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PSA testing in primary care: is it time to change our practice?

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Abstract

Background Historical prostate-specific antigen (PSA)-based screening studies reduced prostate cancer-related deaths but also led to overdiagnosis/overtreatment. Since then, opportunistic PSA testing has increased, and late-stage diagnoses and prostate-cancer related deaths are rising.

Objectives To review current trends regarding PSA testing in primary care and propose a collaborative approach to improve early prostate cancer detection.

Discussion Opportunistic PSA testing patterns vary among General Practitioners (GPs) and Family Doctors (FDs) based on differing guidelines, patient pressure, time constraints and personal views/preferences. However, an organised, risk-adapted strategy, as outlined by the European Association of Urology's guidelines, could facilitate the early diagnosis of significant prostate cancer whilst sparing those unlikely to experience disease-related symptoms from further tests (overdiagnosis) as well as the psychosocial consequences of a cancer diagnosis. This could be achieved by the introduction of national prostate cancer screening programmes, which has been endorsed in the European Commission's publication of the EU Cancer Screening Recommendations. In this scenario, GPs/FDs would still play an important role in supporting men throughout the decision pathway. However, as some men may still request a PSA test from their GP/FD, patient information as well as clear guidance and support to GPs/FDs are needed, including appropriate skills training to facilitate effective counselling and informed decision-making, and the use of risk calculators to inform referral decisions.

Conclusion GPs/FDs play an important role in counselling healthy men eligible to consider PSA testing. However, clear guidance, training and support is required for them to assume this role.

Keywords Screening, Primary care, Prostate cancer, Prostate-specific antigen

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Take home messages

- Opportunistic PSA testing causes even more overdiagnosis/overtreatment than historical, purely PSA-based screening.
- Introducing national screening programmes utilising a risk-adapted approach would facilitate early prostate cancer detection whilst avoiding overdiagnosis/overtreatment.
- With adequate training/guidance, primary care can provide counselling/support to healthy men considering PSA testing throughout the decision pathway.

Introduction

The PSA test is a simple blood-based test to help diagnose prostate cancer at an earlier stage and decrease the number of men dying from the disease. However, it has been the subject of much controversy as it can, in combination with a random systematic prostate biopsy, also identify slow-growing tumours in men who are unlikely to experience any disease-related symptoms during their lives and would therefore face an unnecessary diagnosis (overdiagnosis) as well as the psychosocial consequences of being labelled with a cancer diagnosis, and the associated additional medical tests, treatment and side effects (overtreatment) [1–3], and impact on quality of life (QoL) [4]. These consequences have spawned much debate regarding whether PSA testing does more harm than good [5] and should therefore be avoided as part of quaternary prevention [6], and have also raised concerns among healthy men regarding the potential mortality benefits of PSA testing versus the trade-offs in terms of unnecessary biopsies and likelihood of treatment-related side effects such as incontinence or impotence [7, 8]. As a result, guidance for healthcare professionals was changed, with population-wide PSA-based screening no longer advocated [9]. In the primary care setting, this has led to uncertainty and confusion, and a disparity among guideline recommendations: In some countries, General Practitioners (GPs) and Family Doctors (FDs) have no obligation to offer PSA testing to asymptomatic men [10, 11], while in other countries, GPs/FDs are not recommended to offer an unsolicited PSA test [12] or may only offer a solicited PSA test following a discussion of the possible benefits and harms of PSA testing [13]. There is no EU-level guidance for GPs/FDs on PSA testing. However, a request for a PSA test is common among men visiting their GP/FD. Thus, clear and consistent guidance on PSA testing is required.

Following the cessation of organised PSA-based screening studies, clinical practice patterns have changed globally, with a shift towards PSA testing only in symptomatic men as well as opportunistic testing – conducted outside of an organized screening program, predominantly in men who are unlikely to benefit (i.e. those with a life expectancy of < 10 years). However, in its curable stages, prostate cancer is still asymptomatic. As a result, late-stage diagnoses and prostate cancer-related deaths are rising [14–18]. Moreover, despite current misconceptions, prostate cancer is not an indolent disease as it is currently the third leading cause of death among men in the EU and the second leading cause of death among men in America [19–21].

Over the past decade, knowledge regarding slow-growing versus aggressive prostate cancer has improved, and clinical guidelines for specialists (i.e. Urologists, Oncologists) have evolved. The European Association of Urology (EAU) and the American Urological Association (AUA) guidelines now endorse a risk-adapted approach based on multiple factors, including PSA test result, risk calculators and imaging, with a view to identifying all men with potentially aggressive prostate cancer at an earlier stage, thereby improving outcomes [22–25]. However, as GPs/FDs represent the first point of contact with healthcare service providers for many men, they could play a vital role in counselling and referring men with potentially aggressive prostate cancer to receive specialised hospital-based care, including asymptomatic men who can potentially be cured. Despite this, current guidelines do not provide enough information to busy primary care practices to achieve this goal. Further support and guidance for GPs/FDs is therefore required to ensure all healthy men eligible to consider PSA testing are offered further information and counselling to make an informed decision regarding whether to have a PSA test. Furthermore, in the event of the introduction of national prostate cancer screening programmes, GPs/FDs would play a key role in guiding and supporting patients through the decision pathway following a prostate cancer diagnosis.

This paper provides a summary of the current situation and examines the important role of GPs/FDs in helping to ensure that all men who request or enquire about a PSA test at their GP's/FD's office receive adequate information and counselling to guide their decisions, and that those with potentially aggressive prostate cancer are referred and treated at an earlier stage to improve their chances of cure.

Methods

In 2021, the European Association of Urology (EAU) identified a group of experts with significant interest in the early identification and management of patients with prostate cancer, from both primary care and hospital-based specialists as well as relevant organisations, such as the EAU, World Organization of family doctors -Europe

(WONCA Europe) and European Union of General Practitioners (UEMO), and the European prostate cancer patients organisation, Europa Uomo. The Principle Investigator from the European Randomised Study of Screening for Prostate Cancer (ERSPC) brought in expertise and up-to-date scientific knowledge of the field as a co-author. These experts reviewed relevant literature in the field of prostate cancer, focussing on trends in PSA testing and impact on prostate cancer outcomes as well as guideline recommendations for the use of PSA testing across different regions and timeframes. No systematic literature review was undertaken. Subsequently, the experts convened to review their findings in order to compile recommendations that could facilitate a collaborative approach between hospital-based specialists and primary care practitioners that could help to improve the early detection of prostate cancer both in the absence and presence of national screening programmes.

Trends in PSA testing and prostate cancer deaths

PSA-based screening was introduced in the late 1980s and early 1990s, resulting in a significant reduction in prostate cancer-related deaths [26–29]; however, this was also associated with overdiagnosis and overtreatment, and PSA testing was subsequently discouraged in the early 2010s. At the same time, opportunistic PSA testing took over and was even endorsed in some areas [30]. However, this approach may be more detrimental than organised screening since opportunistic testing typically targets a predominantly elderly population with a shorter life expectancy who are unlikely to derive treatment benefit [31, 32]. Moreover, inappropriate repeat testing is frequent (annually in some countries [33]), even among men with an initial PSA test result of < 1 ng/mL [31]. Interestingly, male GPs/FDs tend to offer more PSA tests than their female counterparts [33, 34], although reasons for this are unclear.

Opportunistic PSA testing patterns also vary between individual GPs/FDs. They are often based on demands and pressure from patients as well as their own preferences and practice methods [33, 35], which may be influenced by conflicting guidelines and advice, as well as mantras perpetuated in the scientific community and the media, such as "PSA testing does not affect mortality rates", "prostate cancer is an old man's disease", "there is no point in PSA testing men over 70 years", "PSA testing does more harm than good", "most men with prostate cancer will die with, but not from, the disease" and "all men would develop prostate cancer if they lived long enough".

In the last decade, and since the decline of PSA testing, the proportion of men diagnosed at an early, and potentially curable stage, has decreased, and late-stage diagnoses and prostate-cancer related deaths are rising [14–18]. Although a direct causal link between PSA testing and prostate cancer deaths cannot be confirmed, changes in PSA testing patterns are likely to be a significant factor.

Interestingly, long-term follow-up data from the European Randomized Study of Screening for Prostate Cancer (ERSPC) show that the relative mortality reduction associated with PSA-based screening is substantial (48% at 16 years for men screened at least twice), and the number needed to screen (NNS) and number needed to treat (NNT) to prevent one prostate cancer death are decreasing [22, 27]. At 9 years of follow-up, the NNS and NNT were 1410 and 48, respectively, whereas at 16 years, these values had reduced to 570 and 18, respectively; this is lower than the NNS observed in breast cancer [36], a setting where organised screening is endorsed and broadly implemented across Europe [37].

Disparities in current guidelines for PSA testing

Variations in guidelines regarding PSA testing are a key concern since they are likely to fuel confusion among GPs/FDs, resulting in significant variations in routine practice.

In primary care, there is no global or EU-level guidance regarding PSA testing and guidelines vary from country to country. In the UK and Australia, PSA testing is not recommended in asymptomatic men [10, 11], and in Germany, DRE is the routine practise, PSA testing is not reimbursed by the healthcare system and so can only be performed at the patient's expense. In the Netherlands and United States, GPs/FDs are not recommended to offer an unsolicited PSA test, with any solicited tests only carried out following a discussion regarding the potential benefits and harms as part of a shared decision-making process [12, 13]. Moreover, there are disparities between primary care guidelines versus those developed for prostate cancer specialists (i.e. Urologists, Oncologists). For example, guidelines and a position statement issued by the EAU in 2021 provide comprehensive guidance to facilitate the early diagnosis of significant (i.e. potentially aggressive) prostate cancer in well-informed men whilst avoiding overdiagnosis/overtreatment of men unlikely to experience prostate cancer-related symptoms during their lifetime. This risk-adapted strategy is illustrated in an algorithm (Fig. 1) and shows how a stepwise approach, starting with a PSA test, incorporates risk calculators and multiparametric magnetic resonance imaging to assess the likelihood of significant prostate cancer and need for further tests or a biopsy. Eligibility criteria for men considering PSA testing are also clearly outlined, along with guidance on time intervals for repeat PSA testing based on age and initial PSA test result [22, 23]. Healthy men

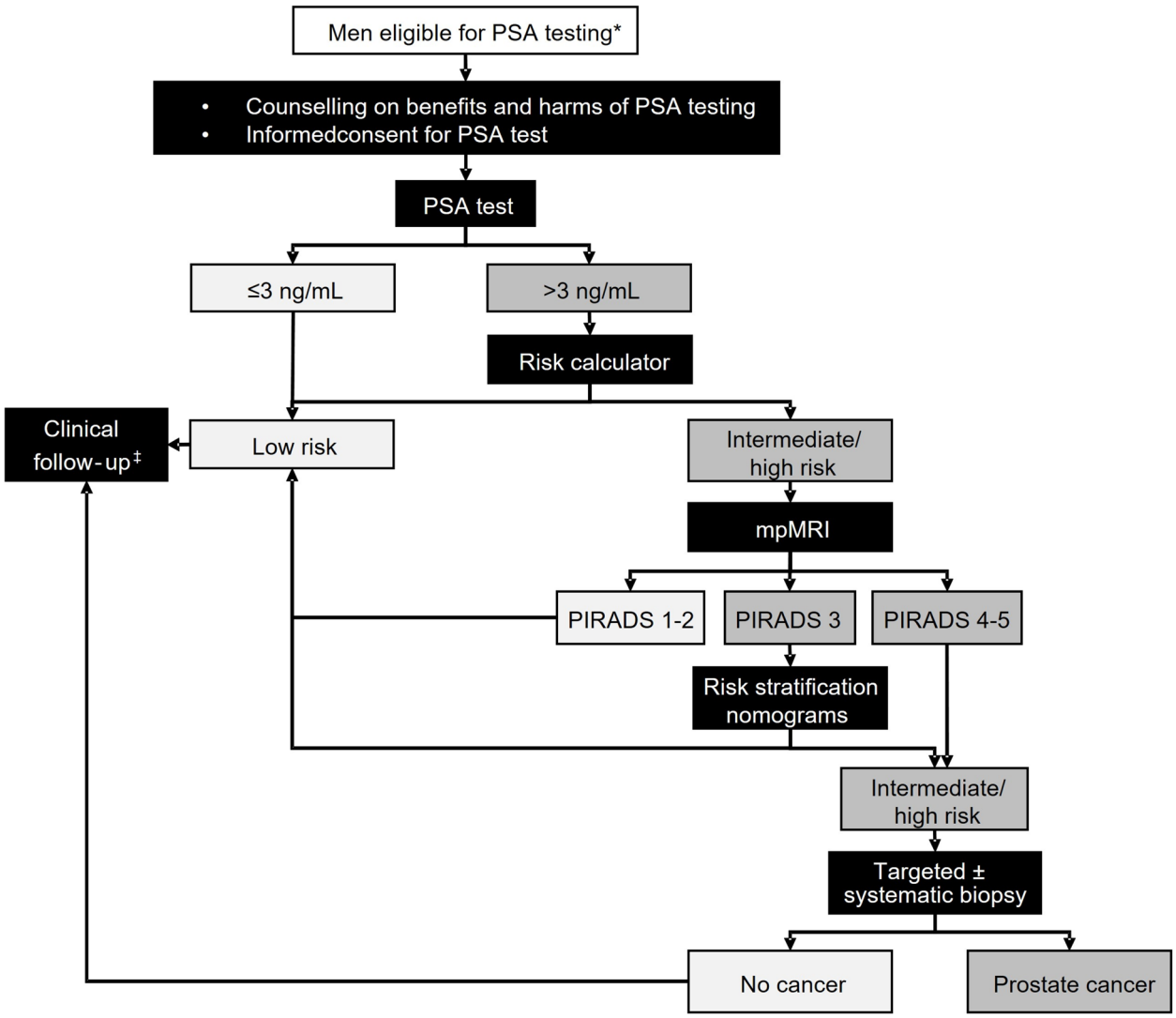

Fig. 1 Risk-adapted algorithm for the early detection of prostate cancer, adapted based on prostate cancer guidelines published by the EAU [22, 23]. *Healthy men with a life expectancy of ≥ 10–15 years AND > 50 years of age OR > 45 years of age with a family history of prostate cancer OR > 45 years of age of African descent OR > 40 years of age carrying BRCA2 mutations. †The patient's values and preferences should always be taken into account as part of a shared decision-making process [22]. ‡ Includes repeat PSA testing after 2–4 years for PSA 1–3 ng/mL or after 5 years for PSA < 1 ng/mL; stop PSA testing in men > 60 years of age with a PSA < 1 ng/mL. EAU, European Association of Urology; mpMRI, multiparametric magnetic resonance imaging; PIRADS, Prostate Imaging-Reporting and Data System; PSA, prostate-specific antigen. [NOTE: Copyright permission attached to submission]

with a life expectancy of ≥ 10–15 years AND > 50 years of age OR > 45 years of age with a family history of prostate cancer OR > 45 years of age of African descent OR > 40 years of age carrying BRCA2 mutations.

This algorithm is now used in several countries, including Norway and Austria, and work is ongoing to collect outcomes data following its use to provide more robust support for this approach [23].

Interestingly, recent data suggest that combining PSA testing with blood or urinary tests that analyse various protein and genetic markers, such as the Stockholm 3 test, the 4 K score, SelectMDx, or Proclarix, following an elevated PSA reduces overdiagnosis and prostate cancer mortality and is cost effective [38–40] thereby corroborating the concept that the net benefit of screening can be improved when PSA testing is combined with newer technologies [41]. Research into new forms of screening and risk stratification beyond PSA levels is ongoing; however currently considered as weak evidence [42, 43].

Finally, Europe's Beating Cancer Plan has led to the European Commission publishing the update of the EU Cancer Screening Recommendations [33] which will

ultimately help facilitate endorsement of a risk-adapted prostate cancer screening programme at an EU level so that it can be incorporated into national cancer plans [23]. Indeed, the European Commission recently issued a report indicating that consideration of the latest scientific evidence could support the extension of targeted screening to prostate cancer [44]. The report also outlines activities and trials that will provide further information to Member States to facilitate the design and implementation of such screening programmes, suggesting that there could be national prostate cancer screening programmes in the near future. Interestingly, organised population-based screening has already been implemented in several regions in Sweden, with more regions due to initiate a similar approach in the next years [37].

The recommendation from the EC to extend the existing screening recommendation from 2003 (breast, cervix and colo-rectal) including prostate, lung and gastric cancer, was discussed in the EU Council with the EU Member States and in the end the EU Council gives green light for EU-wide guidance and collaboration on early detection of prostate cancer [38]. The new recommendation concerning prostate cancer screening is: "Considering the preliminary evidence and the significant amount of ongoing opportunistic screening, countries should consider a stepwise approach, including piloting and further research, to evaluate the feasibility and effectiveness of the implementation of organized programmes aimed at ensuring appropriate management and quality on the basis of PSA testing for men, in combination with additional MRI scanning as a follow up test".

Defining a collaborative approach for early prostate cancer detection

PSA testing is a simple method to facilitate early prostate cancer detection if used properly. Thus, the way forward is not to stop PSA testing but to stop its misuse [45]. Opportunistic testing should not be advocated or used since it has, despite its high cost, no effect on prostate cancer deaths and does not avoid overdiagnosis [46]. Rather, an organised and targeted screening approach is required to ensure eligible men are offered a PSA test since this would facilitate the early diagnosis of significant prostate cancer and also likely reduce the number of unnecessary/opportunistic PSA tests performed among low-risk groups and/or those unlikely to derive any benefit, which could also help alleviate the burden on healthcare costs and resources [47].

The introduction of national prostate cancer screening programmes would provide an effective and proactive approach to raise awareness of prostate cancer and to identify and counsel eligible men, provide PSA testing and, using a risk-adapted strategy such as that outlined by the EAU [23], organise referrals to specialist care for additional tests where required. In this scenario, GPs/FDs would still play an important role in terms of answering any questions that men might have and providing support through the decision pathway for those who go on to receive additional tests and/or a prostate cancer diagnosis.

However, an alternative scenario that could still exist, even in the presence of national screening programmes, is that some men may seek further information and a PSA test directly from their GP/FD. In these cases, men should be provided with relevant information by their GP/FD, such as patient information leaflets and links to dedicated patient information websites [48–56], and then followed-up for further discussion and counselling with their GP/FD so that they are able to make an informed decision regarding whether to have a PSA test, preferably within a national screening programme (if available). As patient information is critical, a proactive approach should also be taken, including the provision of patient information leaflets in hospitals and GP/FD's waiting rooms and information dissemination as part of prostate cancer awareness schemes (e.g. Urology Week, UK Urology Awareness Month and Movember Male Cancer Awareness Month).

GP/FD education and support in this scenario is also important. Firstly, GP/FD's should be aware of the eligibility criteria for PSA testing, as defined by the EAU's guidelines [22]. In addition, the process of counselling men and supporting appropriate discussions regarding PSA testing as part of a shared decision-making process takes time and requires specific skills, but current guidance is limited [1, 50, 57] and this represents a significant unmet need. Moreover, better advice, support and consistent attitudes from healthcare systems and managers are needed [58]. Finally, in cases where men decide to go ahead with a PSA test and receive an elevated test result, referral decisions should be guided by the parameters outlined in national screening programmes, where available. However, in the absence of such programmes, additional information and support are required for GPs/FDs to make these decisions, since referring all men with an elevated PSA leads to overdiagnosis and is associated with significant healthcare costs. Guidance to GPs from Public Health England states that all men with a PSA > 3 ng/mL should be referred [1]. However in the instance of asymptomatic men with a prostate-specific antigen (PSA) level between 3–10 ng/mL and a normal digital rectal examination (DRE) a repeat PSA is allowed [22, 25]. Referral decisions should also be guided by other factors (in addition to PSA level), including age, DRE, family history, anticipated life expectancy and patient preference and other. Risk calculators are simple online

tools that can help support GPs/FDs and patients in this decision-making process since they incorporate several of these parameters to provide a score reflecting the likelihood discovering significant prostate cancer with further examinations and tests [59]. Several risk calculators are available, including those developed by the ERSPC (https://www.prostatecancer-riskcalculator.com/) and the Prostate Cancer Prevention Trial (PCPT; https://riskcalc.org/PCPTRC/), and although they have been largely validated in the secondary care setting, their use in primary care has been shown to almost halve the number of referrals of men with a PSA level of ≥ 3 ng/mL [60]. However, it is always important to keep in mind that a calculator provides an estimate and can be used as a guide rather than the absolute truth for an individual patient. Improved integration between primary and secondary care (e.g. access to tests, patient records, IT systems and resources) could also help to facilitate timely referrals of appropriate patients (i.e. those with an elevated PSA and an anticipated life expectancy of > 10 years who wish to undergo further tests based on their risk calculator results and following a discussion with their GP/FD) and improve the communication and support that they receive. This may be particularly important in geographical locations where access to secondary care is poor and where local primary care provision may assume greater importance.

Conclusions

The introduction of national prostate cancer screening programmes that utilise a risk-adapted strategy such as that outlined by the EAU [23] could facilitate the identification of all men with potentially aggressive prostate cancer at an early stage when they are still asymptomatic, enabling early treatment and potential cure. In this situation, many men could be offered active surveillance instead of treatment, thereby minimising any impact on QoL whilst ensuring their cancer remains under control. In the presence of screening programmes, GPs/FDs could play an important provide additional support for those who receive a prostate cancer diagnosis. advisory role to men throughout the decision pathway and provide additional support for those who receive a prostate cancer diagnosis.

However, as some men may seek further information, patient information as well as clear guidance and support for GPs/FDs are needed to ensure a consistent approach and minimise opportunistic testing. In this scenario, men meeting criteria outlined by the EAU's guidelines [22, 23] could receive adequate information from their GP/FD on prostate cancer, with appropriate follow-up counselling and discussion to allow them to make a well-informed decision regarding whether to have a PSA test, preferably within a national screening programme, if available. The decision to refer men with an elevated PSA should be guided by the parameters outlined in national screening programmes, where available. However, in the absence of such programmes, GPs/FDs should consider multiple factors, including age, family history, anticipated life expectancy, PSA value and patient preference. Here, risk calculators are critical to help support GPs/FDs and patients in this decision-making process. Improved collaboration between hospital-based specialists and primary care could also help to ensure that all men with potentially aggressive prostate cancer receive timely referrals, thereby facilitating an early diagnosis and optimal care to improve their chances of cure.

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Authors' contributions
Study concept and design: FB, HVP, AS, TV, JV, MU, AD, SC, MR Acquisition of data: FB, HVP, AS, SC, MR Analysis and interpretation of data: FB, HVP, AS, SC, MR Drafting of the manuscript: FB, HVP, MR Critical revision of the manuscript for important intellectual content: FB, HVP, AS, TV, JV, MU, AD, SC, MR Statistical analysis: N/A Obtaining funding: N/A Administrative, technical or material support: N/A Supervision: HVP Frederique B. Denijs (FB), Hendrik van Poppel (HVP), Arnulf Stenzl (AS), Tiago Villanueva (TV), Josep M. Vilaseca (JV), Mehmet Ungan (MU), André Deschamps (AD), Sarah Collen (SC), Monique J Roobol (MR).

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The research did not require ethical approval as the study did not use human beings.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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