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The Era of Prostate-specific Antigen-based Personalized Prostate Cancer Screening Has Only Just Begun

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Screening, in medicine, is a strategy used in a population to identify an unrecognized disease in individuals without signs or symptoms. This can include individuals with pre-symptomatic or unrecognized symptomatic disease. As such, screening tests are somewhat unique in that they are performed on persons apparently in good health. (Wikipedia)

Q2 The crux for virtually all cancer screening efforts is the need to apply the screening to the whole population at risk—which in the case of prostate cancer (PCA) is half of the world's population—and to repeat the test frequently to avoid missing the window of curability.

The three most important aims in PCA screening are (1) to limit diagnostic tests to individuals at risk, (2) to detect only PCAs that will significantly harm the individual host during his remaining lifetime, and (3) to detect such tumors within the window of curability.

Measurement of prostate-specific antigen (PSA) is a powerful tool for early PCA detection and has made PCA a prominent representative of mass screening of healthy individuals. Undoubtedly, PSA testing is a key contributor to the reduction in overall prostate cancer mortality during the past decades. However, PSA screening is still controversial because it leads to (1) a significant number of false-positive results and subsequent unnecessary biopsies and (2) detection of clinically indolent tumors and subsequent overtreatment.

In fact, studying the potential of PSA (and of other biomarkers) is heavily influenced by the slow natural history of PCA, particularly when oncologically meaningful endpoints such as metastasis and tumor-specific survival are taken into account. There are many examples of long-term randomized prospective studies that enrolled hundreds of thousands of men but were not able to unequivocally answer the initial study questions. This can be explained in part by the fact that study participants do not abide by the rules for the required long-term follow-up, particularly if the standard of care changes during this time period. PCA is thus an excellent example of a tumor type for which retrospective studies are particularly powerful. Retrospective studies are facilitated by the very high prevalence of prostate cancer, so very large cohorts of retrospective patients can be collected. Very often, significant bias can be prevented in retrospective studies as long as all relevant and possible confounder variables are thoroughly documented and available to investigators.

The Swedish register studies are a remarkable example of how excellent retrospective data can be efficiently utilized to enhance future clinical practice. Between 1974 and 1986, the Malmö Preventive Project invited all men born between 1926 and 1949 who were living in Malmö, Sweden, to undergo baseline evaluation and venipuncture. In total, 21 277 men aged 33–50 yr participated, representing 74% of the eligible population [1]. The Västerbotten Intervention Project (VIP) is an ongoing population-based cohort study initiated in 1986 in which residents of Västerbotten County, Sweden, were invited to undergo a health examination at ages 40, 50, and 60 yr, with blood drawn for cryopreservation [2]. Currently VIP represents more than 57% of the total background population. Among the participants of these studies, men who developed PCA over time were identified

and their blood that was cryopreserved for up to three decades before the last follow-up was reanalyzed for PSA and other kallikreins. Since only a negligible proportion of the participating men underwent PSA testing during this time period, the studies represent an unprecedented resource of real natural PSA history data, which cannot be obtained prospectively.

Earlier pivotal results from these large population-based Swedish register studies, initiated and lead by Hans Lilja, taught us that a single PSA measurement early in life can detect men at risk of developing metastatic PCA and that nearly half of men can be safely managed with only three PSA measurements during their lifetime [1,3]. This series of milestone studies is now successfully continued in this issue of *European Urology* by a paper presented by Stattin et al [2]. The study shows that a four-kallekrein panel provides additional discriminative power for subdivide the group of men with modestly elevated PSA, helping to further reduce the number of unnecessary biopsies [2]. These strategies may bring us several steps closer to (1) limiting screening to men at high risk, (2) diagnosing PCAs that will most likely benefit from invasive therapy, and (3) avoiding missing the window of curability.

Despite these promising data, it is obvious that even the most intelligent use of PSA (and its subforms) cannot solve the problem of overtreatment in PCA. Overtreatment is a multifactorial process, depending not only on tumor biology but also on the life expectancy of the individual patient. Stringent application of the current active surveillance criteria to all applicable patients could save a considerable proportion of men from overtreatment. In addition, it can be expected that even more men can be conservatively

managed in the future by more precise prediction of relevant tumor and host factors. Rapid progress in molecular techniques such as next-generation sequencing raises expectations that in the future we will be able not only to predict individual tumor biology more precisely but also to accurately assess individual life expectancy by identifying genomic factors predisposing to limiting conditions and perhaps even longevity. However, there is collective knowledge of hundreds of millions or even billions of single PSA values and tens of millions of individual histological biopsy results, which may impede the replacement of PSA and Gleason scores by new diagnostic approaches. This is what makes me believe that PSA and Gleason scores will continue to be important in PCA screening and therapy decision-making for a long time, and that evolving techniques will go hand in hand with PSA and Gleason scores rather than replacing them.

Conflicts of interest: The author has nothing to disclose.

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