Prostate cancer screening and its effect on disease-specific mortality has been a topic of debate since the early 1990s. In 2009, after publication of the results of two large randomized prostate cancer screening trials showing contradictory results, the debate continued. Meanwhile, based on the huge amount of data from these two trials it became clear there is no one-size-fits-all for prostate cancer screening. Now, with two recent publications, the debate on whether prostate cancer screening affects mortality can finally be ended. The focus is on how to identify those men that can benefit from screening.

Keywords
Prostate cancer, screening, PSA, mortality, over diagnosis, biopsy, harm/benefit

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Corresponding Author: Monique J Roobol, Erasmus University Medical Center, Department of Urology PO Box 2040, 3000 CA Rotterdam, The Netherlands. E: m.roobol@erasmusmc.nl

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After the outcome of the trials

In daily clinical practice confusion remained and guidelines interpreted the outcome of the trials very differently, with an obvious transatlantic gap. In the US, in 2012, the US Preventative Services Task Force (USPSTF) released a so-called D recommendation against PSA-based screening for all ages. This was not followed by other US organizations, like the American Urological Association (AUA), and also not in Europe. In the US, the general consensus was that PSA screening was allowed as long as men were fully informed about the potential harms and benefits, and that men with a life expectancy <10 years should refrain from (further) testing. On paper this looks logical; however, in daily clinical practice these recommendations are not always easy to follow. For example, data appeared from countries such as the UK and Sweden revealing that men were more frequently tested at higher age, men were often not informed about being tested, and 50% of men with low PSA values (<1.0 ng/ml) were in fact retested within 3 years. While, due to the uncertainty about the effect of PSA-based screening on disease specific mortality, mass screening was discouraged, opportunistic testing was going on, and in fact perhaps causing even more harm. The Swedish arm of the ERSPC trial compared the outcome of organized screening (as was done in the intervention arm of ERSPC) with opportunistic screening (as occurred in the Swedish control arm of ERSPC), and concluded that opportunistic screening resulted in over diagnosis and subsequent over treatment, while there was no effect on the rate of metastatic disease or disease specific mortality.

The end of the debate and focus on what is important

Luckily, two recent publications put, at least in my view, an end to the discussion of whether or not PSA-based screening can save lives. The first publication appeared in the *New England Journal of Medicine* in 2016. For this study, the PSA testing rates in the control arm of the PLCO trial were re-evaluated. It transpired that the proportion of control participants who reported having undergone at least one PSA test before or during the trial, was close to 90%. This implies that the two arms of the trial were in fact, more or less, comparable with respect to the intervention being tested, and it is highly unlikely that such a set-up would be able to demonstrate any effect if present. Very recently, a manuscript using analytic and microsimulation models was published in the Annals of Internal Medicine. The authors concluded that “After differences in implementation and settings are accounted for, the ERSPC and PLCO provide compatible evidence that screening reduces prostate cancer mortality”. Finally, I truly hope the discussion on whether PSA-based screening can save lives (I believe it cant), can stop, and we can now focus on the question: who are those men that can benefit from an early detection of their prostate cancer?

This question has and still is the basis of my scientific work related to prostate cancer. So far, it has led us to important lessons with respect to PSA-based screening as I mentioned earlier. When focusing on risk stratification it is obvious that an elevated PSA level should never trigger biopsy or even imaging, such as magnetic resonance imaging (MRI). Reflex testing is the way to go. Reflex testing is using other available relevant information to assess the individual risk of having potentially life-threatening prostate cancer. Whether this should be done with the use of an additional biomarker (where we should be aware of costs), or multivariate risk prediction tools (often cheaper but perhaps less straightforward to use), is a matter of personal choice while we lack proper head-to-head comparisons. Despite this, the fact remains that it should be done. Multivariate risk prediction has the potential to save 30–50% of unnecessary prostate biopsies or MRIs.

Next to this, diagnosis should be uncoupled from treatment. While, with multivariate risk stratification, we are able to more selectively diagnose potentially life-threatening prostate cancer, over diagnosis, remains an issue. These low risk prostate cancers, often defined as T1C Gleason 6 or even Gleason 7 prostate cancers, with favorable characteristics (e.g., without cribriform growth pattern), should not be treated actively. Instead, these men should be put on active surveillance, a treatment strategy with the aim to switch to active curative treatment if progression should occur.

So, while we now know that PSA-based screening can save lives it is crucial to organize our screening efforts in such a way that we only screen those men that can benefit. My motto with respect to the PSA test is “use responsibly”; stopping PSA testing is not the way to go, but testing every man over and over again is also wrong. With the many ongoing research projects, especially in the field of omics and imaging, I am confident that we will succeed to lower the rate of men suffering and dying from the disease and at the same time avoid men suffering from an unnecessary biopsy or diagnosis.