Personalized Biopsy Schedules for Men With Low-Risk Prostate Cancer Under Active Surveillance*

Anirudh Tomer, MSc[a,*], Daan Nieboer, MSc[b,c], Monique J. Roobol, PhD[c], Anders Bjartell, MD, PhD[d], Ewout W. Steyerberg, PhD[b,e], Dimitris Rizopoulos, PhD[a], Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) consortium[f]

[a] *Department of Biostatistics, Erasmus University Medical Center, Rotterdam, the Netherlands*
[b] *Department of Public Health, Erasmus University Medical Center, Rotterdam, the Netherlands*
[c] *Department of Urology, Erasmus University Medical Center, Rotterdam, the Netherlands*
[d] *Department of Urology, Skåne University Hospital, Malmö, Sweden*
[e] *Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, the Netherlands*
[f] *The Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) consortium members presented in Appendix A*

Abstract

Background: Prostate cancer active surveillance (AS) patients undergo repeat biopsies. Active treatment is advised when biopsy Gleason grade group ≥ 2 (*upgrading*). Many patients never experience upgrading, yet undergo biopsies frequently. Personalized biopsy decisions based on upgrading-risk may reduce patient burden.

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*Word count: abstract (headings excluded) 300; Text 2488; Total 2788

*Corresponding author (Anirudh Tomer): Erasmus MC, kamer flex Na-2823, PO Box 2040, 3000 CA Rotterdam, the Netherlands. Tel: +31 10 70 43393

Email addresses: a.tomer@erasmusmc.nl (Anirudh Tomer, MSc), d.nieboer@erasmusmc.nl (Daan Nieboer, MSc), m.roobol@erasmusmc.nl (Monique J. Roobol, PhD), anders.bjartell@med.lu.se (Anders Bjartell, MD, PhD), e.w.steyerberg@lumc.nl (Ewout W. Steyerberg, PhD), d.rizopoulos@erasmusmc.nl (Dimitris Rizopoulos, PhD)

`Objective`: Develop a risk prediction model and web-application to assist patients/doctors in personalized biopsy decisions.

`Design, Setting, and Participants`: Model development: world's largest AS study PRIAS, 7813 patients, 1134 experienced upgrading; External validation: largest six cohorts of Movember Foundation's GAP3 database ($> 20,000$ patients, 27 centers worldwide); Data: repeat prostate-specific antigen (PSA) and biopsy Gleason grade group.

`Outcome Measurements, and Statistical Analysis`: A Bayesian joint model fitted to PRIAS dataset. This model was validated in GAP3 cohorts using risk prediction error, calibration, area under ROC (AUC). Model and personalized biopsy schedules based on predicted risks were implemented in a web-application.

`Results and Limitations`: Cause-specific cumulative upgrading-risk at year five of follow-up: 35% in PRIAS, at most 50% in GAP3 cohorts. PRIAS based model: PSA velocity was stronger predictor of upgrading (Hazard Ratio: 2.47, 95%CI: 1.93–2.99) than PSA value (Hazard Ratio: 0.99, 95%CI: 0.89–1.11). Validation: Moderate AUC (0.55–0.75) in PRIAS and GAP3 cohorts. Moderate prediction error (0.1–0.3) in GAP3 cohorts where impact of PSA value and velocity on upgrading-risk was similar to PRIAS, but large (0.3–0.45) otherwise. Recalibration of baseline risk required for external cohorts.

`Conclusions`: We successfully developed and validated a model for predicting upgrading-risk, and providing risk-based personalized biopsy decisions, in prostate cancer AS. The model made available via a web-application enables shared decision making of biopsy schedules by comparing fixed and personalized schedules on total biopsies and expected time delay in detecting upgrading.

`Patient Summary`: Personalized prostate biopsies are a novel alternative to fixed one-size-fits-all schedules. The underlying statistical models are made available through a user-friendly web-application and may help to reduce unnecessary prostate biopsies while maintaining cancer control.
Keywords: Active Surveillance, Biopsies, Personalized Medicine, Prostate Cancer, Shared Decision Making

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1. Introduction

Patients with low- and very low-risk screening-detected localized prostate cancer are usually recommended active surveillance (AS) instead of immediate radical treatment [1]. In AS, cancer progression is routinely monitored via prostate-specific antigen (PSA), digital rectal examination, and repeat biopsies. Among these, the strongest indicator of cancer-related outcomes is the biopsy Gleason grade group [2]. When it increases from group 1 (Gleason 3+3) to 2 (Gleason 3+4) or higher, called *upgrading* [3], patients are commonly advised curative treatment [4].

Usually, AS protocols schedule biopsies periodically. Consequently, upgrading is always detected with a time delay (Figure 1). For detecting

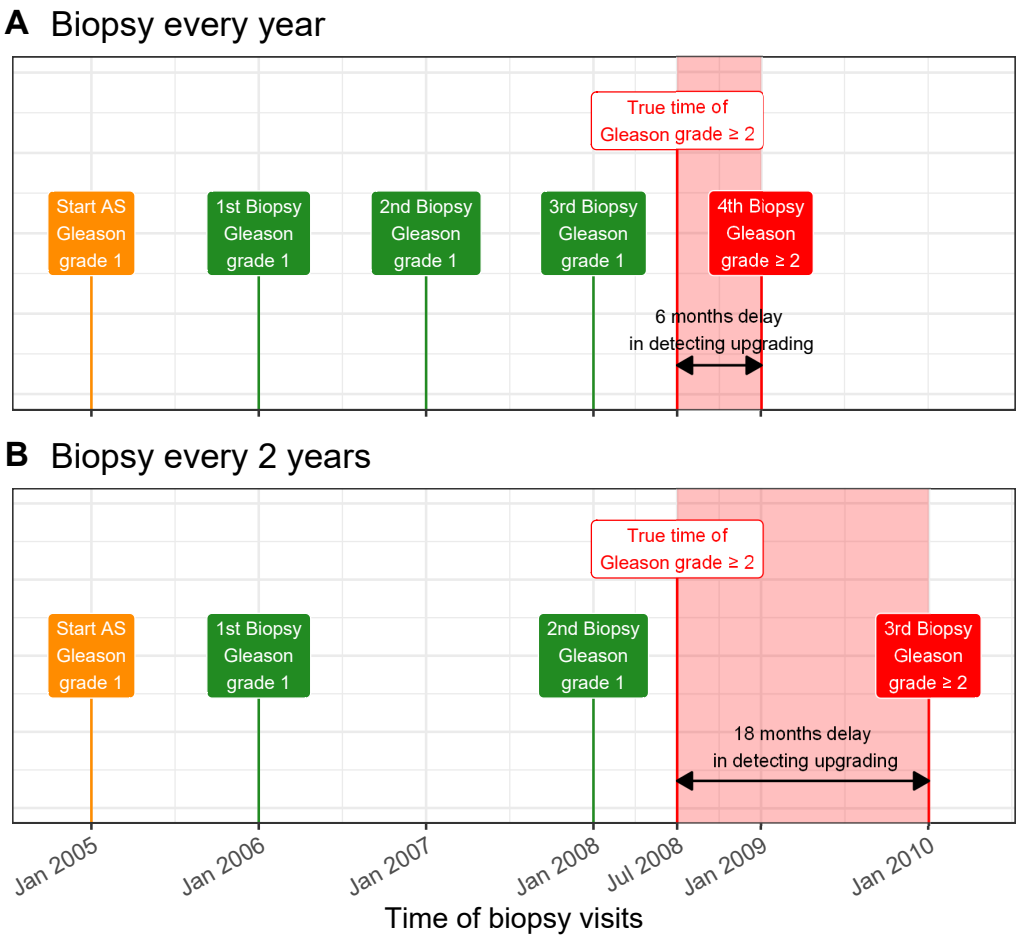

Figure 1: **Trade-off between the number of biopsies and time delay in detecting upgrading (Increase in Gleason grade group from 1 to 2 or higher):** The true time of upgrading for the patient in this figure is July 2008. When biopsies are scheduled annually (**Panel A**), upgrading is detected in January 2009 with a time delay of six months, and a total of four biopsies are scheduled. When biopsies are scheduled biennially (**Panel B**), upgrading is detected in January 2010 with a time delay of 18 months, and a total of three biopsies are scheduled. Since biopsies are conducted periodically, the time of upgrading is observed as an interval. For example, between Jan 2008–Jan 2009 in **Panel A** and between Jan 2008–Jan 2010 in **Panel B**. The phrase 'Gleason grade group' is shortened to 'Gleason grade' for brevity.

upgrading timely, many AS programs schedule fixed and frequent biopsies (e.g., annually) for all patients [5, 6]. However, this leads to unnecessary biopsies in slow/non-progressing patients. Biopsies are invasive, may be painful, and are prone to medical complications such as bleeding and septicemia[7]. Biopsy burden and patient non-compliance to frequent biopsies [8] have raised concerns regarding the optimal biopsy schedule [9, 10]. In this regard, in some cohorts, magnetic resonance imaging (MRI) is employed for targeted biopsies and to study its value for tumor monitoring. Although, due to currently limited AS data, MRI's value is not clear. Others have proposed the option of scheduling biopsies infrequently (e.g., biennially) [9, 11]. However, due to differences in baseline upgrading-risk across cohorts [9], fixed biopsy schemes can still lead to many unnecessary biopsies. A promising alternative to fixed schedules are personalized biopsy schedules based on the patient-specific upgrading-risk (Figure 2).

The first challenge in creating personalized biopsy schedules is developing a statistical model to consolidate accumulated patient data (e.g., PSA, previous biopsy results) into predictions for upgrading-risk. Existing upgrading-risk [12, 13] calculators use only the latest PSA measurement of a patient. Comparatively, more information is captured by considering all repeatedly measured PSA, previous biopsy results, and baseline characteristics of a patient. To this end, a suitable model is the joint model for time-to-event and longitudinal data [14, 15, 16]. A joint model predicts upgrading-risk in a personalized manner. However, a subsequent challenge is translating predicted risks into clinical decisions. For example, a 10% upgrading-risk can be perceived high/low depending upon the patient's age. Patients may also

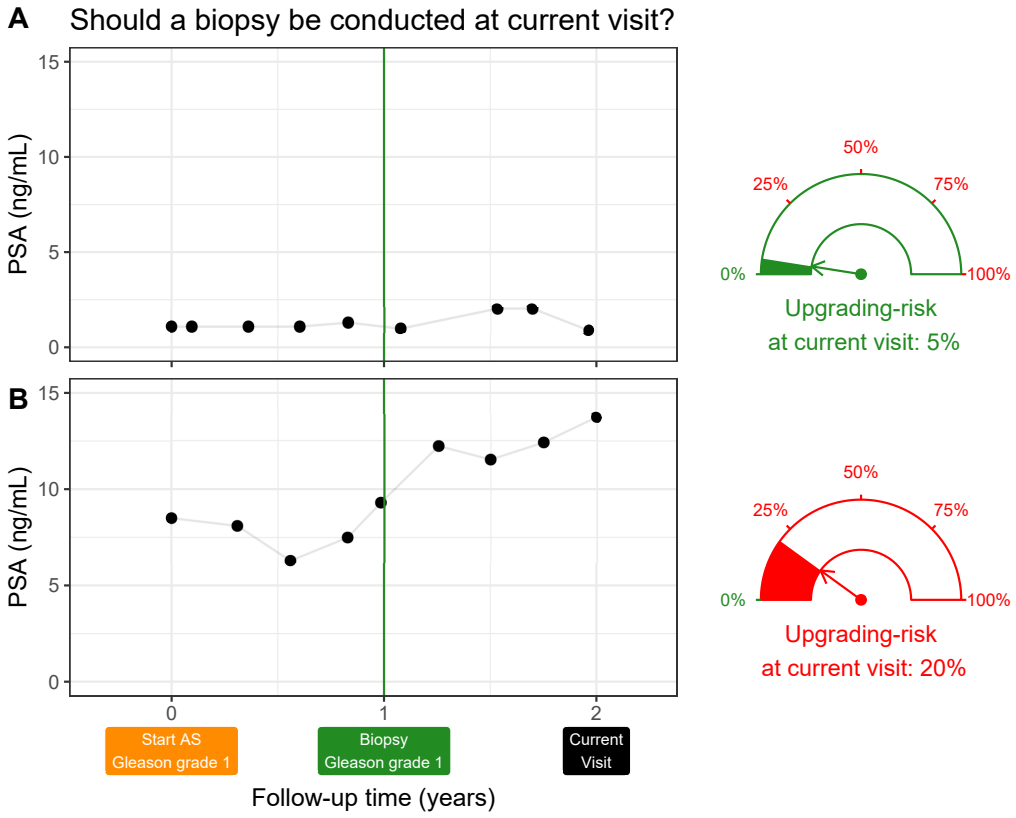

Figure 2: **Motivation for personalized upgrading-risk based decisions of biopsy**: Patient A (**Panel A**) and B (**Panel B**) had their latest biopsy at year one of follow-up (green vertical line). Patient A's prostate-specific antigen (PSA) profile remained stable until his current visit at year two, whereas patient B's profile has shown a rise. Consequently, patient B's upgrading-risk at the current visit (year two) is higher than that of patient A. This makes patient B a more suitable candidate for biopsy than Patient A. Risk estimates in this figure are only illustrative.

weigh risks of upgrading with the potential *consequences* of another biopsy. Two such relevant consequences (Figure 1) are the timing and the total number of planned biopsies (burden), and the time delay in detecting upgrading (smaller is beneficial). The relative importance of these consequences can vary between the patients, and also within a patient over the follow-up period.

The goal of this work is two-fold. First, to develop a robust, generalizable model that gives reliable estimates for individual upgrading-risk in AS. Second, to utilize the predicted upgrading-risks to create personalized biopsy schedules. To facilitate shared decision making of biopsy schedules, we also intend to provide quantitative estimates of the aforementioned *consequences* of opting for a personalized versus the standard fixed schedule. For developing our model, we will use the world's largest AS dataset PRIAS. Subsequently, we want to externally validate our model in the largest six AS cohorts from the Movember Foundation's GAP3 database [17]. Last, we intend to implement our model and methodology in a web-application.

2. Patients and Methods

2.1. Study Cohort

For developing a statistical model to predict upgrading-risk, we used the world's largest AS dataset, Prostate Cancer International Active Surveillance or PRIAS [4], dated April 2019 (Table 1). In PRIAS, PSA was measured quarterly for the first two years of follow-up and semiannually thereafter. Biopsies were scheduled at year one, four, seven, and ten of follow-up. Additional yearly biopsies were scheduled when PSA doubling time was between

zero and ten years.

We selected all 7813 patients who had Gleason grade group 1 at the time of inclusion in PRIAS. Our primary event of interest is an increase in this Gleason grade group observed upon repeat biopsy, called *upgrading* (1134 patients). Upgrading is a trigger for treatment advice in PRIAS. Also, 2250 patients were provided treatment based on their PSA, number of biopsy cores with cancer, or anxiety/other reasons. Our reasons for focusing solely on upgrading are, namely, upgrading is strongly associated with cancer-related outcomes, and other treatment triggers vary between cohorts [5].

For model validation, we selected the following largest (by number of repeated measurements) six cohorts from Movember Foundation's GAP3 database version 3.1 [17]: University of California San Francisco AS (UCSF, version 3.2), University of Toronto AS (Toronto), Johns Hopkins AS (Hopkins), Memorial Sloan Kettering Cancer Center AS (MSKCC), King's College London AS (KCL), and Michigan Urological Surgery Improvement Collaborative AS (MUSIC). Only patients with a Gleason grade group 1 at the time of inclusion in these cohorts were selected. Summary statistics are presented in Supplementary A.2.

2.2. Statistical Model

For developing an upgrading-risk prediction model, the data we utilized from the PRIAS cohort was patient age at inclusion in AS, longitudinally measured PSA, timing of repeat biopsies and Gleason grades, and observed time of upgrading. Analysis of this data required modeling the within-patient correlation for PSA, the association between the Gleason grades and PSA profiles of a patient, and handling missing PSA measurements after a patient

Table 1: **Summary of the PRIAS dataset as of April 2019**. The primary event of interest is upgrading, that is, increase in Gleason grade group from group 1 [2] to 2 or higher. IQR: interquartile range, PSA: prostate-specific antigen. Study protocol URL: `https://www.prias-project.org`

Characteristic	**Value**
Total centers	> 100
Total patients	7813
Upgrading (primary event)	1134
Treatment	2250
Watchful waiting	334
Loss to follow-up	249
Death (unrelated to prostate cancer)	95
Death (related to prostate cancer)	2
Median age at diagnosis (years)	66 (IQR: 61–71)
Median maximum follow-up per patient (years)	1.8 (IQR: 0.9–4.0)
Total PSA measurements	67578
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	15686
Median number of biopsies per patient	2 (IQR: 1–2)

experienced upgrading. In such situations, a commonly used model is the joint model for time-to-event and longitudinal data [14, 15, 16].

Our joint model consisted of two sub-models. First, a linear mixed sub-model [18] for longitudinally measured PSA (log-transformed). Second, a relative-risk sub-model (similar to the Cox model) for obtaining the cause-specific upgrading-risk. We included patient age in both sub-models. In the PSA sub-model, we fitted a unique curve to the PSA measurements of each patient (Panel A, Figure 3). Subsequently, we calculated the mathematical derivative of the patient's fitted PSA profile (Equation 2, Supplementary A), to obtain his follow-up time specific instantaneous PSA velocity (Panel B, Figure 3). This instantaneous velocity is a stronger predictor of upgrading than the widely used average PSA velocity [19]. We modeled the impact of PSA on upgrading-risk by employing fitted PSA value and instantaneous velocity as predictors in the risk sub-model. Also, we included the time of the latest negative biopsy in the risk sub-model (Panel C, Figure 3). The parameters of the two sub-models were estimated jointly (Supplementary A) using the R package **JMbayes** [20].

2.3. Risk Prediction and Model Validation

Our model provides predictions for upgrading-risk over the entire future follow-up period of a patient. Predictions also automatically update over follow-up as more patient data becomes available (Figure 5, Supplementary B). We validated our PRIAS based model internally in the PRIAS cohort, and externally in the largest six GAP3 database cohorts. We employed calibration plots [21, 22] and follow-up *time-dependent* mean absolute risk prediction error or MAPE [23] to graphically and quantitatively evaluate

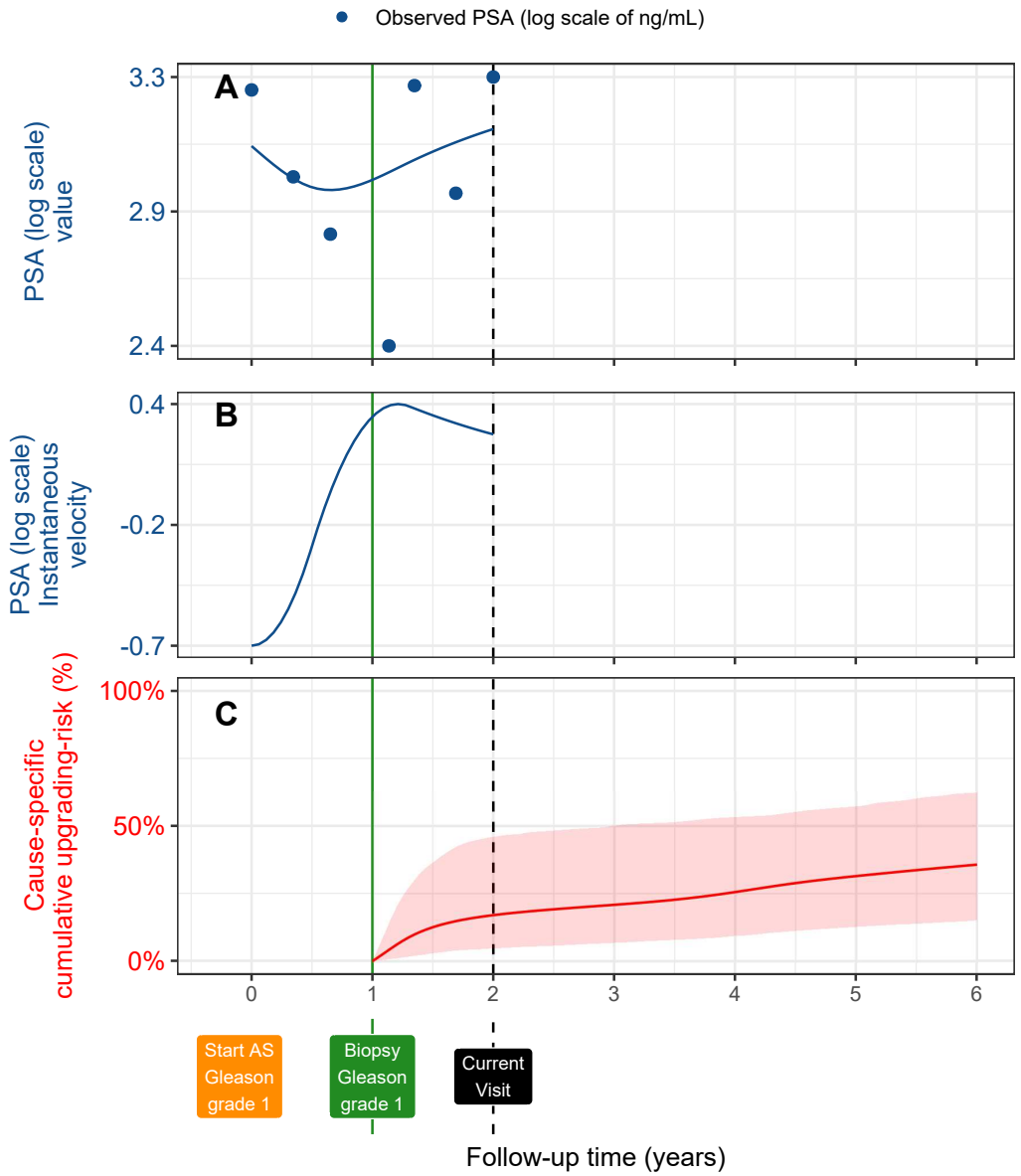

Figure 3: **Illustration of the joint model on a real PRIAS patient**. **Panel A:** Observed PSA (blue dots) and fitted PSA (solid blue line), log-transformed from ng/mL. **Panel B:** Estimated instantaneous velocity of PSA (log-transformed). **Panel C**: Predicted cause-specific cumulative upgrading-risk (95% credible interval shaded). Upgrading is defined as an increase in the Gleason grade group from group 1 [2] to 2 or higher. This upgrading-risk is calculated starting from the time of the latest negative biopsy (vertical green line at year one of follow-up). The joint model estimated it by combining the fitted PSA (log scale) value and instantaneous velocity, and time of the latest negative biopsy. Black dashed line at year two denotes the time of current visit.

our model's risk prediction accuracy, respectively. We assessed our model's ability to discriminate between patients who experience/do not experience upgrading via the time-dependent area under the receiver operating characteristic curve or AUC [23].

The aforementioned *time-dependent* AUC and MAPE [23] are temporal extensions of their standard versions [22] in a longitudinal setting. Specifically, at every six months of follow-up, we calculated a unique AUC and MAPE for predicting upgrading-risk in the subsequent one year (Supplementary B.1). For emulating a realistic situation, we calculated the AUC and MAPE at each follow-up using only the validation data available until that follow-up. Last, to resolve any potential model miscalibration in validation cohorts, we aimed to recalibrate our model's baseline hazard of upgrading (Supplementary B.1), individually for each cohort.

3. Results

The cause-specific cumulative upgrading-risk at year five of follow-up was 35% in PRIAS and at most 50% in validation cohorts (Panel B, Figure 4). Hence, many patients do not require all biopsies planned in the first five years of AS. In the fitted PRIAS model, the adjusted hazard ratio (aHR) of upgrading for an increase in patient age from 61 to 71 years (25-th to 75-th percentile) was 1.45 (95%CI: 1.30–1.63). For an increase in fitted PSA value from 2.36 to 3.07 (25-th to 75-th percentile, log scale), the aHR was 0.99 (95%CI: 0.89–1.11). The strongest predictor of upgrading-risk was instantaneous PSA velocity, with an increase from -0.09 to 0.31 (25-th to 75-th percentile), giving an aHR of 2.47 (95%CI: 1.93–2.99). The aHR for PSA

value and velocity varied between GAP3 cohorts (Supplementary Table 8).

The time-dependent AUC, calibration plot, and time-dependent MAPE of our model are shown in Figure 4, and Supplementary Figure 8. In all cohorts, time-dependent AUC was moderate (0.55 to 0.75) over the whole follow-up period. Time-dependent MAPE was large (0.3 to 0.45) in those cohorts where the impact of PSA on upgrading-risk was different from PRIAS (e.g., MUSIC cohort, Supplementary Table 8), and moderate (0.1 to 0.3) otherwise. In all cohorts, the MAPE decreased rapidly after year one of follow-up. Our model was miscalibrated for validation cohorts (Panel B, Figure 4). Recalibrating the baseline hazard of upgrading in validation cohorts resolved this issue (Supplementary Figure 6). We compared risk predictions from the recalibrated models, with predictions from separately fitted cohort-specific joint models (Supplementary Figure 7). The difference in predictions was lowest in Johns Hopkins cohort (impact of PSA on upgrading-risk similar to PRIAS). Comprehensive results are in Supplementary A.2 and B.

3.1. Personalized Biopsy Schedules

We employed the PRIAS based fitted model to create personalized biopsy schedules for real PRIAS patients. Specifically, first using the model and patient's observed data, we predicted his cumulative upgrading-risk (Figure 5) on all of his future follow-up visits (biannually in PRIAS). Subsequently, we planned biopsies on those future visits where his conditional cumulative upgrading-risk was more than a certain threshold (Supplementary Figure 9). Example personalized schedules based on 5% and 10% risk thresholds are shown in Figure 5, and in Supplementary Figure 10–12. For both personalized and fixed schedules, we estimated the expected time delay in detecting

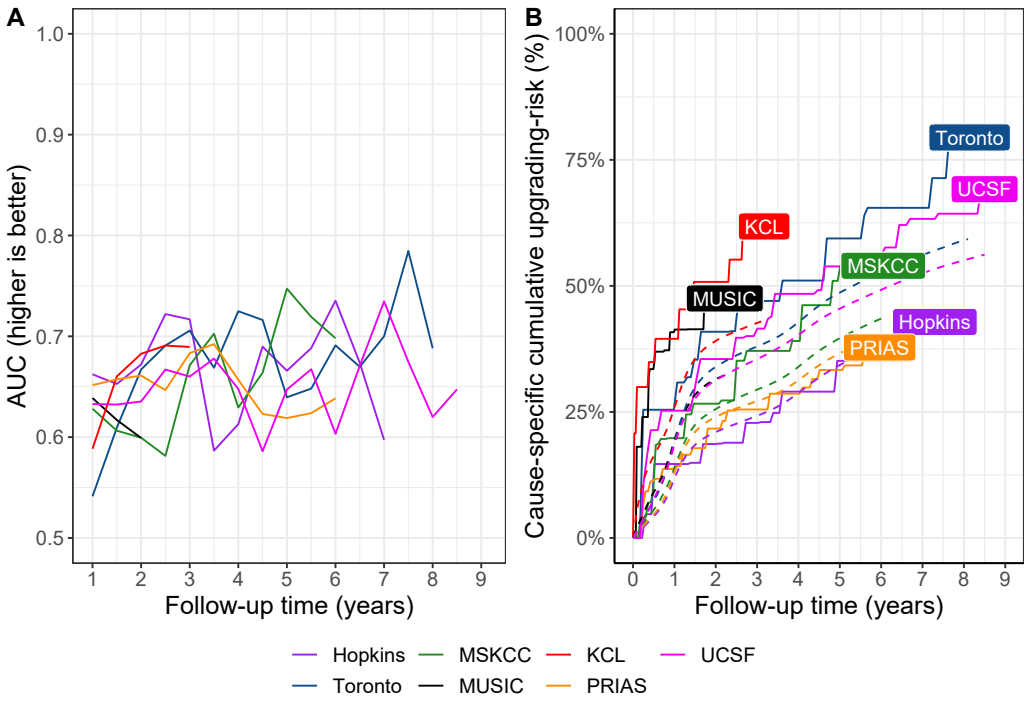

Figure 4: **Model Validation Results**. **Panel A**: time-dependent area under the receiver operating characteristic curve or AUC (measure of discrimination). **Panel B**: calibration-at-large indicates model miscalibration. This is because solid lines depicting the non-parameteric estimate of the cause-specific cumulative upgrading-risk [24], and dashed lines showing the average cause-specific cumulative upgrading-risk obtained using the joint model fitted to the PRIAS dataset, are not overlapping. Recalibrating the baseline hazard of upgrading resolved this issue (Supplementary Figure 6). Full names of Cohorts are *PRIAS*: Prostate Cancer International Active Surveillance, *Toronto*: University of Toronto Active Surveillance, *Hopkins*: 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, *UCSF*: University of California San Francisco AS.

upgrading if the patient progresses before the time of the last planned biopsy (Panel C, Figure 5). This delay is also personalized (Supplementary C.1). That is, even if two different patients are prescribed the same biopsy schedule, their expected delays will depend on their individual upgrading-risk profiles. Patients/doctors can utilize the expected delay and schedule of biopsies as criteria to compare fixed, and different risk-based personalized schedules.

3.2. Web-Application

We implemented our model and personalized schedules in a user-friendly web-application `https://emcbiostatistics.shinyapps.io/prias_biopsy_recommender/`. Currently, the web-application supports PRIAS and the six validation cohorts. Patient data can be entered manually and in Microsoft Excel format. Predictions for upgrading-risk are available for a currently limited, cohort-specific, follow-up period (Supplementary Table 9). The web-application visualizes the timing of biopsies, and expected time delay in detecting upgrading, for personalized schedules based on 5%, 10%, and 15% risk threshold; annual biopsies; biennial biopsies; and PRIAS schedule.

4. Discussion

We successfully developed and externally validated a model for predicting upgrading-risk [3] in prostate cancer AS, and providing risk-based personalized biopsy decisions. Our work has four novel features over earlier risk calculators [15, 25]. First, our model was fitted to the world's largest AS dataset PRIAS and externally validated in the largest six cohorts of the Movember Foundation's GAP3 database [17]. Second, the model predicts a patient's current and future upgrading-risk in a personalized manner. Third,

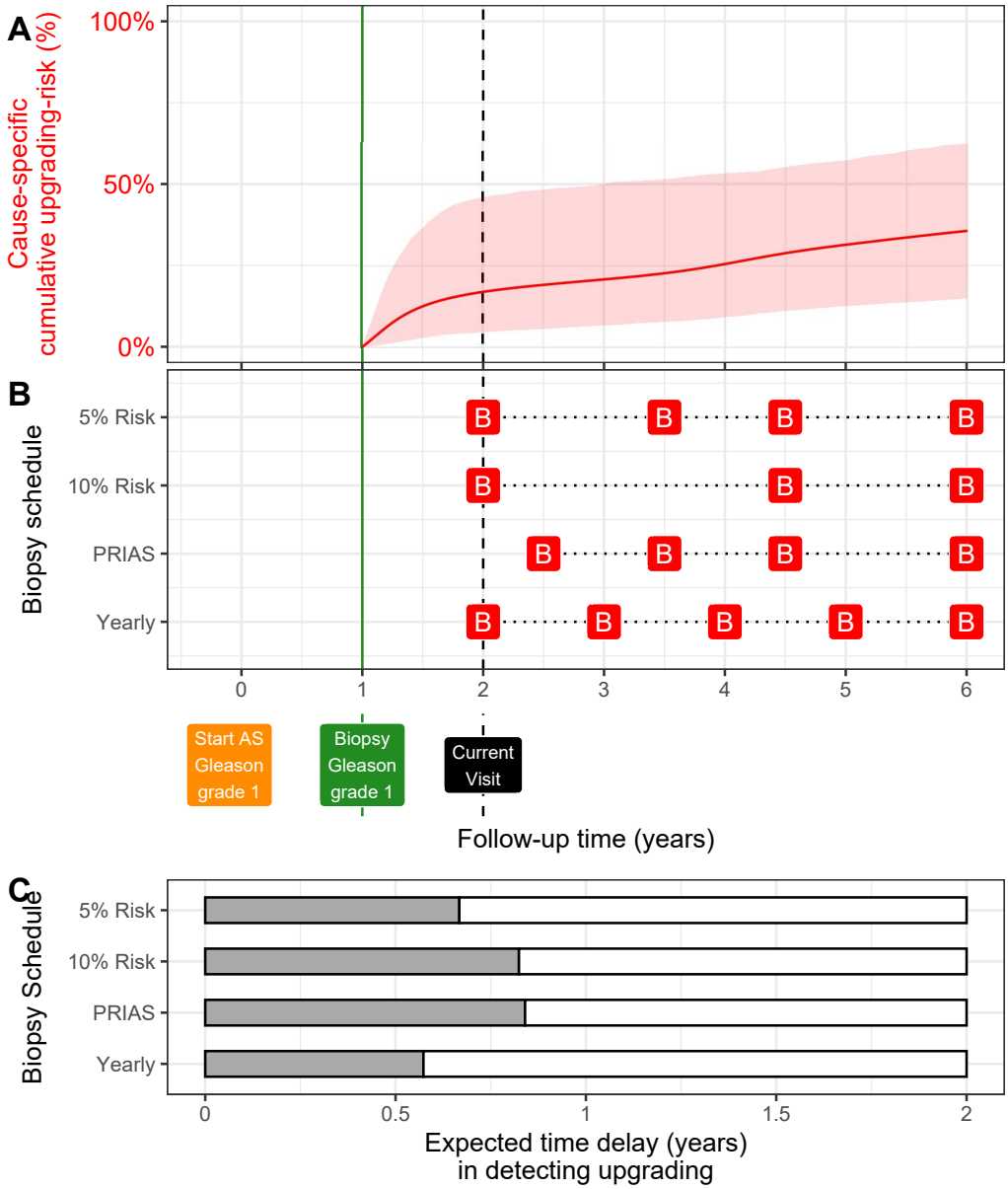

Figure 5: **Illustration of personalized and fixed schedules of biopsies for patient from Figure 3**. **Panel A:** Predicted cumulative upgrading-risk (95% credible interval shaded). **Panel B:** Different biopsy schedules with a red 'B' indicating a future biopsy. Risk: 5% and Risk: 10% are personalized schedules in which a biopsy is planned whenever the conditional cause-specific cumulative upgrading-risk is above 5% or 10% risk, respectively. Green vertical line at year one is the time of the latest negative biopsy. Black dashed line at year two denotes the time of the current visit. **Panel C:** Expected time delay in detecting upgrading (years) if patient progresses before year six. A compulsory biopsy was scheduled at year six (maximum biopsy scheduling time in PRIAS, Supplementary C) in all schedules for a meaningful comparison between them.

using the predicted risks, we created personalized biopsy schedules and also calculated the expected time delay in detecting upgrading (less is beneficial) if that schedule was followed. Thus, patients/doctors can compare schedules before making a choice. Fourth, we implemented our methodology in a user-friendly web-application (`https://emcbiostatistics.shinyapps.io/prias_biopsy_recommender/`) for both PRIAS and validated cohorts.

Our model is useful for numerous patients from PRIAS and validated cohorts. The discrimination ability of our model, exhibited by the *time-dependent* AUC, was moderate (0.55–0.75). This is possible because, unlike the standard AUC [22], the time-dependent AUC utilizes only the validation data available until the time at which it is calculated. The same holds for the time-dependent MAPE (mean absolute prediction error). Although, MAPE varied much more between cohorts than AUC. In cohorts where the effect size for the impact of PSA value and velocity on upgrading-risk was similar to that for PRIAS (e.g., Hopkins cohort), MAPE was moderate. Otherwise, MAPE was large (e.g., KCL and MUSIC cohorts). In all cohorts, MAPE decreased rapidly after year one of follow-up. A plausible reason is that at year one, the validation data also contains those patients who may have been misclassified as Gleason grade group 1 at the time of inclusion in AS. This issue can be obviated by scheduling a compulsory biopsy at year one for all patients (current PRIAS recommendation). Last, we required recalibration of our model's baseline hazard of upgrading for all validation cohorts.

The clinical implications of our work are as follows. First, the cause-specific cumulative upgrading-risk at year five of follow-up was at most 50% in all cohorts (Panel B, Figure 4). That is, many patients may not require

all biopsies planned in the first five years of AS. Given the non-compliance and burden of frequent biopsies [8], the availability of our methodology as a web-application may encourage patients/doctors to consider upgrading-risk based personalized schedules instead. An additional advantage of personalized schedules is that they update as more patient data becomes available over follow-up. We have shown via a simulation study [26] that personalized schedules may reduce, on average, six biopsies compared to annual schedule and two biopsies compared to PRIAS schedule in slow/non-progressing AS patients, while maintaining almost the same time delay in detecting upgrading as PRIAS schedule. Personalized schedules with different risk thresholds indeed have different performance. In this regard, to assist patients/doctors in choosing between fixed schedules and personalized schedules based on different risk thresholds, the web-application provides a patient-specific estimate of the expected time delay in detecting upgrading, for both personalized and fixed schedules. We hope that this will objectively address patient apprehensions regarding adverse outcomes in AS.

This work has certain limitations. Predictions for upgrading-risk, and personalized schedules are available only for a currently limited, cohort-specific, follow-up period (Supplementary Table 9). This problem can be mitigated by refitting the model with new follow-up data in the future. Recently, some cohorts started utilizing MRI to explore the possibility of targeting visible lesions by biopsy. Presently, the GAP3 database has limited MRI follow-up data available. As more such data becomes available, the current model can be extended to include MRI based predictors. We scheduled biopsies using cause-specific cumulative upgrading-risk, which ignores com-

peting events such as treatment based on the number of positive biopsy cores. Employing a competing-risk model may lead to improved personalized schedules. Upgrading is susceptible to inter-observer variation too. Models which account for this variation [15, 27] will be interesting to investigate further. However, even with an enhanced risk prediction model, the methodology for personalized scheduling and calculation of expected time delay (Supplementary C) need not change.

5. Conclusions

We successfully developed and externally validated a model for predicting upgrading-risk, and providing risk-based personalized biopsy decisions, in prostate cancer AS. The model made available via a user-friendly web-application (`https://emcbiostatistics.shinyapps.io/prias_biopsy_recommender/`) enables shared decision making of biopsy schedules by comparing fixed and personalized schedules on total biopsies and expected time delay in detecting upgrading. Novel biomarkers and MRI data can be added as predictors in the model to improve predictions in the future. Recalibration of baseline upgrading-risk is advised for external cohorts.

Author Contributions

Anirudh Tomer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tomer, Nieboer, Roobol, Bjartell, and Rizopoulos

Acquisition of data: Tomer, Nieboer, and Roobol

Analysis and interpretation of data: Tomer, Nieboer, and Rizopoulos

Drafting of the manuscript: Tomer, and Rizopoulos

Critical revision of the manuscript for important intellectual content: Tomer, Nieboer, Roobol, Bjartell, Steyerberg, and Rizopoulos

Statistical analyses: Tomer, Nieboer, Steyerberg, and Rizopoulos

Obtaining funding: Roobol, Steyerberg, and Rizopoulos

Administrative, technical or material support: Nieboer

Supervision: Roobol, and Rizopoulos

Other: none

Acknowledgments

We thank Jozien Helleman from the Department of Urology, Erasmus University Medical Center, for coordinating the project. The first and last authors would like to acknowledge support by Nederlandse Organisatie voor Wetenschappelijk Onderzoek (the national research council of the Netherlands) VIDI grant nr. 016.146.301, and Erasmus University Medical Center funding. Part of this work was carried out on the Dutch national e-infrastructure with the support of SURF Cooperative. The authors also thank the Erasmus University Medical Center's Cancer Computational Biology Center for giving access to their IT-infrastructure and software that was used for the computations and data analysis in this study.

The PRIAS website is funded by the Prostate Cancer Research Foundation, Rotterdam (SWOP). This work was supported by the Movember Foundation. The funder did not play any role in the study design, collection, analysis or interpretation of data, or in the drafting of this paper.

Appendix A. Members of The Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) consortium

Principle Investigators: Bruce Trock (Johns Hopkins University, The James Buchanan Brady Urological Institute, Baltimore, USA), Behfar Ehdaie (Memorial Sloan Kettering Cancer Center, New York, USA), Peter Carroll (University of California San Francisco, San Francisco, USA), Christopher Filson (Emory University School of Medicine, Winship Cancer Institute, Atlanta, USA), Jeri Kim / Christopher Logothetis (MD Anderson Cancer Centre, Houston, USA), Todd Morgan (University of Michigan and Michigan Urological Surgery Improvement Collaborative (MUSIC), Michigan, USA), Laurence Klotz (University of Toronto, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada), Tom Pickles (University of British Columbia, BC Cancer Agency, Vancouver, Canada), Eric Hyndman (University of Calgary, Southern Alberta Institute of Urology, Calgary, Canada), Caroline Moore (University College London & University College London Hospital Trust, London, UK), Vincent Gnanapragasam (University of Cambridge & Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK), Mieke Van Hemelrijck (King's College London, London, UK & Guy's and St Thomas' NHS Foundation Trust, London, UK), Prokar Dasgupta (Guy's and St Thomas' NHS Foundation Trust, London, UK), Chris Bangma (Erasmus Medical Center, Rotterdam, The Netherlands/ representative of Prostate cancer Research International Active Surveillance (PRIAS) consortium), Monique Roobol (Erasmus Medical Center, Rotterdam, The Netherlands/ representative of Prostate cancer Research International Active Surveillance (PRIAS) consortium), Arnauld Villers (Lille University Hospi-

tal Center, Lille, France), Antti Rannikko (Helsinki University and Helsinki University Hospital, Helsinki, Finland), Riccardo Valdagni (Department of Oncology and Hemato-oncology, Università degli Studi di Milano, Radiation Oncology 1 and Prostate Cancer Program, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy), Antoinette Perry (University College Dublin, Dublin, Ireland), Jonas Hugosson (Sahlgrenska University Hospital, Göteborg, Sweden), Jose Rubio-Briones (Instituto Valenciano de Oncología, Valencia, Spain), Anders Bjartell (Skåne University Hospital, Malmö, Sweden), Lukas Hefermehl (Kantonsspital Baden, Baden, Switzerland), Lee Lui Shiong (Singapore General Hospital, Singapore, Singapore), Mark Frydenberg (Monash Health; Monash University, Melbourne, Australia), Yoshiyuki Kakehi / Mikio Sugimoto (Kagawa University Faculty of Medicine, Kagawa, Japan), Byung Ha Chung (Gangnam Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea)

Pathologist: Theo van der Kwast (Princess Margaret Cancer Centre, Toronto, Canada). Technology Research Partners: Henk Obbink (Royal Philips, Eindhoven, the Netherlands), Wim van der Linden (Royal Philips, Eindhoven, the Netherlands), Tim Hulsen (Royal Philips, Eindhoven, the Netherlands), Cees de Jonge (Royal Philips, Eindhoven, the Netherlands).

Advisory Regional statisticians: Mike Kattan (Cleveland Clinic, Cleveland, Ohio, USA), Ji Xinge (Cleveland Clinic, Cleveland, Ohio, USA), Kenneth Muir (University of Manchester, Manchester, UK), Artitaya Lophatananon (University of Manchester, Manchester, UK), Michael Fahey (Epworth HealthCare, Melbourne, Australia), Ewout Steyerberg (Erasmus Medical Center, Rotterdam, The Netherlands), Daan Nieboer (Erasmus Medical Center, Rot-

terdam, The Netherlands); Liying Zhang (University of Toronto, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada)

Executive Regional statisticians: Ewout Steyerberg (Erasmus Medical Center, Rotterdam, The Netherlands), Daan Nieboer (Erasmus Medical Center, Rotterdam, The Netherlands); Kerri Beckmann (King's College London, London, UK & Guy's and St Thomas' NHS Foundation Trust, London, UK), Brian Denton (University of Michigan, Michigan, USA), Andrew Hayen (University of Technology Sydney, Australia), Paul Boutros (Ontario Institute of Cancer Research, Toronto, Ontario, Canada).

Clinical Research Partners' IT Experts: Wei Guo (Johns Hopkins University, The James Buchanan Brady Urological Institute, Baltimore, USA), Nicole Benfante (Memorial Sloan Kettering Cancer Center, New York, USA), Janet Cowan (University of California San Francisco, San Francisco, USA), Dattatraya Patil (Emory University School of Medicine, Winship Cancer Institute, Atlanta, USA), Emily Tolosa (MD Anderson Cancer Centre, Houston, Texas, USA), Tae-Kyung Kim (University of Michigan and Michigan Urological Surgery Improvement Collaborative, Ann Arbor, Michigan, USA), Alexandre Mamedov (University of Toronto, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada), Vincent LaPointe (University of British Columbia, BC Cancer Agency, Vancouver, Canada), Trafford Crump (University of Calgary, Southern Alberta Institute of Urology, Calgary, Canada), Vasilis Stavrinides (University College London & University College London Hospital Trust, London, UK), Jenna Kimberly-Duffell (University of Cambridge & Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK), Aida Santaolalla (King's College London, London, UK & Guy's

and St Thomas' NHS Foundation Trust, London, UK), Daan Nieboer (Erasmus Medical Center, Rotterdam, The Netherlands), Jonathan Olivier (Lille University Hospital Center, Lille, France), Tiziana Rancati (Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy), Helén Ahlgren (Sahlgrenska University Hospital, Göteborg, Sweden), Juanma Mascarós (Instituto Valenciano de Oncología, Valencia, Spain), Annica Löfgren (Skåne University Hospital, Malmö, Sweden), Kurt Lehmann (Kantonsspital Baden, Baden, Switzerland), Catherine Han Lin (Monash University and Epworth HealthCare, Melbourne, Australia), Hiromi Hirama (Kagawa University, Kagawa, Japan), Kwang Suk Lee (Yonsei University College of Medicine, Gangnam Severance Hospital, Seoul, Korea).

Research Advisory Committee: Guido Jenster (Erasmus MC, Rotterdam, the Netherlands), Anssi Auvinen (University of Tampere, Tampere, Finland), Anders Bjartell (Skåne University Hospital, Malmö, Sweden), Masoom Haider (University of Toronto, Toronto, Canada), Kees van Bochove (The Hyve B.V. Utrecht, Utrecht, the Netherlands), Ballentine Carter (Johns Hopkins University, Baltimore, USA – until 2018).

Management team: Sam Gledhill (Movember Foundation, Melbourne, Australia), Mark Buzza / Michelle Kouspou (Movember Foundation, Melbourne, Australia), Chris Bangma (Erasmus Medical Center, Rotterdam, The Netherlands), Monique Roobol (Erasmus Medical Center, Rotterdam, The Netherlands), Sophie Bruinsma / Jozien Helleman (Erasmus Medical Center, Rotterdam, The Netherlands).

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