Dear Editor,

The 2019 European guidelines for prostate cancer recommend that biopsy be omitted when multiparametric MRI of the prostate shows no significant (Prostate Imaging Reporting and Data System [PI-RADS] score ≤2) lesions and clinical suspicion of prostate cancer is low; however, it remains unclear how to define 'low clinical suspicion' and one might assume, that clinical suspicion is usually more than low if a costly investigation such as MRI is ordered. The attempt to establish specific parameters in the post-MRI setting addressing this matter is therefore inevitable. In pooled studies on biopsy-naive patients and patients with prior negative biopsies, it was observed that a Likert/PI-RADS threshold of ≥3 would have missed 11% (95% CI 6–18) of all detected International Society of Urological Pathology (ISUP) grade >2 cancers [1]. In the context of false-negative rates of up to 50% for random systematic biopsies in the pre-MRI era, this missed rate may not sound alarming; however, MRI-invisible prostate cancer (any grade group detected by systematic biopsy) is a frequent clinical finding and its frequency strongly depends on the radiologist’s experience, biopsy indication and technique (number of cores). Although a negative MRI is a reassuring result, it poses a challenge for urologists and patients regarding how to proceed. Some research groups have tried to address this issue, but most reports are based on small cohorts because a ‘biopsy-all’ strategy is no longer the standard of care at most academic centres. While multiparametric prediction models need local recalibration and therefore are often not a practical approach in a clinical setting, PSA density (PSAD) as a single variable has been proposed as a robust and simple predictive tool with which to perform a post-MRI risk assessment [2]. These reports all propose PSAD thresholds based on individual

Fig. 1 For any given PSA density (PSAD) threshold (horizontal axis, logarithmic scale) used to select men for further prostate biopsy, the figure shows the proportion (vertical axis) of: (i) men whose International Society of Urological Pathology (ISUP) grade 1 prostate cancer would go undetected (red line, denominator = 89); (ii) men whose ISUP grade 2–5 prostate cancer would be missed (black line, denominator = 33) with 95% CI (black dotted lines), and (iii) saved biopsies (grey line, denominator = 462). The denominator used to calculate those proportions (0–1) depends on the graph considered (red, black, grey line) and is reported in parentheses (as denominator – x). The yellow line represents the detection rate (vertical axis) of ISUP grade 2–5 cancers, i.e. the proportion of detected ISUP 2–5 grade cancers, in those men selected for further biopsy for any given PSAD threshold. Lower section: overview of the distribution of PSAD in the investigated population. PSAD could not be calculated for four patients. csPCa, clinically significant prostate cancer (ISUP grade 2–5); nsPCa, non-significant prostate cancer (ISUP grade 1).
interpretations of what is an acceptable missed cancer rate. This has resulted in the suggested selection of MRI-negative men for biopsy if PSAD exceeds thresholds of between 0.1 and 0.15 ng/mL\(^2\) [3-5]. Since there is a wide range of concerns among clinicians regarding the management of these men, presentation of the PSAD behaviour in men with negative MRI results that is fully open to different interpretations seems to be a reasonable approach.

We performed an analysis of Scandinavian men from multiple sites referred for prostate cancer diagnostic evaluation. A total of 467 men with no significant lesions on pre-biopsy MRI were included (103 from the prospective, multicentre Stockholm3 phase 1 study [6] and 364 consecutive patients from Stavanger, Norway). All men underwent a biparametric MRI without dynamic contrast. Scans were reported according to the modified PI-RADS (i.e. according to the PI-RADS v2 guidelines, but with the modification that a PI-RADS 3 lesion in the peripheral zone may not be upgraded to PI-RADS 4), and a PI-RADS grade \(\leq 2\) defined no significant lesions. Participants subsequently underwent a transrectal 12-core systematic biopsy. Prostate volume was measured by MRI \((0.52\times h\times w\times l)\) for PSAD calculation.

The mean (sd) age was 68 (6.6) years and the mean (sd) PSA value was 6.3 (5.4) ng/mL. The prevalence of ISUP grade group 1, \(\geq 2\), \(\geq 3\) and \(\geq 4\) prostate cancer in this MRI-negative cohort was 19.1\% \((n = 89)\), 7.1\% \((n = 33)\), 2.6\% \((n = 12)\) and 0.9\% \((n = 4)\), respectively. The negative predictive value for detection of ISUP grade group \(\geq 2\) was 93\% (33/467). Using R statistical software v.3.5.3 (R Foundation for Statistical Computing, Vienna, Austria), we plotted cancer detection, proportion of saved biopsies and cancer risk in the biopsied population according to a range of PSAD thresholds (Fig. 1).

With this analysis, we describe the potential clinical consequences of using PSAD to select men without significant MRI lesions for prostate biopsy. Our findings are in line with the findings reported by Distler et al. [4] and Washino et al. [5], but provide a greater level of detail for the entire range of relevant PSAD thresholds. Depending on the priorities and concerns of urologists and patients, one can focus on the appropriate graph: the black line, if a missed ISUP grade 2–5 cancer poses a major concern, the red line if overdetection is a major issue, and the yellow line for policy-makers to achieve the desired detection rate in the population addressed by their guideline. Some urologists perform whole-gland treatment in patients with ISUP grade 1 cancer and therefore would strongly recommend systematic biopsies in the context of a negative MRI down to a PSAD of 0.05 ng/mL\(^2\), where others would argue for using a higher threshold for omitting biopsies and thus accept a 7% missed rate for ISUP grade \(\geq 2\) by referring to the results of the PROTECT trial [7]. However, our data show that a proportion of patients without MRI-visible lesions can be identified as having a non-negligible risk of significant disease, supporting performing prostate biopsies in such men. This is further supported by European Association of Urology guidelines, which recommend a shared decision-making approach.

In conclusion, some men without significant MRI lesions have an elevated risk of significant prostate cancer and might be identified using PSAD. The chosen PSAD threshold affects cancer (over) detection, cancer risk in the biopsied population and the number of performed biopsy procedures.

**Conflict of Interest**

None declared.

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