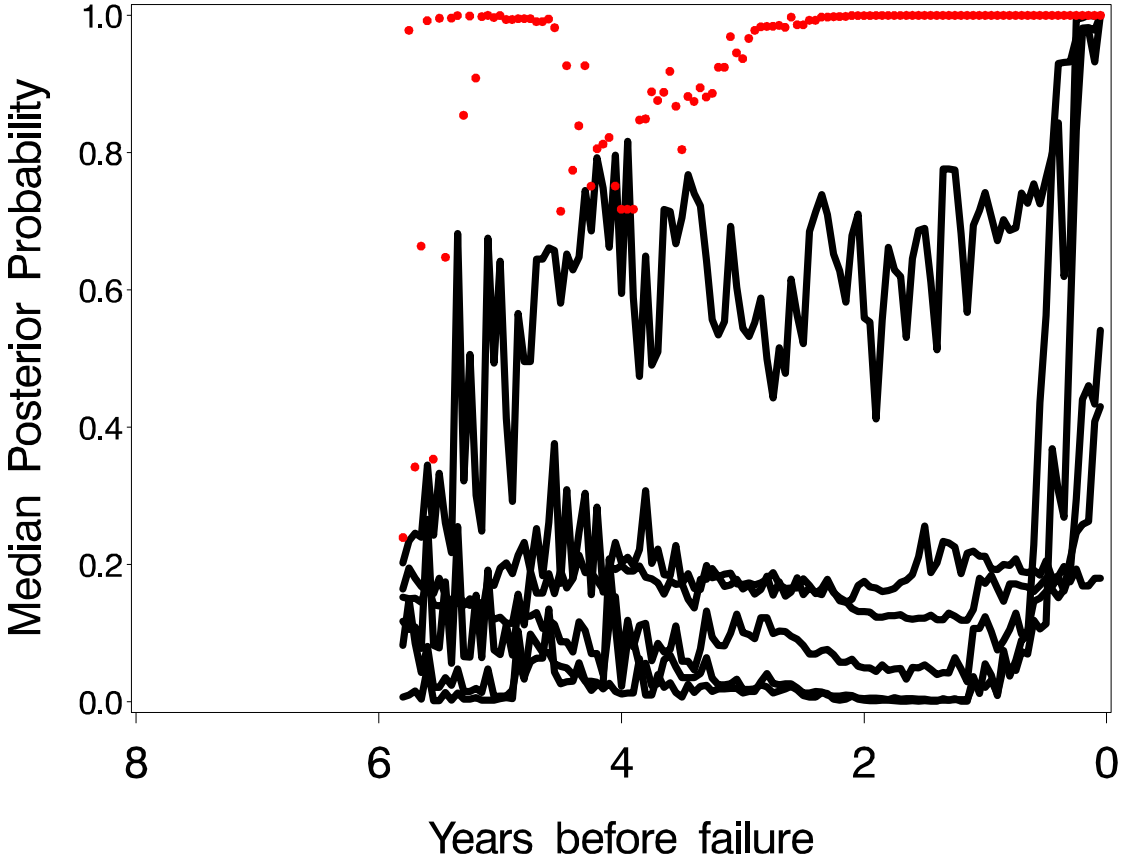
Median posterior probability: Failures

- All four markers, using joint model with uncorrelated markers:



Median posterior probability: Failures

- All four markers, using joint model with correlated markers:



Median posterior probability: Non-failures

- 171 patients in validation set who do not fail
- Median posterior probabilities to fail within the remaining period
- As a function of time: years since transplantation

Median posterior probability: Non-failures

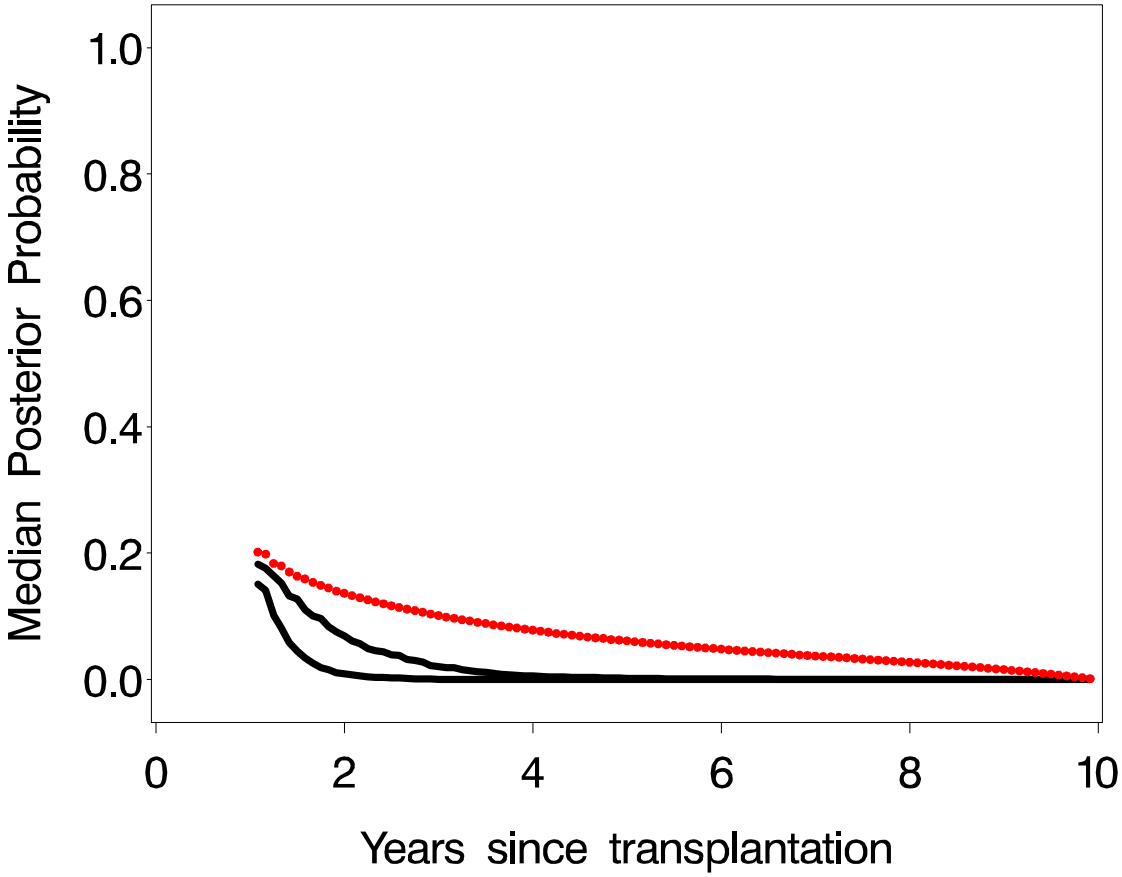
- Only Haematocrit:

Median posterior probability: Non-failures

- Only GFR:

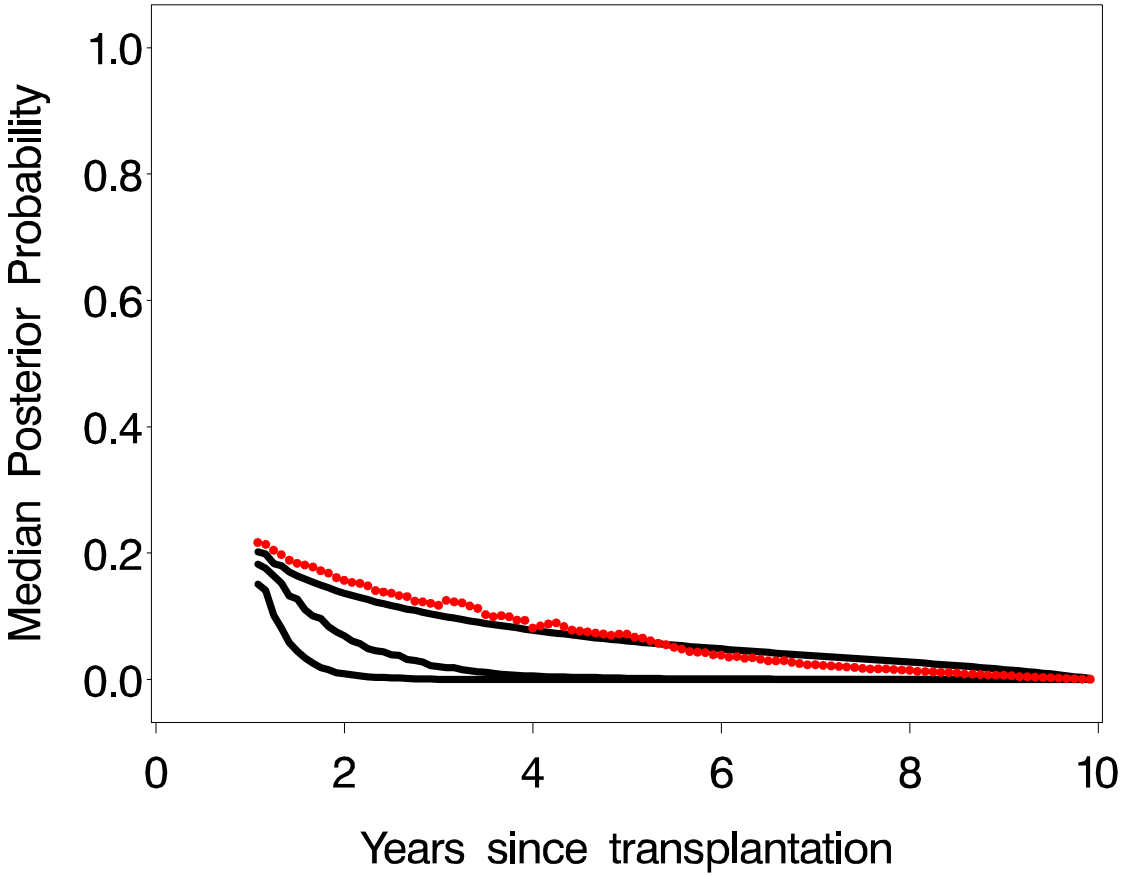
Median posterior probability: Non-failures

- Only Proteinuria:



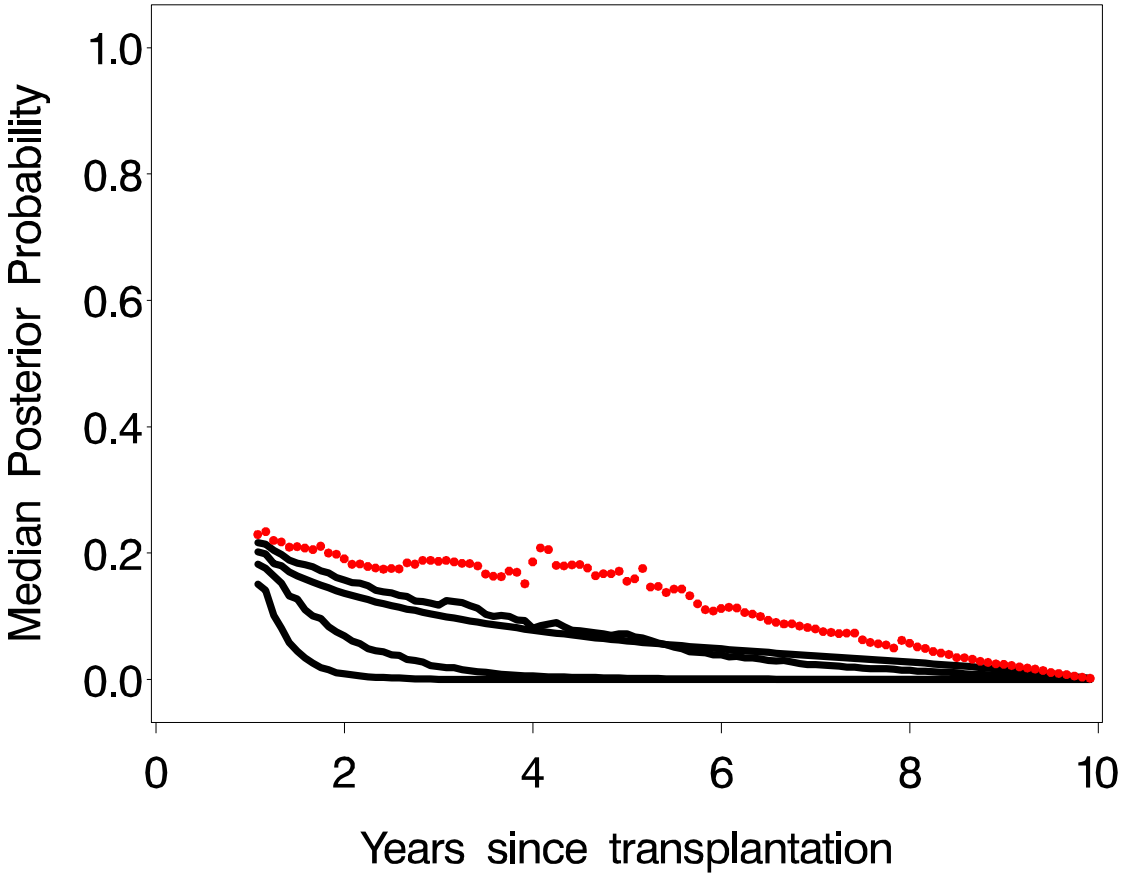
Median posterior probability: Non-failures

- Only Mean Blood Pressure:



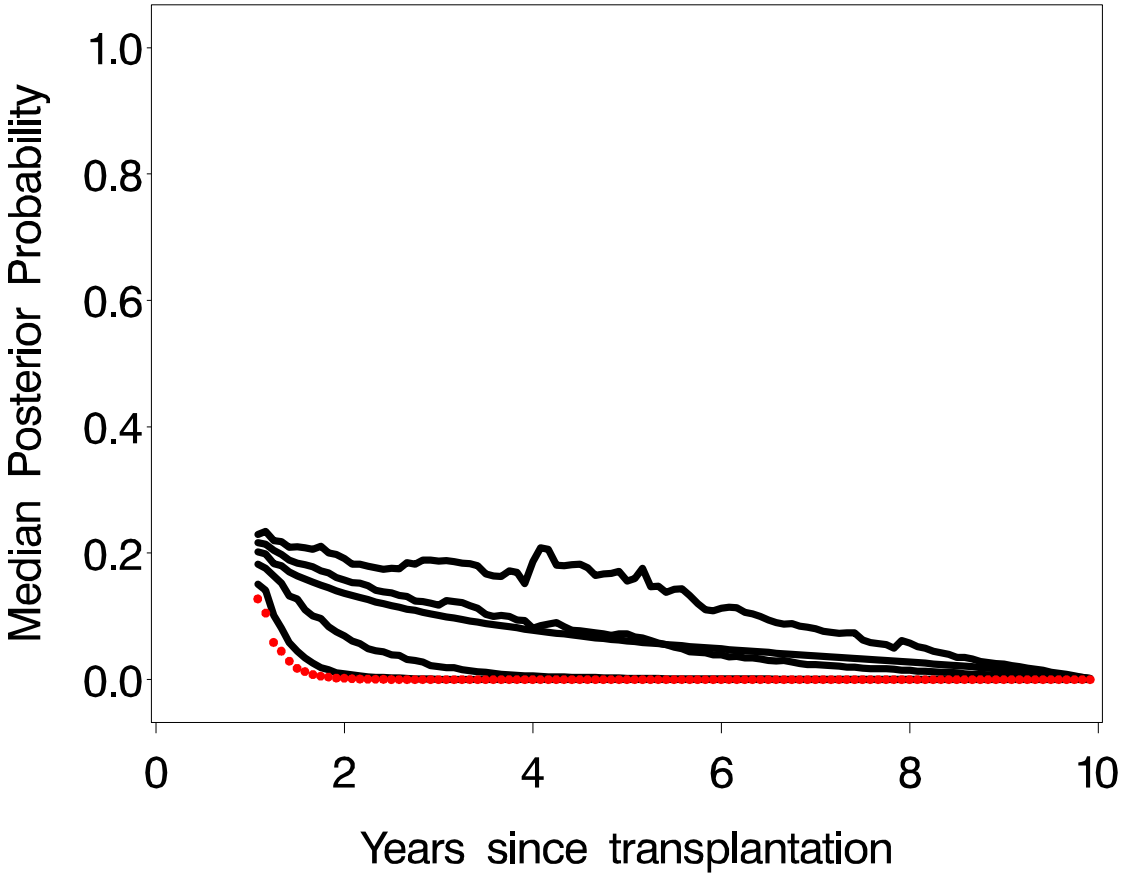
Median posterior probability: Non-failures

- Highest posterior probability over all four markers:



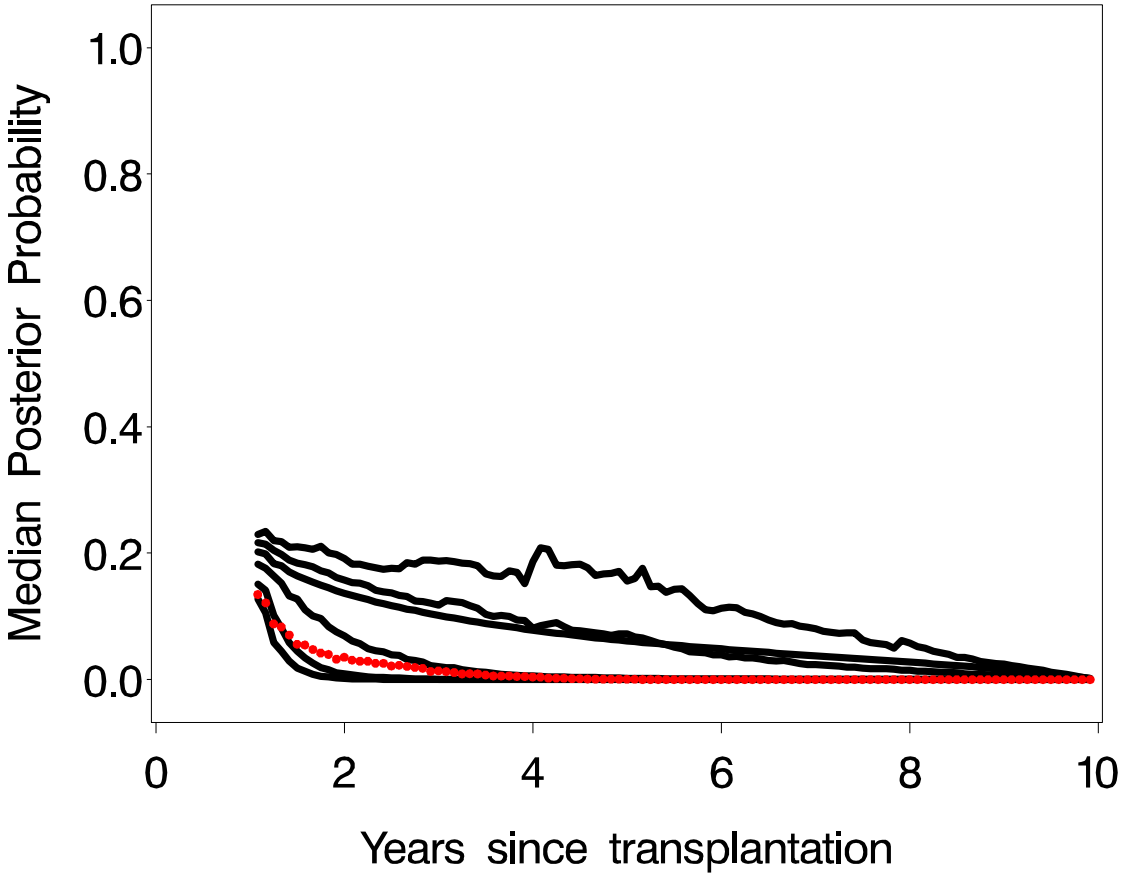
Median posterior probability: Non-failures

- All four markers, using joint model with uncorrelated markers:



Median posterior probability: Non-failures

- All four markers, using joint model with correlated markers:



Conclusions

- Discriminant analysis based on many outcomes, measured longitudinally, in an unbalanced design, is technically possible
- Allowing the longitudinal markers to be correlated considerably improves predictions
- A pattern-mixture approach allows for continuous updating of posterior probabilities
- Various mixed models can be combined and fitted using pairwise fitting approach

The End !