Author’s response to reviews

Title: Benefits and Harms of Prostate Cancer Screening - Predictions of the ONCOTYROL Prostate Cancer Outcome and Policy Model

Authors:

Nikolai Mühlberger (nikolai.muehlberger@umit.at)
Kristijan Boskovic (dr.kristijanboskovic@gmail.com)
Murray D. Krahn (murray.krahn@theta.utoronto.ca)
Karen E. Bremner (karen.bremner@uhnresearch.ca)
Willi Oberaigner (willi.oberaigner@tirol-kliniken.at)
Helmut Klocker (helmut.klocker@tirol-kliniken.at)
Wolfgang Horninger (wolfgang.horninger@tirol-kliniken.at)
Gaby Sroczynski (gaby.sroczynski@umit.at)
Uwe Siebert (uwe.siebert@umit.at; public.health@umit.at)

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UMIT – University for Health Sciences, Medical Informatics and Technology
Department of Public Health, Health Services Research and Health Technology Assessment

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Benefits and Harms of Prostate Cancer Screening – Predictions of the ONCOTYROL Prostate Cancer Outcome and Policy Model

Dear Editors,

Thank you very much for considering our manuscript acceptable for publication after final revisions. We also would like to thank the additionally called in third reviewer for providing helpful comments for the improvement of our manuscript.

On behalf of all authors, I am pleased to submit a third revision of our manuscript. A detailed reply to the reviewer’s comments is provided on the following pages. Changes to the manuscript in response to reviewer’s comments are indicated in the reply as well.

We hope our revisions and answers are suited to resolve all remaining concerns.

Sincerely,

Prof. Dr. Uwe Siebert

Corresponding author:

Uwe Siebert, MD, MPH, MSc, ScD
Professor of Public Health, UMIT
Adjunct Professor of Health Policy and Management, Harvard School of Public Health
Chair, Dept. of Public Health, Health Services Research and Health Technology Assessment
UMIT - University for Health Sciences, Medical Informatics and Technology
Eduard-Wallnoefer-Zentrum 1, A-6060 Hall i.T., Austria
Tel.: +43(0)50-8648-3930, Fax: +43(0)50-8648-6739301; Email: public-health@umit.at
Response to the Reviewer’s Comments

Reviewer 3

We greatly thank this reviewer, who was not involved in the previous review rounds, for providing specific suggestions to improve the readability and focus of the manuscript. In the following we list modifications of the manuscript implemented in response to the reviewer’s comments.

Reviewer’s comment:

The authors have answered and followed most points/advises given by Dr. Etzioni. Dr. Etzioni though wrote that "Beyond this I feel that there are so many results presented that it becomes very hard to keep track. This is partly due to requests from previous reviewers for various sensitivity analyses but it also because the investigators address multiple big questions in this manuscript including how best to screen average versus high-risk strata (which then has to investigate the multiple ways in which a stratum might be higher risk), and how harm-benefit tradeoffs might be affected by triaging low-risk, screen-detected cases to active surveillance. Each of these could constitute its own manuscript. By putting them together in the same manuscript I am a little concerned that each is not getting the full attention it deserves (in fact it is hard to find the results concerning the AS impact in the tables). I would recommend moving some sensitivity analyses to an appendix (e.g. many that are in Table 3) and focus in the manuscript itself on the type of elevated risk (onset, progression, both - which could impact the optimal screening strategy) and on the active surveillance protocol. Perhaps this would make the results section a little more manageable." The authors do not seem to have answered this point.

I agree with Dr. Etzioni that the manuscript would benefit from moving some of the analysis to an appendix and focusing on their most important points. This would make the manuscript stronger and easier to read.

Response:

We fully agree with the reviewer that analyses presented in Table 3 of the previous version of the manuscript can be moved to an appendix. From our point of view this is firstly because the scenario analyses presented in the table might primarily be of interest for modeling experts, and secondly, because the table was situated in between our main result tables with base-case predictions for screening without and with active surveillance (Table 2 and previous Table 4), which may distract the readers’ focus.

In the revised version of the manuscript, we have therefore moved Table 3 to the Appendix, which is now submitted as Additional file 1. In addition to the table, the Appendix also describes methodological details and results of the scenario analyses in order to make it a concluded
section on the performed scenario analyses. As a consequence of moving the scenario analyses to an appendix, former table 4 was renumbered to table 3 in the revised version of the manuscript and the result section on scenario and sensitivity analyses (Page 15, line 12 to page 16, line 2 in the previous version of the manuscript) was modified and shortened, keeping only the essential findings of the scenario analyses in the main manuscript.

The revised passage now reads as follows:

“Results of the scenario analyses evaluating the effect of critical model assumptions on QALDs gained versus no screening are presented in the appendix [see Additional file 1].

Scenarios for screening in men with average PCa risk, which apply more favorable screening assumptions, still predict a negative benefit-harm balance, but with lower losses in QALE. Scenarios for screening in men with familial predisposition, applying more favorable screening assumptions, consistently yield higher gains in QALE except for one-time screening at age 69.

Scenario analyses investigating the effect of familial risk assumptions yield contrary results. When familial risk increases only PCa onset, the benefit-harm balance for men with familial predisposition becomes negative, whereas when only PCa progression is increased, the net benefit of screening considerably exceeds our base-case prediction.”

(Page 15, line 12 – 22)

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