Supplementary Materials for "Personalized Schedules for Burdensome Surveillance Tests"

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Web Appendix A Joint Model for Time-to-Progression and Longitudinal Outcomes

Let the true time of disease progression for the i-th patient be T_i^*. Progression is always observed with interval censoring $l_i < T_i^* \leq r_i$. In patients who obtain progression, r_i and l_i denote the time of their latest and second latest invasive tests. Otherwise, l_i denotes the time of their latest test and $r_i = \infty$. Assuming K auxiliary longitudinal outcomes, let $\boldsymbol{y}_{ki}$ denote the $n_{ki} \times 1$ longitudinal response vector of the k-th outcome, $k \in \{1, \ldots, K\}$. The observed data of all n patients is given by $\mathcal{A}_n = \{l_i, r_i, \boldsymbol{y}_{1i}, \ldots \boldsymbol{y}_{Ki}; i = 1, \ldots, n\}$.

To accommodate longitudinal outcomes of different types in a unified framework, the joint model consists of a generalized linear mixed-effects sub-model (Laird and Ware, 1982). In particular, the conditional distribution of $\boldsymbol{y}_{ki}$ given a vector of patient-specific random effects $\boldsymbol{b}_{ki}$ is assumed to be a member of the exponential family, with linear predictor given by,

$$g_k\big[E\{y_{ki}(t) \mid \boldsymbol{b}_{ki}\}\big] = m_{ki}(t) = \boldsymbol{x}_{ki}^\top(t)\boldsymbol{\beta}_k + \boldsymbol{z}_{ki}^\top(t)\boldsymbol{b}_{ki}, \tag{1}$$

where $g_k(\cdot)$ denotes a known one-to-one monotonic link function, $y_{ki}(t)$ denotes the value of the k-th longitudinal outcome for the i-th patient at time t, and $\boldsymbol{x}_{ki}(t)$ and $\boldsymbol{z}_{ki}(t)$ denote the time-dependent design vectors for the fixed $\boldsymbol{\beta}_k$ and random effects $\boldsymbol{b}_{ki}$, respectively. To account for the association between the different longitudinal outcomes, we link their corresponding random effects. More specifically, the complete vector of random effects $\boldsymbol{b}_i = (\boldsymbol{b}_{1i}^\top, \ldots, \boldsymbol{b}_{Ki}^\top)^\top$ is assumed to follow a multivariate normal distribution with mean zero and variance-covariance matrix W.

For the survival process, we assume that the hazard of progression $h_i(t)$ at a time t depends on a function of the patient and outcome-specific linear predictors

$m_{ki}(t)$ and/or the random effects. More specifically,

$$h_i\{t \mid \mathcal{M}_i(t), \boldsymbol{w}_i(t)\} = h_0(t) \exp\left[\boldsymbol{\gamma}^\top \boldsymbol{w}_i(t) + \sum_{k=1}^{K} f_k\{\mathcal{M}_{ki}(t), \boldsymbol{w}_i(t), \boldsymbol{b}_{ki}, \boldsymbol{\alpha}_k\}\right], \quad t > 0, \tag{2}$$

where $h_0(\cdot)$ denotes the baseline hazard function, $\mathcal{M}_{ki}(t) = \{m_{ki}(s) \mid 0 \leq s < t\}$ denotes the history of the k-th longitudinal process up to t, and $\boldsymbol{w}_i(t)$ is a vector of exogenous, possibly time-varying, covariates with corresponding regression coefficients $\boldsymbol{\gamma}$. Functions $f_k(\cdot)$, parameterized by vector of coefficients $\boldsymbol{\alpha_k}$, specify which features of each longitudinal outcome are included in the linear predictor of the relative-risk model (Brown, 2009; Rizopoulos, 2012; Taylor et al., 2013). Some examples, motivated by the literature (subscripts k dropped for brevity), are:

$$\begin{cases} f\{\mathcal{M}_i(t), \boldsymbol{w}_i(t), \boldsymbol{b}_i, \boldsymbol{\alpha}\} = \alpha m_i(t), \\ f\{\mathcal{M}_i(t), \boldsymbol{w}_i(t), \boldsymbol{b}_i, \boldsymbol{\alpha}\} = \alpha_1 m_i(t) + \alpha_2 m_i'(t), \quad \text{with } m_i'(t) = \frac{\mathrm{d}m_i(t)}{\mathrm{d}t}. \end{cases}$$

These formulations of $f(\cdot)$ postulate that the hazard of progression at time t may be associated with the underlying level $m_i(t)$ of the longitudinal outcome at t, or with both the level and velocity $m_i'(t)$ (e.g., PSA value and velocity in prostate cancer) of the outcome at t. 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).

Web Appendix A.1 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 progression, and all of the longitudinal measurements taken over time are all mutually independent. Under this assumption the posterior distribution of the parameters is given by:

$$\begin{aligned} p(\boldsymbol{\theta}, \boldsymbol{b} \mid \mathcal{D}_n) &\propto \prod_{i=1}^{n} p(l_i, r_i, \boldsymbol{y}_{1i}, \ldots \boldsymbol{y}_{Ki}, \mid \boldsymbol{b}_i, \boldsymbol{\theta}) p(\boldsymbol{b}_i \mid \boldsymbol{\theta}) p(\boldsymbol{\theta}) \\ &\propto \prod_{i=1}^{n} \prod_{k=1}^{K} p(l_i, r_i \mid \boldsymbol{b}_i, \boldsymbol{\theta}) p(\boldsymbol{y}_{ki} \mid \boldsymbol{b}_i, \boldsymbol{\theta}) p(\boldsymbol{b}_i \mid \boldsymbol{\theta}) p(\boldsymbol{\theta}), \\ p(\boldsymbol{b}_i \mid \boldsymbol{\theta}) &= \frac{1}{\sqrt{(2\pi)^{|W|} \det(\boldsymbol{D})}} \exp(\boldsymbol{b}_i^\top \boldsymbol{D}^{-1} \boldsymbol{b}_i), \end{aligned}$$

where, the likelihood contribution of the k-th longitudinal outcome vector $\boldsymbol{y}_{ki}$ for the i-th patient, conditional on the random effects is:

$$p(\boldsymbol{y}_{ki} \mid \boldsymbol{b}_i, \boldsymbol{\theta}) = \prod_{j=1}^{n_{ki}} \exp\left[\frac{y_{kij}\psi_{kij}(\boldsymbol{b}_{ki}) - c_k\{\psi_{kij}(\boldsymbol{b}_{ki})\}}{a_k(\varphi)} - d_k(y_{kij}, \varphi)\right],$$

where n_{ki} are the total number of longitudinal measurements of type k for patient i. The natural and dispersion parameters of the exponential family are denoted by $\psi_{kij}(\boldsymbol{b}_{ki}$ and φ, respectively. In addition, $c_k(\cdot), a_k(\cdot), d_k(\cdot)$ are known functions specifying the member of the exponential family. The likelihood contribution of the time to progression outcome is given by:

$$p(l_i, r_i \mid \boldsymbol{b}_i, \boldsymbol{\theta}) = \exp\Big[-\int_0^{l_i} h_i\big\{s \mid \mathcal{M}_i(t), \boldsymbol{w}_i(t)\big\}\mathrm{d}s\Big] - \exp\Big[-\int_0^{r_i} h_i\big\{s \mid \mathcal{M}_i(t), \boldsymbol{w}_i(t)\big\}\mathrm{d}s\Big]. \tag{3}$$

The integral in (3) 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 effect parameters of the longitudinal model. For scale parameters we inverse Gamma priors. 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 the total number of random effects. For the relative risk model's parameters $\boldsymbol{\gamma}$ and the association parameters $\boldsymbol{\alpha}$, we use independent normal priors with zero mean and variance 100. However, when $\boldsymbol{\alpha}$ becomes high dimensional (e.g., when several functional forms are considered per longitudinal outcome), we opt for a global-local ridge-type shrinkage prior, i.e., for the s-th element of $\boldsymbol{\alpha}$ we assume:

$$\alpha_s \sim \mathcal{N}(0, \tau\psi_s), \quad \tau^{-1} \sim \text{Gamma}(0.1, 0.1), \quad \psi_s^{-1} \sim \text{Gamma}(1, 0.01). \tag{4}$$

The global smoothing parameter τ has sufficiently mass near zero to ensure shrinkage, while the local smoothing parameter ψ_s allows individual coefficients to attain large values. Other options of shrinkage or variable-selection priors could be used as well (Andrinopoulou and Rizopoulos, 2016). Finally, the penalized version of the B-spline approximation to the baseline hazard is specified using the following hierarchical prior for γ_{h_0} (Lang and Brezger, 2004):

$$p(\gamma_{h_0} \mid \tau_h) \propto \tau_h^{\rho(\boldsymbol{K})/2} \exp\Big(-\frac{\tau_h}{2}\gamma_{h_0}^\top \boldsymbol{K}\gamma_{h_0}\Big) \tag{5}$$

where τ_h is the smoothing parameter that takes a Gamma$(1, \tau_{h\delta})$ prior distribution, with a hyper-prior $\tau_{h\delta} \sim$ Gamma$(10^{-3}, 10^{-3})$, which ensures a proper posterior distribution for γ_{h_0}(Jullion and Lambert, 2007), $\boldsymbol{K} = \Delta_r^\top \Delta_r + 10^{-6}\boldsymbol{I}$, with Δ_r denoting the r-th difference penalty matrix, and $\rho(\boldsymbol{K})$ denotes the rank of $\boldsymbol{K}$.

Web Appendix B Joint Model for the PRIAS Dataset Used in Simulation Study

Web Appendix B.1 Dataset

In this work we reused a joint model we previously fitted to the PRIAS dataset (Tomer et al., 2019, 2020). The PRIAS database is not openly accessible. However, access to the database can be requested on the basis of a study proposal approved by the PRIAS steering committee. The website of the PRIAS program is www.prias-project.org. For sake of completeness and reproducibility of results we have presented the PRIAS based model's definition and parameter estimates below. Figure 1 shows the cumulative-risk of progression over the follow-up period.

Web Appendix B.2 Model Specification

Let T_i^* denote the true 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 $\boldsymbol{y}_{di}$ and $\boldsymbol{y}_{pi}$ denote his observed DRE (digital rectal examination) and PSA (prostate-specific antigen) longitudinal measurements, respectively. The observed data of all n patients is denoted by $\mathcal{D}_n = \{l_i, r_i, \boldsymbol{y}_{di}, \boldsymbol{y}_{pi}; i = 1, \ldots, n\}$.

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:

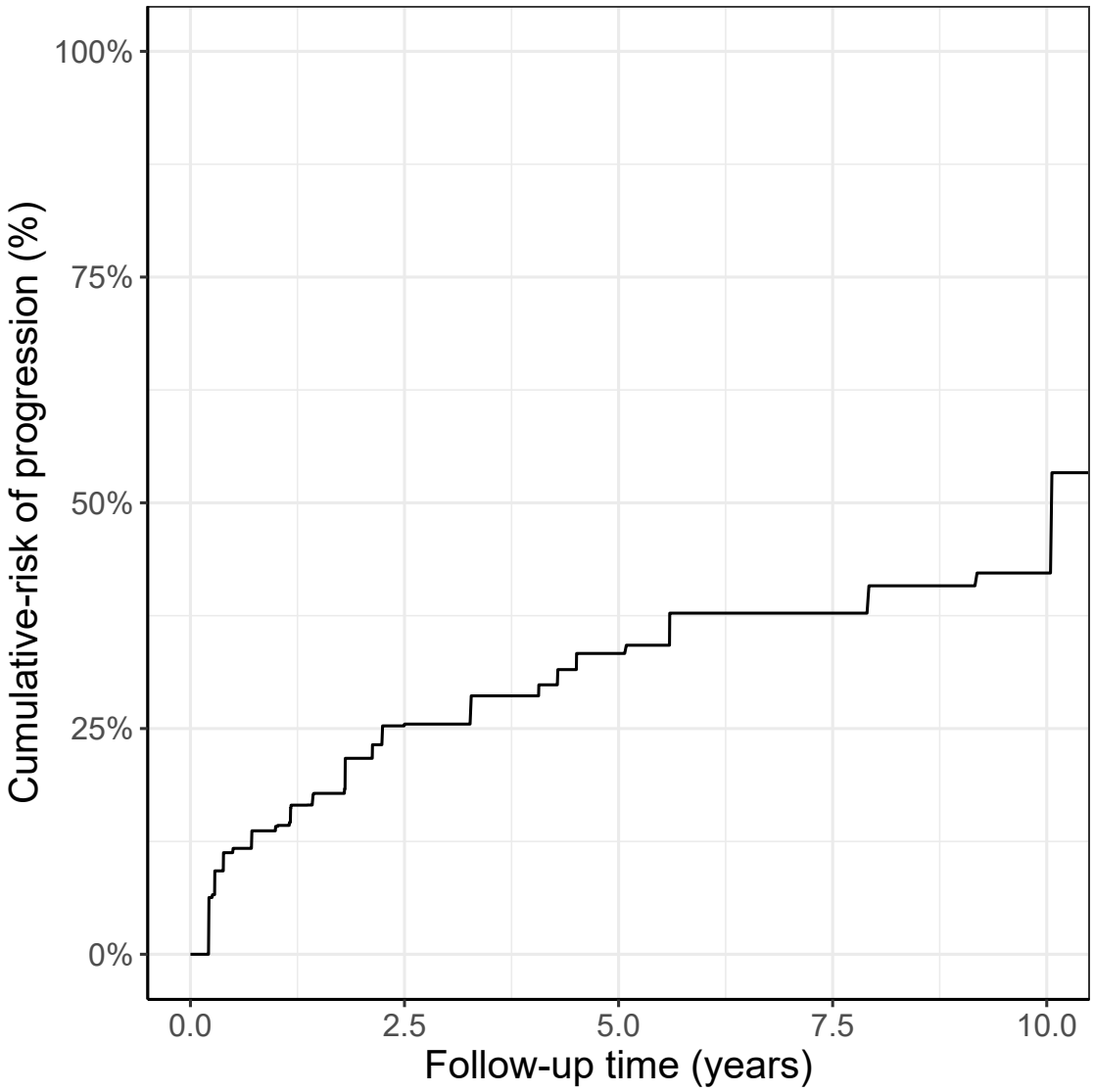
$$\begin{aligned}\text{logit}\big[\Pr\{y_{di}(t) > \text{T1c}\}\big] &= \beta_{0d} + b_{0di} + (\beta_{1d} + b_{1di})t \\ &\quad + \beta_{2d}(\text{Age}_i - 65) + \beta_{3d}(\text{Age}_i - 65)^2 \end{aligned} \tag{6}$$

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 $\{\beta_{0d}, \ldots, \beta_{3d}\}$, 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 (palpable tumor) remain linear over time.

The mixed effects sub-model for PSA is given by:

$$\begin{aligned}\log_2\big\{y_{pi}(t) + 1\big\} &= m_{pi}(t) + \varepsilon_{pi}(t), \\ m_{pi}(t) &= \beta_{0p} + b_{0pi} + \sum_{k=1}^{3}(\beta_{kp} + b_{kpi})B_k(t, \mathcal{K}) \\ &\quad + \beta_{4p}(\text{Age}_i - 65) + \beta_{5p}(\text{Age}_i - 65)^2, \end{aligned} \tag{7}$$

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. We model it non-linearly over time using B-splines (De Boor, 1978). To this end, the B-spline basis function $B_k(t, \mathcal{K})$ has 3 internal knots at $\mathcal{K} = \{0.75, 2.12\}$ years (33-rd and 66-th percentile of observed follow-up times), and boundary knots at 0 and 6.4 years (95-th percentile of the observed follow-up times). The fixed effect parameters are denoted by $\{\beta_{0p}, \ldots, \beta_{5p}\}$, and $\{b_{0pi}, \ldots, b_{3pi}\}$ are the patient specific random effects. The error $\varepsilon_{pi}(t)$ is assumed to be t-distributed with three degrees of freedom (Tomer et al., 2019) and scale σ, and is independent of the random effects.



Web Figure 1: **Estimated cumulative-risk of cancer progression (Tomer et al., 2020)** 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 progression times observed in the PRIAS dataset. Censoring includes death, removal from surveillance on the basis of observed longitudinal data, and patient dropout.

To account for the correlation between the DRE and PSA measurements of a patient, link their corresponding random effects are linked. Specifically, the complete vector of random effects $\boldsymbol{b}_i = (b_{0di}, b_{1di}, b_{0pi}, \ldots, b_{3pi})^\top$ is assumed to follow a multivariate normal distribution with mean zero and variance-covariance matrix $\boldsymbol{W}$.

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

$$h_i(t) = h_0(t) \exp\Big(\gamma_1(\text{Age}_i - 65) + \gamma_2(\text{Age}_i - 65)^2 + \alpha_{1d}\text{logit}\big[\Pr\{y_{di}(t) > \text{T1c}\}\big] + \alpha_{1p} m_{pi}(t) + \alpha_{2p}\frac{\partial m_{pi}(t)}{\partial t}\Big), \tag{8}$$

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 progression. The impact of PSA on the hazard of progression is modeled in two ways: a) the impact of the error free underlying PSA value $m_{pi}(t)$, and b) the impact of the underlying PSA velocity $\partial m_{pi}(t)/\partial t$. 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).

Web Appendix B.3 Parameter Estimates

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

Web Table 1: Estimated variance-covariance matrix $\boldsymbol{W}$ of the random effects $\boldsymbol{b} = (b_{0d}, b_{1d}, b_{0p}, b_{1p}, b_{2p}, b_{3p})$ from the joint model fitted to the PRIAS dataset.

Random Effects	b_{0d}	b_{1d}	b_{0p}	b_{1p}	b_{2p}	b_{3p}
b_{0d}	9.233	-0.183	-0.213	0.082	0.058	0.023
b_{1d}	-0.183	1.259	0.091	0.079	0.145	0.109
b_{0p}	-0.213	0.091	0.247	0.007	0.067	0.018
b_{1p}	0.082	0.079	0.007	0.248	0.264	0.189
b_{2p}	0.058	0.145	0.067	0.264	0.511	0.327
b_{3p}	0.023	0.109	0.018	0.189	0.327	0.380

Web Table 2: Estimated mean and 95% credible interval for the parameters of the longitudinal sub-model (6) for the DRE outcome.

Variable	Mean	Std. Dev	2.5%	97.5%
(Intercept)	-4.407	0.151	-4.716	-4.113
(Age − 65)	0.057	0.009	0.039	0.075
$(\text{Age} - 65)^2$	-0.002	0.001	-0.004	0.000
visitTimeYears	-1.089	0.113	-1.292	-0.866

Web Table 3: Estimated mean and 95% credible interval for the parameters of the longitudinal sub-model (7) for the PSA outcome.

Variable	Mean	Std. Dev	2.5%	97.5%
(Intercept)	2.687	0.007	2.674	2.701
(Age − 65)	0.008	0.001	0.006	0.010
$(\text{Age} - 65)^2$	-0.001	0.000	-0.001	0.000
Spline: [0.00, 0.75] years	0.199	0.009	0.181	0.217
Spline: [0.75, 2.12] years	0.293	0.012	0.269	0.316
Spline: [2.12, 6.4] years	0.379	0.014	0.352	0.406
σ	0.144	0.001	0.142	0.145

For the relative risk sub-model (8), the parameter estimates in Web 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 progression.

Web Table 4: Estimated mean and 95% credible interval for the parameters of the relative risk sub-model (8) of the joint model fitted to the PRIAS dataset.

Variable	Mean	Std. Dev	2.5%	97.5%
(Age − 65)	0.034	0.005	0.025	0.043
$(\text{Age} - 65)^2$	0.000	0.001	-0.001	0.001
$\text{logit}\{\Pr(\text{DRE} > \text{T1c})\}$	0.047	0.014	0.018	0.073
Fitted $\log_2(\text{PSA}+1)$ value	0.024	0.076	-0.125	0.170
Fitted $\log_2(\text{PSA}+1)$ velocity	2.656	0.291	2.090	3.236

As described in Web Appendix A the baseline hazard of the joint model model utilized a cubic P-spline. The knots of this P-spline were placed at the following time points: 0.000, 0.000, 0.000, 0.000, 0.401, 0.801, 1.202, 1.603, 2.003, 2.404, 2.805, 3.205, 3.606, 4.007, 4.407, 4.808, 5.209, 12.542, 12.542, 12.542, 12.542 The parameters of the fitted spline function are given in Web Table 5.

Data of the demonstration patient in Figure 5 of the main manuscript is available in Web Table 6.

We present the predictive performance of the PRIAS based joint model using the area under the receiver operating characteristic curve or AUC (measure of discrimination), and the mean absolute prediction error (MAPE) in Web Table 7. In a joint model these are calculated in a time-dependent manner (Rizopoulos, Molenberghs, and Lesaffre, 2017). More specifically, given the time of latest biopsy t, and history of longitudinal data up to time s, we are interested in a medically relevant time frame $(t, s]$, within which the occurrence of progression is of interest, e.g., 1 year in prostate cancer. That is, $s = t+1$. The AUC and MAPE at every six months (schedule of PSA/DRE measurement follow-up in PRIAS) between year one and year six (roughly the 95-percentile of observed follow-up times) are presented in Web Table 7.

Web Table 5: Estimated parameters of the P-spline function utilized to model the baseline hazard $h_0(t)$ in joint model fitted to the PRIAS dataset. Parameters are named with the prefix 'ps' indicating P-spline parameter.

Variable	Mean	Std. Dev	2.5%	97.5%
ps1	-1.091	0.535	-2.286	-0.235
ps2	-2.113	0.271	-2.638	-1.591
ps3	-2.486	0.308	-3.095	-1.883
ps4	-2.083	0.311	-2.740	-1.483
ps5	-1.918	0.279	-2.460	-1.388
ps6	-2.620	0.265	-3.138	-2.140
ps7	-3.169	0.303	-3.796	-2.580
ps8	-3.416	0.340	-4.075	-2.823
ps9	-3.432	0.345	-4.103	-2.796
ps10	-3.223	0.352	-3.997	-2.573
ps11	-2.840	0.349	-3.577	-2.214
ps12	-2.481	0.350	-3.148	-1.762
ps13	-2.540	0.352	-3.206	-1.840
ps14	-2.841	0.321	-3.447	-2.212
ps15	-3.046	0.381	-3.853	-2.328
ps16	-3.113	0.701	-4.533	-1.796
ps17	-3.195	1.232	-5.894	-0.978

Web Table 6: Data of the demonstration patient in Figure 5 of the main manuscript. Age of the patient at baseline was 60 years and time of last negative biopsy was 3.5 years. DRE: digital rectal examination.

Visit time (years)	PSA	$\log_2(\text{PSA}+1)$	DRE > T1c
0.00	5.7	2.77	1
0.30	3.2	2.09	-
0.68	4.0	2.30	0
0.97	4.6	2.50	-
1.15	2.9	1.92	0
1.47	3.0	1.95	0
1.77	3.3	2.14	-
2.23	3.5	2.12	0
2.58	4.4	2.39	-
3.21	6.1	2.84	0
3.86	5.9	2.81	-
4.32	3.9	2.31	0
5.00	4.4	2.41	-

Web Table 7: Follow-up time dependent, area under the receiver operating characteristic curves (AUC), and mean absolute prediction error (MAPE), with 95% confidence interval in brackets.

Follow-up period (years)	AUC (95% CI)	MAPE (95%CI)
0.0 to 1.0	0.658 [0.620, 0.693]	0.234 [0.229, 0.240]
0.5 to 1.5	0.648 [0.631, 0.663]	0.220 [0.213, 0.226]
1.0 to 2.0	0.624 [0.600, 0.644]	0.151 [0.147, 0.155]
1.5 to 2.5	0.649 [0.604, 0.704]	0.127 [0.118, 0.134]
2.0 to 3.0	0.683 [0.629, 0.729]	0.134 [0.121, 0.143]
2.5 to 3.5	0.681 [0.604, 0.739]	0.115 [0.105, 0.128]
3.0 to 4.0	0.647 [0.600, 0.710]	0.079 [0.073, 0.087]
3.5 to 4.5	0.630 [0.583, 0.668]	0.095 [0.089, 0.101]
4.0 to 5.0	0.614 [0.557, 0.659]	0.104 [0.098, 0.111]
4.5 to 5.5	0.615 [0.541, 0.702]	0.101 [0.088, 0.114]
5.0 to 6.0	0.617 [0.550, 0.713]	0.102 [0.086, 0.121]

Web Appendix C Simulation Study

In the simulation study, we evaluated the following biopsy schedules (Inoue et al., 2018; Loeb et al., 2014): biopsy every year (annual), biopsy according to the PRIAS schedule (PRIAS), personalized biopsy schedules based on two fixed risk thresholds, namely, $\kappa = 10\%$, and automatically chosen $\kappa^*(v)$ (Section 3 of main manuscript), and automatically chosen $\kappa^*\{v \mid E(D) \leq 0.75\}$ with a constraint of 9 months (0.75 years) on expected delay in detecting progression. We compare all the aforementioned schedules on two criteria, namely the number of biopsies they schedule and the corresponding time 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 Web Table 8. Since the simulated cohorts are based on PRIAS, roughly only 50% of the patients progress in the ten year study period. While, we are able to calculate total number of biopsies scheduled in all 500×250 test patients, but the time delay in detection of progression is available only for those patients who progress in ten years (*progressing*). Hence, we show the simulation results separately for *progressing* and *non-progressing* patients.

Web Table 8: **Simulation study results for all patients**: Estimated mean (μ), median (Med), first quartile Q_1, and third quartile Q_3 for number of biopsies (nb) and for the time delay (d) in detection of cancer progression in years, for various biopsy schedules. The delay is equal to the difference between the time of the positive biopsy and the simulated true time of progression. Types of schedules: $\kappa = 10\%$ and $\kappa^*(v)$ schedule a biopsy if the cumulative-risk of cancer progression at a visit is more than 10%, and an automatically chosen threshold, respectively. Schedule $\kappa^*\{v \mid E(D) \leq 0.75\}$ is similar to $\kappa^*(v)$ except that the euclidean distance is minimized under the constraint that expected delay in detecting progression is at most 9 months (0.75 years). Annual corresponds to a schedule of yearly biopsies, and PRIAS corresponds to biopsies as per PRIAS protocol.

Progressing patients (50%)								
Schedule	Q_1^{nb}	μ^{nb}	Med^{nb}	Q_3^{nb}	Q_1^{d}	μ^{d}	Med^{d}	Q_3^{d}
Annual	1	3.71	3	6	0.29	0.55	0.57	0.82
PRIAS	1	2.88	2	4	0.38	0.92	0.74	1.00
$\kappa = 10\%$	1	2.55	2	4	0.45	1.00	0.85	1.33
$\kappa^*(v)$	1	2.46	2	3	0.45	0.89	0.86	1.26
$\kappa^*\{v \mid E(D) \leq 0.75\}$	1	3.39	3	5	0.32	0.61	0.63	0.88
Non-progressing patients (50%)								
Annual	10	10.00	10	10	-	-	-	-
PRIAS	4	6.40	6	8	-	-	-	-
$\kappa = 10\%$	4	4.91	5	6	-	-	-	-
$\kappa^*(v)$	6	6.22	6	7	-	-	-	-
$\kappa^*\{v \mid E(D) \leq 0.75\}$	8	8.68	9	9	-	-	-	-

Web Appendix D Source Code

Web Appendix D.1 Creating Personalized Schedules

The R code for creating personalized schedules can be found at https://github.com/anirudhtomer/prias/blob/master/src/lastpaper/pers_schedule_api.R. This source code is compatible with joint model objects obtained using the R package **JMbayes** (Rizopoulos, 2016). The file contains two functions, namely, 'personalizedSchedule.mvJMbayes' and 'testScheduleConsequences.mvJMbayes'. The parameters of the functions are described in the comments above the function names. In general, the parameters work on the lines of the function survfitJM available in the **JMbayes** package. The function 'personalizedSchedule.mvJMbayes' returns risk-based personalized schedules based on 200 risk thresholds separated by a gap of every 0.5% risk. In addition, it also returns the optimal schedule out of the 200 schedules. The function's capability is not limited to risk-based schedules. Rather, if the parameter 'risk_based_schedules_only' is set to FALSE, then given a grid of follow-up visits via the parameter 'fixed_grid_visits', the function finds the optimal schedule among all possible schedules that can be made based on the grid of the future visits. In some scenarios, users may want to calculate expected number of tests and expected time delay in detecting progression for an already decided schedules of tests. This can be obtained via the second function called 'testScheduleConsequences.mvJMbayes'.

Web Appendix D.2 Running the simulation study

The simulation study can be run by the R scripts in the folder: https://github.com/anirudhtomer/prias/tree/master/src/lastpaper/simulation. The file 'controller_model.R' creates a hypothetical PRIAS like prostate cancer active surveillance study with 1000 patients in it. For this purpose it accepts only one command line parameter, an integer which acts as the seed which is set before generating hypothetical patient profiles. The source code also fits a joint model using the R package **JMbayes** and saves it in a Rdata file. This fitted model can be utilized to create personalized and fixed schedules for the simulated test patients. For this purpose, one can run the R scripts 'controller_schedule_fixed.R' and 'controller_schedule_optimal.R'. These files accept two command line parameters, namely, the seed with which a joint model was fitted earlier, and the hypothetical patient ID of the test patient for which personalized and fixed schedules are to be created. These hypothetical test patient IDs are always between 751 and 1000, i.e., a total of 250 test patients. The file 'controller_schedule_fixed.R' runs annual schedule, biennial schedule, PRIAS schedule, and risk-based personalized schedules using fixed thresholds of 5%, 10% and 15%. Whereas, the file 'controller_schedule_optimal.R' runs the code to find an optimal personalized schedule using a visit-specific threshold, and an optimal personalized schedule using a visit-specific threshold under the constraint that the expected delay in detecting progression is at most 0.75 years.

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