

**PROFESSIONAL
SUPPORT**

Prostate Cancer UK's Best Practice Pathway

Pre-referral guidance

Stage I: Pre-referral

I.1 Risk factors for prostate cancer

Not all men are at the same risk of developing prostate cancer; there are some specific factors that put men at higher than average risk of developing prostate cancer including age, a family history of the disease and obesity (specifically in relation to advanced disease).

Ethnicity

Prostate cancer is the most prevalent cancer in men in the UK; approximately 1 in 8 men living in the UK will get prostate cancer at some point in their life¹. Our research shows that in men of black ethnicity, the risk of getting prostate cancer is doubled to 1 in 4. Asian men have a much lower risk with 1 in 13 men developing prostate cancer². It is not understood why there is a difference in risk amongst different ethnic groups but it could be linked to genetics.

Age

Prostate cancer mostly affects men over 50 and the risk of developing prostate cancer increases with age with a 75% incidence rate in men over 65³. Men under 50 can develop prostate cancer but it is less common. Black men and men with a family history of prostate cancer are more likely to be diagnosed at a younger age^{4,5}.

Family history

Men with a family history of prostate cancer are 2.5 times more likely to develop prostate cancer if their father or brother has been diagnosed compared to men with no relatives that have had the disease⁶.

There is also an increased risk of developing prostate cancer if a man's mother or sister have been diagnosed with breast cancer and had faults in the BRCA1 or BRCA2 gene. These inherited genetic faults have been found to be linked with an increased risk of developing a more aggressive prostate cancer⁷.

Body weight

Being overweight or obese increases a man's risk of developing aggressive or advanced prostate cancer⁸.

I.2 Presentation in primary care

Symptomatic men

Men presenting with the following symptoms should go on to have a PSA test and digital rectal examination (DRE) as per the NICE suspected cancer pathway for referral⁹: lower urinary tract symptoms (difficulty passing urine or a frequent need to pass urine), visible haematuria or erectile dysfunction; and for a small percentage other symptoms may include weight loss, back and/or bone pain⁹.

Asymptomatic men

Most early prostate cancers have no symptoms; general practitioners (GPs) and practice nurses should be aware of the factors that put men at higher than average risk.

The Prostate Cancer Risk Management programme (PCRMP)¹⁰ (see Appendix 1), which is produced by Public Health England, has recently been updated to support primary care professionals in their use of the PSA test with asymptomatic men. Unlike its previous version, it now recommends one referral threshold for PSA value of 3ng/ml for men between the ages of 50 to 69.

Due to different methodologies and accepted levels of evidence, Prostate Cancer UK's PSA consensus¹¹ (see Appendix 2) covers aspects of PSA testing not included in the PCRMP, where robust published evidence is lacking.

Higher than average risk men

Prostate Cancer UK's PSA consensus recommends for GPs to have proactive conversations about prostate cancer risk and the PSA test with men at higher than average risk, especially if they don't often visit their GP¹¹. These men may not know they're at higher risk. Men without symptoms who have a life expectancy of clearly less than 10 years are unlikely to benefit from a PSA test.

1.3 Counselling/Deciding to do the PSA test and other investigations in primary care

Prior to going ahead with a PSA test the following should be covered:

- Exclusion of urinary tract infection (UTI) or sexually transmitted infection (STI)
- Ensure patient is fully counselled about the pros and cons of the PSA test and next steps if the PSA is elevated.

Before actually having the test:

- Advice about refraining from vigorous exercise or sexual activity (including masturbation) 48 hours ahead of a PSA test.

A digital rectal examination (DRE) should also be performed prior to referral to feel for malignancy. Indicators of a clinically malignant cancer will be a firm, hard or craggy feeling prostate on DRE⁹.

Depending on presenting symptoms, GPs may consider performing a DRE prior to a PSA test. It is not necessary to delay giving a PSA test due to a DRE having been performed first as the rise in PSA is minimal following DRE¹². A delay in performing the PSA test could have a detrimental effect on the speed at which a prostate cancer is detected.

1.4 Referral criteria and patient support

The prostate-specific antigen (PSA) level of 3 ng/ml for referral was incorporated into the prostate cancer diagnostic pathway advocated by NICE¹³ and used in the PCRMP guidelines¹⁰. This changed the PSA test threshold for referral for further investigation from age-stratified variable limits to one specific level recommended for men between the ages of 50-69.

The previous system, which used age-specific PSA thresholds, is controversial. It is known that PSA generally increases with age, so age bands were introduced to increase sensitivity of the test in younger men and specificity in older men to reduce over-treatment of an elderly population¹⁴. However, variability in PSA also increases with age, reducing the sensitivity of the test among older men^{14,15}. Other factors affecting PSA levels, such as race, combine to mean that age-specific thresholds do not improve the overall performance of the PSA test in detecting clinically significant cancer¹⁴.

The evidence for a referral threshold of 3ng/ml

In 2015, the UK National Screening Committee (UKNSC) published an external report which included a review of the evidence surrounding predictive values associated with different PSA cut-offs, and also assessed the feasibility of the PSA test for a UK population-wide screening programme¹⁶. The review reported the results of Wolf et al. (2010) who showed that decreasing the cut-off point from 4.0 to 3.0 ng/ml increases sensitivity for detecting any cancer from 21% to 32%, and for detecting high-grade cancer (Gleason 8) from 51% to 68%¹⁷. The UKNSC report states: "lowering the PSA cut-off threshold from 4.0 to 3.0 ng/ml increases test positivity and cancer detection rates but at the expense of lower specificity. Overall,

the results highlight that there is no distinct PSA cut-off to distinguish between the presence and absence of prostate cancer¹⁶.

They also reviewed two large-scale clinical trials that have investigated screening for prostate cancer using the PSA test. **Table 1** below illustrates that the best available clinical evidence to determine a PSA threshold for referral for suspected prostate cancer is between 3 to 4 ng/ml:

Table 1:

Trial	Participants	Threshold (ng/ml)
European Randomized Study of Screening for Prostate Cancer (ERSPC)	162,388	3.0*
Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)	76,685	4.0
Cluster Randomized Trial of PSA Testing for Prostate Cancer (CaP) ¹⁸	419,582	3.0

Table 1. Large-scale trials investigating prostate cancer screening using the PSA test. Details of participant numbers and PSA thresholds are shown. (Adapted from Table 13 of the UKNSC external evidence review.)¹⁶ Note: The CaP trial was not part of the evidence review undertaken by the UKNSC in 2015. This is because this trial published in 2018. *Some centres of this multi-centre trial used a PSA referral value of 4.0 ng/ml.

The Prostate Cancer Prevention Trial (PCPT) also reported that, of their study cohort, approximately 14% of men (397/2757; age range, 62 to 91 years) with a PSA value <3.0 ng/ml and a normal digital rectal examination (DRE) had biopsy-detectable prostate cancer. Moreover, 14% of these men (54/397) had high-grade prostate cancer (here defined as Gleason grade ≥ 7).¹⁹

Managing patient demand

The optimal timed prostate cancer diagnostic pathway²⁰, facilitated and produced by NHS England, recognises that a PSA threshold of 3 ng/ml can increase the numbers of men being referred for suspected prostate cancer. To support centres in their management of these men, the pathway recommends for pre-mpMRI clinical triage. This can enable those men whose PSA level is the result of a urinary tract infection (UTI) to be removed from the referral pathway while they undergo antibiotic treatment. A subsequent PSA test can then be used to either return them to the suspected cancer pathway or remove them from it.

1.5 Other referral factors

A raised PSA alone should not be an indicator for referral to a urologist and other risk factors that should be considered are as follows¹⁰:

- DRE findings and prostate size
- Age (see 1.1)
- Ethnicity (see 1.1)
- Family history (see 1.1)
- Comorbidities
- BMI (see 1.1)
- Any previous PSA or prostate biopsy history

At the point of referral patients should be counselled and informed that they are being referred to a cancer service²¹. They should be given the reasons for the referral decision and provided with reassurance that most people referred will not have a diagnosis of cancer. Those with a very high PSA should be counselled appropriately about the likelihood of a prostate cancer being detected. Other possible outcomes such as benign prostate hyperplasia should also be discussed.

Information should be presented both orally and in an accessible written format in order to promote their active participation in care and self-management²².

Information to be given to the patient should include details about²¹:

- Where they have been referred to and the type of specialist they will see
- When to expect to be contacted with an appointment and how long they should have to wait before seeing a specialist
- What types of tests they may undergo and how long it may take before they should expect to receive the results
- Other sources of information about prostate cancer that can be accessed prior to their appointment with the specialist unit

NICE recommends in its latest Quality Standards that patients are provided with written information encouraging them to attend their appointment with a specialist. This is to avoid missed appointments and ensure an earlier diagnosis²³.

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Appendix I – Public Health England PCRMP information sheet



Public Health
England



Advising well men aged 50 and over about the PSA test for prostate cancer: information for GPs

This Prostate Cancer Risk Management Programme (PCRMP) sheet helps GPs give clear and balanced information to asymptomatic men who ask about prostate specific antigen (PSA) testing. The PSA test is available free to any well man aged 50 and over who requests it.

GPs should use their clinical judgement to manage symptomatic men and those aged under 50 who are considered to have higher risk for prostate cancer.

Prostate cancer

Each year in the UK about 47,000 men are diagnosed with prostate cancer and about 11,000 die from the disease. The most common age of diagnosis is 65 to 69.

Men are at higher risk if they:

- have a family history of prostate cancer
- are of black ethnic origin – lifetime risk 1 in 4 compared to 1 in 8 for white men
- are overweight or obese (specifically for advanced prostate cancers)

Slow-growing tumours are common and may not cause any symptoms or shorten life. Some tested men may therefore face unnecessary anxiety, medical tests and treatments with side-effects.

PSA test

The test aims to detect localised prostate cancer when treatment can be offered that may cure cancer or extend life. It is not usually recommended for asymptomatic men with less than 10 years' life expectancy.

Evidence suggests PSA screening could reduce prostate-cancer related mortality by 21%.

About 3 in 4 men with a raised PSA level ($\geq 3\text{ng/ml}$) will not have cancer. The PSA test can also miss about 15% of cancers.

Before a PSA test men should not have:

- an active urinary infection
- ejaculated in previous 48 hours
- exercised vigorously in previous 48 hours
- had a prostate biopsy in previous 6 weeks

When taking blood:

- ensure specimen will reach laboratory in time for serum to be separated within 16 hours
- send samples to laboratories taking part in UK National External Quality Assessment Service

Digital rectal examination (DRE)

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.

Biopsy

A biopsy can diagnose prostate cancer at an early stage when a cure may be possible.

About 2 out of 5 men describe biopsy as painful. The most common complications (9 out of 10 men) are bleeding and infections. Most men experience blood in urine and sperm after biopsy.

Some prostate cancers will be missed at biopsy (up to 1 in 5 men). If the biopsy is negative, follow-up and additional biopsies may be needed.

Management and treatment

Some men may benefit from treatment for localised prostate cancer. There is no clear evidence as to the best treatment option for localised prostate cancer.

The main treatment options are:

- active surveillance
- watchful waiting
- radical prostatectomy (open, laparoscopic or robotically assisted laparoscopic)
- external beam radiotherapy (EBRT)
- brachytherapy (low and high dose rate)

There are important quality of life differences between each option. The options available depend on the stage of disease, the man's age and general health.

Active surveillance involves repeat PSA testing and biopsies. Surgery and radiotherapy may offer the possibility of a cure but can have significant side-effects.

See *patient information sheet* for summary of the potential benefits and harms of PSA testing.

Appendix 2 - Prostate Cancer UK's PSA Consensus

Consensus statements on PSA testing in asymptomatic men in the UK [HP version]

March 2016

www.prostatecanceruk.org/PSAconsensusHP

The consensus statements

We've produced a set of statements, representing the consensus view of hundreds of health professionals, to support primary health care professionals to use the PSA test more effectively for men without symptoms of prostate cancer. The set of thirteen consensus statements, providing additional guidance to Public Health England's Prostate Cancer Risk Management Programme (PCRMP), will drive improvements in the early detection of prostate cancer in men without symptoms whilst aiming to avoid over treatment and reduce variation in practice.

You can read more about the evidence behind the statements and the methods used to develop the consensus on the 'How the consensus was developed' tab above.

Statement 1:

A man's PSA level should be built into a validated risk assessment tool, when available, alongside other known risk factors to better assess a man's risk of prostate cancer and aid in the decision-making process.

We're working with experts from around the world to change the way prostate cancer is diagnosed across the UK by developing a risk prediction tool for primary care practice.

Statement 2:

Primary healthcare professionals need to be aware of the factors that put men at higher than average risk of prostate cancer.

Increasing age, black ethnicity and a family history of prostate cancer put men at higher than average risk of prostate cancer.

Statement 3:

Primary healthcare professionals need to be prepared to have proactive conversations with men at higher than average risk of prostate cancer about prostate cancer risk and the PSA test.

Statement 4:

Governments and public health agencies have primary responsibility for raising awareness of prostate health and prostate cancer risk factors amongst men in the UK, with relevant contribution from healthcare professionals and charities.

Statement 5:

All men should be able to access PSA testing from the age of 50, but men at higher than average risk of prostate cancer should be able to access the PSA test from the age of 45.

The PCRMP guidance states that "The PSA test is available free to any man aged 50 or over who requests it, after careful consideration of the implications".

Statement 6:

When a PSA test is being considered, primary healthcare professionals should provide balanced information on the pros and cons of the PSA test in order to allow the man to make up his own mind on whether to have the test.

Information on the pros and cons of the PSA test can be found in the PCRMP guidance and on our information page on the PSA test.

Statement 7:

Asymptomatic men with a life expectancy clearly less than 10 years should be recommended against an initial or repeat PSA test as they are unlikely to benefit.

We acknowledge that further work is required to better estimate an individual's life expectancy.

Statement 8:

GPs should offer a digital rectal examination (DRE) to all asymptomatic men who have decided to have a PSA test.

Statement 9:

Asymptomatic men at higher than average risk of prostate cancer who have a PSA test between the ages of 45 and 49 should be referred for further investigations if their PSA level is higher than 2.5ng/ml.

This recommendation is based on the limited evidence currently available, and may need to be reviewed if further information becomes available.

Statement 10:

PSA history and a rising PSA (whilst still under the referral threshold) should be taken into consideration when deciding whether to refer to secondary care.

The PCRMP states the new recommended prostate biopsy referral value for men aged 50-69 years is 3ng/ml.

Statement 11:

Asymptomatic men who have a PSA level below the threshold referral value should not be denied a repeat PSA test. Re-testing intervals should be individualized following a discussion incorporating prostate cancer risk factors.

Statement 12:

Asymptomatic men over 40 should consider a single 'baseline' PSA test to help predict their future prostate cancer risk.

If the PSA level is above the age-specific median value, they should be considered at higher than average risk of prostate cancer and should be encouraged to be re-tested in the future.

The age-specific median value for men aged 40-49 years is 0.7ng/ml.

Statement 13:

The PSA test, even when combined with the DRE, should not be used in a UK population-wide screening programme for asymptomatic men.

Read our policy position on the PSA test, which includes more information on why there is no national screening programme using the PSA test in the UK.