# Screening of Prostate Cancer

5

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## Contents



**Abstract**

In this chapter we aim to give insight in the burden of prostate cancer and the effects of early detection and treatments using ample available data from cancer registries and (randomized) clinical trials. Prostate cancer is the leading cancer type in men, and it occurs mainly at age 60–80 remaining asymptomatic during lifetime in many cases. The impact of a disease determines the need and extent of screening. Large-scale population-based prostate cancer screening trials mainly aimed to demonstrate a reduction in disease-specific mortality. After two decades it became clear that disease-specific mortality could be reduced, but at considerable harms including over diagnosis and related overtreatment. Interpretation of trial data is however hampered by, e.g., prostate-specific antigen (PSA) contamination of the control group and the continuous development of new diagnostic tools and treatment options. Nowadays, prostate cancer morbidity and quality of life are at least equally important as survival. Diagnostic strategies in prostate cancer screening protocols are now directed at trying to detect higher-risk prostate cancers in a really early phase and trying to avoid detection of low-volume, low-grade cancers. The ideal test does not (yet) exist meaning that clinically insignificant tumors will still be diagnosed and significant tumors can be missed. Until more advanced markers and diagnostic tools, less invasive

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treatments, and better active surveillance strategies combined into an individually tailored algorithm demonstrate a substantially better cost-effective impact, the decision whether or not to screen remains a shared decision between men and their physicians.

## The Epidemiology of Prostate Cancer

Globally prostate cancer is the fourth most common cancer with 1.1 million men in 2012 being diagnosed. In developed countries 69.5 per 100,000 men per year were diagnosed with prostate cancer and in less developed countries 14.5 per 100,000 men (Ferlay et al. 2015). In developed countries, prostate-specific antigen (PSA)-based early detection strategies are offered more frequently and are even more frequently applied in people with higher socioeconomic status (Weber et al. 2013; Tabuchi et al. 2015; Guessous et al. 2016). Mortality rates are less variable as compared to incidence rates but are still higher in less developed countries. Mortality rates are generally high in populations of African descent and very low in Asia (Ferlay et al. 2015). As prostate cancer incidence is increasing with age, prostate cancer can be expected to be diagnosed most often in populations with high life expectancy and widely applied PSA-based screening.

Before the early 1980s, prostate cancer was only detected at an early stage by abnormal findings on rectal examination or by transurethral resection for obstructive hyperplasia. In such cases only 43% was locally confined and 25% already was distally metastasized (Johansson et al. 1989). Approximately two out of three men died of their disease (Hsing et al. 2000). In the early 1990s PSA testing became widely available, and prostate cancer could be detected in a much earlier phase. As is often the case with a screen-detected cancer, a person without having any complaints suddenly becomes a cancer patient. In the case of low-grade, low-volume prostate cancer, it is very likely that the tumor will remain asymptomatic even if it is not treated. These tumors are often referred to as clinically insignificant tumors. Criteria defining clinical significance are a primary Gleason score of less than 4 and a tumor core length of less than 6 mm as assessed in systematic TRUS or MRI-guided prostate core biopsies (Stark et al. 2009; Ahmed et al. 2011; Wolters et al. 2011). The earlier a clinically insignificant prostate cancer is detected, the longer the duration of the disease: this is called lead time (Black and Ling 1990; Bokhorst et al. 2015). PSA testing can account for at least 5 years of lead time. In a prospective aging study using a PSA cutoff of 4 ng/mL, it was found that 78% of prostate cancer patients with localized disease could have been diagnosed a median of 4.9 years earlier than their clinical diagnosis and patients with metastatic disease had elevated serum PSA levels as many as 11.2 years earlier than their clinical diagnosis (Carter et al. 1992). But even before the early days of PSA testing, it was clear that high-grade prostate cancers had an up to tenfold higher mortality rate than low-grade prostate cancers (Chodak et al. 1994). Although these tumors account for a minority of early-detected cancers, they are expected to benefit most from early detection and early treatment. Even prostate cancers diagnosed after the age of 75 tend to be later stage tumors with >50% prostate cancer-related death rates (Scosyrev et al. 2012).

Life expectancy plays a major role in choices to be made addressing diagnostics and treatments. Life expectancy has improved significantly over the last three decades. Though screening protocols tend to advice against any PSA testing when life expectancy is less than 10 years, the estimation of one's life expectancy has to take into account many factors like comorbidity, age, socioeconomic status, race, family history, dietary habits, BMI, and even geographics (De Angelis 2014). And even a favorable life expectancy can make decisions difficult: the younger of age, the lower the risk of prostate cancer, whereas the more favorable life expectancy, the higher the chance that even a very low-risk prostate cancer might become clinically relevant. The prostate cancer guideline of the NCCN (National Comprehensive Cancer Network) refers to several tools but emphasizes that for individuals it is challenging to make a good life expectancy estimate (Mohler 2017).

## The Impact of Prostate Cancer

### Life Expectancy

Screening for a disease in an early asymptomatic phase is only relevant if early detection leads to a decrease in morbidity and/or mortality in a significant number of cases: the benefit of screening. This benefit should be in balance with the harms and the costs of the tests and the strategies after diagnosis. A negative test should be reassuring enough: it cannot be accepted to miss too many potentially aggressive tumors. A positive test should in fact only detect a clinically significant tumor. Hence, the number of patients needed to test to prevent one prostate cancer death or to prevent one patient with symptomatic metastatic disease should be in balance. So far the theoretical world.

Parameters reflecting the burden of prostate cancer have changed considerably in the last 30 years. The incidence of prostate cancer has increased, diagnostic tests have improved, and treatments have been refined and became more tailored to the individual. In addition, criteria allowing for active surveillance have been standardized and applicable for a considerable part of newly diagnosed patients.

But what if local prostate cancer is not treated? It is clear that only a minority of the patients will become symptomatic and even a smaller fraction of patients will die within 10 years. But many patients will aim at a favorable perspective with a much longer life expectancy. Recently a Swedish study describing the very long-term follow-up data of patients with local disease followed expectantly demonstrated that even in low-risk tumors prostate cancer-specific survival declined between 15 and 25 years of follow-up from 81% to 31% (Popiolek et al. 2013). Again, life expectancy plays a crucial role.

In most cases curative intent must be seen as a long-term strategy and is only expected to influence overall survival in healthy men with a life expectancy of $>10$ years. New diagnostic tools are therefore aiming at the early detection of intermediate- and high-risk prostate cancers and trying not to detect low-volume low-grade cancers.

### Morbidity

Prostate cancer is characterized in most cases by a long asymptomatic phase. The long-term follow-up data of men aged 65 years or older who were SEER residents and diagnosed with stage T1–T2 prostate cancer during 1992–2009.

($N = 31{,}137$) clearly demonstrate that comorbidity and age account for a vast number of competing causes of mortality (Fig. 1) (Lu-Yao et al. 2015).

But even between the first onset of prostate cancer symptoms and cancer-specific mortality, there are often many years to come in which the patient might suffer from disease-related symptoms like skeletal-related events, anemia, hydronephrosis, and other urinary tract symptoms. Later in life most symptoms will be caused by androgen deprivation therapy and other locoregional or systemic palliative treatments. Patients with local disease can be offered treatments with curative intent. The majority of prostate cancer cases are being treated by radical prostatectomy and different modalities of radiation therapy. Minimal invasive treatments like HIFU, cryotherapy, proton therapy, photodynamic therapy, and organ-sparing focal therapies are still often considered as experimental, lacking long-term oncological results or the application is limited by availability and logistics (Porres et al. 2012; van den Bos et al. 2014). Though cardiovascular risks of anesthesia have improved, a radical prostatectomy is still considered to be major surgery with limited mortality but partly predictable morbidity (Abdollah et al. 2012; Ficarra et al. 2012a, b; Bjorklund et al. 2016). Nerve-sparing, adapted apical dissection and suturing techniques have improved but are not always possible, and preoperative information can differ from intraoperative findings and postoperative results. The better we become in predicting oncological outcomes after treatment and thus treatment necessity, the better patients can accept the functional adverse effects of treatments (Korfage et al. 2006). The better we become in predicting outcome, the better patients can deal with treatment decision and functional and oncological outcome.

While a selective diagnosis of those prostate cancers that are destined to cause harm during a

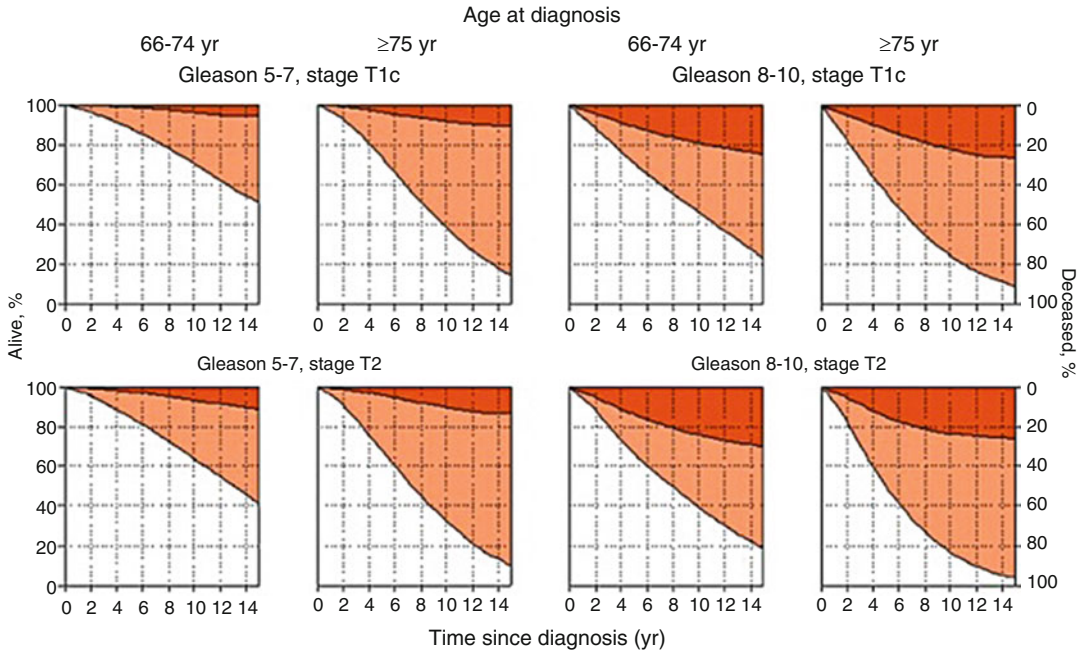


**Fig. 1** Competing risks of death by age at diagnosis, cancer stage, and grade. Dark shading indicates prostate cancer-specific mortality and light shading mortality due to competing causes; non-shaded areas represent the probability of being alive. Results for well-differentiated disease are not shown because estimates were unstable due to limited sample sizes (Re-used with permission)

man's lifetime is the way to go, this is currently not possible. This means that also prostate cancers are being detected that would never cause harm if not detected. To avoid more harm in the form of overtreatment, active surveillance is being applied. A typical active surveillance strategy implies visiting a urologist for three-monthly PSA testing, six-monthly rectal examination, and repeatedly prostate biopsies (e.g., yearly or with two-year intervals or longer). In some cases an MRI is being done potentially providing additional insight in disease progression. Independent on what is being done, each visit will cause some anxiety, although being a cancer patient these visits can also be reassuring. Even though diagnostic tools have improved, selecting the ideal candidate for active surveillance is still a challenge. In practice, 24–40% of the patients being followed by an active surveillance strategy will be treated with curative intent within 5 years after being diagnosed (Tosoian et al. 2016). The reasons can be disease reclassification and progression but also patient anxiety despite a favorable course of the disease. Some men suffer most from the suffering they fear, but might never appear. However, in an active surveillance cohort of 129 men, overall only 6 of 129 men (5%) discontinued active surveillance because of anxiety and distress (Venderbos et al. 2015).

Men with a life expectancy of >10 years and an intermediate- or high-risk prostate cancer, according to D'Amico (1998), often require a more invasive strategy in an effort to cure or postpone cancer-related morbidity. And even when treatment with curative intent is being offered, available prediction tools can be very instructive in getting a good perception of the burden and prospects of the disease. Good examples are the prostate cancer nomogram of the Memorial Sloan Kettering Center website (Center 2017) and Briganti tables (Boehm et al. 2016). Although the technique of radical prostatectomy has improved and radiation therapies have been refined, these treatments still have side effects that

have a major impact on quality of life (QoL) (Whiting et al. 2016; Venderbos 2017). Monitoring QoL remains pivotal in men with prostate cancer in order to facilitate treatment decision making (Villa et al. 2017).

Being cured from prostate cancer makes dealing with the side effects of treatments more acceptable (Korfage et al. 2007). In the case of recurrence or metastasized disease-related morbidity and treatment-related side effects may be harder to deal with. In a time where active surveillance plays an increasing role in local, low-risk disease and a time where delay of systemic treatments in asymptomatic slowly progressing disease is commonly applied, there is growing evidence that even in metastasized prostate cancer, treatment of the primary tumor can be beneficial (Culp et al. 2014), and it is also known that in metastasized prostate cancer, early ADT may offer a slightly better life expectancy. Available systemic treatments have increased and have been accepted for reimbursement. In the past 5 years, a whole range of systemic treatments (Crawford et al. 2015) has demonstrated to add significant time of disease-specific survival to metastasized castration-resistant prostate cancer patients, and results from application of docetaxel in early hormone-naïve metastasized setting have changed daily practice dramatically (Sweeney et al. 2015). Locoregional salvage therapies also promise to be able to postpone systemic treatments (Ost et al. 2016). But still, metastasized prostate cancer is generally considered incurable, and many treatments can add years of survival but potentially with a decrease in quality of life as a tradeoff. Fortunately the knowledge of how to constrain toxicity of the current palliative treatments has increased, and the benefits of treatments like pain relief, prevention of skeletal events, or alleviation of urinary obstruction are clear.

## Prostate Cancer Screening

Screening trials have been initiated in a time where TRUS-guided random, often sextant biopsies were the standard, and PSA testing was not applied as widespread as it is now. The two largest trials addressing population-based screening are the American Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial (Andriole et al. 2009) and the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial (Schroder et al. 2014). During the course of these trials, medical checkups became common practice, and more and more men and physicians became aware of the diagnostic possibilities often without fully realizing the existence of potential downsides. PSA testing and subsequent prostate biopsy and early diagnosis in men randomized to the control arm (contamination) jeopardize the power of randomized trials in showing an effect of PSA-based screening (Shoag et al. 2016a). This is clearly shown in the PLCO trial where it recently became obvious that their initial conclusion of no effect of PSA-based screening on disease-specific mortality cannot be drawn from the data available, due to a very high level of contamination in their control arm Shoag et al. (2016a, b).

It has taken the ERSPC screening trial, in which the effect of contamination was much less as compared to the PLCO, two decades to be able to get insight in the overall impact on metastatic disease and disease-specific mortality. This is as said due to the natural course of the disease, the majority of prostate cancer cases are slow growing cancers which eventually may cause harm depending on life expectancy. Despite the fact that disease-specific mortality and perhaps even more important suffering from metastatic disease is reduced by PSA-based screening, the ideal balance between the reduction of morbidity and death from the disease and the harms of screening leading to overdiagnosis and overtreatment with side effects and deterioration of quality of life has not been established. With the currently available follow-up data in the ERSPC trial, it is shown that in order to prevent one prostate cancer death, 781 men have to be screened and an additional 27 prostate cancers need to be detected as compared to a situation without screening (Schroder et al. 2014). Too many men still undergo unnecessary biopsies (with potential risks like up to 5% of septicemia) and other invasive or costly diagnostic procedures.

The increasing use of the PSA tests in the nineties and the intermediate results of the randomized trials

already showing a considerable increase in the detection of low-risk prostate cancer cases were reasons to draft guidelines on the use of PSA testing in daily clinical practice. In 2002 the follow-up time in both screening trials was still considered to be too short, and the US Preventive Services Task Force (USPSTF) could not conclude whether or not PSA-based screening on prostate cancer should be broadly implemented. In 2008 the USPSTF assigned a grade of D (recommending against screening) for men aged ≥75 years and in 2012 for men of all ages (Force 2002; Force 2008; Moyer and Force 2012). This recommendation is contrary to guidelines from urological associations worldwide that promote shared decision making. Despite the negative advice of USPSTF, data on PSA use for screening purposes from the years after 2012 show that many physicians still regularly perform PSA testing for screening purposes and many men still ask their doctor for a PSA test. Rates of PSA screening tests have declined by 3–10% in all age groups, but what could be worrying is that there are slight changes in grade and stage toward more aggressive and extensive disease which are noticeable. It is however too early to draw any conclusions on potential benefit or harm (Fleshner et al. 2017).

What is however clear is that a purely PSA-based screening approach is not the way to go. Diagnostics have improved dramatically since the last 20 years. To find an answer on the merits of population-based screening if new serum markers, urinary markers, mpMRI imaging, current ultrasound devices, and perhaps even elastometry devices or PET imaging techniques would be applied, large trials would have to be repeated in a time where it will be impossible to randomize well-informed people to a control arm. We can however still apply the data from previous trials in simulation models in order to improve available nomograms and decision aids (Bertsimas et al. 2016).

An example of further exploration on improving screening strategies is the German PROBASE study (Prospective, randomized, risk-adapted Prostate Cancer Early Detection Study Based on a "Baseline" PSA Value in Young Men) in which men (age 45 or 50) with a PSA < 1.5 ng/mL will only need to be screened again after 5 years. Only an elevated baseline PSA will lead to more frequent follow-up screening visits (Arsov et al. 2013).

Another example of risk-based prostate cancer screening is the application of the so-called STHLM3 model (a combination of clinical data, serum biomarkers, and SNPs) in the Stockholm 3 trial which leads to a reduction of the number of biopsies by 32% (95% CI 24–39) while avoiding 44% (35–54) of benign biopsies without compromising the ability to diagnose prostate cancer with a Gleason score of at least 7 (Gronberg et al. 2015). Many of these ongoing trials incorporate a wide diversity of serum markers and imaging modalities, and biobanking facilities will facilitate accelerated testing of future biomarkers in these valuable screening cohorts.

In the UK the so-called CAP study results are being awaited. Initiated in 2002 the Comparison Arm for ProtecT (CAP) cluster randomized controlled trial (RCT) evaluates prostate cancer screening effectiveness by comparing primary care centers allocated to only one round of prostate-specific antigen (PSA) testing (intervention) or standard clinical care. This will give insight in the benefits and harms of one single screening versus repeat screenings (Lane et al. 2010).

Lithuania until now is the only country that has been offering a population-based prostate cancer screening program outside a trial. Since 2006 the Early Prostate Cancer Detection Programme (EPCDP) targets men aged 50–75 years and younger men (>45 years) with a family history of prostate cancer. Their most recent analysis showed an unprecedented increase in prostate cancer incidence: more than sevenfold in two decades with mortality rates remaining relatively stable. Overdiagnosis and overtreatment are a risk, and participating men are to be just as well informed about pros and cons of PSA-based screening as any other man (Gondos et al. 2015).

## Diagnostic Tools for Early Detection: It's all About Risk Stratification

As mentioned before, since the late 1980s diagnostic tools for detection of prostate cancer have evolved thoroughly. Since the application of

prediction tools is everyday practice nowadays, it is important that these tools are continuously improved with up-to-date and externally validated information.

What we have already learned by analyzing available data has been incorporated in guidelines. It is clear that using PSA as a single parameter to calculate the chance of detecting prostate cancer is insufficient. Using PSA density by adding prostate volume accounts for a significant improvement of detection rates and avoiding unnecessary biopsies. This is shown in the analyses in Fig. 2. Based on the Rotterdam data from ERSPC initial screening round, the discrimination improves considerably when next to the PSA level additional relevant pre-biopsy information (like the outcome of DRE and volume assessment) is taken into account. Combining relevant information including prostate volume is the driving force behind the well-known and repeatedly externally validated prostate cancer risk calculator (www.prostatecancer-riskcalulator.com or in app store RPCRC).

Adding findings on rectal examination, results of and the amount of previous prostate biopsies, and previous PSA values in time and taking into account factors like age, positive family history, and Afro-American descent underline the necessity of a multivariable approach and preferably presented in a format that is readily available for clinical application.

Data on pre-biopsy mpMRI support the application of the scan after a first negative set of prostate biopsies but persisting suspicion of prostate cancer as depicted in a recent AUA (American Urological Association) and SAR (Society of Abdominal Radiology) consensus statement (Rosenkrantz et al. 2016). The primary use of mpMRI (Ahmed et al. 2017) is in theory equally attractive but needs further study,

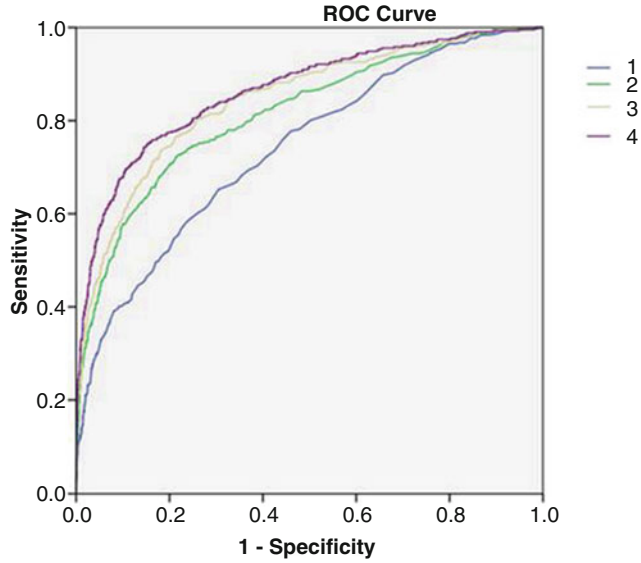


**Fig. 2** The area under the curve (AUR) in a ROC graphic is used to demonstrate the accuracy of a diagnostic test in a certain population. This figure shows the improvement of a PSA test (in a screening cohort of the Rotterdam ERSPC study in 3616 men biopsied and 885 tumors being found) by adding information about digital rectal examination (DRE) findings and transrectal ultrasound (TRUS) findings. Here the performance of the tests to detect Gleason >6 cancers is depicted. Analyses provided by Roobol

| Model # | Model description | AUC | 95% CI |
|---|---|---|---|
| 1 | PSA | 0.74 | 0.71-0.77 |
| 2 | PSA+DRE | 0.82 | 0.79-0.84 |
| 3 | PSA+DRE+DRE assessed volume | 0.85 | 0.82-0.87 |
| 4 | PSA+DRE+TRUS+TRUS assessed volume | 0.86 | 0.84-0.88 |

**Table 1** Relevant new biomarkers and an estimation of performance related to detection of Gleason ≥7 prostate cancer (Murray et al. 2016; Carlsson and Roobol 2017; Hendriks et al. 2017). From each marker an indication is given of the number of unnecessary biopsies that could be avoided ("saved") at the cost of the number of Gleason ≥7 cancers being missed ("missed"). Unfortunately, head-to head comparison of the separate markers is generally not available

| | Diagnosis of GS ≥7 PCa missed (%) | Prostate biopsies avoided (%) |
|---|---|---|
| Free PSA | 23 | 66 |
| PCA3 | 3–13 | 46 |
| PHI | 5 | 36–41 |
| 4 K panel | 1.3–4.7 | 30–58 |
| mCPCs | 6 | 54 |
| STHLM3 model | 0 | 32 |
| MiPS | 1 | 35 |
| SelectMDX | 2 | 42 |
| mpMRI-targeted prostate biopsy | 20 | 27 |
| ERSPC risk calculator 12.5% cutoff | 0 | 33 |

and cost-effectiveness analyses depend on sufficient evidence.

The PROMIS study has demonstrated the potential benefits of mpMRI in a primary diagnostic setting by comparing with template prostate mapping biopsies (Ahmed et al. 2017).

Urinary markers like PCA3 and SelectMDX also can have added value in the case of rising suspicion of prostate cancer, but the added value is modest and misses the advantage of imaging which enables localizing and taking targeted biopsies from areas of suspicion.

The list of other available biomarkers is extensive and grows almost daily. Biomarkers can be roughly subdivided in urinary and serum markers like PSA subforms and genomics or imaging modalities. There are several markers and diagnostics that are promising (Table 1) (Gaudreau et al. 2016; Loeb et al. 2016; Hendriks et al. 2017).

As an example of technical progression, the measurement of circulating tumor cells (mCPCs) is described as a very promising tool but up to now has only been tested in a limited number of men in Chile. The performance of diagnostic tests can differ considerably in different populations, and hence comparing biomarkers and other diagnostic tools should be done with caution.

In addition, an improved pathological grading system like the presence of cribriform growth patterns helps to get a better understanding of disease burden and as such aids in developing better prediction tools (Kweldam et al. 2016).

Performance of mpMRI and other individual markers has been extensively studied, but as said, head-to-head comparison of different markers on large screening cohorts has not sufficiently been done, and so far these innovations have not lead to significant changes in daily clinical practice. Although PHI, PCA3, and certainly mpMRI with targeted biopsies are very promising, a good analysis of cost-effectiveness and when and how often to apply these markers has to be performed before widespread application is justified.

The ultimate goal is a balance between not missing too many high-risk prostate cancers and avoiding unnecessary biopsies. Although imaging techniques like mpMRI improved the detection of high-grade prostate cancer, high-volume Gleason 6 prostate cancer can remain undetected. In patients with a long life expectancy, these tumors might still become clinically significant. New imaging modalities like PET imaging with PSMA or bombesin analogues may have added value in detecting the lower-grade cancers, but this is to be further explored, and until this day we need pathological confirmation by prostate biopsies. In summary, the number of tests and imaging techniques is constantly increasing and shows an increase in the potential to detect high-

grade prostate cancer. However, we must never forget cost-effectiveness and generalizability.

## When to Start and When to Stop Screening

By enriching the cohort of men being at highest risk of having high-grade disease will improve the effectiveness of a screening strategy. Risk factors like age, family history, race/ethnicity, and baseline PSA level in midlife could serve as discriminators to determine the start of screening and rescreening intervals. As prostate cancer is more prevalent at older age, the age at which to start the first prostate cancer screening test should be relatively high. But the higher the age, the higher the chance of missing the opportunity of cure in some cases. The PROBASE study (Arsov et al. 2013) aims to show that an initial screening round in men at age 45–50 could result in deferral of a second screening round by 5 years if initial PSA is $<1.5$ ug/L. In practice however, recommendations concerning when to screen and when not to may be put aside (i.e., PSA testing within the screening interval in the randomized trials or the USPSTF recommendations) by already raised awareness of doctors and first-screen participants or by practical logistics like yearly medical checkup visits for other common health issues.

And the question when to stop screening is also a difficult one. It is clear that high-grade prostate cancers have an up to tenfold higher mortality rate than low-grade prostate cancers (Chodak et al. 1994). Although these tumors account for a minority of early-detected cancers, they are expected to benefit most from early detection and early treatment. Even prostate cancers diagnosed after the age of 75 tend to be later stage tumors with $>50\%$ prostate cancer-related death rates (Scosyrev et al. 2012). Healthy men with a prosperous life expectancy might still benefit from screening at a higher age. This implies that the overall impact on quality of life and cost-effectiveness has to be taken into account (Carlsson et al. 2016). In the end we need to be able to support individual choices incorporating a reliable life expectancy estimate and risk of life threatening prostate cancer in risk calculators and web-based decision aids.

## Conclusions

Randomized controlled trials addressing the merits of population-based prostate cancer screening have shown us that the methods of screening that have been applied need improvement. Much is expected from diagnostic tools being able to detect intermediate- and high-risk prostate cancer in an early still curable way and not detecting prostate cancers that would never in a lifetime of a healthy man would cause symptoms or death. Until the discovery of a prostate cancer treatment with negligible effects on quality of life, screening strategies have to be improved in order to be applied on a population level. These RCTs have given us a huge amount of data that can help us in calculating the extent of potential diagnostic improvement. The available data showed that individual risk stratification is a definite need. Only in this way we can control harms and benefits. Individual prostate cancer screening is here to stay, recommendations on totally avoiding PSA testing for early detection have proven to be ineffective or even counter-effective, and hence it is of upmost importance to apply testing to only those who have a high likelihood of having benefit. The ongoing research on new biomarkers and their combination with clinical data in prediction models is currently the way to go. Obviously, patient wish and expectations should not be forgotten in the decision process, making the decision to screen or not to screen a well-informed individual shared decision. Every individual patient will have to make a personal choice concerning the balance of costs and benefits. And in fact, the first step of this journey starts at the moment he is not yet a prostate cancer patient, the moment he has to decide whether or not he will have his prostate cancer risk evaluated. And to this day the initiative of prostate cancer screening is in general not population based, not by invitation by a government institution, but it is mainly a personal initiative, a dilemma for men and their physicians.

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