1 Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, USA

2 Department of Urology, Cork University Hospital, Ireland

3 University Vita-Salute San Raffaele, Italy

4 Department of Surgery, University College Dublin, Ireland

5 Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sweden

6 Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA

7 Academic Urology Unit, Department of Oncology and Metabolism, University of Sheffield, UK

8 Division of Personalized Early Detection of Prostate Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany

9 Patient and patient advocate, New York, USA

10 Department of Urology, University Hospital, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany

Correspondence to: A J Vickers
vickersa@mskcc.org

Cite this as: *BMJ* 2023;381:e071082
http://dx.doi.org/10.1136/bmj-2022-071082

Current policies on early detection of prostate cancer create overdiagnosis and inequity with minimal benefit

Informed choice approaches lead to high rates of unsystematic PSA testing, especially among those least likely to benefit and most likely to be harmed, argue Andrew Vickers and colleagues

Andrew Vickers, [1] Frank O'Brien, [2] Francesco Montorsi, [3] David Galvin, [4] Ola Bratt, [5] Sigrid Carlsson, [1,5,6] James WF Catto, [7] Agne Krilaviciute, [8] Michael Philbin, [9] Peter Albers[8,10]

Screening for prostate cancer with prostate specific antigen (PSA) remains highly controversial because it is unclear whether the benefits of reduced prostate cancer mortality offset the harms of overdiagnosis and overtreatment. Given this uncertainty, most high income countries have chosen not to implement a national programme of prostate cancer screening, but allow men to obtain a PSA test after a conversation with their physician.

Countries that have adopted screening policies based on shared decision making have seen high rates of PSA testing, particularly among men 70 years or older, who are particularly prone to overdiagnosis[1] but do not benefit from screening.[2] This is one of the reasons why opportunistic screening results in only a small reduction in cancer specific mortality.[3] Moreover, relying on shared decision making to guide PSA testing has led to an uneven distribution, with higher rates of PSA testing among those who are wealthier and more educated.

In 2022 the European Union recommended that organised screening programmes should be extended to prostate cancer.[4] We argue that high income countries should either implement a comprehensive risk based approach to PSA testing, one that is designed to reduce overdiagnosis and overtreatment, or discourage PSA testing through a clear recommendation against screening, along with policies that make it hard to obtain a test without defined urological indications.

Informed choice approach drives high rates of testing

High income countries that have made PSA testing available to men who request it after shared decision making with their physician now have a high prevalence of PSA testing with an inappropriate age distribution (table 1). In the UK, men aged 80-89 are twice as likely to get a PSA test as men in their 50s.[30,31] In France, 30% of men aged over 40 get an annual PSA,[12] with the highest incidence of PSA testing in men over 70.[11] Italy and Germany also have high rates of PSA testing with around half of men aged over 70 having annual PSA.[14,15,19,20] Ireland has particularly high rates of PSA testing, with 500 000 PSA tests performed each year[17] in a population of 600 000 men of screening age.

Table 1 | National recommendations on prostate specific antigen (PSA) screening compared with empirical data on PSA testing in the population*

Country	Recommendation	Current use of PSA testing
Australia	"The PSA test is not suitable for population screening ... We encourage men to speak to their doctor so they can make an informed choice about prostate cancer testing"[5]	High rates of PSA screening (around 20% of men screened annually, about 50% in lifetime) with comparable rates in men aged 75-84 and 45-74[6]
Canada	No population based screening. Policies vary by province. In some, the nationalised health insurance system does not pay for PSA in asymptomatic men; in others testing is free[7]	40-60% of men of screening age have annual testing, with a 50% rate in men aged ≥70.[8 9] Lower rates of testing in people from minorities and those on low incomes or less well educated[10]
France	No national screening programme, but PSA testing available after shared decision making[11]	Around 30% of men ≥40 have had a PSA test in past year.[12] Highest testing rate in men aged over 70, with about 50% having at least one test and 20% having more than 3 tests over three years[11]
Germany	No national screening programme. PSA testing has not been approved by the German statutory health insurance and patients have to pay themselves[13]	Around 75% of men >55 have been tested.[14] Around half of PSA tests are in men aged over 69[15]
Ireland	No national screening programme but PSA testing available after informed consent and shared decision making[16]	Close to 500 000 PSA tests a year[17] with an eligible population of around 600 000[18]
Italy	No national screening programme†	About 75% of men >50 have ever had a PSA test. Highest prevalence of annual testing (roughly 50%) in men aged ≥70[19 20]
Sweden	"The health system should not offer screening for prostate cancer with PSA."[21]† Population based PSA testing programmes are being piloted in some regions[22]	About 70% ever had a PSA test with highest rates in men aged 70-89 (30%-50% over 2 years)[23 24]
Switzerland	No national screening programme†	Around 70% of have been tested, with 40% in the past two years. High rates in older men (around 50% in past 2 years for age ≥70). Testing positively correlated with education, income, and urban location[25]
UK	Screening for prostate cancer is currently not recommended.[26] The NHS has an "informed choice programme": "If you're aged 50 or over and decide to have your PSA levels tested after talking to a GP, the NHS will pay for it"[27]	Strong regional variation in PSA testing[28] and high inequity, with testing inversely correlated with economic deprivation.[29] Testing rates about twice as high in men aged 70-90 (about 40% in past years) as in men aged 50-59 (about 20%)[30 31]
US	"For men aged 55 to 69 years, the decision to undergo periodic prostate-specific antigen (PSA)-based screening for prostate cancer should be an individual one"[32]	About 30% of men receive PSA test each year. Highest rates for men aged 70-79 and considerable screening (~30%) in men aged ≥80.[33 34] Clear evidence of disparities with screening rates associated with education and insurance status[33] and lower rates among people from minority groups[35]

* Note that most studies were unable to distinguish PSA used for screening versus PSA used for clinical reasons, such as follow-up in a patient with prostate cancer. However, the latter will be a small minority of the total and hence are unlikely to influence estimates importantly.

† It is hard to find policy documentation that patients can receive PSA if they request it, but high rates of PSA testing suggest that this is the case.

High rates of PSA testing from "informed choice" policies in high income countries have led to harm from overdiagnosis and overtreatment. In the UK, prostate cancer incidence has increased by about 50% since PSA testing became available in the early 1990sto a current total of 52 000 cases a year.[36] Around 25-50% of men who have prostate cancer detected after PSA testing would have lived out their natural lives without a prostate cancer diagnosis,[37] suggesting that overdiagnosis occurs in about 10 000 men in the UK every year.

A key problem is that, in current routine care—and despite guidelines to the contrary—most men with an abnormal PSA result have prostate biopsy, even though only a minority will have aggressive prostate cancer. Furthermore, most men with biopsy detected cancers have either surgery or radiotherapy (with or without androgen deprivation therapy) even if they have low risk tumours that are unlikely to cause cancer related morbidity or mortality.[38 39] Prostate surgery and radiotherapy are both associated with a high risk of long term urinary, erectile, and bowel dysfunction,[40] while androgen deprivation causes numerous side effects such as fatigue and loss of libido during treatment and increases the long term risk of cardiovascular events.[41] Men who are overdiagnosed thus often experience treatment harms without receiving any benefit.

Approaches to PSA testing that rely on people making an informed choice are likely to reflect and reproduce health inequities in preventive healthcare. Data from Canada, the US, and Switzerland suggest PSA testing is inversely associated with income and education[10 25 33]; in Canada and the US, PSA testing is less common in people from ethnic minorities.[10 35] In the UK and Switzerland, rates of PSA testing are lower in economically deprived areas.[25 29] Although the effects of disparate rates of PSA testing on health outcomes are still unclear, countries should decide who gets offered screening based on a risk assessment rather than leaving it to individuals.

Advantages of a comprehensive, risk based, prostate cancer detection programme

Policy making bodies that advocate for an informed choice or shared decision making model of PSA testing, typically frame their recommendations as contrasting with population based screening. This is generally defined as PSA testing being structured in a similar way to national mammography or colonoscopy programmes: the screening test is provided by a government run body at standardised

intervals with follow-up of abnormal results handled within the national health system. A 2012 statistical modelling study based on evidence from randomised trials suggests that this sort of universal PSA testing programme for men aged 55-69 would reduce prostate cancer mortality by 9 per 1000 men but at the cost of 16 quality-of-life adjusted years per 1000 as a result of harm from overdiagnosis and overtreatment.[42]

A comprehensive, risk based prostate cancer detection programme based on best evidence on how to use PSA testing and manage subsequent diagnostic follow-up and treatment could reduce overdiagnosis and overtreatment.[43-45] Such a programme would restrict testing to men (and those not identifying as male but who have a prostate) aged 50-70, define testing intervals by PSA levels, stop testing early for those with lower PSA, offer biopsy only to those identified as at high risk of aggressive disease after a secondary test (such as magnetic resonance imaging (MRI) or blood markers), and limit treatment to those with high Gleason grade tumours.[43-45] The programme would also have a clear algorithm specifying how these approaches would vary for those at high risk (eg, having a BRCA gene mutation or strong family history).

Such a programme would start by defining, identifying, and inviting eligible people for PSA testing. Management of abnormal results and any subsequent treatment would need to be monitored to ensure protocols were followed (eg, confirmatory or secondary testing with MRI in men with raised PSA levels), rather than passively expecting guidelines to be followed; indeed, our current problems stem largely from practices that go against guideline recommended care.[38 39] Although in the UK most men have a biopsy only after MRI, this is not always the case in other countries, and other elements of the clinical pathway, such as treatment, also need standardisation. As in current informed choice programmes, shared decision making would still take place before testing.[46]

Swedish regional health authorities are piloting a screening programme using this approach.[47] Prevention of overtreatment is not formally part of the programme because Sweden already has extremely high rates of active surveillance, whereby patients with low risk prostate cancer are monitored and start active treatment only on evidence of more aggressive disease.[48] An early randomised evaluation of the Swedish pilot found use of MRI testing before biopsy led to a >50% reduction in overdiagnosisof low grade prostate cancer without a significant difference in the detection of high grade disease.[49]

A comprehensive prostate cancer early detection programme that carefully manages not just testing, but also biopsy and subsequent treatment, could substantially reduce the harms of overdiagnosis and overtreatment that have accompanied PSA screening. About 40% of overdiagnoses currently occur in men aged over 70.[1] The use of MRI[50 51] or secondary markers[52] to determine biopsy in men with raised PSA levels has been shown to reduce both biopsy rates and the overdiagnosis of low grade cancer. In one study, patients with raised PSA levels randomised to biopsy only if they had positive MRI findings had a 30% reduction in the rate of biopsy and a 50% reduction in the overdiagnosis of low grade cancer compared with those randomised to routine biopsy, without reducing the number of aggressive cancers detected.[50] Use of active surveillance reduces treatment rates by 50% or more in men diagnosed with low grade disease.[53]

Most of the benefit of PSA testing on prostate cancer mortality would be retained in a comprehensive, risk adapted early detection programme because best evidence suggests screening older men is ineffective,[2] men who have negative findings in secondary tests such as MRI or blood markers have extremely low mortality from prostate cancer,[54] and conservative management of men with low risk disease does not increase the risk of death from prostate cancer.[55 56]

Moreover, in what might be the central paradox of a PSA based prostate cancer screening policy, implementing a national risk based programme would typically reduce the number of tests compared with the current model. In one risk adapted screening approach,[44] men with initially low PSA levels, constituting about half of the population, would have their PSA tested only three times during their lives, with most others getting tested only every 2-4 years. If implemented in Ireland, for instance, such a programme could reduce the number of PSA tests by at least half compared with contemporary practice. One of the few countries that has implemented a national PSA based programme for early detection of prostate cancer is Lithuania. This has led to a near 80% drop in PSA testing in men aged over 70,[57] the age group for whom PSA screening is most likely to lead to harm and least likely to lead to benefit. An organized early detection programme may also reduce ethnic, socioeconomic, and regional inequalities. For example, in the Swedish randomised trial of PSA testing, reductions in prostate cancer mortality were greater for those with lower educational levels than for those with higher educational levels.[58] Indeed, one of the key benefits of a risk based approach is that it allows better targeting to those at highest risk compared with current informed choice approaches, which are sensitive to affluence and education, as well as undue influence from media coverage, such as celebrities telling their prostate cancer stories.[59]

Restricting access to PSA testing

A reasonable alternative to a comprehensive, risk based prostate cancer early detection programme, is a clear recommendation against PSA screening along with a policy that the PSA test could only be offered by a urologist to patients presenting with urological symptoms, albeit with a possible exception for men at high risk, such as BRCA mutation carriers. This would mean asymptomatic men would not be able to have PSA testing. Such an approach may require governments or public health insurers to do more than refuse reimbursement for the PSA test. For instance, in Germany, PSA tests offered in primary care are not reimbursed by the public health insurance system, yet 75% of German men of screening age have had a PSA test,[14] probably because the test is inexpensive. Specific policies or other mechanisms whereby a national health system could restrict PSA testing are largely untested and would require further research.

Maximising benefit, reducing harm

Although we believe that early detection of prostate cancer should involve shared decision making, the current approach of determining testing by shared decision making has resulted in the worst possible practical outcome of high levels of PSA testing and medical harm, with minimal benefit and inequity. To make better use of PSA testing, policy makers should choose between a comprehensive, risk adapted approach that is specifically designed to reduce overdiagnosis and overtreatment, or restricting PSA testing to people referred to urologists with symptoms. That choice will need to take into account wider patient and public perspective, as well as health economic concerns.

Key messages

- Most high income countries have chosen not to implement a population based prostate cancer screening programme but instead allow men to obtain a PSA test if they wish

- These policies have led to paradoxically high rates of PSA testing, clear medical harm, scant benefit, and inequities
- A national comprehensive, risk based, prostate cancer detection programme that is carefully designed to reduce overdiagnosis and overtreatment would reduce harm, increase benefit and be more equitable
- An alternative approach to reducing harm is to restrict PSA testing to those referred to urologists for symptoms

Contributors and sources: AV is a biostatistician with a special interest in prostate cancer screening and decision theory. FO'B, FM, DG, OB, JC and PA are urologists with expertise in prostate cancer. SC and AK are epidemiologists with expertise in prostate cancer screening. MP has been treated for prostate cancer and is a patient advocate. All authors contributed to the content and writing. AV is the guarantor.

Patient involvement: MP provided patient perspective from the earliest stages of article planning.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare the following: AV is a co-inventor of the 4kscore, a commercial test for predicting prostate biopsy outcome. He receives royalties from sales of the test. He owns stock options in Opko, which offers the test. JC has received reimbursement for consultancy from Astra Zeneca, Ferring, Roche, and Janssen; speaker fees from BMS, MSD, Janssen, Astellas, Nucleix and Roche; honoraria for membership of advisory boards for Ferring, Roche, Gilead, Photocure, BMS, QED therapeutics and Janssen; and research funding from Roche.

Provenance and peer review: Not commissioned; externally peer reviewed.

This work was supported in part by the National Institutes of Health/National Cancer Institute (NIH/NCI) with a Cancer Center Support Grant to Memorial Sloan Kettering Cancer Center (P30 CA008748). SVC was further supported by a career development award grant from the NIH/NCI (K22-CA234400). JWFC is funded by an NIHR research professorship.

1 Vickers AJ, Sjoberg DD, Ulmert D, etal. Empirical estimates of prostate cancer overdiagnosis by age and prostate-specific antigen. *BMC Med* 2014;12:. doi: 10.1186/1741-7015-12-26. pmid: 24512643

2 de Vos II, Meertens A, Hogenhout R, Remmers S, Roobol MJERSPC Rotterdam Study Group. A detailed evaluation of the effect of prostate-specific antigen-based screening on morbidity and mortality of prostate cancer: 21-year follow-up results of the Rotterdam Section of the European Randomised Study of Screening for Prostate Cancer. *Eur Urol* 2023:S0302-2838(23)02669-6. doi: 10.1016/j.eururo.2023.03.016. pmid: 37029074

3 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* 2015;68:-60. doi: 10.1016/j.eururo.2014.12.006. pmid: 25556937

4 European Commission. Proposal for a Council Recommendation on strengthening prevention through early detection: A new EU approach on cancer screening. 2022. https://health.ec.europa.eu/system/files/2022-09/com_2022-474_act_en.pdf

5 Australian Health Ministers' Advisory Council. Prostate cancer screening in Australia. Position statement. 2019. https://www.health.gov.au/sites/default/files/documents/2019/09/prostate-cancer-screening-position-statement.pdf

6 Pathirana T, Sequeira R, Del Mar C, etal. Trends in prostate specific antigen (PSA) testing and prostate cancer incidence and mortality in Australia: a critical analysis. *Cancer Epidemiol* 2022;77:102093. doi: 10.1016/j.canep.2021.102093. pmid: 35026706

7 Canadian Cancer Survivor Network. Screening programs in Canada. 2022. https://survivornet.ca/cancer-type/prostate-cancer/diagnosis-of-prostate-cancer/prostate-cancer-screening/screening-programs/

8 Wang Q, Chen F, Jiang D, Kabani A, Sokoro AAH. Prostate-specific antigen test utilization in a major Canadian city. *Am J Clin Pathol* 2020;153:-80. doi: 10.1093/ajcp/aqaa003. pmid: 32003789

9 Tchir D, Farag M, Szafron M. Prostate-specific antigen (PSA) screening rates and factors associated with screening in eastern Canadian men: findings from cross-sectional survey data. *Can Urol Assoc J* 2020;14:-27. doi: 10.5489/cuaj.6072. pmid: 32017690

10 Gorday W, Sadrzadeh H, de Koning L, Naugler C. Association of sociodemographic factors and prostate-specific antigen (PSA) testing. *Clin Biochem* 2014;47:-9. doi: 10.1016/j.clinbiochem.2014.08.006. pmid: 25130956

11 Braillon A. Prostate-specific antigen testing in France. *JAMA Intern Med* 2013;173:. doi: 10.1001/jamainternmed.2013.10405. pmid: 24276059

12 Tuppin P, Samson S, Fagot-Campagna A, etal. [PSA testing, biopsy and cancer and benign prostate hyperplasia in France]. *Prog Urol* 2014;24:-80. doi: 10.1016/j.purol.2014.03.004. pmid: 24975792

13 Kappen S, Jürgens V, Freitag MH, Winter A. Early detection of prostate cancer using prostate-specific antigen testing: an empirical evaluation among general practitioners and urologists. *Cancer Manag Res* 2019;11:-97. doi: 10.2147/CMAR.S193325. pmid: 31114352

14 Tiedje D, Borowski M, Simbrich A, etal. Decision aid and cost compensation influence uptake of PSA-based early detection without affecting decisional conflict: a cluster randomised trial. *Sci Rep* 2021;11:. doi: 10.1038/s41598-021-02696-z. pmid: 34873188

15 Simbrich A, Semjonow A, Donner-Banzhoff N, Hense HW. [Practice of early detection of prostate cancer: Descriptive survey in preparation for the PSAInForm study]. *Urologe A* 2018;57:-8. doi: 10.1007/s00120-018-0644-0. pmid: 29671079

16 National Cancer Control Programme. National prostate cancer GP referral guideline. 2018. https://www.hse.ie/eng/services/list/5/cancer/profinfo/resources/gpreferrals/nccp-prostate-cancer-gp-referral-guideline.pdf

17 Drummond FJ, Barrett E, Burns R, O'Neill C, Sharp L. The number of tPSA tests continues to rise and variation in testing practices persists: a survey of laboratory services in Ireland 2008-2010. *Ir J Med Sci* 2014;183:-75. doi: 10.1007/s11845-013-1022-y. pmid: 24072433

18 Central Statistics Office. Census of population 2016. Profile 3. An age profile of Ireland. 2017. https://www.cso.ie/en/releasesandpublications/ep/p-cp3oy/cp3/assr/

19 Mirone V, Imbimbo C, Arcaniolo D, etal. Knowledge, attitudes, and practices towards prostate cancer screening amongst men living in the southern Italian peninsula: the Prevention and Research in Oncology (PRO) non-profit Foundation experience. *World J Urol* 2017;35:-62. doi: 10.1007/s00345-017-2074-9. pmid: 28780740

20 D'Ambrosio GG, Campo S, Cancian M, Pecchioli S, Mazzaglia G. Opportunistic prostate-specific antigen screening in Italy: 6 years of monitoring from the Italian general practice database. *Eur J Cancer Prev* 2010;19:-6. doi: 10.1097/CEJ.0b013e32833d944b. pmid: 20679895

21 National Board of Health and Welfare. Prostate cancer—screening with PSA test with or without other complementary test. 2022. https://www.socialstyrelsen.se/kunskapsstod-och-regler/regler-och-riktlinjer/nationella-screeningprogram/slutliga-rekommendationer/prostatacancer/

22 Confederation of Regional Cancer Centres. Organized prostate cancer testing. 2022. https://cancercentrum.se/samverkan/vara-uppdrag/prevention-och-tidig-upptackt/prostata-cancertestning/

23 Enblad AP, Bergengren O, Andrén O, etal. PSA testing patterns in a large Swedish cohort before the implementation of organized PSA testing. *Scand J Urol* 2020;54:-81. doi: 10.1080/21681805.2020.1797871. pmid: 32734806

24 Nordström T, Aly M, Clements MS, Weibull CE, Adolfsson J, Grönberg H. Prostate-specific antigen (PSA) testing is prevalent and increasing in Stockholm County, Sweden, despite no recommendations for PSA screening: results from a population-based study, 2003-2011. *Eur Urol* 2013;63:-25. doi: 10.1016/j.eururo.2012.10.001. pmid: 23083803

25 Guessous I, Cullati S, Fedewa SA, etal. Prostate cancer screening in Switzerland: 20-year trends and socioeconomic disparities. *Prev Med* 2016;82:-91. doi: 10.1016/j.ypmed.2015.11.009. pmid: 26582208

26 UK National Screening Committee. Adult screening programme: prostate cancer. 2020. https://view-health-screening-recommendations.service.gov.uk/prostate-cancer/

27 National Health Service. PSA testing: prostate cancer 2021. https://www.nhs.uk/conditions/prostate-cancer/psa-testing/

28 Young GJ, Harrison S, Turner EL, etal. Prostate-specific antigen (PSA) testing of men in UK general practice: a 10-year longitudinal cohort study. *BMJ Open* 2017;7:e017729. doi: 10.1136/bmjopen-2017-017729. pmid: 29084797

29 Williams N, Hughes LJ, Turner EL, etal. Prostate-specific antigen testing rates remain low in UK general practice: a cross-sectional study in six English cities. *BJU Int* 2011;108:-8. doi: 10.1111/j.1464-410X.2011.10163.x. pmid: 21481132

30 Clift AK, Coupland CA, Hippisley-Cox J. Prostate-specific antigen testing and opportunistic prostate cancer screening: a cohort study in England, 1998-2017. *Br J Gen Pract* 2021;71:-65. doi: 10.3399/bjgp20X713957. pmid: 33431381

31 Nderitu P, Van Hemelrijck M, Ashworth M, etal. Prostate-specific antigen testing in inner London general practices: are those at higher risk most likely to get tested?*BMJ Open* 2016;6:e011356. doi: 10.1136/bmjopen-2016-011356. pmid: 27406644

32 United States Preventive Services Task Force. Prostate cancer: screening. 2018. https://uspreventiveservicestaskforce.org/uspstf/recommendation/prostate-cancer-screening

33 Fedewa SA, Ward EM, Brawley O, Jemal A. Recent patterns of prostate-specific antigen testing for prostate cancer screening in the United States. *JAMA Intern Med* 2017;177:-2. doi: 10.1001/jamainternmed.2017.0340. pmid: 28437537

34 Drazer MW, Huo D, Eggener SE. National prostate cancer screening rates after the 2012 US Preventive Services Task Force Recommendation discouraging prostate-specific antigen-based screening. *J Clin Oncol* 2015;33:-23. doi: 10.1200/JCO.2015.61.6532. pmid: 26056181

35 Kensler KH, Pernar CH, Mahal BA, etal. Racial and ethnic variation in PSA testing and prostate cancer incidence following the 2012 USPSTF recommendation. *J Natl Cancer Inst* 2021;113:-26. doi: 10.1093/jnci/djaa171. pmid: 33146392

36 Cancer Research UK. Prostate cancer incidence statistics. 2022. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/incidence#ref-2

37 Draisma G, Etzioni R, Tsodikov A, etal. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst* 2009;101:-83. doi: 10.1093/jnci/djp001. pmid: 19276453

38 Washington SL, 3rdJeong CW, Lonergan PE, etal. Regional variation in active surveillance for low-risk prostate cancer in the US. *JAMA Netw Open* 2020;3:e2031349. doi: 10.1001/jamanetworkopen.2020.31349. pmid: 33369661

39 Merriel SWD, Hetherington L, Seggie A, etalProstate Cancer UK Expert Reference Group on Active Surveillance. Best practice in active surveillance for men with prostate cancer: a Prostate Cancer UK consensus statement. *BJU Int* 2019;124:-54. doi: 10.1111/bju.14707. pmid: 30742733

40 Lane JA, Donovan JL, Young GJ, etalProstate Testing for Cancer and Treatment (ProtecT) Study Group. Functional and quality of life outcomes of localised prostate cancer treatments (Prostate Testing for Cancer and Treatment [ProtecT] study). *BJU Int* 2022;130:-80. doi: 10.1111/bju.15739. pmid: 35373443

41 Boland J, Choi W, Lee M, Lin J. Cardiovascular toxicity of androgen deprivation therapy. *Curr Cardiol Rep* 2021;23:. doi: 10.1007/s11886-021-01561-9. pmid: 34216282

42 Heijnsdijk EA, Wever EM, Auvinen A, etal. Quality-of-life effects of prostate-specific antigen screening. *N Engl J Med* 2012;367:-605. doi: 10.1056/NEJMoa1201637. pmid: 22894572

43 Van Poppel H, Roobol MJ, Chapple CR, etal. 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* 2021;80:-11. doi: 10.1016/j.eururo.2021.07.024. pmid: 34407909

44 Vickers AJ, Eastham JA, Scardino PT, Lilja H. The Memorial Sloan Kettering Cancer Center recommendations for prostate cancer screening. *Urology* 2016;91:-8. doi: 10.1016/j.urology.2015.12.054. pmid: 26850815

45 Van Poppel H, Hogenhout R, Albers P, van den Bergh RCN, Barentsz JO, Roobol MJ. A European model for an organised risk-stratified early detection programme for prostate cancer. *Eur Urol Oncol* 2021;4:-9. doi: 10.1016/j.euo.2021.06.006. pmid: 34364829

46 Vickers A, Carlsson S, Laudone V, Lilja H. It ain't what you do, it's the way you do it: five golden rules for transforming prostate-specific antigen screening. *Eur Urol* 2014;66:-90. doi: 10.1016/j.eururo.2013.12.049. pmid: 24411991

47 Alterbeck M, Järbur E, Thimansson E, etal. Designing and implementing a population-based organised prostate cancer testing programme. *Eur Urol Focus* 2022;8:-74. doi: 10.1016/j.euf.2022.06.008. pmid: 35811285

48 Ventimiglia E, Bill-Axelson A, Bratt O, Montorsi F, Stattin P, Garmo H. Long-term outcomes among men undergoing active surveillance for prostate cancer in Sweden. *JAMA Netw Open* 2022;5:e2231015. doi: 10.1001/jamanetworkopen.2022.31015. pmid: 36103180

49 Hugosson J, Månsson M, Wallström J, etalGÖTEBORG-2 Trial Investigators. Prostate cancer screening with PSA and MRI followed by targeted biopsy only. *N Engl J Med* 2022;387:-37. doi: 10.1056/NEJMoa2209454. pmid: 36477032

50 Kasivisvanathan V, Rannikko AS, Borghi M, etalPRECISION Study Group Collaborators. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med* 2018;378:-77. doi: 10.1056/NEJMoa1801993. pmid: 29552975

51 Ahmed HU, El-Shater Bosaily A, Brown LC, etalPROMIS study group. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet* 2017;389:-22. doi: 10.1016/S0140-6736(16)32401-1. pmid: 28110982

52 Konety B, Zappala SM, Parekh DJ, etal. The 4Kscore® test reduces prostate biopsy rates in community and academic urology practices. *Rev Urol* 2015;17:-40.pmid: 26839521

53 Perlis N, Klotz L. Contemporary active surveillance: candidate selection, follow-up tools, and expected outcomes. *Urol Clin North Am* 2017;44:-74. doi: 10.1016/j.ucl.2017.07.005. pmid: 29107273

54 Vertosick EA, Häggström C, Sjoberg DD, etal. Prespecified 4-Kallikrein marker model at age 50 or 60 for early detection of lethal prostate cancer in a large population based cohort of asymptomatic men followed for 20 years. *J Urol* 2020;204:-8. doi: 10.1097/JU.0000000000001007. pmid: 32125228

55 Wilt TJ, Jones KM, Barry MJ, etal. Follow-up of prostatectomy versus observation for early prostate cancer. *N Engl J Med* 2017;377:-42. doi: 10.1056/NEJMoa1615869. pmid: 28700844

56 Hamdy FC, Donovan JL, Lane JA, etalProtecT Study Group. Fifteen-year outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med* 2023;388:-58. doi: 10.1056/NEJMoa2214122. pmid: 36912538

57 Patasius A, Krilaviciute A, Smailyte G. Prostate cancer screening with PSA: ten years' experience of population based early prostate cancer detection programme in Lithuania. *J Clin Med* 2020;9:. doi: 10.3390/jcm9123826. pmid: 33255919

58 Hugosson J, Godtman RA, Carlsson SV, etal. 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* 2018;52:-37. doi: 10.1080/21681805.2017.1411392. pmid: 29254399

59 Fry and Turnbull effect" on prostate cancer. *BBC News* 9 Oct 2018. https://www.bbc.co.uk/news/health-45795337