Author's response to reviews

Title: Effects of increasing the PSA cutoff to perform additional biomarker tests before prostate biopsy.

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Author’s response to reviews:

Reply to the reviewers

General comment:

We are grateful for the effort the reviewers and editors have put into reading and commenting on our suggested manuscript. We have addressed each raised point specifically below and adjusted the manuscript accordingly. Further, we have reformatted the abstract as research article and added declarations in line with the editors suggestion. We believe this has improved the text substantially.

Specific comments:

Reviewer #1:
I very much favor the concept you are proposing as I was the second author on the Crawford paper you have referenced. If we can decrease the number of biopsies and unnecessary surgeries by evaluating the abnormal PSA with a biomarker first we will have achieved a great deal. We have debated the 1.5 cutoff for some time. I published a paper in December of 2015 in the International Journal of Clinical Practice (for disclosure, I am the Urology editor) explaining why that number was chosen. Briefly, it was because that appears from the literature to be the point that cancer risk starts to rise. For all the reasons I published, I believe you are on the right track. In addition, only about 25 - 30% of men have that level or higher.

I had only minimal concerns for your article.

Author comment:
We are grateful for this comment which encourage our work. We wholeheartedly agree that risk stratification for prostate cancer needs to be improved. We find the strategy of sequential testing using cheap tests with high negative predictive value first (e.g. PSA with a reasonably low cut-off) and more expensive tests (e.g. S3M, 4K, PHI etc) with better overall predictive properties only in men with increased risk as predicted by the first test very attractive.

Why did you automatically biopsy everyone with a PSA of 3?

Author comment:

The authors are somewhat unsure of the interpretation of this question. In the STHLM3 main study (REF #3), by design, men with either PSA>3 or STHLM3 test >10% had a biopsy. With this follows that biopsy data was complete for men with PSA>3. In men with PSA 1-3, only those with S3M test >10% had a biopsy. To account for this, we performed the Bernoulli experiment (REF 5). This has been demonstrated in previous publications.

For the calculation of e.g. Table 1 however, only men with elevated S3M is included - as stated in the legend. Followingly, men with low S3M test result are excluded from the analysis independent of PSA result.

We clarify this in methods, line 107. “For this analysis we included 3,133 men in the STHLM3 validation cohort with biopsy data and a S3M test ≥10%.”

For this analysis, we believe another reasonable question might also be why we did not also biopsy men with lower PSA in order to better assess the true prevalence of prostate cancer among the entire cohort. However, it would be ethically challenging to perform prostate biopsies also in men with low risk of significant disease.

Do you have data on the biomarker score on patients with a PSA of 3 or above?

Author comment: Yes, we do. We do however believe this calculation is out of the scope of this manuscript. Please refer to Ref 3 and future publications for this.

In the methods portion I would like a deeper explanation of the biomarker. How to get it, and what level denotes risk?

Author comment: We thank the reviewer for this. To clarify this matter, we have added:

“The S3M test is a blood test based on a model including a combination of plasma protein biomarkers (PSA, free PSA, intact PSA, hK2, MSMB, MIC1), genetic polymorphisms (232 SNPs), and clinical variables (age, family, history, previous prostate biopsy, prostate exam). The test gives a prediction on the individual risk of finding Gleason Score ≥7 on prostate biopsies, where ≥10% risk was considered increased risk in the main study. As shown, the exact cut-off used can be chosen to fit different individuals and healthcare systems [5]. As for September 2017, the S3M test is clinically available for analysis at Karolinska University Laboratory, Stockholm, Sweden.”
What were the reasons for not getting a biopsy on a patient with an abnormal S3M?

Author comment: As stated in line 101-103, all men with S3M test indicating ≥10% risk of prostate cancer was recommended a biopsy. For ethical reasons, among men with lower S3M test, only men with PSA >3 was recommended a biopsy.

For clarification we added: “65.0% of participants with high risk followed the recommendation to undergo prostate biopsy during the main study period. For this analysis we included 3,133 men with biopsy data and a S3M test ≥10%.” Row 106-7.

I would like to see more data on the S3M numbers in a table?

Author comment: We agree that the cohort description could be improved. We have added a Table for cohort description (Table 2).

Doesn’t a higher number denote a higher risk of Gleason 7 and higher prostate cancer?

The S3M test estimates the risk of finding a Gleason Score ≥7 cancer at biopsy. For clarity, this information is added, see above.

Reviewer #2:

I thank the authors for a concise report on the "revising" of PSA threshold for high grade prostate cancer detection and its influence on need on extra biopsies and possible considerations on missing significant cancers.

I have few general, more editorial observations:

The abstract is not fully build as stated in the BMC Urology Guidelines:

The abstract should include the following separate sections:

* Background: the context and purpose of the study
* Methods: how the study was performed and statistical tests used
* Results: the main findings
* Conclusions: brief summary and potential implications
* Trial registration

Author comment: The authors acknowledge this. While the manuscript category was changed, we have re-formatted the abstract to follow journal guidelines.
According to the author guidelines, data availability should be stated in the manuscript along with any conditions for access.

Author comment: The authors acknowledge this. A section on Data Availability has been added.

Authors' contributions are missing

Author comment: The authors acknowledge this. A section on Author Contributions has been added.

In addition to the above, I have a few specific recommendations for revisions:

rows 48-49: Something missing in the sentence "Prostate cancer detection rates and proportion saved biopsies using a priori chosen PSA cutoffs"

Author comment: We agree that this sentence is hard to interpret. We have changed it to “Logistic regression models were used to calculate prostate cancer detection rates and proportion saved biopsies.” Row 45.

rows 93-95: What is the basis for the expected 10% risk of having "high risk" Prostate cancer (GS7 or higher) reflected as PSA 3 or more? Add reference for this

Author comment: The authors believe this is important for understanding the STHLM3 study concept. Therefore, we added: “The 10% risk cut-off was chosen while it represent equal sensitivity to detect Gleason Score ≥7 cancer as PSA=3ng/ml, used in major screening studies[5].” Row 97.

rows 107-110: The sentence discussing ERSPC threshold of 3.0 refers to the above text in Methods section and should be transferred there.

Author comment: The authors believe the text would be less easy to understand if transferring the section on the a priori chosen PSA cut-off levels upwards. We have made no change, but if the editor believes it to be indicated, we are happy to change this.

The age range of men in STHLM3 study is fairly wide, 50-69 years. Author comment: The authors do not show the influence of age in finding high risk disease either by PSA criteria or S3M criteria. Would there be differences in men below age of 60 vs. older than 60 in setting the PSA threshold to 1.5 ng/ml?

This is a valid question. In the STHLM3 algorithm, underlying the test result, the patients age is included – as stated in both methods and abstract. Thereby, the effect of age on risk prediction is included in the test. No changes made.

It is fairly well known that GS 3+4 and 4+3 cancers have different survival expectation. In the study cohort, if the high-risk cancer criteria would be set to GS 4+3 or higher, only 3 PCs would be missed if increasing the PSA threshold from 1.0 to 1.5. Even elevating the PSA threshold to
2.0, only 2 more GS 4+3 PCs would be missed. The S3M cutoff to recommend biopsy would not need to be lowered? The number of additional biopsies would increase very little.

Author comment: We are grateful that the reviewer makes this interesting point. Yes, it is true that the risk profile of Gleason Score 4+3 is higher than for Gleason Score 3+4. While men with Gleason Score 3+4 tumors are widely considered having intermediate risk tumors and often are recommended curative treatment, we believe that it could put patients at un-necessary risk if allowing to decrease the sensitivity to detect less Gleason Score 3+4 tumors. However, we have added text to high-light the effect of choosing Gleason Score 4+3 as main endpoint.

Row 131: “A small number of Gleason Score ≥4+3 were detected in low PSA ranges (Table 1). If choosing PSA 2 ng/ml for threshold to perform S3M testing, only 1.0% (3/197) of Gleason Score ≥4+3 cancers would be undetected, but missing also 3.8% (18/472) of Gleason Score 3+4 cancers. Available number of higher-grade cases were to small in low PSA ranges for additional analyses such as in Figure 1 on this endpoint.”

IS there enough statistical power to show the significance of perhaps elevating the PSA threshold to 2.0? How many additional biopsies would then be necessary if the true high grade PC would be considered as GS 4+3 (more contemporary concept than for example the GS7 of Thompson et al 2004)? The authors should report and discuss this.

Author comment: Due to the limited numbers of Gleason Score ≥4+3 cancers listed in Table 1, it is not possible to give the corresponding prediction in Figure 1 for higher-grade endpoints. The general effects of only increasing the PSA threshold without tuning the S3M cutoff is given in Table 1. As above, we argue that it is risky to delay detection of all Gleason Score ≥7 tumors, while there is some evidence of a curative benefit for these men. We refer to the added text-line above.