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Screening for prostate cancer: evidence, ongoing trials, policies and knowledge gaps

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ABSTRACT

Long-term screening with serum prostate-specific antigen (PSA) and systematic prostate biopsies can reduce prostate cancer mortality but leads to unacceptable overdiagnosis. Over the past decade, diagnostic methods have improved and the indolent nature of low-grade prostate cancer has been established. These advances now enable more selective detection of potentially lethal prostate cancer. This non-systematic review summarises relevant diagnostic advances, previous and ongoing screening trials, healthcare policies and important remaining knowledge gaps.

Evidence synthesis and conclusions: The strong association between low serum PSA values and minimal long-term risk of prostate cancer death allows for adjusting screening intervals. Use of risk calculators, biomarkers and MRI to select men with a raised PSA value for biopsy and lesion-targeting rather than systematic prostate biopsies reduce the detection of low-grade cancer and thereby overdiagnosis. These improvements recently led the European Union to recommend its member states to evaluate the feasibility and effectiveness of organised screening programmes for prostate cancer. Nonetheless, important knowledge gaps remain such as the performance of modern diagnostic methods in long-term screening programmes and their impact on mortality. The knowledge gaps are currently being addressed in three large randomised screening trials. Population-based pilot programmes will contribute critical practical experience.

INTRODUCTION

Prostate cancer is one of the leading causes of cancer death in many countries.[1] The disease has a long, asymptomatic, organ-confined stage and is usually incurable when symptomatic. Serum prostate-specific antigen (PSA) testing was introduced in the late 1980s to identify asymptomatic men with prostate cancer.[2] Although serum PSA is a sensitive marker of potentially lethal prostate cancer, its specificity is low.[3] Moderately elevated PSA values (3–10 ng/mL) are more often caused by benign prostatic hyperplasia than prostate cancer.[4 5] As digital rectal examination and transrectal ultrasound cannot rule out clinically significant prostate cancer, a systematic prostate biopsy became the standard diagnostic investigation for men with raised PSA values (≥3 or 4 ng/mL). A European, multinational, randomised screening trial shows that prostate cancer mortality can be reduced by screening but also that the use of systematic biopsies leads to unacceptably high rates of overdiagnosis.[6] As latent, microscopic prostate cancer is common in middle-aged and elderly men,[7] this is not surprising.

Over the past couple of decades, research has been devoted to developing diagnostic methods that more selectively identify men with a potentially lethal prostate cancer. An important progress was the introduction of pre-biopsy MRI and lesion-targeting biopsies.[8–13] Other important advances include biomarkers and nomograms that can aid in identifying men who despite a moderately raised PSA value are unlikely to have a potentially lethal prostate cancer.[14] Moreover, modifications of the Gleason prostate cancer grading system have led to a definition of the lowest grade (Gleason score 6) that now exclusively includes clinically insignificant, slowly progressing cancers with minimal metastatic potential.[15–18]

These advances recently led the Council of the European Union to recommend the member states to evaluate the feasibility and effectiveness of organised prostate cancer screening.[19] Our review summarises the results from previous prostate cancer screening trials, relevant diagnostic research, ongoing prostate cancer screening trials and current healthcare policies, and outlines remaining scientific knowledge gaps and practical issues.

METHODS

PubMed was searched on 2 January 2023 for clinical trials, systematic reviews and meta-analyses with the terms “screening” AND “prostatic neoplasm” OR “prostate cancer” AND (“biopsy” OR “diagnosis” OR “mortality” OR “detection”) published since

1 January 2018. Similar searches were done for the diagnostic methods described in the review. Relevant articles were selected by OB. Additional articles were identified in reference lists. On the same day, a search was done on ClinicalTrials.gov and IRSCTN.com for 'prostate cancer screening' to identify ongoing trials.

EVIDENCE

Previous screening trial results

Except for a few older studies, all randomised prostate cancer screening trials reporting on prostate cancer mortality outcomes used serum PSA as the primary screening test followed by systematic biopsy.[20] Currently relevant trials are summarised below.

The European Randomized Study of Screening for Prostate Cancer (ERSPC)

The multinational European Randomized study of Screening for Prostate Cancer (ERSPC) was initiated in 1993.[21] Recruitment and randomisation procedures differed across countries. Three centres designed population-based effectiveness trials (randomisation before consent) and four centres efficacy trials (consent before randomisation). The core age group for endpoint analyses was 55–69 years at randomisation. The primary endpoint was prostate cancer mortality. Secondary endpoints included metastatic disease and quality of life

The primary screening test was serum PSA. Men with PSA ≥3.0 ng/mL were referred for a systematic prostate biopsy (in Finland, men with PSA 3.0–3.9 ng/mL had an ancillary test to select for biopsy). The screening interval was 4 years in most centres.

After 9 years of median follow-up of 162 242 men, the rate ratio for prostate cancer death in the screening versus the control group was 0.80 (95% CI 0.65 to 0.98). The absolute prostate cancer mortality risk difference was 0.71 prostate cancer deaths per 1000 men. This, together with an excess incidence of 34 prostate cancer cases per 1000 men, translates into 1410 invited men and 48 additional prostate cancer diagnoses (numbers needed to invite and diagnose) to avert one death from prostate cancer.[22] The main results of this and three later publications are shown in table 1.[6 22–24] With longer follow-ups, the absolute prostate cancer mortality risk difference increased and the numbers needed to invite and diagnose decreased. Twelve-year follow-up data from four centres showed a 50% reduction of metastatic disease at the time of diagnosis and a 30% reduction overall, that is, including also metastasis detected during follow-up.[25] An analysis accounting for non-compliance and PSA testing in the control group, based on the Dutch part of ERSPC, shows that the net mortality reduction among screening participants was 51% (intention-to-screen analysis: 32%).[26]

Gothenburg-1 screening trial

The Gothenburg-1 trial started in 1995 as an independent trial but since 1996 constitutes the Swedish branch of the ERSPC. A population-based sample of 20 000 men aged 50–64 years was randomised 1:1 to either biennial PSA screening with a 3 ng/mL threshold for a systematic 6-core biopsy, or to a control group. As many as 93% of the screened men with a PSA ≥3.0 ng/mL had at least one prostate biopsy.[27] Despite that PSA testing was common in the control group (72% had at least 1 PSA test[28]), the Gothenburg-1 trial reported the greatest prostate cancer mortality reduction of all screening trials. After 14 years, the relative reduction was 44% (95% CI 28% to 64%)[27]; the absolute prostate cancer mortality was reduced from 0.9% to 0.5% (difference 0.4%, 95% CI 0.17% to 0.64%).[27] After 22 years, the relative reduction was 29% (95% CI 9.0% to 0.45%) and the absolute reduction was 0.6% (95% CI 0.15% to 1.0%).[29] Younger age at screening start (50–55 years vs 60 years) and primary school education only were both associated with a greater relative mortality reduction.[30–32] The number needed to diagnose to prevent one prostate cancer death was 12 after 14 years and 9 after 22 years.[27 29]

A mere 0.6% of the men with a moderately raised PSA (3–9.9 ng/mL) and a negative first biopsy died from prostate cancer within 20 years.[33] Most men (79%) in the screening group who died from prostate cancer either started screening after the age of 60 years, did not attend or were diagnosed with prostate cancer after screening had stopped.[29] The protective effect of screening on

Table 1 Summary of results from the European Randomized Study of Screening for Prostate Cancer (ERSPC) after 9–16 years of follow-up

Median follow-up (years)	9	11	13	16
Positive predictive value of biopsy (%)	24.1	24.2	24.2	24.2
PCa diagnosed in screening group (No)	5990	6963	7408	8444
PCa diagnosed in control group (No)	4307	5396	6107	7732
Excess PCa incidence per 1000 men	34	35	35	30
Relative PCa mortality reduction (%)	20	21	21	20
Absolute PCa mortality reduction per 1000 men	0.71	1.07	1.28	1.76
Reference number	22	23	24	6

PCa, prostate cancer.

prostate cancer mortality waned off 10–12 years after screening cessation.[34]

The prostate cancer incidence in the control group had after 24 years still not reached the incidence in the screening group, which means that many screening-detected cancers would never have been clinically diagnosed.[31]

The Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial

The PLCO cancer screening trial recruited 76 693 US men aged 55–74 years from 1993 to 2001. Men in the screening group underwent annual PSA testing for 6 years and annual digital rectal examination for 4 years. After 13 years, the relative prostate cancer incidence was 1.12 (95% CI 1.07 to 1.17) and the relative risk of prostate cancer death was 1.09 (95% CI 0.87 to 1.36) in the screening group compared with the control group.[35] These results cannot, however, be used for evaluating the effect of screening versus no screening, as almost half of the enrolled men had been PSA tested before entering the study, 90% of the control men were PSA tested and less than half of the men with raised PSA underwent a prostate biopsy.[36–38]

The Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) trial

The UK-based CAP invited 75 707 men aged 50–69 years for a single PSA test via their primary care practice from 2001 to 2009, of whom 36% participated.[39] A control group of almost 350 000 men received standard care, of whom 25% were PSA-tested at least once.[40] After 10 years, a greater proportion of men in the intervention group (6.0%) than in the control group (3.6%) had been diagnosed with prostate cancer, but there was no difference in prostate cancer mortality (rate ratio 0.96, 95% CI 0.85 to 1.08).

Improved diagnostic methods

PSA for risk stratification

PSA levels within the 'normal' range (<3 ng/mL) at age 45–60 years are strongly associated with up to 25-year risks of advanced, metastatic and lethal prostate cancer.[3 41–47] For example, PSA values below the age-specific median (eg, 1.1 ng/mL at age 60) are associated with 15-year and 25-year risks of lethal prostate cancer far below the population average.[3 41 42 46 47] PSA levels can therefore be used to adapt screening intervals and stop-age to men's predicted long-term risk of lethal prostate cancer.[48 49]

PSA density

Serum PSA is a non-specific test for prostatic disease. Gleason score ≥7 cancer is, however, associated with a higher serum PSA rise per unit volume than Gleason score 6 cancer and benign prostatic tissue.[5 50] This ratio between serum PSA and prostate volume (PSA density) is therefore a better marker for Gleason score ≥7 cancer than serum PSA alone.[51] PSA density can be used for selecting men with an unsuspicious or equivocal prostate MRI for biopsy.[52] Men with a moderately raised PSA value, an unsuspicious MRI and a PSA density <0.1 ng/mL/cm^3 are not more likely to have a Gleason score ≥7 prostate cancer than men in the general population.[52]

Other biomarkers

Conventional serum PSA tests measure both free and complexed forms. Assays detecting free PSA,[53 54] the subfractions intact PSA[55] or −2 proPSA,[56] or the closely related hK2 protein[57] may be used to improve test specificity, either alone or in combination such as in the Prostate Health Index (PHI) and 4Kscore tests.[58–63]

Two statistical models based on biomarker measurements in serum with or without clinical data have been evaluated in large screening populations: the Stockholm-3 test and 4Kscore test. The Stockholm-3 test measures total and free serum PSA, hK2, microseminoprotein-β, macrophage inhibitory cytokine-1, a polygenic risk score calculated from single-nucleotide polymorphisms, age, first-degree family history and previous biopsy.[64] The Stockholm-3 test may reduce unnecessary systematic biopsies by 44% and detection of Gleason score 6 cancer by 17%, compared with a systematic biopsy for all men with PSA ≥3 ng/mL.[64] The test may also be used to select men for MRI, which in a randomised trial reduced the need for MRI by 36%.[65] The Stockholm-3 test has not been externally validated and there has been some variation in the cut-offs and test components.[66–68]

The 4Kscore test is based on measuring free, intact, total PSA and hK2 in blood and information about age, digital rectal examination and prior biopsy.[63] Use of the 4Kscore test decreases unnecessary biopsies by 30%–50% while maintaining >90% detection of Gleason score ≥7 and >97% of Gleason score ≥4+3=7 cancer.[69 70] Furthermore, the 4Kscore predicts a 10–20-year risk of lethal prostate cancer among healthy middle-aged men with 'normal' or moderately high PSA values.[42 46]

MRI and lesion-targeting biopsy

Use of MRI and lesion-targeting biopsies substantially reduce the detection of Gleason score 6 prostate cancer and somewhat increase the detection of Gleason score ≥7 cancer, compared with a systematic prostate biopsy.[10 12 13 71] A systematic review and meta-analysis of 5831 patients from 26 clinical practice studies compared MRI and lesion-targeting biopsies with systematic biopsies and showed a relative detection rate of 0.65 (95% CI 0.55 to 0.77) for Gleason score 6 and 1.3 (95% CI 1.2 to 1.4) for Gleason score ≥7 cancer.[12]

Recently, also data from screening settings have been reported. The population-based Stockholm-3-MRI study randomly allocated 1532 men aged 50–75 years with PSA ≥3 ng/mL to either a systematic biopsy only or an MRI and targeted plus systematic biopsies.[13] Gleason score ≥7 cancer detection was similar in both groups. Gleason score 6 cancer was detected in 4% of the MRI group in 12% of the systematic biopsy group (8% difference, 95% CI 5% to 11%). Fifty-six per cent of the men with PSA ≥3 ng/

mL had an unsuspicious MRI and avoided biopsy. Results from the Gothenburg-2 trial are reported below.[10]

MRI has also been evaluated as the primary screening test: the IP-Prostagram study screened 403 men aged 50–69 years with PSA, transrectal ultrasound and an MRI.[72] All men with at least one positive screening test had a systematic biopsy; men with an MRI or ultrasound lesion also had a targeted biopsy. The diagnostic pathway with an MRI threshold of ≥4 on the 5-tier Prostate Imaging—Reporting and Data System (PI-RADS) score resulted in 10.6% positive tests, 2.7% detection of Gleason score ≥7 cancer and 1.2% Gleason score 6 cancer. A PSA threshold of ≥3 ng/mL resulted in 23.7% positive tests and the detection of Gleason score ≥7 cancer in 1.7% and Gleason score 6 cancer in 1.6% of the men. Similar results were recently reported from the MRI Versus PSA in Prostate Cancer Screening (MVP) study.[73]

Several meta-analyses conclude that prostate MRI without contrast enhancement (bi-parametric MRI) has similar diagnostic accuracy as multiparametric MRI with intravenous contrast medium.[74–78] A pooled analysis of 17 studies directly comparing bi-parametric with multi-parametric MRI showed no significant differences in sensitivity or specificity.[75] In a prospective, paired study of 551 men in a screening trial, bi-parametric MRI was non-inferior to multiparametric MRI, with a relative risk for detection of any prostate cancer 0.99 (95% one-sided CI: 0.95 to 1.0).[79]

Risk calculators

The first wave of diagnostic prostate cancer risk calculators included clinical variables to select men with a moderately raised serum PSA value for biopsy.[80] Few of them are externally validated, which is a prerequisite to properly assess their clinical value.[81–87] Risk calculators also incorporating prostate volume assessed by transrectal ultrasound better identify men with Gleason score ≥7 cancer.[51 88 89] More recently, risk calculators substituting digital rectal examination with MRI have been developed, some of which also include new biomarkers.[90 91] A recent systematic review identified 18 risk calculators incorporating MRI results.[91] All improved prediction of Gleason score ≥7 cancer better than risk calculators without MRI, but only seven were externally validated and even fewer met requirements for routine use.[91]

Ongoing screening trials

Three large, ongoing randomised screening trials and some smaller trials are described below. The designs of the three large trials are summarised in table 2.

Gothenburg-2 trial (Sweden)

Gothenburg-2 is a population-based, randomised screening trial evaluating three main research questions[92]:

- Does a screening algorithm with a pre-biopsy MRI in men with PSA ≥3.0 ng/mL and lesion-targeted biopsies reduce detection of clinically insignificant cancer while maintaining sufficient detection of clinically significant cancer, compared with a systematic biopsy in all men with PSA ≥3.0 ng/mL?
- Does a PSA cut-off of 1.8 ng/mL detect more clinically significant cancer without increasing overdiagnosis?
- Does screening with PSA, pre-biopsy MRI and lesion-targeted biopsies reduce prostate cancer mortality compared with a non-invited control group?

In 2015–2020, 58 225 men aged 50–60 years without a prostate cancer diagnosis were identified from the population register and randomly allocated 2:1 to a screening group or a control group without prior consent (Zelen design). Of 38 775 men in the screening group invited to the first round 17 980 (46%) participated and were further randomly allocated to one of three screening algorithms (figure 1). The men are re-invited with 2–8 years' interval until age 63–76 years. Screening intervals and stop age depend on the PSA value.

Diagnostic outcomes of the first screening round for men with PSA ≥3.0 ng/mL were recently published.[10] In arms 2 and 3 combined (MRI-targeted biopsies only), 2.8% of the invited men had a biopsy, compared with 6.8% in arm 1 (systematic biopsy). Clinically insignificant (Gleason score 3+3=6) cancer was detected in 66 men in arms 2 and 3, and in 72 men in arm 1: relative risk 0.46 (95% CI 0.33 to 0.64), absolute risk difference 0.7%). Gleason score ≥7 cancer was detected in 110 men in arms 2 and 3, and in 68 men in arm 1: relative risk 0.81 (95% CI 0.6 to 1.1), absolute risk difference 0.2%. Of 10 Gleason score 3+4=7 cancers detected on systematic biopsy cores only, 7 were stage T1c and 6 had <5% Gleason pattern 4; none had Gleason score ≥4+3=7. Results from repeated screening rounds are planned for publication in 2023–2024 and prostate cancer mortality data in 2027.

ProScreen (Finland)

The ProScreen trial investigates a screening algorithm including PSA, a four-kallikrein serum panel (4Kscore) and MRI with targeted biopsies. The primary endpoint is prostate cancer mortality after 15 years of follow-up. Secondary endpoints include the cumulative incidences of low-grade cancer and of locally advanced or metastatic prostate cancer after 5 years.

ProScreen covers the target age group 55–63 years in the entire male population of the study areas. A total of 117 000 men (initial protocol: 67 000 men) are randomised 1:3 to a screening group or a control group (inclusion is ongoing). To ensure a representative study population randomisation is done before consent in the screening arm and without consent in the control arm (Zelen design). Men in the screening group with a PSA ≥3.0 ng/mL have a 4Kscore test and those with a positive 4Kscore (≥7.5%) are referred for a prostate MRI (figure 2). Men with a suspicious lesion on MRI (PI-RADS score ≥3) are referred for a targeted prostate biopsy; those with an unsuspicious MRI and a PSA density ≥0.15 ng/mL/cm^3 are referred for a systematic prostate biopsy. Men with PSA <1.0 ng/mL are re-invited after 6 years, men with PSA 1.0–2.9 ng/

Table 2 Summary of the design of ongoing randomised trials of screening for prostate cancer

Trial (reference) and trial groups	Randomisation model and inclusion years Number of men	Start ages (years)	Participation rate	PSA cut-off (ng/ml)	Ancillary test	Pre-biopsy MRI	Standard biopsy protocol	Primary outcome
ProScreen[109]	Before consent 2018–					Yes		PCa mortality
Screening group	29 000	50–63	52%*	3.0	4KScore	Yes	TBx+SBx	
Control group	88 000			Clinical routine	–	Clinical routine	–	
Gothenburg-2[92]	Before consent 2015–2020	50–60				Yes		Clinically insignificant PCa
Screening group	39 000		47%					
Screening arm 1				3.0	–	Yes	SBx+TBx	
Screening arm 2				3.0	–	Yes	TBx	
Screening arm 3				1.8	–	Yes	TBx	
Control group	19 000			Clinical routine	–	Clinical routine	–	
PROBASE[94]	After consent 2014–2019		11%			Yes		Metastatic PCa age 60
Early screening start	23 000	45		3.0	–	Yes	TBx+SBx	
Standard start age	23 000	50		3.0	–	Yes	TBx+SBx	

*Inclusion is ongoing.
PCa, prostate cancer; PSA, prostate-specific amtigen; SBx, systematic biopsy; TBx, targeted biopsy.

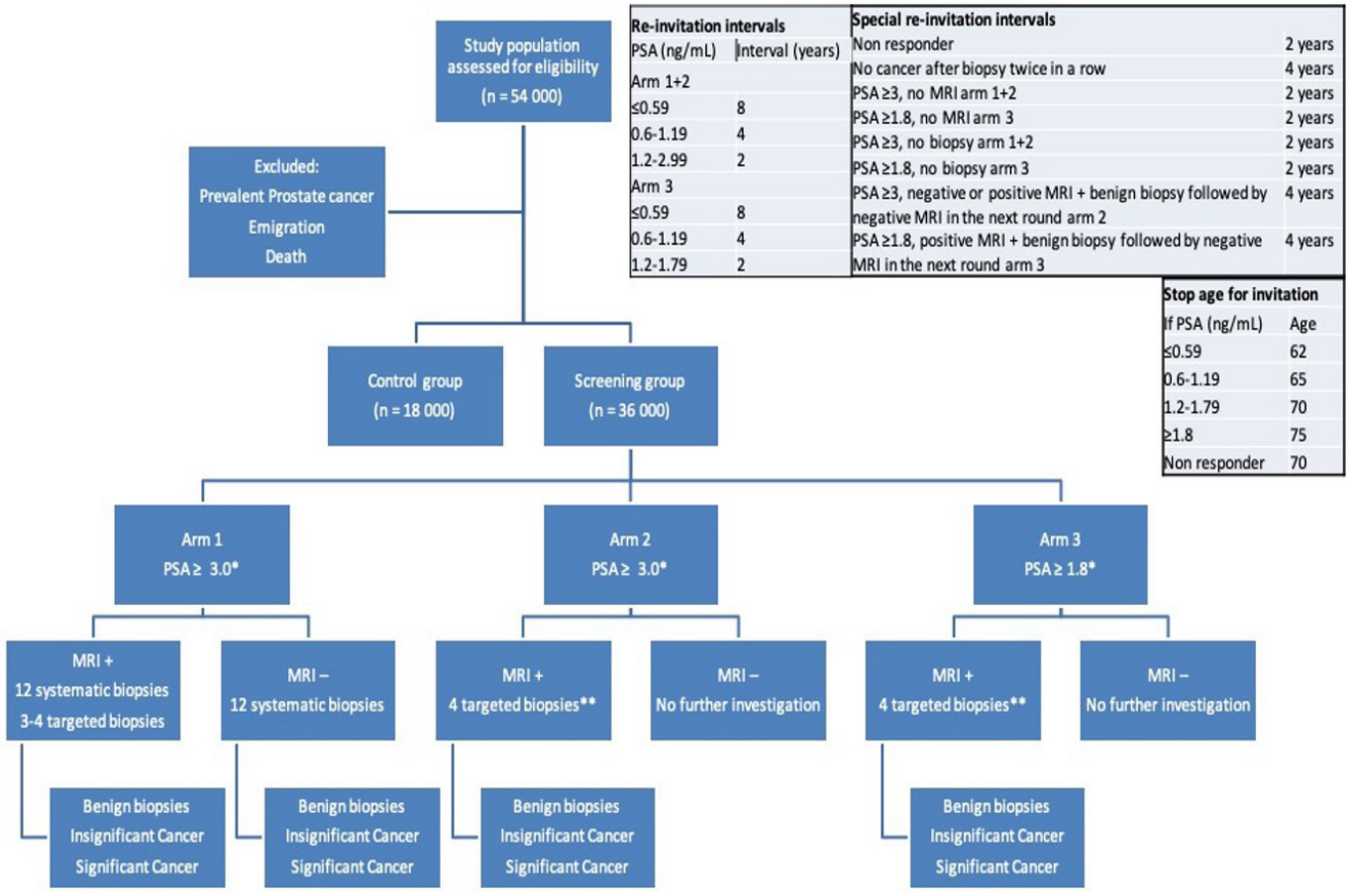

Figure 1 Gothenburg-2 screening trial flow chart. PSA, prostate-specific antigen.

mL after 4 years and men with PSA ≥3.0 ng/mL and no cancer after 2 years. Results from repeated screening rounds are expected within a few years.

The ProScreen trial is embedded in routine clinical practice and the screening intervention is the only component unique to the screening arm. This approach improves feasibility and comparability across the trial arms, reduces costs and facilitates implementation of the study results. Further, changes in clinical diagnostic or therapeutic practices over time are automatically incorporated.

PROBASE (Germany)

PROBASE investigates the efficacy of PSA-based screening with MRI and systematic plus targeted biopsies, comparing start age 45 versus 50 years.[93 94] The

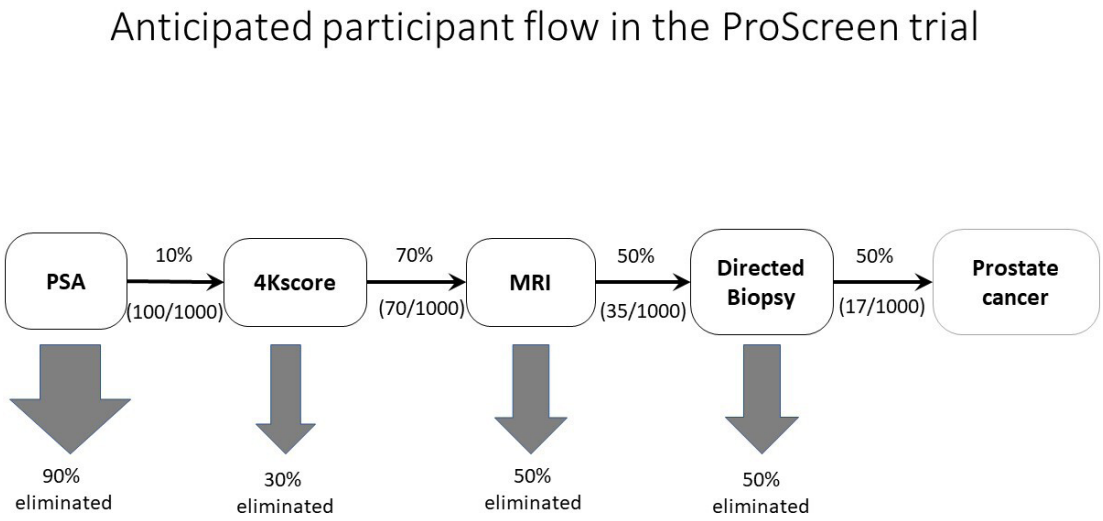

Figure 2 Participant flow through the ProScreen trial and expected distribution of men by test results. PSA, prostate-specific antigen.

primary endpoint is metastatic prostate cancer before age 60 years.

Over 400 000 men were invited from 2014 through 2019, of whom approximately 11% agreed to participate. Of 23 301 participants randomly allocated to screening from age 45 years, 1.5% had an initial PSA ≥3.0 ng/mL. These men had had a second PSA test 2 weeks later; only half of them then still had a PSA ≥3.0 ng/mL. The 179 men with a repeated PSA ≥3.0 ng/mL (0.8% of the initially PSA-tested men) and 7 who did not have a repeat PSA test were referred for MRI and prostate biopsy. Of 120 men who had a biopsy, 33 had Gleason score ≥7 cancer (0.1% of the initially PSA tested men).[93]

Men with PSA <1.5 ng/mL are re-invited after 5 years, men with PSA 1.5–2.9 ng/mL after 2 years. Attendance to scheduled screening visits over the first 6 years varied from 70% to 79% across risk groups.[95]

Other ongoing prostate cancer screening studies

Many non-randomised, prospective prostate cancer screening studies are ongoing. Several evaluate screening of high-risk populations: The UK BARCODE-1 investigates a polygenic risk score for targeting a high-risk population.[96] The international IMPACT trial includes men with a mismatch repair gene or BRCA1/2 mutation.[97 98] Similar studies are ongoing in the USA (eg, NCT05129605, NCT04472338) and Canada (NCT01990521).

Single-arm studies evaluating the feasibility and cost-effectiveness of population-based screening with PSA and MRI include the ReIMAGINE study in the UK[99] and studies in Switzerland (NCT03749993), Czechia (NCT05603351, also evaluating the PHI test to select for MRI) and China (NCT03891732, NCT04251546).

Prostate cancer screening policies

Almost all national healthcare authorities recommend against population-based prostate cancer screening but acknowledge that individual men may weigh the potential benefits and harms of PSA testing differently. Men may therefore be offered testing on request, after appropriate counselling.[100] The US and European Union policies and the unique policies in Lithuania and Sweden are summarised below.

United States Preventive Services Task Force recommendation

The United States Preventive Services Task Force in 2012 recommended against PSA testing of asymptomatic men, regardless of age.[101] In 2018, the recommendation was changed to: 'For men aged 55 to 69 years, the decision to undergo periodic PSA-based screening for prostate cancer should be an individual one and should include discussion of the potential benefits and harms of screening with their clinician'.[102]

European Union recommendation

The 2003 European Union (EU) Council Recommendation for Cancer Screening did not include prostate cancer. Based on an evidence review concluding that screening with PSA testing and bi-parametric MRI for PSA-positive men reduces overdiagnosis and is likely to be cost-effective for many EU member states,[103] and the significant amount of ongoing opportunistic screening, the EU Council in December 2022 recommended that 'countries should consider a stepwise approach, including piloting and further research, to evaluate the feasibility and effectiveness of the implementation of organised programmes aimed at ensuring appropriate management and quality on the basis of PSA testing for men in combination with additional MRI scanning'.[19]

Lithuania: opportunistic PSA screening in primary care

The Lithuanian Early Prostate Cancer Detection Programme started in 2006.[104] A PSA test is offered to all men aged 50–74 years who visit a general practitioner. Men with PSA ≥3 ng/mL are referred to a urologist. During the first 10 years of the programme, 70% of the target population had at least one PSA test.[104] The Lithuanian prostate cancer incidence doubled 2 years after the introduction of the programme.[105]

Sweden: population-based organised prostate cancer testing (OPT)

The Swedish Ministry of Health and Social Affairs in 2018 commissioned the Confederation of Regional Cancer Centres in Sweden to standardise the widespread prostate cancer testing and make it more efficient. The Confederation outlined organised prostate cancer testing (OPT) programmes for men aged 50–74 years within the public, tax-financed, regionally provided healthcare. The first two OPT programmes were launched in 2020 in two of Sweden's most populated regions.[106] As of March 2023, 7 of the 21 regions have started an OPT programme; a further 10 are planned to start over the next year. Men invited to OPT receive a letter with a brief, neutral description of the potential advantages and disadvantages.[49] All steps from invitation to prostate biopsy are organised by an OPT office. PSA testing intervals, use of MRI, indication and extent of prostate biopsies and follow-up are algorithm-based (online supplemental figure 1). All results are registered for quality control and research.[49] A national working group coordinates the programmes and evaluates their outcomes.

DISCUSSION

Scientific knowledge gaps

Important knowledge gaps remain about many aspects related to screening for prostate cancer (Box 1). The PSA test effectively identifies a large proportion of men at very low risk of clinically significant prostate cancer and will most likely remain the primary screening test. However, the optimal PSA threshold for further diagnostic evaluation is not known. Gleason score ≥7 prostate cancer may be detected also in men with PSA below the commonly used biopsy threshold, that is, ≥3.0 or ≥4.0 ng/mL.[64 107] Delaying detection of these cancers in a structured screening

Box 1 Key knowledge gaps about screening for prostate cancer with modern diagnostic methods

- ⇒ How best to inform men about the potential advantages and disadvantages of screening.
- ⇒ Optimal PSA cut-off.
- ⇒ Optimal start and stop ages.
- ⇒ Diagnostic results from repeated screening rounds.
- ⇒ Optimal screening intervals after negative investigations of men with PSA ≥3 ng/mL.
- ⇒ Optimal use of 'intermediate tests' to select men for MRI and biopsy.
- ⇒ Cost-effectiveness of different screening algorithms.
- ⇒ Long-term effects on mortality and overdiagnosis.
- ⇒ Health-economics.

programme may, however, not significantly affect prostate cancer mortality.[108] The ongoing Gothenburg-2 trial is evaluating cancer detection in men with PSA 1.8–2.9 ng/mL.[92]

The use of MRI and lesion-targeted biopsies reduces both the proportion of men who have a prostate biopsy and the detection of low-grade prostate cancer, but current evidence is limited to a single diagnostic evaluation without follow-up testing.[10 12] As most of the benefit from a screening programme is gained from repeated testing,[6 31] results from single testing studies cannot be used to reliably estimate how screening with modern diagnostic methods will affect overdiagnosis and cancer-specific mortality. Diagnostic results from repeated screening rounds in the ongoing screening trials are expected within a few years.[10 93 109]

The optimal start and stop age of a screening programme are not known. Mortality results from the Gothenburg-1 trial suggest that screening should start at age 50–55 years.[31] Diagnostic results from PROBASE show that very few Gleason score ≥7 cancers are detected among men aged 45 years,[93] which suggests that starting at age 45 is not cost-effective. As the protective effect of screening on prostate cancer mortality does not persist more than 10–12 years after screening cessation,[34] stopping screening at age 70 years may be too early for healthy men in countries with a long life expectancy. Results from the ERSPC suggest that selective screening of men aged 70–75 years may lead to the diagnosis of a greater proportion of Gleason score ≥7 cancer than screening of younger men.[110]

Prostate cancer mortality reduction is the definite indicator of screening benefit. A key issue is whether diagnostic outcomes can be used to reliably model mortality and overdiagnosis. Prostate cancer-specific models have been developed,[111 112] but estimating mortality reduction and overdiagnosis from diagnostic results is challenging because these measures can be reliably defined only on a population level. Many cancers currently labelled 'clinically significant' represent overdiagnosis (the man would die before experiencing any cancer symptoms) and some cancers labelled 'clinically insignificant' may over time dedifferentiate and metastasise. On the other hand, if we wait for long-term results from the ongoing trials, their screening algorithms may be obsolete when mortality results become available. It is obviously not possible to prospectively evaluate every refined screening algorithm in a new randomised trial with mortality as the endpoint.

Cost-effectiveness of different screening algorithms will be essential when healthcare authorities decide if, when and how a screening programme is to be implemented. Availability of MRI resources (equipment and qualified staff) is in many countries a limiting factor for implementing MRI-based screening algorithms. It is therefore important to further evaluate biomarkers and risk calculators for the selection of men with a raised PSA for an MRI.[113] The Finnish ProScreen trial evaluates one such biomarker.[109] Healthcare providers short of MRI machines but not staff may use transrectal ultrasound for prostate volume measurement and calculation of PSA density to select men for MRI,[114] but this approach has not yet been prospectively evaluated in a screening context. The length of screening intervals much affects the need for MRI resources. A report from the Gothenburg-2 trial suggests that most men with PSA ≥3.0 ng/mL and a negative MRI do not need to be re-screened for at least 2 years.[115]

Finally, there is scarce evidence for how men who are offered screening are best informed about the potential advantages and disadvantages. This is of course essential for men's choices.[116] Even with modern prostate cancer diagnostics, positive test results, overdiagnosis and overtreatment remain important potential harms. Explaining these issues to laypeople is a challenge.

Practical considerations on implementation

Unorganised PSA testing is less effective and may be more socioeconomically unequal than an organised screening programme.[32 117–123] Organising population-wide testing may, however, be a Herculean challenge. One challenge is related to the simplicity and availability of the primary screening test PSA. Men can easily obtain PSA tests in the screening intervals and after the programme's stop age, but PSA testing and urology consultations in parallel with the screening programme are probably not cost-effective.

The optimal use of prostate MRI in a population-based screening setting differs from its use in the standard clinical setting. A shorter protocol without contrast enhancement (ie, bi-parametric MRI) is clearly advantageous from a resource perspective, but the resulting images may be more difficult for non-expert readers to interpret.[124] Screening usually involves younger men who have smaller prostates with a different signal intensity compared with older men's prostates.[125] Younger men also have a lower prevalence of clinically significant cancer and suspicious MRI lesions.[79] These differences, together with the large variability in MRI interpretation,[126 127] entail a compelling need for quality assurance such as structured training, central review, audits and continuous feedback of biopsy results to reporting radiologists.

Population-based, pilot screening projects were recently recommended by the EU. They will provide experiences that can be used to improve screening algorithms and processes. Such projects are already ongoing in Sweden. Similar, nationally tailored projects will be started within the EU funded PRAISE-U project after a needs-assessment in all

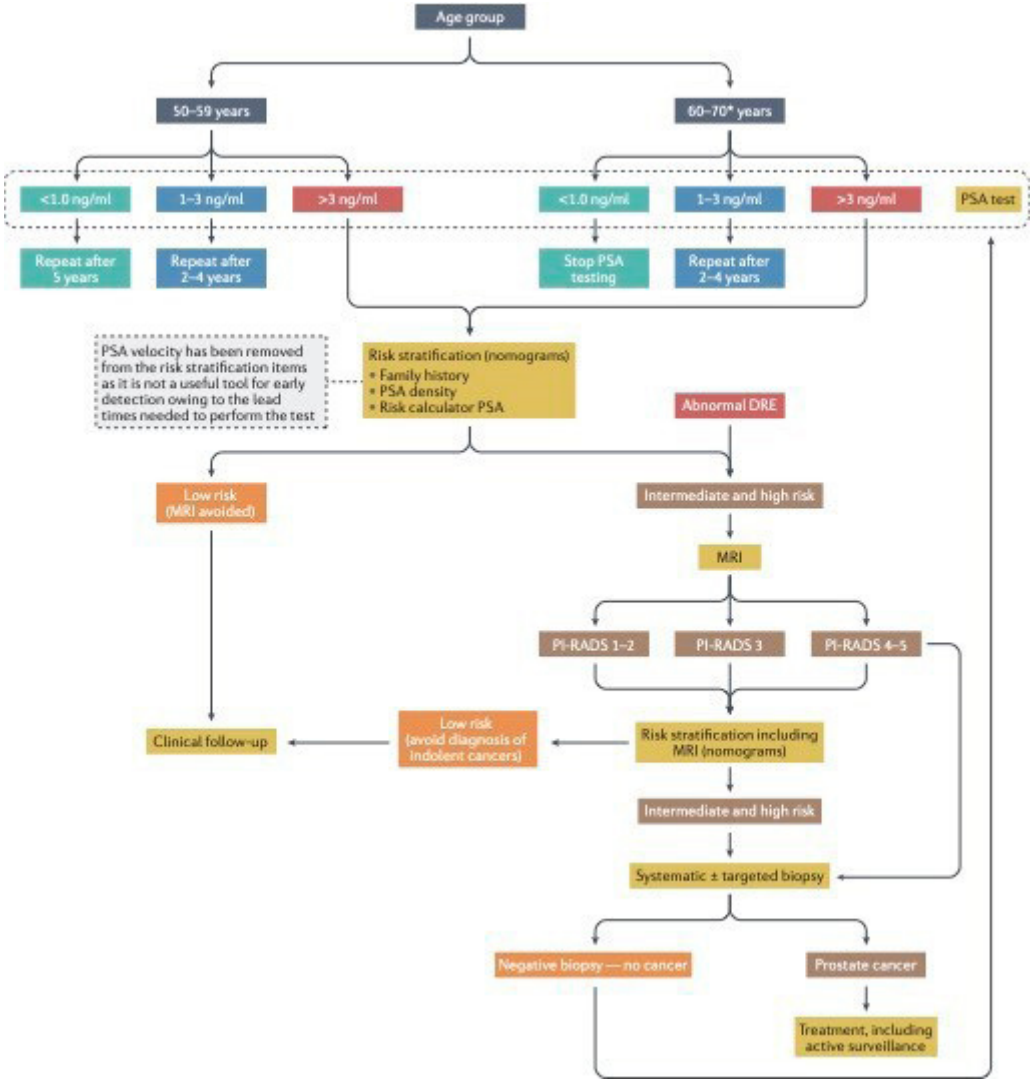

Figure 3 Test algorithm planned for use in the European PRAISE-U project. Reprinted from reference[113] with permission from Springer Nature. PI-RADS, Prostate Imaging—Reporting and Data System; PSA, prostate-specific antigen.

27 EU member states. PRAISE-U will rely on a comprehensive test algorithm with multiple options for risk stratification (figure 3).[113 128] Prerequisites for generating internally and externally valid results include strict adherence to algorithms for PSA testing and diagnostic investigations, and that all results are prospectively registered, analysed and reported, both internally and to some external governance body. Public sharing of protocols, experiences and results is strongly encouraged.

CONCLUSIONS

Screening for prostate cancer using PSA and systematic biopsies reduces prostate cancer-specific mortality but also leads to unacceptable overdiagnosis and overtreatment. Recent advances in diagnostic methods have now reduced these harms. Overdiagnosis can be reduced by risk stratified, organised screening, ancillary testing (risk calculators, biomarkers, MRI) to select men with a raised PSA value for biopsy, and lesion-targeting rather than systematic biopsies. In contrast, the current widespread unorganised PSA testing is ineffective and is more likely to harm than organised screening. Therefore, the EU recently recommended the initiation of pilot projects that evaluate the feasibility and effectiveness of organised screening for prostate cancer. Nonetheless, important knowledge gaps remain. For instance, it is not known to which extent the pre-biopsy selection process and omission of systematic biopsies reduce overdiagnosis or delay detection of curable, potentially lethal cancers that progress to an incurable disease before detection in subsequent screening rounds. Results from ongoing randomised screening trials and population-based pilot screening projects will fill these and some other knowledge gaps over the next few years, but reliable assessment of the impact of screening on cancer mortality requires longer follow-ups.

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Competing interests HL is named on patents on assays for intact PSA and patents on a statistical method to detect prostate cancer (4KScore test) licensed to Arctic Partners that is sublicensed to and commercialised by OPKO Health. HL receives royalties from sales of this test, and has stock in OPKO Health, Arctic Partners, Diaprost AB, and Acousort AB, and is a member of SAB of Fujirebio Diagnostics. RAG has received lecture fees and travel honoraria from IPSEN and Astellas. OB, AA, JW, MH, JH and MJR have no conflicts of interest.

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