Despite the clinical availability of prostate-specific antigen (PSA) screening for nearly a quarter of a century, there are still differences of opinion as to whether such screening is worthwhile. In an attempt to directly address this controversy, early results from two large randomized trials were published in 2009 (1,2). The European Randomized Study of Screening for Prostate Cancer (ERSPC) was a combined analysis of prospective randomized European trials consisting of a total of 162 243 subjects aged 55–69 years who were screened or observed at intervals up to 4 years and recommended for biopsies when the PSA levels were elevated (primarily ≥3.0 ng/mL) (1). The Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) study enrolled 76 693 men aged 55–74 years but screened them on an annual basis and recommended biopsies for PSA levels greater than 4.0 ng/mL (2). The ERSPC study showed a 20% relative reduction in prostate cancer mortality (rate ratio = 0.80, 95% confidence interval = 0.65 to 0.98, P = .04) (1) in the screened group, whereas the PLCO study did not show any statistically significant change in prostate cancer mortality (rate ratio = 1.13, 95% confidence interval = 0.75 to 1.70) (2).

In this issue of the Journal, Zeliadt et al. (3) examine the use of PSA testing in the Veterans Health Administration system following publication of the ERSPC and PLCO studies. They found that PSA testing declined by 5.5–9.1% (2.2–3.0 absolute percentage points) depending on the age group studied. Although the results were statistically significant, they were relatively small in comparison to changes following the release of information from other large clinical trials (4). For example, prescriptions for estrogen use during the 9 months following publication of the negative results from the Women’s Health Initiative declined by 32% (4).

It should come as no surprise that the amount of change in health-care provider and patient behavior following publication of the ERSPC (1) and PLCO (2) studies was more modest than that observed following the Women’s Health Initiative (4). Overdiagnosis and overtreatment are much more common in prostate cancer screening than in screening for breast, colorectal, or cervical cancer (5). For example, nearly one-third to one-half of PSA screened patients may be overdiagnosed [ie, cancer is found in men who would not have clinical symptoms during their lifetime (6,7)], and most of these men with low-risk prostate cancer proceed to aggressive local therapy (eg, surgery or radiation) (8). The net effect is that many men (one-third to one-half of the 82 /1000 men diagnosed by screening) are needlessly treated to realize a moderate benefit (absolute decrease of 0.71 deaths/1000 men), and some may consider this degree of overtreatment too high. Others, however, have interpreted the data as more equivocal (9) and, in the case of some guidelines (10,11), even supportive of screening. When faced with data that could be interpreted as neither strongly supportive nor decidedly unfavorable, it is natural that health-care providers and their patients might not substantially alter their practices in regard to PSA screening and, therefore, the results of Zeliadt et al. (3) should not be unexpected.

The uncertainty and limitations of PSA screening have long been recognized, and the anticipated benefits, if present, have always been thought to be moderate (12,13). These assumptions have been the basis for the requirement for the large sample sizes and extended follow-up in the design of PSA screening trials such as PLCO and ERSPC (1,2). Many have tried to improve on the usefulness of PSA testing by adding other variables (eg, race, family history, or history of prostatic disease) or measures of PSA (eg, free PSA, PSA isoforms, or the rate of rise of PSA levels [PSA velocity]) into the decision-making process, but despite extensive research, no magic formula that incorporates such PSA values or calculations, along with the results of several other variables, has emerged to substantially improve the accuracy of screening. As a consequence, organizations such as the National Comprehensive Cancer Network (NCCN) have recommended that other variables and derivations of PSA testing be considered but have not provided explicit instructions on how they should actually be used (11).

Using the control arm of the Prostate Cancer Prevention Trial that randomly assigned healthy men to finasteride or placebo, Vickers et al. (14) in this issue of the Journal assessed whether information about PSA velocity (change in PSA over an 18- to 24-month period) increased the accuracy of screening when added to standard PSA values, digital rectal examination results, family history of prostate cancer, or a history of a prostate biopsy. The authors found that triggering biopsies based on the commonly recommended PSA velocity threshold of greater than 0.35 ng mL⁻¹ y⁻¹ found in several guidelines (10,11) would lead to a large number of additional biopsies, with close to one in seven men ultimately receiving a biopsy (14) compared with one in 20 men when 4.0 ng/mL is used as the cutoff (15). Because PSA velocity did not enhance outcomes or improve the detection of more aggressive cancers (14), the authors conclude that PSA velocity did not add predictive accuracy beyond PSA values alone and noted that one would be better off lowering the threshold for biopsy rather than adding PSA velocity as a criterion for biopsy (14).

So how do these two studies influence our clinical practices? PSA testing in the Veterans Health Administration system is less frequent than in the general US population (16) and may also differ in other ways compared with the general US health-care system, so we must be careful not to overgeneralize the results of Zeliadt et al. (3). Nonetheless, the data from Zeliadt et al. (3)
suggest that a possible interpretation of the results of the PLCO and ERSPC studies may be that the net results did not clearly argue for or against screening. Under these circumstances, it would be reasonable to continue to adhere to a shared decision-making model between patient and physician, as recommended by most current guidelines (10,11), when determining whether to proceed with PSA screening.

The results from Vickers et al. (10) suggest that using PSA velocity may not provide more information to either physician or patient as we try to come to a decision about interpreting the results of any screening. In addition, PSA velocity measurements take time to acquire, and recognizing that such data add relatively little information may help prevent inappropriate postponement of follow-up in affected patients. Avoiding the wait to acquire subsequent PSA values may also help reduce some of the anxiety associated with testing.

The studies by Zeliadt et al. (3) and Vickers et al. (14) help us refine and focus our clinical approach, but they also remind us that the use of PSA as a screening tool still leaves much to be desired. Indeed, after more than 20 years of PSA screening, it has been estimated that approximately 1 million men may have been unnecessarily treated for clinically insignificant prostate cancer (17). The shortcomings of PSA testing also remind us that there is still much art to the diagnosis and treatment of prostate cancer and that we, like the medieval physician Maimonides, must rely not only on our scientific skills but also on a combination of clear vision, kindness, and sympathy, as we see our patients through this often challenging disease.

References

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