Editorial Commentary

Modifying and personalizing prostate cancer screening

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Comment on: Remmers S, Bangma CH, Godtman RA, *et al.* Relationship Between Baseline Prostate-specific Antigen on Cancer Detection and Prostate Cancer Death: Long-term Follow-up from the European Randomized Study of Screening for Prostate Cancer. Eur Urol 2023;84:503-9.

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The use of prostate-specific antigen (PSA) as a marker for prostate cancer (PCa) screening has been widely debated in literature. Some research argues that in the era of utilizing PSA as a marker for PCa, mortality rates have decreased significantly, implicating its importance in the field (1). However, opposing research indicates the use of PSA is insignificant in the overall effect on mortality, causing more secondary harmful effects than actual benefits from screening (2).

The recent publication by Remmers *et al.* aims to uncover this discrepancy. In this study, the authors evaluated more than 50,000 men between the ages of 55–69 years old who participated in the PCa screening trial—The European Randomized Study of Screening for PCa (ERSPC) (3). The authors specifically assessed the actuarial probability for PCa and for clinically significant PCa (csPCa). The authors concluded that a patient's baseline PSA level at certain age groups is associated with the risk of developing PCa. If a baseline PSA was measured <1.0 ng/mL between ages 55–69 years old, the actuarial probability of developing PCa at 16-year follow-up was shown to be 2.7% and csPCa was 1.3%. The authors stated that this was low enough to suggest no further screening is needed.

The number of men between ages 55–59 years old with a PSA <1.0 ng/mL was 12,825 (50%). For men between the ages of 60–64 years old, 6,579 men (39%) were found to have a PSA <1.0 ng/mL. A total of 4,209 men (33%) between the ages of 65–69 years old were found to have a PSA <1.0 ng/mL. The authors showed that the actuarial probabilities at 16-year follow-up of developing csPCa for these men with a PSA <1 ng/mL ranged from 1.2–1.5% [95% confidence interval (CI)] and no greater than 3% for any PCa, indicating that this PSA level is acceptable for not recommending additional screening.

Another study, the population-based cohort study conducted by Carlsson *et al.* (4), examined 1,756 men aged 60 years old participating in either the screening trial in Gothenburg or in the Malmo Preventive Project. The authors showed very similar results that for men with a PSA <1 ng/mL no further screening is recommended, while for men with a PSA >2 ng/mL, screening should continue. The results of this study are also similar with the study by Preston *et al.* showing that baseline PSA among men aged 40–59 years old could predict PCa specific mortality (5).

In the Remmers study, it was also shown that in men with a PSA <1 ng/mL who were eventually diagnosed with PCa, the median time from screening to diagnosis was 12 years while the median time from diagnosis to death was 1.7 years (3). We agree with the authors that the screening algorithm needs to be improved, and that this should not include lowering the PSA threshold for a prostate biopsy, due to obvious reasons of over diagnosis and overtreatment. Additionally, PSA levels can vary, and there is evidence that lifestyle factors such as sugar-rich diets, long-term aspirin use, and smoking can impact PSA concentrations, affecting its accuracy as a screening tool (6-8). Therefore, relying

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solely on PSA levels is probably not sufficient, and other factors should be incorporated into the screening algorithm. The contemporary screening and diagnosis protocol utilized in modern healthcare is already substantially different than the one used in this study. Currently, we are already aware that the consideration of a patient's biological rather than his chronological age is important. We also know that a man's access to healthcare, prostate volume, his race and family cancer history, are impactful as well. Lastly, the growing use of pre-biopsy prostate magnetic resonance imaging (MRI), and adoption of various molecular testing, has literally changed the game and has impacted screening (9-11). Indeed, risk-adapted screening with incorporation of prostate MRI, is more appropriate, as shown in the PROBASE trial (12).

We commend the authors for publishing this trial and understand that this is a rapidly changing field, where risk adapted PCa screening is more appropriate for going forward. Screening needs to be tailored for each patient, considering various biological, genetic, and social parameters. Additionally, it would need to incorporate anatomical-based testing such as multiparametric MRI and perhaps include molecular/genetic testing in the future, as needed.

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