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 a short introduction to the world's largest active surveillance (AS) program called Prostate Cancer Research International Active Surveillance, abbreviated as PRIAS (Bul et al., 2013), that we use to develop our methodology. We then present an introduction to the joint models for time-to-event and 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

The PRIAS dataset consists of 5270 AS patients, of which 866 observe cancer progression. For each patient, prostate-specific antigen (PSA) measurements (ng/mL) are scheduled every 3 months for first 2 years and every 6 months thereafter. The DRE measurements are scheduled every 6 months. We use the DRE measurements after converting them on a binary scale, namely DRE $>$ T1c and DRE $\leq$ T1c Schröder et al., 1992. On average 5 DRE and 9 PSA measurements have been recorded per patient. Larger values for PSA and/or larger score for DRE, may indicate cancer progression. However, it is the occurrence of biopsy Gleason score larger than 6, that is commonly considered cancer progression. In PRIAS study, 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 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.

Appendix A.2 Model Definition

Let T_i^* denote the true cancer progression time for the i-th patient in PRIAS. Since biopsies are conducted periodically, T_i^* cannot be observed directly and it is only known to fall in an interval $l_i < T_i^* \leq r_i$, where r_i and l_i are the time of the latest and second latest biopsies, respectively, if the progression is observed at the latest biopsy. When the progression is not observed, then l_i is the time of the latest biopsy and $r_i = \infty$. Further, let $\boldsymbol{y}_{di}$, and $\boldsymbol{y}_{pi}$ denote the $n_{di} \times 1$, and $n_{pi} \times 1$ vectors of the DRE, and PSA longitudinal measurements, respectively. For a sample of n patients the observed data is denoted by $\mathcal{D}_n = \{l_i, r_i, \boldsymbol{y}_{di}, \boldsymbol{y}_{pi}; i = 1, \ldots, n\}$.

The patient-specific PSA and DRE measurements over time are modeled using a generalized linear mixed effects model. For the i-th patient, the mixed effects sub-model for DRE is given by:

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

where, t denotes a specific time point in the AS follow-up, Age_i is the age of the i-th patient at the time of inclusion in AS. The fixed effect parameters are denoted by $\{\beta_{0d}, \ldots, \beta_{3d}\}$, and b_{0di}, b_{1di} are the patient specific random effects. With this definition, we assume that the log odds of obtaining a DRE score larger than T1c remain linear over time. An example model fit for DRE is shown in panel A of Figure 1. For the i-th patient, the mixed effects sub-model for PSA is given by:

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

where, $m_{pi}(t)$ denotes the underlying measurement error free value of $\log_2(\text{PSA} + 1)$ transformed (Lin et al., 2000; Pearson et al., 1994) measurements at time t. To accommodate for a non-linear evolution of this value over the follow-up period in AS, we utilize B-splines (De Boor et al., 1978). In Equation (2), $B_k(t, \mathcal{K})$ denotes the k-th basis function of a B-spline with three internal knots at $\mathcal{K} = \{0.1, 0.7, 4\}$ years, and boundary knots at 0 and 5.42 years (0.95 quantile of the observed follow-up times). The fixed effect parameters are denoted by $\{\beta_{0p}, \ldots, \beta_{6p}\}$ and the patient specific random effects are denoted by $\{b_{0pi}, \ldots, b_{4pi}\}$. 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. An example model fit for PSA is shown in panel B of Figure 1. To account for the association between the DRE and PSA measurements, we link their corresponding random effects. More specifically, the complete vector of random effects $\boldsymbol{b}_i = (b_{0di}, b_{0di}, b_{0pi}, \ldots, b_{4pi})^T$ is assumed to follow a multivariate normal distribution with mean zero and 7×7 variance-covariance matrix $\boldsymbol{D}$.

To model the impact of DRE and PSA measurements on the risk of cancer progression, we use a relative risk sub-model. More specifically, the hazard of cancer

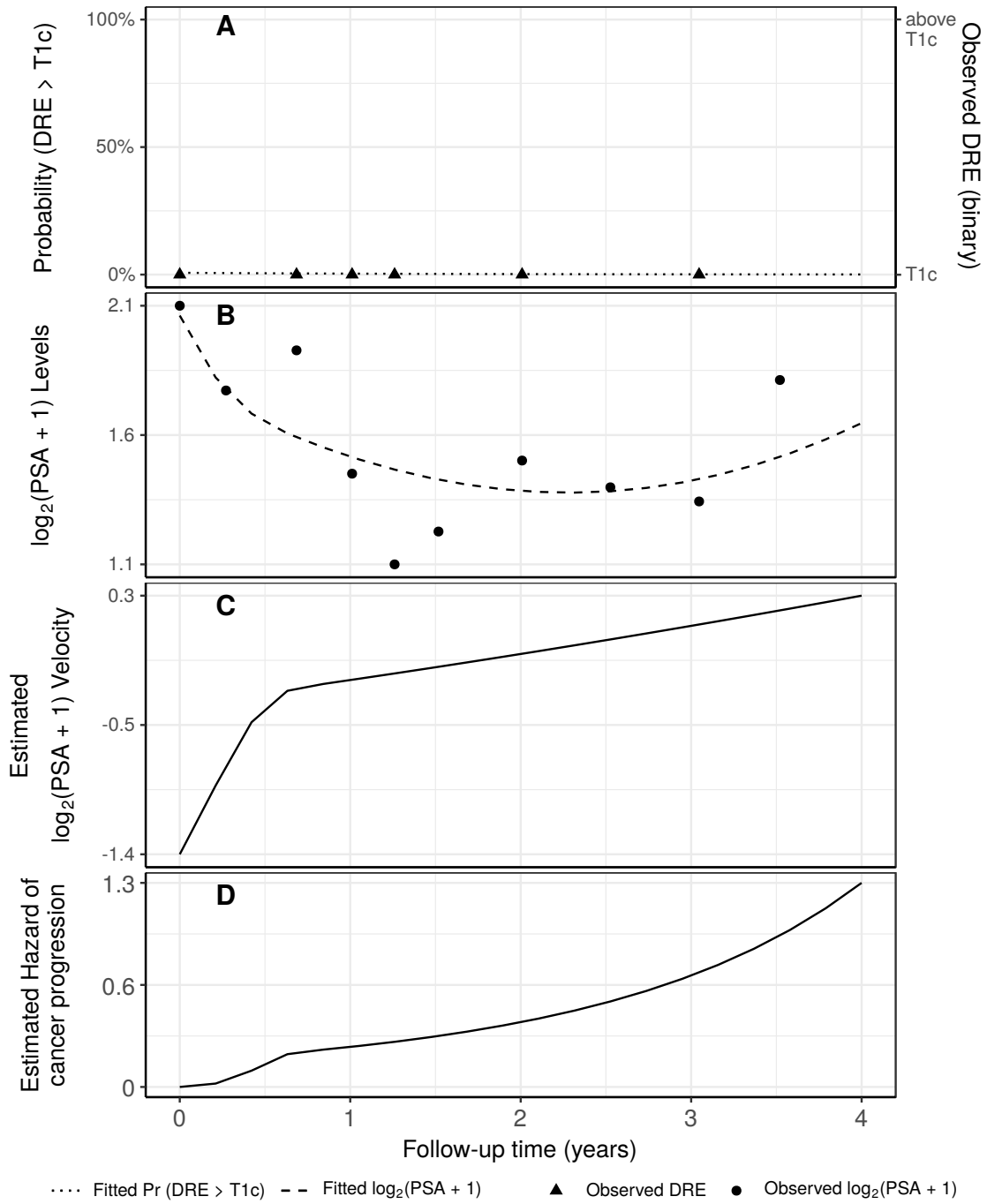

Figure 1: Illustration of the joint model fitted to the PRIAS dataset. **Panel A:** shows the observed DRE scores and the fitted probability of obtaining a DRE score greater than T1c (Equation 1). **Panel B:** shows the observed and fitted $\log_2(\text{PSA}+1)$ levels (Equation 2). **Panel C:** shows 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.

progression $h_i(t)$ at a time t is given by:

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

where, γ_1, γ_2 are the coefficients for the effect of age. The parameter α_{1d} models the impact of log odds of obtaining DRE > T1c on the hazard of cancer progression. The impact of PSA on the hazard of cancer progression is modeled in two ways, namely at any time t the effect of the instantaneous underlying value (dashed line in panel B of Figure 1) of PSA $m_{pi}(t)$ is given by α_{1p}, and the effect of the instantaneous underlying PSA velocity $\partial m_{pi}(t)/\partial t$ (panel C in Figure 1) is given by α_{2p}. Lastly, $h_0(t)$ is the baseline hazard at time t, and is modeled flexibly using P-splines (Eilers and Marx, 1996). More specifically:

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

where $B_q(t, \boldsymbol{v})$ denotes the q-th basis function of a B-spline with knots $\boldsymbol{v} = v_1, \ldots, v_Q$ 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 1.

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 PSA and DRE measurements taken over time are all mutually independent. Under this assumption the posterior distribution of the parameters is given by:

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

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

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

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

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

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

$$p(l_i, r_i \mid \boldsymbol{b}_i, \boldsymbol{\theta}) = \exp\Big\{ - \int_0^{l_i} h_i(s) \mathrm{d}s \Big\} - \exp\Big\{ - \int_0^{r_i} h_i(s) \mathrm{d}s \Big\}. \tag{4}$$

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 $\{\beta_{0d}, \ldots, \beta_{3d}, \beta_{0p}, \ldots, \beta_{6p}\}$, and inverse Gamma prior with shape and rate both equal to 0.01 for the parameter σ^2. For the variance-covariance matrix $\boldsymbol{D}$ 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 B Parameter Estimates from the Joint Model Fitted to the PRIAS Dataset

The posterior parameter estimates for the joint model we fitted to the PRIAS dataset are shown in Table 2 (longitudinal sub-model for DRE outcome), Table 3 (longitudinal sub-model for PSA outcome) and Table 4 (relative risk sub-model), and parameter estimates for the variance-covariance matrix $\boldsymbol{D}$ from the longitudinal sub-model are shown in the following Table 1:

Table 1: Estimated variance-covariance matrix $\boldsymbol{D}$ of the random effects $\boldsymbol{b} = (b_{0d}, b_{1d}, b_{0p}, b_{1p}, b_{2p}, b_{3p}, b_{4p})$ (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}	7.546	-0.564	-0.182	0.075	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 2 we can see that the age of the patient trivially affects the baseline log odds of obtaining a DRE score larger than T1c. In Figure 2 we present the marginal evolution of probability of obtaining a DRE score larger than T1c, 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 score larger than T1c, for nine randomly selected patients in Figure 3.

Table 2: 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	<0.000
(Age − 70)	0.058	0.009	0.041	0.075	<0.000
$(\text{Age} - 70)^2$	-0.001	0.001	-0.003	1.8×10^{-4}	0.076
visitTimeYears	-0.604	0.095	-0.794	-0.437	<0.000

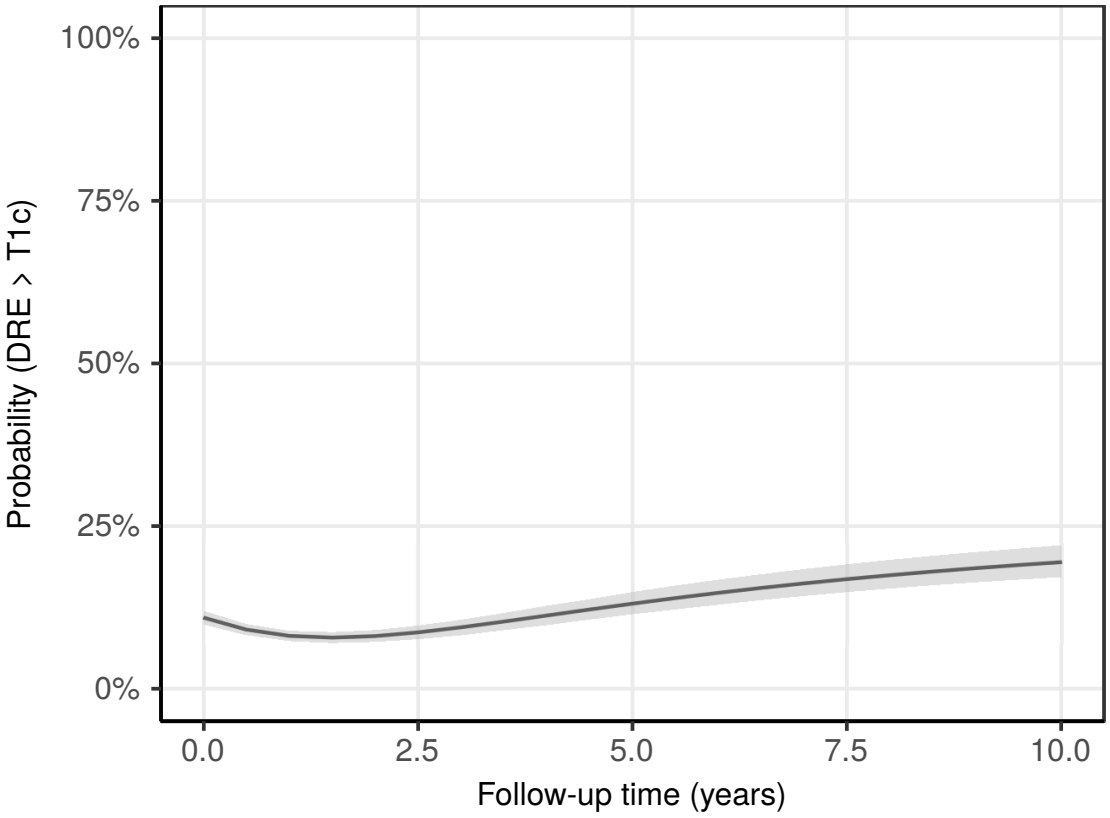

Figure 2: Fitted average probability of obtaining a DRE score larger than T1c with 95% credible interval, over a period of 10 years, for a hypothetical AS patient who is included in AS at the age of 70 years.

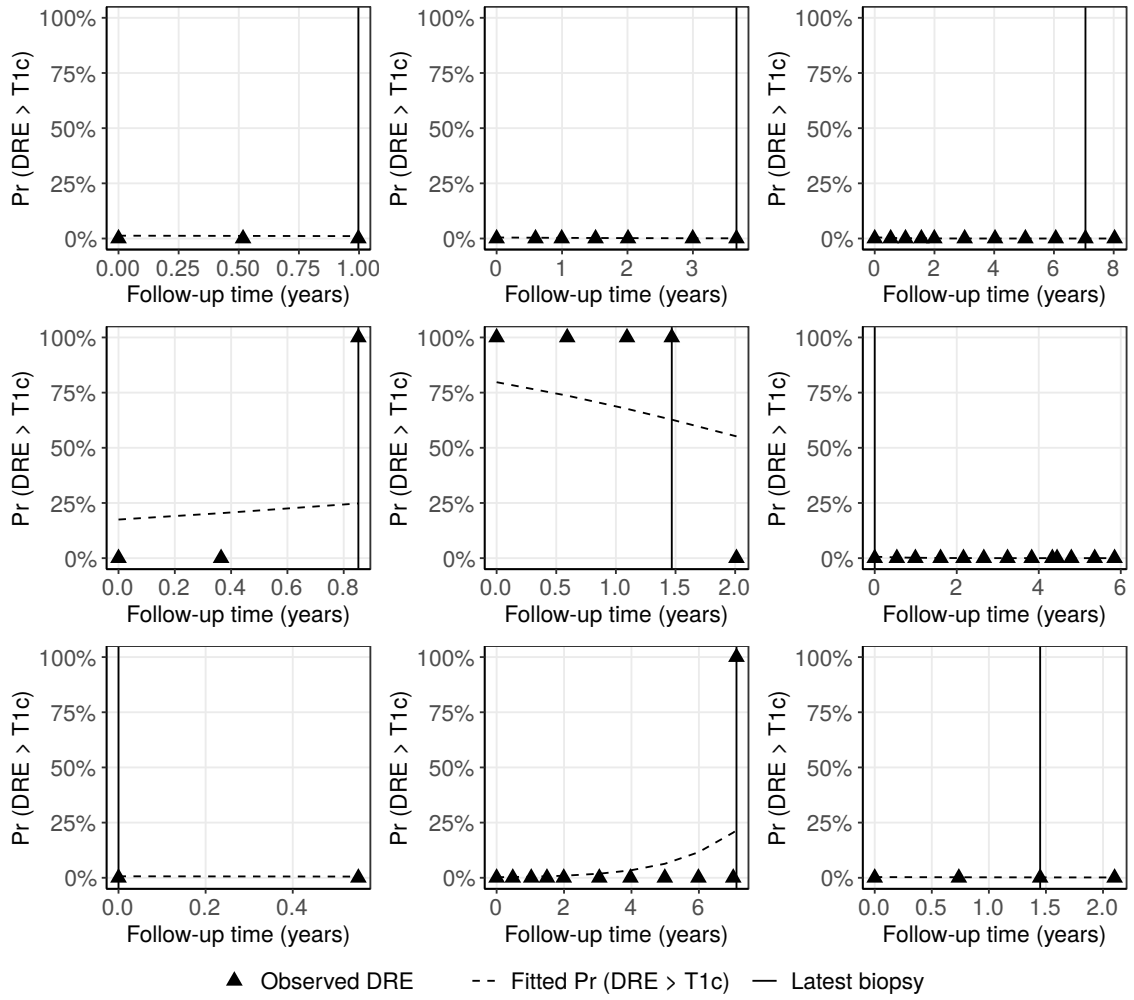

Figure 3: Observed DRE versus fitted probabilities of obtaining a DRE score larger than T1c, for nine randomly selected PRIAS patients. The fitted profiles utilize information from the observed DRE scores, PSA levels, and time of the latest biopsy. Observed DRE scores plotted against 0% probability are equal to T1c. Observed DRE scores plotted against 100% probability are larger than T1c.

For the PSA mixed effects sub-model parameter estimates (see Equation 2), in Table 3 we can see that the age of the patient trivially affects the baseline $\log_2(\text{PSA}+1)$ level. Since the longitudinal evolution of $\log_2(\text{PSA}+1)$ levels is modeled with non-linear terms, the interpretation of the coefficients corresponding to time is not straightforward. In lieu of the interpretation, in Figure 4 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 5.

Table 3: 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	<0.000
$(\text{Age}-70)$	0.003	0.001	0.001	0.005	<0.000
$(\text{Age}-70)^2$	-4.7 $\times 10^{-4}$	9.8 $\times 10^{-5}$	-6.6 $\times 10^{-4}$	-2.7 $\times 10^{-4}$	<0.000
Spline: [0.00, 0.10] years	0.054	0.009	0.037	0.073	<0.000
Spline: [0.10, 0.70] years	0.177	0.012	0.151	0.200	<0.000
Spline: [0.70, 4.00] years	0.194	0.016	0.161	0.225	<0.000
Spline: [4.00, 5.42] years	0.341	0.015	0.312	0.371	<0.000
σ	0.137	0.001	0.135	0.138	

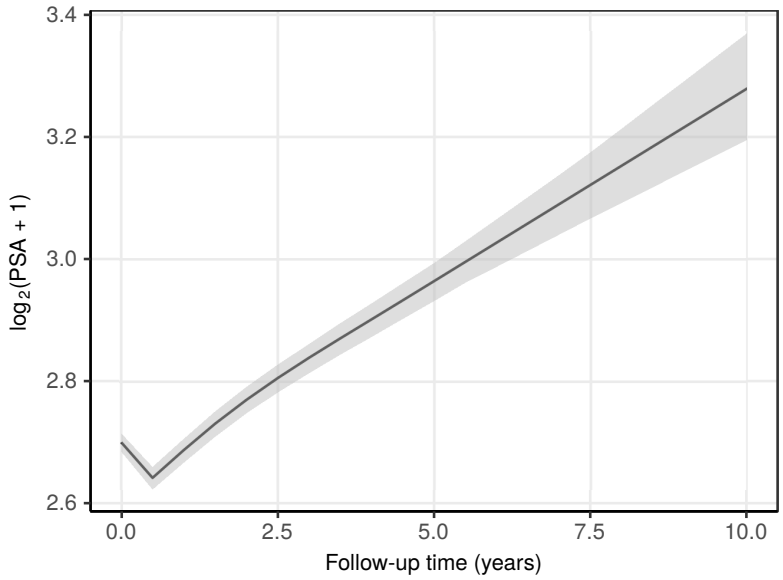

Figure 4: Fitted marginal evolution of $\log_2(\text{PSA}+1)$ levels over a period of 10 years with 95% credible interval, for a hypothetical patient who is included in AS at the age of 70 years.

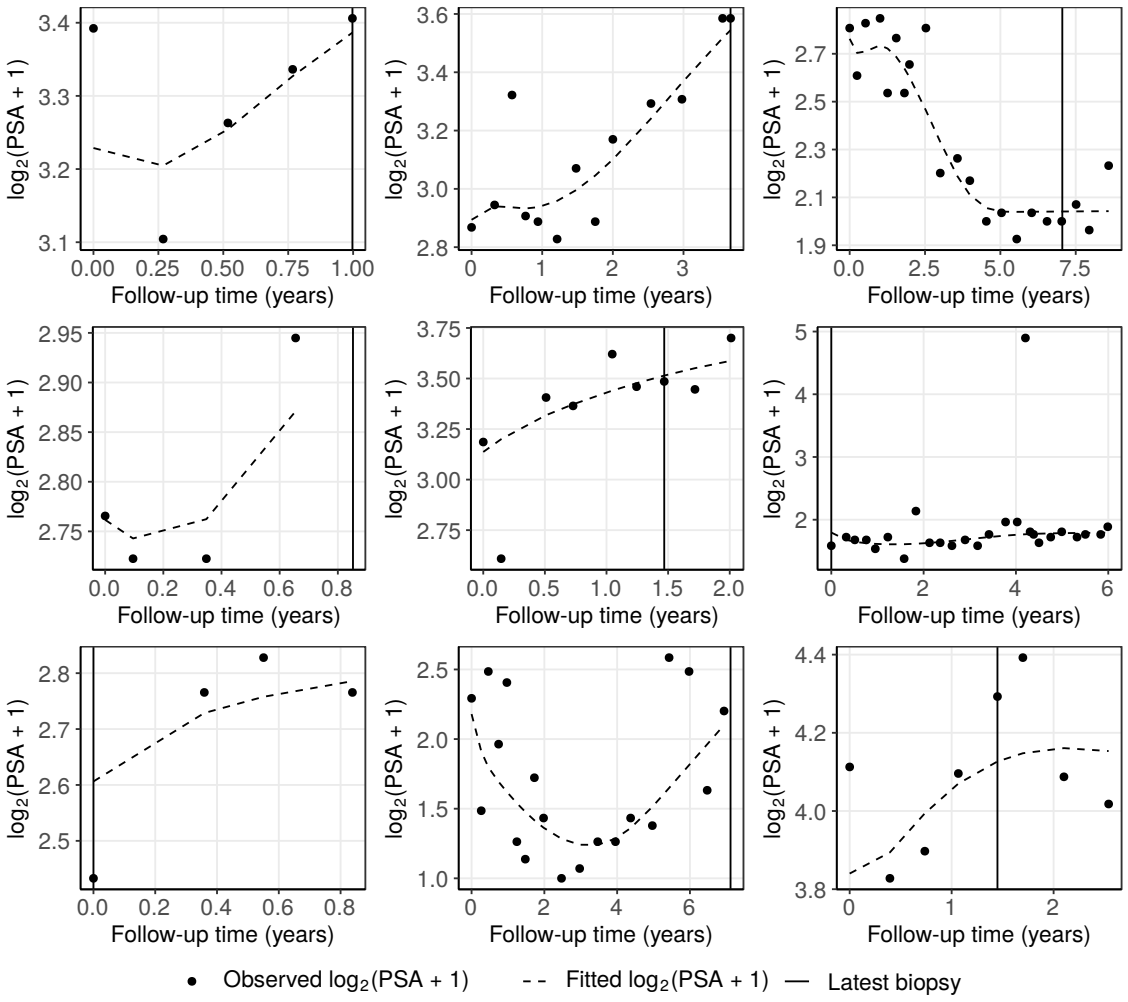

Figure 5: Fitted versus observed $\log_2(\text{PSA} + 1)$ profiles for nine randomly selected PRIAS patients. The fitted profiles utilize information from the observed PSA levels, DRE scores, and time of the latest biopsy.

For the relative risk sub-model (see Equation 3), the parameter estimates in Table 4 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. 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 1.92 fold increase in the hazard of cancer progression. Whereas, an increase in log odds of DRE > T1c from -6.65 to -4.36 (first and third quartiles of the fitted log odds, respectively) corresponds to a 1.40 fold increase in the hazard of cancer progression. An increase in age at the time of inclusion in AS from 65 years to 75 years (first and third quartiles of age in PRIAS dataset) corresponds to a 1.13 fold increase in the hazard of GR.

Table 4: 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
$(\text{Age}-70)$	0.012	0.006	2.3×10^{-4}	0.022	0.045
$(\text{Age}-70)^2$	-0.001	0.001	-0.002	1.6×10^{-4}	0.095
$\text{logit}\{\Pr(\text{DRE} > \text{T1c})\}$	0.147	0.017	0.115	0.183	<0.00
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	<0.00

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

With regards to the choice of the distribution for the error term ε_2 for the PSA measurements (see Equation 2), we attempted fitting multiple joint models differing in error distribution, namely t-distribution with three, four, and five degrees of freedom, and a normal distribution for the error term. However, the model assumptions were best met by the model with t-distribution having three degrees of freedom, for the error terms. The quantile-quantile plot of subject-specific residuals for the corresponding model in Figure 6, shows that the assumption of t-distributed (df=3) errors is reasonably met by the fitted model.

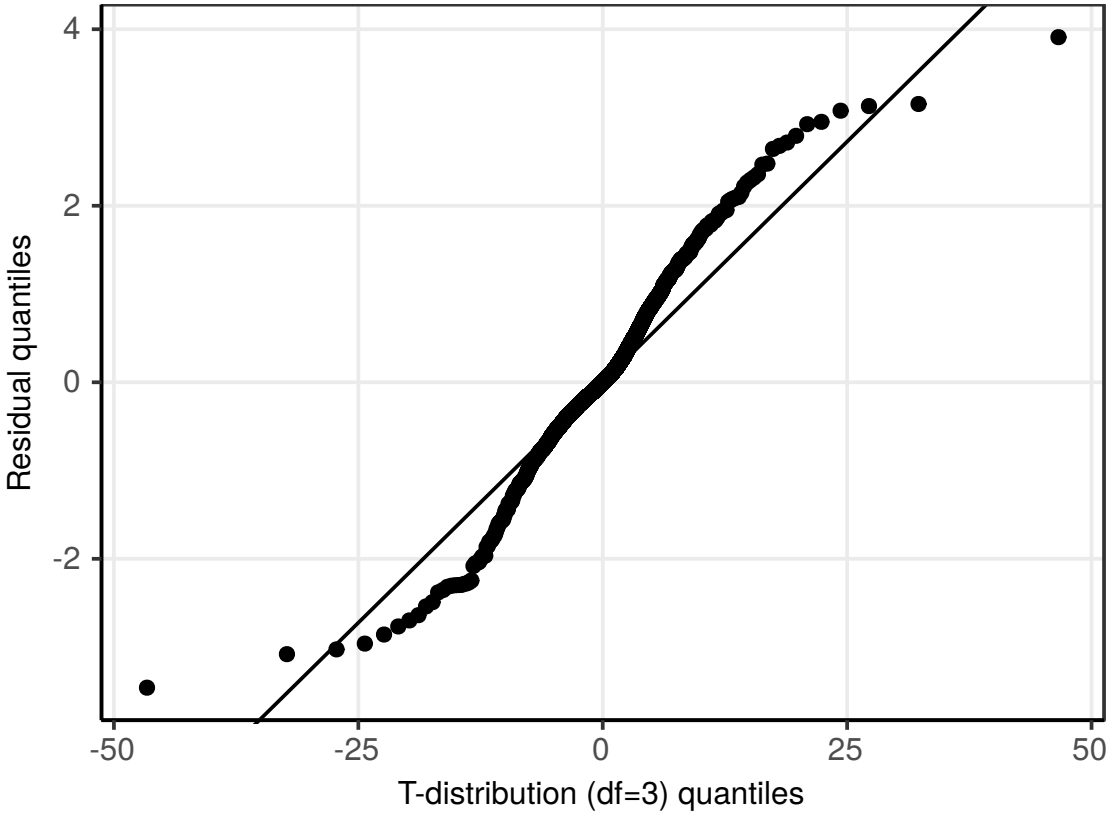

Figure 6: Quantile-quantile plot of subject-specific residuals from the joint model fitted to the PRIAS dataset.

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

In order to compare the predictive performance of a model utilizing information from both DRE and PSA versus a model using information only from PSA, we calculate the area under the receiver operating characteristic curves, also called AUC, and the prediction error for these models (Rizopoulos, Molenberghs, and Lesaffre, 2017). Given the longitudinal nature of the data at hand, in a joint model time dependent AUC and prediction errors are more relevant. Thus, we calculate the AUC and prediction error at year one, year two, year three, year four, and year five (95-percentile of observed cancer progression time) of follow-up in AS. The time window for which the AUC and prediction error are calculated is one year. The resulting AUC are presented in Table 5, and the prediction error are presented in Table 6.

Table 5: Area under the receiver operating characteristic curves (AUC), and 95% confidence interval in brackets. AUC's are calculated for two joint models: first one utilizing information from both DRE and PSA measurements, and second one utilizing information from only PSA measurements.

Year	both DRE and PSA	only PSA
1	0.651 [0.633, 0.663]	0.636 [0.626, 0.648]
2	0.621 [0.610, 0.640]	0.593 [0.584, 0.606]
3	0.748 [0.728, 0.770]	0.716 [0.699, 0.733]
4	0.710 [0.691, 0.736]	0.643 [0.623, 0.660]
5	0.592 [0.577, 0.614]	0.536 [0.517, 0.553]

Table 6: Prediction error, and 95% confidence interval in brackets. Prediction errors are calculated for two joint models: first one utilizing information from both DRE and PSA measurements, and second one utilizing information from only PSA measurements.

Year	both DRE and PSA	only PSA
1	0.055 [0.052, 0.059]	0.056 [0.052, 0.059]
2	0.144 [0.140, 0.148]	0.148 [0.145, 0.153]
3	0.076 [0.075, 0.078]	0.077 [0.075, 0.080]
4	0.076 [0.072, 0.079]	0.077 [0.073, 0.080]
5	0.107 [0.103, 0.112]	0.116 [0.112, 0.122]

Appendix C Source Code

The R code for fitting the joint model to the PRIAS dataset, and for the simulation study, along with sample dataset, and instructions for running the code are available with this paper at the following link:

https://github.com/anirudhtomer/prias/tree/master/src/decision_analytic

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