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Improved Harm/Benefit Ratio and Cost-effectiveness of Prostate Cancer Screening Using New Technologies

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Prostate cancer screening using the prostate-specific antigen (PSA) test leads to a prostate cancer mortality reduction of approximately 20% (intention-to-treat analysis), as demonstrated by the European Randomized Study of Screening for Prostate Cancer (ERSPC) [1], or up to 40% in ideal settings for testing [2]. However, Lithuania is still the only country in Europe that has implemented some form of organized prostate cancer screening program, although in practice biopsy rates for PSA-positive men have been suboptimal [3]. The reason for this reluctance to implement prostate cancer screening in other countries is that PSA testing is accompanied by a substantial number of negative biopsies (false-positive test results) and thus overdiagnosis and overtreatment. In general, approximately 70–80% of the biopsies following a positive PSA test are negative [1] and, depending on the screening protocol, an estimated 23–42% of screening-detected cancers are overdiagnosed, since testing may advance the diagnosis by 10 yr or more [4]. Active surveillance for low-grade disease has therefore become standard practice. New screening methods, more targeted risk-adapted screening and risk calculators, and magnetic resonance imaging (MRI) and/or biomarkers used as reflex tests (after a PSA-positive result) may further help in reducing the harms of screening [5]. These tools can be used to better estimate an individual's risk of finding an aggressive tumor in the near future and therefore unnecessary tests and biopsies and possible overdiagnosis can be prevented.

In this issue of *European Urology*, a study by Hao et al [6] shows that PSA screening followed by reflex testing using the Stockholm3 test and MRI may substantially reduce the harms and costs of screening while maintaining the health benefits from early detection of prostate cancer. Long-term effects of several screening strategies were estimated in the study using a microsimulation model. Although microsimulation models are very complex and often difficult to understand, the authors have done their best to make the model transparent. The model is based on a well-validated and documented model for the USA and was carefully adapted to be specific to the Swedish population and epidemiology. The calibration and validation results have been published before and the model is provided as open source code. The authors show that prostate cancer screening every 4 yr for men between the ages of 55 and 69 4 yr using PSA and then MRI for PSA-positive men followed by a more selective biopsy strategy leads to a 9% reduction in prostate cancer mortality when the men are followed over their lifetime. However, because of the substantial number of MRI scans needed, this is still an expensive strategy (although the incremental cost-effectiveness [ICER] compared to no screening is just above €40 000). Addition of the Stockholm3 test (assumed cost per test of €251) leads to a 60% reduction in the number of MRI scans needed (assumed cost per assessment of €1357), with approximately the same reduction in prostate cancer mortality, and this strategy is cost-effective, with an ICER of €38 894 per quality-adjusted life years gained (given a threshold of €47 218, or 500 000 Swedish Krona). Therefore, the net benefit of screening can be improved when a more expensive test is added to the cheap PSA test. Using the PSA strategy there would be 684 overdiagnosed cases and 494 prostate cancer deaths prevented (1.38 overdiagnoses per prostate cancer death

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prevented). This ratio improves to 469/432 = 1.09 for the strategy using the Stockholm3 test.

In general, the difficulty in quantifying the effects of new technologies is the lack of evidence of long-term effects. It has been demonstrated, for example, that MRI followed by MRI-targeted biopsy induces a grade migration by increasing the detection of high-grade cancers [7,8]. Therefore, a Gleason 7 cancer found via MRI and targeted biopsy is likely to be smaller and of lower risk than a Gleason 7 cancer found using PSA and systematic biopsy, for example. It is not clear to what extent this will influence survival by stage, and therefore this stage migration is not modeled in the present study. In addition, the 9% reduction found in prostate cancer mortality over a lifetime seems rather low compared to the 27–64% found in similar other microsimulation studies that also used lifetime predictions [9,10], so PSA screening is likely to be even more cost-effective than reported here by Hao et al [6]. At present the Stockholm3 test is not available in all countries in Europe, and is mainly used in the Nordic countries. It is expected that its availability will be extended, since several clinical studies are ongoing in other countries.

The present analysis again suggests, among many other studies, that there are ways to implement cost-effective prostate cancer screening programs that result in much less overtreatment then when using age-based PSA screening only, a suggestion that was made decades ago when first results from the trials became apparent, provided that organizers include a specific age category, add MRI and/or other reflex strategies to reduce harms, offer and follow active surveillance guidelines, and have individuals provide detailed quantification of the pros and cons for every step in the screening, assessment, and treatment pathway. There is currently a substantial amount of opportunistic screening in most European countries, including screening of men older than 70 yr, leading to overdiagnosis. Organized screening programs at the ages that will benefit most can possibly decrease the need for opportunistic screening at the older ages at which more harms than benefits can be expected. Therefore, it is time that countries implement wise (pilot) prostate cancer screening programs, with limited screening (eg, three or four times between the ages of 55 and 69 yr) and possibly even extremely long intervals for men whose first PSA test result is below 1 ng/ml. Furthermore, cancer screening programs need an upper age limit as the chance of finding cancers with no or only a marginal increase in net benefits proportionally increases with age. The new European Association of Urology guideline, more detailed risk calculators, studies such as the one by Hao et al [6], and the planned revision of the European Commission guidelines for cancer screening might provide good opportunities to include wise but limited prostate cancer screening programs in the arsenal for cancer screening in Europe. With more than 100 000 men in Europe dying prematurely from the disease each year at present, the absolute benefits (and net benefit) could outweigh some of those for other cancer screening programs at present.

Conflicts of interest: The authors have nothing to disclose.

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