

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 ≥ 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, 7813 patients, 1134 obtained GS7, 100 medical centers in 17 countries, common study protocol and online tool for data collection.

Outcome Measurements, and Statistical Analysis: Prostate-specific anti-

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gen (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. Predictions for GS7 externally validated in five largest AS cohorts (GAP3 database). Predictions utilized to develop risk based biopsy schedules, and then compared with fixed schedules on the basis of total biopsies and expected delay in detection of GS7.

Results and Limitations: Roughly 50% patients do not obtain GS7 in first 10 years in PRIAS. Rate of change of (log-transformed) PSA was a stronger predictor of GS7 (Hazard Ratio: 2.45, 95%CI: 1.83–2.95) than PSA value (Hazard Ratio: 1.00, 95%CI: 0.98–1.02). Internal validation: Time varying area under ROC curve for GS7 prediction ranged between 0.xx and 0.xx, and prediction error between 0.xx and 0.xx. External validation: Results similar to internal validation only for Toronto and Johns Hopkins cohorts.

Conclusions: We developed personalized risk based biopsy schedules as alternative to fixed schedules. For both fixed and personalized schedules we provide total biopsies, time of biopsies, and expected time delay in detection of GS7. Personalized schedules update with more patient data gathered over follow-up.

Patient Summary: Risk based biopsy schedules are a novel alternative to fixed biopsy schedules (e.g., yearly biopsies). They utilize a patient’s PSA history and biopsy history to decide best time of biopsies in future. Such 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 the 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]. In Figure 1 we can see that in the PRIAS and JHAS cohorts, 50% patients do not need such frequent biopsies in first ten years of follow-up. Biopsies are also invasive, painful and prone to medical complications. Biopsy burden and 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 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. Simulation studies

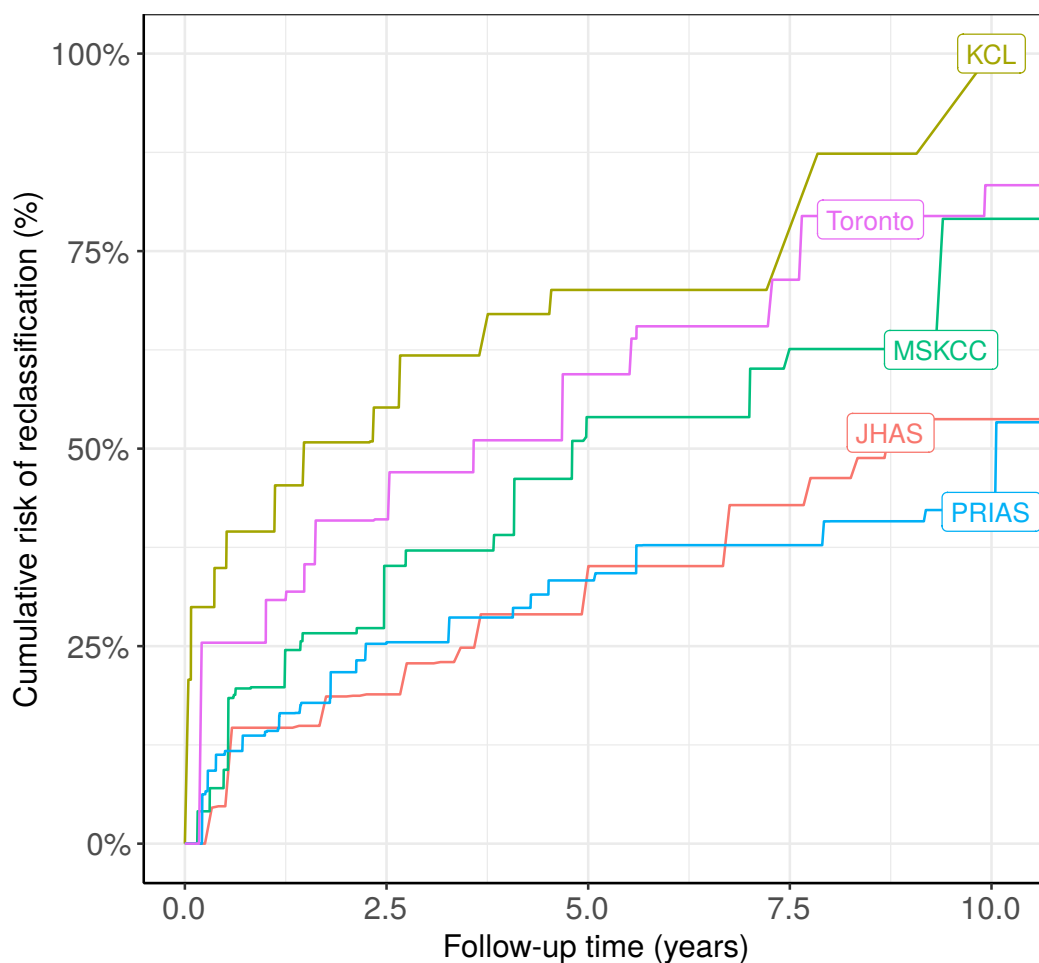


Figure 1: **Estimated cumulative risk of having Gleason ≥ 7 (GS7)** in five of the largest AS studies part of the GAP3 database [8], *JHAS*: Johns Hopkins Active Surveillance, *PRIAS*: Prostate Cancer International Active Surveillance, *Toronto*: University of Toronto Active Surveillance, *MSKCC*: Memorial 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.

26 have shown that personalized schedules may better balance the number of
 27 biopsies per detected GS7 than fixed schedules [10].

28 The first challenge in developing risk-based schedules is consolidating ob-
 29 served patient data (e.g., PSA, previous biopsy results) into GS7 risk esti-
 30 mates. For this previous studies have employed joint models for time-to-event
 31 and longitudinal data [10, 11, 12]. However, translating risk estimates into
 32 clinical decisions is challenging. For example, a 10% risk can be perceived as
 33 high/low depending upon the patient’s age. Patients may also weigh the risk
 34 of GS7 with the potential consequences of another biopsy. Two important
 35 consequences are the timing and total number of biopsies (burden), and the
 36 time delay in the detection of GS7 (smaller is better). These consequences
 37 vary between the patients, and also over the follow-up period for the same
 38 patient.

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

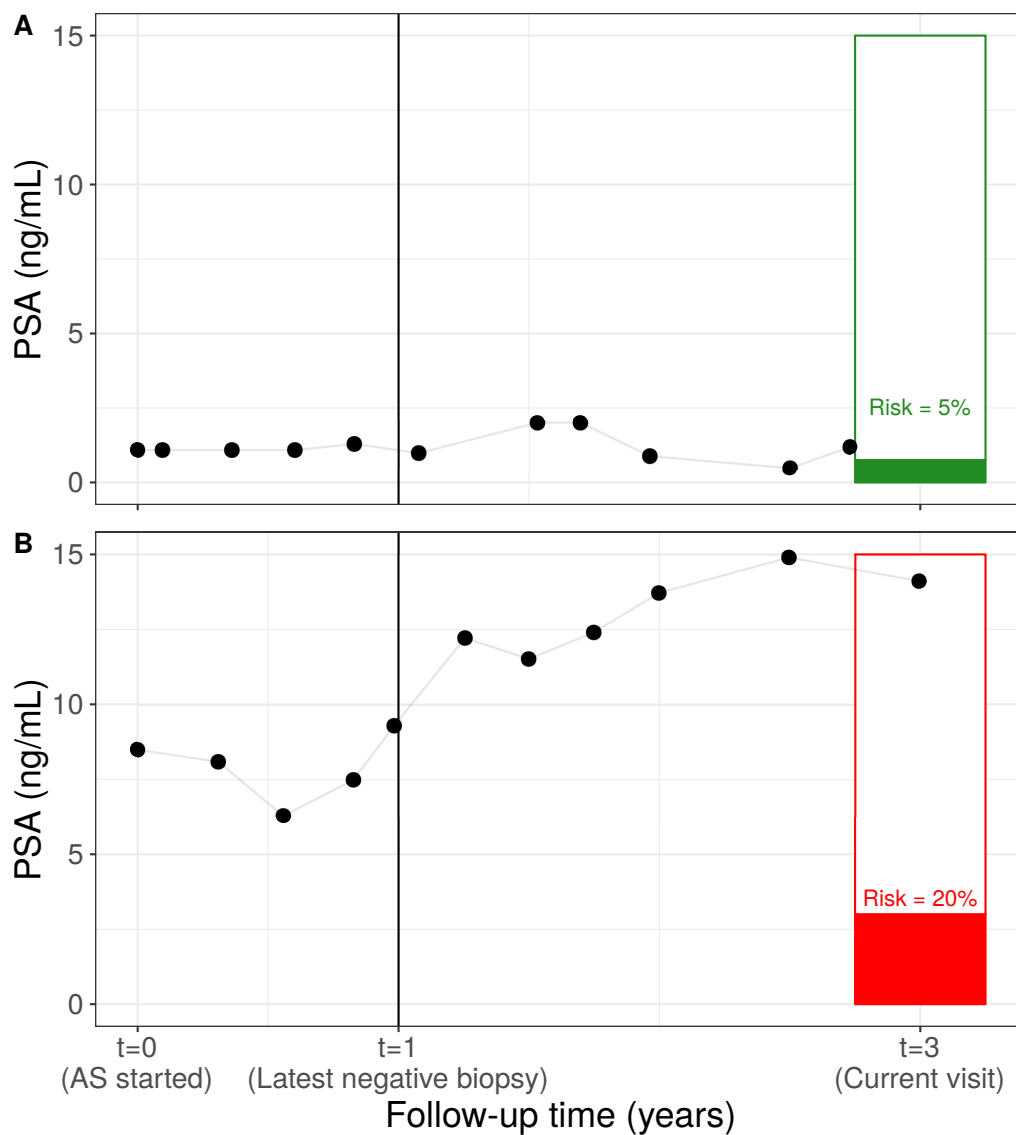


Figure 2: **Motivation for personalized risk-based decisions of biopsy:** Patient A and B had their latest biopsy at year one of follow-up. Patient A's prostate-specific antigen profile remained stable until the current visit time at year three, whereas patient B's profile has shown a rise. Consequently, 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.

50 2. Patients and Methods

51 2.1. Study Cohort

52 Prostate Cancer International Active Surveillance (PRIAS) is an ongoing
 53 prospective cohort study of men with low- and very-low risk PCa diagnoses
 54 [2]. More than 100 medical centers from 17 countries contribute
 55 in PRIAS, using a common study protocol (www.prias-project.org). We
 56 used the data collected between December 2006 (beginning of PRIAS study)
 57 and May 2019. The PSA was measured every three months until year two
 58 of follow-up and every six months thereafter. Biopsy schedule was year one,
 59 four, seven, and ten, and additional yearly biopsies when PSA doubling time
 60 is between three and ten years. The primary event of this work is Gleason ≥ 7
 61 (GS7). It was observed in 1134 patients, but 2250 were provided treatment
 62 (see Table 1). Treatment in absence of GS7 may have been advised on the
 63 basis of PSA, number of biopsy cores with cancer, anxiety, or other reasons.
 64 We focused only on GS7 because of its strong association with cancer-related
 65 outcomes. Due to the periodical nature of biopsies, the time of GS7 was only
 66 known as a time interval in which it 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)

67 2.2. Statistical Methods

68 Our aim was to develop a model for predicting the time of GS7. The
 69 available data for each patient were, age at the start of AS, all observed
 70 PSA measurements, and the history of biopsies. We wanted to account for
 71 the correlation between the PSA measurements of the same patient, and
 72 also their correlation with the time of GS7. An additional complication was
 73 that PSA values were missing once a patient obtained GS7. A commonly
 74 used model to handle these issues is the joint model for time-to-event and
 75 longitudinal data [12, 10, 11].

76 The joint model we utilized, exploited patient-specific random effects
 77 [13] to act as a common source of correlation between the PSA and time
 78 of GS7 outcomes (see Figure 3). Random effects also represented the un-
 79 derlying state of PCa, and were included in both the linear mixed effects
 80 sub-model for $\log_2\{\text{PSA} + 1\}$ transformed measurements, and the relative
 81 risk sub-model (similar to cox model) for time of GS7. In the PSA sub-
 82 model, random effects non-linearly modeled the evolution of PSA over time.
 83 Simultaneously, in the relative risk model they were used indirectly by in-
 84 cluding fitted $\log_2\{\text{PSA} + 1\}$ value and velocity as time dependent covari-
 85 ates. This established the correlation between PSA and time of GS7. Unlike
 86 observed $\log_2\{\text{PSA} + 1\}$ values, the fitted values were free of measurement
 87 errors. The $\log_2\{\text{PSA} + 1\}$ velocity was mathematically derived from fitted
 88 $\log_2\{\text{PSA} + 1\}$ values. Hence, the $\log_2\{\text{PSA} + 1\}$ velocity was also allowed
 89 to change non-linearly over follow-up.

90 The parameters of the two sub-models were estimated jointly using the R
 91 **JMbayes** [14]. This package utilizes the Bayesian methodology to estimate

92 model parameters. The parameters and 95% credible intervals are presented
 93 in Table.. of Appendix.

94 *2.3. Assessment of Predictions of GS7*

95 We validated the predictions of GS7 internally within the PRIAS dataset,
 96 as well as externally in five of the largest AS cohorts part of the GAP3
 97 database [8]. To this end, we utilized the area under the receiver operating
 98 characteristic curve or AUC [15] as a measure of discrimination, and root
 99 mean squared prediction error or RMSPE [15] as a measure of calibration.
 100 Since AS studies are longitudinal in nature, we computed AUC and RMSPE
 101 in a time dependent manner, at a gap of every one year until xx years of
 102 follow-up (95% quantile of observed GS7 times).

103 *2.4. Estimate Risk of GS7 and Consequences of Biopsies*

104 Consider a new patient P shown in Figure ... Using the joint model
 105 fitted to the PRIAS dataset, we obtained his cumulative risk of GS7 over
 106 the entire follow-up period. A biopsy at his current visit may be suggested
 107 if the cumulative risk of GS7 at the current visit is above a certain threshold
 108 (e.g., 10% risk). By repeatedly applying the 10% threshold rule over the
 109 whole follow-up, we obtained his personalized schedule of biopsies. Similar
 110 schedules can be made with another risk threshold. These schedule are not
 111 fixed but are rather updated at each follow-up visit based on newly gathered
 112 patient data.

113 To assist patients in making an informed choice for a schedule, be it
 114 personalized or fixed, we provided them patient-specific consequences of fol-
 115 lowing each schedule. To this end, we first calculated the probability of

116 occurrence of GS7 between successive biopsies of each schedule. Using these
117 probabilities we then obtained the expected delay in detection of GS7 for
118 following that schedule. Thus, patients have a method to compare across
119 various schedules in terms of the personalized burden (time and total biop-
120 sies), and personalized benefit (less delay in detection of GS7 is beneficial).
121 Lastly, we implemented this approach in a web-application.

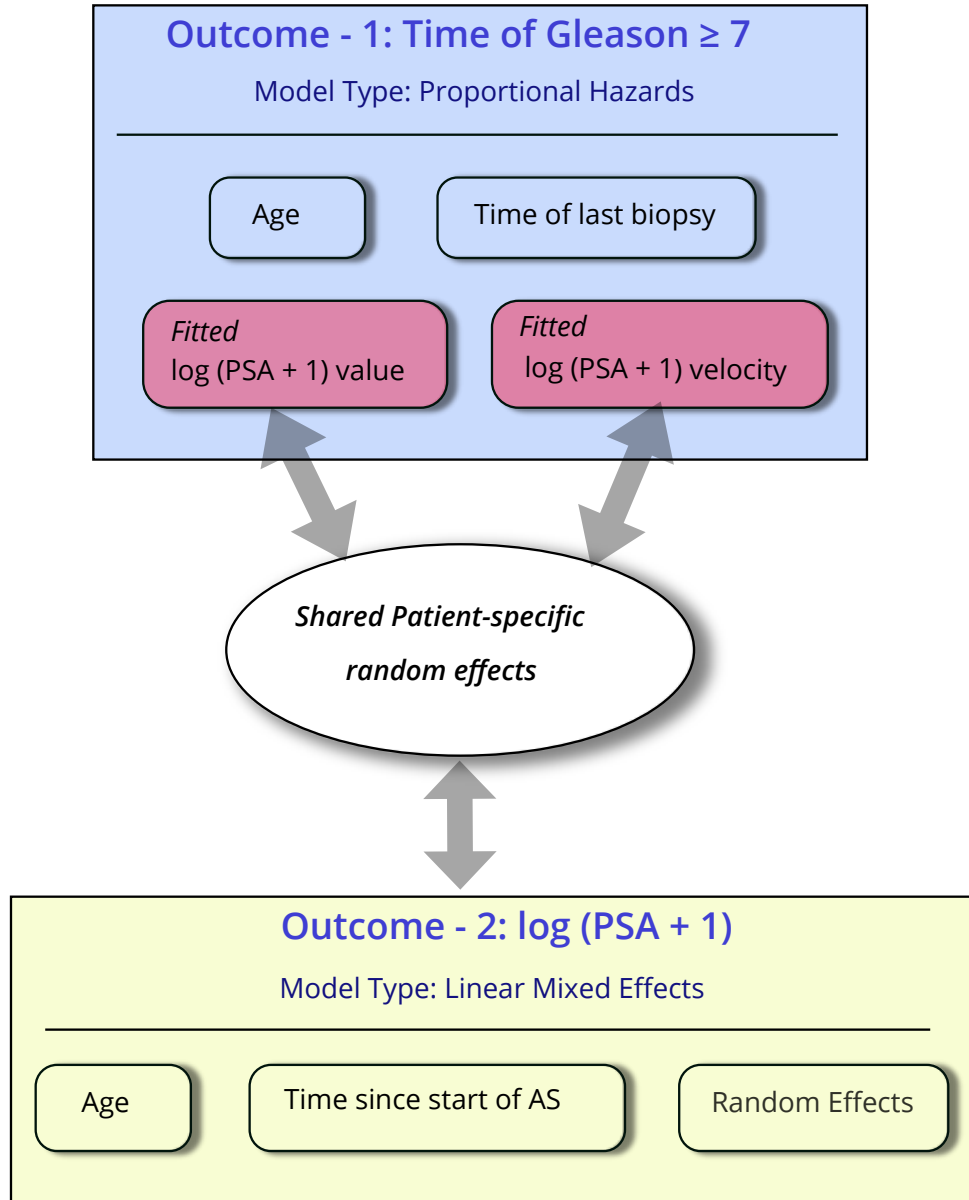


Figure 3: **Diagram of the joint model:** Patient-specific random effects (ellipse in center) are shared between sub-models for all outcomes pertaining to prostate cancer progression. The random effects model the correlation between the outcomes. In the linear mixed effects sub-model for $\log_2\{\text{PSA} + 1\}$ 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.

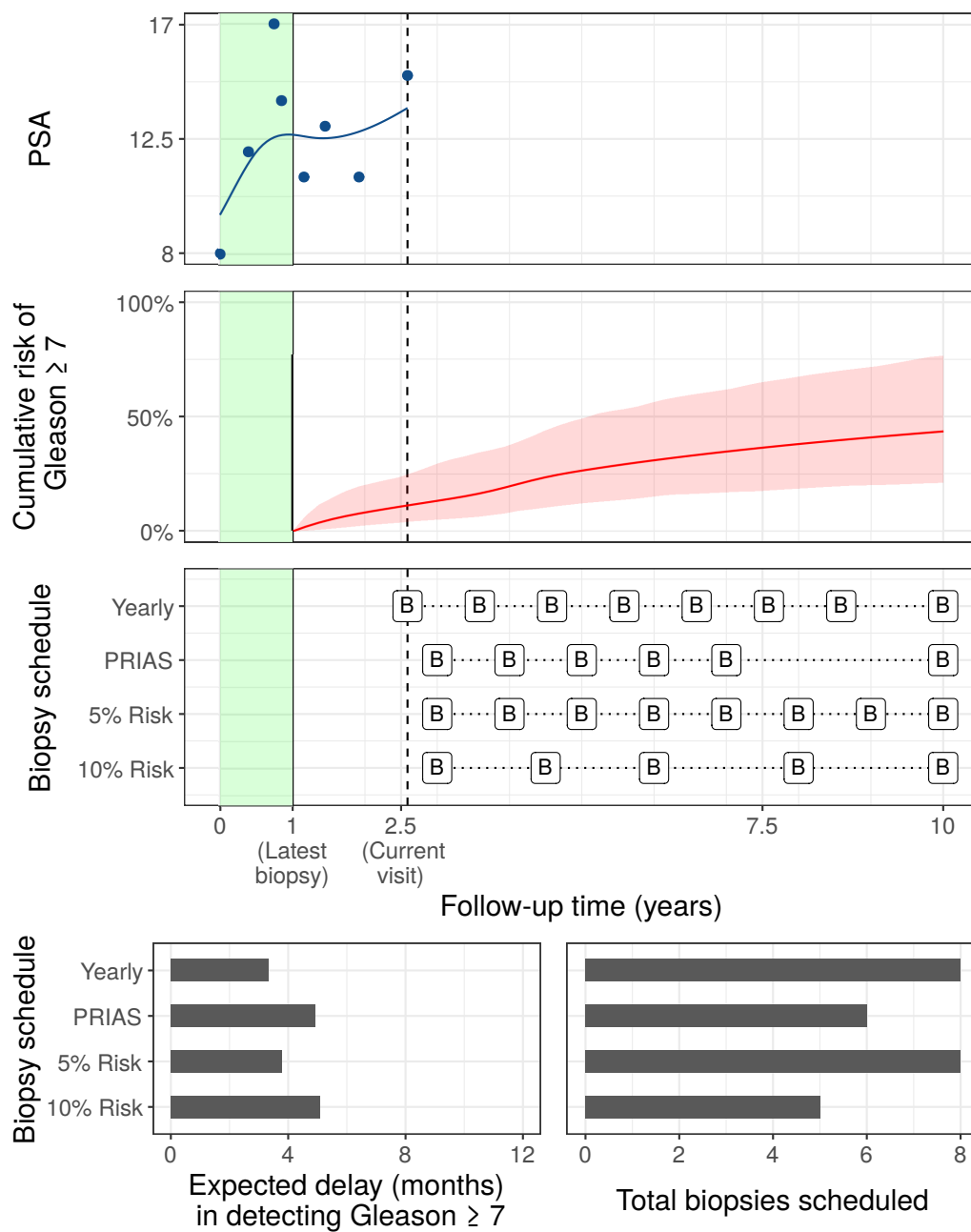


Figure 4

122 3. Results

123 For patients in the PRIAS dataset, the probability of obtaining reclas-
 124 sification within the first five and ten years is 33% and 42%, respectively
 125 (see Figure 1). That is, more than 50% of the patients may not require any
 126 biopsy in the first ten years. We refer to them as *slow progressing* patients
 127 hereafter. For every ten years increase in a patient age the corresponding
 128 adjusted hazard ratio of reclassification is 1.45 (95%CI: 1.29–1.61). For an
 129 increase in fitted $\log_2\{\text{PSA} + 1\}$ value from the first quartile of fitted value
 130 (2.67) to the third quartile (2.82), the corresponding adjusted hazard ratio
 131 of reclassification is 1.00 (95%CI: 0.98–1.02). On the other hand an increase
 132 in fitted $\log_2\{\text{PSA} + 1\}$ velocity from the first quartile of fitted velocity (-
 133 0.04) to the third quartile (0.15), the corresponding adjusted hazard ratio of
 134 reclassification is 2.45 (95%CI: 1.83–2.95). These results indicate that the
 135 velocity of $\log_2\{\text{PSA} + 1\}$ measurements is a stronger predictor of hazard of
 136 reclassification than the $\log_2\{\text{PSA} + 1\}$ value.

137 The time dependent area under the receiver operating characteristic curves
 138 (AUC) and the root mean squared prediction error (RMSPE) with 95% CI
 139 are shown in Figure. The results are comparable for internal and external
 140 validation in cohorts that are similar to the PRIAS cohort. That is, the
 141 model may also be useful for risk prediction in other cohorts such as the
 142 Toronto AS cohort.

143 Using the fitted model we next predict the

Table 2: **Assessment of predictions of Gleason ≥ 7 (GS7) from our model using, area under the receiver operating characteristic curve (AUC), and root mean squared prediction error (RMSPE).**

Characteristic	Value
Total patients	7813
Gleason ≥ 7 (primary event)	1134
Treatment	2250
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Total biopsies	15563
Median number of biopsies per patient	2 (IQR: 1–3)

144 4. Discussion

145 We developed personalized schedules for repeat biopsies in PCa patients
 146 enrolled in AS programs. These schedules were based on a patient’s risk for
 147 having a Gleason ≥ 7 (GS7). Patient- and visit-specific risks of GS7 were
 148 estimated using their entire history of PSA and repeat biopsies, and baseline
 149 characteristics. Consequently, the personalized schedules were updated as
 150 more data was gathered over follow-up. Risk calculators for GS7 are not new
 151 [11, 16]. However, the novelty of our work is that we developed a methodology
 152 for scheduling personalized biopsies using those risks, as well a methodology
 153 to compare schedules, be it personalized or fixed, in simple terms of burden
 154 and benefit. More specifically, for each schedule we provided patients the
 155 times of biopsy and total biopsies (burden), and the delay in detection of
 156 GS7 (less is beneficial) expected due to that schedule. We also implemented
 157 our methodology in a web-application.

158 The proposed joint model accounted for the complex correlation struc-
 159 ture that exists between longitudinal PSA measurements and time of GS7
 160 of a patient. It also accounted for PSA measurements that were missing in
 161 patients who obtained GS7. This model adjusts the risks of GS7 upon a neg-
 162 ative repeat biopsy. Thus complete patient information is consolidated into
 163 a single patient risk profile. Our model is fitted to the world’s largest PCa
 164 AS program, PRIAS. We also validated our model predictions for GS7 in
 165 external cohorts that are part of the GAP3 database [8]. We found that the
 166 discrimination and calibration measures of the predictions from our model
 167 (Table 2) were similar for PRIAS (internal validation), and Toronto and
 168 Johns Hopkins cohorts (external validation). Given the large size of these

169 cohorts, we expect that our model and the methodology will be useful to
170 a large number of AS patients. Extending our model and methodology in
171 other cohorts only requires fitting the model to their AS dataset.

172 The clinical implications of our work are as follows. The median survival
173 time for GS7 is more than ten years in PRIAS, and in some other cohorts
174 (Figure 1). That is, more than 50% of AS patients do not require any biopsy
175 during the first ten years of follow-up. We hope that our work will address
176 patient apprehensions regarding adverse outcomes in AS, in a more objective
177 manner. Many AS programs still utilize a rigorous schedule of yearly biopsies
178 [3]. However, with concerns about non-compliance and burden of biopsies
179 [5], the availability of our web based tool may encourage patients and doctors
180 to consider personalized schedules.

181 Our work has certain limitations. The proposed model is valid only for
182 the first thirteen years of follow-up in PRIAS, whereas GS7 may occur much
183 later in many patients. Due to this issue, the calibration and discrimination
184 measures of predictions were also less accurate in later follow-up periods.
185 These issue can be mitigated by refitting the model as more follow-up data
186 is gathered in PRIAS. While we focused only on GS7, it is susceptible to
187 inter-observer variation. Models which account for this variation [11, 17] will
188 be interesting to investigate further. However, the methodology to schedule
189 biopsies, and to estimate the consequences of following a schedule need not
190 change. There is also a potential for including diagnostic information from
191 novel biomarkers, quality of life measures, and magnetic resonance imaging
192 (MRI). Currently, this data is very sparsely available in the PRIAS dataset.
193 However, in future, adding this information in our model is trivial. This is

194 because modeling correlation for extra outcomes, mainly entails connecting
195 sub-models for the outcomes to shared random effects (see Figure 3). Our
196 model can also be used to schedule MRI scans, since they are expensive in
197 developing countries.

198 5. Conclusions

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

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