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Platinum Priority – Editorial

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Personalized Prostate Cancer Screening Based on a Single Midlife Prostate-specific Antigen Measurement

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Since May, when the United States Preventive Services Task Force (USPSTF) published its final updated recommendation regarding the use of prostate-specific antigen (PSA) to screen for prostate cancer [1], the longstanding PSA debate has been reinvigorated. Some argue that PSA screening sufficiently reduces the burden of death from prostate cancer to warrant widespread implementation. Others, however, believe that the downsides of overdiagnosis and overtreatment outweigh the benefits. For men aged 55–69 yr, the USPSTF did not take sides; it recommended that the decision on whether or not to screen should be an individual one [1].

Rather than contribute another editorial deliberating the merits of PSA screening as it currently exists, we choose to ask an alternative question: how can PSA screening be improved such that the USPSTF would not have to hedge? In this issue of *European Urology*, Preston and colleagues [2] contribute data towards one possible solution: personalized PSA screening. They look at the use of a single PSA measurement in midlife to predict the risk of aggressive prostate cancer in black men (a population that is disproportionately affected by the disease). The authors suggest that such measurements can be used for risk stratification and in turn for the development of personalized screening strategies. Their results support this possibility; they find that a single PSA measurement in midlife is strongly associated with diagnosis of both total and aggressive prostate cancer. The sum of the evidence, including previous literature dealing with both black and white men, indicates that individuals with especially low PSA levels in midlife do need not to undergo screening as frequently as individuals with relatively high PSA levels.

Of course several questions remain regarding the use of midlife PSA levels in developing personalized screening strategies. One is the particular parameters of the screening program. When should the midlife PSA measurement be taken? What PSA cutoffs would dictate varying screening frequencies? What should the frequency of PSA screening be for the different risk groups? A multipronged randomized control trial would provide evidence to address these questions, but it would also be prohibitively expensive and take decades to complete. It will thus be important to leverage existing large-scale observational data from diverse, well-characterized populations to attempt to identify optimal screening parameters.

An additional question to consider is how a personalized screening program based on midlife PSA levels could be further improved. Are there other factors that could be incorporated that would make the program even more effective? Unfortunately, very few convincing risk factors for prostate cancer have been identified. Certainly age, race, and family history could be incorporated into a prediction model with midlife PSA levels, but it has already been shown that midlife PSA levels outperform both race and family history in predicting aggressive prostate cancer [3]. Perhaps a more promising avenue would be genetic adjustment of midlife PSA levels. Were it possible to differentiate individuals with a genetic predisposition to high PSA levels from individuals with high PSA levels as a result of undetected prostate cancer, then PSA testing in

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midlife would have even more predictive power. It could be yet further improved if one could adjust for the genetic determinants of benign prostatic hyperplasia (which, as the authors point out, is associated with an increase in PSA levels). Given that the genetic loci influencing PSA levels probably differ by race [4], it would also be prudent to genetically adjust PSA levels in a race-specific manner. Doing so, and considering race-specific cutoffs for risk stratification, has the potential to be a powerful tool towards determining personalized screening strategies.

That midlife PSA levels predict aggressive prostate cancer suggests that a personalized screening program based on a midlife measurement could improve on standard PSA screening. But could it improve on standard PSA screening enough to introduce a program pervasively? While the authors' findings are promising, the extent to which any personalized screening program would reduce overdiagnosis and overtreatment remains unclear. What magnitude of reduction would be sufficient for the USPSTF to revise their recommendation? Perhaps further research can help to answer the question.

Conflicts of interest: The authors have nothing to disclose.

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