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Review

Evolution of European prostate cancer screening protocols and summary of ongoing trials

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Population-based organised repeated screening for prostate cancer has been found to reduce disease-specific mortality, but with substantial overdiagnosis leading to overtreatment. Although only very few countries have implemented a screening programme on a national level, individual prostate-specific antigen (PSA) testing is common. This opportunistic testing may have little favourable impact, while stressing the side-effects. The classic early detection protocols as were state-of-the-art in the 1990s applied a PSA and digital rectal examination threshold for sextant systematic prostate biopsy, with a fixed interval for re-testing, and limited indication for expectant management. In the three decades since these trials were started, different important improvements have become available in the cascade of screening, indication for biopsy, and treatment. The main developed aspects include: better identification of individuals at risk (using early/baseline PSA, family history, and/or genetic profile), individualised re-testing interval, optimised and individualised starting and stopping age, with gradual invitation at a fixed age rather than invitation of a wider range of age groups, risk stratification for biopsy (using PSA density, risk calculator, magnetic resonance imaging, serum and urine biomarkers, or combinations/sequences), targeted biopsy, transperineal biopsy approach, active surveillance for low-risk prostate cancer, and improved staging of disease. All these developments are suggested to decrease the side-effects of screening, while at least maintaining the advantages, but Level 1 evidence is lacking. The knowledge gained and new developments on early detection are being tested in different prospective screening trials throughout Europe. In addition, the European Union-funded PRostate cancer Awareness and Initiative for Screening in the European Union (PRAISE-U) project will compare and evaluate different screening pilots throughout Europe. Implementation and sustainability will also be addressed. Modern screening approaches may reduce the burden of the second most frequent cause of cancer-related death in European males, while minimising side-effects. Also, less efficacious opportunistic early detection may be indirectly reduced.

Keywords

developments, Europe, evolution, prostate cancer, protocols, screening, trials

Introduction

In 2020, 2.7 million people in the European Union were diagnosed with cancer and 1.3 million people lost their lives to it. Therefore, the European Commission launched the 'Europe beats cancer' plan in 2021 [1]. The initiative intends to cover the entire cycle of the disease, starting from prevention and early diagnosis to survivorship. In an update of the European Council's Recommendation on cancer screening in 2022, prostate cancer (PCa) was included as one of the main conditions of interest. This opened the way to sort out the current harmful opportunistic testing practices and to streamline population-based screening programmes throughout Europe. The PRostate cancer Awareness and Initiative for Screening in the European Union (PRAISE-U) project will implement and compare multiple pilots for population-based PCa screening, in order to evaluate the feasibility and effectiveness of screening for PCa [2].

Classical screening algorithms for PCa have the potential to improve oncological outcomes such as a reduction in metastases and disease-specific mortality rates but may also cause substantial overdiagnosis, resulting in overtreatment [3,4]. In intention-to-screen analyses from the European Randomized Study of Screening for Prostate Cancer (ERSPC), 20% lower disease-specific mortality rates were found. More favourable numbers have been presented for actual screening participants (correction for non-participation) and when corrected for if PSA would never have been checked for (correction for contamination). The advantage of screening is largely dependent on the prevalence of the disease and the specific screening and diagnostic protocol applied [5]. For example, results from the Göteborg trial showed a 29% mortality reduction [5]. However this study invited participants at younger age (Göteborg 50 years, ERSPC 55 years) and used a more frequent screening interval

(Göteborg 2 years, ERSPC 4 years), which both may partly explain the higher mortality reduction rate.

The first screening studies were started in the late 1980s and early 1990s [3,6]. The initial protocols of the Prostate cancer, Lung, Colorectal, Ovarian screening (PLCO) trial and ERSPC screening protocols applied an algorithm with repeated testing using PSA and DRE, proceeding to systematic biopsy when either test was abnormal. Further risk stratification for biopsy was not applied. The indication for active surveillance (AS) for PCa was limited. These algorithms are no longer in line with the current clinical diagnostic strategy.

Since the start of the PLCO and ERSPC, insight on screening has enormously improved and many new technologies have been developed. Both may be used to optimise the cascade of screening, diagnosis, and treatment of PCa. The perfect screening algorithm hypothetically only invites, diagnoses, and treats men who would otherwise develop symptoms from PCa during their lifetime. The improvements are suggested to at least maintain the advantages of screening, while reducing the side-effects. A risk-adapted early detection programme for PCa that incorporates the latest knowledge and technology will have a much more favourable benefit–risk balance, making it more feasible to apply on a population level.

In this review, the main improvements in early detection protocols will be presented. The cascade of identification of men at risk, the diagnostic algorithm, and expectant management with regards to treatment strategy will be discussed. The initial protocols of the PLCO and ERSPC screening protocol were used as comparators. Additionally, an overview of ongoing trials for screening in Europe is presented.

Methods

A narrative review was performed. Highlighted are the most important developments that have impacted early detection programmes for PCa, surpassing the classic algorithms of screening, diagnosis, and treatment used in the large trials of the 1990s.

The improvements were grouped and presented in the following three categories: (i) screening algorithm, (II) diagnostic pathway, and (III) treatment strategy. Topics and the most important references from the literature were included after consensus between the authors (R.C.N.v.d.B, M.J.R., M.J.v.H.).

As a comparator, the approaches as applied in the first protocols of the two large prospective randomised screening trials the PLCO and ERSPC were used [3,6]. Participants in the screening arm of the United States PLCO trial were offered annual PSA testing for 6 years and DRE for 4 years. The subjects and healthcare providers received the results and decided on the type of follow-up evaluation (no fixed threshold for biopsies). Ages 55–74 were invited. The ERSPC applied repeated (2–4 years), PSA-based screening, with a fixed threshold of PSA level (3–4 ng/mL) to advise sextant systematic biopsy, for which men in a core age group of 55–70 years were invited. Thus, for this review, studies applying DRE-only-based screening or just one-time PSA screening (e.g., the Cluster Randomized Trial of PSA Testing for Prostate Cancer [CAP] trial included participants aged 50–69 years who were offered a single PSA test [7]) were considered obsolete. An overview of the most relevant prospective trials currently on population-based screening for PCa is also presented.

Evidence

Screening Algorithm

The following sections are applicable to all men in the screening pathway (early PSA, age to start and stop screening, individual re-screening interval and gradual introduction at fixed age).

Early PSA

Baseline PSA level in blood of men aged 27–52 years was predictive of death due to PCa in a Swedish cohort; 44% (95% CI 34–53%) of deaths occurred in men with a PSA level in the highest 10th of the distribution at 45–49 years (≥1.6 ng/mL) and at 51–55 years (≥2.4 ng/mL) [8]. Comparable values were found by Preston et al. [9] for a study in the USA researching prostate cancer in Black men (age group 40–49 years top 10th PSA level >1.68 ng/mL, age group 50–54 years top 10th PSA level >1.85 ng/mL). For the Swedish study, men with a PSA below the median (age-group 45–49 years median PSA level 0.68 ng/mL; age-group 51–55 years median PSA level 0.85 ng/mL), have a low risk of PCa metastasis two to three decades later. An early PSA test may therefore be used to risk stratify men who benefit of regular screening later.

The Age to Start Screening

In addition to the previous section, starting screening at a relatively young age is important to achieve adequate reductions in PCa mortality. Based on the Göteborg screening trial, which randomised men aged between 50 and 64 years, Carlsson et al. [10] reported that starting at age 55 years approximately doubles the effect size of screening when compared to starting at 60 years.

A study by Hendrix et al. [11] stratified men according to the Prompt Prostate Genetic Score (PGS) and analysed different screening strategies (characterised by age to start screening and screening frequency). It was found that starting screening

at age 55 years is cost-effective while starting at age 45 years is not. Nevertheless, the study also stated that no definitive conclusion could be drawn on whether stratified screening is cost-effective compared to population-based screening.

To allow intensive screening (i.e., more frequent screening) in high-risk groups, it must be offset by less intensive screening of sufficient number of lower-risk individuals. Hence, the proportions of high- and low-risk groups strongly influence cost-effectiveness, with PCa heterogeneity also playing an important role. In the Rotterdam section of the ERSPC, no statistically significant difference in PCa mortality was observed in men aged >70 years when starting screening [12].

The Age to Stop Screening

The cumulative risk of PCa diagnosis increases strongly with age (7.9% at 60 years, 15% at 65 years, and 21% at 70 years) [13]. Vickers et al. [14] reported that PCa overdiagnosis is strongly associated with age and PSA level. The age at which screening may be stopped may also be individualised. Phasing out screening in men with a low PSA level (<1 ng/mL) at relatively young age (±60 years) and with higher PSA levels (2–3 ng/mL) at relatively older age (±70 years) may be an appropriate strategy to improve the balance between harms and benefits. Remmers et al. [15] found that men with a baseline PSA level <2 ng/mL who continue to have low PSA levels at age 68–70 years, are unlikely to benefit of continuation of screening. Getaneh et al. [16] modelled 230 scenarios for screening, varying in starting age, stopping age, and interval, and found that screening at 3-year intervals between the ages of 55–64 years resulted in a 27% PCa mortality reduction and 28 life-years gained per 1000 men, with 36% of screen-detected men over diagnosed. Still, the age to stop screening should also take into account that the risk of being diagnosed with high International Society of Urological Pathology (ISUP) Grade Group (GG) increases with age (ISUP GG ≥3 cancer (vs GG1) 8.5% higher per year) [17].

Individual Rescreening Interval

The first measured PSA is a strong predictor for later risk. Roobol et al. [18] found that the number of cancers detected during two 4-year interval screening rounds was very low; only eight cases in 1017 men who attended all three screening rounds. Gelfond et al. [19] followed 2923 men for a median of 7.5 years; men with a baseline PSA level in the lowest stratum (0.1–1.0 ng/mL) comprised half of the cohort and had only 3.4% risk of PCa, of which most were low risk. Kovac et al. [20] performed a secondary analysis on a PLCO cohort, assessing the long-term risk of any and clinically significant PCa based on baseline PSA. A low actuarial 13-year risk of diagnosis of clinically significant PCa was found for men aged 55–60 years with a baseline PSA level <2 ng/mL (0.4% for PSA level <0.49 ng/mL, 5% for PSA level 0.50–0.99 ng/mL and 5.4% for PSA level 1.00–1.99 ng/mL). These findings suggest that men with a baseline PSA level <2 ng/mL may require less intensive screening than those with a higher baseline PSA level. Randazzo et al. [21] found that in men with a baseline PSA level <3.0 ng/mL, the PSA level was a strong predictor for finding significant PCa (hazard ratio [HR] 6.06 for 1–1.9 vs <1.0 ng/mL, and HR 7.33 for 2–2.9 vs <1.0 ng/mL). If a comparable percentage of significant PCa is aimed to be found during follow-up, relaxing re-testing for men at low risk, while intensifying follow-up for men at higher risk, should be considered. The re-screening interval may be for example 6–8 years for the lowest risk cases and yearly for high-risk cases.

Gradual Introduction at Fixed Age

In most screening trials, a wide range of ages were invited simultaneously for screening. As the reduction of PCa mortality is most pronounced for younger men, gradually introducing screening at a fixed, relatively young age, may therefore be more effective than the results from screening trials simultaneously inviting a wider range of age groups [10].

Identification of Individuals at Risk The following sections apply to identifying men at risk in the screening pathway (family history and genetic profile).

Family History

Positive family history has been associated with a higher incidence and increased aggressiveness of PCa. Hereditary PCa (2.18% of participants) showed a relative risk (RR) of 2.32 for clinically significant PCa [22]. Bratt et al. [23] found that when the father as well as two brothers are affected by PCa, the probability of high-risk PCa at age 65 years was 11.4% (vs population risk 1.4%). This information can be used to select men at increased risk of significant PCa due to their family history and can be used for targeted screening.

Genetic Profile

Men with genetic alterations have a higher risk of developing PCa and this is also associated with more aggressive disease. It was found that 15.6% of men with PCa have pathogenic variants identified in genes tested and 10.9% of men have germline pathogenic variants in DNA repair genes [24]. A standard PCa panel of genes was tested, including those associated with breast cancer genes (BReast CAncer associated gene 1 [*BRCA1*], *BRCA2*, ataxia telangiectasia mutated serine/threonine kinase [*ATM*], checkpoint kinase 2

[*CHEK2*]), hereditary prostate cancer genes (homeobox B13 [*HOXB13*]), Lynch syndrome genes (MutL homolog 1 [*MLH1*], mutS homolog 2 [*MSH2*], *MSH6*, PMS1 homolog 2, mismatch repair system component [*PMS2*], epithelial cell adhesion molecule [*EPCAM*]) and other relevant genes (nibrin [*NBN*] and tumour protein p53 [*TP53*]). Pathogenic variants were most commonly identified in *BRCA2* (4.5%), *CHEK2* (2.2%), *ATM* (1.8%), *BRCA1* (1.1%), *PMS2* (0.6%) and *MSH2* (0.5%). The Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in BRCA1/2 mutation carriers and controls (IMPACT) study evaluates targeted screening using PSA in men with germline BRCA1/2 mutations. The study found a higher incidence of PCa, with men being diagnosed at a younger age in BRCA2 carriers when compared to non-carriers. Although long-term outcomes and impact on oncological endpoints of this study need to be awaited, screening in this group may be an option [25]. Men of African ancestry all over the world demonstrate more unfavourable outcomes due to a combination of biological, environmental, social, and healthcare factors and may also represent a group with additional benefit of screening [26]. However, many men outside the risk groups based on the genetic profile, could benefit from PSA screening, and proposals for modern risk-based screening algorithms do not take genetic profile into account [27]. The first Prostate Cancer Prevention Trial Risk Calculator (PCPTRC) and the PCPTRC 2.0 both also take race into account. When developing the PCPTRC 2.0, Ankerst et al. [28] found that the risk of high-grade disease was related to African American race, among others.

Figure 1 graphically presents a hypothetical situation of individualised phase-in of screening based on risk (genetics, family) and age, individualised re-screening interval based on PSA, and individualised phase-out of screening based on age/life expectancy. This is not included in proposed algorithms for risk-based screening [27].

Diagnostic Pathway

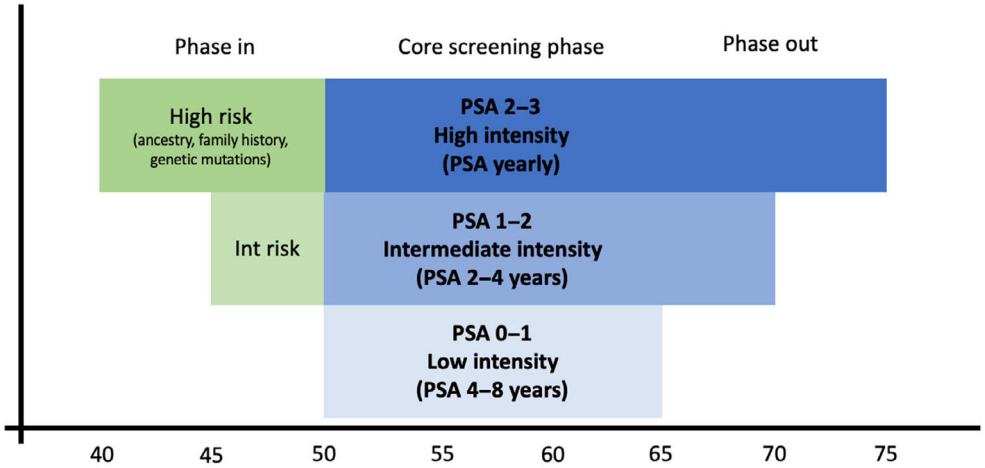
Risk Stratification for Biopsy

PSA Density (PSAD) The PSAD is the PSA level (ng/mL) divided by the prostate gland volume (mL). Nordström et al. [29] found a Gleason score of ≥7 is associated with a higher serum PSA increase per unit volume than a Gleason 6 score or BPH. PSAD is a strong independent predictor of significant PCa and its use is recommended in different clinical scenarios also in combination with other characteristics such as MRI [30].

MRI Kasivisvanathan et al. [31] compared two strategies in patients clinically referred for suspicion of PCa: (i) systematic biopsy for all vs (ii) MRI and targeted biopsy only in those men with MRI suggestive of PCa. In the MRI arm, biopsy indication was reduced (72% vs 100%), more men were diagnosed with cancer classified as significant (38% vs 26%), and less men with PCa classified as insignificant (9% vs 22%).

Hugosson et al. [32] studied this MRI-based pathway in a screening setting. All men with an elevated PSA level received MRI and were then randomised in two groups: (i) all had systematic biopsy as well as targeted biopsy of any MRI lesion vs (ii) only underwent targeted biopsy of any MRI lesion [32]. Men in the MRI-only group had a 54% lower risk of being diagnosed with PCa labelled as insignificant (0.6% vs 1.2%) and a 19% lower risk of being diagnosed with PCa labelled as significant (0.9 vs 1.1%). The significant cancers remaining undetected were generally of intermediate risk and low volume. However, MRI directly

Fig. 1 Schematic representation of individualised phase-in of screening based on risk and age, individualised re-screening interval based on PSA, and individualised phase-out of screening based on PSA and age/life expectancy.



after an elevated PSA level in a screening setting leads to a high percentage of negative MRIs (66%).

Regarding biparametric (bp) vs multiparametric (mp) MRI, 44 articles were analysed in a systematic review and meta-analyses and showed that both have similar accuracy in detecting PCa [33]. The bpMRI (without contrast) is less time-consuming, does not need vascular access and is therefore more comfortable for the patient and cheaper per patient [34]. It may therefore be considered to use bpMRI instead of mpMRI when used in a screening algorithm. Quality control of MRI is essential before any widespread use.

Serum-Based Biomarkers Different risk prediction models incorporating serum biomarkers have been tested to predict the presence of significant PCa. The most well-known scores in which biomarkers are incorporated are: four-kallikrein panel (4K), Prostate Health Index (PHI), and Stockholm3. The 4K score test consists of multiple blood biomarker components: total PSA, free PSA, intact PSA and human kallikrein 2 (hK2) combined with prior biopsy status, age, and DRE results [35]. The PHI score combines total PSA, free PSA and Pro[−2]PSA [36]. The Stockholm3 test consists of a combination of total PSA, free PSA, hk2, prostate secretory protein 94 (PSP-94), growth differentiation factor 15 (GDF-15), >100 genetic markers, and age, family history and prior biopsy status [37].

The diagnostic performance of the models is dependent on the study population and applied thresholds. A review found that the 4K may avoid (systematic) biopsy in 8.7%–64% while missing significant PCa in 1.5%–37%, and the PHI may avoid biopsy in 8.5%–68%, while missing significant PCa in 1.7%–52% [38]. If missing 10% of GG ≥2 cancers would be accepted, a 33% reduction in biopsies would be achieved by using Stockholm3 [39,40]. In men with a moderately elevated PSA but favourable 4K score, the risk of developing metastases on long-term follow-up was low [41].

Urine-Based Biomarkers Different urine-based biomarker essays are also available to predict the likelihood of detecting significant PCa at biopsy, including SelectMDx, ExoDx Prostate Intelliscore (EPI), and MyProstateScore (MPS). The biomarker components include HOXC6, distal-less homeobox 1 (DLX1), prostate cancer antigen 3 (PCA3), ETS transcription factor ERG (ERG), SAM pointed domain containing transcription factor (SPDEF), transmembrane protease, serine 2 (TMPRSS2):ERG, and PSA. The EPI assay is based on the exosomes in urine [42]. It is a quantitative analysis of PCA3, SPDEF-RNA and ERG. McKiernan et al. [42] found a negative predictive value (NPV) of 92% for ruling out clinically significant PCa and would have avoided 26% of biopsies. The PCA3 gene is overexpressed in PCa tissue and is derived from urine after DRE [43]. A study by Gittelman et al. [44] found a NPV of 90% with a cut-off of 25 for the PCA3 score. Alkasab et al. [45] studied the combination of PCA3 with mpMRI and found a NPV of 95% for the combination of mpMRI and low PCA3 scores, while mpMRI only shows a NPV of 83%. Wang et al. [46] performed a meta-analysis encompassing 16 articles and a total of 9952 patients, focusing on urinary biomarker tests. It was found that the SelectMDx, EPI and MPS outperformed PSA serum test with regards to sensitivity, specificity, positive predictive value, NPV, and diagnostic accuracy with EPI having the highest NPV. Concluding, the different assays could reduce the number of biopsies in 26%–44%, while leaving 3.7%–11% of the significant PCa undetected [38].

Risk Calculators (RCs) After initial screening with PSA, different tools have become available to risk stratify men with elevated PSA in whom it is likely that significant PCa is found at prostate biopsy. Roobol et al. [47] studied the application of a RC incorporating PSAD (PSA divided by prostate volume) and DRE in a screening situation and reported a 33% decrease in biopsy indication, with only a few percent of significant PCa cases missed. Remmers et al. [15] reviewed the performance of different RCs; dependent on the threshold used, the Rotterdam Prostate Cancer Risk Calculator could avoid 32–33% of biopsies, leaving 14–25% of insignificant PCa and 5–7% of significant PCa undetected. The PCPTRC 2.0 RC has added the ability to make predictions for low-grade (Gleason score <7) vs high-grade PCa, which can help in the decision to perform a biopsy or not [28].

Gelfond et al. [48] developed a RC based on risk variables identified from the PLCO trial and Selenium and Vitamin E Cancer Prevention Trial (SELECT). This model was externally validated on a San Antonio Biomarkers of Risk (SABOR) cohort. Age, PSA, DRE, family history and African American race were found to be the main clinical variables for predicting a higher risk of PCa. Regarding the 5-year risk prediction, an Akaike information criterion (AIC) of 0.76 was found for the prediction accuracy of any PCa, while it was 0.74 for clinically significant PCa. Clinical variables such as PSAD and DRE can be utilised and integrated in predictive models to improve the biopsy indication over fixed PSA-only thresholds or DRE. In addition, this method enables differentiation between the detection of low- or high-grade disease.

Combinations/Sequences The different sequences and combinations of available tools for risk stratification for biopsy lead to different rates of MRI, biopsy, insignificant PCa, significant PCa, and costs [15,49]. This may be used to balance the early detection strategy when compared to the classic PSA-only-based biopsy indication. Reesink et al. [50] compared the cancer detection rates and number of biopsies indicated for different combinations and sequences of RC

and/or MRI. RC first, followed by MRI left 19% of significant PCa undetected, but avoided 72% of biopsies and 53% of MRIs.

Comparisons Osses et al. [49] provide an overview of the performance of blood-based and urine-based biomarkers, original RCs, RCs including novel biomarkers, MRI, RCs including MRI, biomarkers and MRI combined, and different sequenced/conditional pathways. A maximum of 83% of biopsies and 87% of insignificant PCa could be avoided, although 48% of significant PCa were left undetected.

Wagensveld et al. [51] compared centres with RC-first strategy vs an MRI-first approach in a clinical setting. The rate of cancers labelled as significant PCa was not statistically significantly different (25% vs 24%) between groups, but in the RC-first group more men were diagnosed with PCa labelled as insignificant (13% vs 8.3%), fewer biopsies were avoided in the RC-first group (42% vs 55%), and the number of unnecessary biopsies was also slightly higher in the RC-first group. Cost-effectiveness analysis of the different available pathways are especially relevant in a widespread screening application.

The logistic advantage of biomarkers are the easier use compared to MRI. On the other hand, the disadvantage of biomarkers consist of the fact that still a MRI has to be performed for targeted biopsies in case of PCa suspicion.

Biopsy Strategy

Using MRI to indicate biopsy also opens the possibility of lesion-targeted biopsy cores. The different biopsy strategies (systematic, targeted, combined) lead to different rates of biopsy, insignificant cancer detection, and significant cancer detection. Although the combination of both systematic and targeted cores results in the highest cancer detection rates, targeted only detects only 73% of the insignificant cancers, while still detecting 87% of the significant cancers [52]. The prospective GÖTEBORG-2 shows a RR of 0.81 of finding significant PCa and 0.46 of finding insignificant PCa when MRI-based indication for biopsy and targeted cores are used, when compared to systematic biopsy for all participants. This suggests that the advantages of MRI for clinical patients can be translated to a screening situation [32].

Biopsy Approach

Classic screening studies, such as the ERSPC, used transrectal prostate biopsies. Although the harm of the most frequently reported complications haematospermia and haematuria is mild, a post-biopsy fever rate of 3.9% was reported. Resulting hospital admissions increased from 0.6% in in the period 1993–1996 to 2.1% in 2009–2015 [53]. Currently, the European Association of Urology (EAU) guidelines recommend a transperineal approach due to the low infection rates [30]. A review found a RR of 0.55 for infectious complications [54]. Incorporating transperineal biopsy in the diagnostic pathway after screening may therefore reduce the burden for participants who are screen-positive and are indicated for biopsy.

Treatment Strategy

Expectant Management

Men diagnosed with PCa after screening should only be subjected to the risks of radical therapy when they would become symptomatic during their lifetime when remaining untreated. Men with localised PCa have a very low risk of dying from the disease even when managed expectantly [55,56]. For these cases, an initial strategy of expectant management to avoid or delay the side-effects of curative therapy breaks the link between diagnosis and treatment. This an important step in reducing the harm of overdiagnosis resulting from to screening. At 15 years after starting AS, around half of patients had switched to active therapy [57]. As follow-up criteria to switch to active therapy may have been too strict, future AS protocols aim to individualise and relax criteria [58]. AS is an important development, which reduces the overtreatment and associated side-effects of men diagnosed with low–intermediate risk PCa after screening. Although AS may be applied in patients of all ages, in practice it may be elected less often in younger men.

Patients with PCa with a limited life expectancy are indicated for watchful waiting and should therefore not be invited for screening. Although guidelines mainly take life expectancy into account when recommending expectant management, it may be offered earlier to patients with low-risk disease.

Figure 2 schematically presents the indication for watchful waiting, AS, and active therapy, based on disease risk and life expectancy, using fixed (**A**) or dynamic thresholds (**B**).

Summary of Ongoing Screening Trials

Table 1 [32,59–64] presents an overview and characteristics of the major ongoing and recently closed prospective trials on PCa screening. These trials have in common that there is large focus on the role of MRI and/or biomarker before biopsy.

Trials with Closed Recruitment

The prostate MRI versus PSA screening for prostate cancer detection (MVP) study recruits volunteers via newspapers and radio advertisements in Canada, after which these men are screened via the health service centre. They achieved a

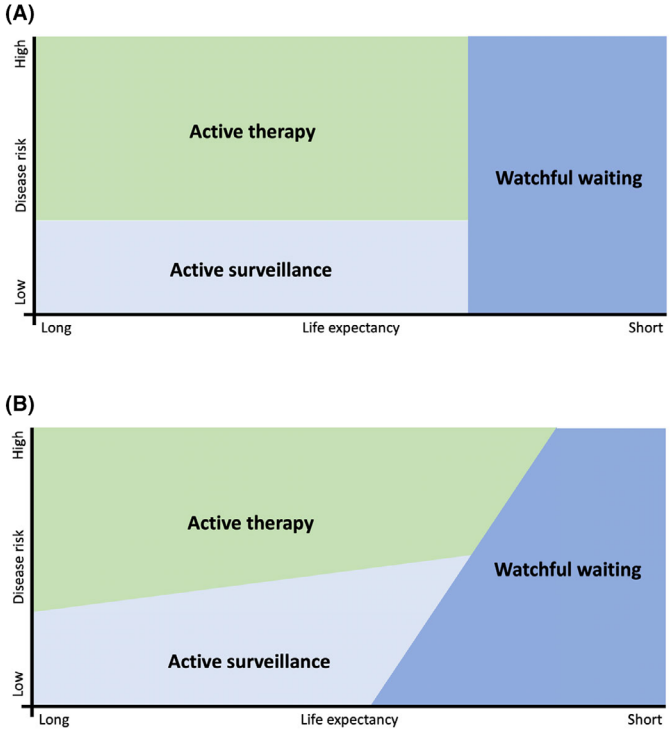


Fig. 2 Schematic representation of the indication for watchful waiting, AS, and active therapy, based on disease risk and life expectancy. (**A**) Fixed thresholds for indications. (**B**) Dynamic thresholds balancing disease risk and life expectancy.

participation rate of 94%. Minimum age is 50 years, with a life expectancy of ≥10 years. Men must not have LUTS to be included. Also, men with abnormal DRE are referred back to the GP. The remaining participants are randomised to a PSA group or MRI group. In the former, men receive a PSA test, with systematic biopsy advised if the PSA level is ≥4.0 ng/mL, but also possible in the PSA range 2.6–4.0 ng/mL. Men randomised to the MRI group receive bpMRI and combined targeted and systematic biopsy in case of Prostate Imaging-Reporting and Data System (PI-RADS) 4–5 lesions. A PSA test is recommended after participation in the MRI arm [59].

The PROBASE study used local German population registries to invite random samples of men aged 45 years. They are randomised between immediate screening vs delayed screening at the age of 50 years. This study achieved a participation of 12%. Based on PSA, participants are assigned in to a low- (PSA level <1.5 ng/mL), intermediate- (PSA level 1.5–2.99 ng/mL) or high-risk (PSA level >3.0 ng/mL) group. The low- and intermediate-risk groups received repeat screening after 5 and 2 years, respectively. Men in the high-risk group received prostate biopsy, with or without mpMRI [60].

The ReIMAGINE (ClinicalTrials.gov identifier: NCT04063566) invites patients aged 50–75 years, identified via databases at partner GP surgeries in the UK. There is no additional information on participation rates. Participants all receive an MRI scan and PSA. The outcomes are reviewed by a trained urologist. In case MRI-visible lesions were identified or the PSAD is ≥0.12 ng/mL/mL the GP is advised to refer the participant to secondary care [61].

The STHLM3-MRI (ClinicalTrials.gov identifier: NCT03377881) randomised men aged 50–74 years, selected randomly via national databases, and applies different screening algorithms, studying cancer detection as main outcome. A participation rate of 41% was found. Eklund et al. [62] presented results of the strategy in which men in the experimental arm had targeted biopsy in case an MRI lesion was seen or systematic biopsy for high STHLM3 biomarker results. While the rates of significant cancer were not statistically significantly different, a 50% reduction in indicated biopsies was reported, with around a third of insignificant cancers found.

Trials with Ongoing Recruitment

The BARCODE1 (ClinicalTrials.gov identifier: NCT03857477) is a screening study in the UK that invites healthy Caucasian men aged 55–69 years for PCa screening based on their genetic profiling. DNA is extracted through saliva samples. After genotyping, a polygenic risk score (PRS) will be

Table 1 Overview of ongoing prospective trials of screening for prostate cancer.

Study	Country	*N*	Protocol focus	References
Closed recruitment				
MVP	Canada	1010	MRI	Nam et al. [59]
PROBASE	Germany	50 000	Baseline PSA young age	Arsov et al. [60]
ReIMAGINE	UK	1000	MRI as primary screening tool	Marsden et al. [61]
STHLM-3	Sweden	12 750	Serum-based biomarker (STHLM3). MRI. TB only	Eklund et al. [62]
Ongoing recruitment				
BARCODE1	UK	5000	Genetic screening	Benafif et al. [63]
GÖTEBORG-2	Sweden	54 000	MRI. TB only	Hugosson et al. [32]
ProScreen	Finland	120 000	Serum-based biomarker (4K). MRI. TB only	Rannikko et al. [64]

TB, targeted biopsies.

calculated. When study participants have a PRS above the 90th centile value, an invitation for MRI and biopsy follows. Participants with a negative biopsy result will have their PSA tested annually. If there is a significant increase in PSA, repeat biopsy will be performed [63].

The GÖTEBORG-2 (International Standard Randomised Controlled Trial Number [ISRCTN] Registry number: ISRCTN94604465) invites men aged 50–60 years for repeated PSA testing in Sweden. If the PSA level is ≥3.0 ng/mL, MRI is performed [32]. Participants are then randomised to a control group in whom systematic and targeted (in case of prostatic lesion) biopsy is performed, or a study group who are only biopsied if MRI shows abnormalities, and a targeted biopsy only strategy is applied.

The ProScreen (ClinicalTrials.gov identifier: NCT03423303) is a Finnish screening initiative inviting men aged 65 years who are identified from the population registry. A three-step strategy is applied, sequencing PSA (≥3.0 ng/mL), 4K kallikrein panel (risk >7.5%), and MRI. If MRI shows abnormalities, targeted biopsies are performed, men with normal MRI but PSAD ≥0.15 ng/mL/mL receive systematic biopsy [64].

The PRAISE-U is not a screening study itself but aims to compare different pilot screening initiatives currently running in Europe [2]. The PRAISE-U consortium has united various experts from different member states in collaboration with the EAU. PRAISE-U aims to get insight and assess needs in member states to design a cost-effective screening algorithm. The diagnostic algorithms in the pilot studies will include an individualised multi-step risk stratification approach. Also, PRAISE-U aims to raise awareness of PCa and its implications. Performance of the screening pilots will be monitored and evaluated to assess applicability in heterogenous European healthcare models. Screening pilot sites will include Ireland, Galicia, Althaia, Poland, and Lithuania. The insights gained will be shared via a knowledge hub.

Two European regions have an ongoing national screening programme [65,66]. The Early Prostate Cancer Detection Programme (EPCDP) in Lithuania started in 2006 through a PSA-test invitation for men aged 50–74 years visiting their GP. When the PSA level was ≥3 ng/mL, patients underwent a DRE and biopsy in case of an abnormal DRE. Cancer detection rate was 10.4–15% among PSA test-positives, and screening participants were more likely to be diagnosed with local disease compared to non-screeners between 2006 and 2015. The Organised Prostate Cancer Testing Programme (OPT) in Sweden started in 2020 with screening in two regions by inviting men aged 50–74 years for a PSA test. Participants undergo an MRI if the PSA level is ≥3 ng/mL and based on the MRI results, they stratified as low- or high-risk indicating biopsy or not.

Discussion

This review summarises the most important potential improvements in the early detection cascade of screening, diagnosis, and treatment that have been introduced over the past three decades. For our screening algorithm the main risk factors include: age related to screening (early PSA, age to start and stop screening), individual re-screening interval and improved identification of individuals at risk (family history, genetic profile) as shown in Table 2. The diagnostic algorithm may be optimised with: improved risk stratification for biopsy (RCs, MRI, biomarkers, combinations/sequences), targeted prostate biopsy, and transperineal biopsy approach. Regarding treatment for men diagnosed with PCa, the main improvement comprises AS for low- to intermediate-risk disease. It can be assumed that incorporating these improvements in a modern screening protocol will at least retain or even improve the advantages of screening for PCa, while importantly reducing side-effects, mainly overdiagnosis with the risk of overtreatment.

Results from the OPT trial in Sweden recently showed that incorporating MRI and PSAD in the pathway avoided >50% of biopsies for men aged 50 years with a PSA level ≥3 ng/mL [67]. These findings contribute to the feasibility of population-based screening.

In the Rotterdam section of the ERPSC, after 21 years follow-up, to reduce one death due to PCa, the number needed to invite (NNI) was 246 and number needed to diagnose (NND) 14; to reduce one metastatic case, NNI was 121 and NND seven [12]. Still, the side effects of screening, mainly overdiagnosis, have been considered by policy makers in most countries to be too large to start population-based screening. The many potential improvements in screening, diagnosis, and treatment may improve the cascade of screening, diagnosis, and treatment. Vickers et al. [68] found that treatment of cases with high Gleason score and higher T stage, at relatively younger age, has the most impact on overall survival. Screening should aim at detecting at an early moment these malignancies that would cause local symptoms, metastases, or death at a later moment during a man's lifetime. By reducing the diagnosis of cases that would not, the main side-effect of overdiagnosis is also reduced, leading to a more favourable benefit–harm ratio of PSA screening. Combining and sequencing different tools for risk stratification into two- or three-tier risk models can be used to balance cancer detection, overdiagnosis of insignificant PCa, and the burden of the diagnostic algorithm on an individual and healthcare level [49]. Risk-adapted screening, diagnosis, and treatment (Fig. 2) approaches have therefore been propagated as a potential future approach for application of screening in Europe. This strategy involves a repeat testing interval based on age and PSA level, and risk stratification for biopsy after an elevated PSA using a two-tier

Table 2 Overview of the main improvements in the early detection cascade of screening, diagnosis, and treatment.

		Classic algorithm for screening, diagnosis, and treatment	Modern algorithm for screening, diagnosis, and treatment	Impact
Screening algorithm	Starting age	Fixed	Individualised, based on risk groups	Increase efficacy
	Stopping age	Fixed	Individualised, based on last PSA	Reduce overdiagnosis
	Risk groups	Age only	Age, optional: baseline PSA, family history, genetic profile	Early identification of men who benefit most
	Re-testing interval	Standard re-testing 2–4 years	Individualised, based on	Relax testing in low risk, intensify testing in high risk
Diagnostic pathway	Indication for biopsy	Fixed PSA threshold and/or abnormal DRE	RC, MRI, biomarkers, combinations/ sequences	Reduce unnecessary biopsy and insignificant cases, maintain significant PCa detection
	Biopsy strategy	Sextant systematic needle biopsy	Targeted biopsy	Reduce overdiagnosis, more PCa labelled as significant
	Biopsy approach	Mainly transrectal biopsy	Transperineal biopsy	Lower risk of infection/sepsis
Treatment strategy	Low- to intermediate-risk disease M0	Limited indication for expectant management of low-risk disease	Standard initial expectant management (AS)	Reduce overtreatment and associated side effects

approach combining PSAD or multivariable RC with biopsy in men with high risk or additional MRI imaging before biopsy indication [27].

Besides reducing rates of metastases and PCa-specific mortality, and improvement in quality of life, the introduction of a population-based screening in men who are most likely to benefit may also reduce opportunistic screening in men who are less likely to benefit from PCa screening. Opportunistic screening has been associated with higher risk of overdiagnosis and overtreatment, and lower adherence to biopsy indications, follow-up recommendations, and treatment advice. A screening protocol could harness the power of PSA and optimise the advantages of screening by applying the most efficient algorithm for identification of men at elevated risk, biopsy indication and strategy, and indications for treatment. Future developments include dynamic and individualised risk indication and follow-up, individualised biopsy decisions and strategies, and wider indication for expectant management.

Different ongoing trials are prospectively incorporating one or more of the improvements in a screening setting. These studies will provide evidence on the impact of an algorithm of early detection applying modern insights regarding screening, diagnosis, and treatment. In addition, the European Union sponsored PRAISE-U consortium will compare and evaluate the performance of screening pilots in different European Union member states.

Decreasing the side-effects of screening, while at least maintaining the advantages, when compared to screening algorithms from three decades ago, may result in a favourable balance of which millions of men may benefit. Even when the long-term oncological outcomes of modern early detection strategies are not yet available, the more favourable harm–benefit ratio may be used to justify introduction of population-based PSA screening. This may reduce the burden of the most frequently diagnosed, and second most lethal form of cancer in males.

Conclusion

Compared to the classic PCa screening algorithm of diagnosis and treatment of PCa developed in the early 1990s, many improvements have been introduced in the management of PCa in clinical practice. These include early identification of risk groups, a focus on screening at relatively young age, different methods for risk stratification for biopsy after elevated PSA, imaging-based targeted biopsy, individualised re-testing interval, and AS for low- to favourable intermediate-risk PCa. Level 1 evidence on how these modern diagnostic and therapeutic developments would impact long-term oncological outcomes when incorporated in a screening algorithm is still largely lacking. It can be assumed that a modern screening protocol will at least retain or even improve the advantages of screening for PCa, while importantly reducing side-effects. Studies and pilots on modern screening are necessary to implement PCa screening on a wider level.

Disclosure of Interests

None.

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Abbreviations: AS, active surveillance; ATM, ATM serine/threonine kinase; bp, biparametric; BRCA, BReast CAncer associated gene; CHEK2, checkpoint kinase 2; EAU, European Association of Urology; EPI, ExoDx Prostate Intelliscore; ERG, ETS transcription factor ERG; ERSPC, European Randomized Study of Screening for Prostate Cancer; GG, Grade Group; hK2, human kallikrein 2; HOX (B13)(C6), homeobox (B13) (C6); HR, hazard ratio; ISRCTN, International Standard Randomised Controlled Trial Number;

ISUP, International Society of Urological Pathology; 4K, four-kallikrein panel; mp, multiparametric; MPS, MyProstateScore; MSH(2)(6), mutS homolog (2) (6); MVP, prostate MRI versus PSA screening for prostate cancer detection (study); NND, number needed to diagnose; NNI, number needed to invite; OPT, Organised Prostate Cancer Testing Programme; PCa, prostate cancer; PCA3, prostate cancer antigen 3; PCPTRC, Prostate Cancer Prevention Trial Risk Calculator; PHI, Prostate Health Index; PLCO, Prostate cancer, Lung, Colorectal, Ovarian screening (trial); PMS2, PMS1 homolog 2, mismatch repair system component; PRAISE-U, PRostate cancer Awareness and Initiative for Screening in the European Union (project); PRS, polygenic risk score; PSAD, PSA density; RC, risk calculator; RR, relative risk; SPDEF, SAM pointed domain containing transcription factor.