Personalized Biopsy Schedules using Joint Models

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Prostate Cancer (PC)

- PC is the 2nd most frequently diagnosed cancer in males worldwide
  - the most frequent in economically developed countries

- Many countries run population screening programs using PSA blood tests
  - to identify men who have developed the disease
  - or men who have high risk of developing it

- However, these programs have resulted to high rates of over-diagnosis and overtreatment
  - standard treatments have serious side-effects

Prostate Cancer Active Surveillance

- To avoid over-treatment, men with low grade prostate cancer are advised active surveillance

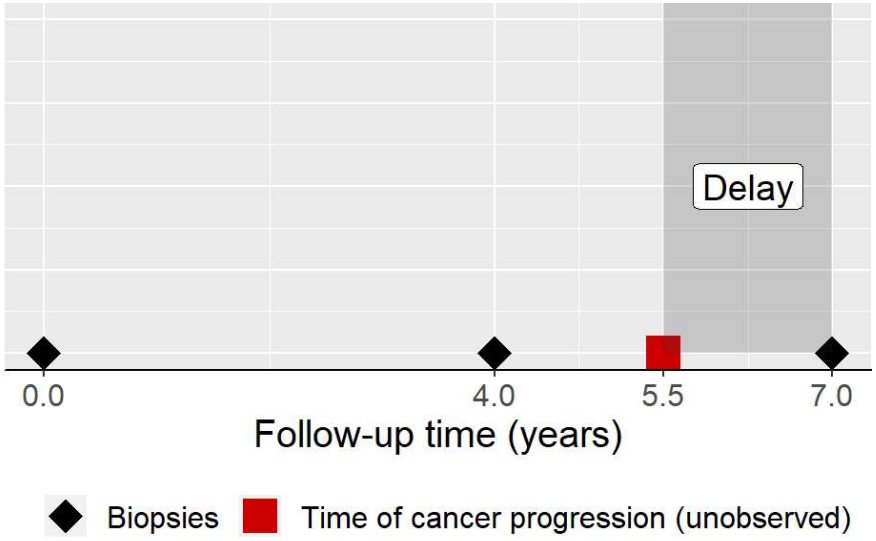
- Cancer progression is tracked via:
  - Prostate-specific antigen measurements
  - Digital rectal examination
  - Biopsies

- Treatment is advised when cancer progression is observed
  - typically via biopsies

Biopsies vs. Delay in Cancer Detection

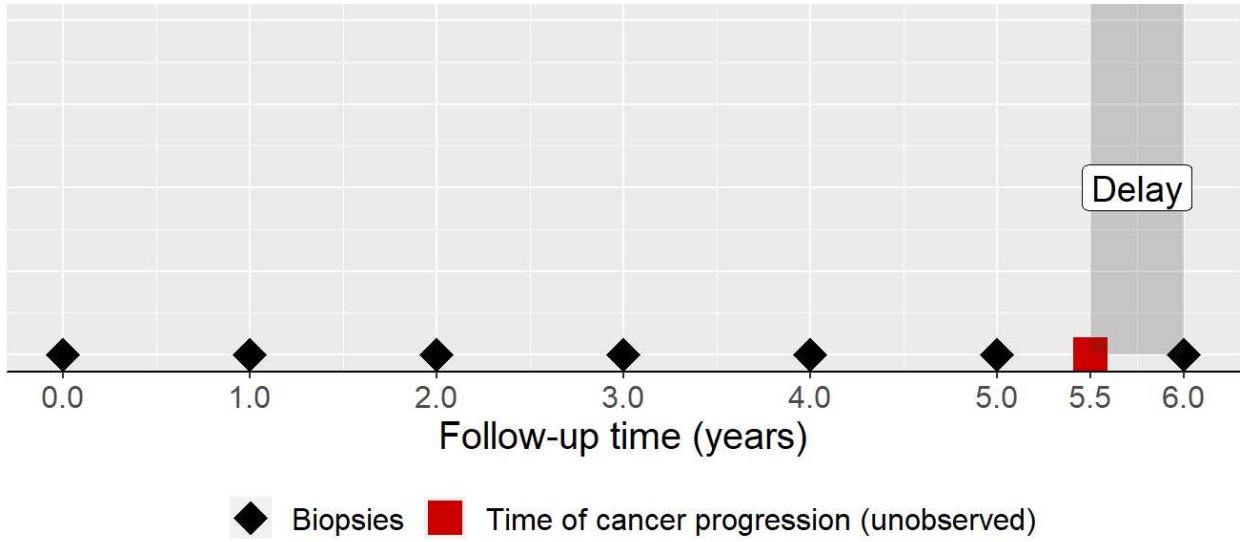
- Biopsies
  - are burdensome (pain, complications)
  - but reliable? sampling errors

- Cancer Progression
  - can only be detected with a certain delay



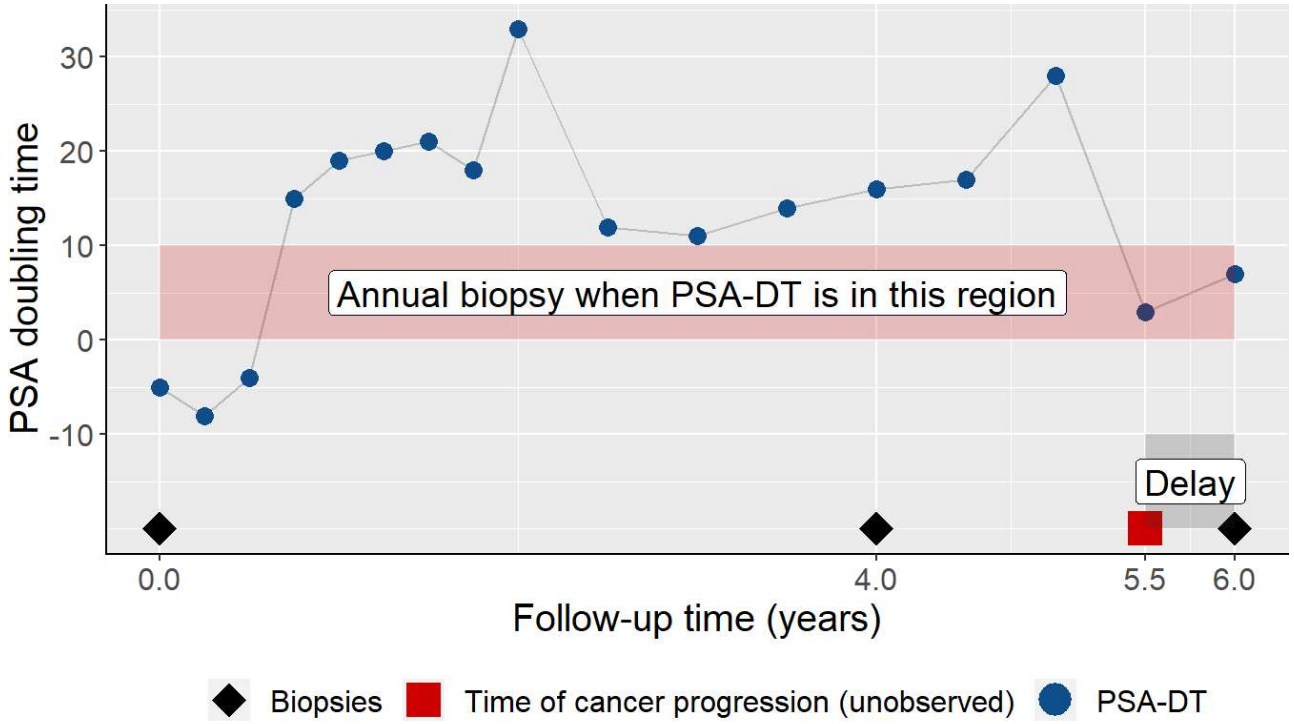
Annual Biopsies

- Focus on minimizing delay
  - maximum delay can be 1 year
- Many unnecessary biopsies for patients who progress slow



Less Frequent Biopsies - 1

- PRIAS
  - every 3 years or
  - annually if PSA doubling time < 10 (try to find faster progressions)



Less Frequent Biopsies - 2

- Still unnecessary biopsies
  - based on simulations, 4-10 unnecessary biopsies for patients with progression >10 years

- PRIAS reports low compliance (~20%) for annual biopsy due to PSA-DT

A New Approach - 1

Considerable room to improve biopsy scheduling

A New Approach - 2

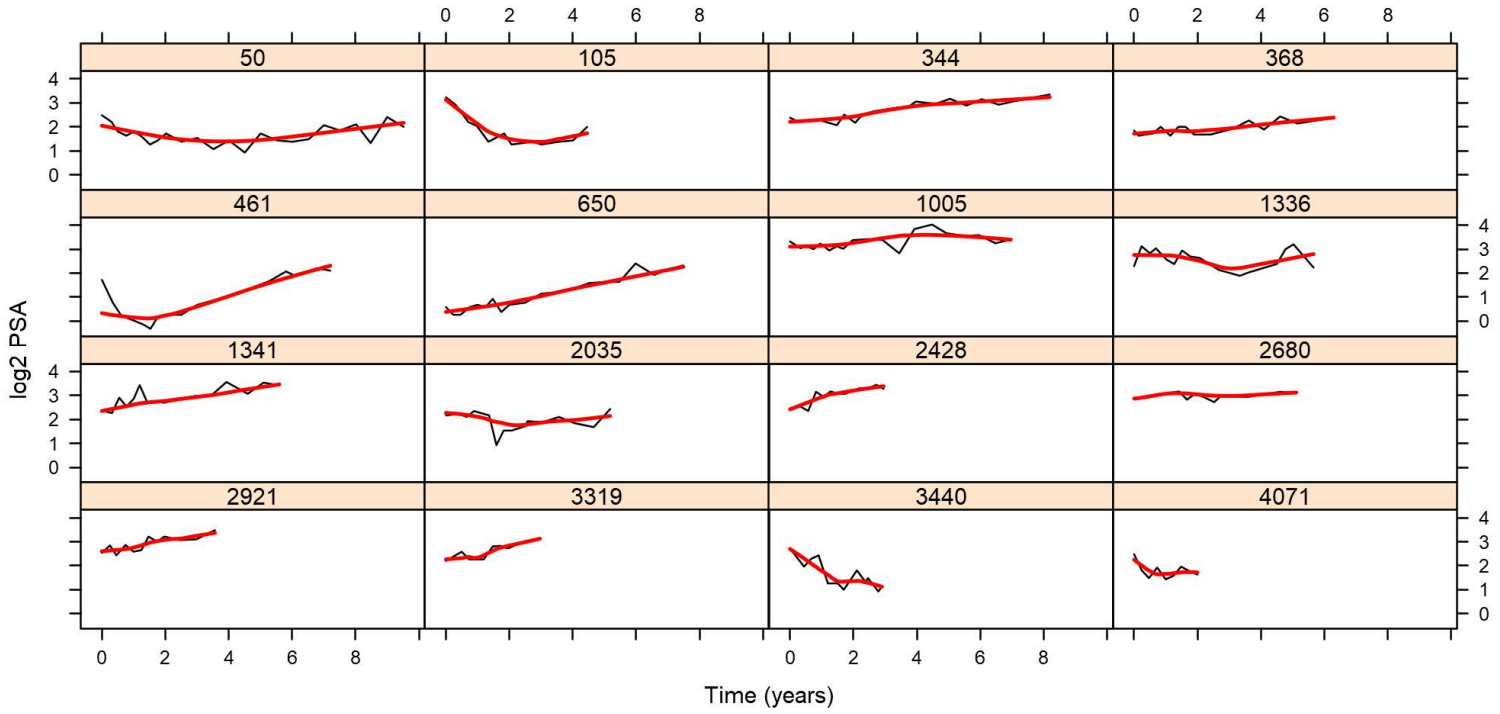
- Scheduling based on individualized risk predictions
  - Progression rate is not only different between patients but also dynamically changes over time for the same patient

- Risk predictions based upon
  - All available PSA (ng/mL) measurements
  - All available DRE (T1c / above T1c) measurements
  - Time and results of previous biopsies

A New Approach - 3

Outcome:

subject PSA



A New Approach - 4

How to better plan biopsies?

- In steps:
  - *How the longitudinal PSA & DRE are related to Gleason reclassification?*
  - *How to combine previous PSA & DRE measurements and biopsies to predict reclassification?*
  - *When to plan the next biopsy?*

Time-varying Covariates

- To answer these questions we need to link
  - the time to Gleason reclassification (survival outcome)
  - the PSA measurements (longitudinal outcome)
  - the DRE measurements (binary outcome)

- Biomarkers are *endogenous* time-varying covariates
  - their future path depends on previous events
  - standard time-varying Cox model not appropriate

Time-varying Covariates (cont'd)

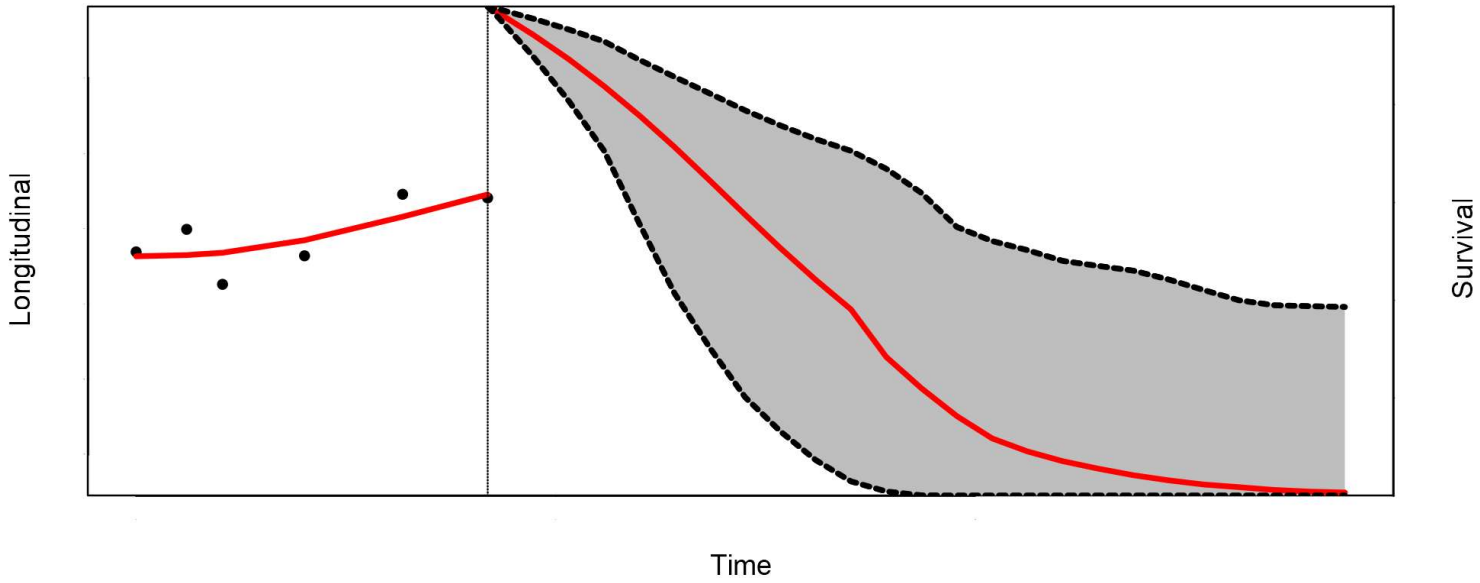
To account for endogeneity we use the framework of

Joint Models for Longitudinal & Survival Data

The Basic Joint Model

Measurements:

1 6 10



The Basic Joint Model (cont'd)

- We need some notation
  - T_i^* the true reclassification time
  - T_i^L last biopsy time point Gleason Score was < 7
  - T_i^R first biopsy time point Gleason Score was ≥ 7
  - $T_i^R = \infty$ for patients who haven't been reclassified yet
  - $\mathbf{y}_{i1}$ vector of longitudinal PSA measurements
  - $\mathcal{Y}_{i1}(t) = \{y_{i1}(s), 0 \leq s < t\}$
  - $\mathbf{y}_{i2}$ vector of longitudinal DRE measurements
  - $\mathcal{Y}_{i2}(t) = \{y_{i2}(s), 0 \leq s < t\}$

The Basic Joint Model (cont'd)

- Formally, we have

$$
\begin{cases}
h_i(t) &= h_0(t)\exp\{\gamma^\top \mathbf{w}_i + \alpha_1\eta_{i1}(t) + \alpha_2\eta_{i2}(t)\} \\
\\
y_{i1}(t) &= \eta_{i1}(t) + \varepsilon_i(t) \\
&= \mathbf{x}_{i1}^\top(t)\beta_1 + \mathbf{z}_{i1}^\top(t)\mathbf{b}_{i1} + \varepsilon_i(t) \\
\\
\log\frac{\Pr\{y_{i2}(t)=1\}}{1-\Pr\{y_{i2}(t)=1\}} &= \eta_{i2}(t) \\
&= \mathbf{x}_{i2}^\top(t)\beta_2 + \mathbf{z}_{i2}^\top(t)\mathbf{b}_{i2} \\
\\
& \{b_{i1}, b_{i2}\} \sim \mathcal{N}(\mathbf{0}, \mathbf{D}), \quad \varepsilon_i(t) \sim \mathcal{N}(0, \sigma^2)
\end{cases}
$$

The Basic Joint Model (cont'd)

- The longitudinal and survival outcomes are jointly modeled

$$p(y_{i1}, y_{i2}, T_i^L, T_i^R) = \int p(y_{i1} \mid b_{i1})\; p(y_{i2} \mid b_{i2}) \left\{ S(T_i^L \mid b_i) - S(T_i^R \mid b_i) \right\} p(b_i)\; db_i$$

  - the random effects b_i explain the interdependencies

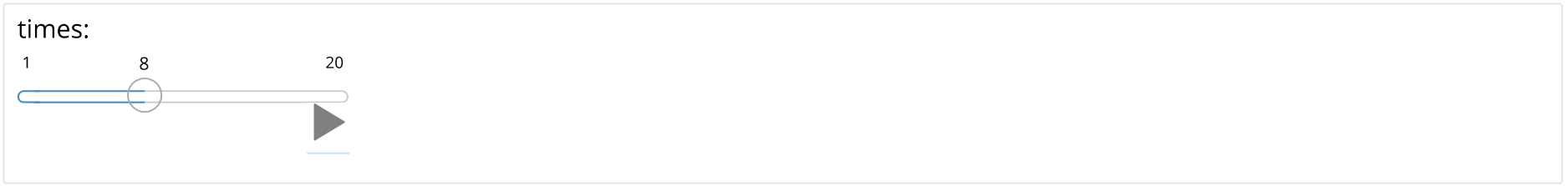
Functional Form

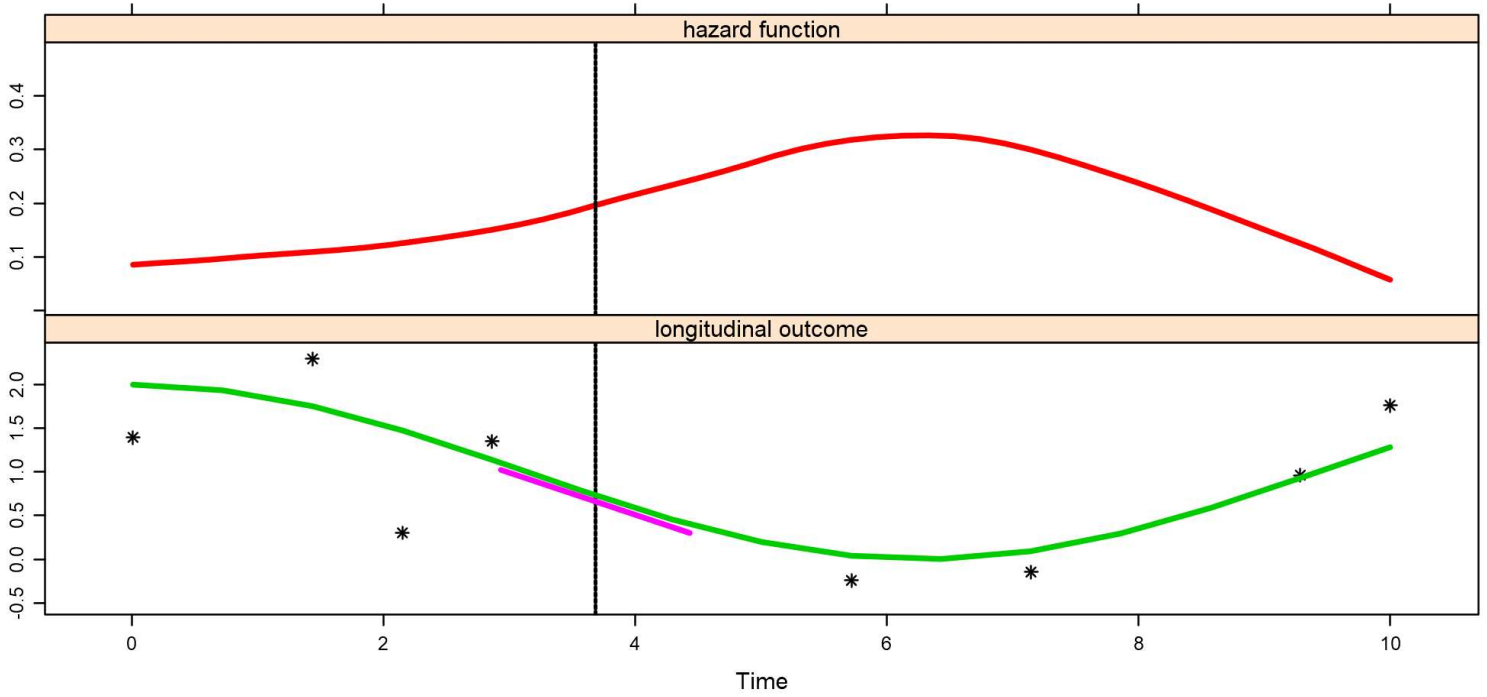
- Biomarker's rate of change
  - fast increasing PSA indicative of progression

$$h_i(t) = h_0(t) \exp\{\gamma^\top \mathbf{w}_i + \alpha_1 \eta_{i1}(t) + \alpha_2 \eta'_{i1}(t)\}$$

where $\eta'_{i1}(t) = \frac{d}{dt}\eta_{i1}(t)$

Functional Form (cont'd)



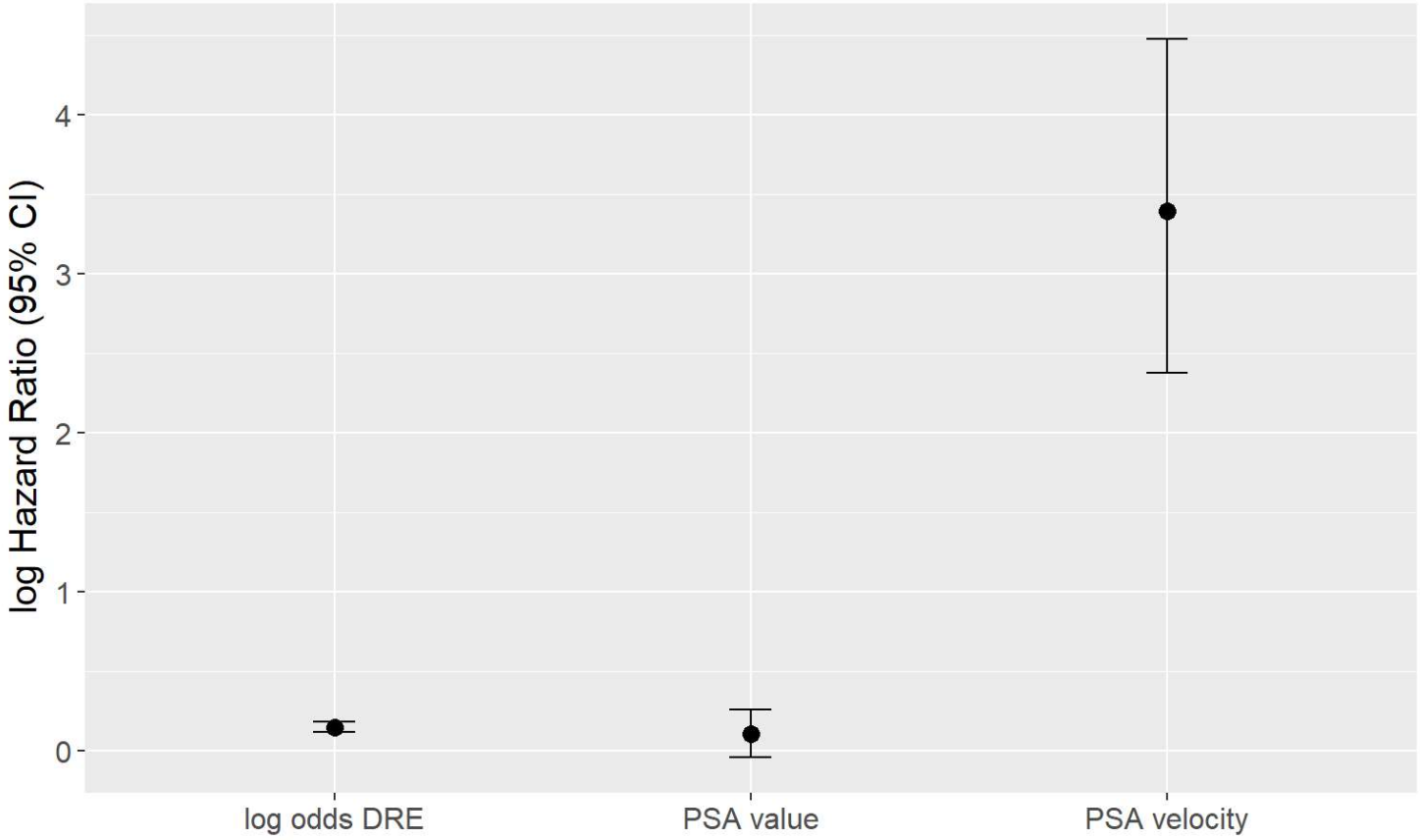


Joint Model for PRIAS - 1

- **Submodel for biomarkers**
  - $\log_2$ PSA trajectories: Age effect + nonlinear evolutions over time
  - DRE > T1c trajectories: Age effect + linear evolutions over time

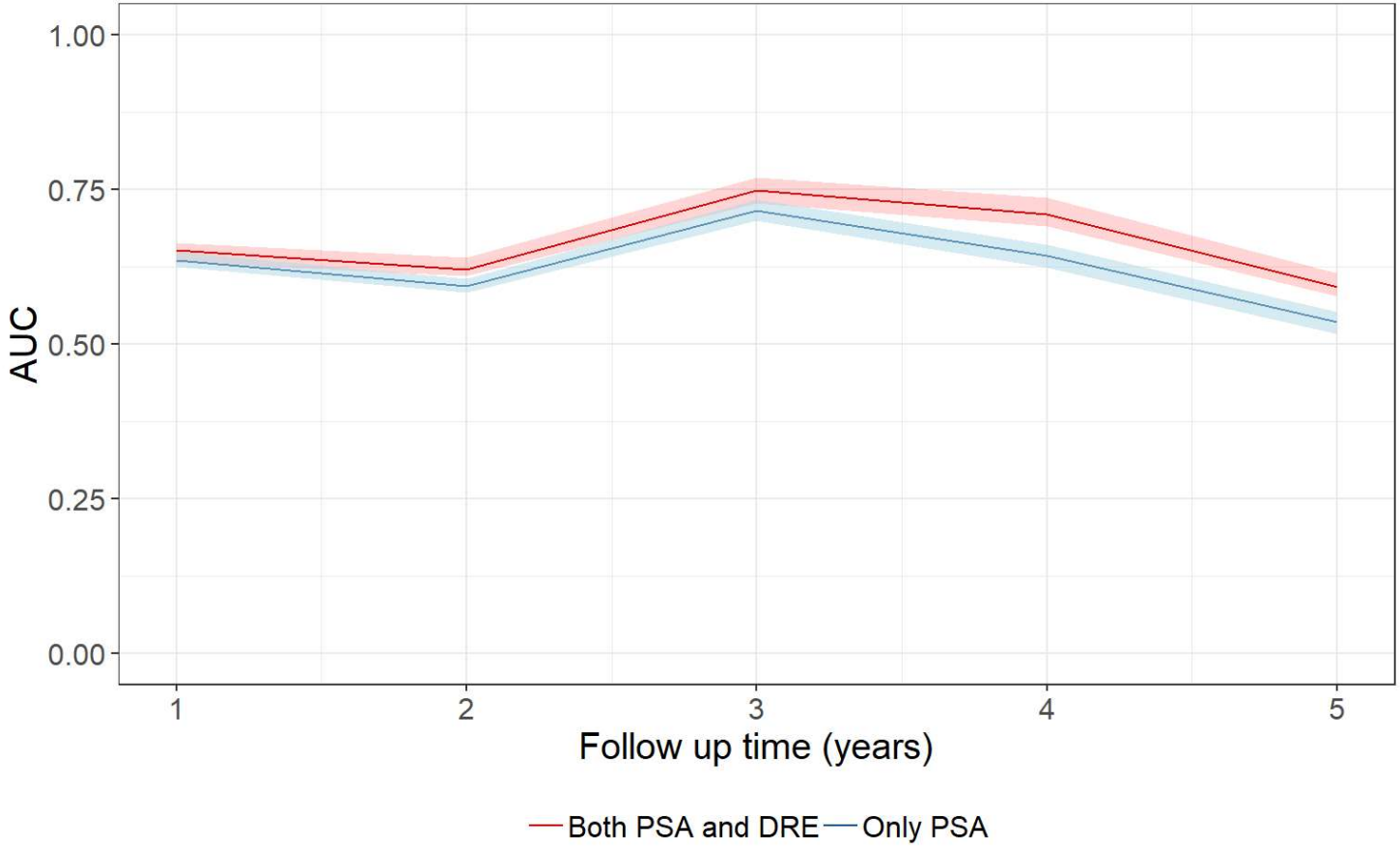
- **Submodel for Risk of Gleason reclassification**
  - Age effect
  - log odds of DRE > T1c
  - $\log_2$ PSA level
  - $\log_2$ PSA velocity

Joint Model for PRIAS - 2



Joint Model for PRIAS - 3

- Area under the receiver operating characteristic curve (AUC)
- Discrimination ability (progression vs. others) in a 1 year time window



Personalized Decision Methodology - 1

- **A new patient, a new visit**
  - At some follow-up time, with a certain history of PSA, DRE and biopsies
  - We combine this information using joint model, to obtain risk of cancer progression at that visit

- **How to select when to perform a biopsy?**
  - **Solution 1:** A fixed treshold, 15% within a year
    - however, the same for all time points

Personalized Decision Methodology - 2

- **How to select when to perform a biopsy?**
  - **Solution 2:** Dynamic treshold based on PRIAS
    - we want both high sensitivity and high positive predictive value
    - basically we don't want too many FP or FN

$$F1 = 2\frac{SN \times PPV}{SN + PPV}$$

    - we select the treshold that maximizes the F1 score

Personalized Decision Methodology - 3

Lets see it in practice...

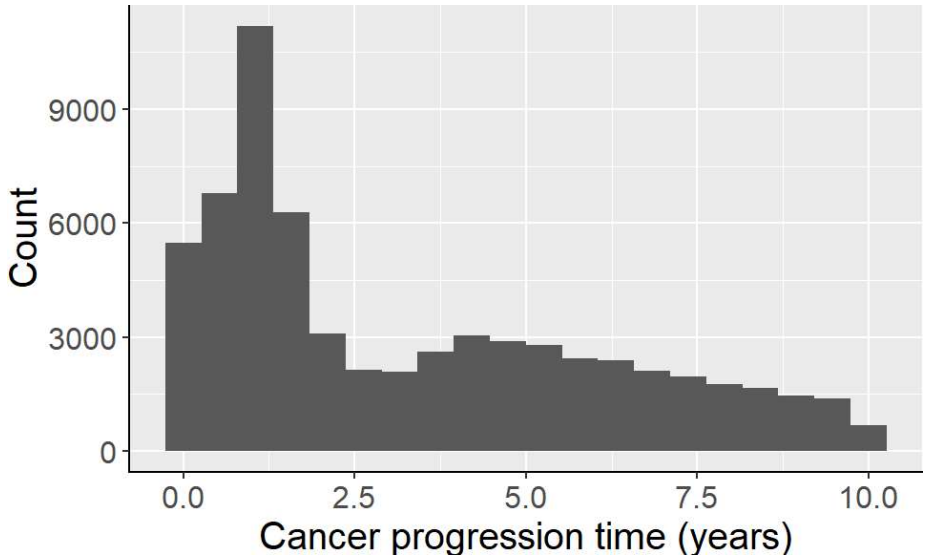
Personalized vs. Fixed Schedules - 1

- Is it better to work with personalized schedules?

- Simulation study:
  - The same characteristics as in PRIAS
  - 500 datasets x (750 training + 250 test) patients

Personalized vs. Fixed Schedules - 2

- For illustration purposes, we define:
  - Slow progression: patients who never progress (50%)
  - Remaining 50%:
    - Fast progression: 30% progression in 0 to 3.5 years
    - Intermediate progression: 20% progression in 3.5 to 10 years



Personalized vs. Fixed Schedules - 3

- Fixed:
  - PRIAS (biopsy every 3 years, and if PSA goes up too fast then annual biopsy)
  - Annual (annual biopsies)

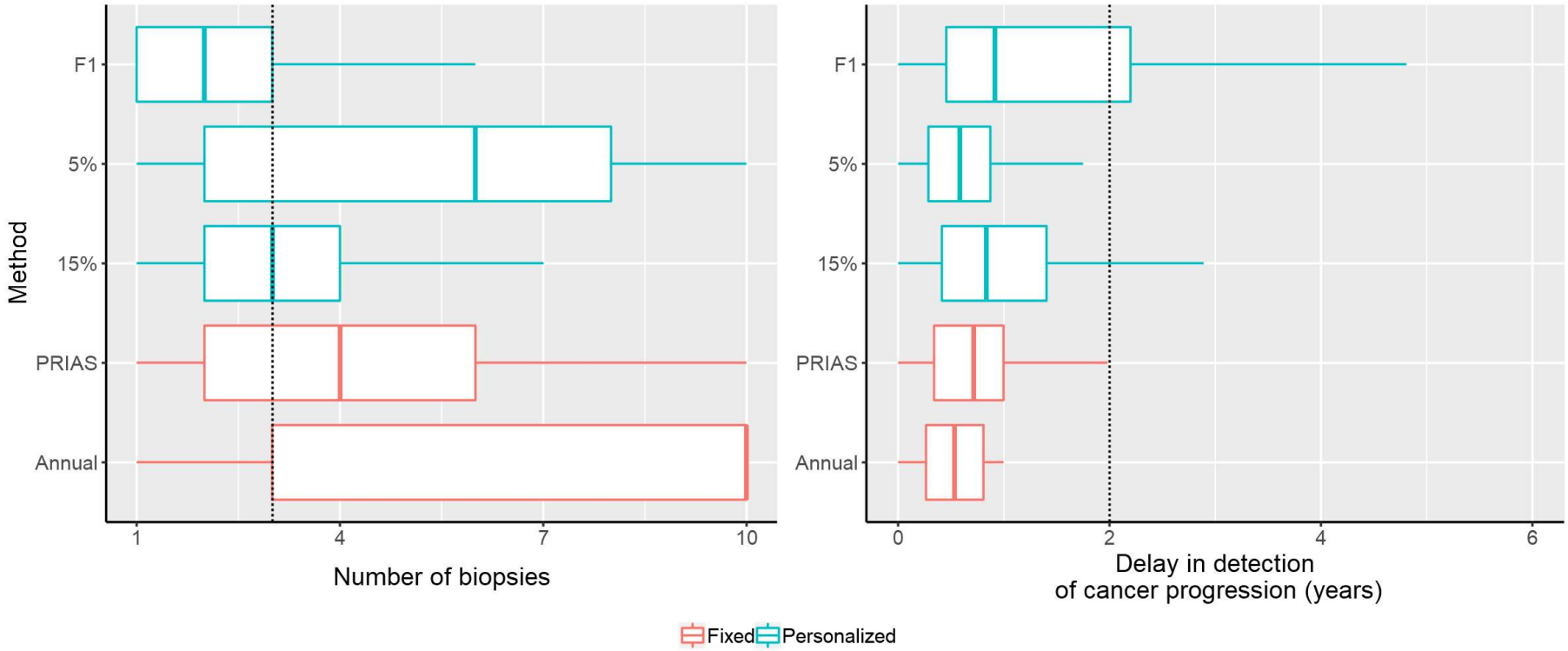
- Personalized (risk based):
  - 5% risk threshold
  - 15% risk threshold
  - time dependent threshold based on F1 score

Personalized vs. Fixed Schedules - 4

- Comparison criteria
  - Number of biopsies until cancer progression
  - Delay in detection of cancer progression

Simulation Results

Patient Selection: All patients | Fast (30% patients) | Intermediate (20% patients) | Slow (50% patients)



Discussion

- Things to improve
  - account for miss-classification

- Biometrics paper available at: https://onlinelibrary.wiley.com/doi/10.1111/biom.12940 (https://onlinelibrary.wiley.com/doi/10.1111/biom.12940)

- Software: available in **JMbayes** on CRAN & GitHub
  - https://cran.r-project.org/package=JMbayes (https://cran.r-project.org/package=JMbayes)
  - https://github.com/drizopoulos/JMbayes (https://github.com/drizopoulos/JMbayes)

Thank you for your attention!

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