

Personalized Schedules for Burdensome Surveillance Tests

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SUMMARY: Gold standard surveillance *tests* for diagnosing disease *progression* (biopsies, endoscopies, etc.) in early-stage chronic non-communicable disease patients (e.g., cancer, lung diseases) are usually invasive. For detecting progression timely, over their lifetime, patients undergo numerous invasive tests planned in a fixed one-size-fits-all manner (e.g., biannually). We present progression-risk based personalized test schedules that aim to balance better the number of tests (burden) and time delay in detecting progression (shorter is beneficial) than fixed schedules. Our motivation comes from the world's largest prostate cancer surveillance study PRIAS.

Using joint models for time-to-event and longitudinal data, we consolidate auxiliary longitudinal data (e.g., biomarkers) and results of previous tests, into individualized future cumulative-risk of progression. We then create personalized schedules by planning tests on future visits where the predicted progression-risk is above a particular *threshold* (e.g., 5% risk). This schedule is updated on each follow-up with newly gathered data. To find the optimal risk threshold, we minimize a utility function of the expected number of tests (burden) and time delay in detecting progression (shorter is beneficial) for different thresholds. We estimate these two quantities in a patient-specific manner for following any schedule, by utilizing the predicted risk profile of the patient. Patients/doctors can employ these quantities to objectively compare various personalized and fixed schedules. Last, we implement our methodology in a web-application for real PRIAS study cancer patients.

KEY WORDS: Chronic NCDs; Invasive diagnostic tests; Joint models; Personalized schedules; Prostate biopsy; Surveillance

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1. Introduction

Chronic non-communicable diseases (e.g., cancer, lung, cardiovascular diseases) cause 60–70% of human deaths worldwide (WHO et al., 2014). Often patients diagnosed with an early-stage disease undergo repeated surveillance *tests* to timely detect disease *progression*, a non-terminal event. Gold standard surveillance tests utilized for this purpose are usually invasive. For example, in prostate cancer surveillance, progression from low to high-grade is detected using biopsies (Bokhorst et al., 2015). Similarly, endoscopies are employed in Barrett’s esophagus (Streitz et al., 1993), colonoscopies for colorectal cancer (Krist et al., 2007), and bronchoscopies for detecting lung transplant (McWilliams et al., 2008) deterioration.

Often fixed schedules (e.g., biannually) are utilized for invasive tests in surveillance (McWilliams et al., 2008; Bokhorst et al., 2015; Krist et al., 2007). Since tests are conducted periodically, there is always a time delay in detecting progression (Figure 1). The frequency/timing of tests and the corresponding time delay in detecting progression, manifest the burden and benefit of test schedules, respectively. Tests are burdensome because they may cause pain and/or severe medical complications (Loeb et al., 2013; Krist et al., 2007), and consequently patients may not always comply with frequent tests (Bokhorst et al., 2015). On the other hand, detecting progression timely can provide a larger window of opportunity for curative treatment. In this regard, one-size-fits-all fixed schedules impose an equal but unnecessary burden on all patients, because many early-stage patients can be slow/non-progressing.

[Figure 1 about here.]

In this work, we aim to balance the number of invasive tests and the time delay in detecting progression better than fixed schedules. Specifically, we intend to create personalized schedules that utilize patient-specific clinical data accumulated over follow-up. In surveillance, this data includes baseline characteristics; previous invasive test results; and auxiliary longitudinal outcomes such as biomarkers, physical examination, and medical imaging measurements,

etc. Previous attempts at personalized scheduling can be divided into three categories. First, heuristic approaches such as decision making flowcharts, e.g., Bokhorst et al. (2015). However, flowcharts discretize continuous clinical outcomes, often exploit only the last measurement, and ignore the measurement error in observed data. Second, partially observable Markov decision processes (Alagoz et al., 2010; Steimle and Denton, 2017) for personalizing test decisions. Although, the curse of dimensionality limits their application with continuous longitudinal outcomes. Third, personalized schedules obtained by optimizing an explicit utility function of the clinical parameters of interest (Bebu and Lachin, 2017; Rizopoulos et al., 2015), including our previous work on scheduling biopsies in prostate cancer (Tomer et al., 2019). In this work, we will employ the third approach.

In our methodology, we first develop a full specification of the joint distribution of the patient-specific longitudinal outcomes and the time of *progression*. To this end, we employ joint models for time-to-event and longitudinal data (Tsiatis and Davidian, 2004; Rizopoulos, 2012) because they are also inherently personalized. Specifically, they exploit patient-specific random effects (Laird and Ware, 1982) to model longitudinal outcomes without discretizing them. Subsequently, we input the accumulated clinical data of a new patient into the fitted model, to obtain their patient-specific cumulative-risk of progression at their current and future follow-up visits. We then create personalized schedules by planning tests on future visits where the predicted conditional cumulative-risk is above a particular *threshold* (e.g., 5% risk). We automate the choice of this threshold and the resulting schedule. Specifically, we optimize a utility function of the expected number of tests (burden) and time delay in detecting progression (shorter is beneficial) for different risk threshold based personalized schedules. We estimate these two quantities in a patient-specific manner for following any schedule, by utilizing the predicted risk profile of the patient. Patients/doctors can employ these quantities to objectively compare various personalized and fixed schedules.

Our work is motivated by the problem of scheduling biopsies (Nieboer et al., 2018) in the world’s largest prostate cancer active surveillance study PRIAS (Bokhorst et al., 2015). It has 7813 patients (1134 cancer progressions) with 104904 longitudinal measurements. At inclusion, patients have low/very-low grade cancer, often over-diagnosed due to prostate-specific antigen (PSA) screening tests (Crawford, 2003). The goal of prostate cancer surveillance is to delay serious treatments (e.g., surgery, chemotherapy) until cancer progresses. For detecting progression, patients are monitored continually via serum PSA (ng/mL), digital rectal examination (DRE) for shape/size of the tumor, and biopsy Gleason grade group (Epstein et al., 2016). Since biopsy results are the strongest indicator of cancer-related outcomes, treatment is commonly advised when patient’s biopsy Gleason grade group increases (cancer progression). The most prescribed schedule of biopsies in prostate cancer surveillance is annual biopsies (Loeb et al., 2014). However, they lead to many unnecessary biopsies in slow/non-progressing patients (50% proportion in some cohorts). Biopsy burden combined with patient non-compliance to frequent biopsies (Bokhorst et al., 2015) has raised concerns regarding the optimal biopsy schedule. Since prostate cancer has the second-highest incidence among all cancers in males (Torre et al., 2015), individualized biopsy schedules can reduce the burden of biopsies numerous patients worldwide.

The rest of the paper is as follows. Section 2 briefly introduces the joint modeling framework. In Section 3, we present the methodology for personalized schedules and then demonstrate them for biopsies in real PRIAS patients in Section 4. Lastly, in Section 5, we show the efficacy of personalized schedules via a realistic simulation study based on PRIAS patients.

2. Joint Model for Time-to-Progression and Longitudinal Outcomes

Let T_i^* denote the true time of disease progression for the i -th patient. Progression is always interval censored $l_i < T_i^* \leq r_i$ (Figure 1), with r_i and l_i denoting the time of the last and second last invasive tests, respectively, when patients progress. In non-progressors, l_i denotes

the time of the last test and $r_i = \infty$. Assuming K auxiliary longitudinal outcomes, let \mathbf{y}_{ki} denote the $n_{ki} \times 1$ longitudinal response vector of the k -th outcome, $k \in \{1, \dots, K\}$. The observed data of all n patients is given by $\mathcal{A}_n = \{l_i, r_i, \mathbf{y}_{1i}, \dots, \mathbf{y}_{Ki}; i = 1, \dots, n\}$.

To accommodate different longitudinal outcomes in a unified framework, the joint model employs a generalized linear mixed-effects sub-model (McCulloch and Neuhaus, 2005). Specifically, the conditional distribution of \mathbf{y}_{ki} given a vector of patient-specific random effects \mathbf{b}_{ki} is assumed to be a member of the exponential family, with linear predictor given by,

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

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

In the survival process, hazard of progression $h_i(t)$ at a time t is assumed to depend on a function of patient and outcome-specific linear predictors $m_{ki}(t)$ and/or the random effects:

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

where $h_0(\cdot)$ denotes the baseline hazard, $\mathcal{M}_{ki}(t) = \{m_{ki}(s) \mid 0 \leq s < t\}$ is the history of the k -th longitudinal process up to t , and $\mathbf{w}_i(t)$ is a vector of exogenous, possibly time-varying covariates with regression coefficients $\boldsymbol{\gamma}$. Functions $f_k(\cdot)$, parameterized by vector of coefficients $\boldsymbol{\alpha}_k$, specify the features of each longitudinal outcome that 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:

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

These formulations of $f(\cdot)$ postulate that the hazard of progression at time t may depend on underlying level $m_i(t)$ of the longitudinal outcome at t , or on both the level and velocity $m'_i(t)$ (e.g., PSA value and velocity in prostate cancer) of the outcome at t . Lastly, the baseline hazard $h_0(t)$ is modeled flexibly using P-splines (Eilers and Marx, 1996). The detailed specification of the baseline hazard, and the joint parameter estimation of the longitudinal and relative-risk sub-models using the Bayesian approach are presented in Web-Appendix A.

3. Personalized Schedule of Invasive Tests for Detecting Progression

3.1 Cumulative-risk of progression

Using the joint model fitted to the available data \mathcal{A}_n , we aim to derive a personalized schedule of invasive tests for a new patient j . The basis for our calculations is the dynamic cumulative risk function. In particular, we let t denote the last time an invasive test was performed and v the current visit time. As in our motivating example, we allow that longitudinal biomarker information can be collected after the last invasive test, i.e., $v \geq t$ (i.e., see Figure 2). The patient-specific cumulative-risk of progression at future time u is defined as:

$$\begin{aligned} R_j(u \mid t, v) &= \Pr\{T_j^* \leq u \mid T_j^* > t, \mathcal{Y}_{1j}(v), \dots, \mathcal{Y}_{Kj}(v), \mathcal{A}_n\} \\ &= \int \int \Pr(T_j^* \leq u \mid T_j^* > t, \mathbf{b}_j, \boldsymbol{\theta}) p\{\mathbf{b}_j \mid T_j^* > t, \mathcal{Y}_{1j}(v), \dots, \mathcal{Y}_{Kj}(v), \boldsymbol{\theta}\} \\ &\quad \times p(\boldsymbol{\theta} \mid \mathcal{A}_n) d\mathbf{b}_j d\boldsymbol{\theta}, \quad u \geq t, \end{aligned} \tag{1}$$

where $\{\mathcal{Y}_{1j}(v), \dots, \mathcal{Y}_{Kj}(v)\}$ denotes the history of observed longitudinal outcomes until the current visit time v . The cumulative risk function $R_j(\cdot)$ dynamically updates over time as more longitudinal data becomes available (Panel B and C, Figure 2).

[Figure 2 about here.]

3.2 Personalized Decision Rule

Our aim is to employ the cumulative-risk function $R_j(\cdot)$ to develop a risk-based personalized schedule of invasive tests for the j -th patient. Typically, the decision to perform such an invasive procedure takes place at the same visit times at which auxiliary data (e.g., biomarkers) are measured. We let $U = \{u_1, \dots, u_L\}$ represent the schedule of such visits (e.g., every six months in prostate cancer for PSA measurement), where $u_1 = v$ is the current visit time. The last time u_L is selected according to the information we have available in the original dataset \mathcal{A}_n . That is, we will only plan tests for the future patient j up to the follow-up time u_L at which we had sufficient number of events in \mathcal{A}_n (e.g., up to the 80% or 90% percentile of progression times).

We propose to take the decision of conducting a test at a future visit time $u_l \in U$ when the cumulative risk of progression exceeds a certain threshold κ , i.e.,

$$Q_j^\kappa(u_l \mid t_l, v) = I\{R_j(u_l \mid t_l, v) \geq \kappa\}, \quad 0 \leq \kappa \leq 1,$$

where $I(\cdot)$ denotes the indicator function. The time point t_l is the time point the last invasive test was performed, i.e., if a test gets planned at time u_l , then the successive test decision at time u_{l+1} is made using an updated cumulative-risk profile (Figure 3). This updated cumulative-risk profile accounts for the possibility that progression may occur after time $u_l < T_j^*$. Hence, the definition of t_l is

$$t_l = \begin{cases} t, & \text{if } l = 1 \\ t_{l-1}, & \text{if } l \geq 2 \text{ and } Q_j^\kappa(u_{l-1} \mid t_{l-1}, v) = 0 \\ u_{l-1}, & \text{if } l \geq 2 \text{ and } Q_j^\kappa(u_{l-1} \mid t_{l-1}, v) = 1 \end{cases}$$

We should note that for all the future decisions we use only the longitudinal information that we have collected up to the current visit $v = u_1$.

3.3 Expected Number of Tests and Time Delay in Detecting Progression

To facilitate shared-decision making, we translate our proposed decision rule, i.e., the choice of a specific κ , into clinically relevant quantities. Namely, for the specific κ value we have selected, we would like to know how many tests we expect to perform in the future for patient j , and if he/she progresses, what will be the expected delay in finding this progression. As explained before, the more tests, the shorter the delay will be but at the expense of increasing patient burden.

To calculate the expected number of tests and expected delay, we first suppose that patient j never progressed in the period $[t, u_L]$. Under this assumption, the subset of future time points in U at which a test is to be performed results into a personalized schedule of planned future tests, given by:

$$\{s_1, \dots, s_{N_j}\} = \{u_l \in U : Q_j^\kappa(u_l | t_l, v) = 1\}, \quad N_j \leq L. \quad (2)$$

Figure 3 depicts this schedule for a hypothetical patient and risk threshold of 12%.

[Figure 3 about here.]

If patient j never progressed in the period $[t, u_L]$, as we initially supposed, we would conduct N_j tests. However, if the patient did progress at some point $T_j^* < u_L$, then we will conduct less tests. We formally define the discrete random variable denoting the number of performed tests in conjunction with the true progression time T_j^* as:

$$\mathcal{N}_j(S^\kappa) = \begin{cases} 1, & \text{if } t < T_j^* \leq s_1, \\ 2, & \text{if } s_1 < T_j^* \leq s_2, \\ \vdots & \\ N_j, & \text{if } s_{N_j-1} < T_j^* \leq s_{N_j}, \end{cases}$$

where $S^\kappa = \{s_1, \dots, s_{N_j}\}$. Then the expected number of future tests for patient j will be the

expected value of $\mathcal{N}_j(S^\kappa)$ that be calculated with the expression:

$$E\{\mathcal{N}_j(S^\kappa)\} = \sum_{n=1}^{N_j} n \times \Pr(s_{n-1} < T_j^* \leq s_n \mid T_j^* \leq s_{N_j}), \quad s_0 = t, \quad (3)$$

where

$$\Pr(s_{n-1} < T_j^* \leq s_n \mid T_j^* \leq s_{N_j}) = \frac{R_j(s_n \mid t, v) - R_j(s_{n-1} \mid t, v)}{R_j(s_{N_j} \mid t, v)}.$$

In an analogous manner we can define the expected delay in finding progression, under the assumption that progression has occurred before u_L . In particular, we first define the random variable that quantifies the time difference between the true progression time T_j^* and the time of the test at which this progression will be observed, i.e.,

$$\mathcal{D}_j(S^\kappa) = \begin{cases} s_1 - T_j^*, & \text{if } t < T_j^* \leq s_1, \\ s_2 - T_j^*, & \text{if } s_1 < T_j^* \leq s_2, \\ \vdots & \\ s_{N_j} - T_j^*, & \text{if } s_{N_j-1} < T_j^* \leq s_{N_j}, \end{cases}$$

The expected delay will be the expected value of $\mathcal{D}_j(S^\kappa)$ given by the expression:

$$E\{\mathcal{D}_j(S^\kappa)\} = \sum_{n=1}^{N_j} \left\{ s_n - E(T_j^* \mid s_{n-1}, s_n, v) \right\} \times \Pr(s_{n-1} < T_j^* \leq s_n \mid T_j^* \leq s_N), \quad (4)$$

where

$$\begin{aligned} E(T_j^* \mid s_{n-1}, s_n, v) &= s_{n-1} \\ &+ \int_{s_{n-1}}^{s_n} \Pr\left\{T_j^* \geq u \mid s_{n-1} < T_j^* \leq s_n, \mathcal{Y}_{1j}(v), \dots, \mathcal{Y}_{Kj}(v), \mathcal{A}_n\right\} du, \end{aligned}$$

where $E(T_j^* \mid s_{n-1}, s_n, v)$ denotes the conditional expected time of progression for the scenario $s_{n-1} < T_j^* \leq s_n$, and is calculated as the area under the corresponding survival curve.

The personalized schedule in (2) is updated as more patient data becomes available over subsequent follow-up visits. The personalized expected number of tests and expected time delay in detecting progression have the advantage that they are updated over follow-up as more patient data becomes available. Since they can be calculated for any schedule, patients and doctors can utilize them to compare schedules before making a decision. Although,

in order to have a fair comparison of time delays between different schedules for the same patient, a compulsory test at a common horizon time point should be planned in all schedules.

3.4 How to Select the Risk Threshold κ

The risk threshold κ controls the timing and the total number of invasive tests in the personalized schedule S^κ . And through the timing and total number of planned tests, κ also indirectly affects the time delay (Figure 1) that may occur in detecting progression if a particular schedule is followed. Hence, κ should be chosen while balancing both the number of invasive tests (burden) and the time delay in detecting progression (less is beneficial).

To facilitate the choice of κ in practice, and in accordance to our developments in the previous section, we translate different choices for this parameter into the expected number of test and expected delay. More specifically, for a specific patient j and at the current visit time v , we can construct the bi-dimensional Euclidean space of the expected total number of invasive tests (x-axis) and the corresponding expected time delay in detecting progression (y-axis) for test schedules planned by varying κ in $[0, 1]$. An example of such a space is given in Figure 4.

[Figure 4 about here.]

The ideal schedule for this patient would be the one that has only one test conducted at exactly the true time of progression T_j^* . In other words, it will have zero time delay. If we would weigh delay and the number of tests as equally important, then we could select as the risk threshold $\kappa^*(v)$ at the current visit time v the threshold that minimizes Euclidean distance between the ideal schedule, i.e., point $(1, 0)$ and the set of points representing the different personalized schedules S^κ corresponding to various, i.e.,

$$\kappa^*(v) = \arg \min_{0 \leq \kappa \leq 1} \sqrt{\left[E\{\mathcal{N}_j(S^\kappa)\} - 1\right]^2 + \left[E\{\mathcal{D}_j(S^\kappa)\} - 0\right]^2}. \quad (5)$$

Additional consequences of following a particular schedule, such as (quality-adjusted) life-

years saved, can also be accommodated in (5). This can be achieved by first setting a point of optimality in a higher dimensional Euclidean space of the aforementioned consequences, and then minimizing the Euclidean distance relative to this point of optimality.

An alternative approach is to constraint one of the two dimensions. For example, depending on the age of patient j , he together with his physician may be willing to schedule a maximum number of future tests or may be apprehensive about having an expected time delay higher than a certain number of months. In such situations, the Euclidean distance in (5) can be minimized under constraints on the expected number of tests and/or expected time delay (Figure 4). An additional benefit of this approach is that it alleviates the issue that the time delay and the number of tests have different units of measurement Cook and Wong (1994).

4. Demonstration of Personalized Schedules

To demonstrate the application of personalized schedules on real patients, we return to the prostate cancer active surveillance dataset, PRIAS, described in Section 1. The current PRIAS protocol for biopsies is fixed biopsies at year one, four, seven, and ten of follow-up, and every five years after that. Additional annual biopsies are scheduled if a patient's PSA doubling-time (Bokhorst et al., 2015) is high. The PSA is measured as per a fixed schedule, quarterly for the first two years, and semi-annually after that. The DRE is also measured semi-annually. The dataset is summarized in Web-Appendix B.

The clinical data that we intend to use consists of longitudinal PSA (continuous: ng/mL) and DRE (binary: tumor palpable or not) measurements, patient age at baseline, history of biopsies, and interval-censored times of cancer progression. The event of interest is cancer progression. We aim to use the accumulated clinical data to build a joint model that can be utilized for creating personalized biopsy schedules in future PRIAS patients.

4.1 Fitting the Joint Model to the PRIAS Dataset

We fit a joint model with $\log_2(\text{PSA} + 1)$ transformed PSA (Lin et al., 2000; Pearson et al., 1994), and DRE as longitudinal outcomes, and cancer progression as the event (Web-Appendix B.3 for exact specification). For PSA, we utilize a linear mixed-effects sub-model wherein PSA profiles are modeled non-linearly over follow-up using B-splines (De Boor, 1978). For DRE, we utilize a logistic mixed-effects sub-model. To link the longitudinal sub-models for the PSA and DRE with the relative-risk sub-model for cancer progression, we include three features of the longitudinal outcomes in the relative-risk sub-model. Specifically, the hazard of cancer progression at time t depends on the fitted instantaneous $\log_2(\text{PSA} + 1)$ value at time t , the estimated instantaneous $\log_2(\text{PSA} + 1)$ velocity at t , and fitted log-odds of having a DRE indicating a palpable tumor at t . We estimated the parameters of our model under the Bayesian framework using the R package **JMbayes** (Rizopoulos, 2016).

The follow-up period of PRIAS is currently limited. Hence, our joint model is able to predict the cumulative-risk of progression only until the year ten of follow-up. The cumulative-risk of progression at year ten in PRIAS is 50% (Web-Figure 1). We found that the strongest predictor for progression in our model is $\log_2(\text{PSA} + 1)$ velocity. Specifically, for an increase in fitted $\log_2(\text{PSA} + 1)$ velocity from -0.03 to 0.15 the adjusted hazard ratio of progression was 1.6 (95%CI: 1.45–1.78). Detailed parameter estimates are in Web-Appendix B.4. Since personalized schedules are risk-based, their overall performance is dependent on the predictive accuracy of the fitted model. In this regard, the PRIAS based model’s time-dependent area under the receiver operating characteristic curve (Rizopoulos, 2011) was moderate (between 0.61 and 0.68) and time-dependent mean absolute prediction error (Rizopoulos, 2011) was moderate to large (between 0.08 and 0.24) over follow-up (Web-Appendix B.6).

4.2 *Personalized Schedules for a Demonstration Patient*

We utilized the joint model fitted to the PRIAS dataset to schedule biopsies in a real PRIAS patient (Figure 5), starting from his current visit at year five, until year ten of follow-up. This patient has not progressed until year 3.5, and hence even if he incurs a delay in detecting progression of up to three years, it may not lead to adverse outcomes (de Carvalho et al., 2017). Also, since his cumulative-risk of progression at year ten is only 16.5%, he is likely to progress slowly. Consequently, few biopsies are planned by risk-based personalized schedules (Panel B, Figure 5). Even if this patient progresses before year ten of follow-up and opts for personalized schedules, not only will he undergo fewer biopsies than annual schedule (Panel C, Figure 5), but his expected delay in detecting progression is also under the aforementioned limit of three years (Panel D, Figure 5).

[Figure 5 about here.]

5. Simulation Study

Although we demonstrated personalized schedules for a real patient, we also intend to analyze and compare personalized and fixed schedules in a full cohort. The criteria for comparison of schedules are the total number of invasive tests planned, and the actual time delay in detection of progression for each schedule. However, due to the periodical nature of schedules, the actual time delay in detection of progression cannot be observed in real-world surveillance. Hence, instead, we compare personalized versus fixed schedules via an extensive simulated randomized clinical trial in which each hypothetical patient undergoes each schedule. To keep our simulation study realistic, we employ the prostate cancer active surveillance scenario. More specifically, our simulated population is manifested by the fitted joint model obtained using the PRIAS cohort (Web-Appendix B.3).

5.1 Simulation Setup

From the simulation population, we first sample 500 datasets, each representing a hypothetical prostate cancer active surveillance 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 longitudinal DRE and PSA measurements at the same follow-up visit times as given in the 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. All test and training patients also observe Type-I censoring at year ten of follow-up (current study period of PRIAS). We next fit a joint model of the same specification as the model fitted to PRIAS (Web-Appendix B.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 surveillance programs, we utilize the corresponding fitted joint models to develop the profiles for cumulative-risk of progression in each of the 500×250 test patients. This cumulative-risk is further used to create personalized biopsy schedules for the test patients. For each test patient, we conduct biopsies using three personalized biopsy schedules. First using a fixed risk threshold of $\kappa^* = 10\%$. Second, an automatically chosen visit-specific threshold $\kappa^*(v)$. Third, an automatic threshold under the constraint that expected delay is less than 9 months (0.75 years) $\kappa^*\{v \mid E(D) \leq 0.75\}$. We also conduct biopsies according to the currently practiced PRIAS and annual schedules. We decide biopsies only on the standard PSA follow-up visits (Section 4) utilizing clinical data accumulated only until that visit. Also, we maintain a minimum recommended gap of one year between consecutive prostate biopsies (Bokhorst et al., 2015). Biopsies are conducted until progression is detected, or the maximum follow-up period at year ten (horizon) is reached. The actual time delay in detection of progression is equal to the time at which progression is detected minus the actual (simulated) time of progression of a patient.

5.2 Results

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 the 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 in Panel A, and Panel B of Figure 6, respectively.

For *progressing* patients (Panel A, Figure 6), the annual schedule leads to the maximum number of biopsies (Median 3, Inter-quartile range or IQR: 1–6). However, it also guarantees a maximum time delay of one year for all patients. The PRIAS protocol schedules much fewer biopsies (Median 1, IQR: 2–4), but also has a higher time delay (Median 0.74, IQR: 0.38–1.00 years). The personalized schedule based on automatically chosen risk threshold $\kappa^*(v)$ schedules fewer biopsies than PRIAS and has a delay (Median 0.96, IQR: 0.60–1.57 years) slightly higher than PRIAS. The mean delay for schedule $\kappa^*\{v \mid E(D) \leq 0.75\}$ is equal to 0.73 years (Median 0.74, IQR: 0.37–0.99 years) and hence works as expected. Unless the patient progresses within the first year of prostate cancer active surveillance, a delay of up to three years may not increase the risk of adverse downstream outcomes in (Inoue et al., 2018; de Carvalho et al., 2017).

The patients who are at the most advantage with the personalized schedules are the *non-progressing* patients (Panel B, Figure 6). For all of these patients, the annual schedule leads to 10 (unnecessary) biopsies. The schedule of the PRIAS program schedules a median of 6 (IQR: 4–8) biopsies. In comparison, the schedule based on automatically chosen risk threshold $\kappa^*(v)$ schedules a median of 5 (IQR: 5–6) biopsies.

[Figure 6 about here.]

6. Discussion

In this paper, we presented a methodology to create personalized schedules for burdensome surveillance *tests*, to detect disease *progression* in early-stage chronic non-communicable diseases. To this end, we utilized the framework of joint models for time-to-event and longitudinal data. Our approach first combines a patient’s auxiliary longitudinal data (e.g., biomarkers) and results from previous invasive tests to estimate the patient-specific cumulative-risk of disease progression over his current and future follow-up time period. Then, using this risk profile, we schedule future invasive tests whenever the patient’s conditional cumulative-risk of progression is predicted to be above a certain threshold. We select this risk threshold automatically in a personalized manner, by optimizing a utility function of the patient-specific consequences of choosing a particular risk threshold based schedule. These consequences are, namely, the number of invasive tests for a particular schedule, and the expected time delay in detection of progression if that schedule is followed. Last, we calculate this expected time delay in a personalized manner for both personalized and fixed schedules to assist patients/doctors in making a more informed decision of choosing a test schedule.

The use of joint models gives our schedules certain advantages. First, joint models utilize individualized random-effects, making our schedules inherently personalized. Second, the patient-specific risk of progression employed by the proposed personalized schedules is estimated by utilizing all observed longitudinal and clinical data of a patient. In addition, the continuous longitudinal outcomes are not discretized, which is commonly a case in Markov Decision Process based (Alagoz et al., 2010; Steimle and Denton, 2017), and flowchart-based test schedules. The third and most significant advantage of our schedules, however, is that they update as more patient data becomes available over follow-up. Last, although this work concerns with the use of personalized schedules in disease surveillance, the methodology is generic for use under a screening setting as well.

Since our schedules are risk-based, we proposed a utility function to automate the choice of a risk threshold based schedule. The utility function that we proposed focused only on two aspects of a schedule, namely the burden and the benefit. In this regard, we chose the number of invasive tests in a schedule (burden) and expected time delay in detection of progression (less is beneficial) because they are easy to interpret and are critical in making the decision of an invasive test. Since we calculate the expected time delay in a patient-specific manner for both personalized and fixed schedules, patients/doctors can compare and choose various risk-based and fixed schedules according to their preferences for the expected burden-benefit ratio. Additional measures such as (quality-adjusted) life-years saved can also be easily added in our utility function.

We evaluated the efficacy of personalized schedules in a full cohort via a realistic simulation randomized clinical trial for prostate cancer active surveillance patients. We observed that the personalized schedule that used an automatically chosen risk threshold using (5) reduced unnecessary biopsies for patients who did not observe progression in the study period, compared to fixed schedules. In contrast, in patients who observed progression, the personalized schedule with automatically chosen risk threshold scheduled fewer biopsies at the cost of having a slightly more time delay in detecting progression than the PRIAS schedule. However, this by no means is the limit of the performance of the personalized schedules. In general, personalized schedules employing models with higher predictive accuracy (both discrimination and calibration) than the PRIAS based model may lead to an even better balance between the number of tests and the time delay in detecting progression.

There are certain limitations of our work. First, in practice, most cohorts observe Type-I right censoring. Hence, the cumulative-risk profiles of patients and the calculation of expected time delay in detection of progression is only possible up to the time of Type-I censoring. This problem can only be resolved as more follow-up data become available over

time. We proposed a joint model which assumes all events other than progression to be non-informative censoring. Alternative models that account for competing risks may lead to better results as they estimate absolute and not the cause-specific risk of progression. However, the methodology for scheduling biopsies need not change. Many surveillance tests are imperfect and prone to inter-observer variation (e.g., biopsy Gleason grade). Models that account for inter-observer variation in diagnostic tests (Balasubramanian and Lagakos, 2003) will be exciting to investigate further.

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SUPPORTING INFORMATION

Web Appendices referenced in this paper are available in the file titled ‘supplementary.pdf’.

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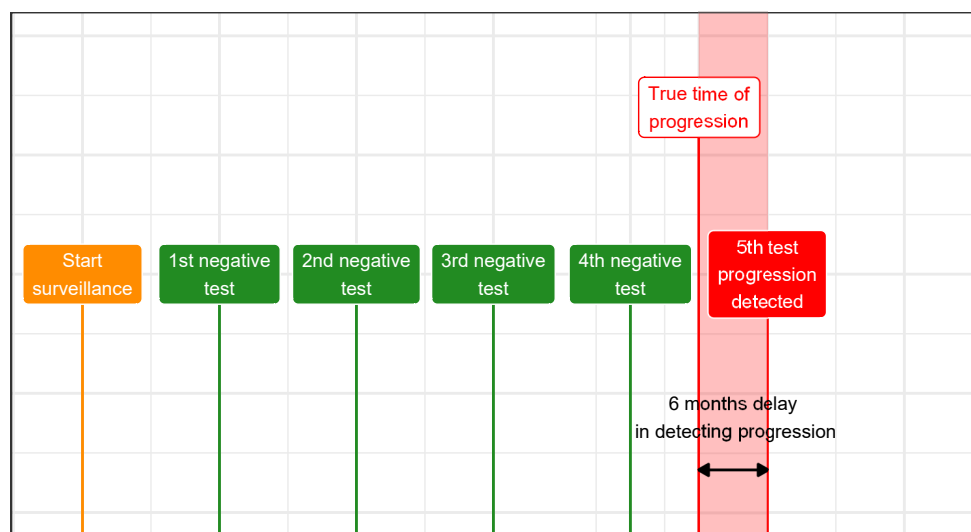
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A Test every year



B Test every 2 years

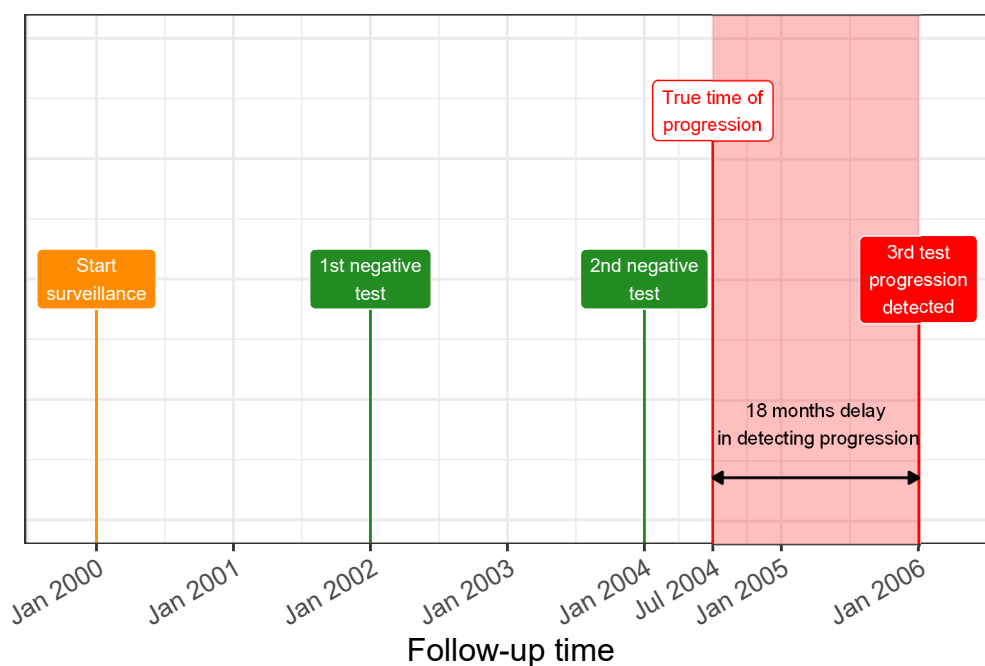


Figure 1. Trade-off between the number of invasive tests and time delay in detecting progression (non-terminal event of interest): The true time of progression for this patient July 2004. More frequent invasive tests in **Panel A** lead to a smaller time delay in detecting progression than less frequent invasive tests in **Panel B**. Since invasive tests are conducted periodically, the time of progression is observed as an interval. For example, between Jan 2004–Jan 2005 in **Panel A** and between Jan 2004–Jan 2006 in **Panel B**.

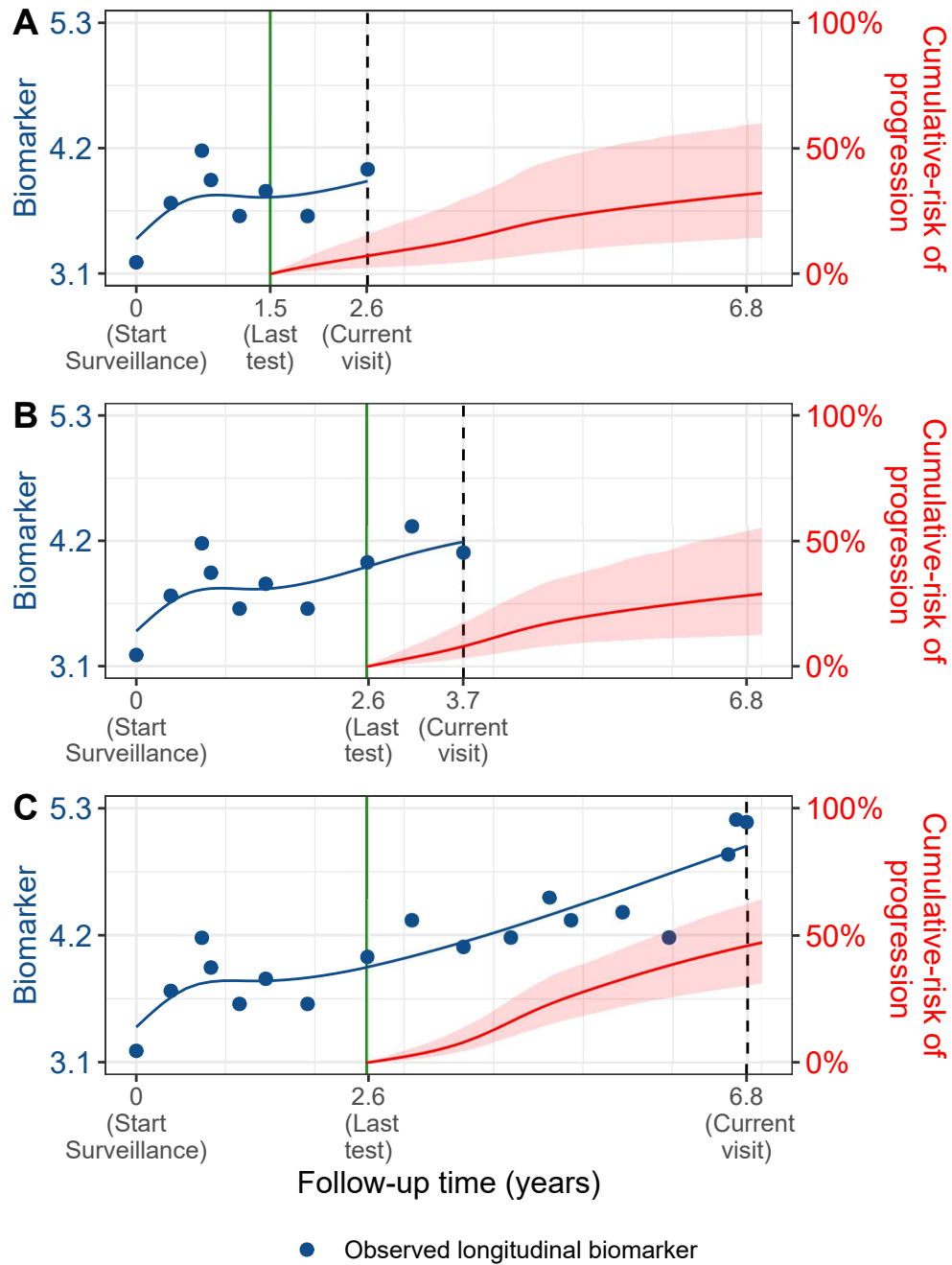


Figure 2. Cumulative-risk of progression changing dynamically over follow-up as more patient data is gathered. A single longitudinal outcome, namely, a continuous biomarker of disease progression, is used for illustration. **Panels A, B and C:** are ordered by the time of the current visit (dashed vertical black line) of a new patient. At each of these visits, we combine the accumulated longitudinal measurements (shown in blue), and last time of negative invasive test (solid vertical green line) to obtain the updated cumulative-risk profile (shown in red) of the patient. All values are illustrative.

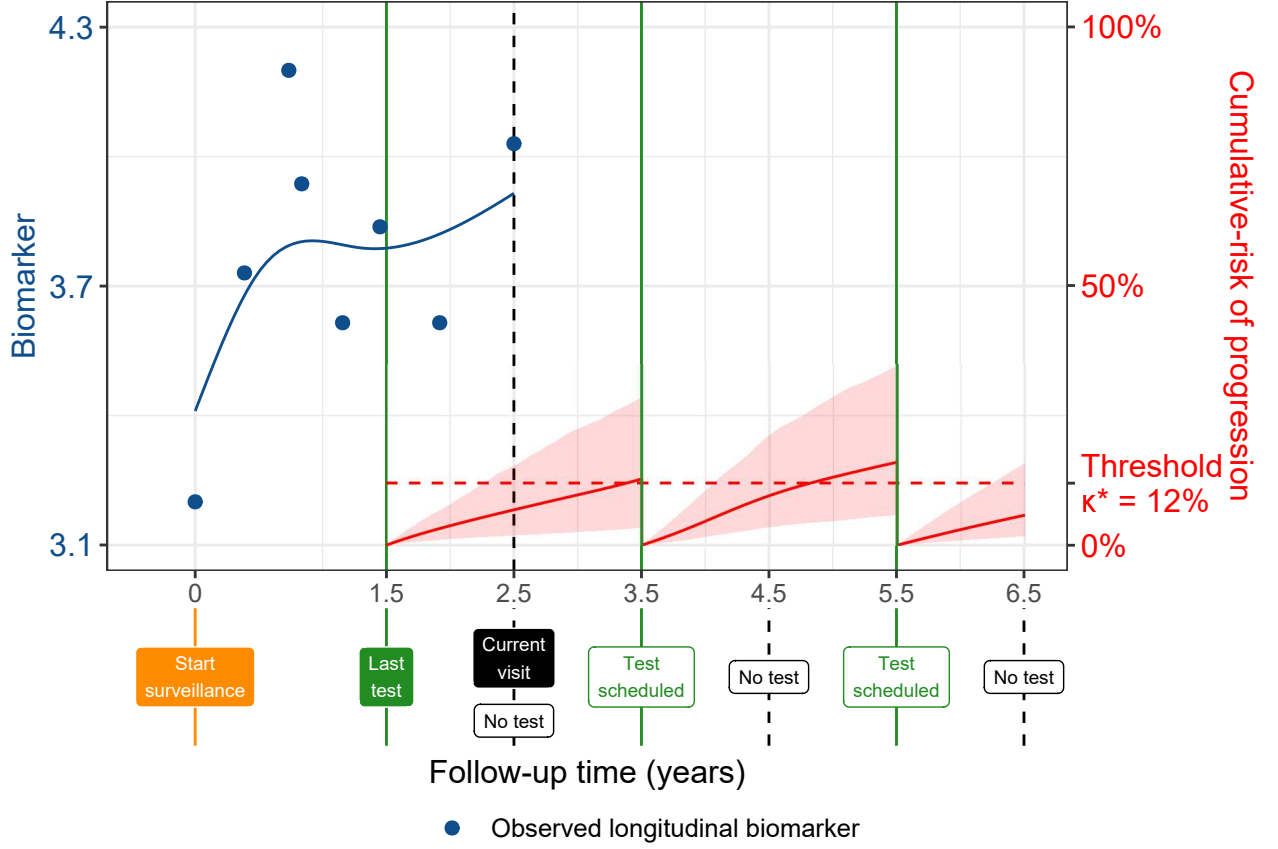


Figure 3. Personalized Invasive Test Schedule Using Patient-specific Conditional Cumulative-risk of Progression. A single longitudinal outcome, namely, a continuous biomarker (observed: blue dots, fitted: blue line) of disease progression is used for illustration. The last test on which progression was not observed was conducted at $t = 1.5$ years. The current visit time of the patient is $v = 2.5$ years. Decisions for invasive test need to be made at a gap of every one year starting from the current visit until a horizon of 6.5 years. That is, $U = \{2.5, 3.5, 4.5, 5.5, 6.5\}$ years. Based on an example risk threshold of 12% ($\kappa = 0.12$) the future test decisions at time points in U lead to a personalized schedule $S_j^{\kappa^*}(U \mid t = 1.5, v = 2.5) = \{3.5, 5.5\}$ years. The conditional cumulative-risk profiles $R_j(u_l \mid t_l, v)$ employed in (??) are shown with red line (confidence interval shaded). It is called ‘conditional’ because, for example, the second test at future time 5.5 years, is scheduled after accounting for the possibility that progression (true time T_j^*) may not have occurred until the time of the previously scheduled test at time $T_j^* > 3.5$ years. All values are illustrative.

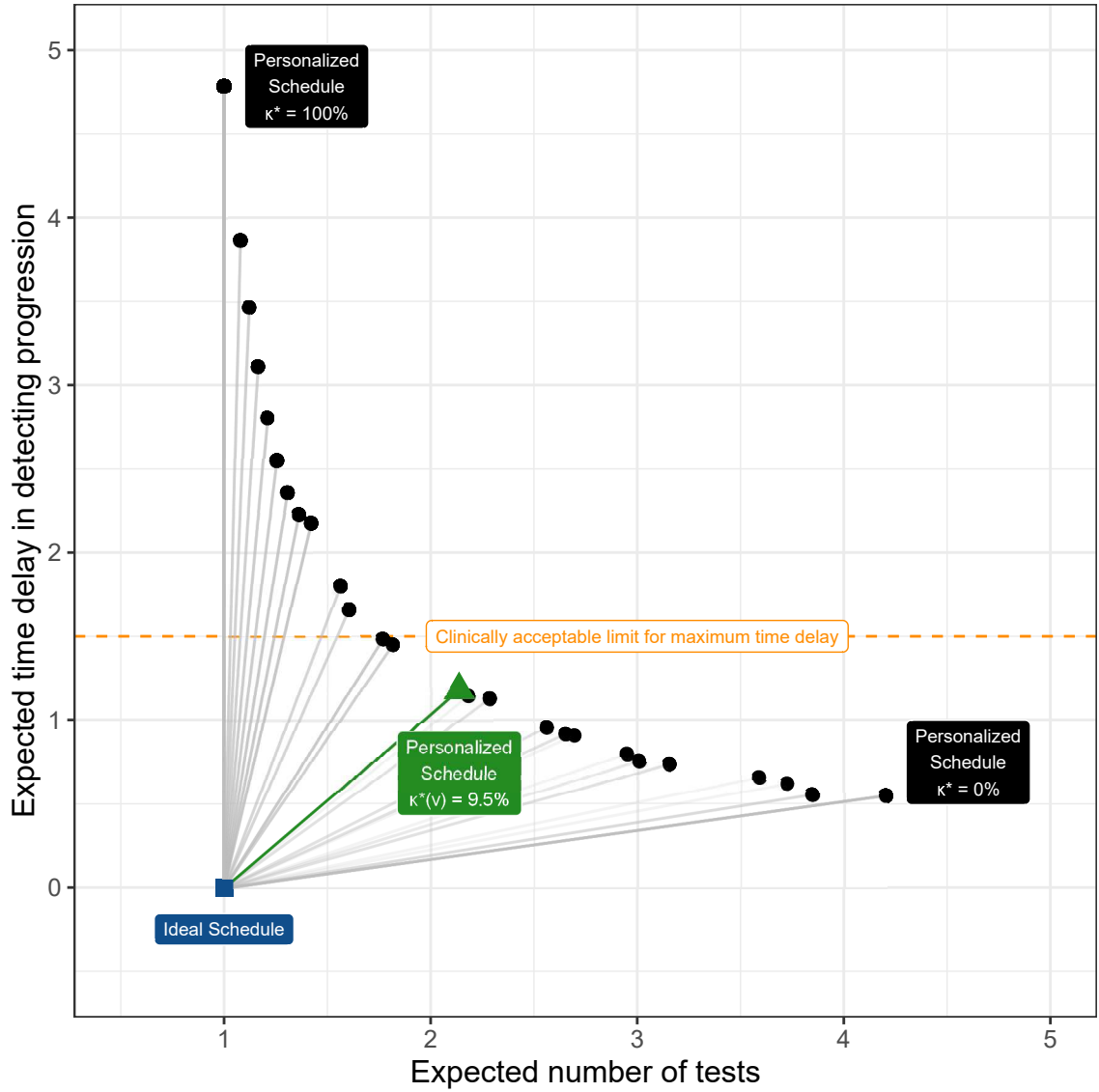


Figure 4. Automatic choice of risk threshold $0 \leq \kappa \leq 1$ using (5). The ideal schedule of tests at point (1,0) is shown as a blue square. It plans exactly one invasive test at the true time of progression T_j^* of a patient and hence leads to a zero time delay in detecting progression. Personalized schedules based on a grid of thresholds chosen between $0 \leq \kappa \leq 1$ are shown with black circles. Higher thresholds lead to fewer tests, but also higher expected time delay. We propose to choose the personalized schedule based on $\kappa^*(v) = 9.5\%$ threshold (green triangle). This is because it has the least Euclidean distance (shown with a green line) to the ideal schedule. It is also possible to find the least distance under a certain clinically acceptable limit on time delay (orange dashed line), or number of tests.

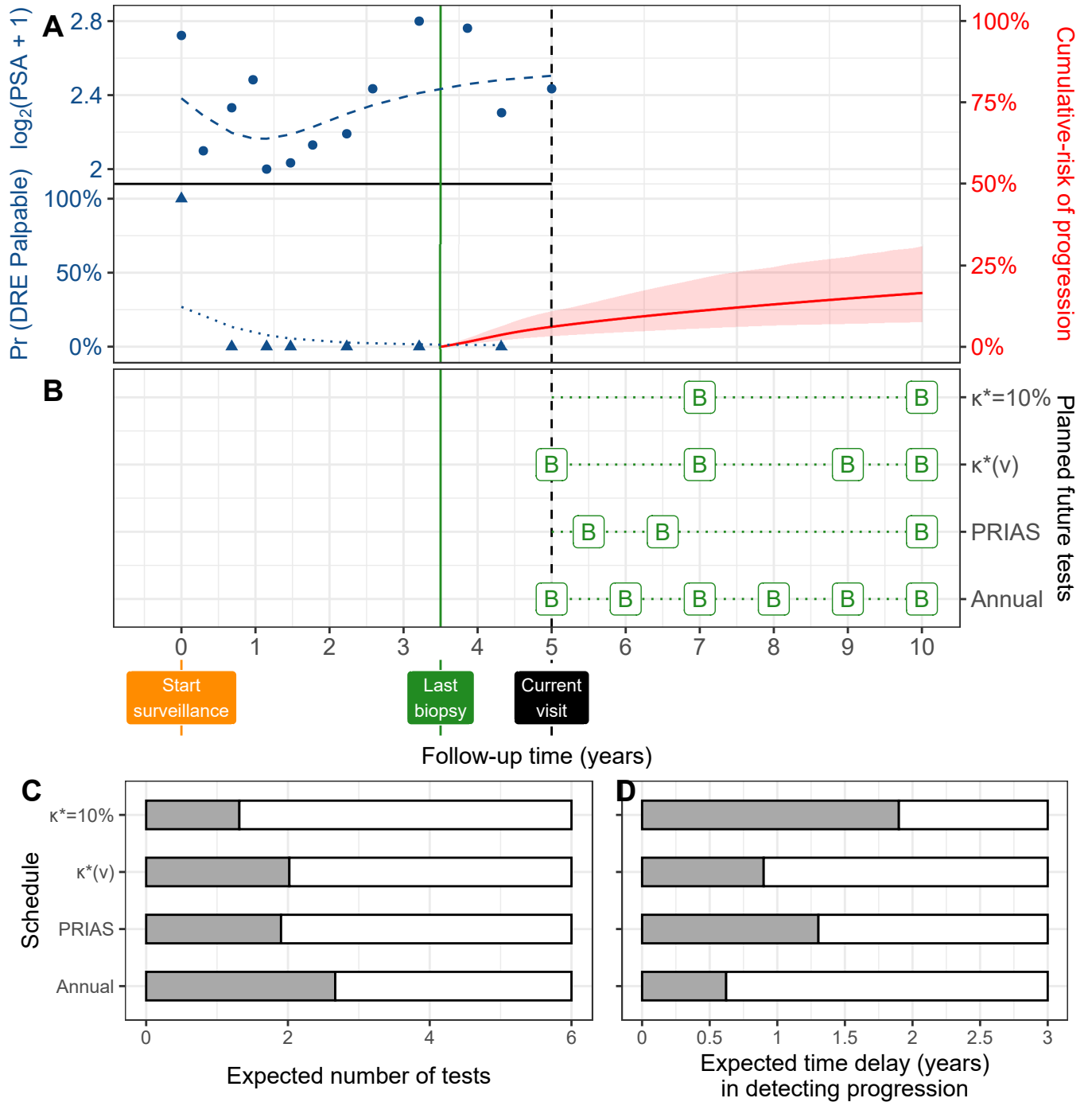


Figure 5. Demonstration of personalized schedules for a real PRIAS patient: In **Panel A**: Time of last negative biopsy is year 3.5 (vertical green solid line). Longitudinal data is repeated DRE (blue triangles) and PSA measurements (blue circles). The current visit is year five (vertical black dashed line). The estimated cumulative-risk profile is shown with a solid red line (95% credible interval is shaded). It is 16.5% at year ten (horizon). In **Panel B**, we visualize different biopsy schedules, with a ‘B’ indicating a biopsy. $\kappa^* = 10\%$ and $\kappa^*(v)$ are personalized biopsy schedules using a fixed risk threshold of 10%, and automatically chosen threshold (5), respectively. PRIAS and Annual denote the PRIAS biopsy schedule (paragraph 2 of Section 4) and annual biopsy schedule. **Panel C,D**: For all schedules we calculate the expected number of tests and expected time delay in detecting progression if the patient progresses before year ten. Since a recommended minimum gap of one year is maintained between biopsies, maximum possible number of tests are six. A delay in detecting progression of up to three years may not lead to adverse outcomes (de Carvalho et al., 2017).

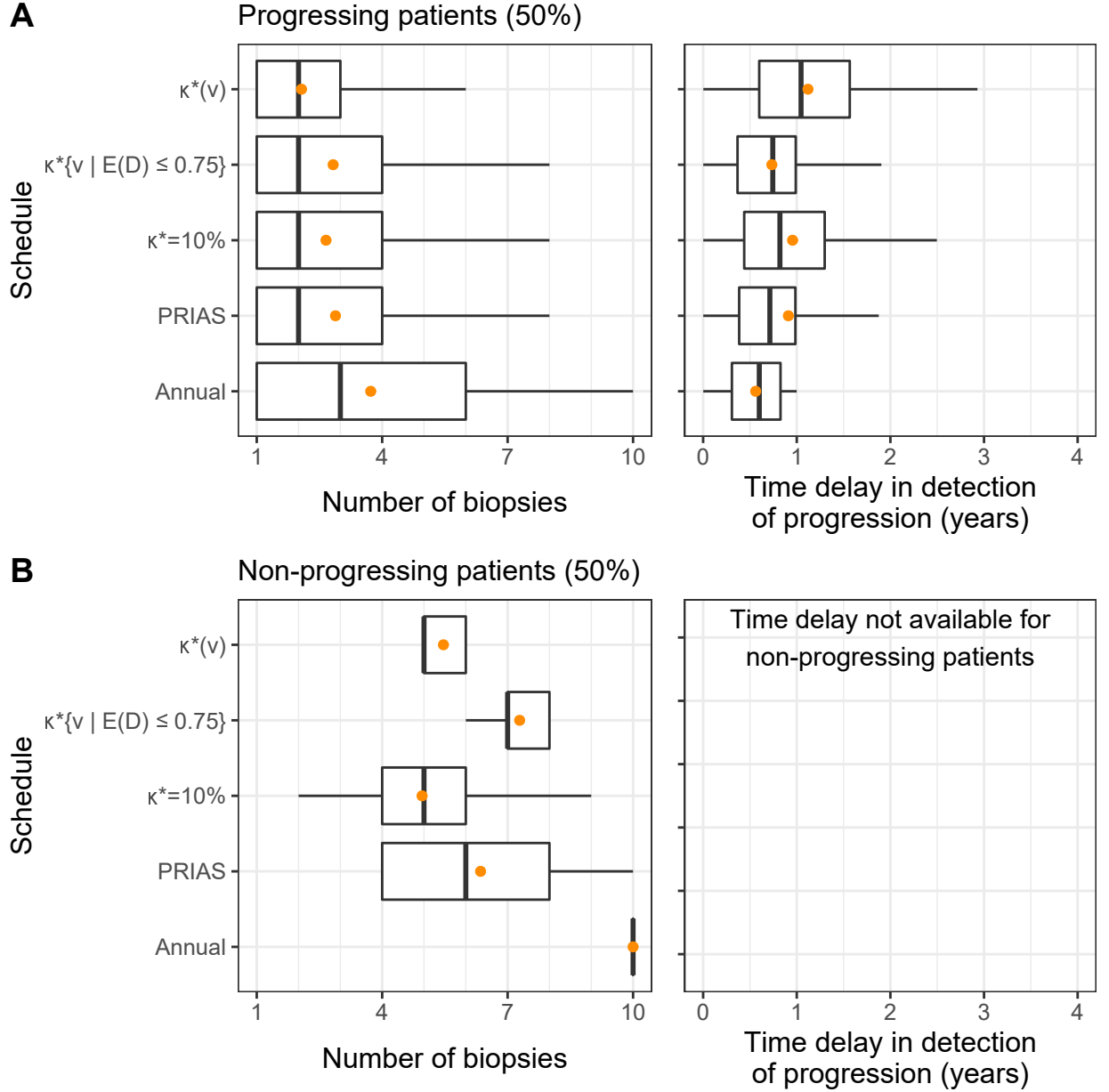


Figure 6. Boxplot showing variation in the number of biopsies, and the time delay in the detection of cancer progression for various biopsy schedules. Mean is indicated by the orange circle. Time delay (years) is calculated as (time of positive biopsy - the true time of cancer progression). Biopsies are conducted until cancer progression is detected. **Panel A:** results for simulated patients who obtained cancer progression in the ten year study period (*progressing*). **Panel B:** results for simulated patients who did not obtain cancer progression in the ten year study period (*non-progressing*). Types of schedules: $\kappa^* = 10\%$ and $\kappa^*(v)$ schedules a biopsy if the cumulative-risk of cancer progression at a visit is more than 10%, and an automatically chosen threshold (5), respectively. Schedule $\kappa^*\{v \mid E(D) \leq 0.75\}$ is similar to $\kappa^*(v)$ except that the euclidean distance in (5) 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 (Section 4).