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Letter to the Editor

Reply by authors: Reducing unnecessary biopsies while detecting clinically significant prostate cancer including cribriform growth with the ERSPC Rotterdam risk calculator and 4Kscore

We thank Benson et al. for their interest in our paper. Although the European Randomized Study of Screening for Prostate Cancer was initiated more than 2 decades ago, consists predominantly of Caucasians, and sextant biopsies were applied it has been shown multiple times that both the Rotterdam Prostate Cancer Risk Calculator (RPCRC) and 4Kscore derived from this data performs well in contemporary settings [1,2]. We agree with the reviewer that a 12-core biopsy with inclusion of target MRI biopsies would be preferable. However, as far as we know there is no cohort available which has the advantages of a being a true population-based screening cohort, has measured the 4Kscore and has the availability on a pathologic evaluation with the latest cribriform findings. As this cohort was used for the development of both the RPCRC and the 4Kscore, we believe this dataset provides the most fair comparison. Moreover, its population-based nature and the fact that men were systematically biopsied based on a fixed screening protocol (PSA $\geq$ 3.0 n/ml) avoiding selection bias (i.e., urologists decide who and when to biopsy) is a benefit in the assessment of the value of different risk prediction tools.

The RPCRC uses prostate volume to predict clinical significant prostate cancer and can be measured with transrectal ultrasound or digital rectal examination. As the digital rectal examination estimated volume in the European Randomized Study of Screening for Prostate Cancer cohort was not available, the transrectal ultrasound measured prostate volume was categorized. This categorization step has been externally validated and showed substantial agreement in prostate volume measurements and had limited impact on the performance of the RPCRC [3]. The relation of PSA density with biopsy outcome is strong. This is supported by the fact that other recently developed nomograms including genetic markers also include prostate volume as an important contributor to the discriminative ability of their models [4,5].

Benson et al. stated that no calibration plots were provided with our analyses. However, the calibration plots are displayed in the supplement of the manuscript, displaying the probability of high-grade disease (ISUP grade 2 with cribriform growth and all ISUP grade $\geq$3).

It is perhaps human nature to assume that novel (often more expensive) biomarkers or models are better than existing more simple risk prediction tools. However, in this case our study showed that both RPCRC and 4Kscore have similar predictive performance and clinical utility.

As clinicians, working in a field where there are so many commercially available biomarkers offered by companies with very active marketing strategies, it must be difficult to make a choice and in addition not to overlook cost-effectiveness. In this context we would like to refer to the remark of Dr. Zappala of May 2018 [6]. Here, Dr. Zappala, representing the company that offers the 4Kscore test in the United States urges physicians and urologists to embrace the 4Kscore Test to any patient with abnormal PSA readings. While we wholeheartedly agree with the need of reflex testing after PSA before deciding to biopsy, we would like to add that it remains crucial to keep an open mind in deciding what tests to use and to consider added value also in relation to costs.

Conflicts of interests

Monique J. Roobol served once as an expert for the European Advisory Board of OPKO health in 2015. This board was dissolved in 2016.

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