

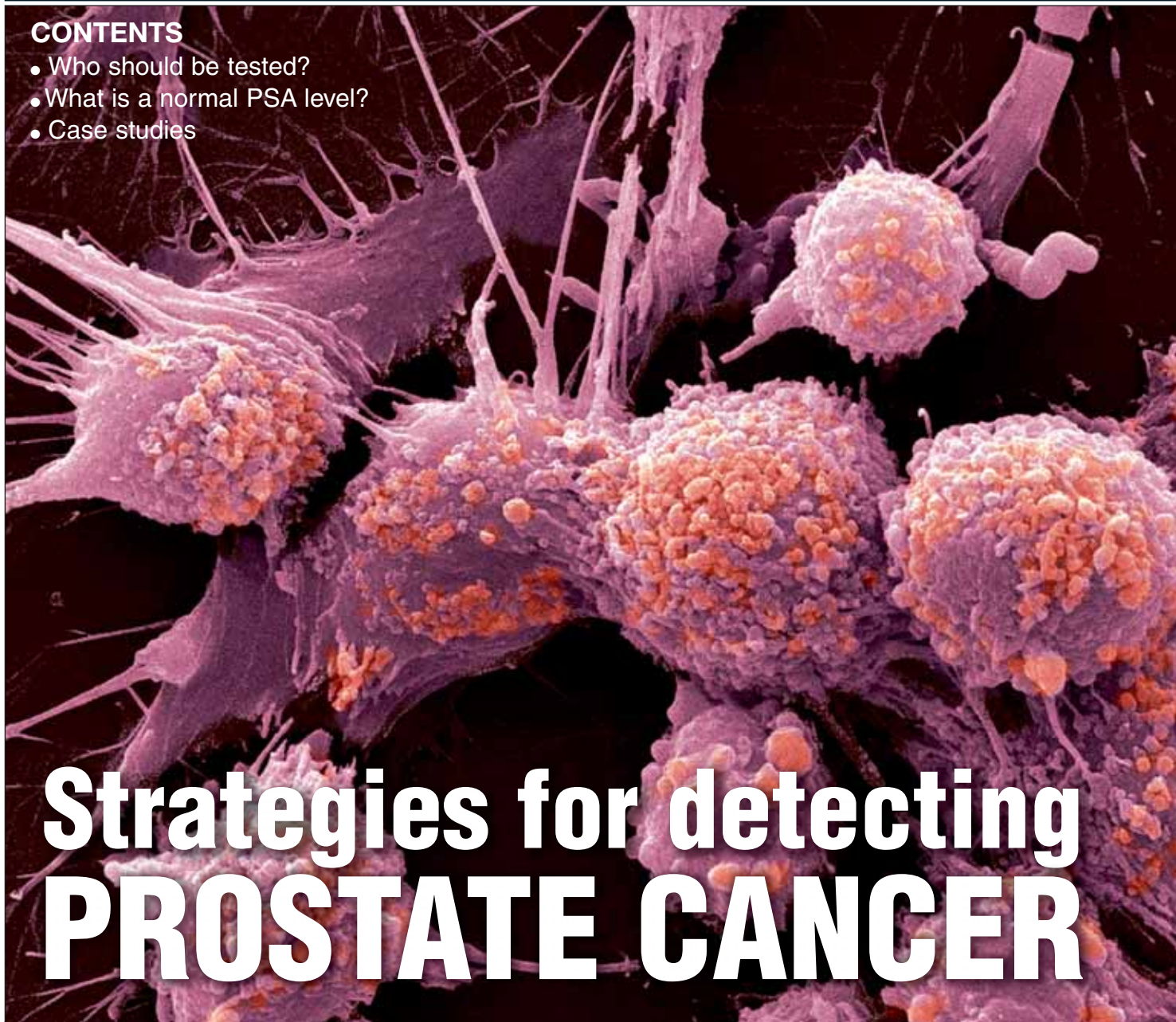
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## Common Sense Pathology

A REGULAR CASE-BASED SERIES ON PRACTICAL PATHOLOGY FOR GPs

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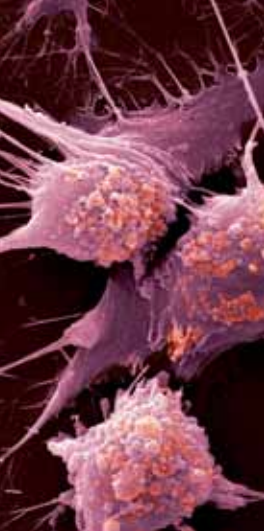


# Strategies for detecting PROSTATE CANCER

A JOINT INITIATIVE OF



Australian  
**Doctor.**



## Strategies for detecting prostate cancer



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### Introduction

Prostate cancer is a significant health issue in Australia. After non-melanoma skin cancer, it is the most commonly diagnosed malignancy in men and it is responsible for as many deaths each year as breast cancer in Australian women. Yet, unlike breast cancer, there is no national screening program despite a widespread understanding that prostate-specific antigen (PSA) testing in conjunction with digital rectal examination (DRE) facilitates early detection of this disease. The controversy is whether the use of such a strategy for mass-population screening directly results in decreased mortality rates. Establishing this relationship is important given the small incidence of adverse events from prostatic biopsy and the fact that many older men will die with prostate cancer rather than of it. In Australia, the approach to testing has been one where testing has been encouraged only with informed consent after the risks and benefits of testing have been discussed.

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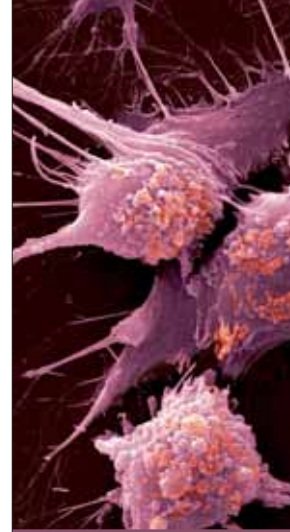
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### Prostate-specific antigen

PSA is a serine protease produced by the prostate gland epithelium to assist in liquefaction of semen. In health, a small percentage of PSA enters the bloodstream so that comparative concentrations in semen to blood are of the order of one million to one.

The most common cause of PSA elevation in the serum is probably benign prostatic hyperplasia (BPH) where an increased amount of PSA is produced by the larger-than-normal gland and, consequently, the amount of PSA escaping into the general circulation is higher than usual. Prostate cancer can also cause elevated serum levels – not necessarily due only to increased PSA production by the malignant cells but also as a result of the disruption of the integrity of the prostate gland, which allows the release of more PSA into the bloodstream. The clinical implications of the aetiology of PSA elevation are twofold: non-malignant prostate disease, such as prostatitis, can elevate the serum PSA through prostatic disruption and organ-confined cancer may not. In other words, PSA is neither 100% specific nor 100% sensitive.

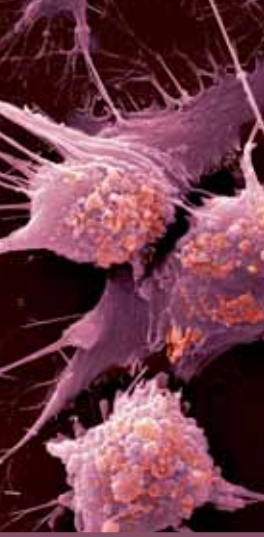
The specificity of PSA can be increased marginally by avoiding testing at times when there is an expected transient rise in serum concentra-

tions, such as within 48 hours of ejaculation and within six weeks of an episode of acute urinary retention or prostatic instrumentation (prostate biopsy or prostate surgery). Strategies devised to increase the discriminating potential of PSA, such as the establishment of age-specific reference intervals and the use of free PSA measurement, will be discussed later in this article.

### Digital rectal examination

As PSA levels may be normal in organ-confined prostate cancer, DRE of the prostate is an important adjunct to PSA testing. Areas of hardness, asymmetry of the gland or loss of the median groove are all important indicators of possible cancer and, irrespective of the PSA result, would prompt referral to a urologist for biopsy and subsequent management. A meta-analysis of studies of prostate cancer screening tests by Mistry et al. in 2003 found that DRE had an overall sensitivity of 53% (range 49-69%) and specificity of 84% (18-99.5%).<sup>1</sup>

ABOUT 15% of men undergoing prostate cancer testing by PSA and DRE will require a prostate biopsy, but about 60% of these initial biopsies will not show cancer when the PSA lies in the 4-10µg/L range.



### **Who should be tested for prostate cancer?**

Mass screening for prostate cancer is not advocated in Australia. Instead, the decision of whom to test is left to clinical judgement. Selecting only symptomatic patients is not a feasible strategy as poor urinary stream and other lower tract symptoms are more often than not associated with BPH while organ-confined prostate cancer is typically asymptomatic.

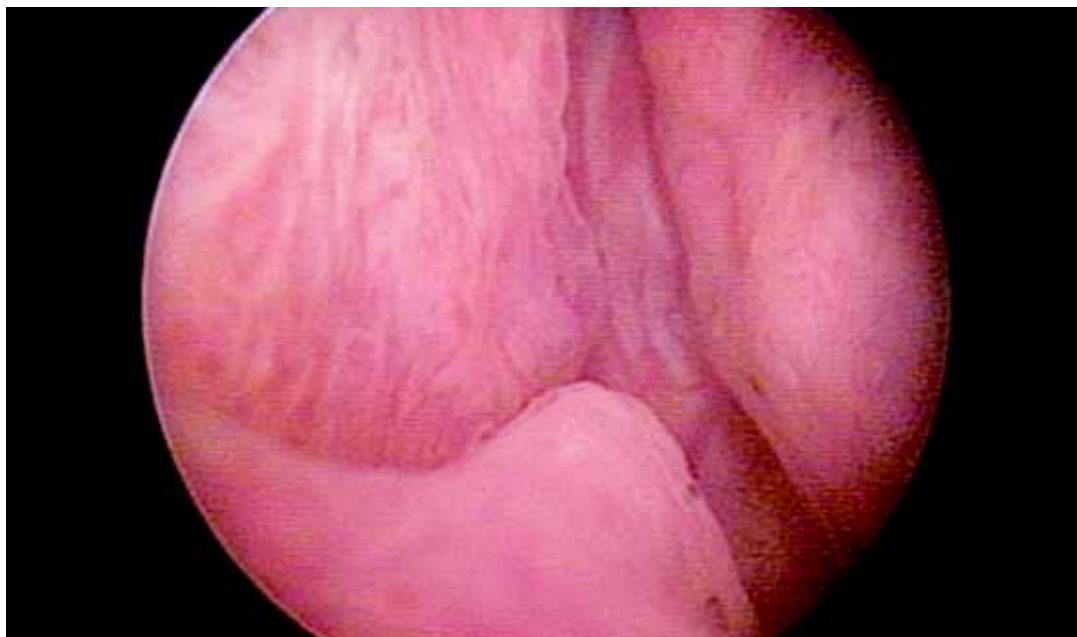
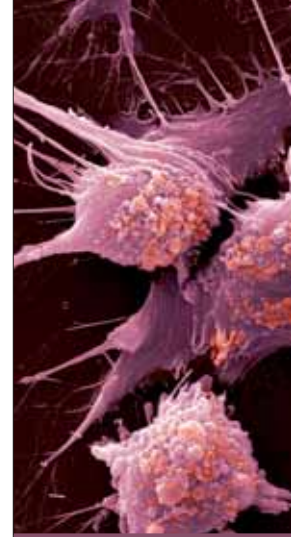
Age is the most significant risk factor for prostate cancer. Diagnosis before the age of 40 is rare but the incidence increases steadily from one in 1000 for men in their 40s to 80 in 1000 for men in their 70s. The risk is 2-3 times higher for those with a first-degree relative (father or brother) diagnosed with prostate cancer before the age of 60.

The Urological Society of Australia and New Zealand supports the selective screening of men based on age. It suggests an annual PSA and DRE in those men between the ages of 50 and 70 years who have a life expectancy of at least 10 years. For men with a positive family history, screening should be considered from 40 years of age. For all individuals, testing should proceed

only after informed consent has been obtained and appropriate counselling has been given regarding the potential risks and limitations of the testing process. Consideration should also be given to the fact that, while the lifetime risk of developing microscopic prostate cancer is 30%, the risk of a cancer becoming apparent or causing problems is only 10% and the lifetime risk of actually dying from prostate cancer is only 2-3%.

### **What is a normal PSA level?**

Total PSA levels above 4µg/L are commonly considered to be abnormal. This threshold was established from a study in the mid-1980s of 472 young men without prostate cancer using one of the first assays available from Hybritech. At levels greater than 4µg/L, the positive predictive value for cancer is of the order of 30% (25% if the total PSA level lies between 4µg/L and 10µg/L and about 60% when the total PSA is greater than 10µg/L). So, although elevated PSA levels may indicate malignancy, the majority of levels between 4µg/L and 10µg/L are due to benign disease, reminding us that PSA is prostate specific but not cancer specific. When prostate



**Endoscopy image showing an enlarged prostate due to benign prostatic hyperplasia.**

cancer is discovered at PSA levels between  $4\mu\text{g/L}$  and  $10\mu\text{g/L}$ , almost 75% of cancers are organ confined, potentially curable and thus worth finding. At levels above  $10\mu\text{g/L}$ , the proportion of organ-confined cancer falls to 50%.

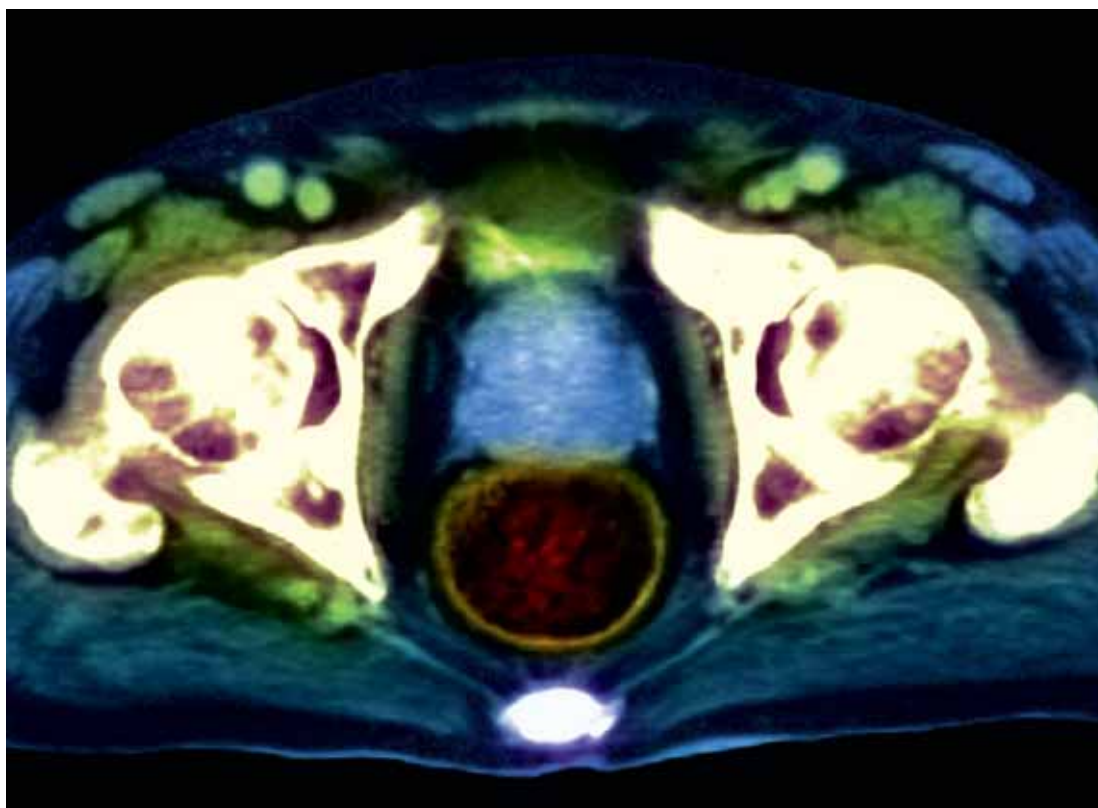
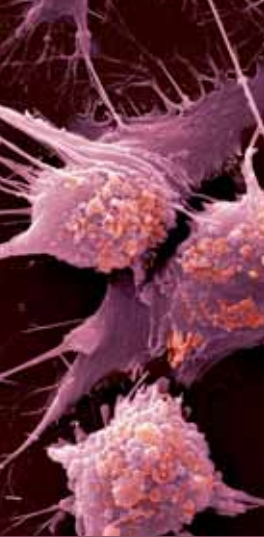
What has not been widely appreciated until recently is that the risk of cancer at PSA levels below  $4\mu\text{g/L}$  is also significant. Of 2950 men in the placebo arm of the Prostate Cancer Prevention Trial, all of whom had a serum PSA level less than  $4\mu\text{g/L}$ , 15% had prostate cancer on biopsy and, of these, 15% were classified as high grade (Gleason score 7 or higher).<sup>2</sup> Further analysis of these figures show that even if a PSA cut-off of  $0.5\mu\text{g/L}$  was used, cancers were still missed. However, the clinical benefit of detecting cancers at such low PSA levels is questionable as the proportion of high-grade lesions in this group was considerably less (12.5% compared with 25% of cancers found in the PSA range of  $3.1\text{--}4\mu\text{g/L}$ ). In deciding which levels of PSA are clinically significant, it should be noted that a moderate incidence of high-grade cancers occurs where the PSA lies between  $2\mu\text{g/L}$  and  $4\mu\text{g/L}$ , a range which is usually defined as normal.

The substantial overlap that exists in PSA levels between men with and without prostate cancer makes it difficult to separate 'normal' from 'abnormal' levels and highlights the trade-off between sensitivity (not missing cancers) and specificity (minimising the number of unnecessary biopsies). The use of age-related reference intervals has been proposed as a way of achieving some balance in the approach to testing.

### **Age-specific reference intervals**

PSA levels increase with age in the absence of prostate cancer and are probably due to the increasing incidence of BPH in older men. Oesterling and colleagues, noting the direct correlation between age, serum PSA concentration and prostatic volume, studied PSA distribution in 471 healthy men and proposed age-specific reference intervals to replace the 'one-size-fits-all' traditional PSA cutoff of  $4\mu\text{g/L}$ .<sup>3</sup> They suggested the following 'normal' ranges:

- 40 to 49 years: 0 to  $2.5\mu\text{g/L}$
- 50 to 59 years: 0 to  $3.5\mu\text{g/L}$
- 60 to 69 years: 0 to  $4.5\mu\text{g/L}$
- 70 to 79 years: 0 to  $6.5\mu\text{g/L}$



Coloured MRI scan of an axial section of the pelvis showing prostate cancer.

These ranges effectively raise the PSA biopsy threshold in older men, increasing specificity and reducing the number of unnecessary biopsies. For younger men, the threshold is lowered to improve sensitivity, especially for early-stage and potentially curable malignancy. The ranges developed by Oesterling are commonly quoted but, where available, analyser-specific ranges should be used, as variations do exist between results produced by different assay methodologies and different assay standardisation.

### PSA density

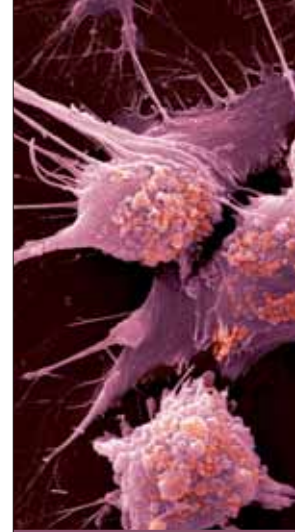
The relationship between prostate volume and PSA level is also the basis for PSA density – the adjustment of PSA levels for the size of the prostate as determined by transrectal ultrasonography (TRUS) or MRI. Difficulties in obtaining accurate and consistent prostate volume assessments limit the application of this strategy.

### PSA velocity

PSA velocity – the rate of increase in PSA over a period of time – is another strategy devised to differentiate between benign disease and prostate cancer. Increases of more than  $0.75\mu\text{g/L}$  per year are generally considered to be abnormal. However, this may also be seen within the range of daily biological variation. Establishing an accurate pattern of increase typically involves multiple samples taken over months to years. Calculating personal PSA doubling times has been proposed as a more practical approach.

### Free-to-total PSA ratio

The majority of PSA in the general circulation is protein bound (mostly to alpha-1-antichymotrypsin), with a small component existing in the free form. Total PSA measurement in serum detects both free and such bound, complexed forms. However, the free, unbound PSA compo-



ment can be measured also. In normal, benign situations, the ratio of free-to-total PSA in the circulation is usually greater than 25%. Although theories exist about differing clearance rates and preferential production of complexed PSA by cancer cells, the explanation behind why low levels of free-to-total PSA ratios are mostly associated with prostate cancer remains unclear. In practice, using the ratio to distinguish BPH from cancer in order to decide when to biopsy is not always straightforward, as there is a 'grey zone' of values that is generally acknowledged as equivocal.

In addition, free PSA is not particularly stable in vitro under normal handling and storage conditions. Analysis is recommended within 24 hours of collection, making retrospective (that is, 'add on') testing unreliable unless serum has been frozen from separation. Bypassing this problem by measuring complexed PSA, which is not unstable under normal conditions, and subtracting this from the total PSA to derive the free PSA is possible, but not all laboratories offer this assay.

## PSA medians

Currently the Australian Medicare Benefits Schedule supports the measurement of free-to-total PSA ratio when the total PSA is equivocal, but does not define what is meant by 'equivocal'. Traditionally, this has been taken to mean total PSA levels of between 4µg/L and 10µg/L but, for reasons discussed previously, levels between the age-specific reference interval and 10µg/L are more appropriate.

However, as demonstrated in the placebo-arm study of the Prostate Cancer Prevention Trial,<sup>2</sup> prostate cancer is seen at lower PSA levels and, in addition, studies such as the Baltimore Longitudinal Study of Aging have shown that men with PSA levels above their age-specific median value (that is, 50th centile for their age group) carry the greatest long-term risk of developing prostate cancer.<sup>4</sup> It is perhaps this group that deserves more attention in the form of free-to-total PSA testing. Age-specific median values are not commonly reported by laboratories at present but have been reported in the literature and, where possible, should relate to the analyser being used to measure it.

## Case 1

Mr A is a 60-year-old man who presents the first time for testing. He has a total PSA of 6µg/L.

### *Is a DRE necessary?*

Yes. DRE provides information additional to PSA measurement.

### *What would be a reasonable approach to the management of this patient?*

It is important to take a history and consider all causes of a raised PSA, including prostatitis and other non-malignant conditions. If an associated infection is suspected, treatment is warranted and the PSA should be remeasured afterwards. The best group of antibiotics in this setting are the quinolones and a suitable regime would be norfloxacin 400mg bd for 14 days.

Even when antibiotics are not prescribed, it is worthwhile to repeat the total PSA to eliminate unrecognised causes of transient PSA elevation. Repeating the test in 3-4 weeks is reasonable although there is no evidence to support this time-frame particularly. The total PSA should be repeated with a free-to-total ratio after the patient has abstained from ejaculation for 48 hours before the blood is taken. If the PSA is still elevated or the free-to-total ratio is low or equivocal then referral to a urologist for assessment and consideration of a prostatic biopsy would be appropriate.

## Case 2

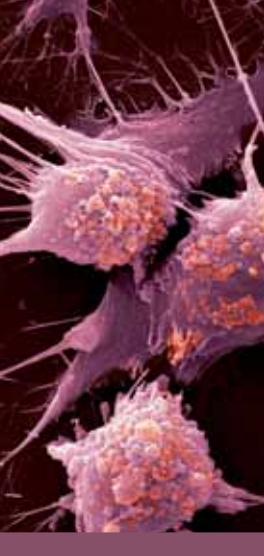
Mr B is a 50-year-old man with a total PSA of 3.1µg/L.

### *Is the free-to-total PSA ratio of use here?*

Yes, the result is above the median for his age, which, according to findings in the Baltimore Longitudinal Study of Aging, for men aged 50-59.9 years is 0.70µg/L. Measuring the ratio here further clarifies his risk.

### *The ratio comes back at 8% (low). What would be a reasonable management plan for this patient?*

A history must be taken, checking particularly for a family history of prostate cancer. This level of PSA is of concern as it is both above the median for his age and is associated with a low free-to-total ratio. This patient would be advised to accept referral to a urologist for consideration of biopsy.



### Case 3

Mr C is a 69-year-old man with a history of ischaemic heart disease, coronary artery bypass grafts and congestive cardiac failure with a total PSA of 9µg/L and a free-to-total ratio of 30% (high). DRE reveals a large, benign gland.

#### *Does he require any follow-up?*

Yes, he should be followed up, given his high PSA level.

#### *What issues should be considered in pursuing the cause of PSA elevation in this patient?*

There is a high likelihood that his elevated PSA is due to largely benign prostatic changes and the risk of cancer may therefore be low. Also, due to his age and co-morbid medical illnesses, he may not have a 10-15-year life expectancy and therefore may not benefit from the early detection and treatment of an asymptomatic prostate cancer.

### KEY POINTS

- Prostate cancer is common but death from prostate cancer is not.
- Age-related testing in the form of an annual PSA and DRE is generally supported from the age of 50 (or 40 if a significant family history exists) in men with at least 10 years' life expectancy after discussion with the patient.
- Age-related reference intervals increase the specificity and sensitivity of PSA for cancer.
- Beware the young man with a borderline PSA and low free-to-total PSA ratio.
- The free-to-total PSA ratio may assist in differentiating between benign conditions of the prostate and malignancy. It is best utilised at PSA levels that lie between the age-relevant median and 10µg/L.

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### FURTHER READING

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