Personalized Biopsies in Prostate Cancer Active Surveillance[☆]

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Abstract

`Background`: Low-risk prostate cancer patients enrolled in active surveillance (AS) undergo repeat biopsies. Treatment often advised when biopsy Gleason $\geq$ 7 (GS7). Many patients never obtain GS7, yet undergo biopsies frequently.

`Objective`: Better balance the number of biopsies and time delay in detection of GS7.

`Design, Setting, and Participants`: World's largest AS study PRIAS,

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7813 patients, 1134 obtained GS7, 100 medical centers in 17 countries, common study protocol.

`Outcome Measurements, and Statistical Analysis`: Prostate-specific antigen (PSA) measured every six months, repeat biopsies every one to three years. Bayesian joint model fitted to the observed time of GS7 and longitudinal PSA measurements. Risk predictions for GS7 externally validated in five largest AS cohorts from GAP3 database. Personalized risk based biopsy schedules developed using GS7 predictions. Total biopsies, time of biopsies and expected time delay in detection of GS7 calculated for various schedules to compare them.

`Results and Limitations`: Roughly 50% patients did not obtain GS7 in first 10 years in PRIAS. PSA velocity was a stronger predictor of GS7 with Hazard Ratio (increase from 1st to 3rd quartile: 2.47; 95%CI: 1.93–2.99, than PSA value (Hazard Ratio: 0.99; 95%CI: 0.89–1.11). Internal validation: Time varying area under ROC curve for GS7 prediction between 0.62 and 0.69, and prediction error between 0.23 and 0.37. External validation: Results similar to internal validation only for Toronto, Memorial Sloan Kettering, and Johns Hopkins AS cohorts.

`Conclusions`: We developed personalized risk based biopsy schedules as alternative to fixed schedules. To assist patients in biopsy decisions we provided total and time of biopsies, and expected time delay in detection of GS7, for fixed and personalized schedules. Personalized schedules update with more patient data over follow-up.

`Patient Summary`: Personalized biopsy schedules are a novel alternative to fixed biopsy schedules (e.g., yearly biopsies). They utilize a patient's PSA

and biopsy history to decide best time of biopsies. Personalized schedules can offer a better balance between number of biopsies and delay in detection of Gleason upgrade than yearly biopsies.

Keywords: Active Surveillance, Biopsies, Personalized Medicine, Prostate Cancer, Shared Decision Making

1. Introduction

Patients with low- and very low-risk screening-detected localized prostate cancer (PCa) are usually advised active surveillance (AS) instead of immediate radical treatment [1]. In AS, PCa progression is routinely monitored via prostate-specific antigen (PSA), digital rectal examination, and the Gleason score from repeat prostate biopsies. Since Gleason score is the strongest indicator of cancer-related outcomes, patients are commonly advised curative treatment when Gleason ≥ 7 (GS7) is detected [2].

Biopsies are conducted periodically, and hence GS7 is always detected with a time delay. The smaller this delay, the larger is the window of opportunity for curative treatment. For timely detection of GS7, many AS programs use fixed biopsy schedules (e.g., annual or biennial biopsies) for all patients [3, 4]. However, many AS patients do not require any biopsy in the first ten years of follow-up (see PRIAS and John's Hopkins AS cohorts in Figure 1). Biopsies are also invasive, painful and prone to medical complications. Biopsy burden combined with patient non-compliance [5] to frequent biopsies, has raised concerns regarding the optimal biopsy schedule [6, 7].

A simple alternative to frequent biopsies is infrequent biopsies. However, studies suggest not reducing biopsy frequency beyond 24 months, to have a sufficient window of opportunity for curative treatment [6, 9]. Although, biopsy every 24 months still leads to five unnecessary biopsies over ten years for 50% patients (Figure 1). A promising alternative to fixed biopsies is biopsies based on personalized risk of GS7. For example, among the two patients shown in Figure 2, patient B is a more suitable candidate for biopsy than patient A, because his risk of GS7 is much higher.

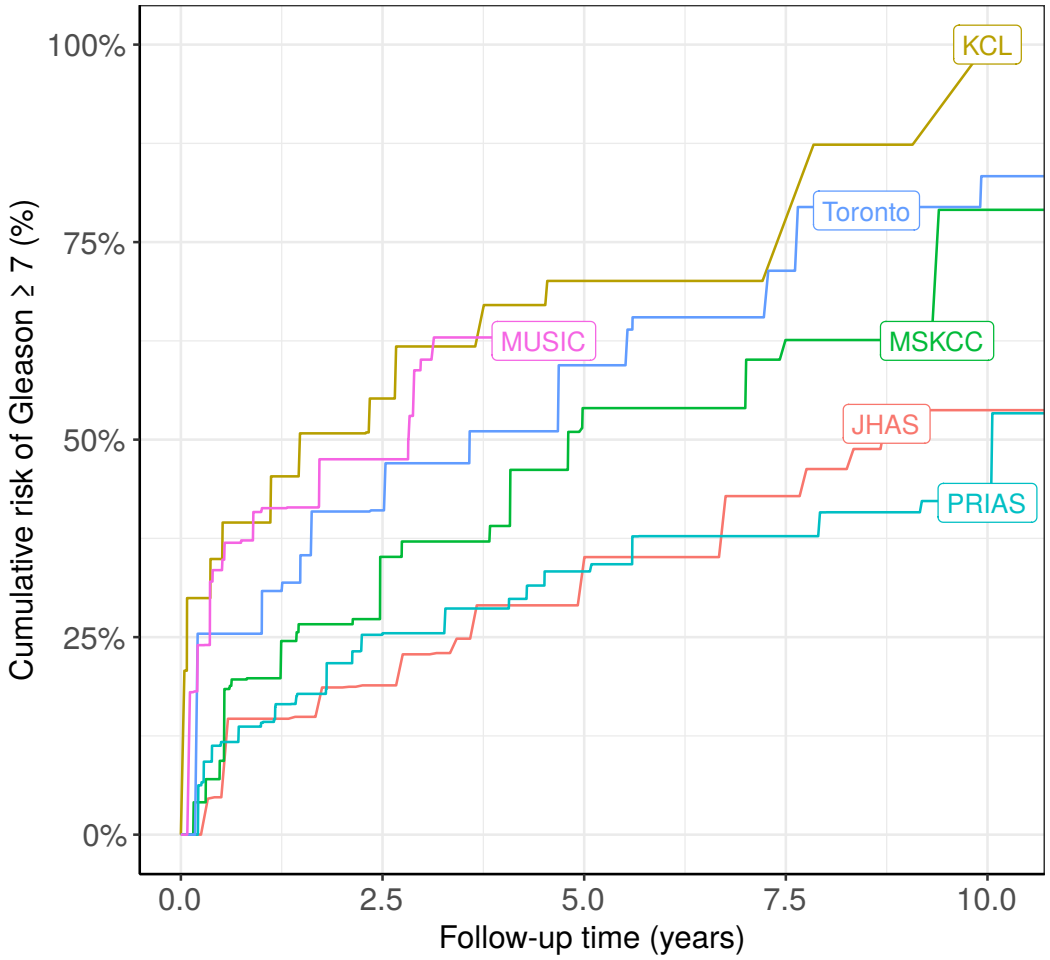

Figure 1: **Estimated cumulative risk of having Gleason $\geq$ 7 (GS7)** in the world's largest AS cohort PRIAS, and five of the largest AS cohorts part of the GAP3 database [8]. Abbreviations are *JHAS*: Johns Hopkins Active Surveillance, *PRIAS*: Prostate Cancer International Active Surveillance, *Toronto*: University of Toronto Active Surveillance, *MSKCC*: Memorial Sloan Kettering Cancer Center Active Surveillance, *KCL*: King's College London Active Surveillance. In the world's largest AS cohort PRIAS and in JHAS, roughly 50% of patients do not obtain GS7 in the first ten years. That is, ideally no biopsies should be prescribed to 50% of the patients in first ten years of AS.

The first challenge in developing risk-based schedules is consolidating observed patient data (e.g., PSA, previous biopsy results) into GS7 risk estimates. Previousy, studies have utilized latest value of PSA to predict the Gleason score [10, 11]. However, in AS the entire trajectory of PSA of a patient is available. To accomodate such longitudinal PSA data, a suitable model is joint model for time-to-event and longitudinal data [12, 13, 14]. A subsequent challenge is to translate risk estimates for GS7 into clinical decisions is challenging. For example, a 10% risk can be perceived as high/low depending upon the patient's age. Patients may also weigh the risk of GS7 with the potential consequences of another biopsy. Two relevant consequences are the timing and total number of biopsies (burden), and the time delay in the detection of GS7 (smaller is better). These consequences vary between the patients, and also over the follow-up period for the same patient.

The goal of this work was to assist patients and doctors in making better decisions of biopsies than fixed and frequent biopsies. We intended to achieve this by providing the patients risk based personalized schedules of biopsies, and to allow them to compare the consequences of each schedule before making a decision. To this end, we took three steps. First we fitted a prediction (joint) model to the world's largest AS dataset, PRIAS [2]. We then externally validated the model predictions in five largest AS cohorts that are part of the GAP3 database. Lastly, we utilized the personalized GS7 risk predictions to calculate the timing and total number of biopsies, and the time delay in the detection of GS7 for risk-based and fixed biopsy schedules.

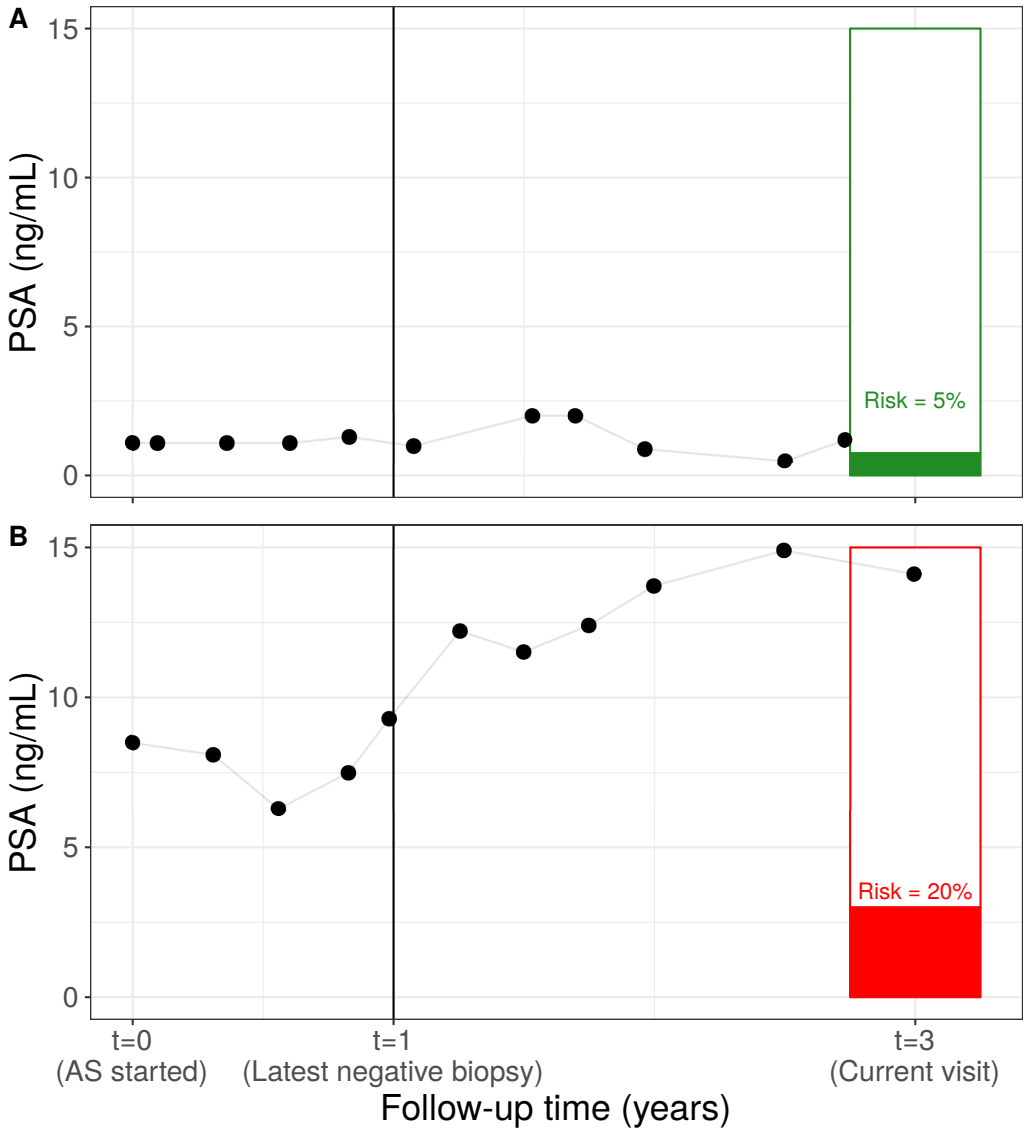

Figure 2: **Motivation for personalized risk-based decisions of biopsy**: Patient A and B had their latest biopsy at year one of follow-up. Patient A's prostate-specific antigen profile remained stable until the current visit time at year three, whereas patient B's profile has shown a rise. Consequently, patient B's estimated cumulative risk of GS7 at year three is higher than that of patient A, making patient B a more suitable candidate for biopsy than Patient A. Risk estimates in this figure are only illustrative.

2. Patients and Methods

2.1. Study Cohort

Prostate Cancer International Active Surveillance (PRIAS) is an ongoing prospective cohort study of men with low- and very-low risk PCa diagnoses [2]. More than 100 medical centers from 17 countries contribute in PRIAS, using a common study protocol (`www.prias-project.org`). We used the data collected between December 2006 (beginning of PRIAS study) and May 2019. The PSA was measured every three months until year two of follow-up and every six months thereafter. Biopsy schedule was year one, four, seven, and ten, and additional yearly biopsies when PSA doubling time was between zero and ten years. The primary event used in this work is Gleason ≥ 7 (GS7) because it is commonly used as a trigger for treatment advice. It was observed in 1134 patients. However, 2250 patients were provided treatment (see Table 1). Treatment in absence of GS7 may have been advised on the basis of PSA, number of biopsy cores with cancer, anxiety, or other reasons. We focused only on GS7 because of its strong association with cancer-related outcomes. Due to the periodical nature of biopsies, the time of GS7 was only available as a time interval in which GS7 occurred.

Table 1: **Patient characteristics for the PRIAS dataset**. The primary event of interest is Gleason ≥ 7. IQR: interquartile range, PSA: prostate-specific antigen.

Characteristic	Value
Total patients	7813
Gleason ≥ 7 (primary event)	1134
Treatment	2250
Watchful waiting	334
Loss to follow-up	250
Death (unrelated to prostate cancer)	95
Death (related to prostate cancer)	2
Median age at diagnosis (years)	61 (IQR: 66–71)
Median follow-up period per patient (years)	1.8 (IQR: 0.9–3.99)
Total PSA measurements	65798
Median number of PSA measurements per patient	6 (IQR: 4–12)
Median PSA value (ng/mL)	5.7 (IQR: 4.1–7.7)
Total biopsies	15563
Median number of biopsies per patient	2 (IQR: 1–3)

2.2. Statistical Methods

Our aim was to develop a model for predicting the time of GS7. The available data for each patient were, age at the start of AS, all observed PSA measurements, and the history of biopsies. We wanted to account for the correlation between the PSA measurements of the same patient, and also their correlation with the time of GS7. An additional complication was that the PSA values were missing once a patient obtained GS7. A commonly used model to handle these issues is the joint model for time-to-event and longitudinal data [14, 12, 13].

The joint model we utilized, exploited patient-specific random effects [15] to act as a common source of correlation between the PSA and time of GS7 outcomes (see Figure 3 and Appendix A.2's Figure 1). Random effects also represented the underlying state of PCa, and were included in both the linear mixed effects sub-model for $\log_2\{\text{PSA} + 1\}$ transformed measurements (see Appendix A.5), and the relative risk sub-model (similar to Cox model) for time of GS7. In the sub-model for PSA, random effects non-linearly modeled the evolution of PSA over time. Simultaneously, in the relative risk model random effects were used indirectly by including fitted $\log_2\{\text{PSA} + 1\}$ value and velocity as time dependent covariates. The $\log_2\{\text{PSA} + 1\}$ velocity was mathematically derived from fitted $\log_2\{\text{PSA} + 1\}$ values. Consequently, the $\log_2\{\text{PSA} + 1\}$ velocity also changed non-linearly over follow-up.

The parameters of the two sub-models were estimated jointly using the R package **JMbayes** [16]. This package utilizes the Bayesian methodology to estimate model parameters.

2.3. Assessment of Predictions of GS7

We validated the risk predictions of GS7 from our model within the PRIAS dataset (internal validation), as well as in five of the largest AS cohorts part of the GAP3 database [8] (external validation). The external cohorts were University of Toronto AS (Toronto), Johns Hopkins AS (JHAS), Memorial Sloan Kettering Cancer Center AS (MSKCC), King's College London AS (KCL), and Michigan Urological Surgery Improvement Collaborative AS (MUSIC). For validation, we utilized the area under the receiver operating characteristic curve or AUC [17] as a measure of discrimination, and root mean squared prediction error or RMSPE [17] as a measure of calibration. Since AS studies are longitudinal in nature, we computed AUC and RMSPE in a time dependent manner, at a gap of every six months (follow-up schedule of PRIAS) until year five (95-percentile of the observed GS7 times in PRIAS) of follow-up.

2.4. Personalized Schedule of Biopsies, and Its Consequences

The key component in development of personalized schedules is the personalized risk of GS7. This risk is predicted for new patients using the joint model fitted to the PRIAS dataset. For example, in Figure 4 we show a new patient whose cumulative-risk of GS7 (Panel B of Figure 4) is calculated at each of his follow-up visits since his latest negative biopsy. This risk is dynamic in the sense that it is updated as more data is gathered over follow-up. Now, suppose that this patient does not intend to cross more than a certain cumulative-risk threshold (e.g., 10% risk) between his successive follow-up visits. To start with, this rule can be first applied at his current visit to schedule a biopsy. If a biopsy gets scheduled at his current visit, then his

cumulative risk profile is updated in order to account for the possibility of not finding GS7 during this biopsy. This process is repeated for each of the future follow-up visits, to obtain an entire personalized schedule of biopsies (Panel C of Figure 4).

To assist patients in making an informed choice for a schedule, be it personalized or fixed, we provided them patient-specific consequences of following each schedule. To this end, we reused the cumulative-risk of GS7 (Panel B of Figure 4). More specifically, for any schedule of biopsies we first split the cumulative-risk profile of the patient for each time period between subsequent biopsies. We then exploited these cumulative-risk profiles to obtain the expected time delay in detection of GS7 in the corresponding time period of the schedule (Equation 5, Appendix C). Lastly, we combined these time delays while accounting for the total risk of GS7 in the corresponding time period, to obtain the expected time delay in detection of GS7 for the schedule. Thus, patients had a method to compare various schedules in terms of the personalized burden (time and total biopsies), and personalized benefit (less delay in detection of GS7 is beneficial). We implemented this approach in a web-application.

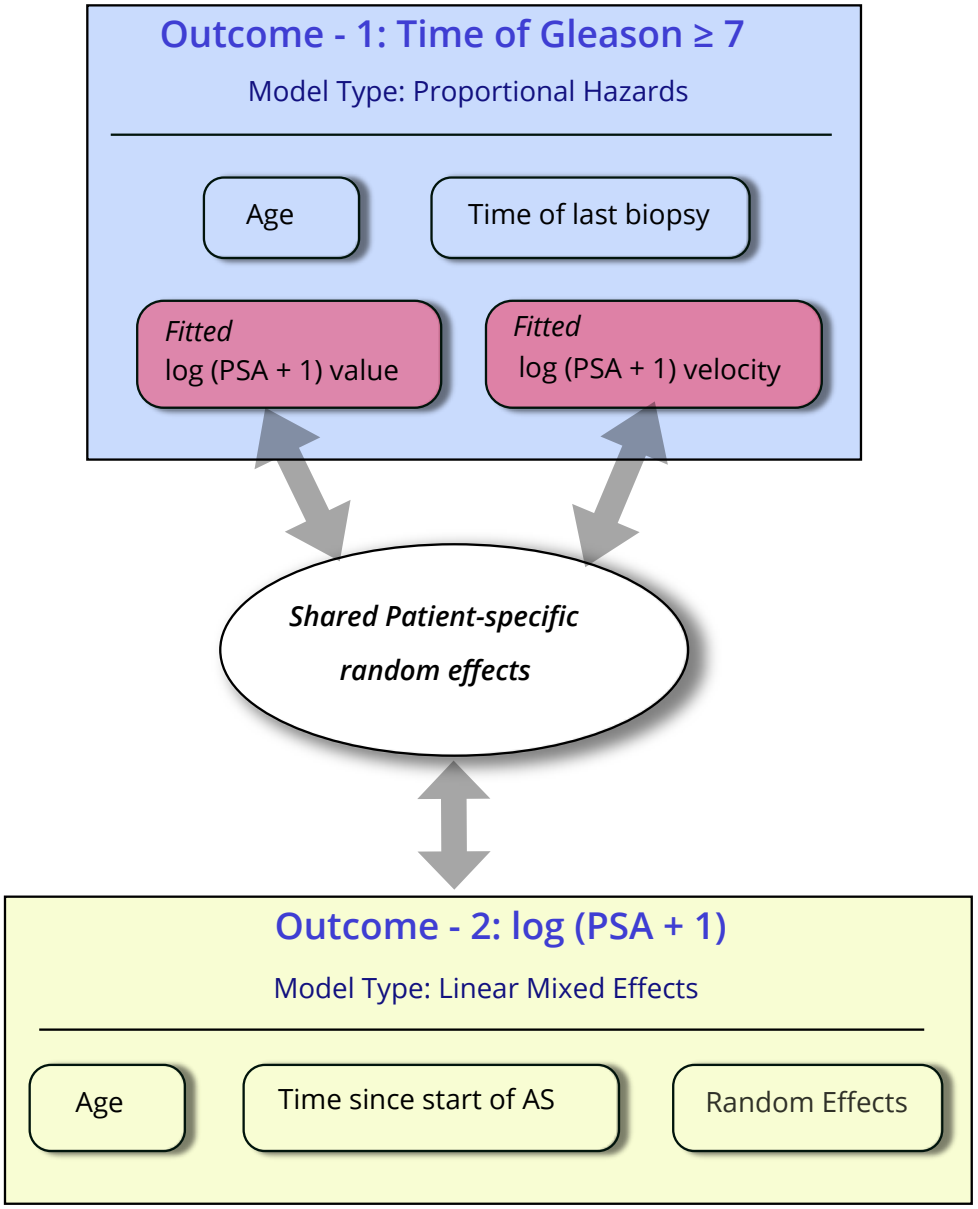

Figure 3: **Diagram of the joint model**: Patient-specific random effects (ellipse in center) are shared between sub-models for all outcomes pertaining to prostate cancer progression. The random effects model the correlation between the outcomes. In the linear mixed effects sub-model for $\log_2\{\text{PSA} + 1\}$ transformed PSA outcome (bottom rectangle), random effects are used as covariates. In the relative-risk sub-model (similar to Cox model) for time of Gleason ≥ 7 (GS7), random effects are utilized indirectly, by including fitted $\log_2\{\text{PSA} + 1\}$ value and velocities as covariates. Age of patient at baseline is included in both sub-models. Parameters of both sub-models are estimated jointly.

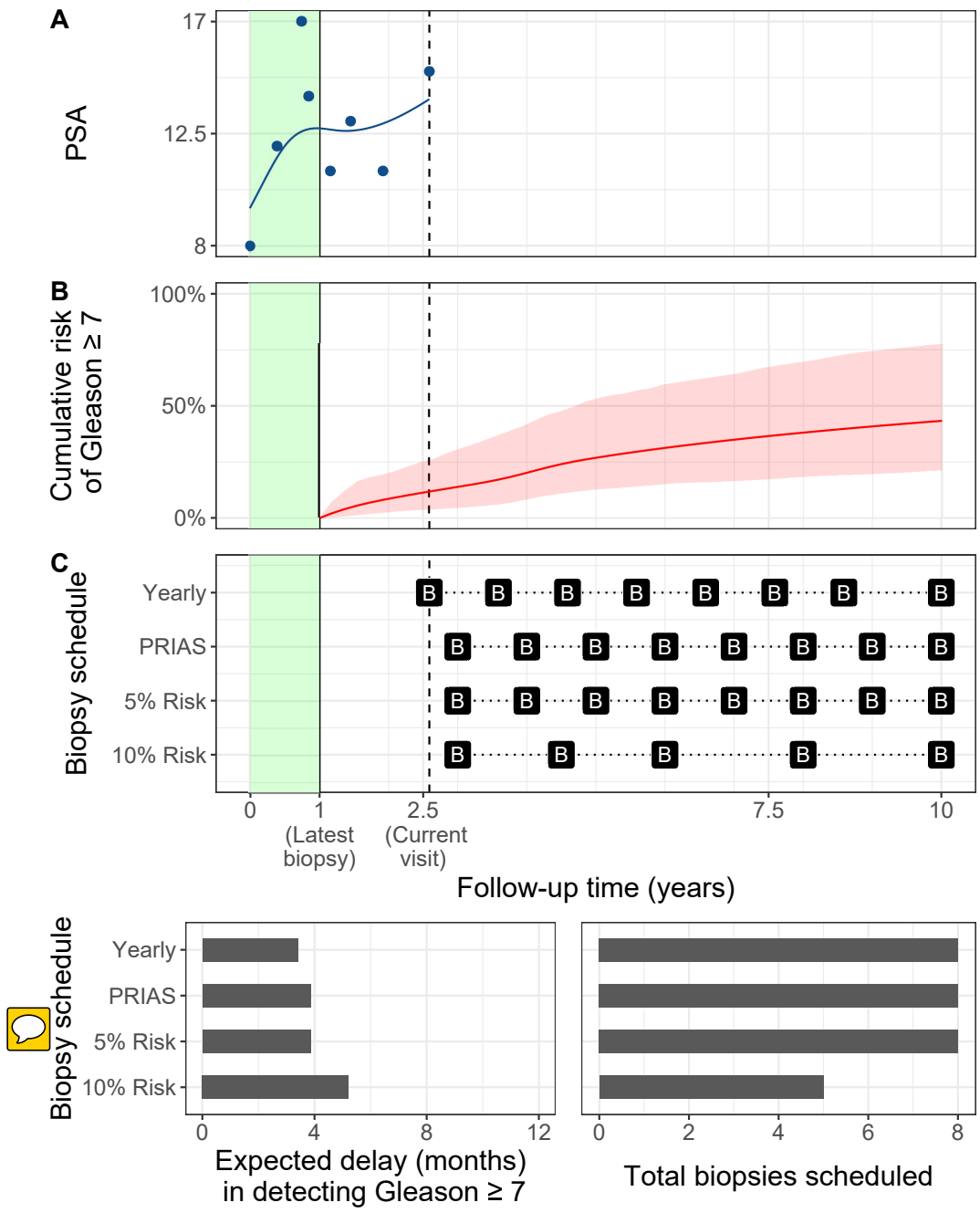

Figure 4: **Personalized and fixed schedules of biopsies for new patient**. **Panel A,B:** show the observed and fitted $\log_2(\text{PSA}+1)$ measurements, and the dynamic cumulative-risk of Gleason ≥ 7 over the follow-up period. **Panel C** shows the personalized and fixed schedules of biopsies with a 'B' indicating the time of biopsy. In the bottom two panels, the various schedules are compared in terms of the number of biopsies they schedule, and the expected delay in detection of Gleason ≥ 7 if they are followed.

3. Results

For patients in the PRIAS dataset, the probability of obtaining reclassification within the first five and ten years 3% and 42%, respectively (see Figure 1). That is, ideally more than 50% of the patients do not require any biopsy in the first ten years. We next discuss the results from the joint model fitted to the PRIAS dataset. For every ten years increase in a patient age the corresponding adjusted hazard ratio of reclassification is 1.45 (95%CI: 1.30–1.63). For an increase in fitted $\log_2\{\text{PSA} + 1\}$ value from the first quartile of fitted values (2.36) to the third quartile (3.07), the corresponding adjusted hazard ratio of reclassification is 0.99 (95%CI: 0.89–1.11). On the other hand an increase in fitted $\log_2\{\text{PSA} + 1\}$ velocity from the first quartile of fitted velocity (-0.09) to the third quartile (0.31), the corresponding adjusted hazard ratio of reclassification is 2.47 (95%CI: 1.93–2.99). These results indicate that the velocity of $\log_2\{\text{PSA} + 1\}$ measurements is a stronger predictor of hazard of reclassification than the $\log_2\{\text{PSA} + 1\}$ value. Detailed parameter estimates are presented in Tables 2, 3 and 5 of Appendix A.4.

Using the joint model fitted to the PRIAS dataset we made risk predictions for GS7 in real PRIAS patients. As shown in Figure 4 of Appendix B, these risk estimates become more accurate as more data is gathered over follow-up. To check the accuracy of these risk predictions, we calculated the time dependent area under the receiver operating characteristic curves (AUC) as a measure of discrimination, and the root mean squared prediction error (RMSPE) as a measure of calibration. These are shown in Figure 5. For predictions within PRIAS (internal validation), the time-dependent AUC was between 0.62 and 0.69, and RMSPE between 0.23 and 0.37 over the

whole follow-up period. For validation in external cohorts, the AUC was similar to the AUC of PRIAS for all cohorts during the first three years of follow-up. The RMPSE however differed much more during the same period. The AS cohorts closest to PRIAS in terms of RMSPE were Johns Hopkins Active Surveillance and Memorial Sloan Kettering Cancer Center Active Surveillance. Detailed AUC and RMSPE results for all cohorts with 95% bootstrapped confidence intervals are presented in Table 6 to Table 11 of Appendix B.

Using the risk predictions for GS7, we developed personalized schedules of biopsy for real PRIAS patients. We maintained a minimum gap of one year between biopsies as advised by the PRIAS protocol. In addition, we scheduled biopsies only for the first ten years follow-up because of limited follow-up data period of PRIAS. A compulsory biopsy was done at year ten of follow-up in all schedules for meaningful comparison of their expected delays in detection of GS7. Various personalized and fixed biopsy schedules for demo patients are shown in Figure 4 and Appendix C's Figure 6, 7, 8 and 9. The biopsies denoted by 'B' show that personalized schedules schedule fewer biopsies than fixed schedules. At the same time the expected time delay in detection of GS7 is less than an year for personalized schedules. We have implemented this approach in a web-application (`https://emcbiostatistics.shinyapps.io/prias_biopsy_recommender/`, and Appendix D) for practical use.

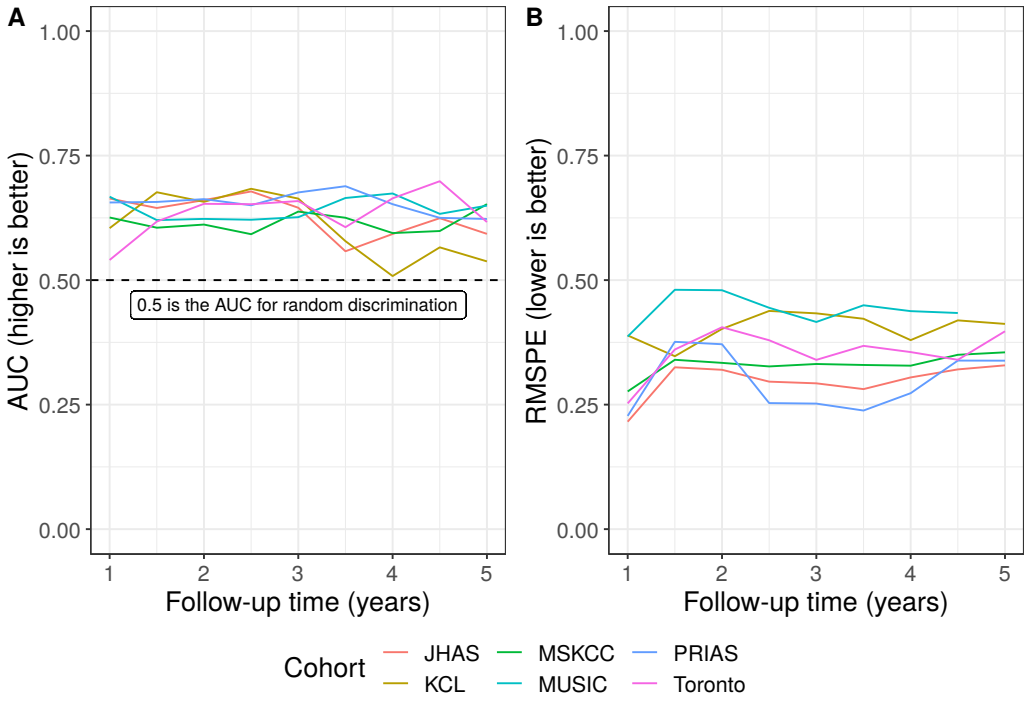

Figure 5: **Validation of predictions of Gleason $\geq$ 7 (GS7)**. In **Panel A** we can see that the time dependent area under the receiver operating characteristic curve or AUC (measure of discrimination) is above 0.5 in PRIAS (internal validation), and in Toronto, JHAS, MSKCC, KCL, and MUSIC AS cohorts (external validation). In **Panel B** we can see that the time dependent root mean squared prediction error or RMSPE (measure of calibration) is similar for PRIAS, and JHAS and Toronto cohorts. The bootstrapped 95% confidence interval for these estimates are presented in Table 6 to Table 11 of Appendix B. Full names of Cohorts are *PRIAS*: Prostate Cancer International Active Surveillance, *Toronto*: University of Toronto Active Surveillance, *JHAS*: Johns Hopkins Active Surveillance, *MSKCC*: Memorial Sloan Kettering Cancer Center Active Surveillance, *KCL*: King's College London Active Surveillance, *MUSIC*: Michigan Urological Surgery Improvement Collaborative Active Surveillance.

4. Discussion

We developed personalized schedules for repeat biopsies in PCa patients enrolled in AS programs. These schedules were based on a patient's risk for having a Gleason ≥ 7 (GS7). Patient- and visit-specific risks of GS7 were estimated using their entire history of PSA and repeat biopsies, and baseline characteristics. Consequently, the personalized schedules were updated as more data was gathered over follow-up. Risk calculators for GS7 are not new [13, 18]. However, the novelty of our work is that we developed a methodology for scheduling personalized biopsies using those risks, and also a methodology to compare schedules, be it personalized or fixed, in simple terms of burden and benefit. More specifically, for each schedule we provided patients the times of biopsy and total biopsies (burden), and the time delay in detection of GS7 (less is beneficial) expected due to that schedule. We also implemented our methodology in a web-application.

The proposed joint model accounted for the complex correlation structure that exists between longitudinal PSA measurements and time of GS7 of a patient. It also accounted for PSA measurements that were missing in patients who obtained GS7. This model adjusts the risks of GS7 upon a negative repeat biopsy. Thus complete patient information in consolidated into a single patient risk profile. Our model is fitted to the world's largest PCa AS program, PRIAS. We also externally validated our model predictions for GS7 in five largest AS cohorts that are part of the GAP3 database [8]. We found that the AUC for predictions of GS7 over the follow-up period (Figure 5) was similar in external cohorts and PRIAS (internal validation). The RMSPE however was similar to PRIAS only for Memorial Sloan Kettering

Cancer Center and Johns Hopkins cohorts. Given the large size of the latter two cohorts, we expect that our model and the methodology will be useful to a large number of AS patients. Extending our model and methodology in other cohorts only requires fitting the model to their AS dataset.

The clinical implications of our work are as follows. The median survival time for GS7 is more than ten years in PRIAS, and in some other cohorts (Figure 1). That is, more than 50% of AS patients do not require any biopsy during the first ten years of follow-up. We hope that our work will address patient apprehensions regarding adverse outcomes in AS, in a more objective manner. Many AS programs still utilize a rigorous schedule of yearly biopsies [3]. However, with concerns about non-compliance and burden of biopsies [5], the availability of our web based tool may encourage patients and doctors to consider personalized schedules.

Our work has certain limitations. The proposed model is valid only for the first ten years of follow-up in PRIAS, whereas GS7 may occur much later in many patients. Due to this issue, we could schedule biopsies only for the first ten years follow-up. In addition, the calibration and discrimination measures of predictions were also less accurate in later follow-up periods. These problems can be mitigated by refitting the model as more follow-up data is gathered in PRIAS. While we focused only on GS7, it is susceptible to inter-observer variation. Models which account for this variation [13, 19] will be interesting to investigate further. However, the methodology to schedule biopsies, and to estimate the consequences of following a schedule need not change. There is also a potential for including diagnostic information from novel biomarkers, quality of life measures, and magnetic resonance imaging

(MRI). Currently, this data is very sparsely available in the PRIAS dataset. However, in future, adding this information in our model is trivial. This is because modeling correlation for extra outcomes, mainly entails connecting sub-models for the outcomes to shared random effects (see Figure 3). Our model can also be used to schedule MRI scans, since they are expensive in developing countries

5. Conclusions

We developed a novel methodology for scheduling biopsies to detect Gleason ≥ 7 (GS7) in PCa patients enrolled in AS. Our methodology consolidates a patient's entire history of PSA and repeat biopsies, and baseline characteristics into risk profile of GS7 over his follow-up period. It then utilizes this risk profile to schedule biopsies in a personalized manner. The personalized schedule is updated as more patient data is gathered over follow-up. To assist patients in making the choice of the best biopsy schedule, we provided them personalized burden (time and total biopsies), and personalized benefit (less time delay in detection of GS7 is beneficial), for both personalized and currently used schedules. Lastly, we implemented this approach in a web-application.

Acknowledgments

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