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Evidence-based Interventions

Proposed clinical guidance

PSA Testing for men aged 80 years and above

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Introduction

The Evidence-based Interventions (EBI) programme is an initiative led by the Academy of Medical Royal Colleges to improve the quality of care. Since its inception in 2018, the programme has been supported by four partners: NHS England, NHS Confederation, the Patients Association and the National Institute for Health and Care Excellence (NICE).

Backed by both doctors and patients, the programme is designed to maximise the value patients get from healthcare. This might mean carrying out fewer interventions — where the benefit of certain tests, treatments and procedures is no longer supported by the evidence — but might also mean increasing activity, where the positive impact of a particular intervention for patients is compelling. And finally, it might mean changing the way a particular condition is diagnosed and then treated.

As well as improving outcomes and reducing patient harm, prioritising evidence-based care means we can improve outcomes, reduce patient harm and minimise unwarranted variation in service provision, as well as freeing up valuable resources for use elsewhere in the NHS. This is more important than ever as the NHS recovers from the impact of COVID-19 and restores services.

These recommendations aim to maximise shared decision making in relation to the investigation and diagnosis of prostate cancer in primary care. Addressing the harm associated with overdiagnosis and overtreatment and the wide variance in care delivery across the country.

The recommendations have been drafted by a panel of senior specialist clinicians. The panel is overseen by an Expert Advisory Committee (EAC) which evaluates the evidence and ensures only those proposals which meet strict criteria are progressed. This committee in turn reports to a Programme Board which makes the ultimate decision on whether a change to the clinical guidance can be made. Their decision is based on feedback from all key stakeholders including patient groups, clinical commissioners, and clinicians. You can find out more about EBI on our website.

We are keen to hear from individuals and organisations with views on this proposal. The engagement period closes on 1 September 2023. These proposals and any views received will be considered by the Programme Board who will reach a conclusion on the practicality and appropriateness of the proposed changes to clinical guidance in Winter 2023.

This guidance relates to those who have a prostate, this includes:

- Cismen (men who identify as male and were assigned male at birth)
- Trans women (women who identify as female and were assigned male at birth)
- Non-binary people who were assigned male at birth
- Some intersex people.

The information has been developed based on guidance and evidence in men. If you are a trans woman, male-assigned non-binary or intersex, some of this information is still relevant to you — but your experience may be slightly different.

Please note for the purposes of this document and to align with the evidence when we use 'men' it refers to all those with a prostate.

Summary of current practice

Prostate cancer is common, up to 1 in 8 men are diagnosed during their lifetime with over 45,000 cases diagnosed each year in England and Wales[1,2]. It is a common cause of cancer-related death globally[3]. In the UK, prostate cancer diagnosis typically begins in primary care with a blood test for serum prostate specific antigen (PSA) and/or a digital rectal examination. A PSA test may be performed in asymptomatic patients concerned about the risk of prostate cancer or in individuals with symptoms localised to the urinary tract or indicative of metastatic disease, who are defined as 'symptomatic' in national guidance[4]. The PSA level that should prompt specialist referral is defined at a fixed threshold for asymptomatic men[5] and at age-specific thresholds for 'symptomatic' men[4]. An age-specific PSA threshold is not defined for men aged over 80 in NICE guideline NG12 due to the lack of evidence in this group; instead 'clinical judgement' is advised[4]. In the absence of specified value for this age-group, individual cancer alliances have devised their own numerical thresholds with significant regional variation[6]. Simple numerical cut-offs miss the bigger picture, including what a referral for suspected prostate cancer is likely to involve, and what factors are important in treatment decisions.

PSA testing is common in men over 80. Testing is often offered to men with lower urinary tract symptoms (LUTS) in line with national guidance, although LUTS are not a reliable symptom of localised prostate cancer and are common in this age-group due to other causes[7]. Many of these men could be considered 'asymptomatic' from the perspective of prostate cancer with PSA testing therefore constituting a form of screening. PSA has a poor specificity in this age-group, meaning many with a raised test will not have cancer. This can result in over-investigation, including prostate biopsy, which carries significant risk. The need of biopsy has partly been mitigated by the introduction of multi-parametric prostate magnetic resonance imaging (MRI), but this is resource intensive.

Prostate cancer is often over-diagnosed in this age-group, meaning that while an individual may have cancer this will not cause symptoms in the patient's lifetime or impact their life expectancy. Individuals need to live at least 10 years to benefit from radical treatment for localised prostate cancer. This will not be true for many, with median life expectancy eight years for a man turning 80 in the UK[8]. The diagnosis and radical treatment of prostate carries a significant risk of side effects that can negatively impact quality of life and it is important that these are avoided where treatment will not improve quality of life or survival[9]. Clinicians and patients are both poor predictors of life expectancy, meaning that some patients with indolent cancers but a high level of comorbidity are 'overtreated'[10].

PSA testing is a highly complex and contentious area, and it is important that primary care clinicians are appropriately supported to allow shared decision making to take place with patients.

This guideline aims to complement NICE guideline NG12[4] by providing detail on the principles that should inform a shared decision making process in men over 80 who are considering, or who have had, a PSA test.

These recommendations aim to ensure:

- Localised prostate cancer is diagnosed in all individuals who would benefit from radical treatment.
- Over-diagnosis and overtreatment are minimised in those who don't have cancer or have clinically insignificant prostate cancer where radical treatment is unlikely to be of benefit and could cause harm.
- Men with metastatic prostate cancer are identified and offered treatment where appropriate.

Recommendations

Scope

This guideline aims to support primary care clinical decision making in men aged over 80 years where PSA testing is being considered or where a PSA test has been performed.

NICE guideline NG12[4] advises that primary care clinicians should use 'clinical judgement' when deciding whether to refer 'symptomatic' men over 80 who have an elevated PSA test.

Recommendations

PSA testing: Framework for shared decision making prior to testing

1. Before a PSA test is performed a shared decision-making process[11] should take place between the patient and the primary care clinician where the limitations of the test and the possible consequences of an abnormal result are discussed[12]. The clinician should consider discussing the following points:

About the PSA test

1.1. PSA can commonly be raised in the absence of prostate cancer (false positive) and occasionally be normal where cancer is present (false negative)

About localised prostate cancer

1.2. Prostate cancer confined to the prostate gland is typically asymptomatic — LUTS are not a reliable symptom of localised prostate cancer.

1.3. Prostate cancer confined to the prostate gland is common, but many cancers diagnosed in this age-group will be clinically insignificant meaning they won't cause symptoms in an individual's lifetime or shorten their life expectancy.

1.4. An individual must live for at least 10 years to benefit from radical treatment of prostate cancer when it is confined to the prostate gland. However, radical treatment can be associated with side effects (e.g. incontinence and erectile dysfunction) that impact quality of life[13].

About metastatic prostate cancer

1.5. When prostate cancer has spread outside the prostate gland there are effective treatments that may help reduce symptoms (but not cure the disease).

PSA testing: Clinical recommendations on testing

1.6. In men over 80, PSA testing should be encouraged where there are symptoms suggestive of metastatic prostate cancer (such as bone pain, unintended weight loss and fatigue).

1.7. In men over 80 without signs of metastatic disease the benefit of PSA testing is uncertain. A PSA test should only be performed in men who want one after an appropriate shared decision-making process (see above). The potential benefits are greater in those with a life expectancy of more than 10 years.

PSA testing: Interpreting test results

1.8. For men ≥80 years of age who have had a PSA test, offer referral via a suspected cancer pathway if:

- the PSA >20 ng/mL;

OR

- the PSA >7.5 ng/mL AND there are symptoms suggestive of metastatic disease (bone pain and/or fatigue and/or significant unintended weight loss).

1.9. If the initial PSA test is between 7.5 – 20 ng/L and there are no symptoms suggestive of metastatic disease, repeat PSA **ONCE** after 6 months in primary care, prior to any secondary care referral.

1.10. When the PSA is repeated, offer referral via the suspected cancer pathway if:

- either criteria in recommendation 1.8 being met;

OR

- PSA has increased significantly (more than doubled), and the patient has a performance status of 0 or 1.

1.11. If patients do not fit the above criteria but concerns remain, seek appropriate support via 'advice and guidance.

Rationale for recommendations

The panel discussed current NICE guidance on PSA testing in 'symptomatic' men and the lack of evidence on the predictive accuracy of age-specific thresholds in this group was acknowledged. The panel considered there was a lack of guidance to support primary care clinicians with 'clinical judgements' on PSA testing and on actioning abnormal results. Panel members underlined how individual cancer alliances have introduced local age-specific thresholds to help address this uncertainty but that this has led to significant regional variation in referral patterns[6]. The panel agreed there was a need for unified recommendations covering men in this age group, and that these would benefit from considering the evidence on prostate cancer treatment and outcomes rather than simply focussing on the predictive accuracy of the PSA test in isolation. It was the panel's opinion that a more holistic view would help mitigate some of the risks associated with over-investigation and over-treatment and have important resource implications.

The panel noted that prostate cancer is a common diagnosis in older men. More than 75% of all prostate cancers are diagnosed in men over 65 years old[14] and it is estimated that approximately 50% of men over 50 years have histological evidence of prostate cancer, rising to almost 80% in men aged over 80 years[15]. The panel noted that for most men, prostate cancer is slow growing and does not cause symptoms during an individual's lifetime and/or affect life expectancy[15,16,17]. The panel noted that there is a particular risk of over-diagnosing and over-treating prostate cancer in men aged over 80 years where the prevalence of cancer is highest, but the proportion of cancers that are clinically significant is lowest.

The role of PSA testing in over-diagnosis was discussed. The panel noted that PSA testing can advance the time of diagnosis, but this may not confer treatment benefits where cancers are indolent, or life expectancy is limited[18]. It was noted that the long-term prognosis for older men with PSA-detected prostate cancer is excellent, including those treated conservatively[19]. Studies looking at prostate cancer specific mortality after radical treatment of localised disease were reviewed, and the panel agreed that those with a life expectancy of less than 10 years are unlikely to derive benefit from radical treatment[20,21,22,23,24,25,26]. The difficulties with predicting life expectancy were noted[27]. Evidence was presented that patients and clinicians do this poorly[28,29,30] and that clinicians often fail to appropriately adjust for comorbidities, leading to a tendency to overestimate survival[10,27]. The panel concluded that early diagnosis, in certain cases, may expose patients to harm through treatments that do not benefit quality of life or survival[18].

The panel discussed the utility of the WHO performance scale — which is simple, widely used, and has good inter-rater reliability — in helping identify those who might benefit from early diagnosis and treatment. The panel considered that only individuals with a performance status under 2 should be offered radical treatment of localised prostate cancer given how long the benefits of treatment take to be realised. It was therefore agreed that performance status would be used as one criterion for screening patients for onwards referral. It was the view of the panel that patients would need to be provided with clear information on the rationale behind the decision-making process and that 'advice and guidance' should be used by primary care where there was clinician or patient uncertainty.

The panel acknowledged that the benefit of radical treatment in men over 80 with the highest performance status will be equivocal and relate, among other things, to the precise histological features of an individual's cancer. These individuals stand to benefit from a histological diagnosis, which can then be used as part of risk prediction algorithms such as Predict Prostate[31] to individualise treatment decisions. The panel noted that even among this group, only approximately 10% of patients receive radical treatment (predominantly radiotherapy) [National Cancer Registration and Analysis Service 2013-2019]. A consensus expert view was taken that the PSA cut-off for the lower 70-79 age group should be used as a threshold for PSA monitoring in primary care, and that men should be referred where their PSA is rapidly rising.

There was considerable discussion on the value of LUTS as a symptom of prostate cancer and it was noted that LUTS continue to form an important part of national guidelines and media health campaigns. Evidence evaluating the diagnostic utility of LUTS was reviewed and the negative association between LUTS and localised prostate cancer diagnosis in screening studies was noted[7]. The findings of a 2013 Cochrane review, which concluded that *'the presence of LUTS, typically due to benign prostatic obstruction, are very common in the ageing male and are not considered to increase prostate cancer risk'*, were considered to be significant[22]. PSA testing for LUTS was noted to be an important factor contributing to over-investigation and overdiagnosis and the panel agreed that this issue should be addressed explicitly in the guidance.

The panel considered the benefits of early hormonal treatment for localised disease in those not fit enough for radical treatment. It was noted that the current evidence only supports early hormonal treatment in those with a baseline PSA > 50 ng/ml and/or a PSA doubling time < 12 months[32]. An age-specific PSA threshold of 20 and repeating PSA measurement in those with a PSA>7.5 at six months (to pick up individuals where PSA is rapidly rising), was considered adequate to ensure all individuals potentially benefitting from early hormonal treatment are seen in secondary care.

The panel agreed on the importance of ensuring all men with suspected metastatic disease are offered referral to secondary care. The panel came to a consensus on the typical symptoms of metastatic disease (bone pain, fatigue, and unintended weight loss) and agreed that even a mildly raised PSA in these individuals should prompt a high index of

suspicion of metastatic cancer. A PSA above the age-specific threshold for the 70-79 age group was agreed upon as a reasonable referral threshold where possible symptoms of metastatic disease exist. The appropriate PSA threshold for detecting metastatic disease in asymptomatic patients was also considered. The available evidence indicates that a PSA threshold of 20ng/ml has a high sensitivity for detecting asymptomatic metastatic disease[33,34].

Patient information

Prostate-specific antigen (PSA) is a blood test used to help detect prostate cancer. It is normally carried out by your GP or in a primary care setting.

For men over 80 we recommend that before carrying out a PSA test your GP (primary care clinician) discusses the test and its implications with you so that together you can make a shared decision about what is best for you. If you do have a PSA test this guidance can also help decide whether a referral to a urologist is likely to be beneficial.

PSA is a protein produced in the prostate. It is therefore entirely normal for you to have a small amount of PSA in your blood. The amount of PSA tends to increase as you age because the prostate gets bigger over time — a bigger prostate releases more protein. Raised levels can sometimes indicate prostate cancer but there are many other reasons why PSA levels may be raised such as, diet, sexual activity, vigorous exercise, recent infection, and some medications.

Men may ask for a PSA test because they are concerned that they could have prostate cancer due to experiencing changes to urine flow or the need to pass urine more frequently, more urgently and overnight. These are known as lower urinary tract symptoms (LUTS). As men age, they can experience LUTS due to age-related enlargements in the prostate. Prostate cancer does not generally cause these symptoms and is typically a silent disease when confined to the prostate gland. For this reason, LUTS should not automatically prompt a PSA test.

A PSA test should be performed on its own merits, when finding and treating early prostate cancer would help improve an individual's life expectancy or quality of life.

Current NICE guidance[4] sets out specific criteria on what PSA levels should trigger a referral to a specialist urology department based on age. For men over 80 years old, the guidance does not provide a specific value but advises clinicians to 'use clinical judgement'. In response, different regions have adopted different numerical cut-offs for this age-group. This has resulted in variation in referral rates across England. This guidance addresses this regional variation by providing national guidance on when to perform a PSA test in this age-group, and what to do with the results.

For cancer that is confined to the prostate, the benefits from treatments such as surgery and radiotherapy are only realised if a man lives another 10 years. Unsurprisingly, for men over 80 diagnosed with prostate cancer, only around 10% will undergo radical treatment.[1]

Diagnosing prostate cancer by prostate biopsy comes with a substantial risk of side effects and serious complications, (blood in semen (93%), blood in urine (66%), pain (44%), fever (18%), and admission to hospital for sepsis (1-2%)) and these need to be balanced against the benefits of making a diagnosis. Treatments can also have side effects, including on sexual, urinary and/or bowel functions and health-related quality of life[13].

These recommendations are designed to minimise the over-investigation, overdiagnosis and overtreatment of early prostate cancer in this age-group while still ensuring those who would benefit from treatment are diagnosed.

In situations where prostate cancer has spread outside of the prostate gland — metastatic disease — hormone treatment may help control symptoms (but do not cure the disease).

Those who display symptoms of metastatic disease or have a very high PSA level, with no metastatic disease symptoms, are likely to benefit from a review by a urologist. The EBI recommendations are designed to ensure all these individuals are identified and referred.

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