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Prostate specific antigen

This article forms part of our 'Tests and results' series for 2011 which aims to provide information about common tests that general practitioners order regularly. It considers areas such as indications, what to tell the patient, what the test can and cannot tell you, and interpretation of results.

Keywords: prostate-specific antigen

What is the prostate specific antigen test?

Prostate specific antigen (PSA) is a glycoprotein produced solely by the prostate. Its function is to liquefy semen. Small amounts leak into the bloodstream, where it can be measured. Prostate specific antigen is tissue-specific but not cancer-specific. Elevated levels can occur in men with benign prostatic hypertrophy (BPH), prostatitis, urinary tract infection or prostatic infarction. Elevation also may occur after prostate biopsy, aggressive digital rectal examination (DRE), ejaculation, bicycle riding and physical exercise.

The use of PSA as a screening test for prostate cancer remains controversial because no double blind, randomised controlled trial has shown that early detection reduces mortality.^{1,2} Despite this controversy, PSA provides valuable information for the general practitioner in everyday clinical practice, including monitoring of treated and untreated prostate cancer and prostatitis.

What are the indications?

Early detection of prostate cancer

Men requesting PSA testing should be counselled about the nature of the test; the information it provides, especially its limitations; and that it is possible to have prostate cancer even if their PSA

is within the 'normal' range. Currently universal screening is not recommended but, if proceeding, the combination of PSA and DRE should be encouraged to improve the predictive value of both as early detection tests.

Monitoring treatment outcomes for prostate cancer

Surgical removal of the prostate (radical prostatectomy) should stop PSA production; PSA levels fall then remain at zero. Persistence of PSA levels or rising PSA after radical surgery indicates a failure to remove the gland completely, cancer recurrence or metastases.

Similarly, a positive response to radiation or hormone treatment should drop PSA levels while any subsequent increase in PSA would suggest disease recurrence or spread.

Watchful waiting

Not all prostate cancer requires treatment and some men with nonaggressive cancers may be managed by 'watchful waiting', including serial PSA testing every 6–12 months. A gradual increase in PSA may suggest disease progression and urological intervention may be considered.

Diagnosing and monitoring prostatitis

Prostatitis can be diagnosed by a sudden rise in PSA levels combined with typical symptoms and signs (deep seated pelvic discomfort; tender, boggy prostate). A return to normal PSA levels 6 weeks after appropriate antibiotic treatment signifies a positive response to treatment.

Contraindications

There are no absolute contraindications to PSA testing. Clinician discretion is required in regards to if and when to test, and the appropriate interval between testing. Most research suggests that PSA testing is not indicated beyond 75 years unless monitoring known cancer.

Precautions

Patients need to understand that PSA is not a diagnostic test. Careful informed consent is required including explanation that invasive investigations (transrectal ultrasound [TRUS] and prostate biopsy) may be needed if PSA levels are elevated.

Medications can impact on PSA levels. Anti-androgens (eg. finasteride, dutasteride) lower PSA levels but alpha-adrenergic blockers (eg. prazosin, terazosin) do not. Cyclophosphamide, methotrexate and some herbal treatments can also affect PSA levels. Urology referrals should include details of any medications being used.

What do I tell the patient?

Informed consent is essential with careful explanation of the pros and cons of testing. The PSA test involves providing a blood sample. No special preparation is required but the test should not be taken within 24 hours of ejaculation or after bicycle riding. Medicare funding is available once every 12 months. Men with symptomatic disease can have more frequent testing.

How is PSA measured?

The PSA test is based on analysis of a single serum sample. Some variations occur between pathology providers based on differing assays. Results are expressed in ng/mL with levels of total PSA >4.0 ng/mL regarded as abnormal. The test should be repeated after 1–3 months if results are markedly different from that expected.

Age specific reference ranges,³ PSA velocity⁴ and free-to-total PSA⁵ can also be useful if considering a diagnosis of prostate cancer.

Suspicious clinical findings such as induration, a nodular prostate or a tender prostate on DRE may help with interpretation of the PSA result.

What do the results mean?

Raised PSA levels occur with BPH, prostate cancer, prostatitis, prostatic infarction, postaggressive DRE, bicycle riding or postejaculation.

Benign enlargement remains the commonest cause overall for raised PSA levels. Surgery such as transurethral resection of prostate (TURP) and less invasive laser treatments can reduce and complicate the interpretation of PSA and PSA kinetics.⁶

A sudden unexpected rise in PSA levels

suggests prostatitis, especially in conjunction with dysuria or pelvic discomfort. Early stream urine postprostate massage may occasionally yield positive culture, but in reality this is uncommon. A tender, slightly boggy prostate is more likely to confirm the diagnosis.

Prostate specific antigen provides no information about the physical characteristics of the prostate gland. Clinical examination with DRE complements PSA and is minimally invasive. Failure to undertake DRE can result in a failure to diagnose prostatitis, a hard craggy gland suspicious of cancer or an enlarged gland with BPH.

A normal blood level does not exclude cancer and patients should be reminded of this test limitation.

Methods to heighten the accuracy of PSA testing are highlighted in *Table 1*.

What are the next steps in management?

The next steps depend on the indication and clinical setting. Although advisable for all men, DRE is essential in assessing a patient with an elevated PSA as it provides valuable additional information.

Early detection of prostate cancer

Men requesting testing for prostate cancer with persistent PSA levels in the 'normal' range (and no suspicious DRE), can be offered annual testing with both PSA and DRE. Men with PSA <1.0 ng/mL on serial annual testing are at low risk of developing prostate cancer and should be reassured. The testing interval could be stretched to 2 yearly when these men reach 65 years of age. A review if symptoms develop could be offered as an alternative.

If the PSA test is unexpectedly elevated and there are no clinical features demanding more urgent investigation, it may be wise to repeat PSA testing after 1–3 months.

Prostate specific antigen (and DRE) are early detection tests used to facilitate a diagnosis of prostate cancer. If abnormal, the patient needs to be counselled about the nature of the findings. If cancer is suspected, urological referral is indicated for further investigation. This will generally consist of TRUS guided prostate biopsy where core samples of suspicious areas in the prostate are obtained and sent for histological analysis and

Gleason score.⁷ Potential side effects from biopsy include pain, infection, prostatitis, haematuria, haematospermia and blood in stools. Adequate analgesia is important and prophylactic antibiotic cover is typical.

If cancer is diagnosed, further staging tests such as a bone scan may be used, especially if PSA levels are >10 ng/mL.⁸

Watchful waiting

Some patients, especially older men, decline specialist opinion and instead opt for 6 monthly monitoring. These patients must be fully counselled about their options and should understand that a tissue diagnosis is necessary to confirm a clinical suspicion of cancer. Patient autonomy needs to be respected, but regular follow up should be encouraged and GPs are advised to use their recall register for 'watchful waiting' patients.

Monitoring disease outcomes

General practitioners have an important role for patients who have locally advanced or metastatic disease, in close liaison with the radiation oncologist and urologist. Regular PSA (eg. 6 monthly) can help monitor the impact of treatments such as brachytherapy, radiation or hormone treatment. A positive response can see PSA return to near zero levels. Although there may be a small transient rise after treatment (termed 'bounce'),⁹ serial measurements showing a gradual rise in PSA may mean disease is recurring or progressing and further pulsed treatments may be indicated.

Management of prostatitis

Treatment with antibiotics and early clinical follow up is indicated. Prostate specific antigen should be repeated after 6 weeks to ensure levels are returning to baseline.

Case study 1

James, aged 51 years, enquired about getting tested for prostate cancer. He has an uncle who developed prostate cancer in his mid 60s and his grandfather had a TURP for BPH. His GP explained the increased risk of a first degree relative developing prostate cancer, what was involved in having a DRE and what the PSA test might reveal. A prostate model was used to assist explanation – with examples of a normal

Table 1. Improving PSA testing

The following methods may heighten the accuracy of PSA testing, are also covered by Medicare and are clinically useful in assessment

Age specific PSA ranges³ are an attempt to improve the interpretation of raised PSA levels by allowing for the natural increase found with advancing years. Prostate specific antigen values are adjusted upward with advancing age. Up to 2.5 ng/mL is regarded as normal for men aged 40–49 years; up to 3.5 ng/mL for men aged 50–59 years; up to 4.5 ng/mL for men aged 60–69 years; and up to 6.5 ng/mL for men aged 70–79 years

Free-to-total PSA ratios⁵ – patients with prostate cancer have more bound PSA and thus lower free-to-total ratios. Ratios under 15% are regarded as more suspicious of cancer. (Note: this can be complex to explain to patients)

Prostate specific antigen velocity⁴ is a measure of annual increases in PSA levels of more than 0.75 ng/mL over at least 2 years. It seeks to improve the specificity of PSA based on the theory that cancer cells produce increased amounts of PSA over time

Note: PSA density¹⁰ is the ratio of serum PSA to prostate volume as measured by TRUS. It is based on the premise that cancer tissue produces higher volumes of serum PSA than benign hyperplastic disease. However, the measurement of prostate volume by TRUS is not readily available in primary care and is subject to observer variability; seriously limiting its usefulness in clinical practice

prostate, a hard craggy mass, a discrete firm nodule and a hypertrophied prostate. James was also advised that the DRE and PSA were early detection tests and could not diagnose or totally exclude prostate cancer. He was told that a normal finding on DRE combined with a low PSA (<1 ng/mL) would suggest a low likelihood of prostate cancer. He agreed to undertake a PSA test and arranged to return after a week for the result and to have a DRE.

James' PSA reading was 0.8 ng/mL. Digital rectal examination felt normal with a gland size of about 35 g, smooth regular consistency and palpable medial sulcus. In light of his family history, he was advised to undertake an annual PSA and DRE and encouraged to maintain a low fat diet and regular exercise.

Over the next 3 years, James' PSA levels rose slightly (0.9, 1.1, 1.4 ng/mL) while his DRE remained normal. He then presented feeling unwell for 3 days. His symptoms were vague but included deep-seated pelvic discomfort as well as slight discomfort on passing urine. He was afebrile with a blood pressure (BP) of 130/78. Cardiovascular, respiratory and superficial abdominal examinations were normal. The potential for a urinary tract or prostatic problem was discussed and options outlined. A PSA test was obtained followed by DRE. The DRE revealed a slightly tender

prostate. After the examination, James was asked to provide a first pass urine sample. Urinalysis was positive for leucocytes and the sample was sent for culture. A provisional diagnosis of prostatitis was made and James was commenced on ciprofloxacin 500 mg twice per day for 2 weeks.

On review 2 days later, James' symptoms had slightly improved, his PSA was 8.5 ng/mL and first pass urine sample grew *Escherichia coli*. He completed the full 2 weeks of antibiotics and his symptoms gradually disappeared. A repeat PSA after 6 weeks showed a level of 2.4 ng/mL and a repeat urine culture was normal. A further PSA test after 6 months was advised.

Case study learning points

Prostatitis remains underdiagnosed in primary care and may be confused with a urinary tract infection. Culture of first pass urine postprostatic massage is rarely positive. The more common diagnostic findings are a tender, boggy prostate on DRE together with a sudden rise in PSA that returns to normal levels after appropriate treatment. Remember to undertake the PSA test before undertaking the DRE as a vigorous prostate examination can alter the PSA result! Always consider prostatitis in men presenting with vague, deep seated pelvic pain. You will never find it if you don't consider it.

Case study 2

Peter was 63 years of age and divorced when diagnosed with prostate cancer. Serial monitoring over the previous 2 years revealed normal DRE but PSA increased from 4.1 ng/mL to 4.9 ng/mL. Before diagnosis, his PSA had reached 5.8 ng/mL and DRE revealed a small nodular area in the left lobe. Peter had been counselled both before and after the annual tests and had initially deferred urology referral.

Peter now accepted urology assessment which involved TRUS and biopsy. Two foci of adenocarcinoma were identified with Gleason scores of 7 and 6. The urologist explained treatment options (radiation treatment, brachytherapy, radical prostatectomy and watchful waiting) and Peter sought further advice from his GP. He elected to undergo nerve sparing radical prostatectomy.

Good urinary continence was achieved after 2 months but no spontaneous erections returned. He was referred to a sexual health specialist and trialled intracavernosal injections but decided against continuing after 6 months. Oral agents provided minimal assistance and were also discontinued with Peter citing a lack of a partner as a factor in his decisions.

Six months postoperation his PSA level had fallen to <0.1 ng/mL and remained there on serial testing over 12 years when he agreed to discontinue regular testing. His comorbidities from ischaemic heart disease and diabetes are now more pressing concerns, while his risk from prostate cancer recurrence is minimal.

Case study 3

Bob, aged 68 years, presented with increasing nocturia and worsening urinary stream. Rectal examination confirmed clinical suspicion of prostatic hypertrophy with a large, smooth 60 g prostate. The PSA level was 6.8 ng/mL. Bob was counselled before and after undertaking the early detection tests and accepted urology referral in view of his and his wife's concerns about prostate cancer. Urology assessment supported the clinical diagnosis of benign prostatic hypertrophy and conservative management was continued. At 12 months, Bob's PSA was 7.1 ng/mL falling to 7.0 ng/mL after a further 12 months. Digital rectal examination remained nonsuspicious with no suggestion of

cancerous nodularity or induration. During this time, his urinary stream had further deteriorated with minimal benefit from alpha-adrenergic blockers.

Further urology referral was made as his symptoms deteriorated with increasing hesitancy and slow stream. Prostate specific antigen level was now 7.4 ng/mL. Bob's urologist advised TURP which eased his urinary flow problems considerably. Initial haematuria was followed by 3 months of mild urinary incontinence before full dryness was achieved. His erectile function deteriorated and he lost ejaculatory capacity but declined sexual health review. Histopathology of prostate chips revealed benign hyperplasia with no evidence of cancer. His nocturia is now twice per night with a good urinary stream.

Resources

- A patient PSA test factsheet is available at Andrology Australia: www.andrologyaustralia.org/pageContent.asp?search=PSA&pageCode=PS1
- UK Cancer Research has patient factsheets and information for GPs: www.cancerresearchuk.org.uk
- The Mayo Clinic has further information on prostate cancer: www.mayoclinic.com/health/prostate-cancer/DS00043/TAB=indepth.

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