Reviewer's report

Title: Improving Prostate Cancer Detection in Veterans through the Development of a Clinical Decision Rule for Prostate Biopsy

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Reviewer: Cesar E Ercole

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General Comment

Thank you for the opportunity to review this manuscript. The question of when to do a prostate biopsy on a patient is a great one, and the effort to try to make the decision with the assistance of readily available biomarkers is commendable. All efforts should be made to make it applicable to the current state of care. This manuscript attempts to provide a clinical decision rule to help make the recommendation to get a biopsy one that is more patient-appropriate and to ensure that resources are used properly. The rule incorporates some patient demographics along with PSA, Hgb, RBC count, and Cr (readily available biomarkers) showing a correlation with high-grade tumors, and does not take into account more typical variables that are PSA related: percent-free PSA, PSA velocity, PSA density, because of “lack of universal acceptance,” per manuscript.

Minor Essential Revisions

1. In the first sentence of the abstract the acronym for the proposed rule is used “HCDR”, the H is not defined.

2. In the first paragraph of the Materials and Methods section, in the sentence that reads “Patients with history of prior genital urgency malignancy…” should probably read “Patients with history of prior genital urinary malignancy....”

3. In the Discussion section, the sentence that starts with “If one were to apply the HDCR....” the word verses is used instead of versus.

Discretionary Revisions

1. The last sentence of the “Materials and Methods: Population, Inclusion/Exclusion Criteria, and Data Sources” states approval from the University of South Florida IRB, although it may be implied, since the patient population is from the VA system, consider mentioning that the VA IRB also approved this study.

Major Compulsory Revisions

1. There is no discussion of patient's life expectancy. The discussion of prostate cancer screening or early detection starts at determining the patient’s life expectancy and comorbidities. In the second case example, it uses a 75 year old
male, prostate cancer screening for this male would not be recommended unless the patient in the scenario has a family history of longevity. The discussion of prostate cancer screening with a PSA at age 75 is not routinely recommended. Are you recommending this rule be used with any patient regardless of age?

2. By definition the clinical diagnosis of higher stage cancers (Stage II, III, and IV) is not done by PSA tests. These are cancers that are noted on abnormal digital rectal exams (DRE). The combination of an abnormal DRE and elevated PSA are what make that patient’s clinical picture more suspicious for higher stage cancers. It would be very concerning if a patient would not be advised to get a biopsy, if the rule does not recommend one within this context. Although the rule may provide support for pathologic high-grade cancer, the importance of a physical exam should be highlighted.

3. The PSA level cut-off is too high. More recently, physicians and advisory panels, including the NCCN Guidelines for Prostate Cancer Early Detection, have recommended using as low as 2.5 ng/dL as the cut-off for recommending a biopsy, and discuss the distinction between men with PSA level #1 and >1 ng/dL for early detection. Some even take it further to say that there is no true safe cut-off to rule out high-grade cancers. Studies have shown that the risk of having high-grade disease has been the same for men with a PSA >4 ng/dL as those with a PSA 2.5 - 4 ng/dL. By using the cut-off of 4 ng/dL, this leaves out a patient population that as stated in the manuscript, is not routinely recommended for biopsy, and therefore most at risk of not having a high-grade cancer detected—potentially at a more treatable stage. Evaluation of this patient population would add strength to this rule as a PSA augmentation strategy and help in the decision to recommend a biopsy for the patient.

4. There is mention of a “profound” decrease in cost for the VA if this rule would have been used, it would be interesting to see a cost analysis and some numbers associated with this claim. Either for the cost of the biopsy (materials to processing) or number of patients that required more care than usual based on complications from the biopsies, such as, hematuria, infection/sepsis, hospital admission, ER visits, and/or retention, to mention a few.

5. The biopsies were classified as with prostate cancer (PC) or non-PC (PIN, BPH, or prostatitis), how were the biopsies with atypical small acinar proliferation (ASAP) classified? Where some of the 352 “repeat biopsies” those that were triggered by ASAP, and if so, it would be interesting to see how applicable the rule is with this population. Also, is the rule limited to first time biopsies? Because the discussion of a repeat biopsy is just as important. Especially, if the patient has a normal DRE and his PSA continues to rise in light of previous negative biopsies and no other triggers for PSA elevation.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.