PSA testing in asymptomatic men

1. PSA testing in asymptomatic men

> "While I'm here, can I have that prostate test done?"

This article is about deciding whether to have a PSA test; shared decision-making and the evidence behind it; how to do the test well; and what to do with the results. Further details about the next steps in diagnosis and follow-up can be found in the *Prostate cancer: diagnosis* and *Prostate cancer: management and long-term consequences* articles.

This article was updated in November 2024.

1.1. Key considerations

- Is this man **symptomatic** or **asymptomatic**?
- Does this man have a significant family history?
- Does this man have additional risk factors that we should consider? For example, the lifetime risk for men of black ethnicity is 1 in 4 compared with 1 in 8 for white men.
- Availability of multiparametric MRI has probably slightly changed the balance of the decision for some men.

1.2. Do we 'screen' for prostate cancer?

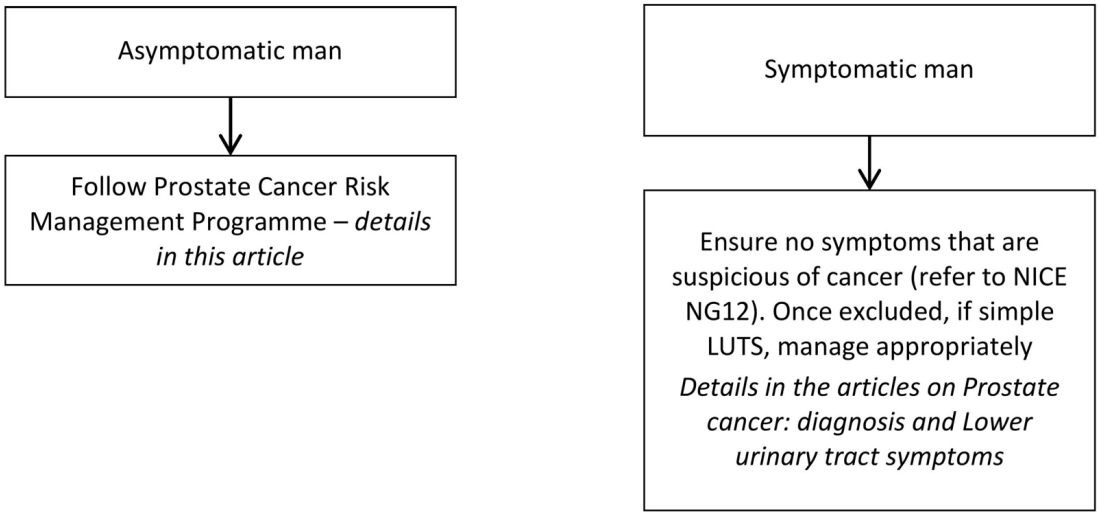
No, the UK National Screening Committee does not recommend systematic PSA screening in asymptomatic men.

There is, however, the Prostate Cancer Risk Management Programme (PCRMP) (updated 2022):

- This allows anyone with a prostate aged 50y or over to ask for a PSA test if they have had the opportunity to make an informed decision.
- We can use clinical discretion for those aged under 50y who we consider may be at additional risk.

The purpose of the PCRMP has been to support us in offering shared decision-making to men requesting a PSA test. The update emphasised the need to check whether men requesting a PSA test have symptoms, defined as lower urinary tract symptoms, erectile dysfunction or visible haematuria, and therefore require a clinical assessment and a decision about whether to

follow NICE NG12 guidance.



In primary care, we currently use digital rectal examination (DRE) and prostate-specific antigen (PSA) levels as our key diagnostic tools, but we seem more hesitant to offer PSA than our international colleagues. This may be due to an awareness of the limitations of PSA, or a desire to not contribute to overdiagnosis of clinically insignificant tumours. From a patient's perspective, this hesitancy may come across as us trying to dissuade or discourage them from taking the test, at a time when the media and some site-specific charities have been encouraging many more men to see their GP and to get a PSA! (BJGP 2023;73 (727):54)

This can lead to some difficult and tense conversations…

1.3. Why don't we have a national screening programme?

The National Screening Committee last reviewed all the available evidence in 2020 and concluded that "**screening is not currently recommended for this condition**" (UK NSC Screening for Prostate Cancer External Review

2020). This was for the following reasons:

- The PSA test is not accurate enough to detect the prostate cancers that need treatment, and can miss some cancers.
- It remains unclear at this time whether MRI +/- PSA is accurate enough to make sufficient difference to change the recommendation.
- There is no single treatment for early prostate cancer that has been demonstrated to be superior, and each available treatment has to be weighed against its side-effects.
- It is unclear how PSA impacts on deaths due to prostate cancer, and it has not been shown to have any impact on all-cause mortality.
- A PSA-based screening programme could cause harm to men as some would be diagnosed with a cancer that would never have become clinically significant during their lives.

For those of you who are interested in the research evidence behind these recommendations, you will find a summary of the 3 key trials at the end of this article.

Men may request a PSA test if they wish, but they should be fully counselled regarding the pros and cons of the test. It may be easy to just tick the PSA box on the blood form, but doing this without adequate explanation is not in any of our patients' best interests. As part of the counselling, we may want to consider and discuss additional risk factors.

1.4. Men with additional risk factors

Some men are at higher risk of prostate cancer death (BMJ 2018;362:k3581, PCRMP 2022). Risk factors include:

- Family history of prostate cancer.
- Black ethnic origin (the lifetime risk is 1 in 4 for men of black ethnicity compared with 1 in 8 for white men and 1 in 12 for Asian men).
- Lower socioeconomic status.

A clinical consensus published in the BJGP in August 2024 deviated from the current guidance. It suggested that, as clinicians, we **should** be aiming to increase awareness of prostate cancer in those at risk (but **shouldn't** be insisting they all have a PSA), and should **proactively** raise prostate cancer risk with men >45y if deemed at the highest risk (BJGP 2024;74:e534).

The National Screening Committee and PCRMP do not advocate a different approach to screening for these groups, but the PCRMP DOES advocate that clinical discretion can be used in deciding whether to test men under the age of 50y who we may consider to be at higher risk.

The National Screening Committee systematic review and meta-analysis could not answer the question of whether screening was of more benefit in ethnicities at higher risk. The BMJ Rapid Recommendation did not advocate a different approach to screening in these groups either.

Impact of family history on risk

- 5–10% of prostate cancers are associated with genetic mutations.
- In those with genetic mutations, onset is often earlier (≤50y).
- Men who develop prostate cancer at an earlier age are more likely to die from it, even when compared with older men with a similar stage of disease.

This information comes from the older PCRMP (2016) – the original reference is from a systematic review and meta-analysis (Int J Cancer

2003;107(5):797). The majority of men involved in the studies included in the meta-analysis were white so this data cannot be extrapolated to men of black ethnicity who already have an increased risk or men of Asian ethnicity who have a lower risk.

Relative affected	Family history	Lifetime risk
None	No family history	8%
Father	Father diagnosed with prostate cancer <60y	20%
	Father diagnosed with prostate cancer ≥60y	12%
Brother	1 brother diagnosed with prostate cancer <60y	25%
	1 brother diagnosed with prostate cancer ≥60y	15%
More than 1 relative	Two first-degree relatives, or one first-degree and one second-degree relative, with prostate cancer (First-degree: father, brother. Second-degree: uncle, grandfather)	30%
	Three or more affected male relatives (no closeness specified)	35–45%

We may want to seek advice from clinical genetics and weigh this information in the balance when making decisions about PSA testing with men.

Men with the *BRCA* gene

Men with the *BRCA* gene are at increased risk of prostate, breast and pancreatic cancer.

Men and women are ***equally likely to inherit and pass on the BRCA genes*** which are autosomal dominant. It is therefore important that we take family histories for male and female family members, and consider the possibility of a *BRCA* mutation in men with prostate cancer at a young age, or in men with aggressive or multiple prostate cancers. But do men who carry the *BRCA* gene have additional clinical needs?

This was the subject of a useful BMJ Practice Pointer (BMJ 2021;375:n2376).

Key messages are:

- All men with suspected/confirmed *BRCA* should have had a clinical genetics assessment and care plan formulated.
- Men with *BRCA* genes have an increased risk of breast cancer and should be breast aware. They also have an increased risk of prostate and pancreatic cancer.
- Men with *BRCA2* (and possibly also *BRCA1*) have an increased risk of developing aggressive prostate cancer. The absolute risk is 27% by the age of 75y. It is not yet known whether PSA screening reduces mortality for these men.
- There is no UK guidance on whether these men should be offered PSA screening, but the European Association of Urology recommends offering PSA screening to men with *BRCA2* from the age of 40y; it does not specify at what interval. The IMPACT study is currently in progress to evaluate whether this is a useful strategy.

All this information will feed into our shared decision-making conversations. So, what process should we follow when a man asks for a test?

1.5. Deciding whether to do the test

The PCRMP states that we should not proactively raise the issue of PSA testing with asymptomatic men.

Here is how we should proceed if asked to do a PSA test:

Please follow the link for a PDF version of the GEMS for download/printing:
PSA testing: GEMS

PSA testing

PCRMP 2022, NICE NG12 2015 (updated 2021)

Red Whale GEMS
Guidelines & Evidence Made Simple

Man aged ≥50y requests PSA test

Does this man have symptoms?

- Lower urinary tract symptoms (LUTS), e.g. nocturia, frequency, hesitancy, urgency or retention
- Erectile dysfunction
- Visible haematuria (in the absence of UTI)

NO

Discuss pros and cons of PSA testing
Offer appropriate written material

Decides against test

End of pathway – can revisit in the future

Decides to have test

PSA not raised

End of pathway – can revisit in the future

YES

Assess symptoms and follow NICE NG12

- *Consider* offering DRE and PSA test
- *Refer on cancer referral pathway if prostate feels malignant on DRE*
- *Consider cancer referral pathway if PSA raised*

NOTE: *visible haematuria may also warrant cancer referral on renal/bladder pathway – see haematuria GEMS*

PSA raised

Refer according to local pathways

- PCRMP 2022 does not state what counts as a 'raised PSA' in the context of screening, though trials used ≥3.0mcg/l as the cut-off
- In many areas, we will refer according to NICE NG12 age-related cut-offs (see below for more details), but we should note that the evidence that sits behind these is based on men with symptoms, NOT screening (asymptomatic) PSA

Can raise PSA	Can lower PSA
Benign prostatic hypertrophy Older age Prostatitis Recent ejaculation Prostate cancer	Obesity Drugs: • 5ARIs (e.g. finasteride) • Aspirin • Statins • Thiazides

Practicalities for doing a PSA test

Men should not have:

- An active urine infection at the time of the test or within the previous 6 weeks
- Ejaculated in the previous 48 hours
- Exercised vigorously, e.g. cycling, in the previous 48 hours
- Had urological intervention, e.g. prostate biopsy/cystoscopy, in the previous 6 weeks

The test must reach the lab in time for serum to be separated within 16 hours (*or be spun down in practice)*

1.6. What constitutes a raised PSA in the context of screening?

That's a tricky one to answer as there is a gap in current UK guidance on this! We therefore suggest you refer according to your locally agreed pathways and PSA cut-off thresholds

Understanding the gap!

The PCRMP states that "most men have a PSA <3.0mcg/l" in its 2022 update, but in its flowchart and guidelines for primary care, it states that men should be referred if their PSA is "raised", offering no specific thresholds. The main screening trials, including PLCO, CAP and ERSPC, used a cut-off of ≥3.0mcg/l as the threshold for further investigation. None of these studies included multi-parametric MRI.

In 2021, NICE updated the suspected cancer referral guidelines (NG12 2021 update) to include age-related cut-offs for PSA at which **symptomatic men** should be referred. Screening trials were excluded from this decision-making process. These are the thresholds that will appear on many of our blood results and referral forms, and, *in practice*, will be the cut-offs that we use for referral of **asymptomatic men**.

NICE NG12 Consider cancer referral pathway in symptomatic men if PSA above age threshold, taking account of individual preferences and comorbidities	
<40y	Use clinical judgement
40–49y	>2.5mcg/l
50–59y	>3.5mcg/l
60–69y	>4.5mcg/l
70–79y	>6.5mcg/l
≥80y	Use clinical judgement

This means that, in practice, for now, if we do a screening PSA in the context of a request from an asymptomatic man, we should refer based on local referral criteria, which in many cases will use the NICE thresholds for symptomatic men.

Do you know your local pathway? Have a look now if not.

1.7. Shared decision-making

So, for men with no symptoms, we need to discuss the pros and cons of testing PSA, and this might include an individualised discussion of their personal risk.

There is a helpful printable leaflet for men produced by the PCRMP (updated 2022) (see also useful resources, below). It suggests we cover the

following issues (taken directly from the leaflet):

Possible advantages	Possible disadvantages
The PSA test may help to: • Pick up prostate cancer before you have symptoms. • Pick up a fast-growing cancer at an early stage when treatment could stop it spreading and causing problems or shortening life.	• Many individuals have a raised PSA without having prostate cancer. • A small proportion of men with a low PSA will later be found to have cancer. • If your PSA is raised, you *may* need a biopsy which can cause side-effects, including bleeding, infections and (rarely) sepsis. • Not ALL men need to have a biopsy. • You may be diagnosed with a slow-growing cancer which would never have caused you any problems or shortened your life. This could cause worry, and you may decide to have treatment you do not need. • Treatments can cause side-effects which can affect you daily for the rest of your life, e.g. urinary, bowel and erection problems. • Neither biopsy nor mpMRI will detect ALL prostate cancers.

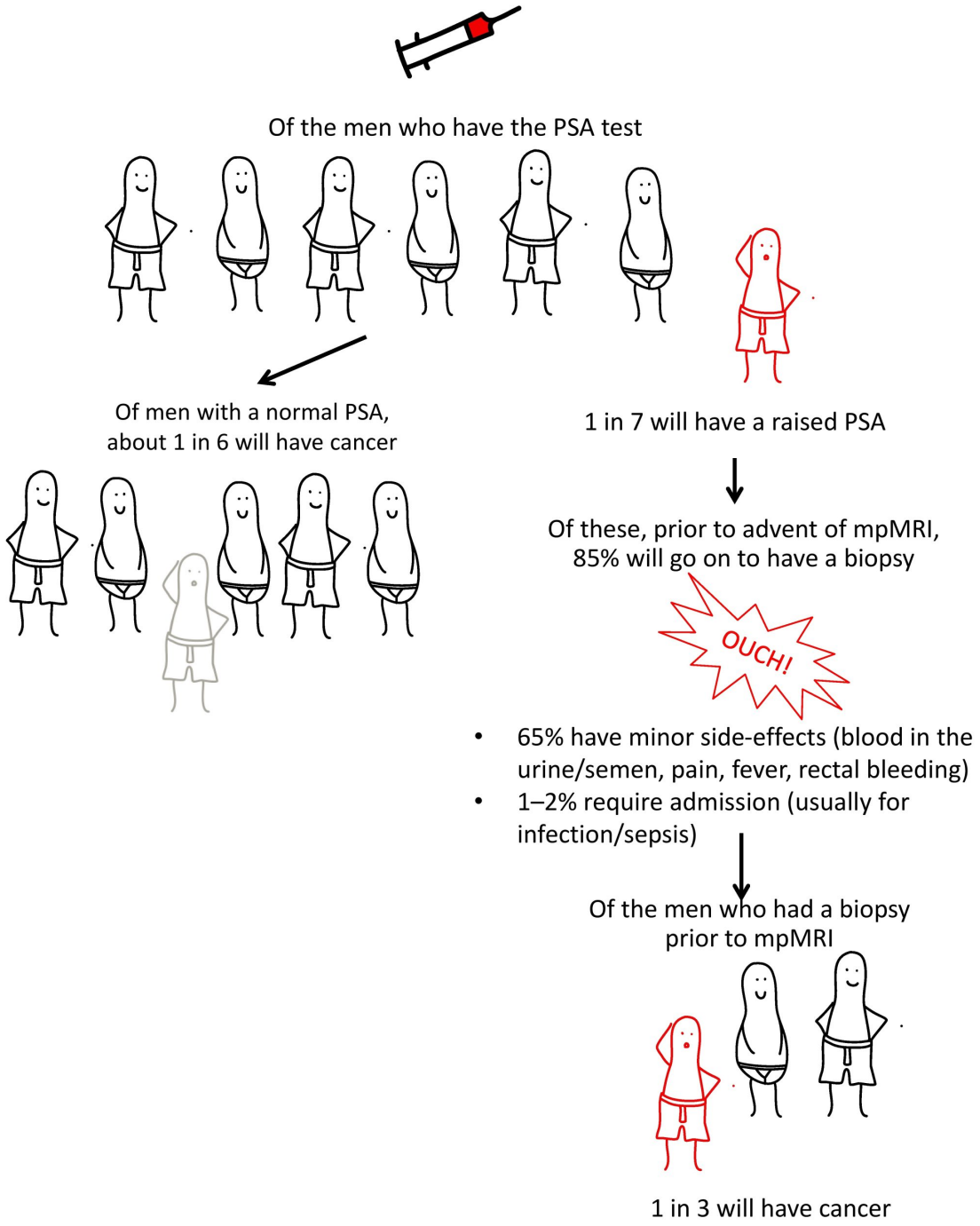
For men who find numbers more helpful, data from the BMJ Rapid Recommendation article suggested we could explain that (BMJ 2018;362:k3581):

- Roughly 1 in 7 asymptomatic men who undergo PSA screening will have an elevated PSA result.
- In trials, 85% of men with a raised PSA proceeded to have a biopsy

(*remember, this number is likely to be smaller but still significant if there is access to mpMRI*).

- 66% of men offered a biopsy because of a raised PSA result will NOT have prostate cancer.
- 15% of men with a normal PSA result will have prostate cancer.
- 2% of men with a normal PSA result will have advanced cancer.

And, if a picture is useful…



For men who want *even* more information/detail on the numbers, the evidence at the end of this article may be helpful – **but, of important note, many of the trials quoted were performed before the advent of multiparametric MRI which has reduced the number of men needing biopsy by about 25%** and may make accurate biopsy more likely as the images are used to identify which sections of the prostate to focus on. Therefore, men having screening are less likely to need a biopsy, and the

over-aggressive treatment of a relatively benign cancer is lower.

Why do these discussions matter?

Almost 40% of men in the UK aged 45–69y have had a PSA, but we do not know how many have discussed the pros and cons of this before testing.

A French study showed that men who received information BEFORE PSA testing were less likely to opt for screening (1000 asymptomatic men aged 50–75y, BJGP 2015;65:236).

Would you want PSA screening?	Intention to undergo screening after no decision aid (control group)	Intention to undergo screening after receiving 2 sides of A4 decision aid (intervention group)
Yes No 'I don't know'	74% 10% 15%	56% 21% 22%

So, information does appear to change men's willingness to have the test.

A link to a UK-specific patient information leaflet can be found in the useful resources, below, as well as a link to MAGICapp which summarises the evidence from the BMJ Rapid Recommendation to support shared decision-making.

1.8. How often should we be retesting PSA in asymptomatic men?

The UK clinical consensus report noted that it hadn't been possible to reach agreement on how often PSA should be retested in an asymptomatic man. It suggested that any decision to retest should be 'risk stratified' – while accepting that no validated risk stratification tools currently exist for this! (BJGP 2024;74:e534)

We suggest that you be guided by local guidelines and by clinical judgement.

1.9. What is the role of digital rectal examination?

The prospect of a DRE can act as a powerful disincentive for some men needing advice about prostate and urinary symptoms. It can also be an issue for men who have been subject to sexual abuse or assault, perhaps a larger percentage of your practice population than you realise. A BJGP article suggests that, in the UK, around 5.6% of men have been subject to sexual assault post-16 years of age (BJGP 2024;74:137).

A DRE may be a key diagnostic step, but used alone is not a reliable screen (this is much more common in the US and Germany than in the UK). A large meta-analysis found that DRE performed poorly in this situation and was no better than flipping a coin (Ann Fam Med 2018;16:149). A press release by the European Association of Urology (March 2023) stated that DRE was not accurate enough to use as a reliable screening test, and that PSA and mpMRI were superior at detecting early disease. There is also some indication that the perception of the need for a DRE may put men off having

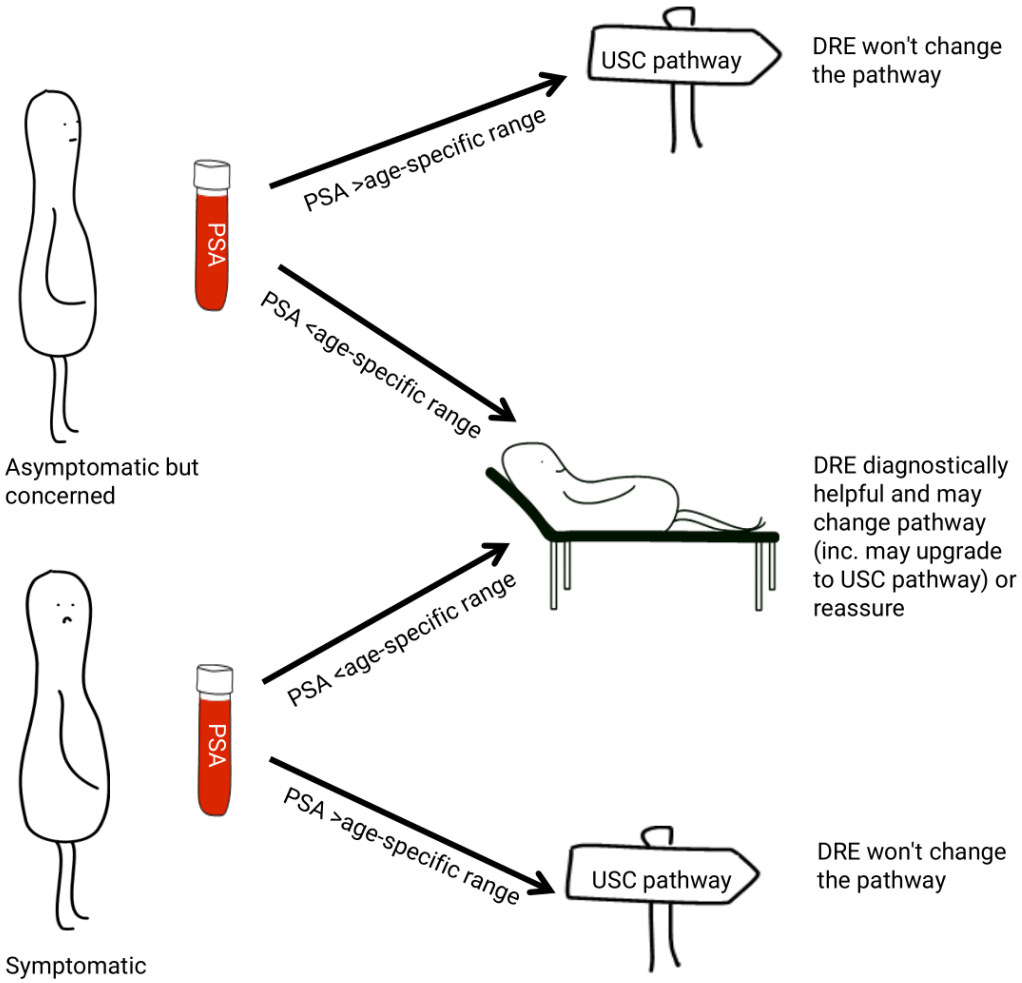
a PSA test.

The PCRMP mentions DRE in its guidance to GPs, but is rather vague, stating that, *"DRE allows assessment of the prostate for signs of prostate cancer (a hard gland, sometimes with palpable nodules) or benign enlargement (smooth, firm, enlarged gland). A gland that feels normal does not exclude a tumour."* So, we should not be using DRE to rule out prostate cancer.

All men with symptoms should be offered a DRE as part of their assessment, and we should refer on the urgent suspected cancer (USC) pathway if the prostate feels malignant, as per NICE guidance (NICE 2015, NG12).

A BJGP article suggested that a more pragmatic approach to DRE may be needed. It suggests that we ask ourselves the question: will a DRE change my management of this man? (BJGP 2024;74:137)

Men with a PSA above the age-specific range, whether symptomatic or asymptomatic, are likely to need referral on a suspected cancer pathway, and the findings from a DRE won't affect that. On the other hand, in men whose PSA is under the age-specific threshold (thus not requiring referral on the cancer pathway), a DRE does have potential diagnostic value. It may identify occult prostate malignancy (needing urgent referral), help diagnose BPH or prostatitis, or offer reassurance if normal.



Some of the screening trials detailed below, e.g. PLCO and some centres in the ERSPC, included combined PSA testing with DRE. This is something we may want to discuss with men as part of the shared decision-making around having the test.

1.10. Risk-prediction tools

Many risk-prediction tools (like QRISK for CVD) that try to assess men's risk of prostate cancer in the next 10 years have been developed. The results for one tool were published in the BJGP. It performed better than age-related PSA thresholds, but it isn't yet clear how we can incorporate this into clinical practice (BJGP 2021;71:e364).

Prostate Cancer UK also offers a 30-second risk checker which was endorsed by NHSE on social media during 2022. We have been unable to identify any pilot or evidence related to this risk checker. If you are over 50y, even without any other risk factors, it identifies that you "may be at higher risk and may want to speak to your GP". It is worth being aware of this as men may attend having used it.

1.11. Multiparametric MRI or biopsy – or both?

NICE recommends that all men referred to urology with a raised PSA who would be eligible for 'radical' (potentially curative) treatment should be offered a multiparametric MRI as a first-step investigation before biopsy (NICE 2019, NG131).

This is an MRI imaging technique that can provide very high-resolution images of the prostate, and can be used as an additional triage step between PSA and prostate biopsy to establish whether prostate biopsy is required. It allows determination of the prostate volume; this then enables PSA density to be calculated, and allows an mpMRI-influenced biopsy that targets areas of the prostate identified as being higher risk (for more details, see *Prostate cancer: diagnosis*).

This is now available in *most* (but not all) parts of the UK, with sites in all 4 home nations. However, even where it is available, it is not used in line with this guidance because of capacity limitations. In areas where it is not available, biopsy may still be the first-line test, but commissioning *should* catch up.

A qualitative study of 22 men and 10 GPs (6 female, 4 male) looked at whether the use of mpMRI was acceptable to patients and GPs. While patients found the experience acceptable, some GPs felt they lacked

enough knowledge about mpMRI. Some expressed concerns that, should this test become accessible via primary care, they may be pressurised to arrange this by asymptomatic men, 'just to be sure' (BJGP 2024;74:e527).

A study assessing the impact of introducing mpMRI followed by targeted biopsy after PSA screening in asymptomatic men found that the addition of mpMRI was non-inferior to standard TRUS biopsy for detecting important cancers, but reduced detection of clinically insignificant cancers (NEJM 2021;385:908).

At this stage, data suggests that using mpMRI as the first test means that biopsy may be avoided by more than 25% of men with a raised PSA.

What does this mean in practice?

The introduction of mpMRI will change the risk–benefit balance of PSA testing, but we don't yet have the data to know how much. It also means there will be an additional cohort of men – those with low-risk mpMRIs – having PSA monitoring in primary care. *Do you have a robust recall system?* You can read more about it and the follow-up required in primary and secondary care in *Prostate cancer: diagnosis*.

1.12. PSA at age 60y and risk of prostate cancer

In an older case–control study from Sweden, researchers followed 1167 men who had had a single PSA test at age 60y. Follow-up was comprehensive, with the men followed until they were 85y and with very few being lost (BMJ 2010;341:c4521).

- **Men whose PSA was <1ng/ml at the age of 60y had a 0.5% risk of**

metastatic cancer by the age of 85y, and a 0.2% risk of death from prostate cancer.

It's a small study of predominantly white men and needs validation, particularly for different racial ethnicities and different ages, but it provides a useful piece of information we can offer to patients who opt for a PSA test at age 60y and have a result of <1ng/ml.

1.13. Summary of the key screening trials

In its 2020 review, the National Screening Committee considered all the available evidence, but took particular weight from the 3 best-designed trials most reflective of the UK population. Note that none of these trials included mpMRI as part of their protocol.

If you want more detail of these trials, see below; *otherwise, feel free to skip this!*

Trial	Outcome	Design
CAP trial (JAMA 2018;319(9):883) (JAMA 2024;331:1460)	After 10y follow-up: • No significant difference in prostate cancer mortality. • Increased detection of low-risk prostate cancer. After 15y follow-up: • Non-significant reduction in prostate cancer mortality (absolute reduction in risk of 0.09%, relative risk 0.97, 95% CI 0.94–1.01).	• UK RCT with >400 000 men aged 50–69y. • Single PSA test vs. no screening.

	• No reduction in all-cause mortality. • Still predominantly detecting low-grade, early-stage, localised cancers.	
ERSPC trial (NEJM 2009;360:1320 and Lancet 2014;384:2027)	After 13y follow-up: • No difference in all-cause mortality. • Small statistically significant reduction in prostate cancer mortality (see below).	• European 8-country RCT with 180 000 men aged 50–74y. • PSA test every 4y vs. no screening.
PLCO trial (NEJM 2009;360:1310 and J Natl Cancer Inst 2012;104:125)	After 13y follow-up: • Screening picked up slightly more cancers (RR 1.12; CI 1.07–1.17). • No difference in mortality between screened and unscreened groups.	Trial design: • US-based RCT with 76 000 men aged 55–74y. • Annual PSA test for 6y and DRE for 4y vs. usual care.

The trial with the lowest risk of bias was felt to be the ERSPC, which showed (BMJ 2018;362:k3519, BMJ 2018;362:k3581, NEJM 2009;360:1320 and Lancet 2014;384:2027):

- **PSA screening has a small, statistically significant impact on prostate cancer-specific mortality:**
    - 781 men need to be screened to prevent 1 prostate cancer death after 13y (confidence intervals mean the number is between 490

and 1929).
    - Similar figures when data reassessed after 18y.
- **PSA screening has no impact on all-cause mortality.**
- PSA screening increases the cancer detection rate but many of these tumours are clinically INSIGNIFICANT – that is, they would not have caused the man any problems in his lifetime.

Over a 10y period, per 1000 men taken from the data with the lower risk of bias (BMJ 2018;362:k3519):

-	All-cause mortality	Prostate cancer-specific mortality	Incidence of prostate cancer (any stage)	Incidence of localised disease	Incid of adva disea
PSA screening	129	2	50	33	10
No PSA screening	129	3	32	19	13

What does this mean in practice?

This isn't new – it supports what we already know. There is currently insufficient evidence to support a national screening programme for prostate cancer using PSA screening.

1.14. The future of prostate cancer screening

Every year, over 44 000 men are diagnosed with prostate cancer and more than 10 000 men die from prostate cancer (Prostate Cancer UK, accessed July 24). There is an understandable push for a viable, effective and safe screening programme.

If PSA by itself isn't viable as a screening tool, how about PSA + something else?

PSA *and* mpMRI?

Multiparametric MRI can now be accessed across 72% of the UK (Prostate Cancer UK data, February 2023). This has sparked debate as to whether a combined strategy of PSA and mpMRI as a two-phase screen is now an option that should be formally evaluated for asymptomatic men.

The aim would be to reduce the detection of clinically insignificant prostate cancer (those with a low risk of death/metastases, but diagnosis still likely to cause emotional/psychological distress), while increasing the detection of clinically significant tumours (those where diagnosis at an earlier stage is likely to have a significant effect on five-year survival).

A Swedish randomised study evaluated whether such a screening algorithm could be effective (NEJM 2022 387:2126). In the GOTEBORG-2 trial, 17 980 men participated in annual PSA testing. Those with a **PSA ≥3ng/ml** were offered an mpMRI and then randomised to either:

- A reference group (which had a targeted biopsy of any suspicious areas on the mpMRI AND a systemic prostate biopsy, regardless of the mpMRI results. *Ouch*!).
- An experimental group (which only had targeted biopsies of any abnormalities on MRI. Men in this group *were* offered a systemic biopsy if their PSA was >10ng/ml).

The study showed that, in men with suspicious findings on mpMRI, performing targeted biopsies alone reduced overdiagnosis by 50% (by reducing the diagnosis of clinically insignificant tumours). This was at a cost of a delay in the diagnosis of intermediate-risk prostate cancers in a small proportion of patients.

A possible additional complication with this strategy is that tumours defined as clinically 'insignificant' on current mpMRI criteria may have a greater likelihood of progressing than those found at biopsy in men who have not had mpMRI (Eur Urol Open Sci 2022;35:59).

PSA + several other tests?

Another Nordic research team, this time from Finland, published some interim findings from its ProScreen study (JAMA 2024;331:1452).

While the primary outcome is prostate cancer mortality at 10 and 15 years follow-up, interim findings suggested some potential benefit to screening. In this study, over 60 000 men aged 50–64y were randomised to either:

- Screening with a PSA. If PSA was ≥3.0, they underwent further blood testing (total PSA, free PSA, intact PSA, and human kallikrein-2). This data was used to produce a 'risk score'. If the risk score was above a threshold, they were sent for mpMRI. If the MRI was graded as higher risk, with a PI RADS score >2, they were offered a targeted biopsy! (See our article *Prostate cancer diagnosis* for more information on mpMRI and the PI RADS score.)
- Control group: usual medical care.

What the study reports is that, vs. the control group, one more high-grade prostate cancer was diagnosed per 196 men screened, and one more low-grade cancer was diagnosed per 909 men screened. However, it is too early

to see what impact this might have on mortality, and the screening process was... quite involved! Importantly, there was also no data provided on harms.

It is likely that the EU's planned prostate screening programme, which it is looking to roll out in the next few years, will follow this multistage approach (Council Recommendation of 9 December 2022 on strengthening prevention through early detection: A new EU approach on cancer screening replacing Council Recommendation 2003/878/EC 2022/C 473/01).

PSA + biomarkers + genetic markers + clinical data?

In August 2022, NICE brought out a briefing document on Stockholm3, a technology designed to 'screen' for prostate cancer in males aged 45–74y (NICE 2022, MIB303).

In fact, this isn't really a screening test. Instead, it is designed to be used either as an additional test in men with a PSA ≥1.5nanograms/ml, or a possibly as a pre-MRI triage tool in secondary care in individuals referred with elevated PSA.

This technology is already being used in the UK, but only via a private route. Our patients may therefore come in seeking our opinion, in which case you'll need to know that a result of ≥11% is considered significant.

The test combines biomarkers, genetic markers and clinical data to generate a risk score:

- Biomarkers include 5 things: total PSA, free PSA and 3 we hadn't heard of.
- Genetic markers: 101 single nucleotide polymorphisms.

- Clinical data includes age, family history and previous prostate biopsy.

Cost

The test is substantially more expensive than a PSA test, at around £350 (excluding VAT) per test vs. £27.75 for a PSA test in primary care.

The studies that were included in this review suggested that Stockholm3, when combined with MRI-targeted biopsy, reduced over-detection without missing clinically significant prostate cancers, and the subsequent reduction in MRIs and biopsies made it cost-effective.

The evidence

If you want to read further, the source research included Eur Urol Focus 2023;7:S2405, J Clinical Oncol 2024;42:262 and JAMA Netw Open 2024;7:e247131. These trials show that Stockholm3 appears to have validity in Central European populations and African American/black, white, hispanic/latino and Asian males in the US. Combined with systemic biopsy in areas without access to mpMRI, it offers pickup of clinically significant prostate cancer comparable to MRI-targeted biopsies based on PSA levels.

In summary

A multimodal approach based on PSA plus ‘other metrics’ sounds promising, but we are still some way off a screening programme being a reality in the NHS!

PSA testing in asymptomatic men

- Is this man symptomatic or asymptomatic?
- Family history and black ethnicity increase the absolute risk of developing prostate cancer, but there is an absence of evidence as to how this information should influence screening.
- **The National Screening Committee does not recommend population-wide PSA screening but, through the PCRMP, allows males aged 50y and over to make an informed choice to have a PSA test.**
- Shared decision-making is key.
- NICE recommends mpMRI as a second-line test for men with raised PSAs for whom curative treatment would be considered. This probably changes the risk–benefit balance.

What do you say when a man asks about a PSA test?
Should this change considering the evidence summarised in this article?

Useful resources:
Websites (all resources are hyperlinked for ease of use in Red Whale Knowledge)

- gov.uk - Prostate Cancer Risk Management Programme (has information for both patients and clinicians)
- PCRMP PSA information leaflet
- MagicApp – prostate cancer screening using PSA (BMJ Rapid Recommendation app to support shared decision-making)
- Prostate Cancer UK risk checker

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