

A discussion on controversies and ethical dilemmas in prostate cancer screening

Satish Chandra Mishra 

Correspondence to

Dr Satish Chandra Mishra,
Department of Surgery, WHO
Collaboration Centre for
Research in Surgical Care
Delivery in LMIC, Bhabha Atomic
Research Centre Hospital,
Mumbai, MH 400094, India;
mishrasatishdr@gmail.com

Received 21 November 2019
Revised 17 May 2020
Accepted 22 May 2020
Published Online First
6 July 2020

ABSTRACT

Prostate cancer (PCa) is one of the the most common cancers in men. A blood test called prostate-specific antigen (PSA) has a potential to pick up this cancer very early and is used for screening of this disease. However, screening for prostate cancer is a matter of debate. Level 1 evidence from randomised controlled trials suggests a reduction in cancer-specific mortality from PCa screening. However, there could be an associated impact on quality of life due to a high proportion of overdiagnosis and overtreatment as part of the screening. The US Preventive Services Task Force (USPSTF) in 2012 recommended that PSA-based PCa screening should not to be offered at any age. However, considering the current evidence, USPSTF recently revised its recommendation to offer the PSA test to men aged 55–69 years with shared decision-making, in line with earlier guidelines from the American Cancer Society and the American Urological Association. A shared decision making is necessary since the PSA test could potentially harm an individual. However, the literature suggests that clinicians often neglect a discussion on this issue before ordering the test. This narrative discusses the main controversies regarding PCa screening including the PSA threshold for biopsy, the concept of overdiagnosis and overtreatment, the practical difficulties of active surveillance, the current level 1 evidence on the mortality benefit of screening, and the associated pitfalls. It offers a detailed discussion on the ethics involved in the PSA test and highlights the barriers to shared decision-making and possible solutions.

INTRODUCTION

Prostate cancer (PCa) is one of the most common cancers in men and a leading cause of cancer death. The tool commonly used for screening of PCa is a blood test called prostate-specific antigen (PSA). While PSA has a potential to pick-up early PCa, it is a controversial screening tool in terms of benefit versus harm. Due to this, in 2012 the US Preventive Services Task Force (USPSTF) issued a grade D recommendation (routine PSA testing not to be offered for PCa screening at any age). However, in 2018 the USPSTF revised its recommendation to grade C (offer PSA test in men aged 55–69 years in shared decision-making).¹ This has put the entire responsibility of difficult pretest counselling on the shoulders of healthcare professionals. The practical difficulties involved in making a layman understand this complex issue partly explains the widespread use of the PSA test without informed consent. This narrative tries to offer a balanced discussion on the merits and limitations of PSA-based screening for PCa, the

ethical principles, and the practical difficulties faced by clinicians in shared decision-making.

PRINCIPLES OF SCREENING

In 1968 Wilson and Jungner identified certain principles of screening which were consolidated further by a Delphi consensus process (table 1).^{2,3}

DISEASE CHARACTERISTICS

Is PCa an important health issue in a defined population?

PCa is the second most common cancer diagnosed and the fifth leading cause of cancer death worldwide, with an estimated 1.3 million new cases (13.7% of cancers diagnosed in men) and 359 000 deaths (6.7% of cancer deaths in men) in 2018. Further, it is the most frequently diagnosed cancer among men in 105 of 185 countries (Americas, Northern and Western Europe, Australia/New Zealand, and Sub-Saharan Africa).⁴ Most men clinically present after the age of 65 years.^{5,6}

Is there an identifiable latent or early symptomatic stage of the disease?

PCa is a heterogenous disease with ‘latent’, ‘slowly progressive’ and ‘aggressive’ variants.^{7,8} The ‘latent’ PCa may not present clinically in the entire lifetime of the patient and is detected either by screening or incidentally in histopathology of prostate tissue removed to relieve lower urinary tract symptoms (LUTS) from an apparently benign enlargement of the prostate (BEP). The ‘aggressive’ variant progresses rapidly, often metastasises before the onset of symptoms, and kills the patient despite interventions. It is the ‘slowly progressive’ variant where early detection and treatment is most useful since it grows slowly with a variable degree of aggressiveness and, if not detected and treated early, may metastasise and kill the patient. It is estimated that the average asymptomatic duration of ‘slowly progressive’ PCa for US white men is 7–12 years.^{9,10}

The ‘slowly progressive’ PCa may present with LUTS and get clinically detected by a palpable abnormality in the prostate (hardness/nodularity) on digital rectal examination (DRE), which has a sensitivity, specificity and positive predictive value of 58%, 96% and 28%, respectively, for PCa.¹¹

However, LUTS is a weak predictor of PCa since it is a common symptom in the elderly due to changes in the bladder or BEP. Further, not all ‘slowly progressive’ PCa may show symptoms. In a randomised study in 2012, Franlund *et al* found a negative association between PCa and LUTS



© Author(s) (or their employer(s)) 2021. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Mishra SC.
J Med Ethics
2021;**47**:152–158.

Table 1 Consolidated screening principles

Screening principles	
Disease characteristics	The condition sought should be an important health problem There should be a recognisable latent or early symptomatic stage The natural history of the condition, including development from latent to declared disease, should be adequately understood The target population for screening should be clearly defined (eg, with an appropriate target age range), identifiable and able to be reached
Test characteristics	There should be a suitable test or examination with all key components specific to the test being accurate (sensitivity, specificity and positive predictive value) and reliable or reproducible The test should be available and acceptable to the population
Intervention characteristics	There should be an available and accepted treatment for patients with recognised disease There should be an agreed policy on who to treat as patients
Programme characteristics	The expected range and magnitude of benefits and harms for participants and society should be clearly defined and acceptable Case-finding should be a continuing process
Ethics of screening	Non-maleficence and beneficence: the programme should be supported by high-quality scientific evidence that the overall benefit of the screening programme outweighs its potential harms. Justice: The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care Respect to autonomy: There should be effective methods for providing screening participants with informed choice, promoting their autonomy and protecting their rights

(PCa was diagnosed in 31% of asymptomatic men and 23% of men with LUTS) and concluded that tests to detect PCa should be independent of LUTS.¹²

Is the natural history of the disease adequately understood?

Based on clinical stage, histopathology grade (Gleason score), PSA isoforms, PSA kinetics, biomarkers and recent imaging modalities such as MRI, we have reasonable knowledge to identify a low risk disease and this has the potential to prevent overtreatment. However, our current knowledge on the natural history of PCa is still inadequate.

TEST CHARACTERISTICS

What are the key components (sensitivity/specificity/predictive value/acceptance) of PSA?

PSA is widely available and is well accepted by the target population.¹³ At 4 ng/mL threshold for biopsy, which is most widely used, PSA has a high sensitivity of 89% for detection of early PCa.^{14 15} Catalona *et al* showed that adding PSA to DRE increased the pick-up rate of organ-confined disease from 30% to 80%.¹⁶ PSA-based screening also causes a migration to favourable clinical stages and histopathological grades. In the European Randomised Study for Screening of Prostate Cancer (ERSPC) Rotterdam the screen arm had better tumour characteristics (84% localised; 0.6% metastatic; 36% in first round, 22% and 12% in subsequent rounds had Gleason score ≥ 7) than the control arm (60% localised; 8% metastatic; 55% had Gleason score ≥ 7).¹⁷ In addition, the PSA level at 60 years was associated with risk of clinical diagnosis of PCa, metastasis and cancer-related death by the age of 85 years, with area under the curve of 0.76, 0.86 and 0.90, respectively, suggesting its potential to detect more aggressive tumours.¹⁸

Biopsy detectable PCa exists at all PSA levels and the detection rate continues to increase as we gradually raise the PSA threshold for biopsy.¹⁹ The threshold of 4 ng/mL was arbitrarily decided by consensus in the 1990s as a reasonable balance between sensitivity and specificity, and was further endorsed by a large multi-centred prospective study in 1994 by Catalona *et al*.²⁰ Catalona subsequently proposed to bring the PSA cut-off to 2.6 ng/mL

since 20% of important and potentially curable PCa could be detected in the PSA range of 2.6–4 ng/mL, with no significant overdiagnosis.²¹ Furthermore, the Prostate Cancer Prevention Trial (PCPT) reported that 15% of participants had a biopsy-detectable PCa at PSA levels <4 ng/mL and 25% of cancers in the PSA range of 3.1–4.0 ng/mL were high grade (Gleason ≥ 7).¹⁹ Similar findings were reported by other studies.^{22 23} The multi-centred ERSPC also used 3 ng/mL as a PSA threshold for biopsy.²⁴ The National Comprehensive Cancer Network (NCCN) guideline on early detection of PCa also recommends a PSA cut-off of 3 ng/mL.²⁵ However, the downside of a low PSA threshold is a huge number of unnecessary biopsies. In the ERSPC trial, three out of four (75%) biopsies triggered by an elevated PSA level were negative for cancer, initiating a debate over the universal acceptance of the PSA cut-off of 3 ng/mL. In this trial, with 86% compliance rate, 24% (17 543) of participants had undergone biopsy.²⁴ Though a prostate biopsy rarely (0.5%) causes serious complications such as urosepsis, the procedure is uncomfortable and minor complications such as bleeding from the urethra or rectal haemorrhage are reported in around half of biopsied men.¹⁹

The PSA level is reported to be influenced by age. It normally increases with age, mainly due to a higher prevalence of BEP. Therefore, age-specific PSA values may have a better discrimination power, particularly for young men with potentially curable cancers. Maintaining a reasonable balance between sensitivity and specificity, the suggested age-specific PSA cut-off values are 2.5 ng/mL (40–49 years), 3.5 ng/mL (50–59 years), 4.5 ng/mL (60–69 years), and 6.5 ng/mL (70–79 years).^{26–29}

PSA threshold may also be influenced by ethnic variations in the prevalence of PCa. The prevalence of microscopic disease in men above 50 years has been reported to be only 15% in Asians as compared with 30% in Caucasians and 48% in African Americans.³⁰ It has been proposed to raise the PSA threshold to 5.5 ng/mL for Asians.^{31 32}

However, the exact role of age-specific and race-specific PSA cut-off is still unclear and guidelines make no recommendation on these. Therefore, it may be more pragmatic to use a PSA cut-off of 4 ng/mL in the recommended age group of 55–69 years.

This cut-off is also supported by the receiver operating curve, balancing the sensitivity and specificity reasonably well.²⁰

At a biopsy threshold ≥ 4 ng/mL, the specificity and positive predictive value of PSA are reported to be 54% and 20–30%, respectively.^{14 15} Since PSA is expressed in both benign and malignant tissue, several benign conditions such as BEP, prostatitis, urinary tract infection, acute urinary retention and prostatic or urethral manipulations can elevate PSA. This lack of specificity for PCa has limited the utility of PSA, especially in the range of 3–10 ng/mL—a diagnostic ‘grey zone’. To improve PSA specificity in the diagnostic grey zone several tools have been proposed which include PSA metrics, PSA isoforms, biomarkers and newer imaging modalities. These include PSA density, PSA velocity, ratio of free to total PSA, the Prostate Health Index, PCA3, 4K test, SelectMDx and MRI. These tools are reported to enhance the specificity of PSA and provide useful adjuncts both in the prevention of negative biopsies as well as the prediction of aggressiveness of PCa.^{33–51} In 2019 the National Institute for Health and Care Excellence (NICE) recommended MRI as the first line investigation in men with suspected clinically localised PCa, and concluded that MRI-influenced prostate biopsy is more cost effective than the systematic prostate biopsy.⁵² It also recommends that PSA density and PSA velocity should be assessed while considering a biopsy in individuals who have a high PSA level but low risk of PCa on MRI.⁵²

Other guidelines also recommend use of these tools as an adjunct in clinical decision-making, particularly in a setting of repeat biopsy or assessment for the nature of intervention.²⁵

INTERVENTION CHARACTERISTICS

What are the key components (availability, acceptability, benefits, risks) of intervention?

PCa treatment modalities are widely available and protocolised.^{52–56} The treatment decision considers the stage of the tumour; the calculated risk of aggressiveness (based on PSA levels, histopathological features such as the Gleason score, biomarkers and imaging), patients’ comorbidities and their preference. For low risk PCa active surveillance (AS) is a recommended option. For organ confined PCa with intermediate or high risk, radical prostatectomy (RP), radiotherapy (RT) or a combination are recommended, with a very high 10 year disease-free survival of 85–95% and overall survival of 80–90%.⁵⁷ For patients not eligible for local curative treatment due to competing comorbidities or short life expectancy, watchful waiting is recommended.

Locally advanced PCa (T3, T4 or N1), defined as either locally infiltrating to the bladder/seminal vesicles or involving regional lymph nodes, are treated by multimodality treatment involving RP, RT and androgen deprivation therapy (ADT), with a good 10 year disease-free survival of up to 48% and overall survival of 58%.⁵⁸ Metastatic cancers are treated by ADT and chemotherapy. The prognosis of metastatic disease is poor with 50% 5 year survival.⁵⁹

The invasive treatment modalities for PCa have few potential side effects on bladder, bowel and sexual functions. Patients undergoing RP are reported to have urinary incontinence (20–50%) and erectile dysfunction (70–90%), and patients treated with RT are reported to have bowel problems (30–35%), erectile dysfunction (41–55%) and urinary incontinence (6–7%).^{60 61} The recent ProtecT trial also reported a higher incidence of urinary incontinence and sexual incontinence with RP (table 2).⁶²

Table 2 Comparison of urinary incontinence and sexual dysfunction in the ProtecT trial

Intervention	Men using ≥ 1 pad/day (%)		Men with firm erections (%)	
	Baseline (1%)		Baseline (67%)	
	6 Months	6 Years	6 Months	6 Years
Radical prostatectomy	46	17	12	17
Radical radiotherapy	5	4	22	27
Active surveillance	4	8	52	30

Is there an agreed policy on who to treat?

For a low risk PCa, defined by serum PSA at diagnosis ≤ 10 ng/mL, Gleason score < 7 with no pattern 4/5 disease, and clinical stage T1 or T2a, AS is a safe option with normal life expectancy and is supported by high levels of evidence and guidelines.^{25 63–67} In AS, men are observed carefully with serial PSA assessments, repeat biopsies and other tests intended to identify early signs of progression. The idea is to avoid or postpone an invasive treatment (RP or RT) without missing the window for curative intervention if there is a disease progression. AS in low risk PCa over a period of 15 years has a disease-specific mortality of only 0.1–1.5%, depending on the definition of low risk.^{66 67}

Randomised controlled trials (RCTs) comparing the outcomes of AS, RP and RT in low-risk PCa report no significant differences in cancer-specific or overall mortality between AS, RP and RT. However, nearly 50% of the AS cohort did require a switchover to RP or RT at 10 years. Further, the treatment arm had lower incidences of disease progression and metastases as compared with AS.⁶⁷

PROGRAMME CHARACTERISTICS

What is the evidence-based expected range and magnitude of benefits and harms for participants and society?

The fundamental question is whether a PCa screening programme improves the clinical outcome? In the USA, from 1993 to 2016 the age-adjusted mortality from PCa dropped by 51%.⁶⁸ This reduction has been attributed to an earlier stage at diagnosis due to PCa screening and advances in treatment.⁶⁹ However, researchers argue that the mortality benefit in the screened group was only an artefact of lead time and length time bias.^{70 71} In an analysis of the ERSPC the estimated lead times were 11–12 years and 6–7 years, if PCa was diagnosed at the age of 50 years and 75 years, respectively.⁷²

In 2009, reports of two large RCTs on PCa screening were published. The Prostate, Lung, Colon and Ovarian (PLCO) trial, involving over 75 000 men, reported no reduction in PCa deaths in the screen group after 13 years of follow-up.⁷³ However, this trial had 50% contamination in the control arm. The ERSPC, with over 160 000 men randomised into screening and no screening (control), provides the largest level 1 evidence to date and reports at 9, 13, and 16 years are available.^{24 74 75} It reported an absolute reduction in cancer-specific mortality though the numbers needed to invite (NNI) and numbers needed to detect (NND) to prevent one cancer death were significantly large. Furthermore, a recent study, after accounting for differences in implementation and settings of the ERSPC and PLCO, concluded that both trials had an estimated 25–30% reduction in cancer-specific mortality in the screened arm.⁷⁶

While there is definite level 1 evidence that PCa screening decreases cancer-specific mortality, it has a potential for overdiagnosis of clinically insignificant tumours. This overdiagnosis

Table 3 Long-term follow-up results of the ERSPC trial

Follow-up period (years)	Reduction in cancer specific mortality (%)	Numbers needed to invite (NNI) to prevent one cancer death	Numbers needed to diagnose (NND) to prevent one cancer death
9	21	1410	48
13	27	781	27
16	25% (at least one screening round attended) 48% (at least two screening rounds attended)	570	18

ERSPC, European Randomised Study for Screening of Prostate Cancer.

may lead to overtreatment with potential for harm. The concern of overdiagnosis stems from the fact that latent PCa is highly prevalent and there is a significant disparity between the prevalence of microscopic disease (33% over 50 years in US white men), clinical presentation (9.5%) and death (3%) due to the cancer.^{30 77} The literature reports overdiagnosis in PCa screening to be 23–67%, depending on the definitions of overdiagnosis used.^{78 79} The prominent ones are PCPT (30% overdiagnosis in PSA range 2.6–10 ng/mL) and ERSPC (48% overdiagnosis in the age group 55–67 years).^{72 80}

Heijnsdijk *et al*, based on 11 years follow-up data of the ERSPC, estimated risk versus benefit of screening and concluded that the PCa screening programme would result in a gain of 52 life-years and 41 quality-adjusted life-years (QALYs) per 1000 men over their lifespan, with a 23% negative impact on the life-years gained because of quality of life (QoL).⁸¹

What is the evidence that PCa screening should be ongoing?

In addition to mortality benefit concluded from the ERSPC trial, its long-term follow-up at 13 and 16 years provides evidence of a significant absolute benefit in PCa mortality and a continuous decrease in NNI and NND (table 3).^{74 75} The NNI and NND were estimated to decrease to 98 and 5, respectively, with lifetime horizon as modelled by Heijnsdijk *et al*.⁸¹

Further, the trend of migration in cancer detection to early stage and favourable grade continues when PSA screening is offered continuously and a ‘reverse migration’ starts when PSA screening is stopped.^{82–86}

The PSA retesting interval is recommended to be guided by the baseline PSA value. Studies recommend a PSA retesting interval of 3–8 years at baseline PSA ≤ 1.00 ng/mL, 4 years at baseline PSA 1–2 ng/mL and yearly at initial PSA > 2 ng/mL.^{87–89} NCCN recommends a PSA testing interval of 2–4 years at PSA < 1 ng/mL and 1–2 years at PSA 1–3 ng/mL.²⁵

EVALUATION FROM A PUBLIC HEALTH POLICY DECISION MAKER'S PERSPECTIVE AND CONSIDERATION OF ETHICAL PRINCIPLES

Does PCa screening stand on principles of non-maleficence (first do no harm) and beneficence (preventing harm)?

The obvious benefits of PCa screening are a reduction in disease-related mortality, an increase in the number of life-years gained, and a reduction in the rate of advanced disease. However, to a

certain extent, the benefits are counterbalanced by harms to QoL resulting from overdiagnosis and overtreatment. Holding to the ethical principal of *primum non nocere* (first, do no harm), most of the clinical guidelines do not make any recommendations for a population-based screening, though all of them have adopted an approach that it is unethical to withhold the PSA test. Further, since the mortality benefit versus QoL risk calculation is value based, screening should be offered only in the context of shared decision-making. The recommended age group in clinical guidelines (50–69 years) is also reasonably balanced since screening in men with a short life expectancy (< 10 years) may not offer a net benefit, and even the harms may outweigh the benefits. Most of the scientific societies adopt an individualised risk adapted strategy based on either a set of individual factors or a baseline PSA.⁹⁰ At the same time many societies have adopted an approach of opportunistic PSA screening.⁵² However, organised screening is reported to have a significantly better mortality outcome.⁹¹

Overdiagnosis usually leads to overtreatment. So, the question ‘should we screen?’ actually originates from ‘must we treat?’. Acceptance rates of AS in eligible patients is reported to range from 15–50% and there has been a gradual rise in the last few years.^{92 93} In a recent RCT 60% of men with low-risk PCa agreed to randomization between AS, RP and RT, with a high compliance (88%) to the assigned protocol.⁶⁷ This suggests that if the clinicians are proactive in offering AS, the majority of patients are ready to accept. However, AS may not be an easy choice for patients and clinicians due to uncertainty of disease progression, risk of loss to follow-up and repeated biopsies. Also, there is a potential psychological harm attached with the labelling. The knowledge of the cancer's existence, lack of treatment, and its uncertain outcome may itself affect QoL with anxiety, depression, uncertainty and a perception of danger.^{94 95} A systematic review concluded that there was possible or definite evidence of psychological harm of labelling in the period soon after diagnosis.⁹⁶ However, other published studies, including the ProtecT trial and a recent systematic review, suggest that patients undergoing AS experience no adverse impact on health-related QoL and only a minority of men on AS switch to radical treatment due to psychological reasons.^{97–100} Further high quality research is required in this area.

One of the important reasons for increasing acceptance towards AS is better prediction of aggressiveness using newer technologies such as multiparametric MRI and genomic biomarkers during the initial assessment and monitoring of disease progression. For risk re-stratification, multiparametric MRI has a sensitivity, specificity, positive predictive value, and negative predictive value of 92.5%, 76%, 81%, and 90%, respectively, and it has significantly reduced the need for serial biopsies.^{101–103}

Does PCa screening stand on the ethical principle of justice (cost effectiveness)?

Cost effectiveness analysis is an important tool to assess a just utilisation of resources. Cost analysis of screening and treatment of PCa has utilised different models using the inputs based on available evidence at the time of analysis. The relatively recent studies have used the results of the ERSPC trial to assess cost effectiveness of screening. One study calculated the cost as US\$16 8611/QALY for men with average risk, and concluded that screening could be cost effective when it is limited to men with five times the average risks.¹⁰⁴ Another study found the lifetime cost of PCa screening and treatment to be \$262 758 per year life gained, and concluded that screening became cost

effective when the lifelong treatment costs were below \$1868 per life-year, or when the NND was 18.¹⁰⁵ The most recent study by Heijnsdijk *et al* found that screening at the age of 55–59 years with 2 year intervals had an incremental cost effectiveness ratio of \$73 000 per QALY gained and considered it optimal. It concluded that PSA-based screening could be cost effective when it is limited to patients aged 55–60 years with intervals of 1 or 2 years, and less cost effective above 63 years because of loss of QALYs due to overdiagnosis.¹⁰⁶ To meet the ethical challenges of justice and beneficence, the American Urological Association recommends screening every 2–4 years based on the ERSPC protocol.³⁶ Similarly, the American Cancer Society recommends a screening interval of 2 years if the PSA value is <2.5 ng/mL and yearly for PSA values of 2.5–4 ng/mL.

As the guidelines recommend offering the PSA test to the age group 60–69 years, screening for nearly half of the population (>60 years) may not be cost effective as per the studies. Moreover, spending over \$100 000 to \$200 000 per QALY may not stand the ethical principles of justice in publicly funded systems with limited resources, when other competing and much more cost effective healthcare opportunities need to be supported. In most of the universal public-funded healthcare systems, including the UK and even countries such as Australia and New Zealand with some of the highest PCa incidence in world, there is no systematic population-based screening programme for PCa and PSA test allowed on the basis of an individual's risk assessment.^{52 107}

Does PCa screening respect patient autonomy?

A decision made in the face of uncertainty necessarily involves trade-offs between different types of risks, and the decision of which types of risk one is willing to tolerate reflects a set of individualised goals and values in life. Men with localised prostate cancer need to make a balanced decision between side effects on urinary, bowel and sexual function, against later risks of metastasis and progression, and their impacts on QoL and length of life. A recent shift in the recommendation of the USPSFT from 'no screening' to 'screening in shared decision-making' is partly a reflection of recent evidence, but it also reflects a respect for patient autonomy. All guidelines are clear that if shared decision-making is not possible, PSA-based screening should not be offered.

To be empowered to take a decision, men need to know about the evidence in favour of screening, recommendations of professional organisations, the accuracy and reliability of PSA and DRE in the diagnosis of PCa, the change in PSA with age and size of prostate gland, the diagnostic grey zone, the cut-off value of PSA applicable to them, the frequency of the PSA test, the risk of overdiagnosis, the process of risk stratification, AS, the treatment protocols and the treatment of side effects. Since the decisions are value-based, the decisions against screening should be equally respected. Also, many patients prefer paternalism and seek their doctors' advice. Provided the physician ensures that the patient has understood the controversy, giving an opinion (if asked), based on patient values during the discussion, does not infringe on the autonomy of the patient.¹⁰⁸ Furthermore, evidence suggests that a man presenting with LUTS is at no additional risk for prostate cancer as compared with those without a urinary symptom, so the same screening protocol should be followed in patients presenting with LUTS.^{12 109}

Shared decision-making implies that the healthcare provider is engaged in the decision-making by assisting the patient in the process, and it needs a dedicated period of time and an unhurried environment to allow the patient to assimilate the

knowledge, ask relevant questions, discuss the issue freely and be able to make an independent decision. The process is often challenging because of constraints of time and the specific skills that it requires. It has been reported that 30–70% of men undergoing a PSA test are not even aware that their physician has ordered this test. Of those who are aware of receiving the test, only 35–50% recall any controversies having been discussed and only a few could understand the essence of the discussion.^{110–112} A public survey reported that only 18% of men undergoing PCa screening recalled that overdiagnosis was discussed.¹¹³ Improvements in the process of shared decision-making is possible by training the healthcare providers and using balanced and unbiased audio-visual aids. Decision aids are particularly useful when the trade-off between benefits and risks requires a subjective judgement. But the clinician should choose the decision aid carefully and should use it to supplement, and not to replace, the discussion. A recent systematic review of 19 eligible trials involving 12 781 men and 12 decision aids found that only three decision aids scored well with all relevant information, and only one of them could clearly facilitate a discussion leading to shared decision-making. The results demonstrate that the majority of prostate cancer decision aids could increase patient knowledge on the subject, but were not specifically geared to facilitate shared decision-making.¹¹⁴

CONCLUSION

PCa screening results in a proven cancer-specific mortality reduction when the patients are followed for more than 10 years. However, there is still a huge potential for overdiagnosis and overtreatment affecting patient QoL, and population-based PCa screening is not cost effective. Overtreatment can be reduced to some extent with AS, which is receiving wider acceptance as multiparametric MRI has improved risk stratification and disease reclassification. To meet the ethical principles of non-maleficence, beneficence and justice, guidelines recommend offering the PSA test to men aged 55–69 years, with at least a 2 year retest interval, and strongly recommend shared decision-making. Most organisations recommend a personalised screening based on a set of individual factors. The limited time available with physicians is a significant barrier for the required discussion and patient empowerment, and there is a lack of balanced decision aids which could facilitate the process of shared decision-making.

Contributors I am the sole author. I conceptualised and developed the project design, surveyed the literature, prepared the draft and finalised the manuscript.

Funding The author has not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement statement No patient was involved in the preparation of this manuscript.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Satish Chandra Mishra <http://orcid.org/0000-0001-6086-6541>

REFERENCES

- 1 Grossman DC, Curry SJ, *et al*, US Preventive Services Task Force. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *JAMA* 2018;319(18):1901–13.
- 2 Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: WHO. *Public Health Paper* 1986;34.

- 3 Dobrow MJ, Hagens V, Chafe R, et al. Consolidated principles for screening based on a systematic review and consensus process. *CMAJ* 2018;190(14):E422–9.
- 4 Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68(6):394–424.
- 5 Ghagane SC, Nerli RB, Hiremath MB, et al. Incidence of prostate cancer at a single tertiary care center in North Karnataka. *Indian J Cancer* 2016;53(3):429–31.
- 6 Brawley OW. Prostate cancer epidemiology in the United States. *World J Urol* 2012;30(2):195–200.
- 7 Waterbor JW, Bueschen AJ. Prostate cancer screening (United States). *Cancer Causes Control* 1995;6(3):267–74.
- 8 Diamandis EP. Prostate cancer screening with prostate-specific antigen testing: more answers or more confusion? *Clin Chem* 2010;56(3):345–51.
- 9 Whittemore AS, Keller JB, Betensky R. Low-grade, latent prostate cancer volume: predictor of clinical cancer incidence? *J Natl Cancer Inst* 1991;83(17):1231–5.
- 10 Etzioni R, Cha R, Feuer EJ, et al. Asymptomatic incidence and duration of prostate cancer. *Am J Epidemiol* 1998;148(8):775–85.
- 11 Mettlin C, Lee F, Drago J, et al. The American Cancer Society national prostate cancer detection project. Findings on the detection of early prostate cancer in 2425 men. *Cancer* 1991;67(12):2949–58.
- 12 Fränlund M, Carlsson S, Stranne J, et al. The absence of voiding symptoms in men with a prostate-specific antigen (PSA) concentration of ≥ 3.0 ng/mL is an independent risk factor for prostate cancer: results from the Gothenburg randomized screening trial. *BJU Int* 2012;110(5):638–43.
- 13 Kirby RS, Kirby MG, Feneley MR, et al. Screening for carcinoma of the prostate: a GP based study. *Br J Urol* 1994;74(1):64–71.
- 14 Brett TD. An analysis of digital rectal examination and serum-prostate-specific antigen in the early detection of prostate cancer in general practice. *Fam Pract* 1998;15(6):529–33.
- 15 Catalona WJ, Smith DS, Ratliff TL, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. *N Engl J Med* 1991;324(17):1156–61.
- 16 Catalona WJ, Richie JP, Ahmann FR, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. *J Urol* 1994;151(5):1283–90.
- 17 van der Crujisen-Koeter IW, Vis AN, Roobol MJ, et al. Comparison of screen detected and clinically diagnosed prostate cancer in the European Randomized Study of Screening for Prostate Cancer, section Rotterdam. *J Urol* 2005;174(1):121–5.
- 18 Vickers AJ, Cronin AM, Bjork T, et al. Prostate specific antigen concentration at age 60 and death or metastasis from prostate cancer: case-control study. *BMJ* 2010;341(sep14 1).
- 19 Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level ≤ 4.0 ng per milliliter. *N Engl J Med* 2004;350(22):2239–46.
- 20 Catalona WJ, Hudson M'liss A, Scardino PT, et al. Selection of optimal prostate specific antigen cutoffs for early detection of prostate cancer: receiver operating characteristic curves. *J Urol* 1994;152(6 Pt 1):2037–42.
- 21 Catalona WJ, Ramos CG, Carvalhal GF, et al. Lowering PSA cutoffs to enhance detection of curable prostate cancer. *Urology* 2000;55(6):791–5.
- 22 Pepe P, Panella P, Savoca F, et al. Prevalence and clinical significance of prostate cancer among 12,682 men with normal digital rectal examination, low PSA levels. *Urol Int* 2007;78(4):308–12.
- 23 Ediz C, Cimen S, Akan S, et al. What should be the PSA threshold value? 2.5 or 4 ng/mL? *Int J Res Med Sci* 2019;7(3):838–42.
- 24 Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360(13):1320–8.
- 25 Carroll PR, Parsons JK, Andriole G, et al. NCCN guidelines insights: prostate cancer early detection, version 2.2016. *J Natl Compr Canc Netw* 2016;14(5):509–19.
- 26 Oesterling JE, Jacobsen SJ, Chute CG, et al. Serum prostate-specific antigen in a community-based population of healthy men. establishment of age-specific reference ranges. *JAMA* 1993;270(7):860–4.
- 27 Morgan TO, Jacobsen SJ, McCarthy WF, et al. Age-specific reference ranges for serum prostate-specific antigen in black men. *N Engl J Med* 1996;335(5):304–10.
- 28 Carter HB. Prostate cancers in men with low PSA levels — must we find them? *N Engl J Med* 2004;350(22):2292–4.
- 29 Nadler RB, Loeb S, Roehl KA, et al. Use of 2.6 ng/ml prostate specific antigen prompt for biopsy in men older than 60 years. *J Urol* 2005;174(6):2154–7.
- 30 Jahn JL, Giovannucci EL, Stampfer MJ. The high prevalence of undiagnosed prostate cancer at autopsy: implications for epidemiology and treatment of prostate cancer in the prostate-specific antigen era. *Int. J. Cancer* 2015;137(12):2795–802.
- 31 Agnihotri S, Mittal RD, Kapoor R, et al. Raising cut-off value of prostate specific antigen (PSA) for biopsy in symptomatic men in India to reduce unnecessary biopsy. *Indian J Med Res* 2014;139(6):851–6.
- 32 Sirisopana K, Sangkum P, Sirisreetreerux P. Optimal prostate-specific antigen (PSA) cut-off value and transrectal ultrasound guided prostate biopsy for the diagnosis of prostate cancer at Ramathibodi Hospital: the first study in Southeast Asia. *J Med Assoc Thai* 2019;102.
- 33 Sfoungaristos S, Katafigiotis I, Perimenis P. The role of PSA density to predict a pathological tumour upgrade between needle biopsy and radical prostatectomy for low risk clinical prostate cancer in the modified Gleason system era. *Can Urol Assoc J* 2013;7(11-12):722–7.
- 34 Seaman EK, Whang IS, Cooner W, et al. Predictive value of prostate-specific antigen density for the presence of micrometastatic carcinoma of the prostate. *Urology* 1994;43(5):645–8.
- 35 D'Amico AV, Chen M-H, Roehl KA, et al. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. *N Engl J Med* 2004;351(2):125–35.
- 36 Carter HB, Ferrucci L, Kettermann A, et al. Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. *J Natl Cancer Inst* 2006;98(21):1521–7.
- 37 Catalona WJ, Partin AW, Slawin KM, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease. *JAMA* 1998;279(19):1542–7.
- 38 Partin AW, Brawer MK, Subong ENP, et al. Prospective evaluation of percent free-PSA and complexed-PSA for early detection of prostate cancer. *Prostate Cancer Prostatic Dis* 1998;1(4):197–203.
- 39 Lee R, Localio AR, Armstrong K, et al. A meta-analysis of the performance characteristics of the free prostate-specific antigen test. *Urology* 2006;67(4):762–8.
- 40 Catalona WJ, Partin AW, Sanda MG, et al. A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate specific antigen range. *J Urol* 2011;185(5):1650–5.
- 41 de la Calle C, Patil D, Wei JT, et al. Multicenter evaluation of the prostate health index to detect aggressive prostate cancer in biopsy naive men. *J Urol* 2015;194(1):65–72.
- 42 Loeb S, Sanda MG, Broyles DL, et al. The prostate health index selectively identifies clinically significant prostate cancer. *J Urol* 2015;193(4):1163–9.
- 43 de la Taille A, Irani J, Graefen M, et al. Clinical evaluation of the PCA3 assay in guiding initial biopsy decisions. *J Urol* 2011;185(6):2119–25.
- 44 Wei JT, Feng Z, Partin AW, et al. Can urinary prostate CANCER3 supplement PSA in the early detection of prostate cancer? *JCO* 2014;32(36):4066–72.
- 45 Stattin P, Vickers AJ, Sjoberg DD, et al. Improving the specificity of screening for lethal prostate cancer using prostate-specific antigen and a panel of kallikrein markers: a nested Case–Control study. *Eur Urol* 2015;68(2):207–13.
- 46 Parekh DJ, Punnen S, Sjoberg DD, et al. A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. *Eur Urol* 2015;68(3):464–70.
- 47 Han C, Liu S, Qin XB, et al. MRI combined with PSA density in detecting clinically significant prostate cancer in patients with PSA serum levels of 4–10ng/mL: biparametric versus multiparametric MRI. *Diagn Interv Imaging* 2020;101(4):235–44.
- 48 Brawer MK, Aramburu EA, Chen GL, et al. The inability of prostate specific antigen index to enhance the predictive value of prostate specific antigen in the diagnosis of prostatic carcinoma. *J Urol* 1993;150(2 Pt 1):369–73.
- 49 Catalona WJ, Southwick PC, Slawin KM, et al. Comparison of percent free PSA, PSA density, and age-specific PSA cutoffs for prostate cancer detection and staging. *Urology* 2000;56(2):255–60.
- 50 Vickers AJ, Savage C, O'Brien MF, et al. Systematic review of pretreatment prostate-specific antigen velocity and doubling time as predictors for prostate cancer. *J Clin Oncol* 2009;27(3):398–403.
- 51 Vickers AJ, Wolters T, Savage CJ, et al. Prostate-specific antigen velocity for early detection of prostate cancer: result from a large, representative, population-based cohort. *Eur Urol* 2009;56(5):753–60.
- 52 Prostate cancer: diagnosis and treatment. London, UK: National Institute for Health and Care Excellence (NICE) 2019.
- 53 Heidenreich A, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localized disease. *Eur Urol* 2011;59(1):61–71.
- 54 Mohler JL, Antonarakis ES, Armstrong AJ, et al. Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2019;17(5):479–505.
- 55 Wolf AMD, Wender RC, Etzioni RB, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. *CA Cancer J Clin* 2010;60(2):70–98.
- 56 Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: American Urological Association. *J Urol* 2013;190:419–26.
- 57 Lee SU, Cho KH, Park W, et al. Clinical outcomes of postoperative radiotherapy following radical prostatectomy in patients with localized prostate cancer: a multicenter retrospective study (KROG 18-01) of a Korean population. *Cancer Res Treat* 2020;52(1):167–80.
- 58 Tosco L, Briganti A, D'Amico AV, et al. Systematic review of systemic therapies and therapeutic combinations with local treatments for high-risk localized prostate cancer. *Eur Urol* 2019;75(1):44–60.
- 59 Balasubramaniam G, Talole S, Mahantshetty U, et al. Prostate cancer: a hospital-based survival study from Mumbai, India. *Asian Pac J Cancer Prev* 2013;14(4):2595–8.
- 60 Madalinska JB, Essink-Bot M-L, de Koning HJ, et al. Health-related quality-of-life effects of radical prostatectomy and primary radiotherapy for screen-detected or clinically diagnosed localized prostate cancer. *JCO* 2001;19(6):1619–28.
- 61 Haglund E, Carlsson S, Stranne J, et al. Urinary incontinence and erectile dysfunction after robotic versus open radical prostatectomy: a prospective, controlled, nonrandomised trial. *Eur Urol* 2015;68(2):216–25.

- 62 Donohy JL, Hamdy FC, Lane JA, *et al.* Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med* 2016;375(15):1425–37.
- 63 Cooperberg MR, Broering JM, Kantoff PW, *et al.* Contemporary trends in low-risk prostate cancer: risk assessment and treatment. *J Urol* 2007;178(3S):S14–19.
- 64 D'Amico AV. Combined-modality staging in predicting prostate-specific antigen outcome after definitive local therapy for men with clinically localized prostate cancer. In: D'Amico AV, ed. *Prostate cancer: principles & practice*. Philadelphia, PA: Lippincott Williams & Wilkins, 2002: 254–68.
- 65 Klotz L, Vesprini D, Sethukavalan P, *et al.* Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *JCO* 2015;33(3):272–7.
- 66 Tosoian JJ, Mamawala M, Epstein JI, *et al.* Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. *JCO* 2015;33(30):3379–85.
- 67 Hamdy FC, Donovan JL, Lane JA, *et al.* 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med* 2016;375(15):1415–24.
- 68 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA A Cancer J Clin* 2019;69(1):7–34.
- 69 Etzioni R, Tsodikov A, Mariotto A, *et al.* Quantifying the role of PSA screening in the US prostate cancer mortality decline. *Cancer Causes Control* 2008;19(2):175–81.
- 70 Dennis LK, Resnick MI. Analysis of recent trends in prostate cancer incidence and mortality. *Prostate* 2000;42(4):247–52.
- 71 Cookson MM. Prostate cancer: screening and early detection. *Cancer Control* 2001;8(2):133–40.
- 72 Draisma G, Boer R, Otto SJ, *et al.* Lead times and overdiagnosis due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst* 2003;95(12):868–78.
- 73 Andriole GL, Crawford ED, Grubb RL, *et al.* Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009;360(13):1310–9.
- 74 Schröder FH, Hugosson J, Roobol MJ, *et al.* Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet* 2014;384(9959):2027–35.
- 75 Hugosson J, Roobol MJ, Månsson M, *et al.* A 16-yr follow-up of the European Randomized Study of Screening for Prostate Cancer. *Eur Urol* 2019;76(1):43–51.
- 76 Tsodikov A, Gulati R, Heijnsdijk EAM, *et al.* Reconciling the effects of screening on prostate cancer mortality in the ERSPC and PLCO trials. *Ann Intern Med* 2017;167(7):449–55.
- 77 Whitmore WF. Localised prostatic cancer: management and detection issues. *Lancet* 1994;343(8908):1263–7.
- 78 Draisma G, Etzioni R, Tsodikov A, *et al.* Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst* 2009;101(6):374–83.
- 79 Welch HG, Black WC. Overdiagnosis in cancer. *J Natl Cancer Inst* 2010;102(9):605–13.
- 80 Lucia MS, Darke AK, Goodman PJ, *et al.* Pathologic characteristics of cancers detected in the prostate cancer prevention trial: implications for prostate cancer detection and chemoprevention. *Cancer Prev Res* 2008;1(3):167–73.
- 81 Heijnsdijk EAM, Wever EM, Auvinen A, *et al.* Quality-of-life effects of prostate-specific antigen screening. *N Engl J Med* 2012;367(7):595–605.
- 82 Desireddi NV, Roehl KA, Loeb S, *et al.* Improved stage and grade-specific progression-free survival rates after radical prostatectomy in the PSA era. *Urology* 2007;70(5):950–5.
- 83 Galper SL, Chen M-H, Catalona WJ, *et al.* Evidence to support a continued stage migration and decrease in prostate cancer specific mortality. *J Urol* 2006;175(3 Pt 1):907–12.
- 84 Dobbis RW, Greenwald DT, Wadhwa H, *et al.* Is prostate cancer stage migration continuing for black men in the PSA era? *Prostate Cancer Prostatic Dis* 2017;20(2):210–5.
- 85 Leyh-Bannurah S-R, Karakiewicz PI, Pompe RS, *et al.* Inverse stage migration patterns in North American patients undergoing local prostate cancer treatment: a contemporary population-based update in light of the 2012 USPSTF recommendations. *World J Urol* 2019;37(3):469–79.
- 86 Onol FF, P Ganapathi H, Rogers T, *et al.* Changing clinical trends in 10 000 robot-assisted laparoscopic prostatectomy patients and impact of the 2012 US Preventive Services Task Force's statement against PSA screening. *BJU Int* 2019;124(6):1014–21.
- 87 Aus G, Damber JE, Khatami A, *et al.* Individualized screening interval for prostate cancer based on prostate-specific antigen level results of a prospective, randomized, population-based study. *Arch Intern Med* 2005;165(16):1857–61.
- 88 Roobol MJ, Roobol DW, Schröder FH. Is additional testing necessary in men with prostate-specific antigen levels of 1.0 ng/mL or less in a population-based screening setting? (ERSPC, section Rotterdam). *Urology* 2005;65(2):343–6.
- 89 Randazzo M, Beatrice J, Huber A, *et al.* A "PSA pyramid" for men with initial prostate-specific antigen ≤ 3 ng/ml: a plea for individualized prostate cancer screening. *Eur Urol* 2015;68(4):591–7.
- 90 Gandaglia G, Albers P, Abrahamsson P-A, *et al.* Structured population-based prostate-specific antigen screening for prostate cancer: the European Association of Urology position in 2019. *Eur Urol* 2019;76(2):142–50.
- 91 Arnsrud Godtman R, Holmberg E, Lilja H, *et al.* Opportunistic testing versus organized prostate-specific antigen screening: outcome after 18 years in the Göteborg randomized population-based prostate cancer screening trial. *Eur Urol* 2015;68(3):354–60.
- 92 Mahal BA, Butler S, Franco I, *et al.* Use of active surveillance or watchful waiting for low-risk prostate cancer and management trends across risk groups in the United States, 2010–2015. *JAMA* 2019;321(7):704–6.
- 93 Ong WL, Evans SM, Evans M, *et al.* Trends in conservative management for low-risk prostate cancer in a population-based cohort of Australian men diagnosed between 2009 and 2016. *Eur Urol Oncol* 2019.
- 94 Wallace M. Uncertainty and quality of life of older men who undergo watchful waiting for prostate cancer. *Oncol Nurs Forum* 2003;30(2):303–9.
- 95 Bergman J, Litwin MS. Quality of life in men undergoing active surveillance for localized prostate cancer. *JNCI Monographs* 2012;2012(45):242–9.
- 96 Cotter AR, Vuong K, Mustelin LL, *et al.* Do psychological harms result from being labelled with an unexpected diagnosis of abdominal aortic aneurysm or prostate cancer through screening? A systematic review. *BMJ Open* 2017;7(12):e017565.
- 97 van den Bergh RCN, Korfae IJ, Bangma CH. Psychological aspects of active surveillance. *Curr Opin Urol* 2012;22(3):237–42.
- 98 Wilcox CB, Gilbourd D, Louie-Johnsun M. Anxiety and health-related quality of life (HRQL) in patients undergoing active surveillance of prostate cancer in an Australian centre. *BJU Int* 2014;113 Suppl 2:64–8.
- 99 Vasarainen H, Lokman U, Ruutu M, *et al.* Prostate cancer active surveillance and health-related quality of life: results of the Finnish arm of the prospective trial. *BJU Int* 2012;109(11):1614–9.
- 100 Bellardita L, Valdagni R, van den Bergh R, *et al.* How does active surveillance for prostate cancer affect quality of life? A systematic review. *Eur Urol* 2015;67(4):637–45.
- 101 Itatani R, Namimoto T, Atsugi S, *et al.* Negative predictive value of multiparametric MRI for prostate cancer detection: outcome of 5-year follow-up in men with negative findings on initial MRI studies. *Eur J Radiol* 2014;83(10):1740–5.
- 102 Schoots IG, Petrides N, Giganti F, *et al.* Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. *Eur Urol* 2015;67(4):627–36.
- 103 Schoots IG, Moore CM, Rouvière O. Role of MRI in low-risk prostate cancer: finding the wolf in sheep's clothing or the sheep in wolf's clothing? *Curr Opin Urol* 2017;27(3):238–45.
- 104 Martin AJ, Lord SJ, Verry HE, *et al.* Risk assessment to guide prostate cancer screening decisions: a cost-effectiveness analysis. *Med J Aust* 2013;198(10):546–50.
- 105 Shteynshlyuger A, Andriole GL. Cost-effectiveness of prostate specific antigen screening in the United States: extrapolating from the European Study of Screening for Prostate Cancer. *J Urol* 2011;185(3):828–32.
- 106 Heijnsdijk EAM, de Carvalho TM, Auvinen A, *et al.* Cost-effectiveness of prostate cancer screening: a simulation study based on ERSPC data. *J Natl Cancer Inst* 2015;107(1).
- 107 Matti B, Zargar-Shoshtari K. Opportunistic prostate cancer screening: a population-based analysis. *Urologic Oncology: Seminars and Original Investigations* 2019:1–8.
- 108 Marshall KG. Prevention. how much harm? how much benefit? The ethics of informed consent for preventive screening programs. *CMAJ* 1996;155(4):377–83.
- 109 Young JM, Muscatello DJ, Ward JE. Are men with lower urinary tract symptoms at increased risk of prostate cancer? A systematic review and critique of the available evidence. *BJU Int* 2000;85(9):1037–48.
- 110 Federman DG, Goyal S, Kamina A, *et al.* Informed consent for PSA screening: does it happen? *Eff Clin Pract* 1999;2(4):152–7.
- 111 Lamplugh M, Gilmore P, Quinlan T, *et al.* PSA testing: are patients aware of what lies ahead? *Ann R Coll Surg Engl* 2006;88(3):284–8.
- 112 Cooper DL, Rollins L, Slocumb T, *et al.* Are men making informed decisions according to the prostate-specific antigen test guidelines? Analysis of the 2015 behavioral risk factor surveillance system. *Am J Mens Health* 2019;13(2):1557988319834843.
- 113 Moynihan R, Nickel B, Hersch J, *et al.* Public opinions about overdiagnosis: a national community survey. *PLoS One* 2015;10(5):e0125165.
- 114 Riikonen JM, Guyatt GH, Kilpeläinen TP, *et al.* Decision aids for prostate cancer screening choice: a systematic review and meta-analysis. *JAMA Intern Med* 2019;179:1072–82.