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May 23, 2018

Professor Michael J. Daniels

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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:

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

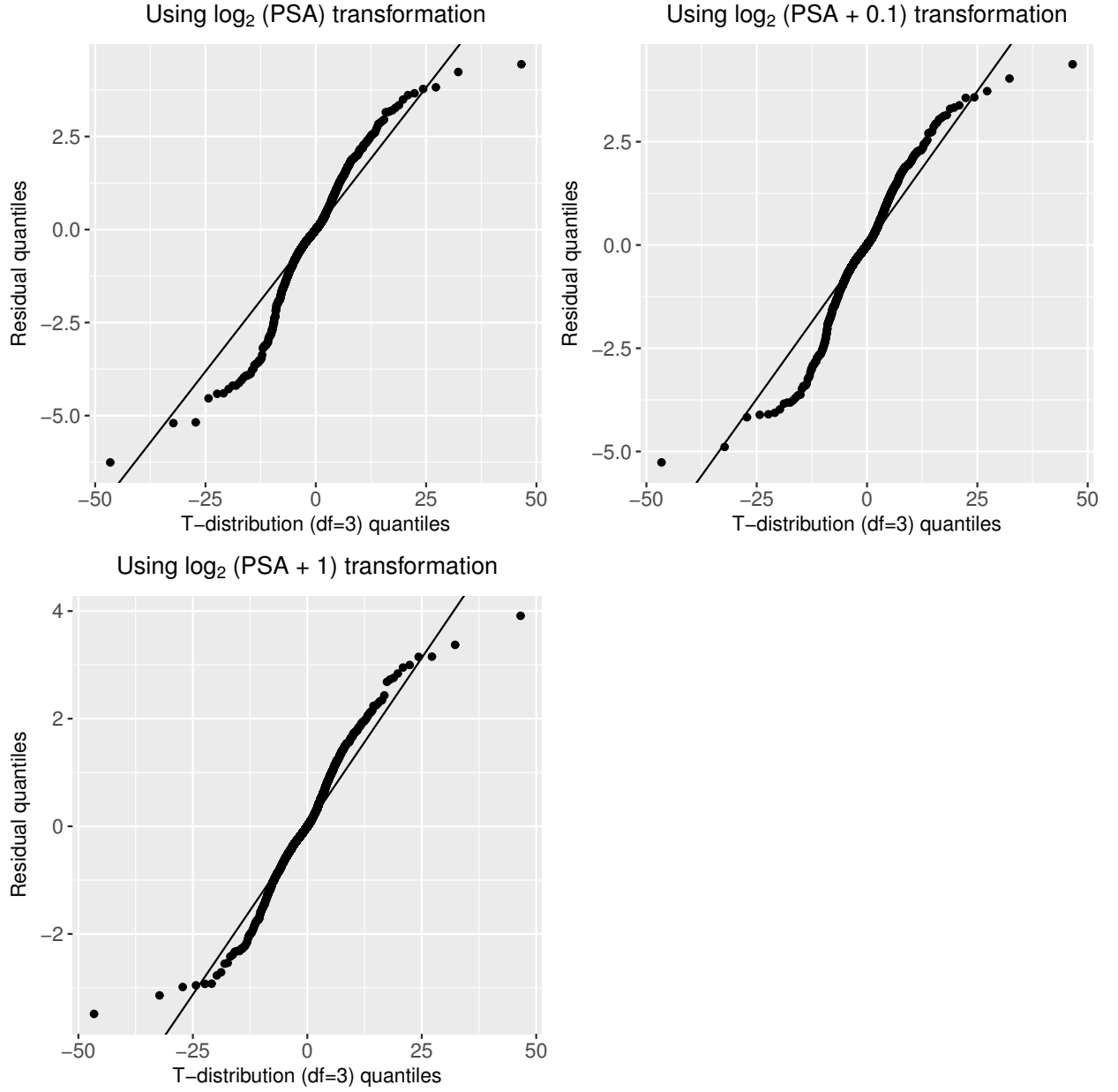   We have now updated the captions of tables and graphs in the revised manuscript. How??????

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. <u>Missing subscript i in Equation 7 of the original manuscript.</u>

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.

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.