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European Association of Urology

Review – Prostate Cancer – Editor's Choice

Prostate-specific Antigen Testing as Part of a Risk-Adapted Early Detection Strategy for Prostate Cancer: European Association of Urology Position and Recommendations for 2021

Hendrik Van Poppel[a,*], *Monique J. Roobol*[b], *Christopher R. Chapple*[c], *James W.F. Catto*[d,e], *James N'Dow*[f,g], *Jens Sønksen*[h,i], *Arnulf Stenzl*[j], *Manfred Wirth*[k]

[a] *Department of Urology, University Hospitals Leuven, Leuven, Belgium;* [b] *Department of Urology, Erasmus University Medical Centre Cancer Institute, Rotterdam, The Netherlands;* [c] *Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK;* [d] *Academic Urology Unit, University of Sheffield, Sheffield, UK;* [e] *Department of Urology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK;* [f] *Academic Urology Unit, University of Aberdeen, Aberdeen, UK;* [g] *Department of Urology, Aberdeen Royal Infirmary, Aberdeen, UK;* [h] *Department of Urology, Copenhagen University Hospital, Herlev and Gentofte, Copenhagen, Denmark;* [i] *Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark;* [j] *Department of Urology, Eberhard Karls University Tübingen, Tübingen, Germany;* [k] *Department of Urology, University Hospital Carl Gustav Carus, Technical University of Dresden, Dresden, Germany*

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Abstract

Background: Recommendations against prostate-specific antigen (PSA) testing in 2012 have increased advanced-stage diagnosis and prostate cancer–specific mortality rates.
Objective: To present the position of the European Association of Urology (EAU) in 2021 and provide recommendations for the use of PSA testing as part of a risk-adapted strategy for the early detection of prostate cancer.
Evidence acquisition: The authors combined their review of relevant literature, including the EAU prostate cancer guidelines 2021 update, with their own knowledge to provide an expert opinion, representing the EAU's position in 2021.
Evidence synthesis: The EAU has developed a risk-adapted early prostate cancer detection strategy for well-informed men based on PSA testing, risk calculators, and multiparametric magnetic resonance imaging, which can differentiate significant from insignificant prostate cancer. This approach largely avoids the overdiagnosis/overtreatment of men unlikely to experience disease-related symptoms during their lifetime and facilitates an early diagnosis of men with significant cancer to receive active treatment. It also reduces advanced-stage diagnosis, thereby potentially reducing prostate cancer–specific mortality and improving quality of life. Education is required among urologists, general practitioners, radiologists, policy makers, and healthy men, including endorsement by the European Commission to adapt the European Council's screening recommendations in its 2022 plan and requests to individual countries for its incorporation into national cancer plans.
Conclusions: This risk-adapted approach for the early detection of prostate cancer will reverse current unfavourable trends and ultimately save lives.

* Corresponding author. Department of Urology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium. Tel.: +32 16 34 16 11; Fax: +32 16 34 69 31.
E-mail address: hendrik.vanpoppel@kuleuven.be (H. Van Poppel).

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Patient summary: The European Association of Urology has developed a patient information leaflet and algorithm for the early diagnosis of prostate cancer. It can identify men who do not need magnetic resonance imaging or a biopsy and those who would not show any symptoms versus those with more aggressive disease who require further tests/treatment. We need to raise awareness of this algorithm to ensure that all well-informed men at risk of significant prostate cancer are offered a prostate-specific antigen test.

1. Introduction

Prostate cancer is the most common male cancer in Europe, with an estimated 450 000 new cases and 107 000 deaths reported in 2018 [1]. The prostate-specific antigen (PSA) test, introduced in the late 1980s and early 1990s, provides an easy and inexpensive method to identify asymptomatic men who might harbour prostate cancer at an earlier stage, thereby increasing the chances of cure and ultimately reducing prostate cancer–specific mortality [2]. Data from large randomised controlled trials support the beneficial effects of PSA testing: In the European Randomised study of Screening for Prostate Cancer (ERSPC), which included 182 160 men (162 389 within a predefined core age group of 55–69 yr), PSA screening significantly reduced prostate cancer–specific mortality by 20% at 16 yr of follow-up (rate ratio [RR] 0.80, 95% confidence interval [CI] 0.72–0.89) [3]. Similarly, in the Göteborg population-based prostate cancer screening trial, which represented the Swedish arm of the ERSPC from 1996 onwards and included 20 000 men aged 50–64 yr, PSA screening was associated with a 35% reduction in prostate cancer–specific mortality at 18 yr of follow-up (RR for death 0.65, 95% CI 0.49–0.87) [4]. In the ERSPC, a subgroup analysis (Rotterdam pilot 1 study cohort, n = 1134) at 19 yr of follow-up showed that PSA screening resulted in a decrease in both prostate cancer–specific mortality (–52%) and progression to metastatic disease (–54%; Fig. 1) [2]. Although the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial failed to show a reduction in prostate cancer–specific mortality, a recent modelling analysis showed that the ERSPC and PLCO trials provide compatible evidence that PSA screening reduces prostate cancer–specific mortality [5]. In contrast, prior to the introduction of PSA testing, one in every two to three men diagnosed with prostate cancer died from their disease [6].

As with many blood-based biomarker tests, false positive and false negative results can occur. PSA can also be elevated in some benign conditions, such as benign prostatic hyperplasia and prostatitis. Moreover, prostate cancer detected because of an elevated PSA level does not always mandate active treatment. Indeed, many screen-detected cancers can be indolent, and in some patients, comorbidities and/or a relatively short anticipated life expectancy may negate the benefits of active treatment. However, when mass PSA testing was initially introduced, there was insufficient knowledge to discriminate between significant and insignificant cancer, and a prostate cancer diagnosis automatically led to active treatment, which can cause a range of side effects, including mainly urinary incontinence and erectile dysfunction [7]. Thus, although these mass screening programmes were effective in reducing prostate cancer–specific mortality rates [8], they also resulted in many unnecessary repeat tests (PSA tests as well as the burdensome prostate biopsies), as well as the overdiagnosis and overtreatment of many asymptomatic men with

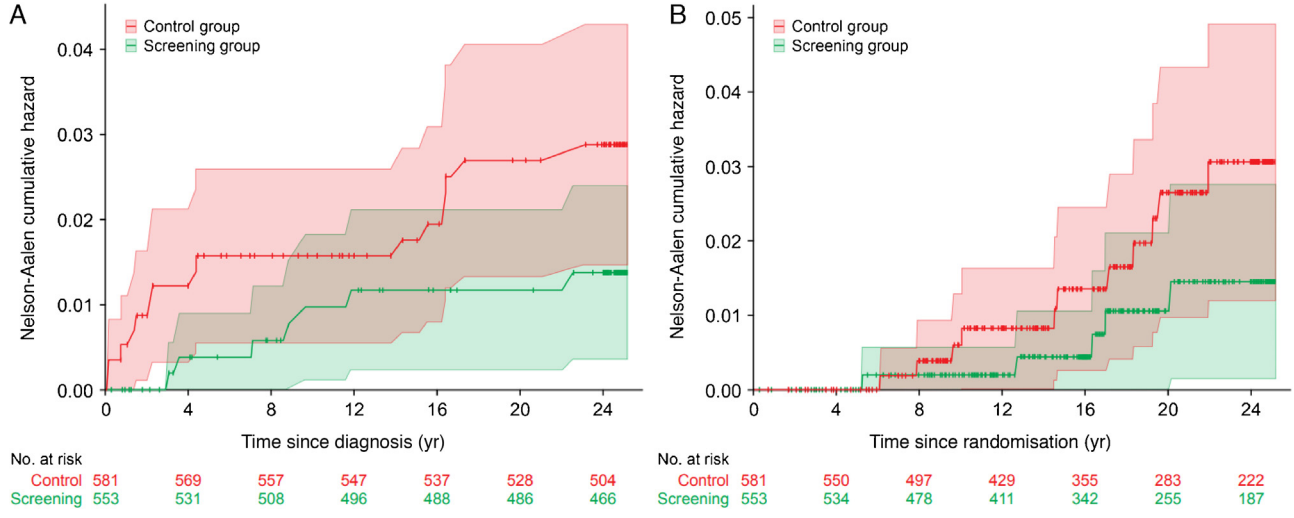

Fig. 1 – Reduction in (A) progression to M+ prostate cancer (54%) and (B) prostate cancer–specific mortality (52%) due to PSA screening in the Rotterdam cohort (n = 1134) of ERSPC at 19 yr of follow-up [2].
ERSPC = European Randomised study of Screening for Prostate Cancer; M+ = metastatic; PSA = prostate-specific antigen.

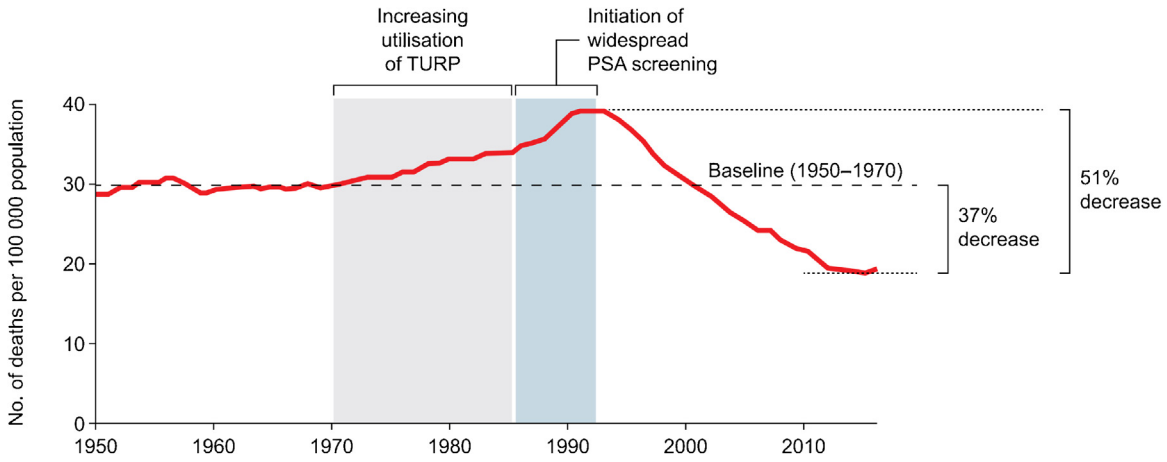

Fig. 2 – Prostate cancer–specific mortality rates in the USA from 1950 to 2019 [8]. PSA = prostate-specific antigen; TURP = transurethral resection of the prostate. Reproduced with permission.

indolent prostate cancer that would not have presented symptomatically during their lifetime and would not have led to prostate cancer–related death [9].

This unnecessary testing, overdiagnosis and overtreatment of prostate cancer eventually resulted in a reversal in guidance, most notably by the US Preventive Service Task Force (USPSTF) in 2012 [10]. These recommendations provided an update to those published in 2002 and 2008, and highlight the shift away from recommendations for PSA-based screening. In 2002, the USPSTF advised that there was good evidence for the use of PSA testing to detect early-stage cancer but, based on mixed or inconclusive evidence regarding its impact on health outcomes, concluded that there was insufficient evidence to recommend either for or against the use of PSA testing [11]. Similar recommendations were provided in 2008, with the added guidance that men >75 yr of age should not be screened for prostate cancer [12]. However, in 2012, the USPSTF recommended against PSA-based screening for prostate cancer for all men, regardless of age, except for surveillance purposes in those with a prior prostate cancer diagnosis [10].

Following these recommendations, the decreasing prostate cancer–specific mortality rates observed over the previous two decades plateaued (Fig. 2) [8]. In the USA, these recommendations led to a significant decline in PSA testing [13] as well as a stage "reverse migration", with a decrease in the diagnosis of localised prostate cancer and a rise in the diagnosis of locally advanced and metastatic disease reported in 2017, ie, 5 yr after the USPSTF 2012 recommendations were issued (Fig. 3) [14–16]. In recent years, increases in late-stage diagnoses and prostate cancer–specific mortality rates have also been reported in other countries. For example, the UK has seen a 17% increase in prostate cancer–specific mortality over 10 yr to 2015 [17]. In Germany, a comparison of patients in 2008–2010 with those in 2017 showed a 20% increase (from 29% to 49.4%) in patients with T3 prostate tumours and a four-fold increase (from 4.5% to 16.9%) in those with lymph node metastasis [18]. Although a definitive causal link between trends in PSA testing and a rise in late-stage diagnosis and prostate cancer–specific mortality rates cannot be proven, it is likely the simplest explanation. In these countries and across Europe, prostate cancer now ranks as the third biggest cause of cancer-related death in men [1,17,18], although globally it now ranks second [19].

In 2018, the USPSTF published a further update to its recommendations, largely based on the publication of longer follow-up data from large screening trials and emerging evidence that the use of active surveillance in low-risk prostate cancer reduces the harms associated with overtreatment due to screening. The USPSTF now recommends that the decision to undergo PSA testing in men aged 55–69 yr should be an individual one based on a discussion with their clinician regarding the relative benefits and harms, although it still recommends against PSA screening in younger men (40–55 yr) or in those of >70 yr [20]. It is hoped that these updated recommendations, along with those issued by the European Association of Urology (EAU) [21], will help reverse the current unfavourable trends.

It is also worth noting that in the absence of widespread, organised PSA testing, opportunistic testing has become common practice in a number of EU member states. However, emerging evidence suggests that this approach has little effect on prostate cancer–specific mortality but is associated with more overdiagnosis than organised risk-adapted PSA testing [22]. This lack of effect is largely caused by testing men who will not benefit (ie, those with life expectancy of <10 yr) without proper informed decision-making [23,24] and repeated testing in men who are not at risk of developing significant prostate cancer [25,26].

Finally, another factor to consider when looking at recent prostate cancer diagnosis and mortality trends is the impact of COVID-19, given the redeployment of medical resources to help fight the pandemic and COVID-19–specific updates to oncology guidelines to deprioritise all oncology screening, including PSA testing, and to defer the diagnosis and

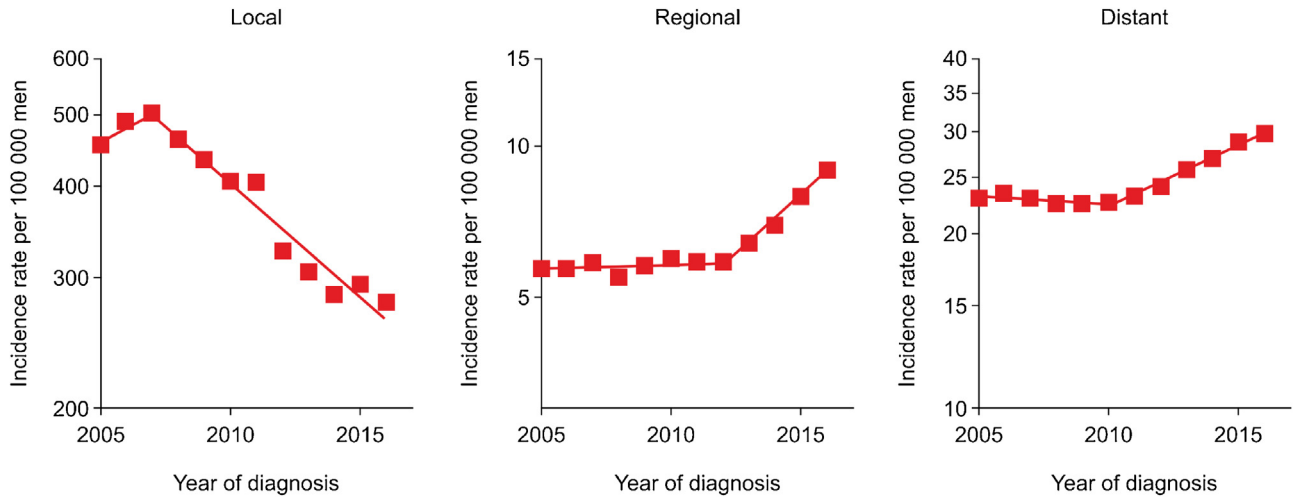

Fig. 3 – Stage migration in prostate cancer diagnoses in the USA after the USPSTF recommendations against PSA screening in 2012 [14].
PSA = prostate-specific antigen; USPSTF = United States Preventive Service Task Force.
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treatment of patients considered to be at low risk of clinical harm [27]. Indeed, the impact of the pandemic is already being seen in several countries, including Belgium and The Netherlands, where prostate cancer diagnoses were 15% lower in 2020 than in the previous year [28,29]. In the USA, the greatest reduction in PSA testing was observed in April 2020, with 56% fewer tests performed than in April 2019 [30]; similar findings were also reported in the UK [31]. Unfortunately, as the COVID-19 pandemic is not yet over, the long-term effects of COVID-19 on prostate cancer diagnosis, treatment and outcomes, including the potential impact on subsequent prostate cancer–specific mortality rates, are yet to be elucidated fully.

Taken together, these findings warrant a change in our approach to reverse the trends outlined above and improve outcomes for men diagnosed with prostate cancer. Fortunately, we now have the tools to hand to make these changes. As an oncology community, we have much greater knowledge on the best use of PSA testing, as well as risk calculators, biomarkers, and technologies, to help differentiate between significant and insignificant cancers in order to reduce overdiagnosis and overtreatment [32–34]. As such, this paper describes the EAU's position in 2021 and provides clear recommendations for the effective use of PSA testing as part of a risk-adapted strategy to improve the early detection of prostate cancer.

2. Rationale for the early detection of prostate cancer

The early detection of significant prostate cancer is highly likely to reduce prostate cancer–specific mortality rates as well as the proportion of men diagnosed with advanced/metastatic disease. However, the effects of even immediate action will not be seen for 5–10 yr due to the high proportion of men who have already received a late diagnosis in the past decade.

Overdiagnosis can be reduced by using a risk-adapted early detection strategy based on PSA values combined with risk calculators and multiparametric magnetic resonance imaging (mpMRI) [21], in order to differentiate significant from insignificant prostate cancer and modify the management approach accordingly. As a result, many early diagnoses of prostate cancer can be managed by active surveillance, preventing overtreatment. Those with a less favourable risk profile may receive local treatment, with fewer side effects and better outcomes than if the disease was diagnosed and treated at a later stage, thereby improving or maintaining the patient's quality of life (QoL) [21]. Moreover, improving knowledge among men about prostate cancer and PSA testing, including awareness that an early significant prostate cancer diagnosis can be managed effectively, often with active surveillance, and avoid adverse outcomes, should provide reassurance and encourage men to have a PSA test when appropriate and after counselling. Conversely, a diagnosis of advanced or castration-resistant prostate cancer (CRPC) typically necessitates the use of chemotherapy; novel hormonal therapies such as abiraterone (given with prednisolone), apalutamide, darolutamide or enzalutamide; radium 223 dichloride (Ra223) or lutetium-177 prostate-specific membrane antigen-targeted radioligand therapy; the poly-ADP ribose polymerase inhibitor olaparib; and bone-targeted agents, such as bisphosphonates or denosumab, for men with bone metastases [21], all of which can be associated with significant toxicity and impairment in QoL.

The management of advanced prostate cancer is also associated with a significant economic burden. Treatment of early significant prostate cancer with radical prostatectomy is approximately €10 000–15 000 [35]. In contrast, management of CRPC, which typically includes drug costs as well as costs of resources associated with outpatient management, inpatient hospitalisations, supportive care and palliative radiotherapy, is approximately €140 000 per patient per year [36].

Recommendation:

- A risk-adapted strategy for the early detection of prostate cancer will allow for a tailored approach to management and avoid overdiagnosis and overtreatment.

3. A risk-adapted approach for the early detection of prostate cancer

The EAU has developed an algorithm to outline a risk-adapted approach for the early detection of prostate cancer (Fig. 4). This algorithm is intended for use in well-informed men of >50 yr and a life expectancy of >10–15 yr (Table 1). Men with a known elevated risk of prostate cancer (ie, those aged >45 yr of African descent or a family history of prostate cancer and those aged >40 yr carrying the BRCA2 mutation) are not included in our algorithm and should follow the recommended pathway outlined in the EAU guidelines [21].

This algorithm clearly illustrates how an early diagnosis of significant prostate cancer can be achieved, whilst avoiding overdiagnosis and overtreatment. Using this approach, following a clinical risk assessment and appropriate counselling, the PSA test represents the first step to identify a large proportion of men with a low PSA value (ie, ≤3 ng/ml) who require no further immediate investigations for either 2–4 yr (for those with a PSA value of 1–3 ng/ml) or 5 yr (for those with a PSA value of <1 ng/ml and <60 yr old). For those with an initial PSA test of >3 ng/ml, the use of a risk stratification nomogram (which considers factors such as age, family history, digital rectal examination and prostate volume [PSA density] in a risk calculator) will identify a subgroup of men (approximately 35% of all men with an initial PSA test of >3 ng/ml [37]) as those with a low risk who require clinical follow-up only, thereby avoiding the need for further testing, including MRI and biopsy. Men with a PSA value of >3 ng/ml classified as intermediate or high risk would then undergo mpMRI, resulting in the identification of a further subgroup (approximately 54% of all men undergoing MRI [37]) with a Prostate Imaging Reporting and Data System (PIRADS) score of 1–2 consid-

Table 1 – Summary of current EAU guidelines for prostate cancer PSA testing and early diagnosis [21]

Do not subject men to PSA testing without counselling them on the potential risks and benefits
Offer an individualised risk-adapted strategy for early detection to a well-informed man with life expectancy of at least 10–15 yr
Offer early PSA testing to well-informed men at an elevated risk of having prostate cancer:
1. Men >50 yr of age
2. Men >45 yr of age with a family history of prostate cancer
3. Men of African descent >45 yr of age
4. Men carrying BRCA2 mutations >40 yr of age
Stop early diagnosis of prostate cancer based on life expectancy and PS; men who have life expectancy of <15 yr are unlikely to benefit

EAU = European Association of Urology; PS = performance status; PSA = prostate-specific antigen.

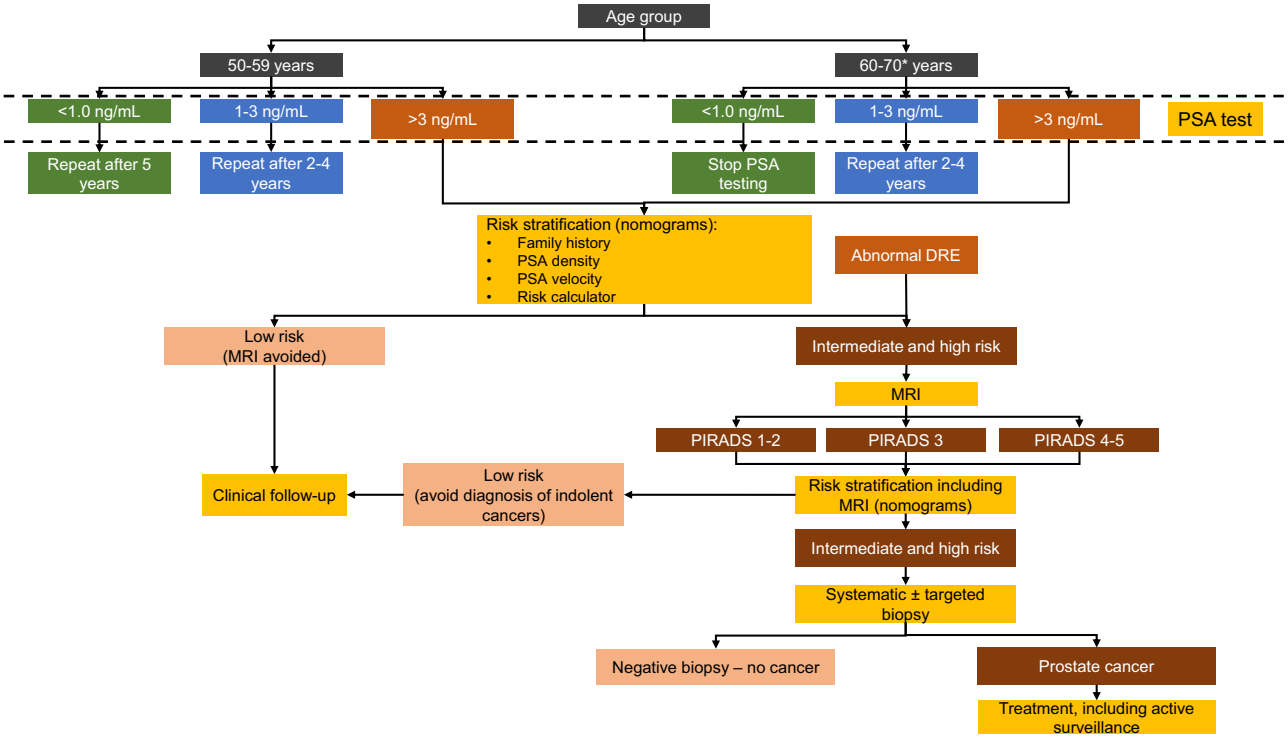

Fig. 4 – Risk-adapted algorithm for the early detection of prostate cancer, adapted based on prostate cancer guidelines published by the EAU [21]. The patient's values and preferences should always be taken into account as part of a shared decision-making process [21].
DRE = digital rectal examination; EAU = European Association of Urology; MRI = magnetic resonance imaging; PIRADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen.
***Healthy men >70 yr without important comorbidities and a life expectancy of >10-15 yr may continue PSA testing.**

ered to be at a low risk of having significant prostate cancer and requiring clinical follow-up only. Further risk stratification of those with a PIRADS score of 3, using PSA density as well as other clinical parameters, would also identify an additional subgroup requiring clinical follow-up only (a PIRADS score of 1, 2 or 'low-risk' 3 accounts for approximately 57% of men assessed by PIRADS [37]). The remaining subgroup of the original population could therefore be considered as truly intermediate or a high risk and should proceed to targeted and/or systematic biopsy. It is also worth noting that, in this subgroup, among those who will eventually be diagnosed with prostate cancer, those with a positive diagnosis and a favourable grading group (approximately 25% of all confirmed diagnoses [37]) could be eligible for active surveillance rather than active treatment. However, all final treatment decisions should also take into account the patient's values and preferences as part of a shared decision-making process [21].

This algorithm therefore demonstrates how PSA testing can be used more intelligently with the incorporation of risk calculators, such as those developed by the ERSPC and the Prostate cancer Prevention Trial (PCPT) [38], as well as mpMRI and PIRADS score [39–42], to reduce the number of men proceeding to biopsy. The proposed differing time intervals for repeat PSA testing based on age and initial PSA test result reflect the likelihood of a future diagnosis of clinically significant cancer [43] and therefore help to avoid false positive biopsies. The choice of risk calculator to be used also requires careful consideration. Although the ERSPC risk calculator has been validated extensively and might therefore be considered superior, a recalibration step may be required in order to take into consideration regional variations in prevalence and the relationship between PSA and prostate cancer risk [44,45].

The collection of outcomes data following the use of this algorithm will provide more robust support for our risk-adapted approach, and this work is ongoing. In addition, MR image quality and assessment are areas where improvements and education are required, possibly by the use of expert centres and/or the incorporation of artificial intelligence into the radiology workflow [46]. Various technologies and biomarkers are also in development that, if validated, could be incorporated into this algorithm to further refine our approach in the future [47]. However, we should not wait for results from ongoing or future clinical trials—we must act now by adopting the risk-adapted strategy outlined here, which represents the optimal approach based on the tools that we have available today and will allow us to optimise the early diagnosis of significant prostate cancer, which will hopefully improve the long-term outcomes for these patients.

Recommendations:

- The EAU's algorithm outlines a risk-adapted strategy for the early detection of prostate cancer and represents the optimal approach for the early diagnosis of significant prostate cancer based on the tools that we have available today.
- This algorithm should be adopted to help improve the long-term outcomes for patients with prostate cancer.

4. Education for key stakeholders

The effective uptake and use of our risk-adapted strategy requires a broad collaborative effort to inform and educate multiple stakeholders, including urologists, general practitioners (GPs), radiologists, policy makers and the healthy male population.

To facilitate this, the EAU has produced white papers [7] and recommendation articles for the European Union (EU) and European Commission (EC), and has also lobbied in the European Parliament (during the European Prostate Cancer Awareness Day in 2017, 2019 and 2020) for the EC to endorse a risk-adapted strategy for the early detection of prostate cancer so that requests can be made to EU member states to incorporate it into their national cancer plans [48]. Finally, the EAU is partnering with the innovative Partnership for Action Against Cancer (iPAAC) with its cancer prevention work package, which will complement the EAU's drive for individualising a risk-adapted approach for the early detection of significant prostate cancer [49].

The EAU has also compiled information to allow healthy men to learn more about prostate cancer so that they can decide whether to have a PSA test. This information also provides details of the likely additional tests they would undergo in the event of an elevated PSA result as well as information on the various treatments for those who receive a positive diagnosis of prostate cancer, including the role of active surveillance, an established—but frequently underutilised—treatment option for men with localised, favourable-risk prostate cancer. This information can be found on a dedicated patient information website, which is available in multiple languages [50] and in a patient leaflet.

Recommendation:

- Key stakeholders, including urologists, GPs, radiologists, policy makers and healthy men, need to be educated about the benefits and potential drawbacks of a risk-adapted strategy for the early detection of significant prostate cancer in order to ensure its effective uptake and use.

5. Hope for the future

With increasing knowledge and awareness regarding the need for the early detection of significant prostate cancer, we are gathering momentum in our efforts that will likely improve the prognosis of men diagnosed with prostate cancer in the future. At an EU level, the EC's Beating Cancer Plan, drafted in 2020, sets out a new EU approach to cancer prevention, treatment and care. Following a period of public consultation, the plan was presented in February 2021 and is structured around four key action areas: prevention, early detection, diagnosis and treatment, and QoL. Although the early detection section focuses on efforts to improve screening for breast, cervical and colorectal cancers, the report also states the following: "Extending targeted cancer

screening beyond breast, colorectal and cervical cancer to include additional cancers, such as prostate, lung and gastric cancer, will be considered. This work will be informed by advice from the EC's Group of Chief Scientific Advisors, prepared by early 2022 at the latest. It will consider the latest developments in cancer screening technologies, and assess advances in personalised medicine, AI, big data and other technologies, as well as operational quality assurance" [51].

As prostate cancer is the second biggest cause of cancer-related death in men globally [19], it is imperative that Europe's Beating Cancer Plan includes a risk-adapted strategy for the early detection of prostate cancer. The EAU is therefore committed to continuing its efforts to ensure that when the EC revises its 2003 recommendations, it will also include prostate cancer early detection in the 2022 version of its plan. However, it is worth noting that although the inclusion of prostate cancer early detection in this plan would represent a significant achievement, work would still be required at a country level since member states are responsible for their own health policies, and a request from the EC would not automatically lead to the inclusion of the EAU's proposed strategy in their national cancer plans.

Recommendation:

- The 2022 version of the EC's Beating Cancer Plan should include the EAU's risk-adapted strategy for the early detection of prostate cancer.

6. Conclusions

Taken together, the information provided here summarises the EAU's position and recommendations in 2021 that the organisation believes will improve the early detection and differentiation of significant prostate cancer, reduce prostate cancer-related morbidity, improve QoL and ultimately save many lives.

The EAU's risk-adapted strategy for well-informed men, which incorporates the use of medical tools and technologies, facilitates the identification of significant versus insignificant cancers and may avoid overdiagnosis and overtreatment. Importantly, the EAU's approach could optimise QoL for many men since those diagnosed with insignificant cancer can safely avoid any further treatment or undergo active surveillance (ie, low impact on QoL) and those with significant cancer would be diagnosed earlier, making them eligible for local treatment (ie, less impact on QoL than if the disease was diagnosed at a later stage). This, in turn, reduces the number of men diagnosed with advanced prostate cancer who would be subjected to a range of drugs, including chemotherapy, androgen deprivation therapy, DNA damage repair targeting therapy, theranostics and bone-targeted agents, all of which are associated with significant toxicity (ie, significant impairment in QoL). Reducing the number of men diagnosed with advanced disease could also reduce prostate cancer–specific mortality rates and the economic burden of prostate cancer management.

Finally, GPs, policy makers and the healthy male population all need to be educated about prostate cancer and the benefits of early detection. There should be no uninformed mass screening programmes; rather, well-informed healthy men meeting the criteria outlined in the current EAU guidelines [21] should be offered a PSA test. However, as a next step, our risk-adapted strategy needs to be endorsed by the EC so that requests can be made at a country level for its incorporation into national cancer plans, thereby promoting a European roll-out for the effective use of PSA testing as part of a risk-adapted strategy that will facilitate the early detection of significant prostate cancer and hopefully save many lives.

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Study concept and design: Van Poppel, Roobol, Wirth.
Acquisition of data: Van Poppel, Roobol.
Analysis and interpretation of data: Van Poppel, Roobol, Chapple, Catto, N'Dow, Sønksen, Stenzl, Wirth.
Drafting of the manuscript: Van Poppel, Roobol.
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