Serum PSA-based early detection of prostate cancer in Europe and globally: past, present and future

Hendrik Van Poppel, Tit Albreht, Partha Basu, Renée Hogenhout, Sarah Collen and Monique Roobol

Abstract | In the pre-PSA-detection era, a large proportion of men were diagnosed with metastatic prostate cancer and died of the disease; after the introduction of the serum PSA test, randomized controlled prostate cancer screening trials in the USA and Europe were conducted to assess the effect of PSA screening on prostate cancer mortality. Contradictory outcomes of the trials and the accompanying overdiagnosis resulted in recommendations against prostate cancer screening by organizations such as the United States Preventive Services Task Force. These recommendations were followed by a decline in PSA testing and a rise in late-stage diagnosis and prostate cancer mortality. Re-evaluation of the randomized trials, which accounted for contamination, showed that PSA-based screening does indeed reduce prostate cancer mortality; however, the debate about whether to screen or not to screen continues because of the considerable overdiagnosis that occurs using PSA-based screening. Meanwhile, awareness among the population of prostate cancer as a potentially lethal disease stimulates opportunistic screening practices that further increase overdiagnosis without the benefit of mortality reduction. However, in the past decade, new screening tools have been developed that make the classic PSA-only-based screening an outdated strategy. With improved use of PSA, in combination with age, prostate volume and with the application of prostate cancer risk calculators, a risk-adapted strategy enables improved stratification of men with prostate cancer and avoidance of unnecessary diagnostic procedures. This combination used with advanced detection techniques (such as MRI and targeted biopsy), can reduce overdiagnosis. Moreover, new biomarkers are becoming available and will enable further improvements in risk stratification.

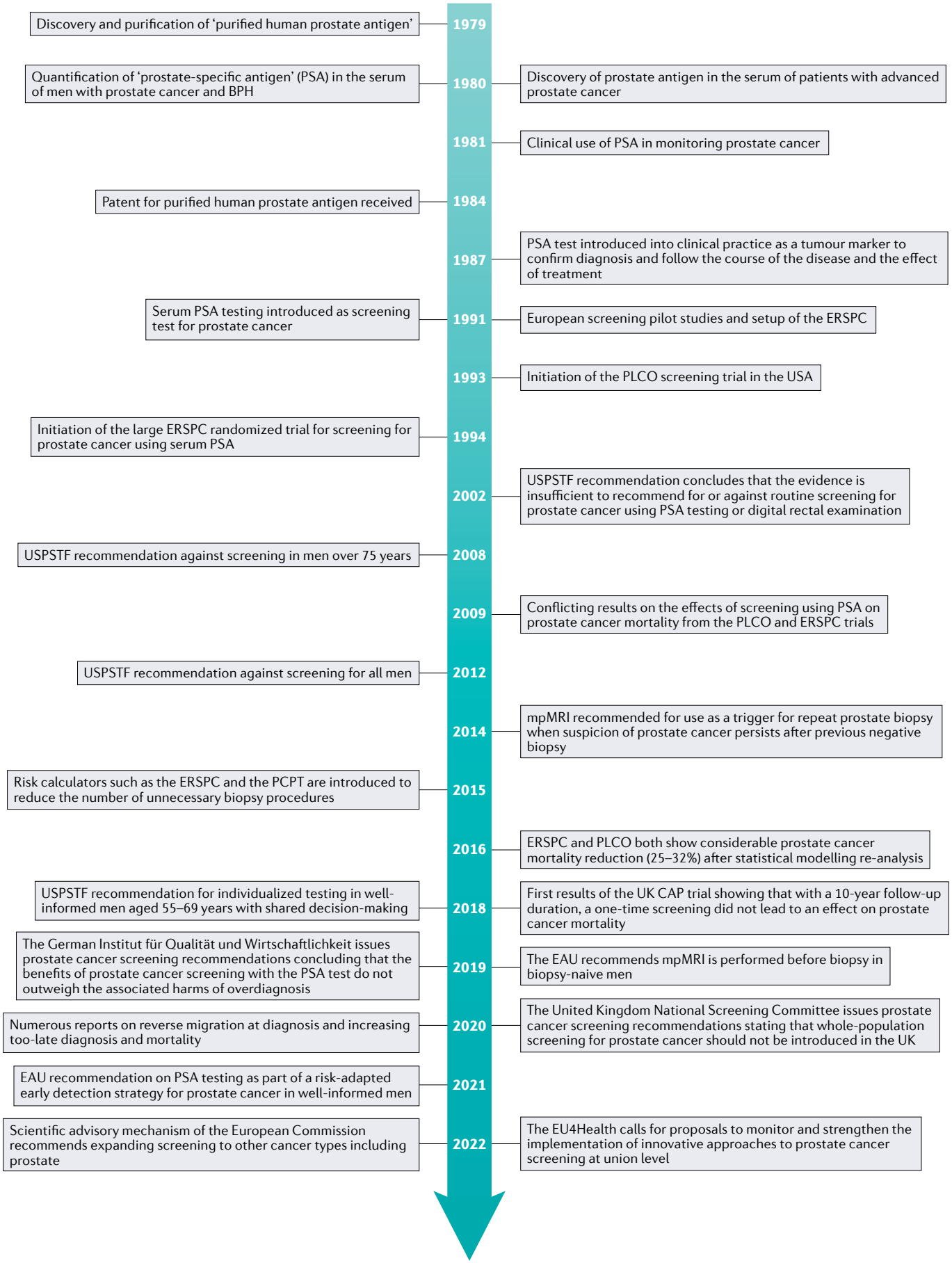
Cancer-screening programmes, such as those for breast, cervical and colorectal cancer, are designed to reduce late-stage diagnoses and cancer-specific mortality, but not to reduce overall mortality. Furthermore, demonstrating an overall mortality reduction through cancer screening is difficult because individual cancer constitutes only a small proportion of all causes of death[1]. Diagnosis of malignant diseases at an early stage using screening has obvious benefits: high possibility of cure, less aggressive treatment options, reduced disease progression to advanced or metastatic stages, improved quality of life, and reduced disease-specific mortality. However, screening also causes identification of cancers that would never result in clinical symptoms or mortality if they remained untreated[2]. Treatment of these overdiagnosed cancers can negatively affect quality of life and not finding them at all would be a better outcome[3]. The question of the benefits and harms of screening are particularly pertinent in prostate cancer with the use of serum PSA as a screening tool.

Research into an antigen in human semen to characterize prostatic diseases had been ongoing since the 1970s but the discovery of purified human prostate antigen was reported in 1979 (REF.[4]) and was subsequently found in the sera of patients with advanced prostate cancer in 1980 (REF.[5]). Also in 1980, quantification of 'prostate-specific antigen' (PSA) in the serum of men with prostate cancer and BPH was reported using a sensitive enzyme immunoassay[6]. The serum PSA test was first used for monitoring patients with prostate cancer in in 1981 (REF.[7]); the PSA test was originally designed for monitoring the progression of prostate cancer and the response to therapy, and not as a screening tool to detect the disease. The test can be used to effectively identify elevated serum PSA levels, which are commonly observed in prostate cancer, but, importantly, are also found in some benign conditions such as BPH (in which the PSA level is related to the prostate volume) and prostatitis, as both conditions are associated with increased amounts of PSA in the bloodstream[8]. In 1984 the patent for 'purified human prostate antigen' was received[9,10]. In 1987, the serum PSA test was introduced into clinical practice as a tumour marker, not as a screening tool, but to confirm diagnosis and follow the course of the disease and the effect of treatment[11]. To attempt to mitigate the fact that prostate cancer was often beyond cure at the time of diagnosis, serum PSA testing, a simple, fully developed, stable, objective and inexpensive blood-based test[12] was reported as a screening tool for prostate cancer in 1991 (REF.[13]) (FIG. 1). The test was cheap, reasonably sensitive and required minimal infrastructural investments[14].

In this Perspective, we describe the use of PSA testing for prostate cancer screening in the past few decades, noting the benefits and pitfalls of historical population-based screening programmes and the current difficulties that have occurred as a result and the lessons learned. In addition, based on knowledge gained during this period, we propose a way forward for the rational use of PSA testing as part of a risk-adapted strategy for the early detection of aggressive prostate cancer.

The past: the PSA screening era

The PSA screening era began in 1993, with the initiation of two large randomized controlled trials[15,16], and follow-up assessment is still ongoing (FIG. 1). At that time, no guidelines on screening were available.


1979
Discovery and purification of 'purified human prostate antigen'
1980
Quantification of 'prostate-specific antigen' (PSA) in the serum of men with prostate cancer and BPH
Discovery of prostate antigen in the serum of patients with advanced prostate cancer
1981
Clinical use of PSA in monitoring prostate cancer
1984
Patent for purified human prostate antigen received
1987
PSA test introduced into clinical practice as a tumour marker to confirm diagnosis and follow the course of the disease and the effect of treatment
1991
Serum PSA testing introduced as screening test for prostate cancer
European screening pilot studies and setup of the ERSPC
1993
Initiation of the PLCO screening trial in the USA
1994
Initiation of the large ERSPC randomized trial for screening for prostate cancer using serum PSA
2002
USPSTF recommendation concludes that the evidence is insufficient to recommend for or against routine screening for prostate cancer using PSA testing or digital rectal examination
2008
USPSTF recommendation against screening in men over 75 years
2009
Conflicting results on the effects of screening using PSA on prostate cancer mortality from the PLCO and ERSPC trials
2012
USPSTF recommendation against screening for all men
2014
mpMRI recommended for use as a trigger for repeat prostate biopsy when suspicion of prostate cancer persists after previous negative biopsy
2015
Risk calculators such as the ERSPC and the PCPT are introduced to reduce the number of unnecessary biopsy procedures
2016
ERSPC and PLCO both show considerable prostate cancer mortality reduction (25–32%) after statistical modelling re-analysis
2018
USPSTF recommendation for individualized testing in well-informed men aged 55–69 years with shared decision-making
First results of the UK CAP trial showing that with a 10-year follow-up duration, a one-time screening did not lead to an effect on prostate cancer mortality
2019
The German Institut für Qualität und Wirtschaftlichkeit issues prostate cancer screening recommendations concluding that the benefits of prostate cancer screening with the PSA test do not outweigh the associated harms of overdiagnosis
The EAU recommends mpMRI is performed before biopsy in biopsy-naive men
2020
Numerous reports on reverse migration at diagnosis and increasing too-late diagnosis and mortality
The United Kingdom National Screening Committee issues prostate cancer screening recommendations stating that whole-population screening for prostate cancer should not be introduced in the UK
2021
EAU recommendation on PSA testing as part of a risk-adapted early detection strategy for prostate cancer in well-informed men
2022
Scientific advisory mechanism of the European Commission recommends expanding screening to other cancer types including prostate
The EU4Health calls for proposals to monitor and strengthen the implementation of innovative approaches to prostate cancer screening at union level

◀ Fig. 1 | **Timeline of the discovery and the use of PSA for prostate cancer screening.** EAU, European Association of Urology; ERSPC, European Randomized Screening for Prostate Cancer; mpMRI, multiparametric MRI; PCPT, Prostate Cancer Prevention Trial; PLCO, Prostate, Lung, Colorectal and Ovarian; USPSTF, United States Preventive Services Task Force.

Establishment of prostate cancer screening trials. In the pre-PSA testing era, when a digital rectal examination (DRE) was the only screening tool available, 30–35% of men had bone metastasis at the time of diagnosis; furthermore, of every 2–3 patients with prostate cancer, one died of their disease[17]. After the PSA test was introduced into clinical practice as a tumour marker[11] the number of newly diagnosed prostate cancers rose rapidly. In the Netherlands, age-adjusted incidence rates increased from 63 to 104 per 100,000 person-years in the period 1989–2006 (REF.[18]). In the early 1990s, PSA-based screening trials[15,16] were designed to assess the effect of screening on prostate cancer-specific mortality. Initial data had shown that the disease was diagnosed most frequently at a stage when it was amenable for cure when using the PSA test[15,19,20]. Whether screening would eventually lead to a prostate cancer mortality reduction was unclear.

In 1991, a paper on the usefulness of serum PSA testing in the detection and staging of prostate cancer was published[13]. The conclusions drawn from this study were that the combination of DRE and the serum PSA test, with additional testing (ultrasonography and biopsy) performed in patients with abnormal findings, provided a better method of detecting prostate cancer than DRE alone. After this publication, the path to a large screening trial was open, as a cheap and acceptable test that could be implemented on a large scale was available, forming the basis for the design of the European Randomized study of Screening for Prostate Cancer (ERSPC)[21]. A pilot study was conducted in the Netherlands between 1991 and 1993 to test feasibility and logistics[19]. Soon after, in 1994, the ERSPC started in eight centres across Europe[21]. In 1993, a prostate cancer screening study, the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial, was also initiated in the USA by the National Cancer Institute, which designed and sponsored the trial. The aim of the PLCO is to determine the effects of screening on cancer-related mortality in men and women aged 55–74 years[20].

The ERSPC[15] and PLCO[16] trials showed overall similarity in design in terms of being multicentre (8 versus 10 centres), the core age range assessed (50–69 years old versus 55–74 years old), PSA cut-off value (≥3 ng/ml versus >4 ng/ml) and primary end point (prostate cancer-specific mortality), with a major difference being that, in the PLCO trial, the execution of the prostate biopsy was performed by the physician, whereas in the ERSPC, this procedure was done in the screening centres, strictly following pre-defined biopsy indications. These differences could have caused the observed difference in compliance with the biopsy protocol: average compliance with biopsy in ERSPC was 86%, whereas it was 35% in PLCO[22,23]. As the primary outcome of both trials was prostate cancer-specific mortality, a long period of waiting followed before the first results were published.

Effect of screening programmes. As the PSA-based screening trials were being undertaken, the incidence of prostate cancer increased rapidly in the general population in places where PSA testing had become popular, mainly in the USA, Australia and western Europe[24]. Since the mid-1990s, especially in high-income countries in northern and western Europe, prostate cancer-specific mortality decreased[25], probably owing to the increased use of PSA testing and advances in treatment[26]. During the same period, mortality from prostate cancer increased in central and eastern Europe, where limited use of PSA testing might have had a role. Indeed, incidence rates are in general threefold higher in high-income than in low-income countries, to which most countries in central Europe belong[27]. PSA testing can be limited by financial constraints, a lack of awareness and accessibility to PSA testing sites.

In 2009, the results from both screening trials were published[15,16] (FIG. 1). The ERSPC trial showed a relative risk reduction of 20% in prostate cancer-specific mortality by screening and 30% reduction of metastatic disease at diagnosis using PSA-based testing[15]; however, no effect of screening was observed in the PLCO trial[16]. In response to these contradictory results and the considerable rates of overdiagnosis (~50%) and related overtreatment that was found in both studies, the recommendations on PSA testing changed.

To address identified gaps in the 2002 recommendation from the United States Preventive Services Task Force (USPSTF)[28], in which they concluded that the evidence was insufficient to recommend for or against routine screening for prostate cancer using PSA testing or DRE, and despite the fact that the results of the trial were not yet available, in 2008, the USPSTF published recommendations against screening for men ≥75 years[29] and for all men in 2012 (REF.[30]). These decisions resulted from new evidence[30] on the benefits and harms of PSA-based screening for prostate cancer, as well as the benefits and harms of treatment of localized disease. Subsequently, a decrease in the diagnosis of local-stage prostate cancer and an increase in regional-stage and advanced-stage diagnoses (reverse stage migration) was observed: for local-stage disease, incidence rates per 100,000 men aged 50 years and older increased from 456.4 (95% CI 454.2–458.6) in 2005 to 506.1 (95% CI 503.9–508.3) in 2007 and then decreased in subsequent years to 279.2 (95% CI 277.7–280.6) in 2016. For regional-stage disease, incidence generally increased throughout the study period, from 5.7 (95% CI 5.4–5.9) in 2005 to 9.0 (95% CI 8.8–9.3) in 2016. For distant-stage disease, incidence rates slightly declined from 23.1 (95% CI 22.6–23.6) in 2005 to 22.4 (95% CI 21.9–22.9) in 2008 but then went on to increase to 29.7 (95% CI 29.2–30.2) in 2016 (REF.[31]), which could be attributed to reduced screening; however, other factors, including excess body weight (incidence of which increased during the 1970s and is associated with fatal prostate cancer) could also have had an effect[31].

Recommendations were issued in Europe by the German Institut für Qualität und Wirtschaftlichkeit in 2019 (REF.[32]), which concluded that the benefits of prostate cancer screening with the PSA test do not outweigh the associated harms of overdiagnosis, and the United Kingdom National Screening Committee in 2020, which stated that whole-population screening for prostate cancer should not be introduced in the UK[33] (FIG. 1). These recommendations were based on systematic reviews and a meta-analysis highlighting the harms of PSA-based prostate cancer screening outweighing the benefits[34,35]. As in the USA, in Europe, the issuing of these recommendations coincided with subsequent stage migration; for example, in Germany the percentage of primarily diagnosed locally advanced disease (cT3) increased from 29% in 2008 to 49% in 2017, and the percentage of nodal disease at diagnosis from 4.5% to 16.9% in the same period[36].

In 2016, the discrepant effect on mortality found in the two studies[15,16] led to a re-evaluation of the control arm of the PLCO study, in which 90% of men had at least one PSA test (contamination).

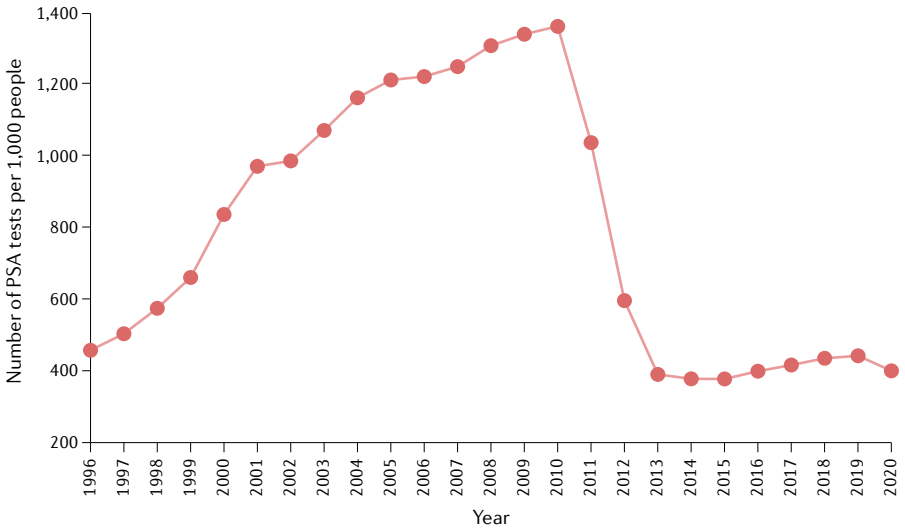


Fig. 2 | **The number of PSA tests over time in Belgium[53].** The graph illustrates the increasing number of PSA tests performed between 1996 and 2010 followed by a steep decline from 2011 onwards, followed by a stabilization at a level equal to that in 1996. Data from Rijksinstituut voor Ziekte-en Invaliditeitsverzekering (RIZIV/INAMI) statistical department[53]; graph adapted from an original graphical representation from E. Briers (personal communication).

This high level of contamination implies that the intervention under study (that is PSA testing) was actually applied in both arms of the trial. This occurrence seriously reduces the power of a trial to show an effect of the intervention on the main end point, in this case prostate cancer-specific mortality[37]. When the differences in implementation and settings were accounted for, combined analysis of data from both the ERSPC and the PLCO studies showed that PSA-based screening reduces prostate cancer-specific mortality. After accounting for differences in implementation the trials showed a 25–30% reduced risk of prostate cancer death in ERSPC (men aged 55–69 years) and a 27–32% reduced risk of prostate cancer death in PLCO (men aged 55–74 years) compared with no screening[38].

Thereafter, in 2018, the USPSTF shifted towards supporting individualized testing in well-informed men aged 55–69 years after discussion of the potential benefits and harms (shared decision-making)[39].

In Europe in general, the ERSPC results were taken as a basis for recommendations. The strong changes in the USA (from no screening at all towards screening in men aged 55–69 after informed consent) were not seen in Europe. Since 2010, the European Association of Urology (EAU) recommendation has been that if a man is fully informed about the advantages and disadvantages he should not be denied a PSA test[40]. Meanwhile, in 2018, the first results of the UK CAP trial became available, showing that with a 10-year follow-up duration, a one-time screening did not lead to an effect on prostate cancer mortality[41] (FIG. 1). Longer follow-up assessment is needed to evaluate the effect of a one-time screening test, but the ERSPC results show that future population-based programmes must be designed, including repeated testing and increased follow-up monitoring duration.

Overall, the two historical PSA-based screening trials[15,16] in Europe and the USA have provided evidence of the benefits of repeated PSA testing to reduce late-stage diagnoses (that is stage migration) and prostate cancer-specific mortality[42–44]. However, these screening protocols were developed almost 30 years ago, in which an abnormal PSA value led to further investigations, such as prostate biopsy sampling, and to overdiagnosis, and are, therefore, outdated when it comes to the harm:benefit ratio, given the scientific advances that have been made since.

The present: 2012–2022

In the past few years, PSA testing in healthy men at risk of prostate cancer but without suspicion of this disease has reduced, but the amount of opportunistic screening has increased. In 2012, the USPSTF made the landmark decision to change their recommendation to no screening at all, which has affected screening since its publication (FIG. 1).

Effect of reduced PSA screening. PSA testing was generally discouraged and many primary care physicians dissuaded healthy men from being tested owing to widespread claims that PSA testing is not beneficial[45]. These claims were based on the harms associated with overdiagnosis and overtreatment that had been observed in historical screening protocols, which considerably reduced quality of life owing to urinary, bowel and sexual complications of active treatment[46]. The mostly individual beliefs on the harms and benefits of PSA testing by both groups of general practitioners and urologists after the publication of the two randomized trials[15,16] were followed by a decline in the use of PSA sampling and, in some countries, the withdrawal of reimbursement policies by national health services. For example, in Belgium, PSA testing is only reimbursed if the man is the son of a father who was diagnosed with prostate cancer before the age of 65 years or to monitor a biopsy-proven prostate cancer[47].

In Europe, during the 1990s and early 2000s, PSA testing rates were relatively low (compared with practices in the USA). In Europe, the lack of evidence for screening — and the potential harms — were recognized, which is indicated in the wording of the European guidelines[48]. However, in the USA, public awareness about prostate cancer is greater than in Europe, owing to celebrities being open about their prostate cancer diagnosis, prostate cancer support groups, public fundraising events and television advertisements from pharmaceutical companies. This increased awareness has led to a very considerable direct patient demand to be tested[49].

Data in a 2003 paper showed that the proportion of men who had ever had one PSA test ranged from 7% (in Spain and Finland in the 1990s) to 36% (in Italy in 2001)[50]. Data on contamination[51] in the ongoing PLCO trial were increasingly emphasized, but in the following years, the rate of PSA testing increased. Data on opportunistic testing from the UK covering a period from 1998 up to 2017 showed that the cumulative proportion of uptake of opportunistic PSA screening was 44% in men aged 40–77 years[52]. Data from Belgium show a clear increase in PSA testing between 1996 and 2010 followed by a steep decrease between 2010 and 2013, when testing levels off[53] (FIG. 2). Incidence of prostate cancer in Belgium and the Netherlands show a decline after the negative recommendations towards PSA testing were announced[54,55] (FIG. 3). As well as a decrease in diagnoses, a 'reverse stage migration' occurred, in which more men

were diagnosed with advanced or late-stage prostate cancer and died from the disease more frequently than before the negative recommendations, both in the USA and in Europe[56–59]. In the USA, between 2008 and 2016, the mean percentage of men screened decreased (from 61.8% to 50.5%) and the mean incidence of metastatic prostate cancer at diagnosis increased (6.4–9.0 per 100.000, $P < 0.001$)[60].

In many countries, prostate cancer became the second most prevalent cancer after lung cancer, and killed more men than colorectal cancer, for which incidence rates are declining. In the UK, a 17% increase in prostate cancer-specific mortality was noted in 10 years (1995–2005), and more men died from prostate cancer than women from breast cancer[61]. These measures of disease-specific mortality are relative but, nevertheless, clearly show the increasing effect of prostate cancer mortality[62]. Unfortunately, in the misuse of PSA testing driven by a lack of an organized and standardized approach is thought to result in even higher rates of overdiagnosis than the previous population-wide PSA screening trials, while hardly affecting prostate cancer mortality[63,64]. However, although PSA screening was declining, men in the general population became increasingly aware of PSA testing and its ability to detect prostate cancer as a potentially lethal disease[65]. Subsequently, opportunistic screening increased, unfortunately, largely in men who are unlikely to derive any benefit based on subjective reasons such as fear of missing out because relatives and neighbours are having a test, urinary complaints that are not related to prostate cancer, or simply because they want a PSA test as they getting older[66–68]. However, screening in an organized manner, at the population level, should have an effect that is much closer to the effect observed in the randomized trials, that is, a reduction in overdiagnosis and death[63].

To date, to our knowledge, only one country globally offers organized PSA testing at a population-based level, and that is Lithuania, which has one of the highest prevalences of prostate cancer[69]. The nationwide screening programme is based on an awareness campaign recommending that healthy men have their PSA tested in order to avoid late diagnosis and prostate cancer death. The programme was started in 2006, and offers 3-yearly testing to men aged 50–75 years with a relatively high coverage (exceeding 70% between 2006 and 2010). This programme has resulted in a continuous decrease in diagnosis of advanced prostate cancer of 11.1% per year[70]. However, opportunistic testing occurred in this programme, resulting in only a modest reduction in prostate cancer mortality[70]. Despite this mortality reduction from prostate cancer in Lithuania, the harms caused by overdiagnosis and overtreatment are likely to be high, as a no risk-adapted approach has been followed for the downstream management of men with concerning PSA levels[71].

Before 2013, guidelines recommended against PSA screening for men with an average risk of prostate cancer diagnosis[72] or a cautious approach of engaging them in informed and shared decision-making by their physicians and proceeding with a PSA test based on each man's values and preferences[73].

From 2013 onwards, both the American Urological Association and EAU guidelines

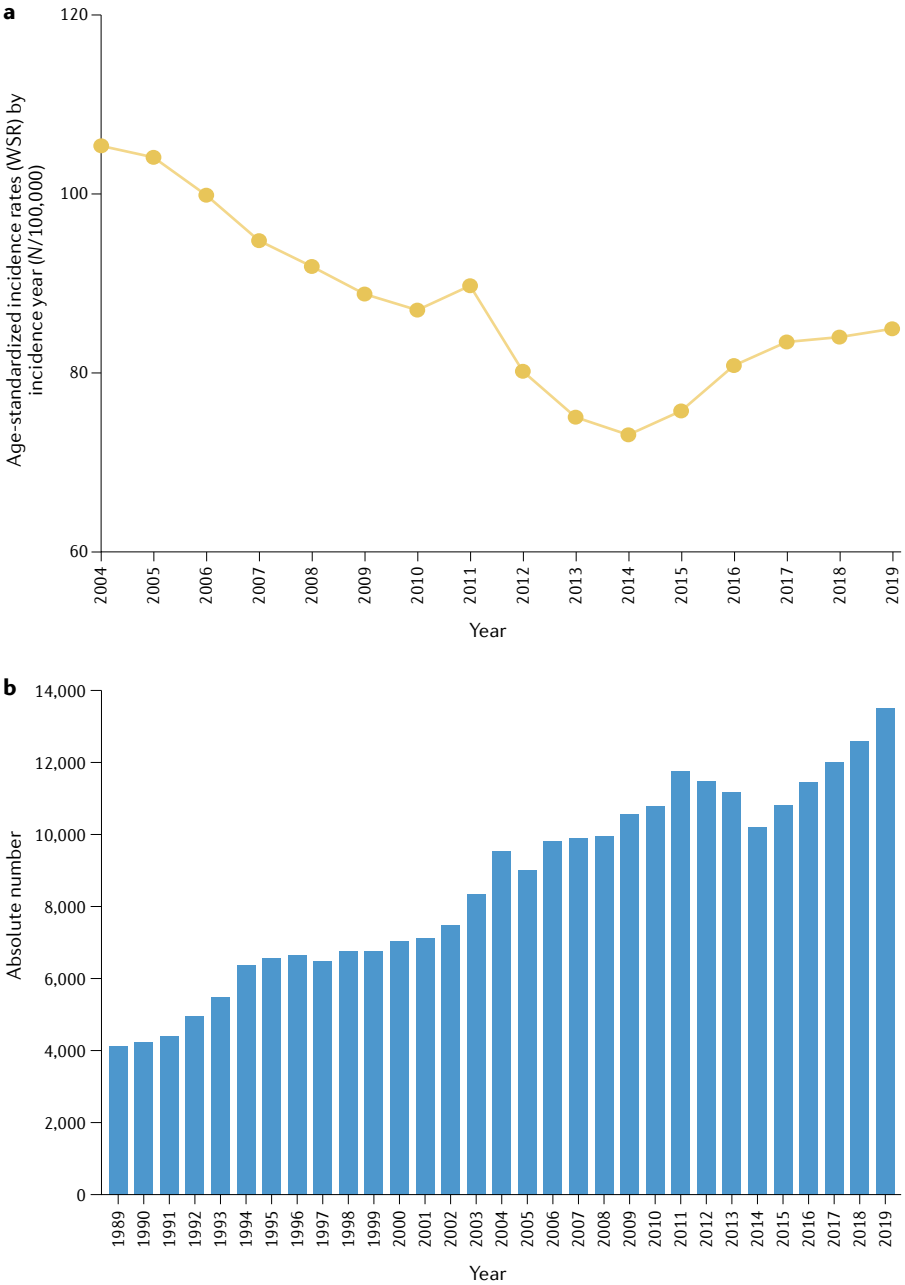
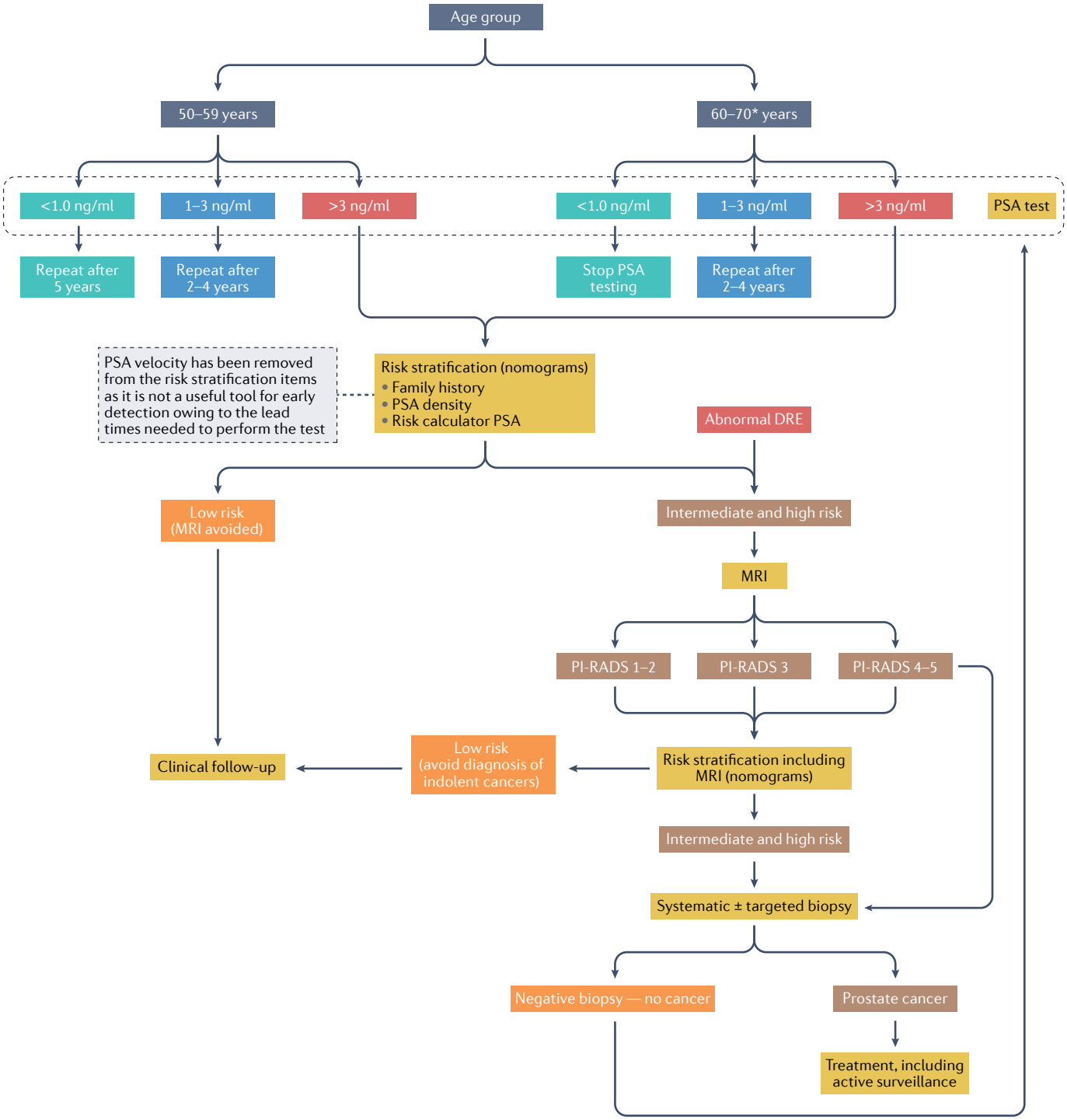


Fig. 3 | **Prostate cancer incidence over time in Belgium[54] and the Netherlands[55]. a** | Prostate cancer diagnoses in Belgium (2002–2019), showing the age-standardized incidence rate using the world standard rate (WSR; expressed as the number of new cases per 100,000 person-years) and indicating the reduction in prostate cancer diagnoses between 2005 and 2014. Data from Belgian Cancer Registry. Cancer Fact Sheet: Prostate Cancer[54]. **b** | Prostate cancer diagnoses in the Netherlands (1989–2019) showing the decline in numbers of prostate cancer diagnoses between 2010 and 2015. Data from Integraal Kankercentrum Nederland. Prostaatkanker in Nederland[55].



have agreed on using an individualized risk-adapted strategy for well-informed men up to 69 years old or remaining life-expectancy of 10–15 years[74–77]. These men are at an elevated risk of having prostate cancer, as they are over 50 years of age, over 45 years of age with a family history of prostate cancer, have African ancestry and are over 45 years of age, or carry *BRCA2* mutations and are over 40 years of age[77]. These men can be offered PSA testing as an individualized strategy for early detection.

New risk stratification tools have gradually been included in this strategy over the past few years. First, prostate volume was integrated as PSA density (PSA divided by prostate volume in grams) and a cut-off was established at 0.15 to distinguish high increased PSA values caused by cancer or by benign prostatic diseases[78,79]. Second, in 2014, multiparametric MRI (mpMRI) was recommended for use as a trigger for repeat prostate biopsy when suspicion of prostate cancer persisted after previous negative biopsy[80]. In 2015, the use of risk calculators such as the ERSPC[81] and Prostate Cancer Prevention Trial risk calculator 2.0 (REF.[82]) were introduced to reduce the number of unnecessary biopsy procedures. These risk stratification nomograms include age, family history, DRE and prostate volume (PSA density)[83,84]. The value of mpMRI in detecting clinically significant prostate cancers and reducing overdiagnosis was increasingly recognized and performing upfront mpMRI (that is, in a diagnostic

◀ Fig. 4 | **Adapted algorithm of the risk-adapted strategy for the early detection of prostate cancer from the EAU[88].** This strategy combines the proven effect of the PSA test derived from the European Randomized study of Screening for Prostate Cancer in reducing prostate cancer-specific mortality and metastatic disease[89] with new risk stratification tools to improve the success of the PSA test and, at the same time, reduce unnecessary testing, overdiagnosis and subsequent overtreatment. The PSA test in itself is a powerful stratification tool to establish a baseline PSA level among healthy men. Then, further reflex testing is strongly advised to reduce the rate of false-positive PSA tests. One of the simplest but strongest predictors of the presence of prostate cancer that is used is PSA density[92], which can be obtained by transrectal ultrasonography or digital rectal examination (DRE)[93,94]. These risk calculators are easy to use and freely available online to every clinician. Here, PSA velocity is not a recommended risk-stratification item as it is not a useful tool for early detection, owing to the lead times needed to perform the test. Those with low-risk disease are then recommended to undergo a form of watchful waiting using interval PSA testing, because of a small risk of missing clinically significant prostate cancer and the fact that one-time screening does not reduce prostate cancer-specific mortality[43,93]. Men at an intermediate risk or high risk should not undergo immediate biopsy but should be offered MRI of the prostate first. Lesions with a Prostate Imaging–Reporting and Data System (PI-RADS) score of 1 or 2 do not cause suspicion of cancer, a PI-RADS score of 3 is termed equivocal, and PI-RADS 4 and 5 lesions are likely to be malignant. Both will definitely need to be biopsied. To decrease the number of negative and insignificant prostate biopsy outcomes for PI-RADS 3 lesions, PSA density might again be used to determine whether a biopsy should be done[98,99]. Also, risk calculators that include MRI results and PSA density are recommended at this stage to reduce unnecessary biopsy procedures and to avoid missing clinically significant cancers in men with non-suspicious MRI[86]. Men who are excluded from biopsy sampling because their disease is low risk and men in whom the biopsy is unlikely to yield cancer according to the results of the risk stratification tools and MRI are not dismissed definitely but should undergo clinical follow-up monitoring as a precaution. From those who show cancer on the biopsy, men with high-risk prostate cancer will be best managed with active treatment such as radical prostatectomy or radiotherapy. To reduce overtreatment, men with low-grade prostate cancer can undergo active surveillance. Adapted with permission from REF.[88], Elsevier.

setting) was recommended as a standard of care for prostate cancer diagnosis[85]. In 2019, mpMRI was recommended to be performed before prostate biopsy in biopsy-naive men by the EAU[86,87] (FIG. 1).

Thus, the recommendations for prostate cancer screening and downstream management gradually became more rational. Recognizing the harms associated with overdiagnosis and overtreatment meant that the trend was towards a more risk-adapted approach rather than 'one-size-fits-all'.

Current and emerging approaches. In 2021, the EAU published a risk-adapted individualized strategy for early detection of prostate cancer structured in an easy-to-follow flowchart[88] (FIGS. 1,4). This strategy combines the proven effect of the PSA test derived from the ERSPC in reducing prostate cancer-specific mortality and metastatic disease[89] with new risk stratification tools to improve the success of the PSA test and, at the same time, reduce unnecessary testing, overdiagnosis and subsequent overtreatment; however, some adaptations to this strategy might be pertinent to further improve the utility of PSA testing (FIG. 4).

Initially, the PSA test in itself provides a powerful stratification tool for establishing a baseline PSA level among healthy men. Thereafter, further risk stratification using reflex testing is strongly advised, which can be done with commercially available risk calculators, such as the 4Kscore or the Prostate Health Index, along with family history[90,91]. Reflex testing is advised to reduce the rate of false-positive PSA tests, that is, an elevated PSA level mostly caused by BPH. Considering availability and costs, one of the simplest but strongest predictors of the presence of prostate cancer that is used is PSA density[92]. This predictor, which relates PSA level to prostate volume, can be obtained by transrectal ultrasonography or even during DRE[93,94] and is frequently included in risk calculators, such as those developed by the ERSPC[93] and the Prostate Cancer Prevention Trial[95]. These risk calculators are easy to use and freely available online to every clinician. Risk calculators improve the predictive accuracy of PSA testing[84] by categorizing men at low risk, intermediate risk, or high risk of having clinically significant cancer. As an adaptation of the original strategy, PSA velocity is not a recommended risk-stratification item as it is not a useful tool for early detection, owing to the lead times needed to perform the test. Those with low-risk disease are then recommended to undergo clinical follow-up monitoring in the form of watchful waiting using interval PSA testing (every 2–4 or 5 years), because of a small risk of missing clinically significant prostate cancer and the fact that one-time screening does not reduce prostate cancer-specific mortality[41,96]. Men at an intermediate risk or high risk should not undergo immediate biopsy but should be offered MRI of the prostate first. Images are assessed using the Prostate Imaging–Reporting and Data System (PI-RADS), indicating the likelihood of clinically significant cancer[97]. Lesions with a PI-RADS score of 1 or 2 do not cause suspicion of cancer, a PI-RADS score of 3 is termed equivocal, and PI-RADS 4 and 5 lesions are likely to be malignant. The EAU nomogram suggests that men with any PI-RADS lesions should undergo further risk stratification, which includes MRI; however, as an adaptation to this flow chart, we suggest that PI-RADS 4–5 lesions will definitely need to be sampled using systematic and/or targeted biopsies. To decrease the number of negative and insignificant prostate biopsy outcomes for PI-RADS 3 lesions, PSA density might again be used to determine whether a biopsy should be done or not[98,99]. Also, risk calculators that include MRI results and PSA density are recommended at this stage to reduce unnecessary biopsy procedures and to avoid missing clinically significant cancers in men with non-suspicious MRI[86]. As an adaptation to this algorithm, men who have a negative biopsy then undergo PSA testing again, in order to monitor their risk. Men who are excluded from biopsy sampling because their disease is low risk and men in whom the biopsy is unlikely to yield cancer according to the results of the risk-stratification tools and MRI are not definitely dismissed but should undergo clinical follow-up monitoring as a precaution. From those who show cancer on the biopsy, men with high-grade prostate cancer will be best managed with active treatment such as radical prostatectomy or radiotherapy. To reduce overtreatment, men with low-grade prostate cancer can undergo active surveillance (FIG. 4). Active surveillance is becoming increasingly acceptable to patients and physicians and its use has increased over the years[100].

Despite these advances, the recommendations against PSA testing in response to the contradictory outcomes of the leading PSA screening trials from the past and the high levels of overdiagnosis have had a long-lasting negative effect[31,101]. Many health-care providers remain reluctant to return to PSA testing[102] as they have reservations about implementing current knowledge and resulting guidelines, and a desire to wait for results of clinical trials that include the new risk-stratification tools remains. However, waiting for the outcomes of new trials could take at least another decade before any changes are made to current practice, in which inefficient

opportunistic screening is expanding whereas the number of men diagnosed with prostate cancer at a late stage continues to increase. Primary-care physicians should continue to keep up to date concerning current knowledge and be encouraged to discuss PSA testing with their patients[103,104]. Otherwise, a situation could arise in which men considering PSA testing receive inconsistent advice and care, which enables the possibility of opportunistic testing being undertaken.

The future: risk-adapted PSA testing

The future implementation of risk-adapted PSA testing will enable early detection of clinically significant prostate cancer while avoiding further investigations in men with a low risk of having this disease.

The need for screening. A more rational approach to early prostate cancer detection than is currently in place is obviously needed as, globally, countries are confronted with increasing elderly populations[105] in whom prostate cancer-specific mortality is highest[106]. In early 2018, a total of 101.1 million middle-aged people (≥65 years old) lived in the 28 EU countries, which is almost one-fifth (19.7%) of the total population; during the next three decades, this figure is projected to rise up to 149.2 million inhabitants in 2050 (28.5% of the total population)[107]. Lessons from previous decades on avoiding overdiagnosis and overtreatment and how to halt non-organized and opportunistic screening have been learned[108,109]. This improved knowledge will help to reverse current increasing trends in prostate cancer mortality in eastern Europe and to hopefully reinitiate a decline in stabilizing trends in the rest of the world[25].

Modelling has already been conducted to assess the cost-effectiveness of risk-adapted early detection of prostate cancer[110–112]. The assumptions used in modelling are always debatable, but these studies can be used to draw some useful conclusions about ideal age ranges for screening and the use of MRI before biopsy[111,112]. In a systematic review of modelling studies, ten studies were included[110]. In four of the studies, cost-effective screening strategies were identified, including a single screen at 55 years old, annual or 2-yearly screens starting at 55 years old and, important to note, delayed radical treatment by the identification of low-grade and some intermediate-grade cancers that do not require immediate active treatment and are, therefore, amenable to active surveillance should be included. Cost implications for health systems in high-income regions are considerable as the elderly population in these places is large and cancer is becoming a greater problem than other medical conditions[113].

New technologies for prostate cancer detection. The scientific advances made to date, such as risk stratification using risk calculators and MRI and use of novel urine and blood biomarkers that have become available, now need to be embraced and included in an ever-improving risk-adapted approach for the early detection of prostate cancer. New tests for early detection of prostate cancer show great potential. For example, the Stockholm3 (STHLM3) test, which combines five plasma protein markers (total PSA, free PSA, free hK2, prostatic secretory protein of 94 amino acids and growth/differentiation factor 15), >100 genetic markers, and clinical data (such as age, previous biopsy results and family history) to determine the risk of aggressive prostate cancer (defined as Gleason Score ≥7 (International Society of Urological Pathology Grade Group 3)). The test is applicable to men aged 50–70 years and has been validated in 60,000 men in the STHLM3 study[114,115]. The STHLM3 model performed significantly better than PSA alone for detection of Gleason score ≥7 ($P<0.0001$ area under the curve for PSA alone 0.56 (95% CI 0.55–0.60); area under the curve for STHLM3 0.74 (95% CI 0.72–0.75))[114]. Using STHLM3 instead of current clinical practice could substantially reduce the number of biopsies performed while maintaining the same sensitivity of diagnosing clinically significant prostate cancer[116]. Comparison of biopsy results in 56,282 men who underwent PSA testing according to current clinical practice in Stockholm in 2011 with the 47,688 men enrolled in the STHLM3 validation cohort between 2012 and 2015 showed that STHLM3 enabled diagnosis of Gleason score ≥7 prostate cancer with the same sensitivity as current practice. Furthermore, use of STHLM3 was estimated to reduce diagnosis of Gleason score 6 cancers by 23% (95% CI 6–40%) and the number of men who would undergo biopsy sampling by 53% (95% CI 41–65%), and would enable avoidance of 76% (95% CI 67–81%) of biopsies[116].

Important work is being conducted to advance the accurate early detection of clinically significant prostate cancer, which will further enhance future early detection protocols. Examples include advances in biopsy technique using MRI lesion-targeted biopsies[117] and the application of artificial intelligence algorithms to aid prostate cancer detection and classification as well as improve imaging interpretation quality control[118]. Moreover, fast biparametric MRI has been evaluated as a potential replacement for costly and time-consuming mpMRI and showed no inferiority in a screening setting[119,120]. Also, personalized early detection is increasingly becoming a reality and will only improve over time[121]. These developments could further improve the currently presented risk-adapted strategy and should be implemented now, rather than waiting >10 years until mature data from ongoing trials[122] are reported, because the incidence of metastatic disease and mortality will probably have further increased or remained stagnant, rather than improving.

Challenges to new detection strategies. Challenges to implementing new detection strategies exist. For example, a lack of patient education and health literacy is a barrier to PSA testing that needs to be overcome regarding patient understanding, although good patient information materials do exist[123,124]. Shared decision-making between the patient and physician before PSA testing is crucial for improving understanding; for example, understanding and acceptance of active surveillance will be improved by including it in the list of treatment options given in the counselling session that precedes the testing. Another challenge is that information on the smart use of PSA does not always reach primary-care practitioners and dissemination of information and education on the use of risk calculators (which are already used with other conditions, such as cardiovascular diseases[125]) needs to be improved. With increasing pressures on the health workforce, physician time and skill constraints to ensure appropriate counselling are also challenging[126]. However, when proper training in communication is available, the shared decision-making process can actually become time effective, in addition to being beneficial to both patient and physician[127]. Education of policy makers, health-care professionals and patients is urgently needed for the endorsement and effective rollout of the risk-adapted PSA-testing approach.

The risk-adapted approach has the potential to reduce the burden of unnecessary testing and overdiagnosis. The use of individualized active surveillance for men who have a low-grade prostate cancer minimizes the possible negative effect on the quality of life[128]. However, the challenges of implementing a risk-adapted screening strategy must be acknowledged. Implementation across different health-care

systems requires different approaches; also, the need for appropriate infrastructure, training and quality assurance procedures must be considered to ensure effective integration into current cancer care services. Access to MRI expertise and artificial intelligence might be a challenge in some European member states owing to financial constraints within the different health systems. Risk stratification must be accessible globally, meaning that tools such as the freely available risk calculators or even PSA density need to be attainable. Any update of the European Union Council recommendations on screening will need to foresee appropriate financial support from funding programmes such as the EU4Health programme (which has called for proposals to monitor and strengthen the implementation of innovative approaches to prostate cancer screening at union level), but also the European Social Fund Plus, the European Regional and Development Fund, and Horizon Europe.

With an ageing population, the effects of prostate cancer will only increase in the absence of a clearly defined testing strategy. The update of the 2003 European Union Council recommendations on screening in 2022 provides a way for the European Union to address this challenge and to consider extending the screening programmes (which, since 2003, have recommended screening for breast, cervical and colorectal cancer) to include prostate cancer (FIG. 1). Guidelines on a risk-adapted approach for the early detection of prostate cancer will, therefore, support a clearly defined strategy across the European Union.

Conclusions

The tools needed to implement a risk-adapted strategy for the early detection of prostate cancer in healthy well-informed men are available and have the potential to positively affect current trends in prostate cancer-specific mortality and ultimately save many lives. Risk-adapted PSA testing entails a baseline, commonly available and low-cost PSA test that determines further action. If this baseline PSA level indicates that additional testing is needed, then the next step is not to directly continue with MRI and/or prostate biopsy but to initiate reflex testing to reduce the rate of false-positive PSA tests. Thus, PSA density (either alone or in combination with additional biomarkers) is a powerful risk-assessment tool, use of which could result in avoidance of a considerable number of unnecessary MRI procedures and/or prostate biopsies. This risk-stratification step means that invasive testing is only done in those men at an elevated risk of having a potentially life-threatening prostate cancer if left undetected and untreated.

The tools incorporated into a risk-adapted screening strategy, such as risk-adapted PSA testing, risk calculators and mpMRI, effectively exclude men who will not benefit from any early detection practices, such as those men who do not have prostate cancer or those men with a high risk of having indolent prostate cancer. These men can be spared further tests and, therefore, lessen the concerns that persist regarding overdiagnosis and related overtreatment. This approach can be adapted to reflect regional variations in prostate cancer risk as well as available health-care resources. Appropriate infrastructure and training and quality assurance procedures are essential for its success.

Future scientific advances will further refine and improve current models and should be implemented now. The PSA test is a non-invasive, inexpensive test that has been proven effective in reducing prostate cancer mortality; thus, it can serve as a simple first step in assessing well-informed men of their risk of prostate cancer (as part of this risk-adapted approach) and should not be dismissed because of a historical, outdated way of using PSA. The aim is to implement a risk-adapted strategy as a population-based programme with a standardized set of tests, but with the flexibility to be tailored to reflect regional variations in prostate cancer risk and health-care resources, to produce the first individually tailored oncology screening programme.

Hendrik Van Poppel[1]✉, *Tit Albreht*[2,3], *Partha Basu*[4], *Renée Hogenhout*[5], *Sarah Collen*[6] *and Monique Roobol*[5]

[1]*Department of Urology, Katholieke Universiteit Leuven, Leuven, Belgium.*

[2]*National Institute of Public Health, Ljubljana, Slovenia.*

[3]*Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia.*

[4]*International Agency for Research on Cancer, Lyon, France.*

[5]*Erasmus University Medical Center, Cancer Institute, Rotterdam, Netherlands.*

[6]*European Association of Urology, Arnhem, Netherlands.*

✉*e-mail: hendrik.vanpoppel@kuleuven.be*

https://doi.org/10.1038/s41585-022-00638-6

Published online: 16 August 2022

1. Stang, A. & Jöckel, K. H. The impact of cancer screening on all-cause mortality: what is the best we can expect? *Dtsch. Arztebl Int.* **115**, 481–486 (2018).
2. Loeb, S. et al. Overdiagnosis and overtreatment of prostate cancer. *Eur. Urol.* **65**, 1046–1055 (2014).
3. Aizer, A. A. et al. Cost implications and complications of overtreatment of low-risk prostate cancer in the United States. *J. Natl Compr. Cancer Netw.* **13**, 61–68 (2015).
4. Wang, M. C. et al. Purification of a human prostate specific antigen. *Investig. Urol.* **17**, 159–163 (1979).
5. Papsidero, L. D. et al. A prostate antigen in sera of prostatic cancer patients. *Cancer Res.* **40**, 2428–2432 (1980).
6. Kuriyama, M. et al. Quantitation of prostate-specific antigen in serum by a sensitive enzyme immunoassay. *Cancer Res.* **40**, 4658–4662 (1980).
7. Kuriyama, M. et al. Use of human prostate-specific antigen in monitoring prostate cancer. *Cancer Res.* **41**, 3874–3876 (1981).
8. Nadler, R. B., Humphrey, P. A., Smith, D. S., Catalona, W. J. & Ratliff, T. L. Effect of inflammation and benign prostatic hyperplasia on elevated serum prostate specific antigen levels. *J. Urol.* **154**, 407–413 (1995).
9. Ming-Chu, T. Prostate specific antigen (PSA): the historical perspective. *MJM* https://doi.org/10.26443/mjm.v2i2.564 (1996).
10. Chu, T. M., Wang M. C. & Papsidero, L. Purified human prostate antigen United States Patent and Trademark Office. https://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&p=1&u=%2Fnetahtml%2FPTO%2Fsearch-bool.html&r=5&f=G&l=50&co1=AND&d=PTXT&s1=316954.AP.&OS=APN/316954&RS=APN/316954 (1984).
11. Stamey, T. A. et al. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N. Engl. J. Med.* **317**, 909–916 (1987).
12. Roth, J. A., Gulati, R., Gore, J. L., Cooperberg, M. R. & Etzioni, R. Economic analysis of prostate-specific antigen screening and selective treatment strategies. *JAMA Oncol.* **2**, 890–898 (2016).
13. Catalona, W. J. et al. Measurement of prostate-specific antigen serum as a screening test for prostate cancer. *N. Engl. J. Med.* **324**, 1156–1161 (1991).
14. Thompson, I. M., Ernst, J. J., Gangai, M. P. & Spence, C. R. Adenocarcinoma of the prostate: results of routine urological screening. *J. Urol.* **132**, 690–692 (1984).
15. Schröder, F. H. et al. Screening and prostate-cancer mortality in a randomized European study. *N. Engl. J. Med.* **360**, 1320–1328 (2009).
16. Andriole, G. L. et al. Mortality results from a randomized prostate-cancer screening trial. *N. Engl. J. Med.* **360**, 1310–1319 (2009).
17. Hsing, A. W., Tsao, L. & Devesa, S. S. International trends and patterns of prostate cancer incidence and mortality. *Int. J. Cancer* **85**, 60–67 (2000).
18. RGHM Cremers, H. E. et al. Prostate cancer: trends in incidence, survival and mortality in the Netherlands, 1989–2006. *Eur. J. Urol.* **46**, 2077–2087 (2010).
19. Roobol, M. J., Kirkels, W. J. & Schöder, F. H. Features and preliminary results of the Dutch centre of the ERSPC (Rotterdam, the Netherlands). *BJU Int* https://doi.org/10.1111/j.1464-410X.2003.04390.x (2004).
20. National Cancer Institute. Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO). *NIH* https://prevention.cancer.gov/major-programs/prostate-lung-colorectal-and-ovarian-cancer-screening-trial (2020).
21. The European Randomized study of Screening for Prostate Cancer. ERSPC Background. *ERSPC* https://www.erspc.org/prostate-cancer/erspc-background/#study-protocol (2021).
22. Schröder, F. H. & Roobol, M. J. ERSPC and PLCO prostate cancer screening studies: what are the differences? *Eur. Urol.* **58**, 46–52 (2010).
23. de Koning, H. J. et al. The efficacy of prostate-specific antigen screening: impact of key components in the ERSPC and PLCO trials. *Cancer* **124**, 1197–1206 (2018).
24. Welch, H. G. & Albertsen, P. C. Reconsidering prostate cancer mortality — the future of PSA screening. *N. Engl. J. Med.* **382**, 1557–1563 (2020).
25. Culp, M. B., Soerjomataram, I., Efstathiou, J. A., Bray, F. & Jemal, A. Recent global patterns in prostate cancer incidence and mortality rates. *Eur. Urol.* **77**, 38–52 (2020).
26. Carioli, G. et al. European cancer mortality predictions for the year 2020 with a focus on prostate cancer. *Ann. Oncol.* **31**, 650–658 (2020).
27. Sung, H. et al. Global cancer statistics 2020: GLOBOCAN Estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer J. Clin.* **71**, 209–249 (2021).

28. U.S. Preventive Services Task Force. Screening for prostate cancer: recommendation and rationale. *Ann. Intern. Med.* **137**, 915–916 (2002).
29. U.S. Preventive Services Task Force. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *Ann. Intern. Med.* **149**, 185–191 (2008).
30. Moyer, V. A. Screening for Prostate Cancer: US Preventive Services Task Force recommendation statement. *Ann. Intern. Med.* **157**, 120–134 (2012).
31. Jemal, A., Culp, M. B., Ma, J., Islami, F. & Fedewa, S. A. Prostate cancer incidence 5 years after US Preventive Services Task Force recommendations against screening. *J. Natl Inst.* **113**, 64–71 (2021).
32. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Prostate cancer screening with the PSA test. *IQWIG* https://www.iqwig.de/projekte/s19-01.html (2020).
33. UK National Screening Committee. Screening for prostate cancer. *UK National Screening Committee* https://view-health-screening-recommendations.service.gov.uk/document/424/download (2020).
34. Ilic, D. et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. *BMJ* **362**, K3519 (2018).
35. Tikkinen, K. et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a clinical practice guideline. *BMJ* **362**, K3581 (2018).
36. Lenzen-Schulte, M. Prostatakrebs-screening: Prüffall PSA-test. *Dtsch. Arztebl* **117**, 1–2 (2020).
37. Shoag, J. E., Mittal, S., Hu, J. C. & Reevaluating, P. S. A. Testing rates in the PLCO trial. *N. Engl. J. Med.* **374**, 1795–1796 (2016).
38. Tsodikov, A. et al. Reconciling the effects of screening on prostate cancer mortality in the ERSPC and PLCO trials. *Ann. Intern. Med.* **167**, 449–455 (2017).
39. Grossman, D. C. et al. Screening for prostate cancer: US preventive services task force recommendation statement. *JAMA* **319**, 1901–1913 (2018).
40. European Association of Urology. Archive of the Prostate Cancer guideline. *EAU* https://uroweb.org/guidelines/archive/prostate-cancer (2020).
41. Martin, R. M. et al. CAP Trial Group effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: the CAP randomized clinical trial. *JAMA* **319**, 883–895 (2018).
42. Hugosson, J. et al. Eighteen-year follow-up of the Göteborg randomized population-based prostate cancer screening trial: effect of sociodemographic variables on participation, prostate cancer incidence and mortality. *Scand. J. Urol.* **52**, 27–37 (2018).
43. Hugosson, J. et al. A 16-yr follow-up of the European randomized study of screening for prostate cancer. *Eur. Urol.* **76**, 43–51 (2019).
44. Pinsky, P. F. et al. Extended follow-up for prostate cancer incidence and mortality among participants in the Prostate, Lung, Colorectal and Ovarian randomized cancer screening trial. *BJU Int.* **123**, 854–860 (2019).
45. Roobol., M. J. Screening for prostate cancer: are organized screening programs necessary? *Trans. Androl. Urol.* **7**, 4–11 (2018).
46. Heijnsdijk, E. A. M. et al. Quality-of-life effects of prostate-specific antigen screening. *N. Engl. J. Med.* **367**, 595–605 (2012).
47. RIZIV/INAMI, National Institute for Health and Disability Insurance (NIHDI), Nomenclature of medical acts in Belgium, Chapter V, 11 clinical biology (2021).
48. Heidenreich, A. et al. Early detection of prostate cancer: European Association of Urology recommendation. *Eur. Urol.* **64**, 347–354 (2013).
49. Yard, D. H. PSA testing: why the U.S. and Europe differ. *Renal & Urology News* https://www.renalandurologynews.com/home/news/urology/prostate-cancer/psa-testing-why-the-u-s-and-europe-differ/ (2011).
50. Ciatto, S. et al. Contamination by opportunistic screening in the European Randomized Study of Prostate Cancer Screening. *BJU Int.* **92** (Suppl 2), 97–100 (2003).
51. Pinsky, P. F. et al. Assessing contamination and compliance in the prostate component of the prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial. *Clin. Trials* **7**, 303–311 (2010).
52. Clift, A. K., Coupland, C. A. C. & Hippisley-Cox, J. Prostate-specific antigen testing and opportunistic prostate cancer screening: a cohort study in England, 1998–2017. *Br. J. Gen. Pract.* **71**, e157–e165 (2021).
53. Rijksinstituut voor Ziekte-en Invaliditeitsverzekering (RIZIV/INAMI) statistical department. *Statistieken geneeskundige verzorging* https://www.riziv.fgov.be/nl/statistieken/geneesk-verzorging/Paginas/default.aspx (2020).
54. Belgian Cancer Registry. Cancer Fact Sheet: Prostate Cancer. *Belgian Cancer Registry* https://kankerregister.org/media/docs/CancerFactSheets/2019/Cancer_Fact_Sheet_ProstateCancer_2019.pdf (2019).
55. Integraal Kankercentrum Nederland. Prostaatkanker in Nederland. *Integraal Kankercentrum Nederland* https://iknl.nl/prostaatkanker-in-nederland (2020).
56. Fleshner, K., Carlsson, S. V. & Roobol, M.J. The effect of the USPSTF PSA screening recommendation on prostate cancer incidence patterns in the USA. *Nat. Rev. Urol.* **14**, 26–37 (2017).
57. Bandini, M. et al. Increase in the annual rate of newly diagnosed metastatic prostate cancer: a contemporary analysis of the surveillance, epidemiology and end result database. *Eur. Urol. Oncol.* **1**, 314–320 (2018).
58. Siegel, D. A., O'Neil, M. E., Richards, T. B., Dowling, N. F. & Weir, H. K. Prostate cancer incidence and survival, by stage and race/ethnicity — United States, 2001–2017. *MMWR Morb. Mortal. Wkly. Rep.* **69**, 1473–1480 (2020).
59. Ferlay, J. et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. *Eur. J. Cancer* **103**, 356–387 (2018).
60. Sharma, V., Venkataramana, A., Comulada, W. S., Litwin, M. S. & Saigal, C. Association of reductions in PSA screening across states with increased metastatic prostate cancer in the United States. *J. Clin. Oncol.* **39**, 228 (2021).
61. Prostate Cancer UK. We call on UK to step up as new figures show prostate cancer now a bigger killer than breast cancer. *Prostate Cancer UK* https://prostatecanceruk.org/about-us/news-and-views/2018/2/we-call-on-uk-to-step-up-as-new-figures-show-prostate-cancer-now-a-bigger-killer-than-breast-cancer (2018).
62. Butler, E. B., Kelly, S. P., Coupland, V. H., Rosenberg, P. S. & Cook, M. B. Fatal prostate cancer incidence trends in the United States and England by race, stage, and treatment. *Br. J. Cancer* **123**, 487–494 (2020).
63. Arnsrud Godtman, R., Holmberg, E., Lilja, H., Stranne, J. & Hugosson, J. Opportunistic testing versus organized prostate-specific antigen screening: outcome after 18 years in the Göteborg randomized population-based prostate cancer screening trial. *Eur. Urol.* **68**, 354–360 (2015).
64. Pickles, K., Carter, S. M. & Rychetnik, L. C. Doctors' approaches to PSA testing and overdiagnosis in primary healthcare: a qualitative study. *BMJ Open* **5**, e006367 (2015).
65. Guessous, I. et al. Prostate cancer screening in Switzerland: 20-year trends and socioeconomic disparities. *Prev. Med.* **82**, 83–91 (2016).
66. Jessen, K., Sondergaard, J., Veldt Larsen, P. & Thomsen, J. L. Danish general practitioners' use of prostate-specific antigen in opportunistic screening for prostate cancer: a survey comprising 174 GPs. *Int. J. Fam. Med.* https://doi.org/10.1155/2013/540707 (2013).
67. Matti, B. & Zargar-Shoshtari, K. Opportunistic prostate cancer screening: a population-based analysis. *Urol. Oncol.* **38**, 393–400 (2020).
68. Fossa, S. D. & Eri, L. M. Norske legers rutiner for opportunistisk screening for prostatekreft. *Tidsskr. Nor. Laegeforen.* **199**, 3572–3576 (1999).
69. Bertuccio, P. et al. Mortality trends from urologic cancers in Europe over the period 1980–2017 and a projection to 2025. *Eur. Urol. Oncol.* **4**, 677–696 (2021).
70. Patasius, A. & Smailyte, G. Changing incidence and stage distribution of prostate cancer in a Lithuanian population — evidence from national PSA-based screening program. *Int. J. Environ. Res. Public Health* **16**, 4856 (2019).
71. Patasius, A. et al. Prostate cancer incidence and mortality in the Baltic states Belarus, the Russian Federation and Ukraine. *BMJ Open.* **9**, e031856 (2019).
72. Moyer, V. A. & U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann. Intern. Med.* **157**, 120–134 (2012).
73. Basch, E. et al. Screening for prostate cancer with prostate-specific antigen testing: American Society of Clinical Oncology provisional clinical opinion. *J. Clin. Oncol.* **30**, 3020–3025 (2012).
74. Wolf, A. M. et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. *CA Cancer J. Clin.* **60**, 70–98 (2010).
75. Carter, H. B. et al. Early detection of prostate cancer: AUA Guideline. *J. Urol.* **190**, 419–426 (2013).
76. National Comprehensive Cancer Network. Prostate Cancer Early Detection. *NCCN* http://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf (2021).
77. Mottet, N. et al. EAU-EANM-ESTRO-SIOG Guidelines on Prostate Cancer — 2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur. Urol.* **79**, 243–262 (2021).
78. Rommel, F. M. et al. The use of prostate specific antigen and prostate specific antigen density in the diagnosis of prostate cancer in community based urology practice. *J. Urol.* **151**, 88–93 (1994).
79. Nordström, T., Akre, O., Aly, M., Grönberg, H. & Eklund, M. Prostate-specific antigen (PSA) density in the diagnostic algorithm of prostate cancer. *Prostate Cancer Prostatic Dis.* **21**, 57–63 (2018).
80. Abd-Alazeez, M. et al. The accuracy of multiparametric MRI in men with negative biopsy and elevated PSA level — can it rule out clinically significant prostate cancer? *Urol. Oncol.* **32**, 45.e17–e22 (2014).
81. Stichting Wetenschappelijk Onderzoek Prostaatkanker, Reeuwijk. Your Prostate Cancer Risk Calculator. *prostatecancer-riskcalculator.com* https://www.prostatecancer-riskcalculator.com/assess-your-risk-of-prostate-cancer (2022).
82. Ankerst, D. P. et al. The Prostate Cancer Prevention Trial Risk Calculator 2.0 for the prediction of low- versus high-grade prostate cancer. *Urology* **83**, 1362–1367 (2014).
83. Roobol., M. J. Rescreening policies and risk calculator. *J. Nat. Rev. Urol.* **11**, 429–430 (2014).
84. Louie, K. S., Seigneurin, A., Cathcart, P. & Sasieni, P. Do prostate cancer risk models improve the predictive accuracy of PSA screening? A meta-analysis. *Ann. Oncol.* **26**, 848–864 (2015).
85. Stabile, A. et al. Multiparametric MRI for prostate cancer diagnosis: current status and future directions. *Nat. Rev. Urol.* **17**, 41–61 (2020).
86. Alberts, A. R. et al. Prediction of high-grade prostate cancer following multiparametric magnetic resonance imaging improving the Rotterdam European Randomized study of screening for prostate cancer risk calculators. *Eur. Urol.* **75**, 310–318 (2019).
87. Mottet N, et al. EAU guidelines: EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer (EAU Guidelines Office, 2019).
88. Van Poppel, H. et al. Prostate-specific antigen testing as part of a risk-adapted early detection strategy for prostate cancer: European Association of Urology position and recommendations for 2021. *Eur. Urol.* **80**, 703–711 (2021).
89. Schröder, F. H. et al. Screening for prostate cancer decreases the risk of developing metastatic disease: findings from the European randomized study of screening for prostate cancer (ERSPC). *Eur. Urol.* **62**, 745–752 (2012).
90. Vickers, A. J. et al. A panel of kallikrein markers can reduce unnecessary biopsy for prostate cancer: data from the European randomized study of prostate cancer screening in Göteborg, Sweden. *BMC Med.* **6**, 19 (2008).
91. Jansen, F. H. et al. Prostate-specific antigen (PSA) isoform p2PSA in combination with total PSA and free PSA improves diagnostic accuracy in prostate cancer detection. *Eur. Urol.* **57**, 921–927 (2010).
92. Osses, D. F., Roobol, M. J. & Schoots., I. G. Prediction medicine: biomarkers, risk calculators and magnetic resonance imaging as risk stratification tools in prostate cancer diagnosis. *Int. J. Mol. Sci.* **20**, 1637 (2019).
93. Roobol, M. J. et al. Prediction of prostate cancer risk: the role of prostate volume and digital rectal examination in the ERSPC risk calculators. *Eur. Urol.* **61**, 577–583 (2012).
94. Pereira-Azevedo, N. et al. Prospective evaluation on the effect of interobserver variability of digital rectal examination on the performance of the Rotterdam prostate cancer risk calculator. *Int. J. Urol.* **24**, 826–832 (2017).
95. Ankerst, D. P. et al. Prostate Cancer Prevention Trial risk calculator 2.0 for the prediction of low- vs high-grade prostate cancer. *Urology* **83**, 1362–1368 (2014).
96. Mannaerts, C. K. et al. Prostate cancer risk assessment in biopsy-naive patients: the Rotterdam prostate cancer risk calculator in multiparametric magnetic resonance imaging-transrectal ultrasound (TRUS) fusion biopsy and systematic TRUS biopsy. *Eur. Urol. Oncol.* **1**, 109–117 (2018).

97. Weinreb, J. C. et al. PI-RADS prostate imaging-reporting and data system: 2015, version 2. *Eur. Urol.* **69**, 16–40 (2016).
98. Pagniez, M. A. et al. Predictive factors of missed clinically significant prostate cancers in men with negative magnetic resonance imaging: a systematic review and meta-analysis. *J. Urol.* **204**, 24–32 (2020).
99. Ullrich, T. et al. Risk stratification of equivocal lesions on multiparametric magnetic resonance imaging of the prostate. *J. Urol.* **199**, 691–698 (2018).
100. Shill, D. K., Roobol, M. J., Ehdaie, B., Vickers, A. J. & Carlsson, S. V. Active surveillance for prostate cancer. *Trans. Androl. Urol.* **10**, 2809–2819 (2021).
101. Desai, M. M. et al. Trends in incidence of metastatic prostate cancer in the US. *JAMA Netw. Open* **5**, e222246 (2022).
102. Ross, L. E., Hall, I. J., Howard, D. L., Rim, S. H. & Richardson, L. C. Primary care physicians beliefs about prostate-specific antigen evidence uncertainty, screening efficacy, and test use. *J. Natl Med. Assoc.* **110**, 491–500 (2018).
103. Drummond, F. J., Carsin, A.-E., Sharp, L. & Comber, H. Factors prompting PSA-testing of asymptomatic men in a country with no guidelines: a national survey of general practitioners. *BMC Fam. Pract.* **10**, 1–12 (2009).
104. Kappen, S., Jurgens, V., Freitag, M. H. & Winter, A. Early detection of prostate cancer using prostate-specific antigen testing: an empirical evaluation among general practitioners and urologists. *Cancer Manag. Res.* **11**, 3079–3097 (2019).
105. Cajka., P. Issues of an ageing population in European Union. *Environ. Sci. Eng. B.* **1**, 966–970 (2012).
106. Rawla., P. Epidemiology of prostate cancer. *World J. Urol.* **10**, 63–89 (2019).
107. Eurostat. Ageing Europe — looking at the lives of older people in the EU — 2019 edition. (2019)
108. Getaneh, A. M. et al. Assessment of harms, benefits, and cost-effectiveness of prostate cancer screening: a micro-simulation study of 230 scenarios. *Cancer Med.* **9**, 7742–7750 (2020).
109. Carlsson, S. V. et al. Estimating the harms and benefits of prostate cancer screening as used in common practice versus recommended good practice: a microsimulation screening analysis. *Cancer* **122**, 3386–3393 (2016).
110. Sanghera, S. et al. Cost-effectiveness of prostate cancer screening: a systematic review of decision-analytical models. *BMC Cancer* **18**, 84 (2018).
111. Callender, T. et al. Benefit, harm, and cost-effectiveness associated with magnetic resonance imaging before biopsy in age-based and risk-stratified screening for prostate cancer. *JAMA Netw. Open* **4**, e2037657 (2021).
112. de Rooij, M. et al. Cost-effectiveness of magnetic resonance (MR) imaging and MR-guided targeted biopsy versus systematic transrectal ultrasound-guided biopsy in diagnosing prostate cancer: a modelling study from a health care perspective. *Eur. Urol.* **66**, 430–436 (2014).
113. Yusuf, S. et al. Modifiable risk factors, cardiovascular disease, and mortality in 155722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet* **395**, 795–808 (2020).
114. Grönberg, H. et al. Prostate cancer screening in men aged 50–69 years (STHLM3): a prospective population-based diagnostic study. *Lancet Oncol.* **16**, P1667–P1676 (2015).
115. Mortezavi, A. et al. Head-to-head comparison of conventional, and image- and biomarker-based prostate cancer risk calculators. *Eur. Urol. Focus.* **7**, 546–553 (2021).
116. Eklund, M. et al. The Stockholm-3 (STHLM3) model can improve prostate cancer diagnostics in men aged 50–69 yr compared with current prostate cancer testing. *Eur. Urol. Focus.* **4**, 707–710 (2018).
117. Eklund, M. et al. MRI-targeted or standard biopsy in prostate cancer screening. *N. Engl. J. Med.* **385**, 908–920 (2021).
118. Twilt, J. J. et al. Artificial intelligence based algorithms for prostate cancer classification and detection on magnetic resonance imaging: a narrative review. *Diagnostics* **11**, 959 (2021).
119. Knaapila, J. et al. Negative predictive value of biparametric prostate magnetic resonance imaging in excluding significant prostate cancer: a pooled data analysis based on clinical data from four prospective, registered studies. *Eur. Urol. Focus.* **7**, 522–531 (2021).
120. Wallström, J. et al. Bi- or multiparametric MRI in a sequential screening program for prostate cancer with PSA followed by MRI? Results from the Goteborg prostate cancer screening 2 trial. *Eur. Radiol.* **31**, 8692–8702 (2021).
121. Remmers, S. & Roobol, M. J. Personalized strategies in population screening for prostate cancer. *Int. J. Cancer* **147**, 2977–2987 (2020).
122. Van Poppel, H. et al. A European model for an organised risk-stratified early detection programme for prostate cancer. *Eur. Urol. Oncol.* **5**, P731–P739 (2021).
123. European Association of Urology. Information for patients: prostate cancer. *EAU* https://patients.uroweb.org/wp-content/uploads/2018/12/12-July-2018_Prostate-cancer.pdf (2014).
124. National Health Service. PSA testing and prostate cancer: advice for well men aged 50 and over. *NHS* https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/856976/PSA_testing_for_prostate_cancer_information_for_well_men.pdf (2020).
125. Xavier, R. et al. Risk prediction tools in cardiovascular disease prevention: a report from the ESC Prevention of CVD Programme led by the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). *Eur. J. Prev. Cardiol.* **26**, 1534–1544 (2019).
126. Mishra, S. C. A discussion on controversies and ethical dilemmas in prostate cancer screening. *J. Med. Ethics* **47**, 152–158 (2021).
127. Légaré, F. & Thompson-Leduc, P. Twelve myths about shared decision making. *Patient Educ. Couns.* **96**, 281–286 (2014).
128. Roobol, M. J. Active surveillance for prostate cancer — will the discoveries of the last 5 years change the future? *Transl. Androl. Urol.* **10**, 2828–2831 (2021).

Author contributions
H.V.P., R.H. and M.R. researched data for the article. H.V.P., T.A., P.B., R.H. and M.R. contributed substantially to discussion of the content. H.V.P., R.H., M.R. and S.C. wrote the article. H.V.P., T.A., P.B., R.H. and M.R. reviewed and/or edited the manuscript before submission.

Competing interests
The authors declare no competing interests.

Disclaimer
Where authors are identified as personnel of the International Agency for Research on Cancer or the World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer or the World Health Organization.

Peer review information
Nature Reviews Urology thanks Quoc-Dien Trinh, Mara Koelker and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

RELATED LINKS
EU4Health: https://health.ec.europa.eu/funding/eu4health-programme-2021-2027-vision-healthier-european-union_en