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May 23, 2018

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Dear Professor Daniels,

We are writing to you with respect to the manuscript #BIOM2017609M, titled "Personalized Schedules for Surveillance of Low-Risk Prostate Cancer Patients" submitted to *Biometrics* 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 several changes in the revised version of the manuscript. In particular, we updated the joint model fitted to the PRIAS dataset to account for heavy tailed negative residuals evident in the quantile-quantile plot. To this end, we transformed the longitudinal outcome using a $\log_2(\text{PSA}+1)$ transformation instead of the original $\log_2 \text{PSA}$ transformation. We have updated the captions of figures and tables to make them more informative. We have also uploaded the R code with example data in a zip file, and moved the Supplementary Materials section to be the last numbered section before Acknowledgments. The previous version was 20.4 pages long and you have asked us to reduce that to 20 pages (including the body of manuscript, acknowledgments, and references). While we have included new pieces of information according to the suggestions of the reviewers, we have managed to reduce the length of the paper to 20.4 pages. We hope that this is acceptable. Please find enclosed a detailed point-by-point response to the Reviewers' comments.

Yours sincerely,

the Authors

Response to 2nd Referee's Comments

We would like to thank the Referee for his/her 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 Sections 5 and 6, Web Appendix A.2, C and D. In addition, changes regarding the specific comments have been made throughout the text.

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

Major Concerns Shared by the 2nd Referee

1. Heavier tailed negative residuals in the quantile-quantile plot.

   We would like to thank the Referee for motivating us to check the model fit. As the Referee noted, the quantile-quantile plot for the residuals from the original model (left panel of Figure) shows heavy tailed negative residuals. Following the suggestion of the Referee we transformed the longitudinal outcome using a $\log_2(\text{PSA} + 0.1)$ transformation instead of the original $\log_2(\text{PSA})$ transformation. In addition, we also tried $\log_2(\text{PSA} + 1)$ transformation (Lin et al., 2000; Pearson et al., 1994). The resulting quantile-quantile plots of the residuals in shown in Figure 1. Since the residuals from the model with $\log_2(\text{PSA}+1)$ transformation met the assumptions best, we use it in the revised version of the manuscript. The corresponding longitudinal sub-model of the joint model we fit is given by:

$$\begin{aligned}\log_2(\text{PSA}_i + 1)(t) = \beta_0 + \beta_1(\text{Age}_i - 70) + \beta_2(\text{Age}_i - 70)^2 + \sum_{k=1}^{4} \beta_{k+2} B_k(t, \mathcal{K}) \\ + b_{i0} + b_{i1} B_7(t, 0.1) + b_{i2} B_8(t, 0.1) + \varepsilon_i(t),\end{aligned} \tag{1}$$

   where the error $\varepsilon_i(t)$ is assumed to be t-distributed with three degrees of freedom and scale σ.

Minor Concerns Shared by the 2nd Referee

1. More informative captions for Table 1 and Figure 3-5.

   We have updated the captions of Table 1 and Figure 3-5 in the revised manuscript. The revised captions along with Table/Figures are shown in Table 1 and Figure 2-4 in this reply letter.

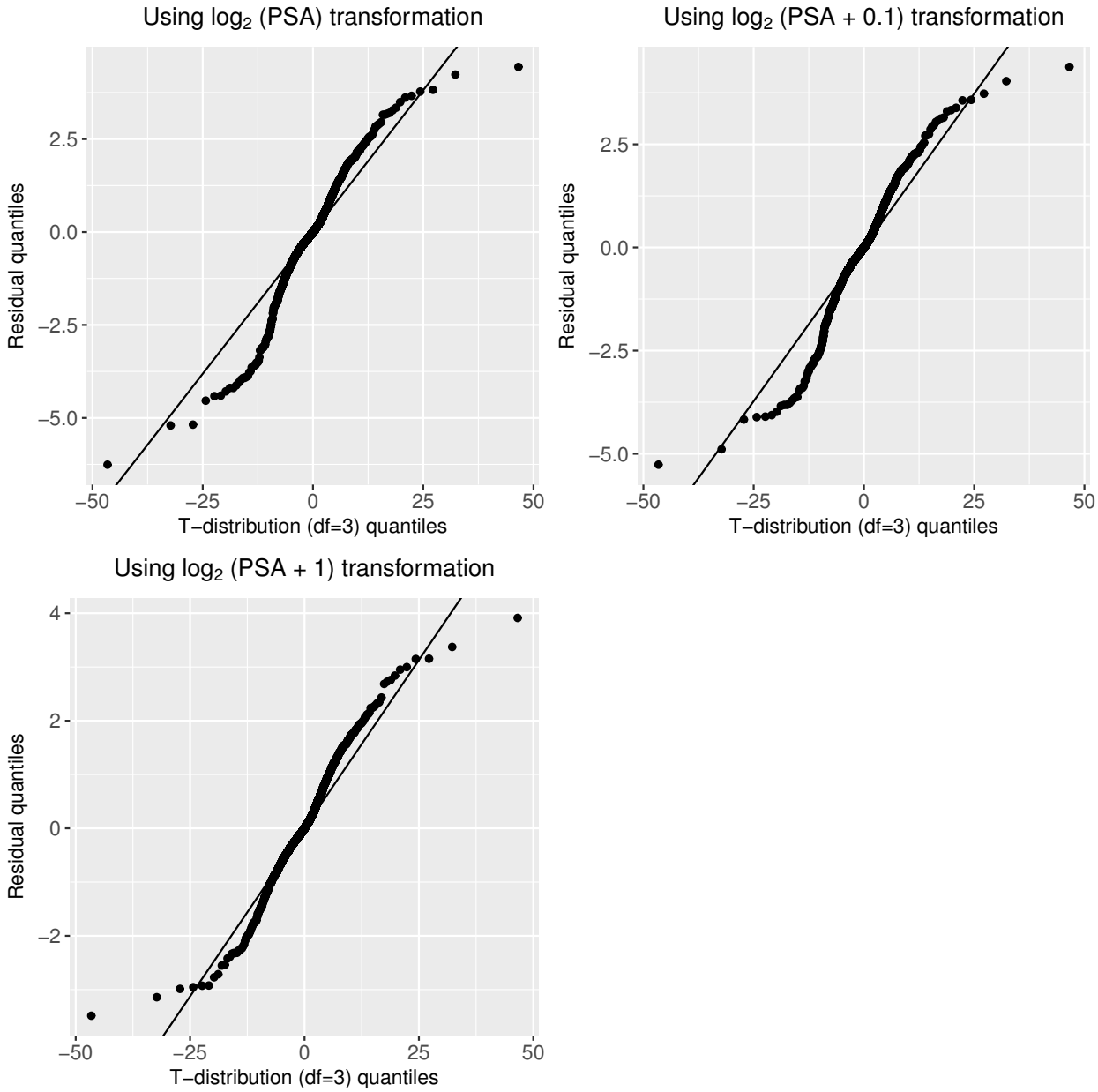

Figure 1: Quantile-quantile plots of subject specific residuals obtained from joint models with $\log_2(\text{PSA})$, $\log_2(\text{PSA}+0.1)$, and $\log_2(\text{PSA}+1)$ transformed longitudinal outcome, and an assumption of t-distributed (df=3) errors, fitted to the PRIAS data set.

2. Missing subscript i in Equation 7 of the original manuscript.

   We thank the Referee for noticing this error. Equation (1) in this reply letter shows the new

equation that we use in the revised version of the manuscript.

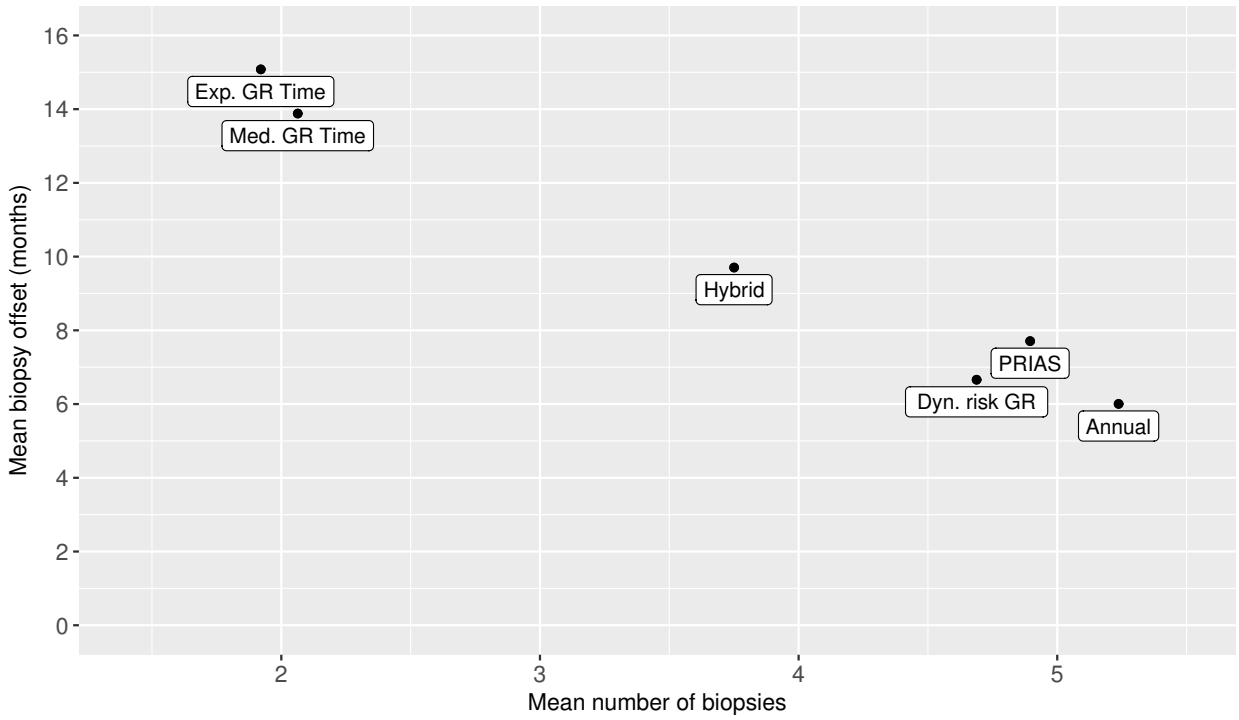

Figure 2: Estimated mean number of biopsies conducted until PCa is detected, and mean offset (difference in time at which PCa progression is detected and the true time of PCa progression, in months) for various biopsy schedules, obtained from the simulation study with 500 simulated datasets. Types of personalized schedules: expected time of GR (Exp. GR time), median time of GR (Med. GR time), schedules based on dynamic risk of GR (Dyn. risk GR), a hybrid approach between median time of GR and dynamic risk of GR (Hybrid). Annual corresponds to a schedule of yearly biopsies and PRIAS corresponds to biopsies as per PRIAS protocol.

Table 1: Estimated mean and standard deviation of the number of biopsies N_j^S conducted until PCa is detected, and offset O_j^S (difference in time at which PCa progression is detected and the true time of PCa progression, in months) for various biopsy schedules, obtained from the simulation study with 500 simulated datasets. Types of personalized schedules: expected time of GR (Exp. GR time), median time of GR (Med. GR time), schedules based on dynamic risk of GR (Dyn. risk GR), a hybrid approach between median time of GR and dynamic risk of GR (Hybrid). Annual corresponds to a schedule of yearly biopsies and PRIAS corresponds to biopsies as per PRIAS protocol. Patients in subgroup G_1 have the fastest PCa progression rate, whereas patients in subgroup G_3 have the slowest PCa progression rate.

a) All hypothetical subgroups				
Schedule	$E(N_j^S)$	$E(O_j^S)$	SD(N_j^S)	SD(O_j^S)
Annual	5.24	6.01	2.53	3.46
PRIAS	4.90	7.71	2.36	6.31
Dyn. risk GR	4.69	6.66	2.19	4.38
Hybrid	3.75	9.70	1.71	7.25
Med. GR time	2.06	13.88	1.41	11.80
Exp. GR time	1.92	15.08	1.19	12.11
b) Hypothetical subgroup G_1				
Schedule	$E(N_j^S)$	$E(O_j^S)$	SD(N_j^S)	SD(O_j^S)
Annual	4.32	6.02	3.13	3.44
PRIAS	4.07	7.44	2.88	6.11
Dyn. risk GR	3.85	6.75	2.69	4.44
Hybrid	3.25	10.25	2.16	8.07
Med. GR time	1.84	20.66	1.76	14.62
Exp. GR time	1.72	21.65	1.47	14.75
c) Hypothetical subgroup G_2				
Schedule	$E(N_j^S)$	$E(O_j^S)$	SD(N_j^S)	SD(O_j^S)
Annual	5.18	5.98	2.13	3.47
PRIAS	4.85	7.70	2.00	6.29
Dyn. risk GR	4.63	6.66	1.82	4.37
Hybrid	3.68	10.32	1.37	7.45
Med. GR time	1.89	12.33	1.16	9.44
Exp. GR time	1.77	13.54	0.98	9.83
d) Hypothetical subgroup G_3				
Schedule	$E(N_j^S)$	$E(O_j^S)$	SD(N_j^S)	SD(O_j^S)
Annual	6.20	6.02	1.76	3.46
PRIAS	5.76	7.98	1.71	6.51
Dyn. risk GR	5.58	6.58	1.56	4.33
Hybrid	4.32	8.55	1.26	5.91
Med. GR time	2.45	8.70	1.15	6.32
Exp. GR time	2.27	10.09	0.99	7.47

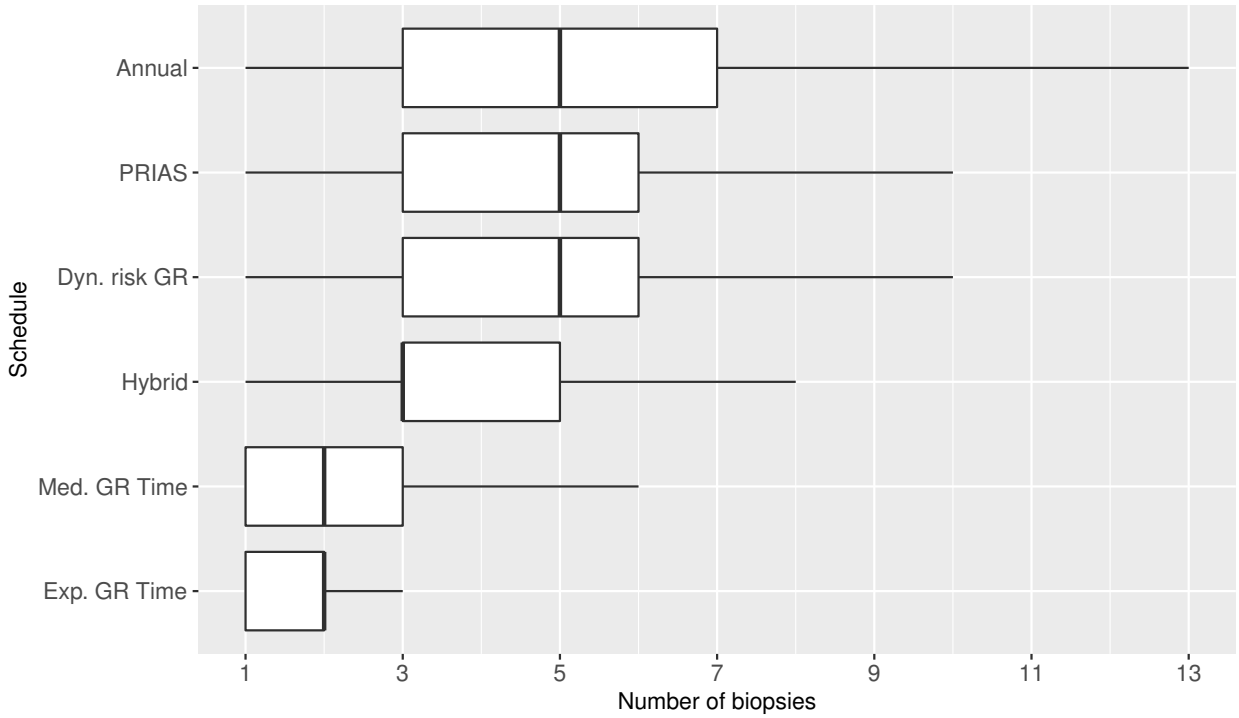

Figure 3: Boxplot showing variation in number of biopsies conducted by various biopsy schedules until PCa progression is detected, obtained from the simulation study with 500 simulated datasets. Types of personalized schedules: expected time of GR (Exp. GR time), median time of GR (Med. GR time), schedules based on dynamic risk of GR (Dyn. risk GR), a hybrid approach between median time of GR and dynamic risk of GR (Hybrid). Annual corresponds to a schedule of yearly biopsies and PRIAS corresponds to biopsies as per PRIAS protocol.

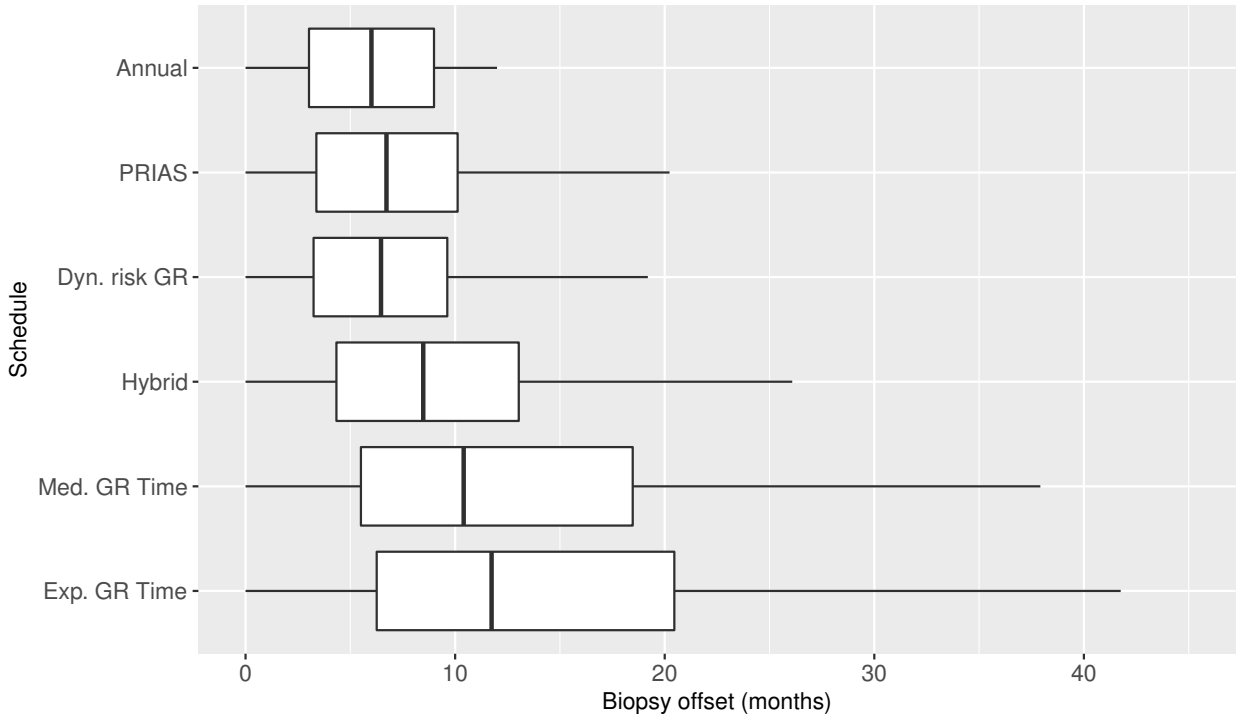

Figure 4: Boxplot showing variation in biopsy offset (difference in time at which PCa progression is detected and the true time of PCa progression, in months) for various schedules, obtained from the simulation study with 500 simulated datasets. Types of personalized schedules: expected time of GR (Exp. GR time), median time of GR (Med. GR time), schedules based on dynamic risk of GR (Dyn. risk GR), a hybrid approach between median time of GR and dynamic risk of GR (Hybrid). Annual corresponds to a schedule of yearly biopsies and PRIAS corresponds to biopsies as per PRIAS protocol.

References

Lin, Haiqun et al. (2000). "A latent class mixed model for analysing biomarker trajectories with irregularly scheduled observations". In: *Statistics in Medicine* 19.10, pp. 1303–1318.

Pearson, Jay D et al. (1994). "Mixed-effects regression models for studying the natural history of prostate disease". In: *Statistics in Medicine* 13.5-7, pp. 587–601.