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Brief Correspondence

Structured Population-based Prostate-specific Antigen Screening for Prostate Cancer: The European Association of Urology Position in 2019

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Abstract

Prostate cancer (PCa) is one of the first three causes of cancer mortality in Europe. Screening in asymptomatic men (aged 55–69 yr) using prostate-specific antigen (PSA) is associated with a migration toward lower staged disease and a reduction in cancer-specific mortality. By 20 yr after testing, around 100 men need to be screened to prevent one PCa death. While this ratio is smaller than for breast and colon cancer, the long natural history of PCa means many men die from other causes. As such, the nonselective use of PSA testing and radical treatments can lead to overdiagnosis and overtreatment. The European Association of Urology (EAU) supports measures to encourage appropriate PCa detection through PSA testing, while reducing overdiagnosis and overtreatment. These goals may be achieved using personalized risk-stratified approaches. For diagnosis, the greatest benefit from early detection is likely to come in men assessed using baseline PSA levels at the age of 45 yr to individualize screening intervals. Multiparametric magnetic resonance imaging as well as risk calculators based on family history, ethnicity, digital rectal examination, and prostate volume should be considered to triage the need for biopsy, thus reducing the risk of overdiagnosis. For treatment, the EAU advocates balancing patient's life expectancy and cancer's mortality risk when deciding an approach. Active surveillance is encouraged in well-informed patients with low-risk and some intermediate-risk cancers, as it decreases the risks of overtreatment without compromising oncological outcomes. Conversely, the EAU advocates radical treatment in suitable men with more aggressive PCa. Multimodal treatment should be considered in locally advanced or high-grade cancers.

Patient summary: Implementation of prostate-specific antigen (PSA)-based screening should be considered at a population level. Men at risk of prostate cancer should have a baseline PSA blood test (eg, at 45 yr). The level of this test, combined with family history, ethnicity, and other factors, can be used to determine subsequent follow-up. Magnetic resonance imaging scans and novel biomarkers should be used to determine which men need biopsy and how any cancers should be treated.

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1. Introduction

Prostate cancer (PCa) is the most common solid cancer with >450 000 new cases and is among the first three causes of cancer mortality with approximately 107 000 deaths in Europe in the year 2018 [1,2]. Multiple rounds of prostate-specific antigen (PSA) screening might allow for earlier detection of clinically significant disease, thus reducing the incidence of metastatic PCa. This, in turn, might lead to a reduction in cancer-specific mortality in the long term [3–10]. However, PSA-based screening is associated with overdiagnosis (as high as 40%; in which men would not have the potential to develop metastases during follow-up) and overtreatment (namely, the lack of benefit as well as unnecessary harms for the treatment of overdiagnosed cases) [11–14]. Given these risks, in 2012 the US Preventive Services Task Force (USPSTF) released a recommendation against nonselective PSA screening [15]. Although many urological societies disagreed with this view [16,17], the consequence of this recommendation was a reduction in the use of PSA for early detection [18]. While PCa mortality had decreased for two decades since the introduction of PSA [2], the incidence of advanced disease and, possibly, cancer-related mortality began to rise after the year 2012 [19]. For example, a decrease of 10–18% in PSA screening rates in the USA was associated with fewer new cases of PCa and fewer men receiving local treatment (from 69% to 54%) [20]. Similarly, the reduction in the use of PSA testing was associated with higher rates of advanced disease at diagnosis (eg, 6% increase in the number of patients with metastatic PCa) [21–25]. Moreover, additional evidence suggests a long-term benefit of PSA in terms of reduction of cancer-specific mortality [8,9]. At almost 20-yr follow-up, the number of patients needed to be screened and diagnosed to prevent one PCa death were 101 and 13, respectively, and is lower than the number of patients requiring breast and colon cancer screening [3,6]. Taken together, these findings led different organizations to reconsider their views on early detection (Table 1). In particular, the European Association of Urology (EAU) recommended that baseline PSA should be obtained at the age of 45–50 yr to initiate an individualized risk-adapted early detection strategy in well-informed men with life expectancy of ≥10 yr [26]. The USPSTF updated its recommendations in 2018 to allow men aged between 55 and 69 yr a choice to undergo PSA-based screening (grade C) [27]. The evidence for PSA screening is derived from trials that included upfront biopsy for all men with elevated PSA levels and did not consider multiparametric magnetic resonance imaging (mpMRI) or additional risk stratification tools. Recent changes in the diagnostic and therapeutic pathways of early PCa (such as the use of mpMRI and MRI-targeted biopsy, availability of novel biomarkers, active surveillance, and less aggressive treatments) could reduce the risks of overdiagnosis and overtreatment without compromising cure rates for aggressive cancers. This, together with long-term data supporting the benefit of PSA screening in terms of reduction in cancer-specific mortality with an acceptable number to diagnose and treat [3,6,10], has prompted the EAU to produce a position paper to support the implementation of PSA-based screening at a population level corroborated by an overview of the scientific background.

2. Impact of PSA screening on mortality

2.1. Statement

Screening based on multiple PSA testing rounds reduces PCa-specific mortality in asymptomatic men aged between 55 and 69 yr.

Table 1 – Available recommendations and guidelines on early detection of prostate cancer (PCa)

Organization	Year	Recommendation	PSA testing intervals
EAU	2018	Offer an individualized risk-adapted strategy for early detection to a well-informed man with a good performance status and life expectancy of at least 10–15 yr Stop early diagnosis of PCa based on life expectancy and PSA; men who have life expectancy of <15 yr are unlikely to benefit	Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of 2 yr for those initially at risk: PSA >1 ng/ml at 40 yr of age PSA >2 ng/ml at 60 yr of age Postpone follow-up to 8 yr in those not at risk
American Urological Association	2018	For men aged 55–69 yr, the decision to undergo PSA screening involves weighing the benefits of reducing the rate of metastatic PCa and prevention of PCa death against the known potential harms associated with screening and treatment; the Panel strongly recommends shared decision making for men aged 55–69 yr who are considering PSA screening The panel does not recommend routine PSA screening in men aged 70 + yr or any man with <10–15 yr life expectancy	To reduce the harms of screening, a routine screening interval of 2 yr or more may be preferred over annual screening in men who have participated in shared decision making and decided on screening
USPSTF	2018	For men aged 55–69 yr, the decision to undergo periodic PSA screening should be an individual one; before deciding whether to be screened, men should have an opportunity to discuss the potential benefits and harms of screening with their clinician, and to incorporate their values and preferences in the decision The USPSTF recommends against PSA-based screening for PCa in men 70 yr and older	NA

EAU = European Association of Urology; NA = not available; PSA = prostate-specific antigen; USPSTF = US Preventive Services Task Force.

2.2. Scientific background

A single PSA test is useful to stratify surveillance and subsequent risk, but is not enough to prevent PCa mortality [11]. Therefore, structured screening programs based on repeated measurements of PSA over time are needed to produce stage migration [28,29] and, in turn, reduction in risks of developing metastases and cancer-specific mortality [4,10]. Of note, screen-detected localized PCa is characterized by an excellent prognosis, where the Prostate Testing for Cancer and Treatment (ProtecT) trial demonstrated that in men with localized disease detected by PSA screening, cancer-specific survival rates exceeded 99% at 10-yr follow-up regardless of the therapeutic approach (active monitoring vs surgery vs radiotherapy) [30]. Moreover, identification of patients with more aggressive disease would increase the proportion of men eligible for curative-intent therapies such as radical prostatectomy, which are associated with a survival benefit at long-term follow-up [31].

The role of screening based on multiple PSA testing rounds has been assessed by two large prospective trials [4,10,32,33]. The European Randomised Study of Screening for Prostate Cancer (ERSPC) trial randomized 182 000 men aged 50–74 yr in eight European countries to PSA screening versus control between the years 1993 and 2003 [4,10]. The main trigger for prostate biopsy was represented by PSA levels above the cut-off of 3 ng/ml. Although compulsory criteria for participation were defined, minor variations in the screening protocol between centers were accepted [10]. For example, while the majority of centers used a 4-yr screening interval, this ranged between 2 (Sweden and France) and 7 yr (Belgium). At 16-yr follow-up, PSA screening was associated with a relative reduction of 20% in cancer-specific mortality [10]. Moreover, the absolute difference in PCa mortality between trial arms increased from 14% at 13 yr to 18% at 16 yr. The number of cases needed to be screened for averting one cancer-related death declined from 742 at 13 yr to 570 at 16 yr. Similarly, the number of patients needed to be diagnosed to prevent one PCa death progressively declined according to the length of follow-up and was 18 in the 16-yr update of the ERSPC trial [10]. When considering ERSPC cohorts with longer follow-up, the number of patients needed to be diagnosed to prevent one PCa death further decreased to 13 at 18-yr follow-up [6]. In particular, the Goteborg screening trial evaluated approximately 20 000 men randomized to organized PSA testing every 2 yr versus opportunistic testing, and reported that organized screening was associated with a relative reduction in the risk of dying from PCa of 42% at 18 yr [6]. Similarly, the Rotterdam pilot 1 study evaluated >1100 men randomized to PSA screening versus control, and reported that the screening arm exhibited a 50% reduced risk of experiencing metastases and of dying from PCa as compared with the control arm at 19-yr follow-up [3].

The second trial assessing the role of PSA screening was the prostate arm of the Prostate, Long, Colorectal and Ovarian Cancer Screening Trial (PLCO), which randomized >76 000 men aged 55–74 yr to annual PSA testing for 6 yr versus usual care between 1993 and 2001 [32]. A prostate biopsy was recommended when the PSA level was >4.0 ng/ml. After almost 17 yr of follow-up, no differences in mortality were detected between the two arms, where 333 versus 352 men died from PCa in the intervention versus control groups, respectively [33]. Although the results of this study do not support screening, the design of the PLCO trial has been criticized heavily. Approximately half the patients in the trial had undergone PSA testing before randomization [32]. Moreover, up to 80% of the participants in the control group without baseline screening contamination reported having undergone at least one PSA test during the trial, and overall, the proportion of control participants who received a PSA test before or during the trial approached 90% [34]. Therefore, this randomized study cannot be considered as an unbiased assessment of the efficacy of PSA screening versus no screening. Recent modeling efforts that accounted for differences in the study design between the PLCO and ERSPC trials suggest that the efficacy of screening in the PLCO study might be consistent with what was observed in the ERSPC trial, with a relative risk reduction in PCa mortality ranging between 25% and 30% [5]. Finally, the results of two meta-analyses of randomized studies assessing the role of PSA screening have been published recently [8,9]. These investigations demonstrate that, when considering studies at a low risk of bias, PSA screening leads to a small but significant reduction in the risk of dying from PCa over 10 yr.

3. Overdiagnosis and overtreatment

3.1. What are overdiagnosis and overtreatment

3.1.1. Statement

The risk of overdiagnosis and overtreatment represent the main barriers for the implementation of PSA screening policies at a population level.

3.1.2. Scientific background

Overdiagnosis is defined as the identification of a disease in asymptomatic men that would not have caused symptoms during their lifetime [35]. Overdetection is particularly important in PCa given the long natural history of many cancers and risks of competing mortality from other causes [36]. The risk of overdetection is mainly driven by the high prevalence of low-grade PCa in healthy men with a normal digital rectal examination (DRE). For example, the Prostate Cancer Prevention Trial demonstrated that >15% of American men older than 55 yr with a PSA value of ≤4 ng/ml and a normal DRE harbor a PCa at prostate biopsy, where the vast majority of cases are represented by low-grade diseases [37]. In this context, the Cluster Randomized Trial of PSA Testing for PCa, which included >419 000 men aged 50–69 yr in 573 primary care practices in the UK, demonstrated that a single PSA screening versus usual care was associated with a significantly higher risk of detecting a grade group 1 PCa. Moreover, the risk of overdiagnosis estimated using the excess incidence method exceeded 40% in this prospective study [8,11]. These observations are in line with the findings of the PLCO and ERSPC trials, and show

that the implementation of screening policies based on total PSA alone would lead to substantial numbers of unnecessary biopsies and detection of insignificant cancers, which might be followed by overtreatment [14]. The risk of overdiagnosis applies particularly to men with short life expectancy or those with lower PSA values [12], where the beneficial effect of curative-intent therapeutic approaches is limited (or absent) [13]. Therefore, measures aimed at minimizing the risk of overdiagnosis and overtreatment while maximizing the benefits of PSA screening in terms of reduction of PCa-specific mortality are urgently needed.

3.2. *Reducing the risk of overdiagnosis and overtreatment: early detection strategies*

3.2.1. *Statement*

A risk-adapted early detection strategy based on PSA values at the age of 45 yr should be offered to well-informed men with life expectancy of ≥10 yr, where screening intervals should be individualized according to baseline PSA levels. Risk calculators based on PSA, family history, ethnicity, DRE, and prostate volume can assist physicians in the identification of men who should receive prostate biopsy, reducing the risk of overdiagnosis.

3.2.2. *Scientific background*

Prospective cohort studies suggest that baseline PSA obtained at the age of 45 yr can safely allow for risk stratification of future screening intensity [38–41]. Patients with a baseline PSA value of <1 ng/ml at the age of 45–49 yr have a very low risk of experiencing metastasis and of dying from PCa at 20-yr follow-up (0.24% and 0.17%, respectively). This is substantially lower than what was observed in men with baseline PSA levels in the highest 10% (namely, ≥1.6 ng/ml), where the 20-yr risk of metastasis and cancer-specific mortality were higher than 4% and 2%, respectively [42]. Although individuals with a family history of PCa or African-American men should be considered at an increased risk of having PCa, PSA at the age of 45 yr represents the most powerful tool for risk stratification for early screening [43,44]. Therefore, a baseline PSA value at the age of 45 yr should be obtained to identify men more likely to experience metastases and cancer-specific mortality regardless of family history and ethnicity. Moreover, screening intervals should be adapted according to baseline PSA levels to minimize overdiagnosis, without increasing the risk of missing significant diseases. In particular, men with a PSA value of <1 ng/ml at the age of 45 yr should be reassured regarding the low risk of experiencing an aggressive PCa during their lifetime. In these individuals, the screening interval could be up to 8 yr to reduce overdiagnosis [16,28]. Conversely, more intensive screening with PSA testing every 2–4 yr should be scheduled in men with higher baseline PSA levels (Fig. 1) [16].

PSA should be considered in the context of other clinical characteristics such as age, family history, ethnicity, DRE, and prostate volume [45]. Of note, several tools such as Rotterdam ERSPC risk calculators account for these parameters [46]. The use of risk stratification tools may allow up to 34% of men to safely avoid prostate biopsy and, diagnosis of up to 20% of insignificant PCa could be avoided (at the cost of missing only 2% significant disease) [47]. These models have been updated recently to include information obtained at mpMRI [48].

Finally, PSA screening should be discouraged in men with short life expectancy, where the risk of dying from other causes is higher than the probability of experiencing PCa mortality [13]. Although the EAU guidelines suggest that

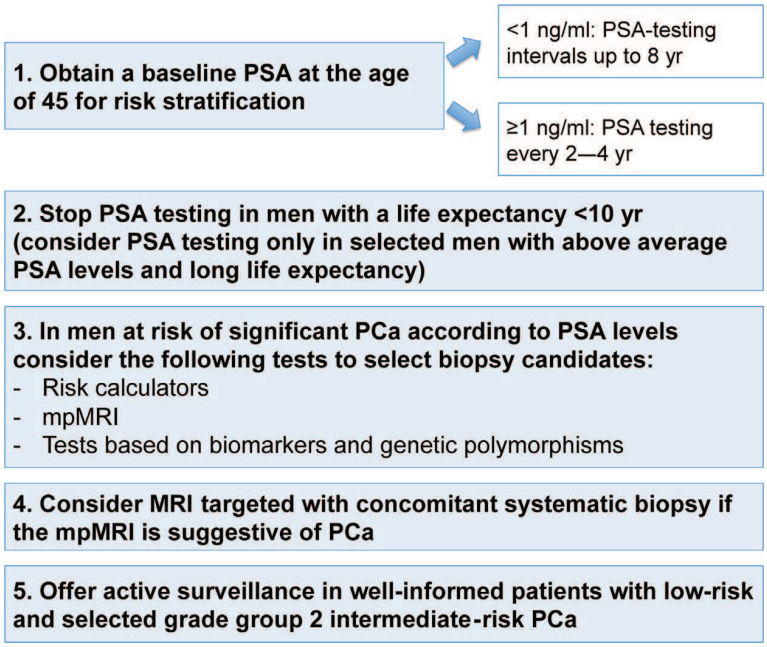

Fig. 1 – Proposed flowchart to reduce the risk of overdiagnosis and overtreatment in well-informed men receiving PSA-based screening. mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PCa = prostate cancer; PSA = prostate-specific antigen.

PSA should be offered to men with life expectancy of ≥10 yr [16], stopping screening even earlier would further reduce the risk of overdiagnosis in selected men [12,49,50]. In this context, previous studies demonstrated that any decrease in mortality associated with PSA screening in men older than 70 yr might be offset by the risk of overdiagnosis [50]. Therefore, screening should be considered only in selected men older than 70 yr with above average PSA levels and long life expectancy to minimize the risk of overdiagnosis [28].

4. Role of mpMRI in selecting men for biopsy

4.1. Statement

Multiparametric MRI can safely improve selection of men for prostate biopsy. The performance of mpMRI for PCa detection and risk estimation is improved by using it in men at risk of clinically significant disease before prostate biopsy.

4.2. Scientific background

The introduction of mpMRI has changed the diagnostic pathway for PCa. This imaging modality is characterized by high sensitivity and a negative predictive value for aggressive disease (namely, grade group ≥2) [51,52], and the ability to reduce detection of insignificant PCa [53]. Multiparametric MRI has been proposed as a follow-up test to identify men at risk of clinically significant PCa who should receive a prostate biopsy. A recent multicenter investigation found that the use of mpMRI would allow 27% of men to avoid a prostate biopsy, with a reduction of 5% in the risk of overdiagnosis [53]. These findings were confirmed by a large multicenter randomized trial aimed at comparing mpMRI with or without target biopsy versus an upfront biopsy in men with elevated PSA levels. MRI-targeted biopsies detected a higher proportion of significant PCa than ultrasound-guided random biopsies (38% vs 26%). Moreover, a reduction of 13% in the risk of diagnosing an insignificant disease was observed, and implementation of a biopsy strategy based on MRI results would allow for saving up to 28% unnecessary biopsies [54]. Recent studies suggest that the implementation of an early detection strategy where prostate biopsies are proposed exclusively to men considered at increased risk of PCa based on PSA with positive mpMRI would avoid up to two-thirds of biopsies and low-grade PCa diagnoses (namely, overdiagnosis), while maintaining the detection of clinically significant disease of the standard approach based on prostate biopsy in all men with elevated PSA levels [55,56].

5. Novel molecular tests

5.1. Statement

Novel tests based on biomarkers and genetic polymorphisms can improve the selection of men with significant PCa, and reduce the number of unnecessary prostate biopsies and detection of insignificant disease.

5.2. Scientific background

A risk-based model that combines PSA, single nucleotide polymorphisms, clinical parameters, and plasma biomarkers has recently been proposed as a first-line screening test (namely, STHLM3) [57]. This tool was developed with the aim of increasing specificity as compared with PSA alone, without decreasing the sensitivity to diagnose significant PCa. When evaluated in 150 000 Swedish men aged 50–69 yr, this test performed substantially better than PSA alone for the detection of high-grade disease. Moreover, the use of the STHLM3 was associated with a reduction of >30% in the number of prostate biopsies and of 17% in the diagnosis of low-grade disease [58–60].

Other molecular biomarkers (eg, Prostate Health Index, 4Kscore, PCA3, and SelecMDx) have been proposed over the past decade and are currently available for clinicians to identify men who harbor significant PCa. These tools are typically based on algorithms that evaluate the expression of total PSA, PSA isoforms, or other kallikreins together with clinical information. These markers are characterized by high specificity for clinically significant PCa (namely, grade group ≥2) and might further reduce the number of unnecessary biopsies, thus decreasing the risk of overdiagnosis [61–64]. Nonetheless, they should not be considered as alternatives to PSA, and they are intended to be used as reflex tests in men with elevated PSA levels who might be considered for prostate biopsy. Their implementation in the diagnostic pathway of PCa and integration with other tools such as mpMRI might reduce to a minimum the number of unnecessary biopsies in men with elevated PSA levels without increasing the risk of missing significant diseases [65,66].

6. Reducing the risk of overtreatment: risk-adjusted therapies

6.1. Statement

Current diagnostic and staging tools can be used to estimate cancer-specific mortality risk in men with PCa. Individual patients should be treated using a risk-stratified approach, taking their life expectancy and their cancer's mortality risk into account. Active surveillance in well-informed patients with low-risk and selected grade group 2 intermediate-risk PCa reduces the risk of overtreatment without compromising oncological outcomes.

6.2. Scientific background

Deferred treatments such as active surveillance can diminish the burden of side effects in men with low-risk and selected grade group 2 intermediate-risk PCa, where patients can safely be included in active surveillance programs with the aim of reducing the risk of overtreatment without losing the window of curability [67,68]. This approach allows for sparing treatment-related side effects in up to 65% of patients with low-risk disease at 15-yr

follow-up [68]. Nowadays, only 5% of active surveillance candidates, according to the PRIAS protocol, receive radical prostatectomy at tertiary referral European centers [69]. Moreover, the use of active surveillance in low-risk patients increased from 14% to 42% from 2010 to 2015 in the USA [70], where it represents the most common management approach in this setting. Focal therapy has been proposed in low- and intermediate-risk patients to treat the index lesion, decreasing the risk of side effects and impairments in quality of life compared with whole-gland therapies [71,72]. Nonetheless, this approach should still be considered as investigational due to the lack of long-term data [73].

7. Prerequisites for the implementation of an effective PSA-based screening program

In order to successfully implement PSA-based screening programs at a large scale aimed at detecting clinically significant PCa without increasing the risk of overdiagnosis, some prerequisites need to be fulfilled.

First, PSA testing should not be considered without counseling men on the potential risks and benefits of this approach [26], where the availability of an objective and thoroughly tested information leaflet might play a crucial role in the successful implementation of a screening program. For example, men should be counseled regarding the potential harms related to prostate biopsy, overdiagnosis, and overtreatment, as well as the risk of missing a significant PCa. In addition, eligible men should be aware of the implications of baseline PSA at the age of 45 yr to individualize future PSA testing intervals. Of note, the recommendation to perform a baseline PSA test should not translate into a more intense use of PSA at any age. This is particularly true when considering individuals less likely to benefit from early detection (ie, those with limited life expectancy), where PSA testing might hamper the cost effectiveness of screening programs [29]. In this context, previous population-based studies showed that up to one out of three of these individuals received PSA testing despite the absence of clinical benefits [74,75]. As such, education of patients and their physicians is the key to reduce unnecessary (and potentially harmful) assessments and implement an effective PSA-based screening program.

Second, mpMRI should be used to identify men at risk of clinically significant PCa to be considered for a prostate biopsy. However, available data are based on studies including individuals evaluated at tertiary referral centers [54], where a higher detection rate of clinically significant PCa at mpMRI and MRI-targeted biopsy is observed [76,77]. Therefore, they might not be generalizable to other settings. Nonetheless, recent data show that lesion characterization at imaging improved over time even in a community-based health system [78]. The role of mpMRI in the screening setting will be prospectively tested by an ongoing randomized trial: the ProScreen study is currently randomizing men aged 55–67 yr to PSA followed by mpMRI in case of an increased risk of clinically significant PCa versus control. Prostate biopsy should be performed exclusively in men with a malignancy-suspected finding at mpMRI. The results of this trial are needed to further assess the role of mpMRI in minimizing the risk of overdiagnosis without missing significant PCa [79].

Third, different population-based observational studies support the prognostic value of baseline PSA for risk stratification of screening intensity [39,42,80]. Nonetheless, this approach still needs to be tested in a prospective randomized trial. Under this light, the PROBASE trial is currently randomizing patients and will clarify the impact of starting PSA screening at the age of 45 versus 50 yr, followed by a risk-adapted strategy that includes the use of mpMRI before biopsy, on the risk of metastases at 15-yr follow-up [81].

Finally, although several studies support the use of risk calculators, imaging (ie, mpMRI), and novel tests based on biomarkers and genetic polymorphisms to reduce the number of unnecessary biopsies and detection of clinically insignificant PCa [47,48,54,56,64], the optimal combination of these tools is still unclear and needs to be tested in a prospective setting.

8. Conclusions

Organized, population-based PSA screening programs should be implemented at a European level to reduce PCa mortality. A risk-adapted strategy based on PSA values at the age of 45 yr should be offered to well-informed men, in whom screening intervals should be individualized according to baseline PSA levels. PSA testing should be stopped in men with life expectancy of $<$10 yr to minimize the risk of overdiagnosis. Multiparametric MRI should be included in the early detection pathway as a triage test to safely improve selection of men for prostate biopsy. Risk calculators, biomarkers, and genetic polymorphisms can further improve the identification of men with significant PCa and reduce the risk of overdiagnosis. Active surveillance in patients with low-risk and some grade group 2 intermediate-risk PCa reduces the risk of overtreatment.

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Study concept and design: van Poppel, Gandaglia, Albers, Abrahamsson, Briganti, Catto, Chapple, Montorsi, Mottet, Roobol, Sønksen, Wirth.
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