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Dear Professor Cipriano,

We are writing to you with respect to the manuscript #MDM-19-037, titled "Personalized Decision Making for Biopsies in Prostate Cancer Active Surveillance Programs" submitted to *Medical Decision Making* and the reports we received after its review. We would like to thank you for giving us the opportunity to submit a revised version of our paper that tackles the weaknesses of the previous version.

Following the recommendations from the Reviewers, we have made changes in the revised version of the manuscript. In particular, we have added explanations for the model equations to make them accessible to a wider audience. We have also discussed the impact of the increasing use of MRI on the findings reported in our paper. The "clean" version of the manuscript is titled "main_manuscript.pdf", the manuscript with highlighted changes is titled "edited_manuscript.pdf", and the appendices are compiled into a file titled "supplementary.pdf".

Please find enclosed a detailed point-by-point response to the Reviewers' comments.

Yours sincerely,

the Authors

Response to 1st Referee's Comments

We would like to thank the Referee for their constructive comments, which have allowed us to considerably improve our paper. The main differences of the new version of the manuscript compared to the previous one can be found in the section titled "Study Population".

You may find below our responses to the specific issues raised.

1. Risk calculator for the clinicians for bringing the concept to practice

   We thank the Referee for their suggestion of a risk calculator. We have already developed a web-application for this purpose (Figure 1). In this web-application doctors can load patient data via CSV files (and other formats such as SPSS files). To aid in shared decision making, the web-application not only estimates the cumulative risk of cancer progression at the current visit, but also on future visits. These estimates are time-dynamic, that is, they get updated as additional patient data is collected over time. In addition, patient-specific fitted PSA and DRE profiles and their future predictions are also provided.

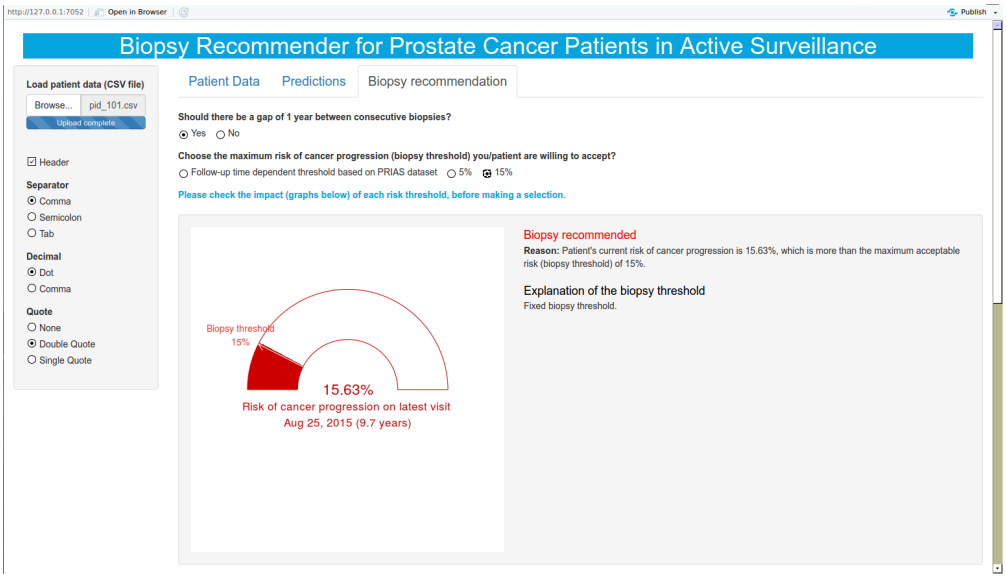

Figure 1: Web-based risk calculator for prediction of risk of prostate cancer progression.

Although the web-application is ready, our model requires further validation. To this end, we are currently validating it using active surveillance data from the GAP3 database (Bruinsma

et al., 2018). The GAP3 database consists of patient data from multiple active surveillance cohorts around the world. Based on some of the initial validation results, we expect that the web-application and our model will also be useful in other cohorts that have a protocol and patient population similar to that of PRIAS.

2. Model robustness to Gleason score misclassification

We thank the Referee for motivating us to check the robustness of our model against Gleason score misclassification. A biopsy Gleason score can be misclassified to be less (or more) than the pathological score that is obtained after prostatectomy. Ignoring such misclassification will affect the parameter estimates as well risk predictions. However, since joint models utilize a relative risk sub-model for modeling time-to-event data, their robustness to misclassification is similar to relative risk models (e.g., Cox proportional hazards model). We next discuss the challenges in accounting for Gleason misclassification.

The impact of Gleason misclassification on our parameter estimates depends upon the misclassification rate as well as the difference between the time at which the underlying (pathological) Gleason score becomes 7 and the time of biopsy. When this time gap is larger it is more likely that disease has progressed. Consequently, the likelihood that a Gleason score higher than 7 is misclassified as Gleason 6 will become lower. The bias in parameter estimates is also directly proportional to the rate of misclassification. However, in general there is little consensus on the rate of Gleason misclassification. Estimates vary between 20% to slightly over 50% (Cookson et al., 1997; Lattouf and Saad, 2002; Melia et al., 2006; Pinthus et al., 2006; Ploussard et al., 2010), which is likely due to variation between centers in terms of both patient population and policies. Thus, the right approach to account for misclassification is to find the misclassification rate specific to the PRIAS program and utilize it to model pathological Gleason score as an outcome in our model (Balasubramanian and Lagakos, 2003; Coley et al., 2017; Meier, Richardson, and Hughes, 2003). However, in the PRIAS dataset such information is available only for the patients who opted for radical prostatectomy. In such patients it is roughly 4.5%, which is much less than the misclassification rates reported in the studies cited above. One possible explanation for a low rate is that such cases may be scrutinized more. We currently lack information on misclassification rate in a random sample of the population (rate potentially higher than 4.5%). Hence, accounting for Gleason misclassification in the model is currently not feasible.

Despite this, the proposed model and the parameter estimates are quite useful for predicting upgrade in biopsy Gleason score, which is the primary clinically relevant endpoint in most

active surveillance programs.

3. Typos on page 6, line 44

   We thank the Referee for pointing out the error. The new text is:

> **Data Accessibility:** The PRIAS database is not openly accessible. However, access to the database can be requested on the basis of a study proposal approved by the PRIAS steering committee. The website of the PRIAS program is `www.prias-project.org`.

Response to 2nd Referee's Comments

We would like to thank the Referee for their constructive comments, which have allowed us to considerably improve our paper. The main differences of the new version of the manuscript compared to the previous one can be found in the "Discussion" section.

You may find below our responses to the specific issues raised.

1. Impact of the increased use of MRIs on our risk calculator

   We agree with the Referee that this is an important issue. In the recent years the use of MRIs to decide biopsies has increased. However, currently MRI data is extremely sparsely available in the PRIAS dataset. Hence, it may not be useful to include it in our model. However, in the next few years we expect to have enough MRI data, such as volume of the prostate tumor in the PRIAS dataset. This data can then be used as a third biomarker in our model, alongside PSA (prostate-specific antigen) and DRE (digital rectal examination) measurements. It is likely that this extended model will lead to improved risk predictions (better AUC and prediction error) than a model which uses information from MRIs alone.

   The current model (without MRI data) can also be used to decide the time of conducting an MRI. This is especially relevant for patients in developing countries, where an MRI scan is still expensive.

   We have added the aforementioned points briefly in the discussion section of the manuscript.

2. Use of patient characteristics, and quality of life in the simulation

   We agree with the Referee that this is an important issue. Currently, the model fitted to the PRIAS dataset, which is also used as the simulation model, accounts for patient age. The Referee also noted the importance of other factors such as having a first degree relative with cancer. However, this factor has been found to be predictive of cancer progression only in African-American patients (Goh et al., 2013; Telang et al., 2017). This is also evident by the fact that PRIAS and many other surveillance programs do not utilize this information in their biopsy protocols (Bokhorst et al., 2016; Nieboer et al., 2018). In addition, patients who have a higher risk of an aggressive form of cancer are usually not recommended active surveillance. Hence the proposed model is relevant only for low-risk prostate cancer patients eligible for active surveillance. An exception are the active surveillance patients who are old and/or have

comorbid illnesses. Currently, such patients may be removed from active surveillance and are instead offered the less intensive watchful waiting (Bokhorst et al., 2016) option. While it is possible to model watchful waiting as a competing risk in our model, but this falls outside the scope of the current work.

How the findings of the model should be utilized in the larger clinical context and what additional work will be needed before the model can be used clinically?

The use of our model and the proposed approach in practice requires further work. A first step will be to initiate studies to look at feasibility acceptability and usability of the personalized approach in daily clinical practice. Biopsy decision making may include other factors such quality of life, patient preferences etc., which are not included in this model. However having an objective estimate (cancer progression risk) next to patient and care giver considerations (subjective) will aid shared decision making. To facilitate such shared decision making we have developed a web-application for clinicians (see Figure 2). We expect to hand it over to clinicians after an external validation of our model in active surveillance cohorts similar to PRIAS. This latter work is currently under progress.

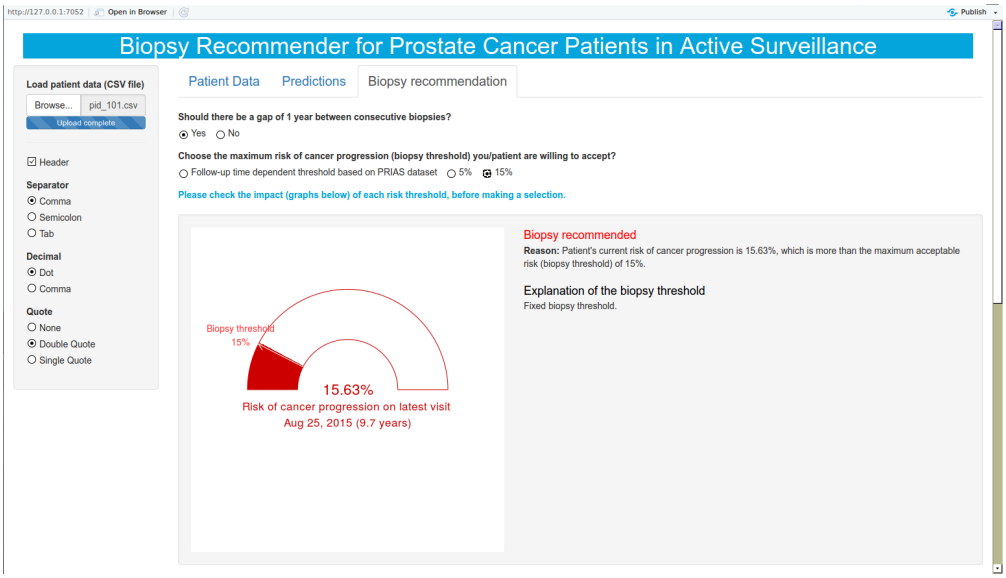

Figure 2: Web-based risk calculator for prediction of risk of prostate cancer progression.

Response to 3rd Referee's Comments

We would like to thank the Referee for their constructive comments, which have allowed us to considerably improve our paper. The main differences of the new version of the manuscript compared to the previous one can be found in the section titled "Methods".

You may find below our responses to the specific issues raised.

1. Base 2 logarithm transformation for PSA

   In many prostate cancer surveillance programs, and specifically in the world's largest surveillance program PRIAS (Prostate Cancer International Active Surveillance), $\log_2$ PSA values have been used for analysis. The reason is that this transformation provides an easy interpretation of the slope of the regression line that is fitted individually for each patient's $\log_2$ PSA levels. More specifically, the inverse of the slope of this regression line is known as the PSA doubling time (Roberts et al., 2001). Although we model PSA levels non-linearly using B-splines (De Boor, 1978), we decided to retain the $\log_2$ PSA transformation for familiarity.

   It is important to note that using $\log_2$ PSA transformation leads to the same model fit as with $\log_e$ PSA transformation. This is because logarithms with different bases are scalar multiples of each other.

2,3. Better explanation of the equations in the Methods section

   We would like to thank the Referee for motivating us to describe these in details. We have added the following text (shaded) in the Methods section.

   What are internal knots and boundary knots?

   > ... our B-spline basis function $B_k(t, \mathcal{K})$ has 3 internal knots at $\mathcal{K} = \{0.1, 0.7, 4\}$ years, and boundary knots at 0 and 5.42 years (95-th percentile of the observed follow-up times). This specification allows fitting the $\log_2(\text{PSA} + 1)$ levels in a piecewise manner for each patient separately. The internal and boundary knots specify the different time periods (analogously pieces) of this piecewise nonlinear curve. ...

   Formula 6 on page 12 could also benefit casual readers with a little hand holding:

$$
\begin{aligned}
\mathrm{F}_1(t,s,\kappa) &= 2\frac{\mathrm{TPR}(t,s,\kappa)\ \mathrm{PPV}(t,s,\kappa)}{\mathrm{TPR}(t,s,\kappa)+\mathrm{PPV}(t,s,\kappa)},\\
\mathrm{TPR}(t,s,\kappa) &= \Pr\big\{R_j(s\mid t)>\kappa \mid t<T_j^*\le s\big\},\\
\mathrm{PPV}(t,s,\kappa) &= \Pr\big\{t<T_j^*\le s \mid R_j(s\mid t)>\kappa\big\},
\end{aligned}
\tag{1}
$$

where, $\mathrm{TPR}(t,s,\kappa)$ and $\mathrm{PPV}(t,s,\kappa)$ are the time dependent true positive rate and positive predictive value, respectively. These values are unique for each combination of the time period $(t,s]$ and the risk threshold κ that is used to discriminate between the patients whose cancer progresses in this time period versus the patients whose cancer does not progress. The same holds true for the resulting F_1 score denoted by $\mathrm{F}_1(t,s,\kappa)$. The F_1 score ranges between 0 and 1, where a value equal to 1 indicates perfect TPR and PPV. Thus the highest F_1 score is desired in each time period $(t,s]$. This can be achieved by choosing a risk threshold κ which maximizes $\mathrm{F}_1(t,s,\kappa)$. That is, during a patient's visit at time s, given that his latest biopsy was at time t, the visit-specific risk threshold to decide a biopsy is given by $\kappa = \arg\max_\kappa \mathrm{F}_1(t,s,\kappa)$. ...

Authors should state why they chose to center age at the value of 70:

... Age_i is the age of the i-th patient at the time of inclusion in AS. We have centered the Age variable around the median age of 70 years for better convergence during parameter estimation...

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