

Medical Decision Making

Personalized Decision Making for Biopsies in Prostate Cancer Active Surveillance Programs

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SAGE

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Abstract

Background. Low-risk prostate cancer patients enrolled in active surveillance programs commonly undergo biopsies for examination of cancer progression. Biopsies are conducted as per a fixed and frequent schedule (e.g., annual biopsies). Since biopsies are burdensome, patients do not always comply with the schedule, which increases the risk of delayed detection of cancer progression.

Objective. Our aim is to better balance the number of biopsies (burden) and the delay in detection of cancer progression (less is beneficial), by personalizing the decision of conducting biopsies.

Data Sources. We use patient data of the world's largest active surveillance program (PRIAS). It enrolled 5270 patients, had 866 cancer progressions, and an average of nine prostate-specific antigen (PSA) and five digital rectal examination (DRE) measurements per patient.

Methods. Using joint models for time-to-event and longitudinal data, we model the historical DRE and PSA measurements, and biopsy results of a patient at each follow-up visit. This results in a visit and patient-specific cumulative risk of cancer progression. If this risk is above a certain threshold, we schedule a biopsy. We compare this personalized approach with the currently practiced biopsy schedules via an extensive and realistic simulation study, based on a replica of the patients from the PRIAS program.

Results. The personalized approach saved a median of six biopsies (median: 4, IQR: 2–5), compared to the annual schedule (median: 10, IQR: 3–10). However, the delay in detection of progression (years) is similar for the personalized (median: 0.7, IQR: 0.3–1.0) and the annual schedule (median: 0.5, IQR: 0.3–0.8).

Conclusions. We conclude that personalized schedules provide substantially better balance in the number of biopsies per detected progression for men with low-risk prostate cancer.

Keywords

Active surveillance, biopsy, joint models, personalized medical decisions, prostate cancer

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Introduction

Prostate cancer is the second most frequently diagnosed cancer in men worldwide¹. In prostate cancer screening programs, many of the diagnosed tumors are clinically insignificant (over-diagnosed)². To avoid further over-treatment, patients diagnosed with low-grade prostate cancer are commonly advised to join active surveillance (AS) programs. In AS, invasive treatments such as surgery are delayed until cancer progresses. Cancer progression is routinely monitored via serum prostate-specific antigen (PSA) measurements, a protein biomarker; digital rectal examination (DRE) measurements, a measure of the size and location of the tumor; and biopsies.

While larger values for PSA and/or DRE, may indicate cancer progression, biopsies are the most reliable cancer progression examination technique used in AS. When a patient's biopsy Gleason score becomes larger than 6 (positive biopsy, cancer progression detected), AS is stopped and the patient is advised treatment³. However, biopsies are invasive, painful, and prone to medical complications^{4,5}. Hence, they are conducted intermittently until a positive biopsy. Consequently, at the time of a positive biopsy, cancer progression may be observed with a delay of unknown duration. This delay is defined as the difference between the time of the positive biopsy and the unobserved true time of cancer progression. Thus, the decision to conduct biopsies requires a compromise between the burden of biopsy and the potential delay in the detection of cancer progression.

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In AS, a delay in the detection of cancer progression around 12 to 14 months is assumed to be unlikely to substantially increase the risk of adverse downstream outcomes^{6,7}. However, for biopsies, there is little consensus on the time gap between them⁸⁻¹⁰. Many AS programs focus on minimizing the delay in the detection of cancer progression, by scheduling biopsies annually for all patients. A drawback of annual biopsies, and other currently practiced fixed/heuristic schedules⁸⁻¹⁰, is that they ignore the large variation in the time of cancer progression of AS patients. While they may work well for patients who progress early (*fast progressing*) in AS, but for a large proportion of patients who do not progress, or progress late (*slow progressing*) in AS, many unnecessary burdensome biopsies are scheduled. To mediate the burden between the *fast* and *slow progressing* patients, the world's largest AS program, Prostate Cancer Research International Active Surveillance¹¹ (PRIAS), schedules annual biopsies only for patients with a low PSA doubling time³. For everyone else, PRIAS schedules biopsies at following fixed follow-up times: year one, four, seven, and ten, and every five years thereafter. Despite this effort in PRIAS, patients may get scheduled for four to ten biopsies over a period of ten years. Therefore, compliance for biopsies is low in PRIAS³. This can lead to a delay in the detection of cancer progression, and reduce the effectiveness of AS.

We aim to better balance the number of biopsies (more are burdensome), and the delay in the detection of cancer progression (less is beneficial), than currently practiced schedules. We intend to achieve this by personalizing the decision to conduct biopsies (see Figure 1). These decisions are made at a patient's pre-scheduled follow-up visits for DRE and PSA measurements. To develop the personalized decision making methodology, we utilize the data of the patients enrolled in the PRIAS study. We model this data and develop the personalized approach using joint models for time-to-event and longitudinal data^{12,13}. In order to compare the personalized approach with current schedules, we conduct an extensive simulation study based on a replica of the patients from the PRIAS program.

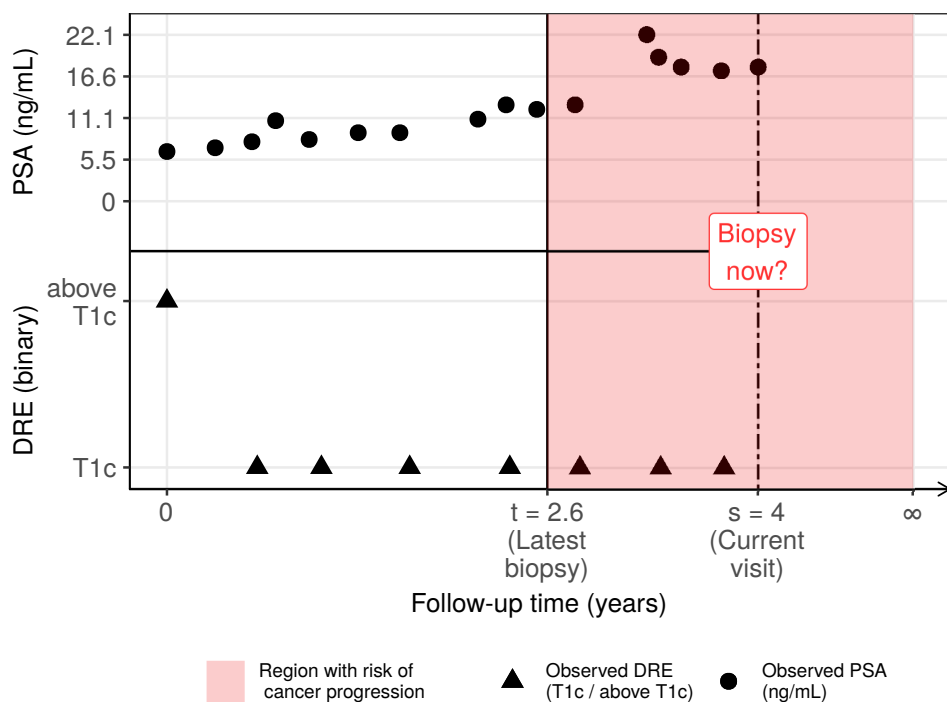


Figure 1. The personalized decision making problem: Available data of a patient j , who had his latest negative biopsy at $t = 2.6$ years. The shaded region shows the time period in which the patient is at risk of cancer progression. His current pre-scheduled follow-up visit for measurement of DRE and PSA is at $s = 4$ years. Using his entire history of DRE $\mathcal{Y}_{dj}(s)$ and PSA $\mathcal{Y}_{pj}(s)$ measurements up to the current visit s , and the time of the latest biopsy t , we intend to make a decision on scheduling a biopsy at the current visit.

Methods

Study Population

To develop our methodology we use the data of prostate cancer patients from the world's largest AS study called PRIAS¹¹ (see Table 1). More than 100 medical centers from 17 countries worldwide contribute to the collection of data, utilizing a common study protocol and a web-based tool, both available at www.prias-project.org. We use data collected over a period of ten years, between December 2006 (beginning of PRIAS study) and December 2016. The primary event of interest is cancer progression detected upon a positive biopsy. The time of cancer progression is interval censored because biopsies are

Table 1. Summary statistics for the PRIAS dataset. The primary event of interest is cancer progression. A DRE measurement equal to T1c¹⁴ indicates a clinically inapparent tumor which is not palpable or visible by imaging, while tumors with DRE > T1c are palpable. The abbreviation IQR means interquartile range.

Data	Value
Total patients	5270
Cancer progression (primary event)	866
Loss to follow-up (anxiety or unknown)	685
Patient removal on the basis of PSA and DRE	464
Death (unrelated to prostate cancer)	61
Death (related to prostate cancer)	2
Median Age (years)	70 (IQR: 65–75)
Total PSA measurements	46015
Median number of PSA measurements per patient	7 (IQR: 7–12)
Median PSA value (ng/mL)	5.6 (IQR: 4.0–7.5)
Total DRE measurements	25606
Median number of DRE measurements per patient	4 (IQR: 3–7)
DRE = T1c (%)	23538/25606 (92%)

scheduled periodically. Biopsies are scheduled as per the PRIAS protocol (see **Introduction**). There are three types of competing events, namely death, removal of patients from AS on the basis of their observed DRE and PSA measurements, and loss to follow-up. We assume these three types of events to be censored observations (see Appendix A.5 for details). However, our model allows removal of patients to depend on observed longitudinal data and baseline covariates of the patient. Under the aforementioned assumption of censoring, Figure 2 shows the cumulative risk of cancer progression over the study follow-up period.

For all patients, PSA measurements (ng/mL) are scheduled every 3 months for the first 2 years and every 6 months thereafter. The DRE measurements are scheduled every 6 months. We use the DRE measurements as DRE = T1c versus DRE > T1c. A DRE measurement equal to T1c¹⁴ indicates a clinically inapparent tumor which is not palpable or visible by imaging, while tumors with DRE > T1c are palpable.

Data Accessibility: The PRIAS database is not openly accessible. However, access to the database on the basis of a by the PRIAS steering committee approved study proposal can be requested via the contact links on the website of the PRIAS program www.prias-project.org.

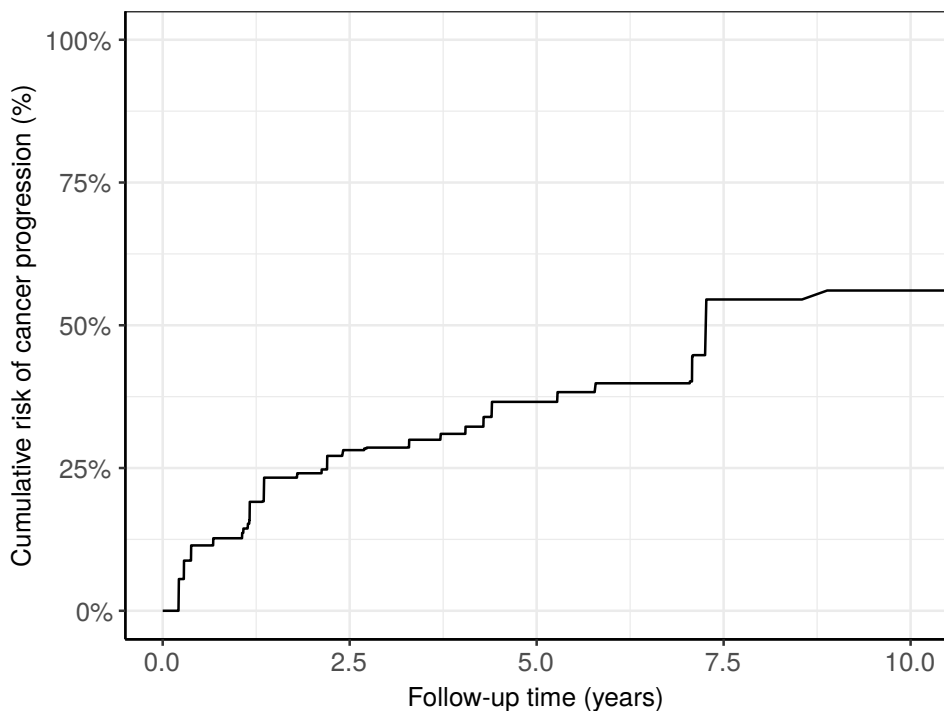


Figure 2. Estimated cumulative risk of cancer progression in AS for patients in the Prostate Cancer Research International Active Surveillance (PRIAS) dataset. Nearly 50% patients (*slow progressing*) do not progress in the ten year follow-up period. Cumulative risk is estimated using nonparametric maximum likelihood estimation¹⁵, to account for interval censored cancer progression times observed in the PRIAS dataset. Censoring includes death, removal from AS on the basis of observed longitudinal data, and patient dropout.

A Bivariate Joint Model for the Longitudinal PSA, and DRE Measurements, and Time of Cancer Progression

Let T_i^* denote the true cancer progression time of the i -th patient included in PRIAS. Since biopsies are conducted periodically, T_i^* is observed with interval censoring $l_i < T_i^* \leq r_i$. When progression is observed for the patient at his latest biopsy time r_i , then l_i denotes the time of the second latest biopsy. Otherwise, l_i denotes the time of the latest biopsy and $r_i = \infty$. Let \mathbf{y}_{di} and \mathbf{y}_{pi} denote his observed DRE and PSA longitudinal measurements, respectively. The observed data of all n patients is denoted by $\mathcal{D}_n = \{l_i, r_i, \mathbf{y}_{di}, \mathbf{y}_{pi}; i = 1, \dots, n\}$.

In our joint model, the patient-specific DRE and PSA measurements over time are modeled using a bivariate generalized linear mixed effects

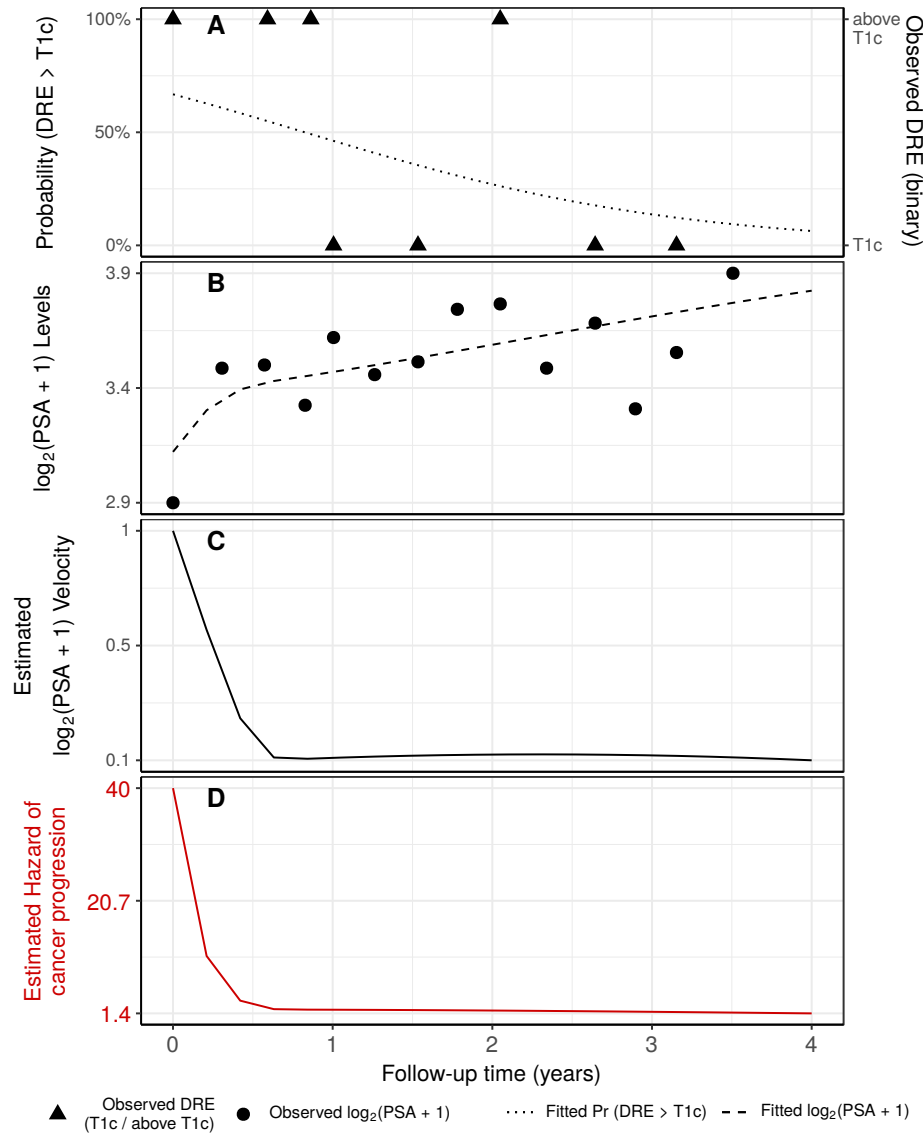


Figure 3. Illustration of the joint model fitted to the PRIAS dataset. Panel A: shows the observed DRE measurements and the fitted probability of obtaining DRE > T1c (Equation 1) for i -th patient. Panel B: shows the observed and fitted $\log_2(\text{PSA} + 1)$ measurements (Equation 2). Panel C: shows the estimated $\log_2(\text{PSA} + 1)$ velocity (velocity cannot be observed directly) over time. The hazard function (Equation 3) shown in Panel D, depends on the fitted log odds of having a DRE > T1c, and the fitted $\log_2(\text{PSA} + 1)$ value and velocity.

sub-model. The sub-model for DRE is given by (see Panel A, Figure 3):

$$\begin{aligned} \text{logit}[\Pr\{y_{di}(t) > \text{T1c}\}] = & \beta_{0d} + b_{0di} + (\beta_{1d} + b_{1di})t \\ & + \beta_{2d}(\text{Age}_i - 70) + \beta_{3d}(\text{Age}_i - 70)^2 \end{aligned} \quad (1)$$

where, t denotes the follow-up visit time, and Age_i is the age of the i -th patient at the time of inclusion in AS. The fixed effect parameters are denoted by $\{\beta_{0d}, \dots, \beta_{3d}\}$, and $\{b_{0di}, b_{1di}\}$ are the patient specific random effects. With this definition, we assume that the patient-specific log odds of obtaining a DRE measurement larger than T1c remain linear over time.

The mixed effects sub-model for PSA is given by (see Panel B, Figure 3):

$$\begin{aligned} \log_2 \{y_{pi}(t) + 1\} = & m_{pi}(t) + \varepsilon_{pi}(t), \\ m_{pi}(t) = & \beta_{0p} + b_{0pi} + \sum_{k=1}^4 (\beta_{kp} + b_{kpi}) B_k(t, \mathcal{K}) \\ & + \beta_{5p}(\text{Age}_i - 70) + \beta_{6p}(\text{Age}_i - 70)^2, \end{aligned} \quad (2)$$

where, $m_{pi}(t)$ denotes the underlying measurement error free value of $\log_2(\text{PSA} + 1)$ transformed^{16,17} measurements at time t . We model it non-linearly over time using B-splines¹⁸. To this end, our B-spline basis function $B_k(t, \mathcal{K})$ has 3 internal knots at $\mathcal{K} = \{0.1, 0.7, 4\}$ years, and boundary knots at 0 and 5.42 years (95-th percentile of the observed follow-up times). The fixed effect parameters are denoted by $\{\beta_{0p}, \dots, \beta_{6p}\}$, and $\{b_{0pi}, \dots, b_{4pi}\}$ are the patient specific random effects. The error $\varepsilon_{pi}(t)$ is assumed to be t-distributed with three degrees of freedom (see Appendix B.1) and scale σ , and is independent of the random effects.

To account for the correlation between the DRE and PSA measurements of a patient, we link their corresponding random effects. More specifically, the complete vector of random effects $\mathbf{b}_i = (b_{0di}, b_{1di}, b_{0pi}, \dots, b_{4pi})^T$ is assumed to follow a multivariate normal distribution with mean zero and variance-covariance matrix \mathbf{D} .

To model the impact of DRE and PSA measurements on the risk of cancer progression, our joint model uses a relative risk sub-model. More specifically, the hazard of cancer progression $h_i(t)$ at a time t is given by

(see Panel D, Figure 3):

$$h_i(t) = h_0(t) \exp \left(\gamma_1(\text{Age}_i - 70) + \gamma_2(\text{Age}_i - 70)^2 + \alpha_{1d} \logit[\Pr\{y_{di}(t) > \text{T1c}\}] + \alpha_{1p} m_{pi}(t) + \alpha_{2p} \frac{\partial m_{pi}(t)}{\partial t} \right), \quad (3)$$

where, γ_1, γ_2 are the parameters for the effect of age. The parameter α_{1d} models the impact of log odds of obtaining a DRE > T1c on the hazard of cancer progression. The impact of PSA on the hazard of cancer progression is modeled in two ways: a) the impact of the error free underlying PSA value $m_{pi}(t)$ (see Panel B, Figure 3), and b) the impact of the underlying PSA velocity $\partial m_{pi}(t)/\partial t$ (see Panel C, Figure 3). The corresponding parameters are α_{1p} and α_{2p} , respectively. Lastly, $h_0(t)$ is the baseline hazard at time t , and is modeled flexibly using P-splines¹⁹. The detailed specification of the baseline hazard $h_0(t)$, and the joint parameter estimation of the two sub-models using the Bayesian approach (R package **JMbayes**²⁰) are presented in Appendix A of the supplementary material.

Personalized Decisions for Biopsy

Let us assume that a decision of conducting a biopsy is to be made for a new patient j shown in Figure 1, at his current follow-up visit time s . Let $t \leq s$ be the time of his latest negative biopsy. Let $\mathcal{Y}_{dj}(s)$ and $\mathcal{Y}_{pj}(s)$ denote his observed DRE and PSA measurements up to the current visit, respectively. From the observed measurements we want to extract the underlying measurement error free trend of $\log_2(\text{PSA} + 1)$ values and velocity, and the log odds of obtaining DRE > T1c. We intend to combine them to inform us when the cancer progression is to be expected (see Figure 4), and to further guide the decision making on whether to conduct a biopsy at the current follow-up visit. The combined information is given by the following posterior predictive distribution $g(T_j^*)$ of his time of cancer progression $T_j^* > t$ (see Appendix A.4 for details):

$$g(T_j^*) = p\{T_j^* \mid T_j^* > t, \mathcal{Y}_{dj}(s), \mathcal{Y}_{pj}(s), \mathcal{D}_n\}. \quad (4)$$

The distribution $g(T_j^*)$ is not only patient-specific, but also updates as extra information is recorded at future follow-up visits.

A key ingredient in the decision of conducting a biopsy for patient j at the current follow-up visit time s is the personalized cumulative risk of

observing a cancer progression at time s (illustrated in Figure 4). This risk can be derived from the posterior predictive distribution $g(T_j^*)^{21}$, and is given by:

$$R_j(s | t) = \Pr\{T_j^* \leq s \mid T_j^* > t, \mathcal{Y}_{dj}(s), \mathcal{Y}_{pj}(s), \mathcal{D}_n\}, \quad s \geq t. \quad (5)$$

A simple and straightforward approach to decide upon conducting a biopsy for patient j at the current follow-up visit would be to do so if his personalized cumulative risk of cancer progression at the visit is higher than a certain threshold $0 \leq \kappa \leq 1$. For example, as shown in Panel B of Figure 4, biopsy at a visit may be scheduled if the personalized cumulative risk is higher than 10% (example risk threshold). This decision making process is iterated over the follow-up period, incorporating on each subsequent visit the newly observed data, until a positive biopsy is observed. Subsequently, an entire personalized schedule of biopsies for each patient can be obtained.

The choice of the risk threshold dictates the schedule of biopsies and has to be made on each subsequent follow-up visit of a patient. In this regard, a straightforward approach is choosing a fixed risk threshold, such as 5% or 10% risk, at all follow-up visits. Fixed risk thresholds may be chosen by patients and/or doctors according to how they weigh the relative harms of doing an unnecessary biopsy versus a missed cancer progression (e.g., 10% threshold means a 1:9 ratio) if the biopsy is not conducted²². An alternative approach is that at each follow-up visit a unique threshold is chosen on the basis of its classification accuracy. More specifically, given the time of latest biopsy t of patient j , and his current visit time s we find a visit-specific biopsy threshold κ , which gives the highest cancer progression detection rate (true positive rate, or TPR) for the period $(t, s]$. However, we also intend to balance for unnecessary biopsies (high false positive rate), or a low number of correct detections (high false negative rate) when the false positive rate is minimized. An approach to mitigating these issues is to maximize the TPR and positive predictive value (PPV) simultaneously. To this end, we utilize the F_1 score, which is a composite of both TPR and PPV (estimated as in Rizopoulos et al., 2017²³), and is

defined as:

$$F_1(t, s, \kappa) = 2 \frac{\text{TPR}(t, s, \kappa) \text{PPV}(t, s, \kappa)}{\text{TPR}(t, s, \kappa) + \text{PPV}(t, s, \kappa)},$$

$$\text{TPR}(t, s, \kappa) = \Pr\{R_j(s | t) > \kappa \mid t < T_j^* \leq s\},$$

$$\text{PPV}(t, s, \kappa) = \Pr\{t < T_j^* \leq s \mid R_j(s | t) > \kappa\}. \quad (6)$$

The F_1 score ranges between 0 and 1, where a value of 1 signifies perfect TPR and PPV. Since a high F_1 score is desired, the visit-specific risk threshold $\kappa = \arg \max_{\kappa} F_1(t, s, \kappa)$. The criteria on which we evaluate the personalized schedules based on fixed risk threshold at all visits, as well as visit-specific risk threshold using F_1 score, is the total number of biopsies scheduled, and the delay in detection of cancer progression (details in **Results**).

Simulation Study

Although the personalized decision making approach is motivated by the PRIAS study, it is not possible to evaluate it directly on the PRIAS dataset. This is because the patients in PRIAS have already had their biopsies as per the PRIAS protocol. In addition, the true time of cancer progression is interval or right censored for all patients, making it impossible to correctly estimate the delay in detection of cancer progression due to a particular schedule. To this end, we conduct an extensive simulation study to find the utility of personalized, PRIAS, and fixed/heuristic schedules. For a realistic comparison, we simulate patient data from the joint model fitted to the PRIAS dataset. The simulated population has the same ten year follow-up period as the PRIAS study. In addition, the estimated relations between DRE and PSA measurements, and the risk of cancer progression are retained in the simulated population.

From this population, we first sample 500 datasets, each representing a hypothetical AS program with 1000 patients in it. We generate a true cancer progression time for each of the 500×1000 patients and then sample a set of DRE and PSA measurements at the same follow-up visit times as given in PRIAS protocol. We then split each dataset into training (750 patients) and test (250 patients) parts, and generate a random and noninformative censoring time for the training patients. We next fit a joint model of the specification given in Equations (1), (2), and (3) to each of

the 500 training datasets and obtain MCMC samples from the 500 sets of the posterior distribution of the parameters.

In each of the 500 hypothetical AS programs, we utilize the corresponding fitted joint models to develop cancer progression risk profiles for each of the 500×250 test patients. We make the decision of biopsies for patients at their pre-scheduled follow-up visits for DRE and PSA measurements (see **Study Population**), on the basis of their estimated personalized cumulative risk of cancer progression. These decisions are made iteratively until a positive biopsy is observed. A recommended gap of one year between consecutive biopsies³ is also maintained. Subsequently, for each patient, an entire personalized schedule of biopsies is obtained.

We evaluate and compare both personalized and currently practiced schedules of biopsies in this simulation study. Comparison of the schedules is based on the number of biopsies scheduled and the corresponding delay in the detection of cancer progression. We evaluate the following currently practiced fixed/heuristic schedules: biopsy annually, biopsy every one and a half years, biopsy every two years and biopsy every three years. We also evaluate the biopsy schedule of the PRIAS program (see **Introduction**). For the personalized biopsy schedules, we evaluate schedules based on three fixed risk thresholds: 5%, 10%, and 15%, corresponding to a missed cancer progression being 19, 9, and 5.5 times more harmful than an unnecessary biopsy²², respectively. We also implement a personalized schedule where for each patient, visit-specific risk thresholds are chosen using F_1 score.

Results

From the joint model fitted to the PRIAS dataset, we found that both $\log_2\{\text{PSA} + 1\}$ velocity, and \log odds of having $\text{DRE} > \text{T1c}$ were significantly associated with the hazard of cancer progression. For any patient, an increase in $\log_2\{\text{PSA} + 1\}$ velocity from -0.03 to 0.16 (first and third quartiles of the fitted velocities, respectively) corresponds to a 1.94 fold increase in the hazard of cancer progression. Whereas, an increase in odds of $\text{DRE} > \text{T1c}$ from -6.650 to -4.356 (first and third quartiles of the fitted log odds, respectively) corresponds to a 1.40 fold increase in the hazard of cancer progression. Detailed results pertaining to the fitted joint model are presented in Appendix B.

Comparison of Various Approaches for Biopsies

From the simulation study, we obtain the number of biopsies and the delay in detection of cancer progression for each of the 500×250 test patients using different schedules. Figure 5 shows that the personalized and PRIAS approaches fall in the region of better balance between the median number of biopsies and the median delay than fixed/heuristic schedules. We next evaluate these schedules on the basis of both median and interquartile range (IQR) of the number of biopsies and delay (see Figure 6). For brevity, only the most widely used annual and PRIAS schedules, the proposed personalized approach with fixed risk thresholds of 5% and 10%, and visit-specific threshold chosen using F_1 score are discussed next (see Appendix C for remaining).

Since patients have varying cancer progression speeds, the impact of each schedule also varies with it. In order to highlight these differences, we divide results for three types of patients, as per their time of cancer progression. They are *fast*, *intermediate*, and *slow progressing* patients. Although such a division may be imperfect and can only be done retrospectively in a simulation setting, we show results for these three groups for the purpose of illustration. Roughly 50% of the patients did not obtain cancer progression in the ten year follow-up period of the simulation study. We assume these patients to be *slow progressing* patients. We assume *fast progressing* patients are the ones with an initially misdiagnosed state of cancer²⁴ or high-risk patients who choose AS instead of immediate treatment upon diagnosis. These are roughly 30% of the population, having a cancer progression time less than 3.5 years. We label the remaining 20% patients as *intermediate progressing* patients.

For *fast progressing* patients (Panel A, Figure 6), we note that the personalized schedules with a fixed 10% risk threshold and visit-specific threshold chosen using F_1 score, reduce one biopsy for 50% of the patients, compared to PRIAS and annual schedule. Despite this, the delay (years) is similar for the personalized schedule with fixed 10% risk threshold (median: 0.7, IQR: 0.3–1.0), and the commonly used annual (median: 0.6, IQR: 0.3–0.9) and PRIAS (median: 0.7, IQR: 0.3–1.0) schedules.

For *intermediate progressing* patients (Panel A, Figure 6), we note that the delay (years) due to personalized schedule with fixed 5% risk threshold (median: 0.6, IQR: 0.3–0.9) is comparable to that of annual

schedule (median 0.5, IQR: 0.2–0.7). However, it schedules fewer biopsies (median: 6, IQR: 5–7) than the annual schedule (median: 7, IQR: 5–8). The delay (years) for PRIAS (median: 0.7, IQR: 0.3–1.3) and personalized schedule with fixed 10% risk (median: 0.7, IQR: 0.4–1.3) are similar, but the personalized approach schedules one less biopsy for 50% of the patients. Although the approach with visit-specific risk threshold chosen using F_1 score schedules fewer biopsies than the 10% fixed risk approach, it also has a higher delay.

The patients who are at the most advantage with the personalized schedules are the *slow progressing* patients. These are a total of 50% patients who did not progress during the entire study. Hence, the delay is not available for these patients (Panel C of Figure 6). For all of these patients, annual schedule leads to 10 (unnecessary) biopsies. The schedule of the PRIAS program schedules a median of six biopsies (IQR: 4–8). In comparison, the biopsies scheduled by the personalized schedules using fixed 10% risk threshold (median: 4, IQR: 4–6) and visit-specific risk chosen using F_1 score (median: 2, IQR: 2–4), are much fewer.

Overall, we observed that the personalized schedule which uses a 10% risk threshold at all follow-up visits is dominant over the PRIAS schedule, biennial schedule of biopsies, and biopsies every one and a half years (see Appendix C for the latter two schedules). This personalized schedule not only schedules fewer biopsies than the aforementioned currently practiced schedules, but the delay in detection of cancer progression is also either equal or less. The personalized schedule which uses risk threshold chosen on the basis of classification accuracy (F_1 score) is dominant over the triennial schedule (see Appendix C) of biopsies. The personalized schedule which uses a 5% risk threshold schedules fewer biopsies than the annual schedule, while the delay is only trivially more than the annual schedule.

Discussion

We proposed a methodology which better balances the number of biopsies, and the delay in detection of cancer progression than the currently practiced biopsy schedules, for low-risk prostate cancer patients enrolled in active surveillance (AS) programs. The proposed methodology combines a patient's observed DRE and PSA measurements, and the time of the latest biopsy, into a personalized cancer progression risk function.

If the cumulative risk of cancer progression at a follow-up visit is above a certain threshold, then a biopsy is scheduled. We conducted an extensive simulation study, based on a replica of the patients from the PRIAS program, to compare this personalized approach for biopsies with the currently practiced biopsy schedules. We found personalized schedules to be dominant over many of the current biopsy schedules (see **Results**).

The main reason for the better performance of personalized schedules is that they account for the variation in cancer progression rate between patients, and also over time within the same patient. In contrast, the existing fixed/heuristic schedules ignore that roughly 50% patients never progress in the first ten years of follow-up (*slow progressing* patients) and do not require biopsies. The *fast progressing* patients require early detection. However, existing methods of identifying these patients, such as the use of PSA doubling time in PRIAS, inappropriately assume that PSA evolves linearly over time. Thus, they may not correctly identify such patients. The personalized approach, however, models the PSA profiles non-linearly. Furthermore, it appends information from PSA with information from DRE and previous biopsy results and combines them into single a cancer progression risk function. The risk function is a finer quantitative measure than individual data measurements observed for the patients. In comparison to decision making with flowcharts, the risk as a single measure of a patient's underlying state of cancer may facilitate shared decision making for biopsies.

Existing work on reducing the burden of biopsies in AS primarily advocates less frequent heuristic schedules of biopsies⁶ (e.g., biopsies biennially instead of annually). To our knowledge, risk-based biopsy schedules have barely been explored yet in AS^{9,10}. The part of our results pertaining to the fixed/heuristic schedules is comparable with corresponding results obtained in existing work⁶, even though the AS cohorts are not the same. Thus, we anticipate similar validity for the results pertaining to the personalized schedules.

A limitation of the personalized approach is that the choice of risk threshold is not straightforward, as different thresholds lead to different combinations of the number of biopsies and the delay in detection of cancer progression. An approach is to choose a risk threshold which leads to personalized schedule dominant (e.g., 10% risk) over the currently practiced schedules, for a given delay. Since personalized biopsy

schedules are less burdensome, they may lead to better compliance. A second limitation is that the results that we presented are valid only in a 10 year follow-up period, whereas prostate cancer is a slow progressing disease. Thus more detailed results, especially for *slow progressing* patients cannot be estimated. However, very few AS cohorts have a longer follow-period than PRIAS⁹. Another limitation is that our results are not valid when the patient data is missing not at random (MNAR).

There are multiple ways to extend the personalized decision making approach. One such way is to account for competing risks (see Table 1) in the joint model. Since biopsy Gleason grading is susceptible to inter-observer variation²⁵, accounting for it in our model will also be interesting to investigate further. To improve the decision making methodology, future consequences of a biopsy can be accounted in the model by combining Markov decision processes with joint models for time-to-event and longitudinal data. There is also a potential for including diagnostic information from magnetic resonance imaging (MRI), and quality of life measures in our model. However, given the scarceness of such information in the dataset, including it in the current model may not be feasible. We intend to further validate our results in a multi-center AS cohort, and subsequently develop a web application to assist in making shared decisions for biopsies.

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Declaration of conflicting interests

The Authors declare that there is no conflict of interest.

Supplemental material

Supplementary material for this article, containing Appendix A–D are available in the file 'supplementary.pdf'.

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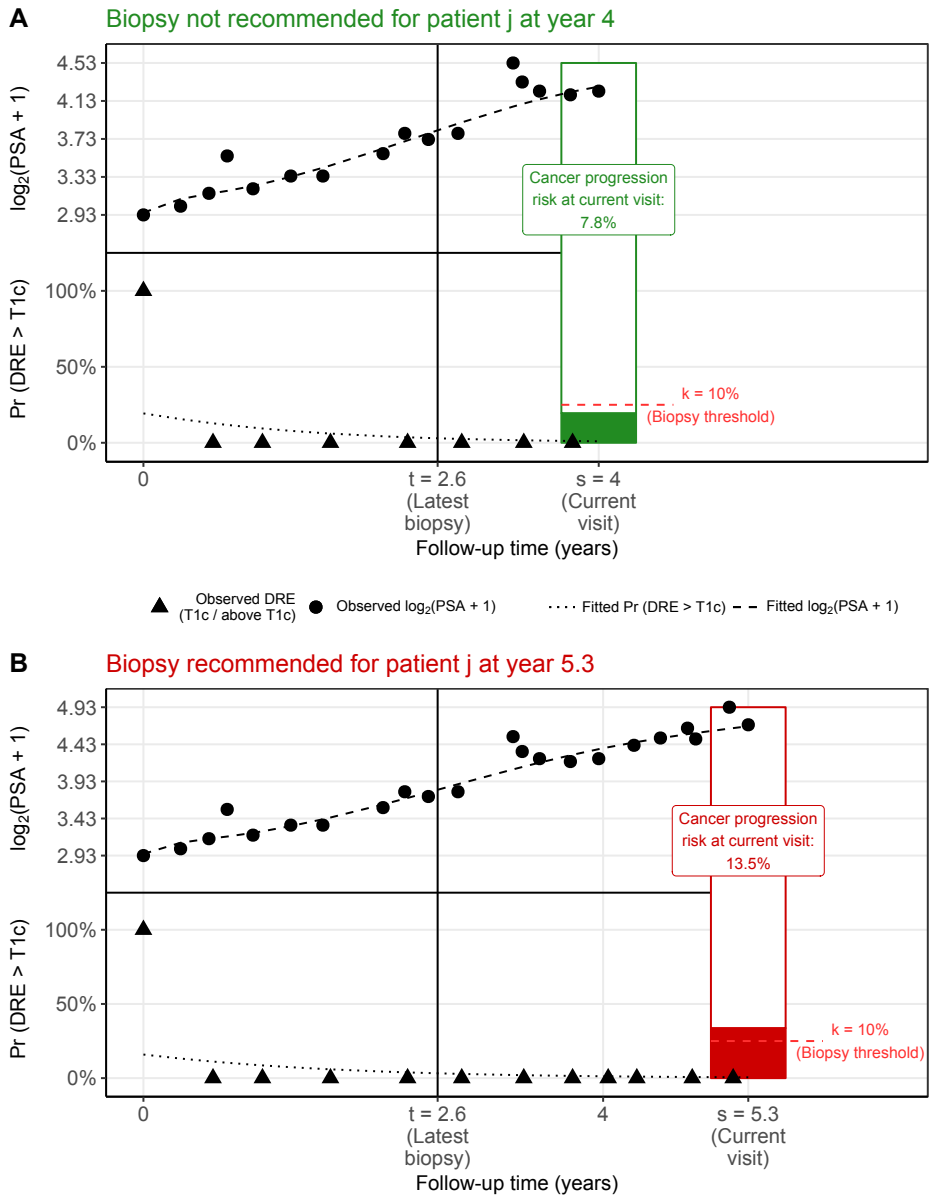


Figure 4. Illustration of personalized decision of biopsy for patient j at two different follow-up visits. Biopsy is recommended if the personalized cumulative risk of cancer progression estimated from the joint model fitted to the observed data of the patient, is higher than the example risk threshold for biopsy ($\kappa = 10\%$). **Panel A:** biopsy is not recommended for the patient j at the follow-up visit time $s = 4$ years, because his estimated personalized cumulative risk of cancer progression (7.8%) is less than the threshold. **Panel B:** biopsy is recommended for the patient j at the follow-up visit time $s = 5.3$ years, because his estimated personalized cumulative risk of cancer progression (13.5%) is more than the threshold.

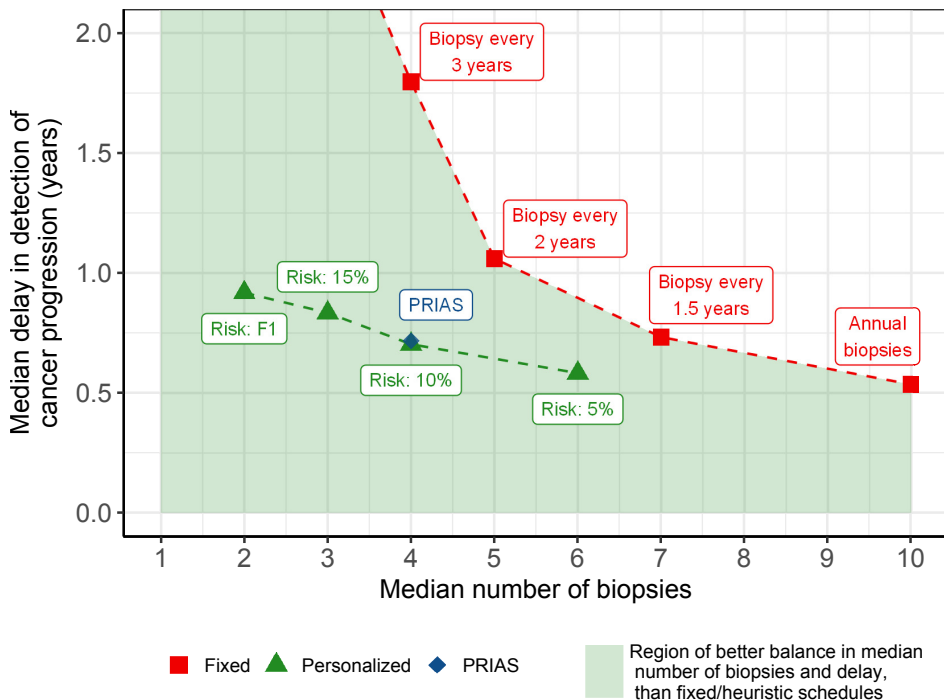


Figure 5. Burden-biopsy frontier: Median number of biopsies (X-axis), and median delay in detection of cancer progression (in years, Y-axis), estimated from the simulation study. Results for currently practiced fixed/heuristic biopsy schedules are shown by red squares, for PRIAS schedule by a blue rhombus, and for personalized schedules by green triangles. **Types of personalized schedules:** Risk: 15%, Risk: 10%, and Risk: 5% approaches, schedule a biopsy if the cumulative risk of cancer progression at a visit is more than 15%, 10%, and 5%, respectively. Risk: F1 works similar as previous, except that for each patient, a visit-specific risk threshold is chosen by maximizing F₁ score (see [Methods](#)). The green shaded region depicts the region of better balance in the median number of biopsies and median delay than the currently practiced fixed/heuristic schedules.

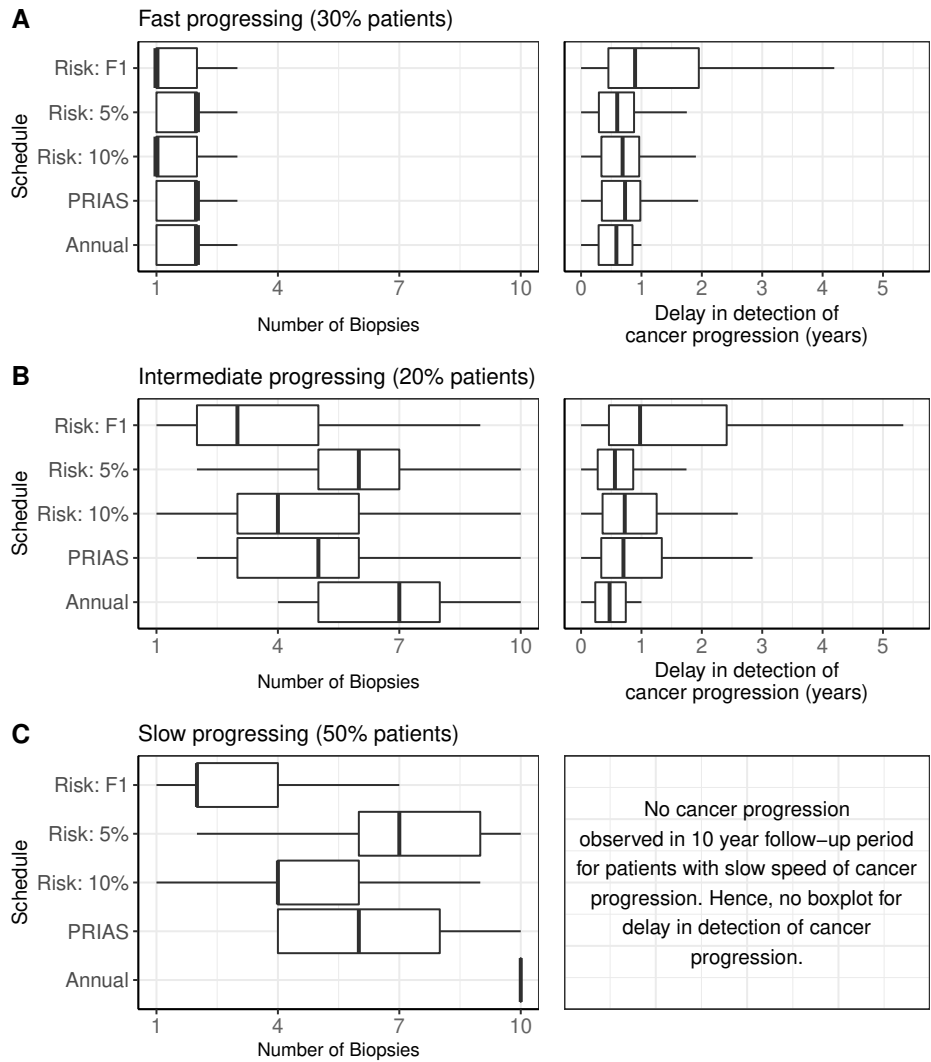


Figure 6. Boxplot showing variation in the number of biopsies, and the delay in detection of cancer progression, in years (time of positive biopsy - true time of cancer progression) for various biopsy schedules. Biopsies are conducted until cancer progression is detected. **Panel A:** results for simulated patients who had a faster speed of cancer progression, with progression times between 0 and 3.5 years. **Panel B:** results for simulated patients who had an intermediate speed of cancer progression, with progression times between 3.5 and 10 years. **Panel C:** results for simulated patients who did not have cancer progression in the ten years of follow-up. **Types of personalized schedules:** Risk: 10% and Risk: 5% approaches, schedule a biopsy if the cumulative risk of cancer progression at a visit is more than 10% and 5%, respectively. Risk: F1 works similar as previous, except that a visit-specific risk threshold is chosen by maximizing F₁ score (see [Methods](#)). Annual corresponds to a schedule of yearly biopsies and PRIAS corresponds to biopsies as per PRIAS protocol (see [Introduction](#)).

Supplementary Materials for “Personalized Decision Making for Biopsies in Prostate Cancer Active Surveillance Programs”

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Appendix A A Bivariate Joint Model for the Longitudinal PSA, and DRE Measurements, and Time to Cancer Progression

In this appendix section, we first provide an introduction to the world’s largest active surveillance (AS) program called Prostate Cancer Research International Active Surveillance, abbreviated as PRIAS (Bokhorst et al., 2016), that we use to develop our methodology. We then present an introduction to the joint models for time-to-event and bivariate longitudinal data (Rizopoulos, 2012; Tsiatis and Davidian, 2004), that we fit to the PRIAS dataset. Lastly, we present the parameter estimation for our model using the Bayesian approach.

Appendix A.1 PRIAS Dataset

To develop our methodology we use the data of prostate cancer patients (see Table 1) from the world’s largest AS study called PRIAS (Bokhorst et al., 2016). More than 100 medical centers from 17 countries worldwide contribute to the collection of data, utilizing a common study protocol and a web-based tool, both available at www.prias-project.org. We use data collected over a period of ten years, between December 2006 (beginning of PRIAS study) and December 2016. The primary event of interest is cancer progression detected upon a positive biopsy. Biopsies are scheduled at the following fixed follow-up times (measured since inclusion in AS): year 1, 4, 7, and 10, and every 5 years thereafter. An annual schedule of biopsies is prescribed to those patients who have a PSA (prostate-specific antigen) doubling time between 0 and 10 years. The PSA doubling time at any point during follow-up is measured as the inverse of the slope of the regression line through the base two logarithm of the observed PSA values. The time of cancer progression is

Table 1: **Summary statistics for the PRIAS dataset.** The primary event of interest is cancer progression. A DRE measurement equal to T1c (Schröder et al., 1992) indicates a clinically inapparent tumor which is not palpable or visible by imaging, while tumors with $\text{DRE} > \text{T1c}$ are palpable. The abbreviation IQR means interquartile range.

Data	Value
Total patients	5270
Cancer progression (primary event)	866
Loss to follow-up (anxiety or unknown)	685
Patient removal on the basis of PSA and DRE	464
Death (unrelated to prostate cancer)	61
Death (related to prostate cancer)	2
Median Age (years)	70 (IQR: 65–75)
Total PSA measurements	46015
Median number of PSA measurements per patient	7 (IQR: 7–12)
Median PSA value (ng/mL)	5.6 (IQR: 4.0–7.5)
Total DRE measurements	25606
Median number of DRE measurements per patient	4 (IQR: 3–7)
DRE = T1c (%)	23538/25606 (92%)

interval censored because biopsies are scheduled periodically. There are three types of competing events, namely death, removal of patients from AS on the basis of their observed DRE and PSA measurements, and loss to follow-up. We assume these three types of events to be censored observations (see Appendix A.5 for details). However, our model allows removal of patients to depend on observed longitudinal data and baseline covariates of the patient. Under the aforementioned assumption of censoring, Figure 1 shows the cumulative risk of cancer progression over the study follow-up period.

For all patients, PSA measurements (ng/mL) are scheduled every 3 months for the first 2 years and every 6 months thereafter. The DRE measurements are scheduled every 6 months. We use the DRE measurements as $\text{DRE} = \text{T1c}$ versus $\text{DRE} > \text{T1c}$. A DRE measurement equal to T1c (Schröder et al., 1992) indicates a clinically inapparent tumor which is not palpable or visible by imaging, while tumors with $\text{DRE} > \text{T1c}$ are palpable.

Data Accessibility: The PRIAS database is not openly accessible. However, access to the database on the basis of a by the PRIAS steering committee approved study proposal can be requested via the contact links on the website of the PRIAS program www.prias-project.org.

Appendix A.2 Model Definition

Let T_i^* denote the true cancer progression time of the i -th patient included in PRIAS. Since biopsies are conducted periodically, T_i^* is observed with interval censoring $l_i < T_i^* \leq r_i$. When progression is observed for the patient at his latest biopsy time r_i , then l_i denotes the time of the second latest biopsy. Otherwise, l_i denotes the time of the latest biopsy and $r_i = \infty$. Let \mathbf{y}_{di} and \mathbf{y}_{pi} denote his observed DRE and PSA longitudinal measurements, respectively. The observed data of all n patients is denoted by $\mathcal{D}_n = \{l_i, r_i, \mathbf{y}_{di}, \mathbf{y}_{pi}; i = 1, \dots, n\}$.

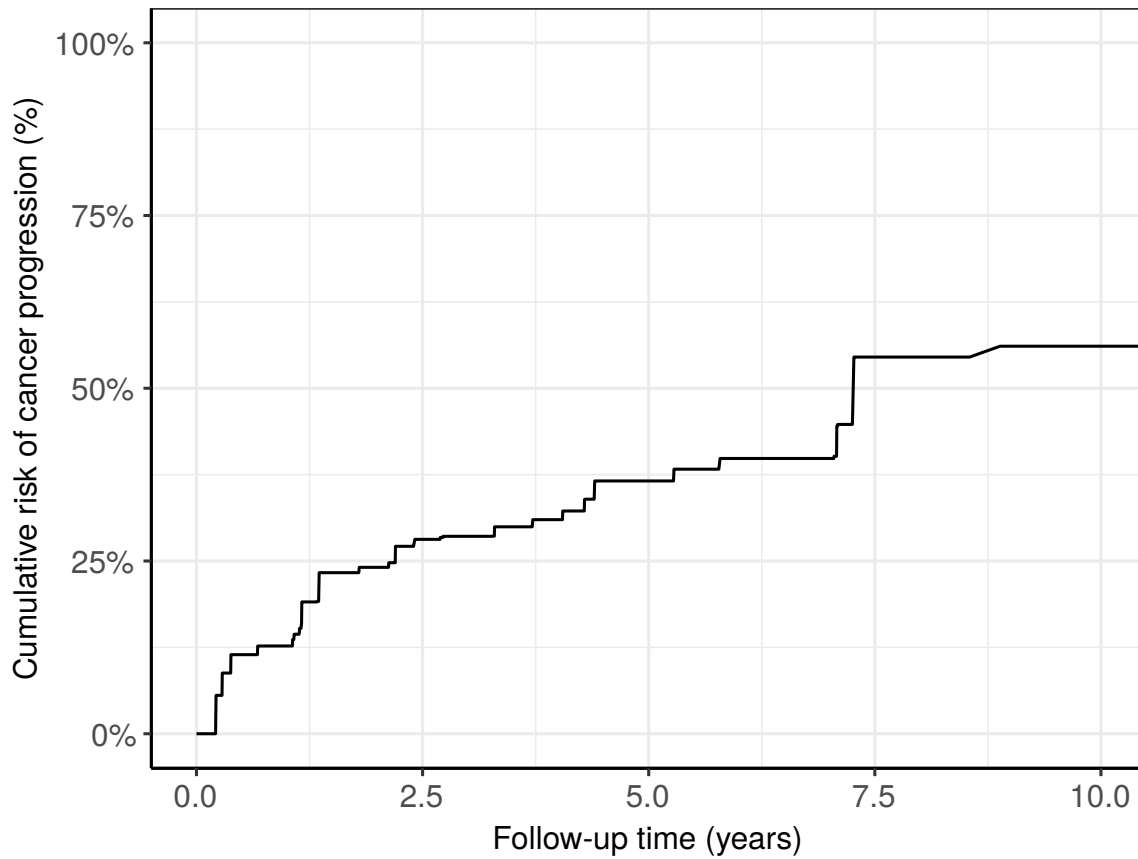


Figure 1: **Estimated cumulative risk of cancer progression in AS** for patients in the Prostate Cancer Research International Active Surveillance (PRIAS) dataset. Nearly 50% patients (*slow progressing*) do not progress in the ten year follow-up period. Cumulative risk is estimated using nonparametric maximum likelihood estimation (Turnbull, 1976), to account for interval censored cancer progression times observed in the PRIAS dataset. Censoring includes death, removal from AS on the basis of observed longitudinal data, and patient dropout.

In our joint model, the patient-specific DRE and PSA measurements over time are modeled using a bivariate generalized linear mixed effects sub-model. The sub-model for DRE is given by (see Panel A, Figure 2):

$$\begin{aligned} \text{logit}[\Pr\{y_{di}(t) > \text{T1c}\}] = & \beta_{0d} + b_{0di} + (\beta_{1d} + b_{1di})t \\ & + \beta_{2d}(\text{Age}_i - 70) + \beta_{3d}(\text{Age}_i - 70)^2 \end{aligned} \quad (1)$$

where, t denotes the follow-up visit time, and Age_i is the age of the i -th patient at the time of inclusion in AS. The fixed effect parameters are denoted by $\{\beta_{0d}, \dots, \beta_{3d}\}$, and $\{b_{0di}, b_{1di}\}$ are the patient specific random effects. With this definition, we assume that the patient-specific log odds of obtaining a DRE measurement larger than T1c remain linear over time.

The mixed effects sub-model for PSA is given by (see Panel B, Figure 2):

$$\begin{aligned} \log_2 \{y_{pi}(t) + 1\} = & m_{pi}(t) + \varepsilon_{pi}(t), \\ m_{pi}(t) = & \beta_{0p} + b_{0pi} + \sum_{k=1}^4 (\beta_{kp} + b_{kpi})B_k(t, \mathcal{K}) \\ & + \beta_{5p}(\text{Age}_i - 70) + \beta_{6p}(\text{Age}_i - 70)^2, \end{aligned} \quad (2)$$

where, $m_{pi}(t)$ denotes the underlying measurement error free value of $\log_2(\text{PSA} + 1)$

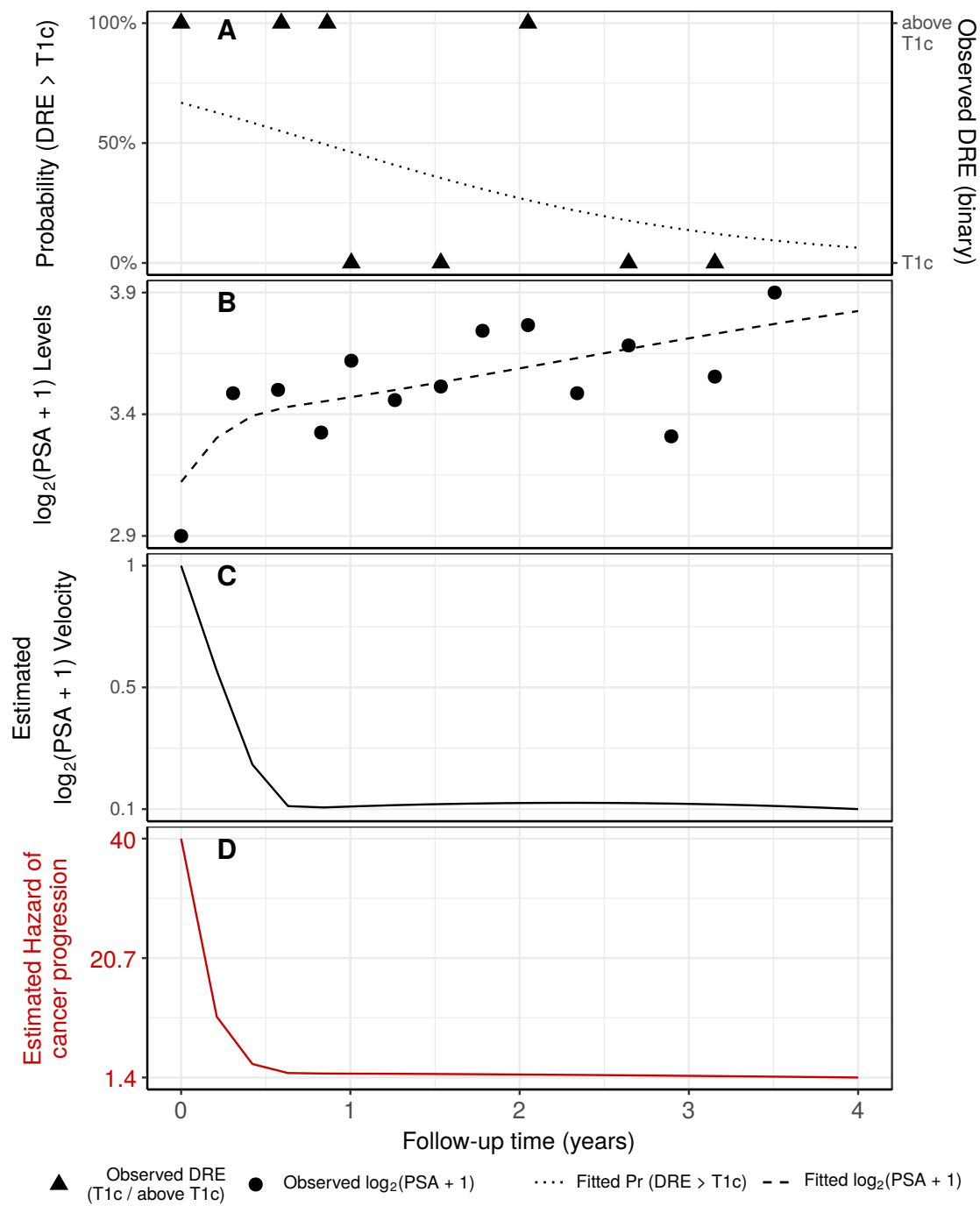


Figure 2: **Illustration of the joint model fitted to the PRIAS dataset.** **Panel A:** shows the observed DRE measurements and the fitted probability of obtaining DRE > T1c (Equation 1) for . **Panel B:** shows the observed and fitted $\log_2(\text{PSA} + 1)$ measurements (Equation 2). **Panel C:** shows the estimated $\log_2(\text{PSA} + 1)$ velocity (velocity cannot be observed directly) over time. The hazard function (Equation 3) shown in **Panel D**, depends on the fitted log odds of having a DRE > T1c, and the fitted $\log_2(\text{PSA} + 1)$ value and velocity.

transformed (Lin et al., 2000; Pearson et al., 1994) measurements at time t . We model it non-linearly over time using B-splines (De Boor, 1978). To this end, our B-spline basis function $B_k(t, \mathcal{K})$ has 3 internal knots at $\mathcal{K} = \{0.1, 0.7, 4\}$ years, and boundary knots at 0 and 5.42 years (95-th percentile of the observed follow-up times). The fixed effect parameters are denoted by $\{\beta_{0p}, \dots, \beta_{6p}\}$, and $\{b_{0pi}, \dots, b_{4pi}\}$ are the

patient specific random effects. The error $\varepsilon_{pi}(t)$ is assumed to be t-distributed with three degrees of freedom (see Appendix B.1) and scale σ , and is independent of the random effects.

To account for the correlation between the DRE and PSA measurements of a patient, we link their corresponding random effects. More specifically, the complete vector of random effects $\mathbf{b}_i = (b_{0di}, b_{1di}, b_{0pi}, \dots, b_{4pi})^T$ is assumed to follow a multivariate normal distribution with mean zero and variance-covariance matrix \mathbf{D} .

To model the impact of DRE and PSA measurements on the risk of cancer progression, our joint model uses a relative risk sub-model. More specifically, the hazard of cancer progression $h_i(t)$ at a time t is given by (see Panel D, Figure 2):

$$h_i(t) = h_0(t) \exp \left(\gamma_1(\text{Age}_i - 70) + \gamma_2(\text{Age}_i - 70)^2 + \alpha_{1d} \text{logit}[\Pr\{y_{di}(t) > \text{T1c}\}] + \alpha_{1p} m_{pi}(t) + \alpha_{2p} \frac{\partial m_{pi}(t)}{\partial t} \right), \quad (3)$$

where, γ_1, γ_2 are the parameters for the effect of age. The parameter α_{1d} models the impact of log odds of obtaining a DRE > T1c on the hazard of cancer progression. The impact of PSA on the hazard of cancer progression is modeled in two ways: a) the impact of the error free underlying PSA value $m_{pi}(t)$ (see Panel B, Figure 2), and b) the impact of the underlying PSA velocity $\partial m_{pi}(t)/\partial t$ (see Panel C, Figure 2). The corresponding parameters are α_{1p} and α_{2p} , respectively. Lastly, $h_0(t)$ is the baseline hazard at time t , and is modeled flexibly using P-splines (Eilers and Marx, 1996). More specifically:

$$\log h_0(t) = \gamma_{h_0,0} + \sum_{q=1}^Q \gamma_{h_0,q} B_q(t, \mathbf{v}),$$

where $B_q(t, \mathbf{v})$ denotes the q -th basis function of a B-spline with knots $\mathbf{v} = v_1, \dots, v_Q$ and vector of spline coefficients γ_{h_0} . To avoid choosing the number and position of knots in the spline, a relatively high number of knots (e.g., 15 to 20) are chosen and the corresponding B-spline regression coefficients γ_{h_0} are penalized using a differences penalty (Eilers and Marx, 1996). An example fitted hazard is shown in panel D of Figure 2.

Appendix A.3 Parameter Estimation

We estimate the parameters of the joint model using Markov chain Monte Carlo (MCMC) methods under the Bayesian framework. Let $\boldsymbol{\theta}$ denote the vector of all of the parameters of the joint model. The joint model postulates that given the random effects, the time to cancer progression, and the DRE and PSA measurements taken over time are all mutually independent. Under this assumption the posterior distribution of the parameters is given by:

$$\begin{aligned} p(\boldsymbol{\theta}, \mathbf{b} \mid \mathcal{D}_n) &\propto \prod_{i=1}^n p(l_i, r_i, \mathbf{y}_{di}, \mathbf{y}_{pi} \mid \mathbf{b}_i, \boldsymbol{\theta}) p(\mathbf{b}_i \mid \boldsymbol{\theta}) p(\boldsymbol{\theta}) \\ &\propto \prod_{i=1}^n p(l_i, r_i \mid \mathbf{b}_i, \boldsymbol{\theta}) p(\mathbf{y}_{di} \mid \mathbf{b}_i, \boldsymbol{\theta}) p(\mathbf{y}_{pi} \mid \mathbf{b}_i, \boldsymbol{\theta}) p(\mathbf{b}_i \mid \boldsymbol{\theta}) p(\boldsymbol{\theta}), \\ p(\mathbf{b}_i \mid \boldsymbol{\theta}) &= \frac{1}{\sqrt{(2\pi)^q \det(\mathbf{D})}} \exp(\mathbf{b}_i^T \mathbf{D}^{-1} \mathbf{b}_i), \end{aligned}$$

where, the likelihood contribution of the DRE outcome, conditional on the random effects is:

$$p(\mathbf{y}_{di} | \mathbf{b}_i, \boldsymbol{\theta}) = \prod_{k=1}^{n_{di}} \frac{\exp \left[-\text{logit} \{ \Pr(y_{dik} > \text{T1c}) \} I(y_{dik} = \text{T1c}) \right]}{1 + \exp \left[-\text{logit} \{ \Pr(y_{dik} > \text{T1c}) \} \right]},$$

where $I(\cdot)$ is an indicator function which takes the value 1 if the k -th repeated DRE measurement $y_{dik} = \text{T1c}$, and takes the value 0 otherwise. The likelihood contribution of the PSA outcome, conditional on the random effects is:

$$p(\mathbf{y}_{pi} | \mathbf{b}_i, \boldsymbol{\theta}) = \frac{1}{(\sqrt{2\pi}\sigma^2)^{n_{pi}}} \exp \left(-\frac{\|\mathbf{y}_{pi} - \mathbf{m}_{pi}\|^2}{\sigma^2} \right),$$

The likelihood contribution of the time to cancer progression outcome is given by:

$$p(l_i, r_i | \mathbf{b}_i, \boldsymbol{\theta}) = \exp \left\{ -\int_0^{l_i} h_i(s) ds \right\} - \exp \left\{ -\int_0^{r_i} h_i(s) ds \right\}. \quad (4)$$

The integral in (4) does not have a closed-form solution, and therefore we use a 15-point Gauss-Kronrod quadrature rule to approximate it.

We use independent normal priors with zero mean and variance 100 for the fixed effects $\{\beta_{0d}, \dots, \beta_{3d}, \beta_{0p}, \dots, \beta_{6p}\}$, and inverse Gamma prior with shape and rate both equal to 0.01 for the parameter σ^2 . For the variance-covariance matrix \mathbf{D} of the random effects we take inverse Wishart prior with an identity scale matrix and degrees of freedom equal to 7 (number of random effects). For the relative risk model's parameters $\{\gamma_1, \gamma_2\}$ and the association parameters $\{\alpha_{1d}, \alpha_{1p}, \alpha_{2p}\}$, we use independent normal priors with zero mean and variance 100.

Appendix A.4 Personalized Posterior Predictive Distribution of Time of Cancer Progression

Let us assume a new patient j , for whom we need to make a personalized biopsy decision. Let his current follow-up visit time be s , latest time of biopsy be $t \leq s$, observed vectors of DRE and PSA measurements be $\mathcal{Y}_{dj}(s)$ and $\mathcal{Y}_{pj}(s)$, respectively. The combined information from the observed data is given by the following posterior predictive distribution $g(T_j^*)$ of his time of cancer progression T_j^* :

$$\begin{aligned} g(T_j^*) &= p\{T_j^* | T_j^* > t, \mathcal{Y}_{dj}(s), \mathcal{Y}_{pj}(s), \mathcal{D}_n\} \\ &= \int \int p(T_j^* | T_j^* > t, \mathbf{b}_j, \boldsymbol{\theta}) \\ &\quad \times p\{\mathbf{b}_j | T_j^* > t, \mathcal{Y}_{dj}(s), \mathcal{Y}_{pj}(s), \boldsymbol{\theta}\} p(\boldsymbol{\theta} | \mathcal{D}_n) d\mathbf{b}_j d\boldsymbol{\theta}. \end{aligned}$$

The distribution $g(T_j^*)$ depends on observed data of the patient $\mathcal{Y}_{dj}(s)$ and $\mathcal{Y}_{pj}(s)$, as well information from the PRIAS dataset \mathcal{D}_n via the posterior distribution of random effects \mathbf{b}_j and posterior distribution of the vector of all parameters $\boldsymbol{\theta}$, respectively.

The distribution can be estimated as detailed in Rizopoulos, Molenberghs, and Lesaffre, (2017). However, majority of the prostate cancer patients do not progress in the ten year follow-up period of PRIAS (see Figure 1). Consequently, the personalized density function of cancer progression $g(T_j^*)$ can only be estimated for time points falling within the ten year follow-up.

Appendix A.5 PSA Dependent Biopsy Schedule of PRIAS, and Competing Risks

PSA dependent interval censored time of cancer progression: The true time of cancer progression T_i^* is not known for any of the patients in PRIAS. In order to detect cancer progression, PRIAS uses a fixed schedule of biopsies wherein biopsies are conducted at year one, year four, year seven and year ten of follow-up, and every five years thereafter. However, PRIAS switches to a more frequent annual biopsy schedule for faster-progressing patients. These are patients with PSA doubling time (PSA-DT) between 0 and 10 years, which is measured as the inverse of the slope of the regression line through the base two logarithm of PSA values. Thus, the interval $l_i < T_i^* \leq r_i$ in which cancer progression is detected depends on the observed PSA values.

Competing events: The primary event of interest in this paper is cancer progression observed via a positive biopsy. There are three types of competing events, namely death of 63 patients, of which 61 died from non prostate cancer related reasons; removal of 464 patients from AS on the basis of their observed DRE and PSA measurements; and loss to follow-up of 685 patients because of patient anxiety or unknown reasons. Death from non cancer related reasons impedes occurrence of cancer progression, and is indeed a competing event.

The number of patients obtaining the event death is small compared to the number of patients who obtain the primary event cancer progression. Hence in this paper considering death as non-informative censoring may be viable. We also consider loss to follow-up as non-informative censoring, which may not always be true. This is especially the case when the reason of loss to follow-up is unknown. However, when the reason of loss to follow-up is patient anxiety, it is often on the basis of their observed results. Given the large number of loss to follow-up patients, considering these patients as censored is a limitation of our work. However, the problem of unknown reason of dropout is not specific to only our model. For the remaining patients who are removed from AS on the basis their observed longitudinal data, the removal does not impede occurrence of cancer progression. In the next paragraph we show that the removal of these patients is non-informative about the parameters of the model for the true time of cancer progression.

Given the aforementioned issues of PSA dependent interval censoring and removal of patients on the basis of their observed longitudinal data is natural to question in this scenario if the parameters of the joint model are affected by these two. However, because the parameters of the joint model are estimated using a full likelihood approach (Tsiatis and Davidian, 2004), the joint model allows the schedule of biopsies, as well as censoring to depend upon the observed DRE and PSA measurements (e.g., via PSA-DT), under the condition that the model is correctly specified. To show this, consider the following full general specification of the joint model that we use. Let $\mathbf{y}_{di}, \mathbf{y}_{pi}$ denote the observed DRE and PSA measurements for the i -th patient, and l_i, r_i denote the two time points of the interval in which GR occurs for the i -th patient. In addition let T_i^S and $\mathcal{V}_{di}, \mathcal{V}_{pi}$ denote the schedule of biopsies, and the schedule of DRE and PSA measurements, respectively. Let G_i^* denote the time of removal from AS without observing cancer progression. Under the assumption that $T_i^S, G_i^*, \mathcal{V}_{di}, \mathcal{V}_{pi}$ may depend upon only the observed data $\mathbf{y}_{di}, \mathbf{y}_{pi}$,

the joint likelihood of the various processes is given by:

$$p(\mathbf{y}_{di}, \mathbf{y}_{pi}, l_i, r_i, T_i^S, G_i^*, \mathcal{V}_{di}, \mathcal{V}_{pi} \mid \boldsymbol{\theta}, \boldsymbol{\psi}) = p(\mathbf{y}_{di}, \mathbf{y}_{pi}, l_i, r_i \mid \boldsymbol{\theta}) \\ \times p(T_i^S, G_i^*, \mathcal{V}_{di}, \mathcal{V}_{pi} \mid \mathbf{y}_{di}, \mathbf{y}_{pi}, \boldsymbol{\psi}).$$

From this decomposition we can see that even if the processes $T_i^S, G_i^*, \mathcal{V}_{di}, \mathcal{V}_{pi}$ may be determined from $\mathbf{y}_{di}, \mathbf{y}_{pi}$, if we are interested in the parameters $\boldsymbol{\theta}$ of the joint distribution of longitudinal and event outcomes, we can maximize the likelihood based on the first term and ignore the second term. In other words, the second term will not carry information for $\boldsymbol{\theta}$. Lastly, since we use a full likelihood approach with an interval censoring specification, the estimates that we obtain are consistent and asymptotically unbiased (Gentleman and Geyer, 1994), despite the interval censoring observed.

Appendix B Parameter Estimates from the Joint Model Fitted to the PRIAS Dataset

We fit a joint model to the PRIAS dataset using the R package **JMbayes** (Rizopoulos, 2016). The corresponding posterior parameter estimates are shown in Table 3 (longitudinal sub-model for DRE outcome), Table 4 (longitudinal sub-model for PSA outcome) and Table 5 (relative risk sub-model). The parameter estimates for the variance-covariance matrix \mathbf{D} from the longitudinal sub-model are shown in the following Table 2:

Table 2: Estimated variance-covariance matrix \mathbf{D} of the random effects $\mathbf{b} = (b_{0d}, b_{1d}, b_{0p}, b_{1p}, b_{2p}, b_{3p}, b_{4p})$ (see Appendix A.2) from the joint model fitted to the PRIAS dataset. The variances of the random effects are highlighted along the diagonal of the variance-covariance matrix.

Random Effects	b_{0d}	b_{1d}	b_{0p}	b_{1p}	b_{2p}	b_{3p}	b_{4p}
b_{0d}	7.55	-0.56	-0.18	0.08	0.084	0.003	-0.019
b_{1d}	-0.564	1.379	0.081	0.119	0.165	0.266	0.219
b_{0p}	-0.182	0.081	0.208	0.031	0.034	0.068	0.014
b_{1p}	0.075	0.119	0.031	0.224	0.109	0.158	0.088
b_{2p}	0.084	0.165	0.034	0.109	0.293	0.324	0.238
b_{3p}	0.003	0.266	0.068	0.158	0.324	0.480	0.312
b_{4p}	-0.019	0.219	0.014	0.088	0.238	0.312	0.290

For the DRE mixed effects sub-model (see Equation 1) parameter estimates, in Table 3 we can see that the age of the patient trivially affects the baseline log odds of obtaining a DRE measurement larger than T1c. In Figure 3 we present the marginal evolution of log odds of obtaining a DRE larger than T1c, and the corresponding marginal probability, over a period of 10 years for a hypothetical AS patient who is included in AS at the age of 70 years. In addition, we present plots of observed DRE versus fitted probabilities of obtaining a DRE measurement larger than T1c, for nine randomly selected patients in Figure 4.

Table 3: Estimated mean and 95% credible interval for the parameters of the longitudinal sub-model (see Equation 1) for the DRE outcome.

Variable	Mean	Std. Dev	2.5%	97.5%	P
(Intercept)	-4.017	0.136	-4.270	-3.763	<0.001
(Age - 70)	0.058	0.009	0.041	0.075	<0.001
(Age - 70) ²	-0.001	0.001	-0.003	0.000	0.076
visitTimeYears	-0.604	0.095	-0.794	-0.437	<0.001

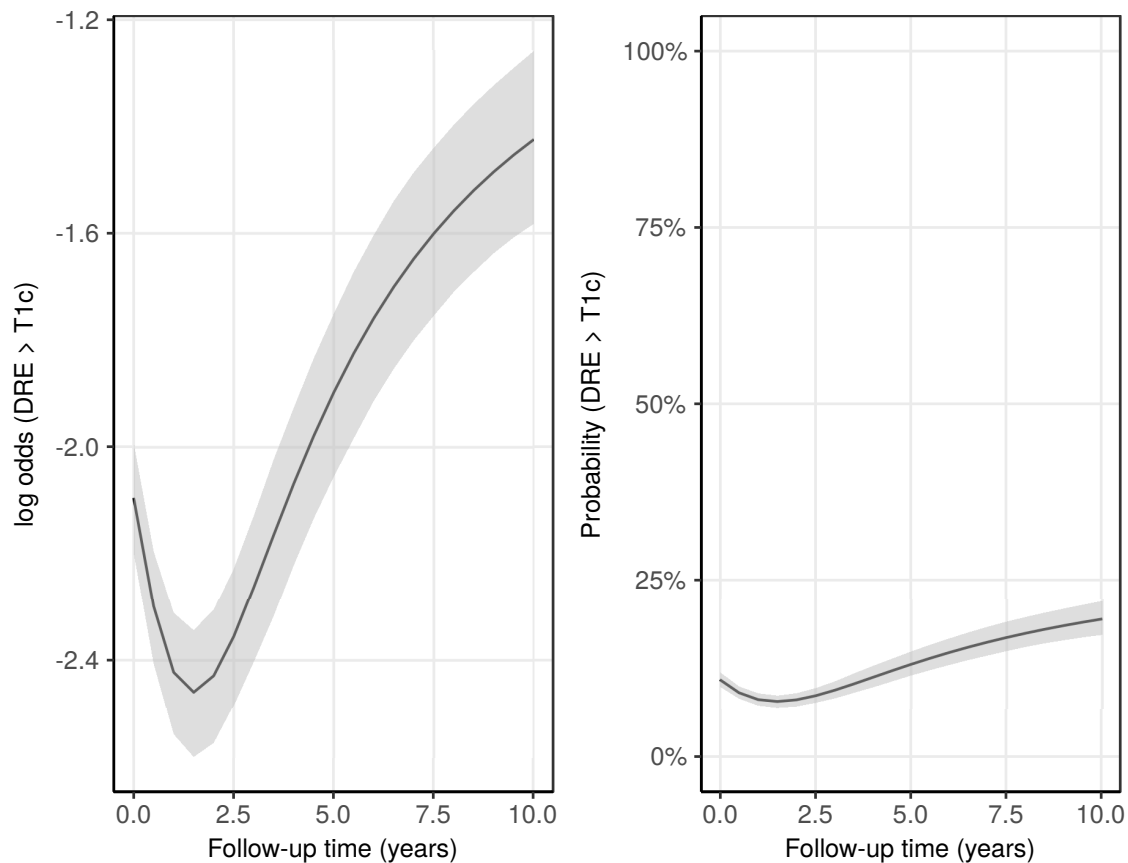


Figure 3: Fitted marginal evolution of the log odds of obtaining a DRE larger than T1c, and the corresponding marginal probability, with 95% credible interval. These results are for a hypothetical AS patient who is included in AS at the age of 70 years.

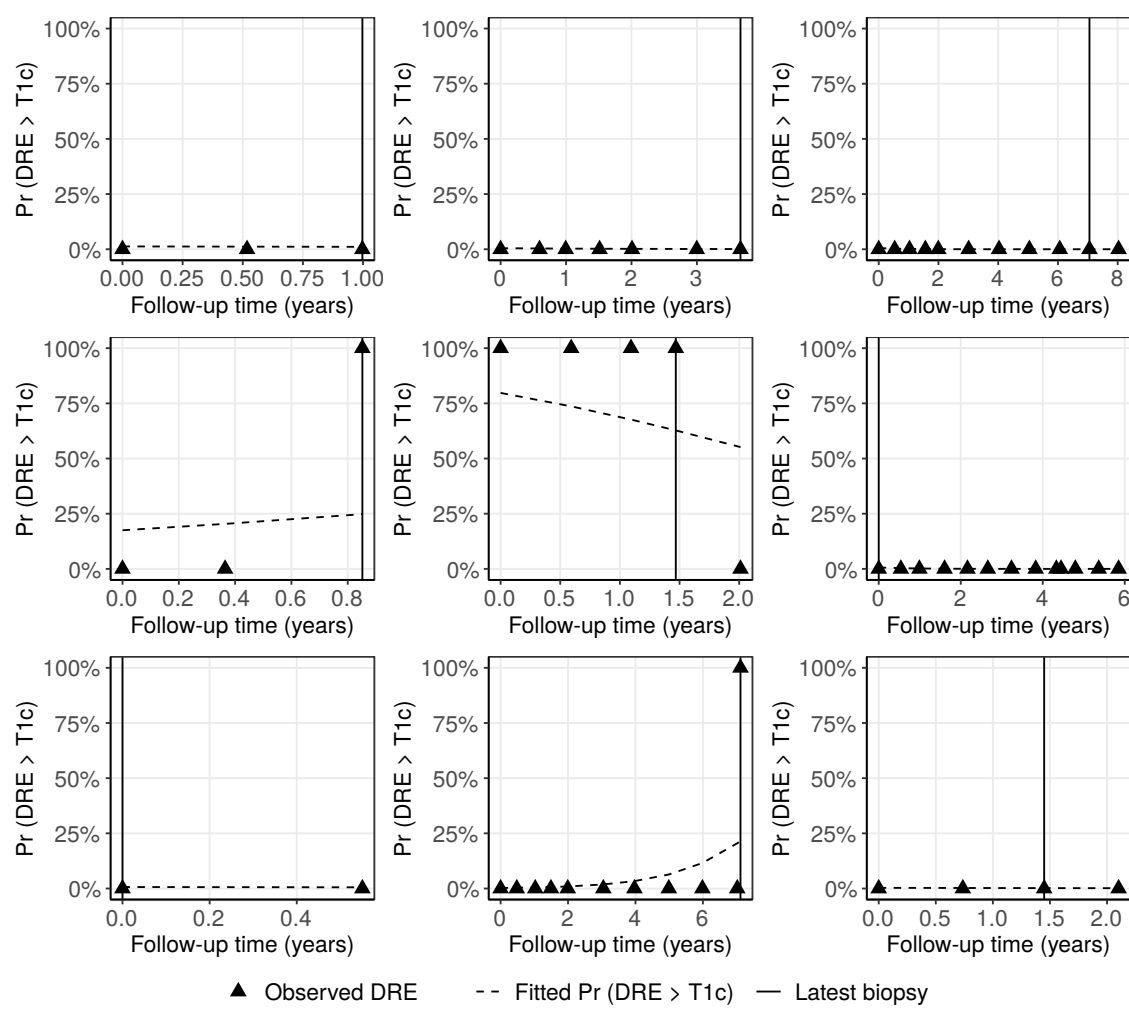


Figure 4: Observed DRE versus fitted probabilities of obtaining a DRE measurement larger than T1c, for nine randomly selected PRIAS patients. The fitted profiles utilize information from the observed DRE measurements, PSA measurements, and time of the latest biopsy. Observed DRE measurements plotted against 0% probability are equal to T1c. Observed DRE measurements plotted against 100% probability are larger than T1c.

For the PSA mixed effects sub-model parameter estimates (see Equation 2), in Table 4 we can see that the age of the patient trivially affects the baseline $\log_2(\text{PSA} + 1)$ measurement. Since the longitudinal evolution of $\log_2(\text{PSA} + 1)$ measurements is modeled with non-linear terms, the interpretation of the coefficients corresponding to time is not straightforward. In lieu of the interpretation, in Figure 5 we present the fitted marginal evolution of $\log_2(\text{PSA} + 1)$ over a period of 10 years for a hypothetical patient who is included in AS at the age of 70 years. In addition, we present plots of observed versus fitted PSA profiles for nine randomly selected patients in Figure 6.

Table 4: Estimated mean and 95% credible interval for the parameters of the longitudinal sub-model (see Equation 2) for the PSA outcome.

Variable	Mean	Std. Dev	2.5%	97.5%	P
(Intercept)	2.701	0.008	2.686	2.716	<0.001
(Age - 70)	0.003	0.001	0.001	0.005	<0.001
(Age - 70) ²	-4.7×10^{-4}	9.8×10^{-5}	-6.6×10^{-4}	-2.7×10^{-4}	<0.001
Spline: [0.00, 0.10] years	0.054	0.009	0.037	0.073	<0.001
Spline: [0.10, 0.70] years	0.177	0.012	0.151	0.200	<0.001
Spline: [0.70, 4.00] years	0.194	0.016	0.161	0.225	<0.001
Spline: [4.00, 5.42] years	0.341	0.015	0.312	0.371	<0.001
σ	0.137	0.001	0.135	0.138	

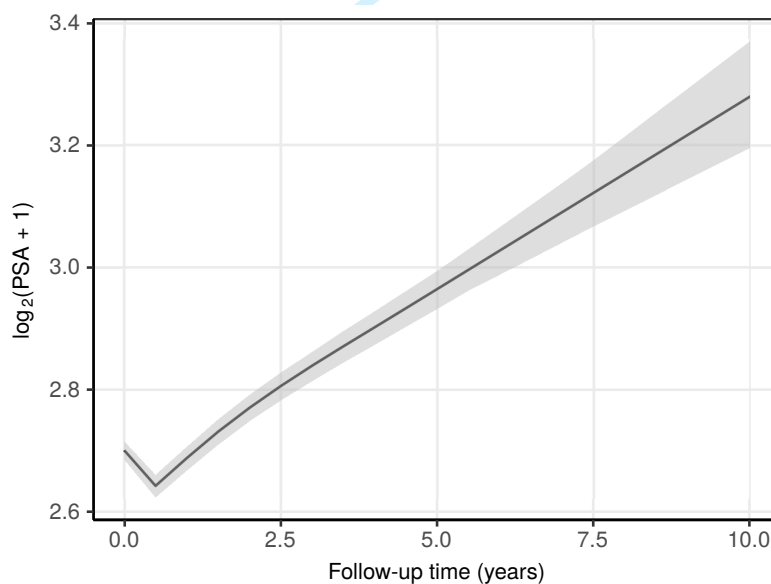


Figure 5: Fitted marginal evolution of $\log_2(\text{PSA} + 1)$ measurements over a period of 10 years with 95% credible interval, for a hypothetical patient who is included in AS at the age of 70 years.

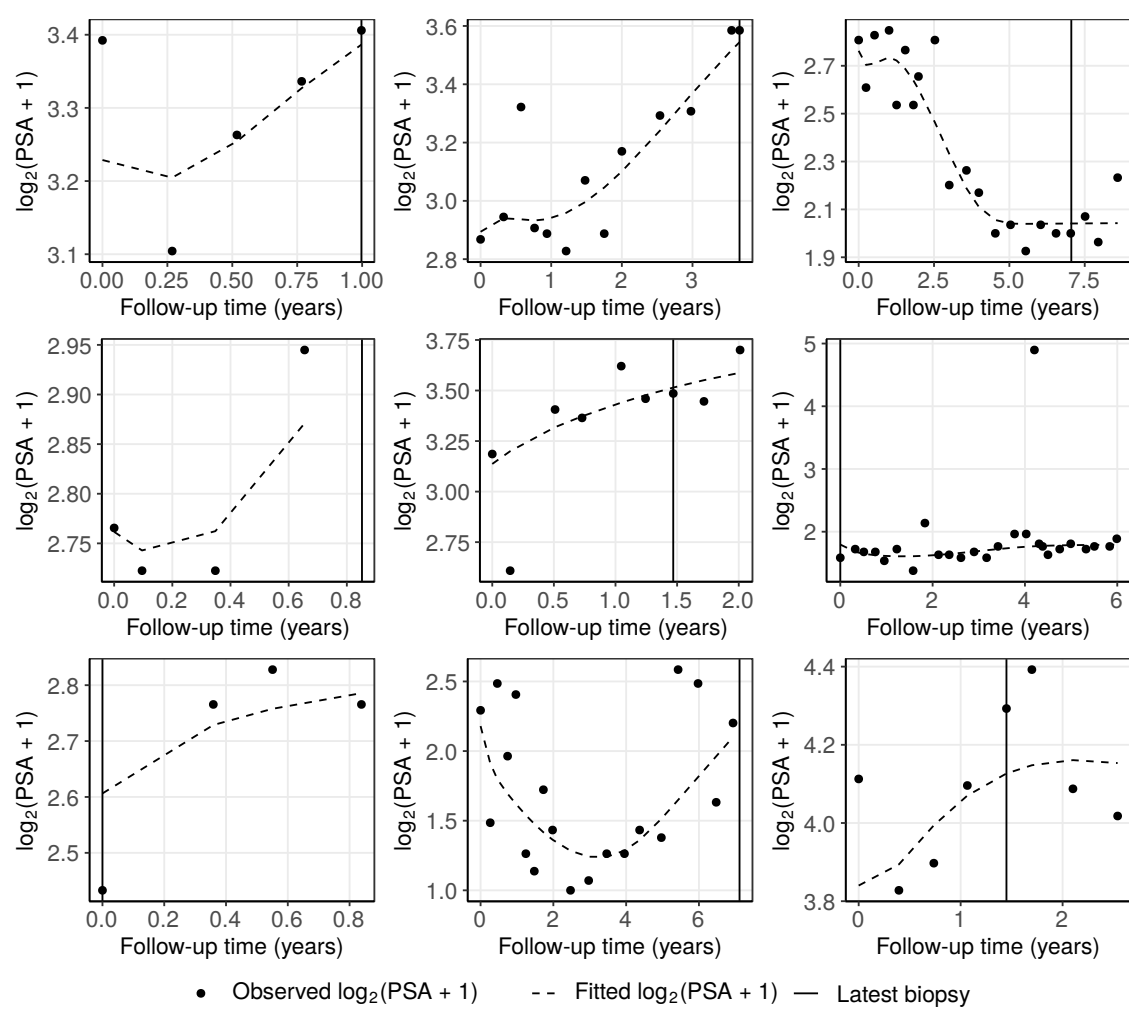


Figure 6: Fitted versus observed $\log_2(\text{PSA} + 1)$ profiles for nine randomly selected PRIAS patients. The fitted profiles utilize information from the observed PSA measurements, DRE measurements, and time of the latest biopsy.

For the relative risk sub-model (see Equation 3), the parameter estimates in Table 5 show that both $\log_2(\text{PSA} + 1)$ velocity, and the log odds of having DRE > T1c were significantly associated with the hazard of cancer progression.

Table 5: Estimated mean and 95% credible interval for the parameters of the relative risk sub-model (see Equation 3) of the joint model fitted to the PRIAS dataset.

Variable	Mean	Std. Dev	2.5%	97.5%	P
(Age – 70)	0.012	0.006	0.000	0.022	0.045
(Age – 70) ²	-0.001	0.001	-0.002	0.000	0.095
$\text{logit}\{\text{Pr}(\text{DRE} > \text{T1c})\}$	0.147	0.017	0.115	0.183	<0.001
Fitted $\log_2(\text{PSA} + 1)$ value	0.104	0.078	-0.044	0.256	0.193
Fitted $\log_2(\text{PSA} + 1)$ velocity	3.396	0.564	2.376	4.475	<0.001

It is important to note that since age, $\log_2(\text{PSA} + 1)$ value and velocity, and log odds of DRE > T1c are all measured on different scales, a comparison between the corresponding parameter estimates is not easy. To this end, in Table 6, we present the hazard (of cancer progression) ratio, for an increase in the aforementioned variables from their first to the third quartile. For example, an increase in log odds of DRE > T1c, from -6.650 to -4.356 (fitted first and third quartiles) corresponds to a hazard ratio of 1.402. The interpretation for the rest is similar.

Table 6: Hazard (of cancer progression) ratio and 95% credible interval (CI), for an increase in the variables of relative risk sub-model, from their first quartile (Q_1) to their third quartile (Q_3). Except for age, quartiles for all other variables are based on their fitted values obtained from the joint model fitted to the PRIAS dataset.

Variable	Q_1	Q_3	Hazard ratio [95% CI]
Age	65	75	1.129 [1.002, 1.251]
$\text{logit}\{\text{Pr}(\text{DRE} > \text{T1c})\}$	-6.650	-4.356	1.402 [1.301, 1.521]
$\log_2(\text{PSA} + 1)$ value	2.336	3.053	1.079 [0.969, 1.201]
$\log_2(\text{PSA} + 1)$ velocity	-0.032	0.161	1.938 [1.582, 2.372]

Appendix B.1 Assumption of t-distributed (df=3) Error Terms

With regards to the choice of the distribution for the error term ε_p for the PSA measurements (see Equation 2), we attempted fitting multiple joint models differing in error distribution, namely t-distribution with three, and four degrees of freedom, and a normal distribution for the error term. However, the model assumption for the error term were best met by the model with t-distribution having three degrees of freedom. The quantile-quantile plot of subject-specific residuals for the corresponding model in Panel A of Figure 7, shows that the assumption of t-distributed (df=3) errors is reasonably met by the fitted model.

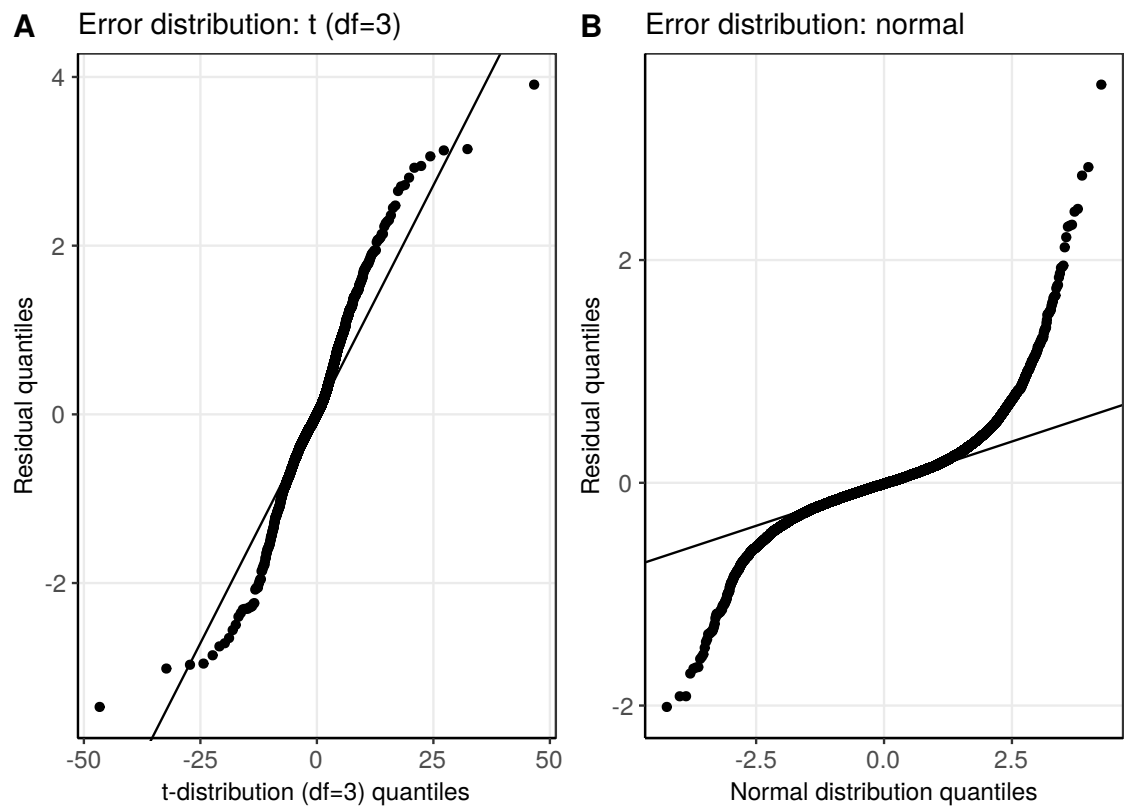


Figure 7: Quantile-quantile plot of subject-specific residuals from the joint models fitted to the PRIAS dataset. **Panel A:** model assuming a t-distribution (df=3) for the error term ε_p . **Panel B:** model assuming a normal distribution for the error term ε_p .

Appendix B.2 Predictive Performance of the Joint Model Fitted to the PRIAS dataset

We evaluate the predictive performance of our model using two measures: the area under the receiver operating characteristic curve (AUC), and the prediction error. Given the longitudinal nature of the data at hand, in a joint model time dependent AUC and prediction errors are more relevant. More specifically, given the time of latest biopsy t , and history of DRE and PSA measurements up to time s , we are interested in a medically relevant time frame $(t, s]$, within which the occurrence of cancer progression is of interest. In the case of prostate cancer, at any point in time it is of interest to identify patients who may have obtained cancer progression in the last one year ($s - t = 1$). Using data of the patients from the PRIAS study, we calculate the AUC and prediction error (see Rizopoulos, Molenberghs, and Lesaffre, (2017) for estimation) at the following time points (s): year one, year two, year three, year four, and year five (95-percentile of observed cancer progression times) of follow-up in AS. The resulting AUC, and prediction error are presented in Table 7.

Table 7: Area under the receiver operating characteristic curves (AUC), and prediction error, with 95% confidence interval in brackets.

Follow-up year	AUC	Prediction Error
1	0.651 [0.633, 0.663]	0.055 [0.052, 0.059]
2	0.621 [0.610, 0.640]	0.144 [0.140, 0.148]
3	0.748 [0.728, 0.770]	0.076 [0.075, 0.078]
4	0.710 [0.691, 0.736]	0.076 [0.072, 0.079]
5	0.592 [0.577, 0.614]	0.107 [0.103, 0.112]

Appendix C Full Results of the Simulation Study

In the simulation study, we evaluate the following in-practice fixed/heuristic approaches (Inoue et al., 2018; Loeb et al., 2014) for biopsies: biopsy every year, biopsy every one and a half years, biopsy every two years and biopsy every three years. For the personalized biopsy approach we evaluate three fixed risk thresholds: 5%, 10% and 15%, and a risk threshold chosen using F_1 score. Lastly, we also evaluate the PRIAS schedule of biopsies. We compare all the aforementioned schedules on two criteria, namely the number of biopsies they schedule and the corresponding delay in detection of cancer progression, in years (time of positive biopsy - true time of cancer progression). The corresponding results, using 500×250 test patients are presented in Table 8.

Table 8: **Simulation study results for all patients:** Estimated first, second (median), and third quartiles for number of biopsies (Q_1^{nb} , Q_2^{nb} , Q_3^{nb}) and for the delay in detection of cancer progression (Q_1^{delay} , Q_2^{delay} , Q_3^{delay}), in years, for various biopsy schedules. The delay is equal to the difference between the time of the positive biopsy and the unobserved true time of progression. The results in the table are obtained from test patients of our simulation study.

In-practice schedules	Q_1^{nb}	Q_2^{nb}	Q_3^{nb}	Q_1^{delay}	Q_2^{delay}	Q_3^{delay}
Every year (annual)	3	10	10	0.3	0.5	0.8
Every 1.5 years	2	7	7	0.4	0.7	1.1
Every 2 years	2	5	5	0.6	1.1	1.5
Every 3 years	1	4	4	1.1	1.8	2.3
PRIAS	2	4	6	0.3	0.7	1.0
Personalized approach						
Risk threshold: 5%	2	6	8	0.3	0.6	0.9
Risk threshold: 10%	2	4	5	0.3	0.7	1.0
Risk threshold: 15%	2	3	4	0.4	0.8	1.4
Risk using F_1 score	1	2	3	0.5	0.9	2.2

Since patients have varying cancer progression speeds, the impact of each schedule also varies with it. In order to highlight these differences, we divide results for three types of patients, as per their time of cancer progression. They are *fast*, *intermediate*, and *slow progressing* patients. Although such a division may be imperfect and can only be done retrospectively in a simulation setting, we show results for these three groups for the purpose of illustration. Roughly 50% of the patients did not obtain cancer progression in the ten year follow-up period of the simulation study. We assume these patients to be *slow progressing* patients. We assume *fast progressing* patients are the ones with an initially misdiagnosed state of cancer (Cooperberg et al., 2011) or high-risk patients who choose AS instead of immediate treatment upon diagnosis. These are roughly 30% of the population, having a cancer progression time less than 3.5 years. We label the remaining 20% patients as *intermediate progressing* patients. Table 9, Table 10, and Table 11 show the results for the *fast*, *intermediate*, and *slow progressing* patients, respectively.

Table 9: **Simulation study results for *fast progressing* patients (30% of all patients):** Estimated first, second (median), and third quartiles for number of biopsies (Q_1^{nb} , Q_2^{nb} , Q_3^{nb}) and for the delay in detection of cancer progression (Q_1^{delay} , Q_2^{delay} , Q_3^{delay}), in years, for various biopsy schedules. The delay is equal to the difference between the time of the positive biopsy and the unobserved true time of progression. The results in the table are obtained from the *fast progressing* test patients of our simulation study.

In-practice schedules	Q_1^{nb}	Q_2^{nb}	Q_3^{nb}	Q_1^{delay}	Q_2^{delay}	Q_3^{delay}
Every year (annual)	1	2	2	0.3	0.6	0.9
Every 1.5 years	1	1	2	0.4	0.8	1.2
Every 2 years	1	1	1	0.7	1.1	1.5
Every 3 years	1	1	1	1.5	2.0	2.5
PRIAS	1	2	2	0.3	0.7	1.0
Personalized approach						
Risk threshold: 5%	1	2	2	0.3	0.6	0.9
Risk threshold: 10%	1	1	2	0.3	0.7	1.0
Risk threshold: 15%	1	1	2	0.4	0.8	1.2
Risk using F_1 score	1	1	2	0.5	0.9	2.0

Table 10: **Simulation study results for *intermediate progressing* patients (20% of all patients):** Estimated first, second (median), and third quartiles for number of biopsies (Q_1^{nb} , Q_2^{nb} , Q_3^{nb}) and for the delay in detection of cancer progression (Q_1^{delay} , Q_2^{delay} , Q_3^{delay}), in years, for various biopsy schedules. The delay is equal to the difference between the time of the positive biopsy and the unobserved true time of progression. The results in the table are obtained from the *intermediate progressing* test patients of our simulation study.

In-practice schedules	Q_1^{nb}	Q_2^{nb}	Q_3^{nb}	Q_1^{delay}	Q_2^{delay}	Q_3^{delay}
Every year (annual)	5	7	8	0.2	0.5	0.7
Every 1.5 years	4	5	6	0.3	0.7	1.0
Every 2 years	3	4	4	0.4	1.0	1.5
Every 3 years	2	3	3	0.6	1.3	2.0
PRIAS	3	5	6	0.3	0.7	1.3
Personalized approach						
Risk threshold: 5%	5	6	7	0.3	0.6	0.9
Risk threshold: 10%	3	4	6	0.4	0.7	1.3
Risk threshold: 15%	3	3	5	0.4	0.8	1.7
Risk using F_1 score	2	3	5	0.5	1.0	2.4

Table 11: **Simulation study results for *slow progressing* patients (50% of all patients):** Estimated first, second (median), and third quartiles for number of biopsies (Q_1^{nb} , Q_2^{nb} , Q_3^{nb}) and for the delay in detection of cancer progression (Q_1^{delay} , Q_2^{delay} , Q_3^{delay}), in years, for various biopsy schedules. The delay is equal to the difference between the time of the positive biopsy and the unobserved true time of progression. The results in the table are obtained from the *slow progressing* test patients of our simulation study. Since no cancer progression is observed in the ten year follow-up period for these patients, delay cannot be estimated, and hence is not reported.

In-practice schedules	Q_1^{nb}	Q_2^{nb}	Q_3^{nb}	Q_1^{delay}	Q_2^{delay}	Q_3^{delay}
Every year (annual)	10	10	10			
Every 1.5 years	7	7	7			
Every 2 years	5	5	5			
Every 3 years	4	4	4			
PRIAS	4	6	8			
Personalized approach						
Risk threshold: 5%	6	7	9			
Risk threshold: 10%	4	4	6			
Risk threshold: 15%	2	3	4			
Risk using F_1 score	2	2	4			

Appendix D Source Code

The R code for fitting the joint model to the PRIAS dataset, and for the simulation study are available at https://github.com/anirudhtomer/prias/tree/master/src/decision_analytic. We refer to this location as ‘DATA_HOME’ in the rest of this document.

Appendix D.1 Fitting the joint model to the PRIAS dataset

Accessing the dataset: The PRIAS dataset is not openly accessible. However, access to the database can be requested via the contact links at www.prias-project.org.

Formatting the dataset: This dataset however is in the so-called wide format and also requires removal of incorrect entries. This can be done via the R script [DATA_HOME/fittingModel/dataset_cleaning.R](#). This will lead to two R objects, namely ‘prias.id’ and ‘prias_long’. The ‘prias.id’ object contains information about time of cancer progression for PRIAS patients. The ‘prias_long’ object contains longitudinal PSA, DRE measurements, time of biopsies and results of biopsies.

Fitting the joint model: We use a joint model for time to event and bivariate longitudinal data to model the evolution of PSA and DRE measurements over time, and to simultaneously model their association with the risk of cancer progression. The R package we use for this purpose is called **JMbayes** (<https://cran.r-project.org/web/packages/JMbayes/JMbayes.pdf>). The API we use, however, are currently not hosted on CRAN, and can be found here: <https://github.com/drizopoulos/JMbayes>. The joint model can be fitted via the script [DATA_HOME/fittingModel/psa_dre_jointAnalysis.R](#). It takes roughly 6 hours to run on an Intel core-i5 machine with 4 cores, and 8GB of RAM.

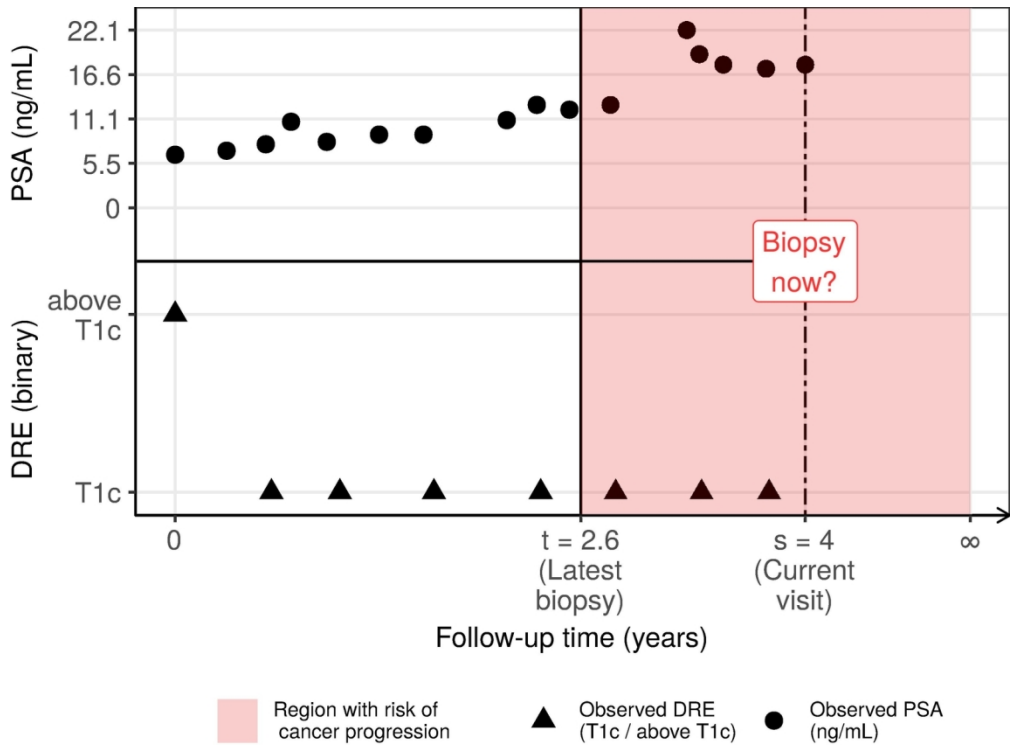
The graphs presented in the main manuscript, and the supplementary material can be generated by the scripts [DATA_HOME/fittingModel/demographs.R](#), and [DATA_HOME/fittingModel/modelDiagnostic.R](#), respectively.

Appendix D.2 Running the simulation study

The simulation study can be run by the following script: [DATA_HOME/simulationStudy/controller.R](#). Although it depends on other files, the code should run without errors as long as the directory structure is maintained. An entire simulation study may take weeks to run. However, this can be controlled via the variable ‘dataSetNums’ in the script. Graphs related to simulation study results can be generated from the scripts [DATA_HOME/simulationStudy/decisionMakingGraph.R](#) and [DATA_HOME/simulationStudy/produceResults.R](#).

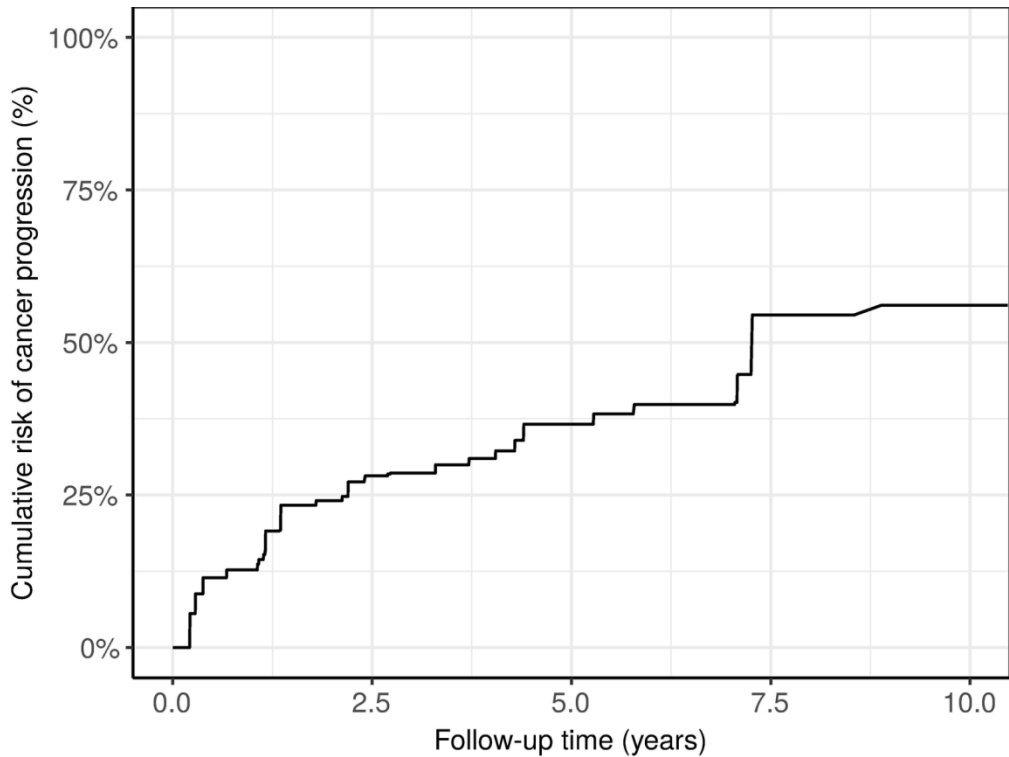
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The personalized decision making problem: Available data of a patient j , who had his latest negative biopsy at $t=2.6$ years. The shaded region shows the time period in which the patient is at risk of cancer progression. His current pre-scheduled follow-up visit for measurement of DRE and PSA is at $s=4$ years. Using his entire history of DRE $Y_{\{dj\}}(s)$ and PSA $Y_{\{pj\}}(s)$ measurements up to the current visit s , and the time of the latest biopsy t , we intend to make a decision on scheduling a biopsy at the current visit.

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Estimated cumulative risk of cancer progression in AS for patients in the Prostate Cancer Research International Active Surveillance (PRIAS) dataset. Nearly 50% patients (slow progressing) do not progress in the ten year follow-up period. Cumulative risk is estimated using nonparametric maximum likelihood estimation, to account for interval censored cancer progression times observed in the PRIAS dataset. Censoring includes death, removal from AS on the basis of observed longitudinal data, and patient dropout.

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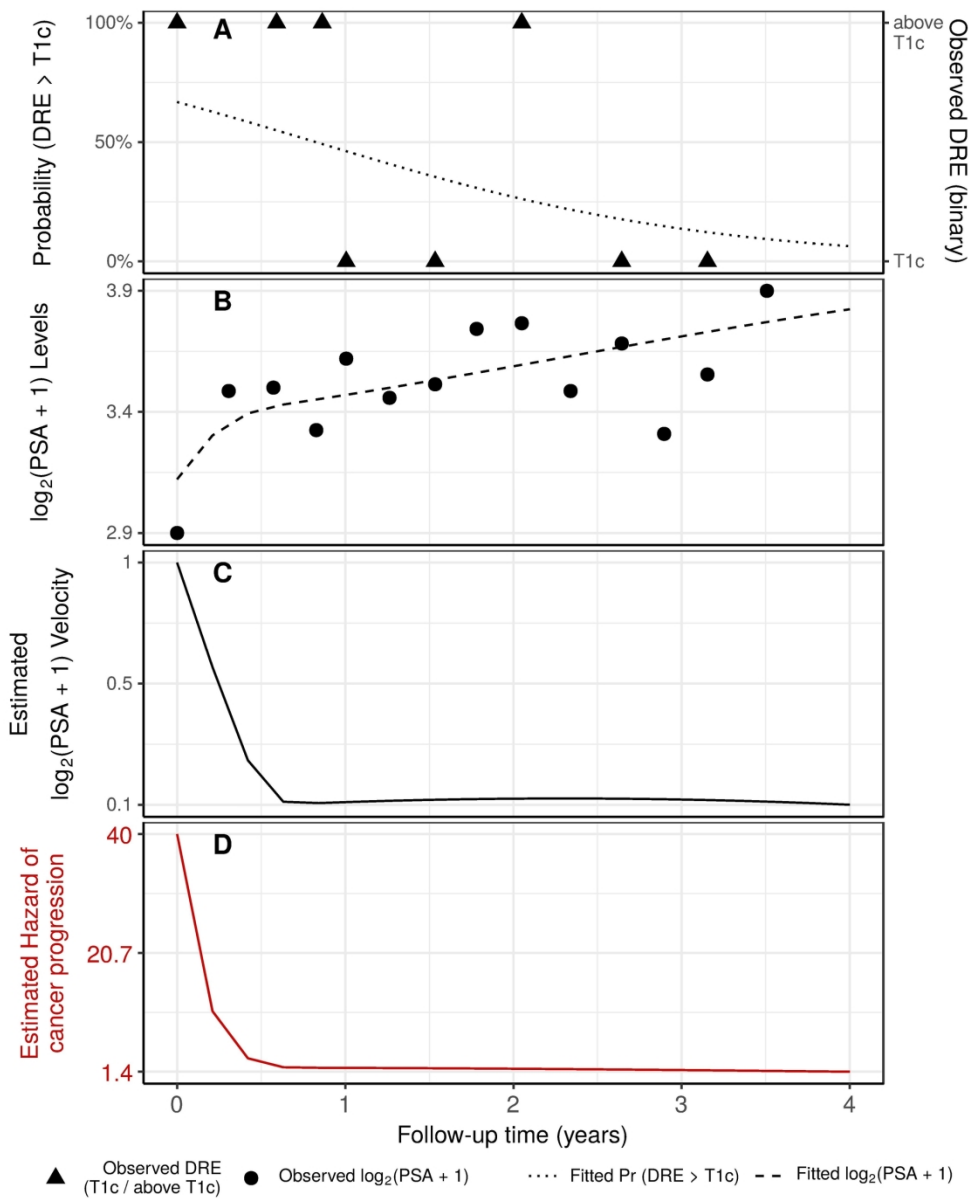


Illustration of the joint model fitted to the PRIAS dataset. Panel A: shows the observed DRE measurements and the fitted probability of obtaining DRE > T1c for i-th patient. Panel B: shows the observed and fitted $\log_2(\text{PSA} + 1)$ measurements. Panel C: shows the estimated $\log_2(\text{PSA} + 1)$ velocity (velocity cannot be observed directly) over time. The hazard function shown in Panel D, depends on the fitted log odds of having a DRE > T1c, and the fitted $\log_2(\text{PSA} + 1)$ value and velocity.

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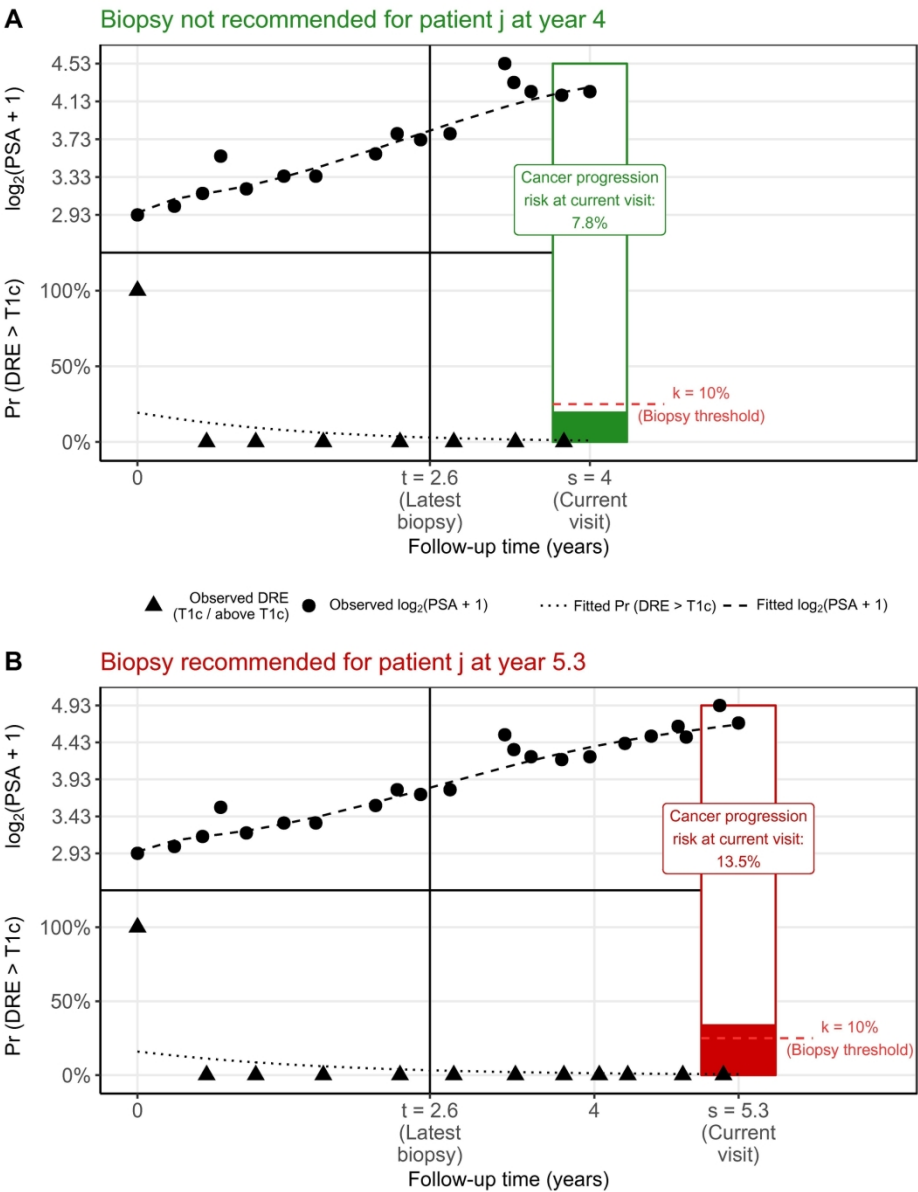
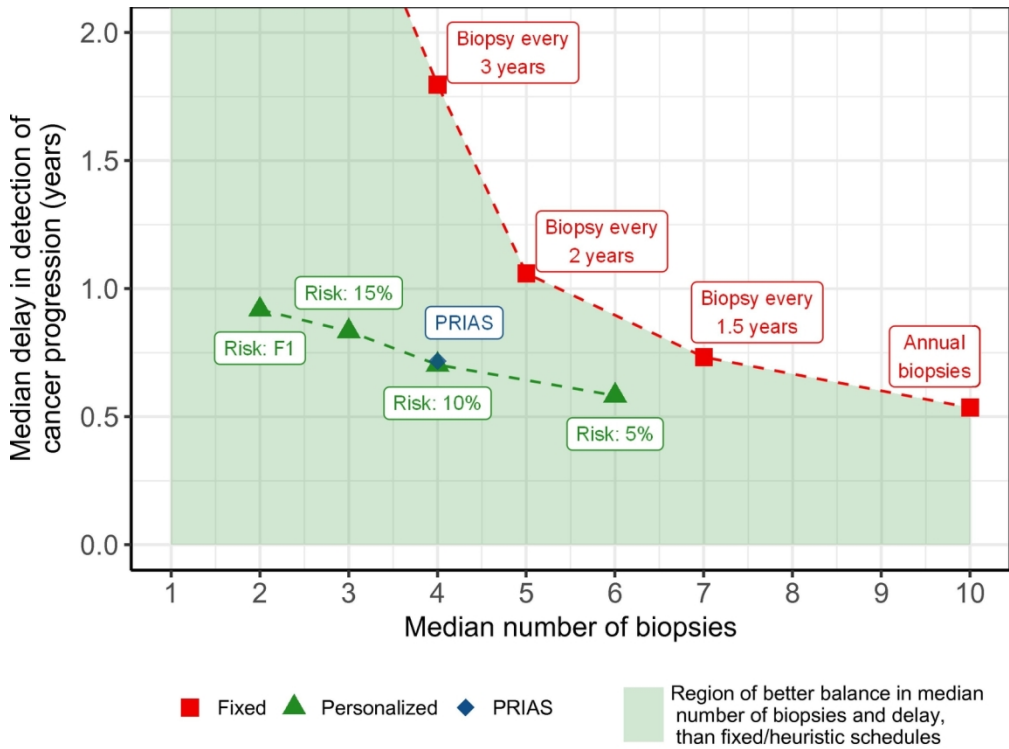


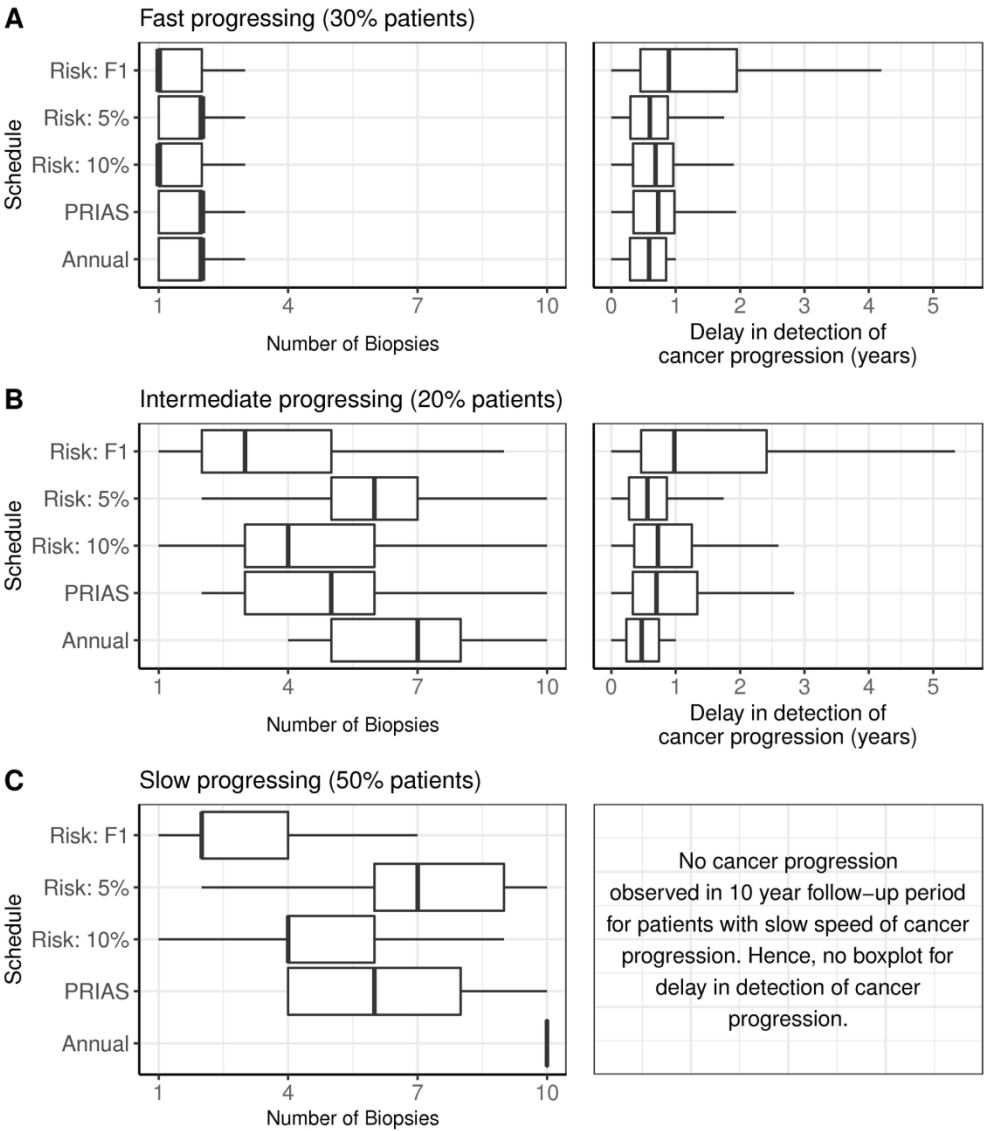
Illustration of personalized decision of biopsy for patient j at two different follow-up visits. Biopsy is recommended if the personalized cumulative risk of cancer progression estimated from the joint model fitted to the observed data of the patient, is higher than the example risk threshold for biopsy ($k=10\%$). Panel A: biopsy is not recommended for the patient j at the follow-up visit time $s=4$ years, because his estimated personalized cumulative risk of cancer progression (7.8%) is less than the threshold. Panel B: biopsy is recommended for the patient j at the follow-up visit time $s=5.3$ years, because his estimated personalized cumulative risk of cancer progression (13.5%) is more than the threshold.

177x228mm (300 x 300 DPI)



Burden-biopsy frontier: Median number of biopsies (X-axis), and median delay in detection of cancer progression (in years, Y-axis), estimated from the simulation study. Results for currently practiced fixed/heuristic biopsy schedules are shown by red squares, for PRIAS schedule by a blue rhombus, and for personalized schedules by green triangles. Types of personalized schedules: Risk: 15%, Risk: 10%, and Risk: 5% approaches, schedule a biopsy if the cumulative risk of cancer progression at a visit is more than 15%, 10%, and 5%, respectively. Risk: F1 works similar as previous, except that for each patient, a visit-specific risk threshold is chosen by maximizing F1 score. The green shaded region depicts the region of better balance in the median number of biopsies and median delay than the currently practiced fixed/heuristic schedules.

139x104mm (300 x 300 DPI)



Boxplot showing variation in the number of biopsies, and the delay in detection of cancer progression, in years (time of positive biopsy - true time of cancer progression) for various biopsy schedules. Biopsies are conducted until cancer progression is detected. Panel A: results for simulated patients who had a faster speed of cancer progression, with progression times between 0 and 3.5 years. Panel B: results for simulated patients who had an intermediate speed of cancer progression, with progression times between 3.5 and 10 years. Panel C: results for simulated patients who did not have cancer progression in the ten years of follow-up. Types of personalized schedules: Risk: 10% and Risk: 5% approaches, schedule a biopsy if the cumulative risk of cancer progression at a visit is more than 10% and 5%, respectively. Risk: F1 works similar as previous, except that a visit-specific risk threshold is chosen by maximizing F1 score. Annual corresponds to a schedule of yearly biopsies and PRIAS corresponds to biopsies as per PRIAS protocol.

177x203mm (300 x 300 DPI)