PERSPECTIVE

MARCO DE SWART

Enforce the clinical guidelines

Prostate-specific antigen is not a bad test, it is just improperly applied, says **Monique Roobol**.

In developed countries, prostate cancer is the most common cancer in men (excluding non-melanoma skin cancer). In the United States alone, there will be 220,800 new cases and about 27,540 deaths from the disease in 2015 (ref. 1).

Not all prostate cancers are the same. Some cases are very aggressive, causing painful bone metastases and turning deadly, whereas others can stay dormant throughout the patient's life. This means that prostate cancer is only the second biggest cause of cancer deaths in US men, behind less-common lung cancer. So although a man's lifetime risk of being diagnosed with prostate cancer is 1 in 7, the risk of dying from prostate cancer is only 1 in 38.

A lot of prostate cancers are, therefore, overdiagnosed: they are unlikely to ever cause harm, let alone death. This overdiagnosis is initiated by the liberal application of a cheap, easy to apply and sensitive blood test: the prostate-specific antigen (PSA) test. And, crucially, that this test is given to too many men or too often, against best-practice guidelines.

To understand the current situation, it is helpful to outline the history of the test. From the mid-1980s until the early 1990s, PSA was officially used only to monitor the course of prostate cancer in men who were already diagnosed. At the time, prostate cancer was a life-threatening disease: one in every two or three patients died. In 1994, a team from Washington University School of Medicine in St Louis, Missouri, showed that adding a PSA test to a digital rectal examination increased the rate of early detection of the cancer — when the disease is confined to the prostate — by 78% (ref. 2). The same year, the US Food and Drug Administration approved this test combination to help detect cancer, and it was rapidly adopted. Physicians were able to actively seek out the disease, and it soon became clear that prostate cancer was actually very common.

These findings raised two questions. First, is it possible to reduce prostate-cancer mortality if the PSA test is introduced as a screening tool? And second, is it possible to reduce the side-effects of PSA screening, including overdiagnosis? To address these questions, two randomized trials — one in the United States[3] and one in Europe[4] — were initiated. Both trials have reported on the effect of PSA testing on prostate-cancer mortality several times over the years, and have always contradicted each other (although it is generally accepted that within the US trial contamination substantially limited researchers' ability to identify a clinically significant screening benefit). This lack of consensus and the considerable risk of overdiagnosis associated with PSA-based screening are the main reasons that screening for prostate cancer is still highly controversial, and why there are so few population-based government-initiated screening programmes.

What has become much clearer, however, is how to use the PSA test in such a way that the side effects are reduced. There are numerous papers describing how and when to use the PSA test. One of these outlined five golden rules[5]. PSA testing should not be carried out without pretest counselling and explicit consent. Do not test in circumstances where screening clearly has no benefit — if a man has an estimated life expectancy of less than 10–15 years, or if he is over 60 years old and has a PSA-level of less than 1 nanogram per millilitre. The decision to perform a prostate biopsy — the next stage in a cancer diagnosis — should be taken based on multiple parameters and not solely on the PSA level. And a diagnosis of prostate cancer should not automatically lead to treatment.

Most of these recommendations have been included in the various national or regional guidelines on prostate-cancer screening, but are not being followed. American Urological Association (AUA) guidelines published in August stated that "screening patterns have been inappropriate and require modification"[6]. The same holds for Europe, where modern screening practices go against the European Association of Urology (EAU) guidelines. Notably, the highest screening rates are seen in men aged 75 or older, and men with a PSA of less than 1 nanogram per millilitre are being tested much too frequently[7].

THE TIME HAS COME TO ACTUALLY IMPLEMENT THE EVIDENCE-BASED GUIDELINES INTO CLINICAL PRACTICE.

There are benefits to using the PSA test, including a reduction in incidence of metastatic disease[8] and in prostate-cancer mortality. But too many physicians are applying the test opportunistically and inappropriately. Doing so only highlights the much-debated drawbacks. But, when used judiciously and according to a fixed algorithm, these flaws can be avoided.

The time has come to actually implement the evidence-based guidelines into clinical practice. Medical associations should better communicate the best practice around PSA testing and strengthen the education of doctors — particularly general practitioners (GPs) who are usually the first point of contact, but are rarely up to date with the latest publications. GP requests for testing should be actively monitored to ensure the message is understood, rather than waiting for registry data to see if there has been an effect.

There is ample knowledge of how to streamline individual testing of men who have been appropriately informed. The PSA test is a key part of the urologist's toolkit. By implementing the EAU and AUA guidelines on prostate-cancer screening into clinical practice and stopping its misuse, we can prevent the loss of a screening test that has the potential to bring benefit to many men. ■

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1. American Cancer Society. *What are the Key Statistics About Prostate Cancer?* go.nature.com/lu3JwJ (ACS, 2015).
2. Catalona, W. J. *et al. J. Urol.* **151,** 1283–1290 (1994).
3. Andriole, G. L. *et al. J. Natl Cancer Inst.* **104,** 125–132 (2012).
4. Schröder, F. H. *et al. Lancet.* **384,** 2027–2035 (2014).
5. Vickers, A., Carlsson, S., Laudone, V. & Lilja, H. *Eur. Urol.* **66,** 188–190 (2014).
6. Eggener, S. E., Cifu, A. S. & Nabhan C. *J. Am. Med. Assoc.* **314,** 825–826 (2015).
7. Nordström, T. *et al. Eur. Urol.* **63,** 419–425 (2013).
8. Schröder, F. H. *et al. Eur Urol.* **62,** 745–752 (2012).