

***Prostate specific antigen  
(PSA) near patient testing  
for diagnosis and  
management of prostate  
cancer***

**May 2005**

MSAC Application 1068

**Assessment report**

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

#### **MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.**

This report was prepared by the Medical Services Advisory Committee with the assistance of Dr Omar Abdulwadud, Ms Ornella Clavisi, Ms Anne Parkhill, Ms Sharon King, and Dr Jillian Broadbear from the Institute of Health Services Research and Mr Andrew Dalton (Health Economist) of AD Health Pty Ltd. The report was edited by Dr Alana Mitchell, ScienceLink Pty Ltd. The report was endorsed by the Minister for Health and Ageing on 4 July 2005.

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# Contents

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<b>Executive summary</b> .....	<b>v</b>
<b>Introduction</b> .....	<b>1</b>
<b>Background</b> .....	<b>2</b>
The procedure .....	3
Clinical need/burden of disease.....	6
Reference standard.....	7
Comparator .....	7
Marketing status of the technology .....	7
Current reimbursement arrangement.....	7
<b>Approach to assessment</b> .....	<b>9</b>
Review of literature.....	9
Expert advice .....	16
<b>Results of assessment</b> .....	<b>17</b>
Is it safe? .....	18
Is it effective? .....	18
What are the economic considerations? .....	21
<b>Conclusions</b> .....	<b>23</b>
Safety.....	23
Effectiveness.....	23
Cost-effectiveness .....	23
<b>Recommendation</b> .....	<b>24</b>
<b>Appendix A MSAC terms of reference and membership</b> .....	<b>25</b>
<b>Appendix B Advisory Panel</b> .....	<b>27</b>
<b>Appendix C Search strategies</b> .....	<b>29</b>
<b>Appendix D Internet sites searched</b> .....	<b>31</b>
<b>Appendix E Study included for critical appraisal</b> .....	<b>34</b>
<b>Appendix F Studies excluded from critical appraisal</b> .....	<b>35</b>
<b>Abbreviations</b> .....	<b>39</b>
<b>References</b> .....	<b>40</b>

## Tables

Table 1	The Australian Cancer Network Working Party on Management of Localised Prostate Cancer (2003) clinical practice guidelines for the management of localised prostate cancer .....	6
Table 2	The total number of services for PSA testing under MBS item numbers 66655, 66656 and 66659 (Australia) .....	8
Table 3	Electronic databases used in this review.....	9
Table 4	Inclusion and exclusion criteria for diagnostic accuracy of PSA near patient testing.....	10
Table 5	Inclusion and exclusion criteria for patient management and health outcomes following PSA near patient testing .....	10
Table 6	Criteria and definitions for assessing validity of diagnostic studies .....	11
Table 7	The generic relationship between results of the diagnostic test and disease status .....	12
Table 8	Evidence dimensions.....	14
Table 9	Designations of levels of evidence .....	15
Table 10	Validity criteria according to study design.....	15
Table 11	Descriptive characteristics of the included primary study (Berg et al 2001).....	18
Table 12	Validity of included primary study .....	20
Table 13	Outcomes measured and results of PSA testing (Berg et al 2001) .....	20
Table 14	Additional information on costs provided by the Applicant.....	22
Table C1	Cost-effectiveness terms for Medline .....	29

## Figures

Figure 1	Flowchart demonstrating the selection process for the effectiveness search .....	17
Figure 2	PSA one-step test system used in Berg et al (2001) .....	19

# Executive summary

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## The procedure

### Prostate specific antigen testing

Prostate specific antigen (PSA) is an enzyme (protein) produced by the prostate gland of adult men. If the prostate gland is enlarged, diseased or infected increased amounts of PSA circulate in the bloodstream and can be measured.

Testing for PSA in blood is usually performed by immunoassay. The PSA level in the blood is expressed in units of nanogram per millilitre (ng/mL) and in most diagnostic laboratories the turn-around time is less than 24 hours.

Funding for PSA testing is currently available through Medicare and the test is listed on the Pathology Services Table as items 66655, 66656 and 66659. The test is usually performed in accredited Pathology Laboratory (categories GX, GY and B) but may be performed under the supervision of other medical practitioners in suitably accredited category M (general practitioner) or category S (medical specialist) laboratories.

The application was for a PSA test for indications that are already listed on the MBS and no higher funding is sought. It proposed PSA testing should be performed by specialists in their offices for the diagnosis and management of prostate cancer. This review evaluated the available evidence concerning PSA point of care testing by specialist clinicians for the diagnosis and management of prostate cancer by all methods, including the Qualigen FastPack<sup>TM</sup> PSA Immunoassay and FastPack<sup>TM</sup> Analyzer, for which the application was made.

### Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the Institute of Health Services Research, Monash University, conducted a systematic review of the literature on the value of PSA near patient testing by specialists for diagnosis and management of prostate cancer. An Advisory Panel with expertise in this area then evaluated the evidence and provided advice to the MSAC.

# **MSAC's assessment of Prostate Specific Antigen (PSA) near patient testing for diagnosis and management of prostate cancer**

## **Clinical need**

The prostate is a gland in the male that surrounds the neck of the bladder and the urethra and contributes to the seminal fluid a secretion that contains acid phosphatase, citric acid and proteolytic enzymes. In men over 50 years, the gland can become enlarged due to benign prostate hyperplasia, hypertrophy or malignant prostate cancer. The development of malignant prostate cancer is slow and is linked with age, family history, certain diets and exposure to occupational toxins.

The symptoms of prostate cancer include problems with micturition, slow urine flow with trickling at the end, increased urinary frequency (mostly at night), a burning sensation on micturition, pain in the back or thigh and blood in the urine.

In Australia, prostate cancer is the most common cancer in men and the second most common cause of cancer death. In 2000, there were 10, 512 new cases (age-standardised incidence rate of 124.9 per 100,000), and 2,665 deaths (age-standardised mortality rate of 35.9 per 100,000) from prostate cancer.

## **Reference standard**

Histology was the appropriate reference standard to validate the diagnostic performance of PSA near patient testing.

## **Comparator**

The comparator was the current practice namely, PSA testing by accredited pathology laboratories or any other PSA testing method outside of a laboratory setting.

## **Safety**

A broad literature search failed to identify any relevant studies on the safety, psychological or psychosocial impact of PSA near patient testing.

## **Effectiveness**

To date, there was one published study that had marginally addressed the concept of PSA near patient testing. It was a pilot study of PSA testing in a pharmacy setting and was conducted in the context of screening in a city with a population of 100,000. The study failed to fully meet the eligibility criteria and did not answer the primary research questions for the current review.

In conclusion, there is insufficient evidence to indicate that PSA near patient testing by specialists is superior to PSA testing in a laboratory setting. Further research is needed to evaluate the safety, effectiveness and cost effectiveness of PSA near patient testing.

Notably, although the 18 month trial currently underway in primary care setting does not include PSA testing, it could provide practical information on the clinical effectiveness, cost effectiveness and safety of near patient testing in general.

### **Cost-effectiveness**

Insufficient evidence exists upon which to base an economic evaluation of PSA near patient testing. Due to limited data on the relative effectiveness of PSA near patient testing compared with laboratory testing, it was not possible to estimate the cost-effectiveness of the test.

However, it is relevant to note that the applicant had provided an estimate of the cost per test of point of care PSA testing that was higher than that of current laboratory cost.

These observations do not support a cost-effective finding for PSA near patient testing.

### **Recommendation**

MSAC recommended that on the strength of evidence pertaining to the safety, effectiveness and cost effectiveness of prostate specific antigen testing for the diagnosis and management of prostate cancer, the current funding arrangements remain unchanged.

The Minister for Health and Ageing endorsed MSAC's recommendation on 4 July 2005.





# Introduction

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The Medical Services Advisory Committee (MSAC) has reviewed the use of prostate specific antigen (PSA) near patient testing by specialists for diagnosis and management of prostate cancer. The MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. The MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

The MSAC's terms of reference and membership are presented in Appendix A. The MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for the safety, effectiveness and cost-effectiveness of PSA near patient testing by specialists for diagnosis and management of prostate cancer. Explicitly, the research questions were:

- Compared with the current PSA testing method, what is the diagnostic accuracy and patient-related benefit of PSA near patient testing by specialists for diagnosis and management of prostate cancer?
- What are the implications of PSA near patient testing by specialists for clinical practice, quality control and patient management?
- What is the economic significance of funding PSA near patient testing by specialists in the context of an Australian setting in the event that effectiveness of this diagnostic test is established?

# Background

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## Intended purpose

Accredited pathology laboratories in Australia currently perform PSA testing. The application is for a PSA test for indications that are already listed on the MBS and no higher funding is sought. It proposes PSA testing by specialists in their offices (not primary care settings) for the diagnosis and management of prostate cancer. The profile of the proposed technology is described under 'Marketing status of the technology'.

Generally, near patient testing is defined as a pathological test performed in the doctor's surgery during the consultation time to produce immediate results to assist in the care of the patient (Department of Health and Ageing, 2004). Near patient testing may also be called bedside or point of care testing.

This review evaluated the available evidence concerning PSA near patient testing by specialist clinicians for the diagnosis and management of prostate cancer by all methods, including the Qualigen FastPack™ PSA Immunoassay and FastPack™ Analyzer, for which the current application is made.

## Prostate specific antigen

Prostate specific antigen is an enzyme (protein) involved in the liquefaction of seminal fluid that is produced by the prostate gland. It is found free in blood serum, but is most commonly detected by immunoassay bound to its substrate, anti-chymotrypsin. Both free and bound PSA have been associated with variations in the measurement of PSA, which has a half-life of 2–3 days (Sheehan 1998).

PSA has been used as a biological marker for prostate cancer since the 1980s. The normal prostate releases small amounts of PSA and a cancerous prostate releases large amounts of PSA into the bloodstream. Thus, the level of PSA in the bloodstream may indicate the presence of abnormal cancerous cells in the prostate. PSA levels above 4 ng/mL indicate an abnormality (Sheehan 1998), although it has been shown that two-thirds of all patients detected with elevated PSA levels do not have prostate cancer (The Cancer Council Australia 2004).

PSA is also produced in the peri-urethral and peri-anal glands and breast tissue of men. PSA is not specific to the type of tumour (benign or malignant). Moreover, elevated PSA level is also a marker of conditions other than prostate cancer, such as urinary retention and prostatitis (Cookson 2001, Sheehan 1998). A biopsy is needed to confirm that a patient has prostate cancer.

## The procedure

### Prostate specific antigen testing

Attempts have been made to clarify the diagnosis of prostate cancer using alternative methods to total PSA levels in the blood. These alternative methods have included analysis of PSA velocity, PSA density, the ratio of free to bound PSA and reverse transcription (RT)-PCR of PSA (Cookson 2001, Sheehan 1998).

- PSA velocity refers to the rate of increase in PSA levels in the blood over time. It has been suggested that a PSA velocity increase of greater than 20% per year increases the likelihood that the patient has prostate cancer. However this measurement of PSA has been shown to be of limited use.
- PSA density refers to the levels of PSA produced in the blood serum divided by the prostate volume. PSA density was thought to be a way of distinguishing between prostate cancer and benign prostate hypertrophy (BPH). The PSA density for patients with prostate cancer is usually ten times greater than that of BPH patients. A cut-off point of 0.15 is generally used, whereby a value of less than 0.15 is more likely to be benign and one greater than 0.15 is more likely to be prostate cancer. This measure has been criticized for being highly variable and too difficult to allow accurate determination of the cancer type.
- The percentage of free PSA is a measure of the amount of PSA that circulates in the bloodstream unbound to its substrate. Free PSA has been shown to be lower in patients with prostate cancer than those with BPH.
- RT-PCR of PSA is a measure of the amount of PSA mRNA in the bloodstream and indicates the prostate cancer's level of aggression.

PSA testing has been shown to be moderately accurate when compared to the reference standard of a prostate biopsy. When the PSA cut-off point is set at 4 ng/mL, the sensitivity, specificity, positive likelihood ratio (LR+) and the negative likelihood ratio (LR-) are 86%, 33%, 1.28 and 0.42, respectively. Furthermore, the sensitivity of the test increases when the patient's age and the type of PSA measurement are taken into account. An increase in age of the patients (from 40–49 years to  $\geq 70$  years) increased the sensitivity from 75 to 90, however this was accompanied by decreases in specificity from 55 to 27, in LR+ from 1.68 to 1.23 and in LR- from 0.45 to 0.37.

The sensitivity can be further improved by lowering the cut-off value, however this lowers the specificity of the test (Hoffman et al 2002). The sensitivity of the PSA test can also be increased by including measurements of free to bound PSA, PSA density and the rates of change in the PSA velocity (The Cancer Council Australia 2004, Hobbs et al 1997).

## **Current procedure for detection and diagnosis of prostate cancer**

### **Diagnosis of prostate cancer**

There are different tests for the diagnosis of prostate cancer. They include a blood test (PSA testing), digital rectal examination (DRE) and biopsy. However a biopsy is the only method of diagnosis to confirm prostate cancer (Australian Prostate Cancer Collaboration 2003).

#### **1. Blood test (PSA testing)**

The blood test for the detection of PSA levels has been described.

#### **2. Digital rectal examination**

Digital rectal examination (DRE) is a procedure to examine the surface of the prostate gland across the rectal wall by inserting a finger into the rectum. A normal prostate gland usually has a soft surface. A malignancy usually causes the surface of the gland to become hard and often asymmetrical or stony (Oncologychannel 2004). Limitations of the effectiveness of this test include subjective differences between doctors and the likelihood that abnormalities of the prostate gland will be missed (The Cancer Council Australia 2004).

#### **3. Prostate biopsy**

Prostate biopsy is a surgical procedure whereby a small piece of prostate tissue is removed for microscopic examination (Medical Network Inc. 2005).

Prostate biopsy is recommended when a DRE reveals a lump or some other abnormality in the prostate or if a blood test reveals that the levels of certain markers, such as PSA, are above normal (Medical Network Inc. 2005). However, there is variability in the site of sampling that may cause a malignant region to be missed (The Cancer Council Australia 2004).

The procedure can be performed by inserting a needle through the perineum or the wall of the rectum, or by cytoscopy. Before the procedure is performed, the patient may be given a sedative to help him relax and will be required to have an enema. Patients undergoing cytoscopy will be given either general or local anaesthesia. The patient will be given antibiotics to lower the risk of infection (Medical Network Inc. 2005).

## **Treatment of prostate cancer**

In clinical practice, different treatment options are available for patients with localised prostate cancer. Treatment decisions are based on the nature of the cancer, the patient's general state of health and personal preferences, and the benefits and risks of all options, including no treatment at all. Prostate cancer can be treated with surgery, radiation, hormones and chemotherapy. In the earliest stages of the disease, a prostatectomy and radiation are often sufficient to eliminate the threat of this disease. Once the disease has progressed to metastatic cancer, treatment usually involves hormonal therapy. Hormone therapy suppresses prostate cancer growth by suppressing androgen levels in the body (Burke 2002).

## Post-treatment management of prostate cancer

The two methods commonly used to evaluate tumour progression and treatment outcomes are histological monitoring and biochemical measures such as serum PSA level (Australian Cancer Network Working Party on Management of Localised Prostate Cancer 2003).

Histological monitoring has become less common as an intermediate end point for survival data. Both the findings of positive surgical margins and positive repeat biopsy post radiotherapy have been shown to have inter-observer variation and poorer predictive value as an indicator for clinical failure than PSA levels (Australian Cancer Network Working Party on Management of Localised Prostate Cancer 2003).

The PSA test has dramatically refined definitions of treatment failure. An increasing PSA level after treatment indicates persistent local disease, development of subclinical metastases or both. Biochemical relapse may precede clinical failure by months to years. Rising PSA levels have become intermediate end points, where the effectiveness of treatment can be evaluated much sooner than evidence of clinical failure or mortality. The interval from biochemical failure to clinical failure has also been shown to be predictable on the basis of the rate of increase of PSA. However, the definition of biochemical failure varies between studies. For example, some studies use a rise above 1.0 ng/mL as evidence of biochemical failure while others require a rise of more than 4.0 ng/mL or a relative rise in the PSA level as their index (Australian Cancer Network Working Party on Management of Localised Prostate Cancer 2003).

## Management guidelines

The Australian Cancer Network Working Party on Management of Localised Prostate Cancer (2003) has produced evidence-based clinical practice guidelines for the management of localised prostate cancer (Table 1). This guideline is accredited and published by the National Health and Medical Research Council (NHMRC). The guideline is adapted from the American Urological Association (AUA) guidelines.

**Table 1 The Australian Cancer Network Working Party on Management of Localised Prostate Cancer (2003) clinical practice guidelines for the management of localised prostate cancer**

Recommendations	Type of recommendation	Remarks
Assess patient's life expectancy, overall health status and tumour characteristics before treatment decisions	Standard <sup>a</sup>	Necessary before any treatment decisions could be made
Provide information on benefits and harms of available treatments to patients	Standard <sup>a</sup>	Inform and discuss about the commonly accepted initial interventions (radical prostatectomy, radiotherapy and no initial treatment), estimates for benefits and harms of each intervention, less commonly-used treatments (eg cryotherapy), and the degree to which they are supported by evidence
Incorporate patient preferences into treatment decisions	Standard <sup>a</sup>	To determine treatment, consider patient's preference and the benefits and harms of the different interventions. Recognise psychosocial factors (the need for education towards therapeutic choices optimal for the individual patient)
Treatment recommendations	Options <sup>b</sup>	Treatment options include radical prostatectomy, radiotherapy and no treatment. Radiotherapy includes external beam and interstitial radiotherapy (brachytherapy). To date, no sufficient evidence suggests the superiority of any one form of treatment for localised prostate cancer.

<sup>a</sup> A policy was considered a standard if the health and economic outcomes of the alternative interventions are sufficiently well-known to permit meaningful decisions and there is virtual unanimity about which intervention is preferred

<sup>b</sup> A policy was considered an option if the health and economic outcomes of the interventions were not sufficiently well known to permit meaningful decisions, preferences among the outcomes were not known and patient's preferences were divided among alternative interventions, and/or patients were indifferent about the alternative interventions

## Clinical need/burden of disease

The prostate is a gland in the male that surrounds the neck of the bladder and the urethra and contributes to the seminal fluid a secretion that contains acid phosphatase, citric acid and proteolytic enzymes. For men over the age of 50, the gland can become enlarged for reasons such as benign prostatic hyperplasia, hypertrophy or malignant prostate cancer. Malignant prostate cancer is sometimes slow in development and is linked with age, family history, certain diets and exposure to occupational toxins (Lavelle 2003, The Cancer Council South Australia 2003).

The symptoms of prostate cancer are centred on having difficulty urinating and include problems in commencing the flow of urine, slow urine flow with trickling at the end, urinary frequency (particularly nocturia), dysuria, pain in the back or thigh and blood in the urine (Lavelle 2003, The Cancer Council South Australia 2003).

## Incidence, prevalence and mortality

The risk of prostate cancer increases with increasing age and family history (Australian Institute of Health and Welfare 2003). The prevalence of prostate cancer in older men is 50–70 per cent and there is a fourfold increase in the risk of prostate cancer if a brother or father has prostate cancer. Foods high in fat (particularly animal fat) and vitamin A and foods low in vitamin D are linked to an increased risk of prostate cancer. Furthermore, the level of testosterone and activity of the enzyme 5-alpha reductase are also associated with the incidence of prostate cancer (Sheehan 1998).

Figures from the year 2000 (Australian Institute of Health and Welfare 2003) show that there were 10, 512 new cases (age-standardised incidence rate of 124.9 per 100,000) in

Australia, and 2, 665 deaths from prostate cancer (age-standardised mortality rate of 35.9 per 100,000).

## Reference standard

Histology was the reference standard. The procedure involves taking and examining tissue samples from the prostate for any abnormality and cancerous cells.

## Comparator

The comparator is PSA testing by accredited pathology laboratories or any other PSA testing method conducted outside the laboratory setting.

## Marketing status of the technology

The FastPack™ PSA Immunoassay and FastPack™ Analyzer System for PSA testing is not exempt from the regulatory requirements of the Therapeutic Goods Act 1989. The device has been registered with the Therapeutic Goods Administration (registration number AUSTL 97228) under the name of 'Qualigen INC in vitro diagnostic kits of human or IGIN (various)'.

The FastPack™ PSA Immunoassay and the FastPack™ Analyzer System have been granted marketing clearance in the United States, subject to the general controls provisions of the Federal Food and Drug Administration. The general controls provisions of the Act, which include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Explicitly, it was cleared for marketing for the following indications:

The FastPack™ PSA Immunoassay is a paramagnetic particle chemiluminescence immunoassay for the in vitro quantitative determination of prostate specific antigen (PSA) in human serum. This PSA Immunoassay is indicated as an aid in the management of patients with prostate cancer and is designed for use with the FastPack™ Analyzer System.

The device was not cleared to be used as a point of care test or for use in physicians' offices, but as a prescription device for use by trained technicians in a hospital laboratory.

## Current reimbursement arrangement

Currently there is listing on the Australian Medicare Benefits Schedule (MBS) for PSA testing. Under the current arrangement, the test is listed on the Pathology Services Table as items 66655, 66656 and 66659. The test is usually performed by an accredited pathology laboratory (categories GX, GY and B), but may be performed under the supervision of other medical practitioners in suitably accredited category M (general practitioner) or category S (medical specialist) laboratories. Item number 66655 provides one test per patient episode in a 12-month period to determine the PSA level. A test done under Item number 66656 is for quantitation of PSA to monitor previously diagnosed prostate disease (including a test described in item 66655). A test carried out

under Item number 66659 should be for quantitation of 2 or more fractions of PSA and any derived index including (if performed) a test described in item 66656, in the follow-up of a PSA result which lies in the equivocal range of the particular method of assay used to determine the level. Moreover, Item number 66659 covers one patient episode in a 12-month period.

Table 2 shows the total number of PSA tests used in Australia under MBS item numbers 66655, 66656 and 66659 between 2001 and 2003. In 2003 alone, a total of 535,054, 327,891, and 20,667 services were claimed, respectively.

**Table 2 The total number of services for PSA testing in Australia**

MBS Item number	Total services		
	2001	2002	2003
66655	535,054	490,611	535,054
66656	504,356	305,024	327,891
66659	21,887	15,047	20,667

Source: <http://www7.health.gov.au/pubs/mbs/mbsnov03/index.html> [Assessed date: 6 August 2004]



# Approach to assessment

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## Review of literature

A search was conducted during the months of October and November 2004 to identify the relevant published studies and reviews. No restrictions (language or year of publication) were applied to the search strategy. Table 3 details the electronic databases searched.

**Table 3 Electronic databases used in this review**

Database	Period covered in literature
Cochrane Library	4th Quarter 2004
EBM Reviews	October 12 2004
Biological Abstracts	1980 to August 2004
PubMed (Cancerlit subset)	1966 to 7 September 2004
CINAHL	1982 to September week 4 2004
EMBASE	1980 to 2004 week 41
Medline in-process and other non-indexed citations	October 4 2004
Premedline	October 5 2004
Current Contents	October 7 2004
Australian Medical Index	October 10 2004

We conducted further Internet searches of relevant Health Technology Assessment websites, clinical trials registers and other relevant websites (Appendix D). In addition, the reference sections of the retrieved studies and those describing PSA testing in general terms were hand searched and examined.

The broad search strategy used in Medline is shown in Appendix C. This search strategy was further modified and adapted for the other databases. In the entire database search, the primary focus was on the two key core terms 'PSA' and 'point of care'. An information specialist with many years of experience performed the searches.

## Selection criteria

The following criteria were developed *a priori* to determine eligibility of relevant studies assessing diagnostic accuracy of PSA near patient testing (Table 4) and for articles evaluating patient management or health outcomes (Table 5). These inclusion and exclusion criteria were based on those agreed upon by both MSAC and the members of the Advisory Panel for the current assessment.

**Table 4 Inclusion and exclusion criteria for diagnostic accuracy of PSA near patient testing**

<b>Part 1: Test accuracy</b>		
<b>Question: Compared with the current PSA testing method by accredited pathology laboratories, what is the diagnostic accuracy of PSA near patient testing?</b>		
<b>Characteristic</b>	<b>Inclusion</b>	<b>Exclusion</b>
Patients	Men with prostate cancer	None defined
Test	PSA near patient testing for diagnosis or management of prostate cancer	PSA testing for screening purpose
Reference standard	Biopsy (histology)	Digital rectal examination, imaging prostate cancer
Outcomes	Accuracy of PSA near patient testing (sensitivity, specificity and their derivatives). The information should be available to allow the formation of the diagnostic two by two table with four cells (true positive, true negative, false positive and false negatives)	None defined
Study design	Cross-sectional studies that report the diagnostic characteristics in an independent blind comparison of PSA near patient testing and an appropriate reference standard in consecutively selected patients. If such studies do not exist, those in which an independent blind or objective comparison in non-consecutively selected patients was reported or where the reference standard was not applied to all patients will be included. If none of the studies above exists, studies reporting diagnostic accuracy without a reference standard in a consecutively selected case series might be considered for inclusion.	Narrative reviews, editorials and other opinion pieces, articles identified as preliminary reports when results are published in later versions, articles in abstract form only and case reports
Publication	English language articles	None defined

**Table 5 Inclusion and exclusion criteria for patient management and health outcomes following PSA near patient testing**

<b>Part 2: Patient management and health outcomes following PSA near patient testing</b>		
<b>Question: What are the effects of PSA near patient testing on patient management and health outcomes?</b>		
<b>Characteristics</b>	<b>Inclusion</b>	<b>Exclusion</b>
Patients	Men with prostate cancer	None defined
Intervention (test)	PSA near patient testing	PSA testing for screening purpose
Comparator	Current PSA testing methods by accredited pathology laboratories or any other method	None defined
Outcomes	Patient health outcomes following PSA near patient testing (eg morbidity, mortality, quality of life, etc) Safety or adverse events associated with PSA near patient testing The impact of PSA near patient testing on quality control and patient management	None defined
Study design	Health technology assessments, systematic reviews, meta-analyses and randomised controlled trials (RCTs) will be sought initially. If these are unavailable, other controlled trials, comparative studies and cohort studies may be assessed. Case series of consecutively selected patients may be considered for inclusion as the last resort	Narrative reviews, editorials and other opinion pieces, articles identified as preliminary reports when results are published in later versions, articles in abstract form only and case reports
Publication	English-language articles, or well-designed RCTs published in any language	None defined

## Assessment of validity

Articles meeting the inclusion criteria for assessment of effectiveness underwent critical appraisal to evaluate the potential for bias of their study designs. Critical appraisal was performed using the methods described below.

### Effectiveness

Two factors are important in determining the effectiveness of a diagnostic test:

- Accuracy of the test, ie the diagnostic characteristics sensitivity, specificity and their derivatives
- Patient management and outcomes following the test, ie the usefulness of the test in improving outcomes for patients.

### Part 1: Diagnostic accuracy of prostate specific antigen near patient testing

The most rigorous study design for assessing the validity of a diagnostic test is considered to be a prospective blind comparison of the test and a reference standard in a consecutive series of patients from a relevant clinical population (Jaeschke et al 1994a, Sackett et al 2000). The Cochrane Methods Working Group on Systematic Review of Screening and Diagnostic Tests (1996) expand on this definition and recommend six criteria for assessing the validity of evidence. Based on these criteria, the validity of the methodology of the included study was assessed against the checklist presented in Table 6. Studies meeting all of the criteria are considered the most rigorous and least susceptible to bias.

**Table 6** Criteria and definitions for assessing validity of diagnostic studies

Validity criteria	Definition
Test is compared with an appropriate reference standard (gold standard)	Patients in the study should have undergone both the diagnostic test in question and a reference test that would provide confirmatory proof that they do or do not have the target disorder
Appropriate spectrum of consecutive patients	Study included patients who would normally receive the test in clinical practice, ie patients covering the spectrum of mild to severe cases of the target disorder, early and late cases, and patients with other, commonly confused diagnosis. An inappropriate spectrum compares patients already known to have the disorder with a group of normal non-diseased patients (case-control) or with patients diagnosed with another condition
Masked assessment of study and reference tests results	The study test and the reference test should be interpreted separately by persons unaware of the results of the other (avoidance of review bias)
All study subjects tested with both study and reference tests	The reference test should be applied regardless of a positive or negative result from the study test (avoidance of work-up/verification bias)
Study test measured independently of clinical information	The person interpreting the test should be masked to clinical history and results of any other tests performed previously
Reference test measured prior to any interventions	No treatment interventions should be initiated prior to the application of the reference (or study) test

The most appropriate reference standard to verify the presence or absence of prostate cancer is histology.

A cross-sectional prospective study would be considered the most appropriate study design to assess the accuracy of PSA near patient testing for diagnosis and management of prostate cancer in terms of its accuracy in predicting treatment outcome (failure or success).

### Reporting accuracy outcomes

The diagnostic characteristics, such as sensitivity, specificity and their derivatives, of PSA near patient testing were reviewed from the single included primary study.

The accuracy of a diagnostic test is primarily determined by its ability to identify the target disorder compared to the most appropriate reference standard. Accuracy is measured by diagnostic characteristics such as sensitivity and specificity. Minimum requirements for computing sensitivity are sufficient data to compute the proportion of subjects with the disorder whose tests were correctly identified as positive. For specificity, data are required to compute the proportion of patients without the disorder whose tests were correctly identified as negative.

Diagnostic test results are presented in two-by-two tables as shown in Table 7. Individuals who test positive for the disease in both the study test under investigation and the reference test are represented in cell 'a' and are called true positives (TP). Individuals without the disease who test negative in both tests (the 'd' cell) are called true negatives (TN).

A diagnostic test may produce discordance between the test result and the true disease status of the subject. When this occurs, a false result is reported. Cell 'b' and 'c' in Table 7 illustrate these situations. In the former, the test is positive in individuals without the disease, in the latter case, the test is negative in diseased individuals. These two sets of false results are called false positives (FP) and false negatives (FN), respectively.

**Table 7 The generic relationship between results of the diagnostic test and disease status**

Study test result	True disease status (reference standard)		Total
	Diseased	Not diseased	
Positive	a	b	a+b
Negative	c	d	c+d
Total	a+c	b+d	a+b+c+d

Abbreviations: a = number of diseased individuals detected by the test; b = number of individuals without disease detected by the test; c = number of diseased individuals not detected by the test; d = number of individuals without disease not detected by the test; a+b = total number of individuals testing positive; c+d = total number of individuals testing negative; a+c = total number of diseased individuals; b+d = total number of individuals without disease; a+b+c+d = total number of individuals studied.

Sensitivity is the proportion of diseased individuals who test positive. It is a measure of the probability of correctly diagnosing a case, or the probability that any given case will be identified by the test (refer to Table 7).

$$Sensitivity = \frac{a}{a+c} = \frac{TP}{TP+FN}$$

Specificity is the proportion of individuals without disease who test negative. It is the probability of correctly identifying a non-diseased person with the study test.

$$\text{Specificity} = \frac{d}{b + d} = \frac{TN}{TN + FP}$$

The complement of specificity is called the false positive rate (FPR).

$$\text{FPR} = 1 - \text{Specificity}$$

The predictive accuracy of a diagnostic test is defined in terms of two components, depending on the test results (Sackett et al 2000).

A positive predictive accuracy (value) is the proportion of people with a positive test who have the target disorder. This can be denoted by:

$$\text{PPV} = \frac{a}{a + b} = \frac{TP}{TP + FP}$$

A negative predictive accuracy (value) is the proportion of people with a negative test who are free of the target disorder. This can be denoted by:

$$\text{NPV} = \frac{d}{c + d} = \frac{TN}{FN + TN}$$

Likelihood ratios (LR) indicate by how much a given diagnostic test result will raise or lower the pre-test probability of the target disorder. Likelihood ratios express the odds that a given level of a test result would be expected in a patient with the condition compared to one without the condition.

The likelihood ratio for a positive test result (LR +) is related to sensitivity and the FPR:

$$\text{LR} + = \frac{\text{Sen}}{\text{FPR}}$$

The likelihood ratio for a negative test result (LR-) expresses the odds that a given finding would not occur in a patient without, as opposed to with, the target condition and is calculated by:

$$\text{LR} - = \frac{1 - \text{Sen}}{\text{Spe}}$$

A general guide to interpreting likelihood ratios is provided in Jaeschke et al (1994b). Large positive likelihood ratios of 10 or more and small negative likelihood ratios of <0.1 indicate large, and often conclusive, changes in disease likelihood, ie large changes from pre- to post-test probability of having the condition. LR+ values of 5–10 and LR- values of 0.1–0.2 indicate moderate changes in pre- to post-test probability. LR+ values of 2–5 and LR- values of 0.5–0.2 indicate small, but sometimes clinically important, changes in probability. If LR+ is below 2 and LR- is above 0.5, then there is little or no likelihood that the presence of disease will be diagnosed as a result of the test.

## Part 2: Patient outcomes following prostate specific antigen near patient testing

Detection of the pathology of the diagnostic procedure under consideration is not the only indicator of the usefulness of the test. Unless application of the procedure improves patient management options and ultimately patient health outcomes, its usefulness is considered limited (Sackett et al 2000). The ideal method for assessing patient outcomes following use of the diagnostic test is an RCT that compares outcomes of patients who have had the test with outcomes from those patients who have not had the test and who have been followed up for an appropriate length of time to measure patient relevant morbidity, quality of life and mortality. Thus, the ideal study design to determine or monitor the effectiveness of PSA near patient testing is an RCT comparing outcomes of patients allocated to PSA near patient testing and patients allocated to testing at accredited pathology laboratory. Unfortunately, no studies of this type were identified in the systematic literature search.

The evidence presented in the included primary study was assessed and classified using the dimensions of evidence defined in NHMRC (2000).

These dimensions (Table 8) consider important aspects of the evidence supporting a particular intervention and include three domains covering: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

**Table 8 Evidence dimensions**

Dimensions	Definition
Strength of the evidence - Level - Quality - Statistical precision	The study design used, as an indicator of the degree to which bias has been eliminated by design <sup>a</sup> The methods used by investigators to minimise bias within a study design The p-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

<sup>a</sup>See Table 9

The three sub-domains – level, quality and statistical precision – are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 9.

**Table 9 Designations of levels of evidence**

Levels of evidence <sup>a</sup>	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

<sup>a</sup> Modified from NHMRC (2000)

The included study underwent critical appraisal involving evaluation of aspects of study design for susceptibility to bias. A list of criteria used to evaluate the validity of the primary research evidence included in this report is outlined in Table 10. These criteria are based on a list assembled by the NHS Centre for Reviews and Dissemination (2001) to evaluate the validity of evidence from various study designs.

**Table 10 Validity criteria according to study design**

Study design	Validity criteria <sup>a</sup>
Randomised controlled trial	Randomised method; allocation concealment; blinding of patients, investigators and outcome assessors; proportion lost to follow-up; intention to treat analysis
Cohort	Prospective/retrospective; comparable groups at inception; identification and adjustment for confounding factors; blind outcome assessment; sufficient duration of follow-up; proportion lost to follow-up
Case-control	Explicit definition of cases; adequate details of selection of controls; comparable groups with respect to confounding factors; interventions and other exposures assessed in same way for cases and controls; appropriate statistical analysis
Case series	Indication was comparable across patients; diseases severity was comparable across patients; explicit entry criteria; outcome assessed in all patients; follow up time uniform; outcomes assessed objectively; outcomes assessed in a blinded manner; outcome measures quantified

<sup>a</sup> Modified from NHS Centre for Reviews and Dissemination (2001)

## Data extraction

Two reviewers independently examined 1,472 titles and abstracts identified on searching and included as appropriate. Once the full texts of the included studies were obtained, three reviewers independently assessed each article. Any discrepancies between reviewers in selection and evaluation were discussed and resolved through consensus. Only one primary study passed the evaluation process and data were extracted using standardised instruments.

## Data analysis

No relevant data were available from the included primary study to answer the primary research questions. As a result, no proper analysis could be conducted. However, the main descriptive information from the study was summarised and included.

## **Expert advice**

An Advisory Panel with expertise in PSA, diagnostics and consumer matters was established to evaluate the evidence and provide advice to MSAC. To select members for Advisory Panels, MSAC's practice is to approach the relevant medical colleges, specialist societies and associations and consumer bodies for nominees. The membership list of the Advisory Panel for the current assessment is provided in Appendix B.



# Results of assessment

## Search results

A breakdown of the articles identified, excluded and included from the search strategies is shown in Figure 1. The search strategy identified a total of 1,472 citations. Two reviewers conducted an initial assessment of the titles and abstracts independently and articles that clearly failed to meet the selection criteria were excluded. Ambiguous citations and articles judged relevant were included in the next assessment stage and three reviewers examined the full texts independently. Any discrepancies in the selection process among the reviewers were resolved by consensus. In total, 39 full text articles were obtained and thoroughly read. Thirty-seven of the 39 did not meet the inclusion criteria, including two studies provided by the applicant. Of the remaining two studies, one was later excluded after the study methodology was established by communication with the authors (Gjengsto et al 2004). As a result only one primary study marginally pertinent to the research questions was appraised and included in this report (Appendix E). Excluded studies and the reasons for their exclusion are listed in Appendix F.

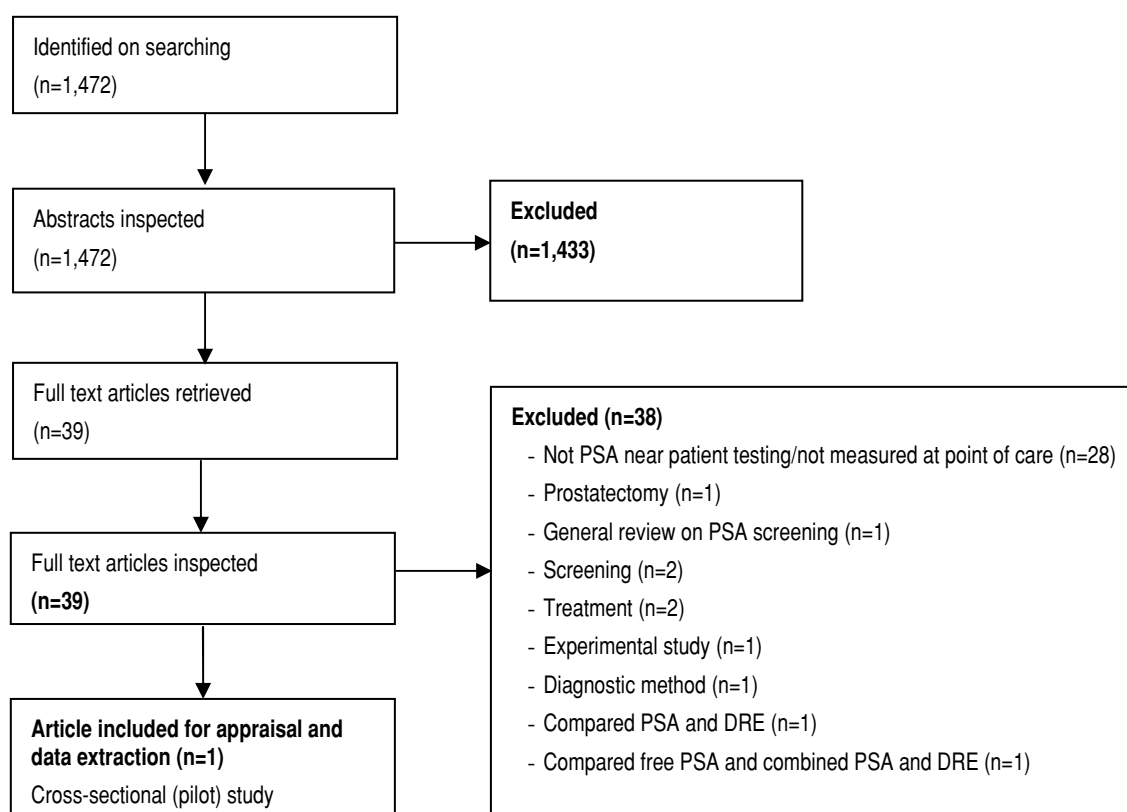


Figure 1 Flowchart demonstrating the selection process for the effectiveness search

## Is it safe?

No studies that addressed the safety of PSA near patient testing by specialists were identified. However, as the test usually requires a blood sample, the only risks to patients are a pricking sensation when the needle is initially inserted (Medical Network Inc. 2004), a small bruise at the puncture site and, rarely, phlebitis after the blood sample is taken (Medical Network Inc. 2004).

## Psychological impact of prostate specific antigen near patient testing

PSA testing at a point of care may have a significant psychological impact on patients. Australia has guidelines that highlight the importance of psychosocial factors for patients undergoing diagnosis or being diagnosed with prostate cancer (Australian Cancer Network Working Party on Management of Localised Prostate Cancer 2003, National Breast Cancer Centre and National Cancer Control Initiative 2004, Australian Prostate Cancer Collaboration 2003). No studies that addressed the psychological or psychosocial impact of PSA near patient testing by specialists were identified.

## Is it effective?

The characteristics of the one included primary study (Berg et al 2001) are summarised in Table 11. The study represents level IV evidence according to the NHMRC criteria (Table 9) and does not answer the key research questions for this assessment.

**Table 11 Descriptive characteristics of the included primary study (Berg et al 2001)**

Aspect of study design	Pilot study (cross-sectional study)
Setting	Jena, Germany
Patient group	All men aged 45 to 75 years living in Jena with a population of 100,000 Average age 59.4 (8.9) years
PSA test	PSA one-step test system for EDTA whole blood and capillary blood was used Free one-step PSA test at 28 pharmacies for one month (1–31 March 1999) was provided to all men residing in Jena city. Urologists and an extensive information campaign also supported the study The PSA testing procedure involved two drops of capillary blood on the indicator strip to which 5 drops of a diluting agent are added. Incubation time was 12 minutes. PSA concentrations above the cut-off point of 4.0 ng/mL indicated by a positive colour change (pink). A colour change of the control zone confirms that the test has been correctly performed The PSA test strips were donated by Cardimac GmbH and Hoyer-Madaus GmbH in Germany
Comparison	Men with positive PSA test results were followed by a quantitative PSA assay Histology was done for those with positive results with the one-step PSA test system
Outcome measured	Test acceptance rate, PSA level and prostate cancer. Subjects also completed a questionnaire (age, education level, occupation); information about testing, motivation and willingness to pay for the test

## Part 1: Diagnostic accuracy of prostate specific antigen near patient testing

The accuracy of PSA near patient testing could not be assessed properly from the primary study (Berg et al 2001). Not all positive PSA results (n=348) were confirmed by serum based quantitative assay (or histology) and the FPs were not reported. Similarly, no

data were available for FNs and TNs because the majority with negative PSA test results (85%) were not confirmed by serum based quantitative assay or histology. Notably, the authors reported that the one-step PSA test had a specificity and sensitivity of 81.3% and 91.1%, respectively. However, this could not be verified based on their raw data. Hence, the diagnostic performance of PSA near patient testing has not yet been properly evaluated and reported in the literature.

### Validity of the primary study

Critical appraisal of the included study against the validity criteria is summarised in Table 12. The cross-sectional study is considered the most useful study design for assessing the association between test results and presence or absence of disease (Knotterus & van Weel et al 2002).

Berg et al (2001) conducted a cross-sectional study to examine the value of a new one-step PSA test system (Figure 2) to improve the acceptance rate and effectiveness of medical check-ups for prostate cancer. The study was conducted in the context of screening and has significant methodological weaknesses. Some of these were:

- failure of the investigators to apply the appropriate reference standard (serum based quantitative assay or histology) to all patients to validate the PSA test results
- failure of patient recruitment to meet the specified inclusion criteria
- performance of the study in a pharmacy setting, ie outside the usual clinical environment
- failure to compare the PSA test results against laboratory-based or any other PSA testing method. Only those with positive PSA results (n=348 or 15%) were further investigated. The majority of men with negative PSA results (n=1,974 or 85%) were not followed and their test results were not validated by serum-based quantitative assay or appropriate reference standard (biopsy).

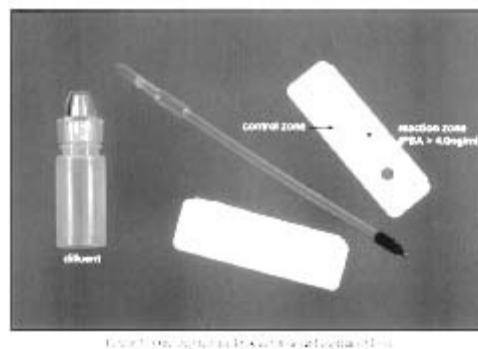


Figure 2 PSA one-step test system used in Berg et al (2001)

**Table 12 Validity of included primary study**

Study	Design	Verification of test result with appropriate reference	Subjects tested with both study test and reference	Appropriate spectrum of consecutive patients	Masked assessment of study and reference results	Study test measured independently of clinical information	Reference measured prior to change in intervention
Berg et al (2001)	Pilot study of one month duration	Yes, for those with positive PSA test result: serum-based quantitative assay and histology	No, those with negative PSA test results did not receive reference test	Not consecutive	No	No	No

## Part 2: Patient health outcomes following prostate specific antigen near patient testing

No RCTs were identified assessing patient outcomes following PSA near patient testing. Moreover, the included primary study (Berg et al 2001) had no prospective data on the vital patient outcomes of quality of life, mortality or prostate cancer following testing. The only patient outcome data reported was cross-sectional and was the number of men diagnosed with prostate cancer following a short study period. The main outcomes measured in Berg et al (2001) are summarised in Table 13.

**Table 13 Outcomes measured and results of PSA testing (Berg et al 2001)**

Outcomes measured	Results
Number of tests during study period	During one month, a total of 2,322 tests (83 tests per pharmacy) were conducted of which 2,119 were in the target age group (45–75 years)
PSA test result	85% (1,974) negative and 15% (348) positive
Consultation with Urologist	Within 8 weeks after the end of the study, 83 of 348 (23.4%) subjects with a positive one-step test reading consulted urologists
Prevalence of prostate cancer among participants	After the end of study, of 2,119 subjects in the target group, 14 cases (0.66%) of prostate carcinoma were confirmed by histology

## Summary of research evidence

For this assessment, one primary study was identified and appraised. The study had several methodological deficiencies. The available evidence related to PSA near patient testing is outlined below.

## Diagnostic accuracy of prostate specific antigen near patient testing

There is insufficient evidence available to support the diagnostic characteristics of PSA near patient testing by specialists for the diagnosis and management of prostate cancer.

## **Patient health outcomes following prostate specific antigen near patient testing**

No RCTs have assessed patient health outcomes following PSA near patient testing. Notably, patient outcomes should be assessed over a long period of time. The appraised primary study (Berg et al 2001) was conducted for only one month and did not examine patient outcomes prospectively over a long period of time. Hence, on the basis of current evidence, the long-term benefits of PSA near patient testing on patient health outcomes or its impact on patient management are unknown.

## **What are the economic considerations?**

The economic evaluation seeks to determine whether PSA near patient testing offers good value for money in Australia. As outlined in the protocol for this evaluation, value for money is determined by an assessment of the cost/benefit ratio of PSA near patient testing compared to the service it would replace, namely PSA testing by an accredited pathology laboratory or any other PSA testing method outside a laboratory setting. In essence, to justify a recommendation for listing, the service must either produce the same health outcomes at a lower cost, or provide improved health outcomes of sufficient magnitude to justify any additional cost.

Equivalence or superiority of PSA near patient testing relative to the comparator can be established through assessment of sensitivity and specificity (refer 'Assessment of validity' section). However, this only establishes the relative performance of the two testing procedures and does not express outcomes in units or measures that enable interpretation of its value for money. To determine the value for money of any differences in performance requires expression of the difference in performance in terms of the impacts upon health outcomes. For example, life-years saved, quality-adjusted life-years (QALYs), or even progression-free months. When expressed in this form, the value per dollar can be more readily assessed.

Clearly the fundamental difficulty in endeavouring to determine the cost-effectiveness of PSA near patient testing is the lack of randomised controlled trials that have assessed patient health outcomes following PSA near patient testing. As previously noted, the appraised primary study (Berg et al 2001) was not sufficiently rigorous to allow the establishment of relative efficacy. Without data on the relative effectiveness of PSA near patient testing, it is not possible to estimate the cost-effectiveness of the test.

Independently of the appraisal of the evidence, Some additional comment on the economics of the application is provided independently of the appraisal of the evidence. The nature of the benefits claimed by the applicant does not support an economic evaluation against health outcomes. The benefits claimed may be summarised as reduced administrative costs and reduced stress for patients through faster processing of results, and reduced administrative costs. Both neither the foundation and nor the magnitude of these claims are not supported. For instance, if patient stress is a function of the time taken to receive pathology results, under PSA near patient testing it may be expected that patient stress will rise as the time of consultation approaches. Under this hypothesis, the level of stress would not have changed but merely have been brought forward in time. Other dimensions of claimed benefits relating to patient convenience are not usually subsidised by taxation revenue.



# Conclusions

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Our search strategy included several databases, health technology assessment and clinical trial websites, the Internet and the reference section of general studies on PSA testing. The comprehensive searching of the literature failed to identify any articles evaluating PSA near patient testing in a real clinical environment, including that of specialists in their offices, for diagnosis and management of prostate cancer. Only one marginally relevant study was identified and it did not answer the primary research questions.

The US Food and Drug Administration was a source of pertinent information about the named technology. It stated that in the US, the device was not cleared for use as a point of care test or in the offices of physicians, but as a prescription device for use by trained technicians in a hospital laboratory.

## Safety

A comprehensive literature search failed to identify any studies on the safety of PSA near patient testing. However, the risks to patients are expected to be negligible, as the PSA test only requires a blood sample. The psychological or psychosocial impact of PSA near patient testing has not been evaluated and reported.

## Effectiveness

There has been only one published study on PSA near patient testing reported. The study was based in Germany and used a one-step PSA test strip for EDTA whole blood or capillary blood. There were no studies on other devices for PSA near patient testing, so the diagnostic performance and the impact of PSA near patient testing on patient outcomes could not be assessed and established. Further research is needed to evaluate the safety, effectiveness and cost-effectiveness of PSA near patient testing.

The Australian government is currently funding an 18-month-trial of near patient testing in a primary care setting. The trial will evaluate a number of research questions pertinent to near patient testing and is expected to be completed in November 2006. Although the PSA test is not included in the trial, the results could provide significant information on the safety, effectiveness and cost-effectiveness of near patient testing in general.

## Cost-effectiveness

Insufficient evidence exists upon which to base an economic evaluation of PSA near patient testing. It is relevant to note, however, that the applicant has estimated the cost per test of PSA testing to be higher than that of laboratory testing and has not claimed improved health outcomes as conventionally defined for reimbursement applications.

## **Recommendation**

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MSAC recommended that on the strength of evidence pertaining to the safety, effectiveness and cost effectiveness of prostate specific antigen testing for the diagnosis and management of prostate cancer, the current funding arrangements remain unchanged.

The Minister for Health and Ageing endorsed MSAC's recommendation on 4 July 2005.



# Appendix A MSAC terms of reference and membership

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MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or Affiliation
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Bruce Barraclough	general surgery
Professor Syd Bell	pathology
Dr. Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr. Gerry FitzGerald	Australian Health Ministers' Advisory Council representative
Dr. Kwun Gong	thoracic medicine
Associate Professor Jane Hall	health economics
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Dr Debra Graves	pathology
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Dr. Ewa Piejko	general practice
Mrs. Sheila Rimmer	consumer representative
Professor Jeffrey Robinson	obstetrics and gynaecology
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Ms Rosemary Huxtable	Medicare Benefits Branch, Department of Health and Ageing
Professor Ken Thomson	radiology
Dr Douglas Travis	urology
Professor Alan Lopez	epidemiology
Associate Professor Donald Perry-Keene	endocrinology
Professor Michael Solomon	colorectal medicine

<http://www7.health.gov.au/msac/membership.htm#a>

## Appendix B Advisory Panel

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### Advisory Panel for MSAC application 1068: The use of PSA near patient testing for diagnosis and management of prostate cancer

<b>Professor Brendon Kearney (Chair)</b> MBBS, FRACP, FRACMA Executive Director Clinical Systems Department of Human Services	MSAC Member
<b>Professor Sydney Bell</b> MD, BS, FRCPA, FAFPHM (RACP) Area Director of Microbiology South East Sydney Area Health Service RANDWICK, NSW	MSAC member
<b>Dr Peter Swindle</b> Urological Surgeon Mater Prostate Cancer Research Centre Mater Medical Research Institute Mater Private Clinic South Brisbane QLD	Nominated by the Australian and New Zealand Association of Urological Surgeons
<b>Dr Justin Vivian</b>  Western Urology Leederville WA	Nominated by the Australian and New Zealand Association of Urological Surgeons

Dr Martin Stockler

Nominated by the Medical Oncology Group  
of Australia

MBBS, MSc, FRACP

Senior Lecturer,

Cancer Medicine and Clinical  
Epidemiology, University of Sydney

Co-Director of Cancer trials,

NHMRC Clinical Trials Centre,  
University of Sydney

Medical Oncologist, Sydney Cancer  
Centre, RPA & Concord Hospitals

Director, Cancer Trials NSW, The Cancer  
Council (NSW)

**Associate Professor Mark Frydenberg** Co-opted member

MBBS, FRACS

Chairman Department of Urology

Monash Medical Centre

Clinical Associate Professor

Department of Surgery, Monash  
University

Malvern VIC

**Mr Max Gardner** (Deceased)

Vaucluse NSW

Nominated by the Consumers' Health  
Forum of Australia

**Dr Jane Cook**

Observer

MSAC Medical Advisor

Medicare Benefits Branch

Department of Health & Ageing

Canberra City ACT

## Appendix C Search strategies

The literature searches were devised to be broad enough to identify all possible terminology to describe near patient testing. The two core terms were 'point of care testing' (near patient testing) and 'prostate specific antigen' (PSA). These two core terms were combined during searching. The search was conducted during October and November 2004. The Medline search strategy is shown in Table C1.

### Core terms

Table C1	Cost-effectiveness terms for Medline
1	Point-of-Care Systems/
2	point of care test\$.mp
3	poct.mp.
4	pct.mp.
5	(near adj2 patient adj2 test\$).mp
6	npt.mp.
7	decentrali?ed test\$.mp.
8	(ancillary adj2 test\$).mp.
9	(alternat\$ adj2 site\$ adj2 test\$).mp
10	(patient adj2 focu\$ adj2 test\$).mp
11	(bedside\$ adj2 test\$).mp.
12	(satellite adj2 test\$).mp
13	(onsite adj2 test\$).mp
14	(peripheral adj2 test\$).mp
15	(extra adj2 laborator\$ adj2 test\$).mp
16	(physician\$ adj2 office adj2 test\$).mp.
17	(office adj2 patholog\$).mp.
18	(office adj2 laborator\$).mp.
19	(desktop adj2 technolog\$).mp.
20	(desk adj2 top adj2 technolog\$).mp.
21	(desktop adj2 laborator\$).mp.
22	(desk adj2 top adj laborator\$).mp.
23	(set adj2 testing).mp.
24	(rapid adj test\$).mp.
25	(laborator\$ adj2 setting\$).mp.
26	(laborator\$ adj setting\$).mp.
27	(near adj5 bedside).mp.
28	poc.mp.
29	(point adj2 care adj5 test\$).mp.
30	point of care.mp.
31	Physicians' Offices/
32	Office Visits/
33	Or/1-32

**Table C1 (cont'd) Cost-effectiveness terms for Medline**

34	Prostate-Specific Antigen/
35	psa.mp.
36	(prostate adj2 specific adj2 antigen\$).mp
37	(prostate adj2 cancer adj2 specific adj2 antigen\$).mp.
38	kallikrein hk3.mp
39	(hk3 adj2 kallikrein\$).mp
40	hk3.mp
41	(gamma adj2 seminoprotein).mp
42	semenogelase\$.mp
43	semenogelin\$.mp
44	seminin.mp
45	exp Antigens, Neoplasm/
46	Prostate-Specific Antigen/
47	psa.mp.
48	(prostate adj2 specific adj2 antigen\$).mp
49	(prostate adj2 cancer adj2 specific adj2 antigen\$).mp.
50	kallikrein hk3.mp
51	(hk3 adj2 kallikrein\$).mp
52	hk3.mp
53	(gamma adj2 seminoprotein).mp
54	semenogelase\$.mp
55	semenogelin\$.mp
56	Or/34-56
57	33 and 56

\$=truncation symbol to represent a series of letters at the end of a word segment.

()= nested terms to be searched together.

adj=terms must be close to one another in the record.

.tw = textword, search term used as free text keyword anywhere in the Medline record.

.mp = textword, keyword in the text of the title, abstract or subject heading fields

and/or=Boolean operators 'AND' and 'OR'

## Appendix D Internet sites searched

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### Relevant HTA websites

Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé (AÉTMIS)  
<http://www.aetmis.gouv.qc.ca/> [Accessed 15 October 2004]

Agency for Healthcare Research and Quality <http://www.ahrq.gov/>  
[Accessed 15 October 2004]

Alberta Heritage Foundation for Medical Research (AHFMR)  
<http://www.ahfmr.ab.ca/index.html> [Accessed 15 October 2004]

BCBS Technology Evaluation Centre <http://www.bcbs.com/tec/index.html>

Canadian Coordinating Office for Health Technology Assessment (CCOHTA)  
<http://www.ccohta.ca/> [Accessed 17 September 2004]

Danish Centre for Evaluation and Health Technology Assessment <http://www.dihta.dk/>  
[Accessed 15 October 2004]

EUROSCAN <http://www.ad.bham.ac.uk/euroscan/index.asp>  
[Accessed 15 October 2004]

Finnish Office for Health Care Technology Assessment  
<http://www.stakes.fi/finohta/e/> [Accessed 15 October 2004]

Health Council of the Netherlands <http://www.gr.nl/index.php>  
[Accessed 15 October 2004]

Institute for Clinical Systems Improvement  
[http://www.icsi.org/knowledge/browse\\_bydate.asp?catID=107](http://www.icsi.org/knowledge/browse_bydate.asp?catID=107)  
[Accessed 15 October 2004]

Institute of Technology Assessment of the Austrian Academy of Science  
<http://www.oew.ac.at/ita/welcome.htm> [Accessed 15 October 2004]

International Network of Agencies for Health Technology Assessment (INHATA)  
[http://www.inahta.org/inahta\\_web/index.asp](http://www.inahta.org/inahta_web/index.asp) [Accessed 17 September 2004]

National Coordinating Centre for Health Technology Assessment (NCCHTA)  
<http://www.hta.nhsweb.nhs.uk/> [Accessed 15 October 2004]

National Horizon Scanning Centre <http://www.publichealth.bham.ac.uk/horizon/>  
[Accessed 15 October 2004]

National Institute for Clinical Excellence (NICE) <http://www.nice.org.uk/>  
[Accessed 15 October 2004]

New Zealand Health Technology Assessment (NZHTA) <http://nzhta.chmeds.ac.nz/>  
[Accessed 15 October 2004]

NHS Centre for Reviews and Dissemination, University of York.  
<http://www.york.ac.uk/inst/crd/crddatabases.htm> [Accessed 17 September 2004]

Point of Care: The Journal of Near-Patient Testing & Technology  
<http://www.poctjournal.com> [Accessed 14 September 2004]

Swiss Network for Health Technology Assessment (SNHTA)  
<http://www.snhta.ch/home/portal.php> [Accessed 15 October 2004]

Technology Assessment at McGill <http://www.mcgill.ca/tau/>  
[Accessed 15 October 2004]

The Centre for Health Services and Policy Research (CHSPR) <http://www.chspr.ubc.ca/>  
[Accessed 15 October 2004]

The Norwegian Centre for Health Technology Assessment (SMM)  
<http://www.oslo.sintef.no/smm/news/FramesetNews.htm> [Accessed 15 October 2004]

The Swedish Council on Technology Assessment in Health Care (SBU)  
<http://www.sbu.se/www/index.asp> [Accessed 15 October 2004]

## Clinical trial register websites

American Society of Clinical Oncology (ASCO) <http://www.asco.org>  
[Accessed 14 September 2004]

Centre Watch Clinical Trials Listing Service <http://www.centerwatch.com/>  
[Accessed 24 August 2004]

Clinical Trials.com <http://clinicaltrials.com/> [Accessed 24 August 2004]

Clinical Trials.gov <http://clinicaltrials.gov/> [Accessed 24 August 2004]

Current Controlled Trials <http://www.controlled-trials.com/>  
[Accessed 24, 30 August 2004]

FDA Clinical trials <http://www.fda.gov/oc/oha/default.htm#clinical>  
[Accessed 15 October 2004]

NHMRC Clinical Trial Registry <http://www.ctc.usyd.edu.au/trials/trials.htm>  
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Society for Clinical Trials <http://www.sctweb.org/> [Accessed 30 August 2004]

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UKCCCR Register of Cancer Trials  
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US National Cancer Institute - Clinical Trials <http://www.cancer.gov/clinicaltrials>  
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# Appendix E Study included for critical appraisal

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## Primary study

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# Abbreviations

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ACN	Australian Cancer Network
AUA	American Urological Association
AIWH	Australian Institute of Health and Welfare
BPH	benign prostate hypertrophy
CT	computerised tomography
DRE	digital rectal examination
EDTA	ethylene diamine tetra acetic-acid
FDA	Food and Drug Administration
FN	false negative
FP	false positive
HTA	health technology Assessment
LR–	likelihood ratio, negative
LR+	likelihood ratio, positive
MBS	Medicare Benefits Schedule
NHMRC	National Health and Medical Research Council (Australia)
MSAC	Medical Services Advisory Committee
NPV	negative predictive value
PPV	positive predictive value
PSA	prostate specific antigen
RCT	randomised control trial
RT	reverse transcriptase
TN	True negative
TP	true positive
TRUS	transrectal ultrasound
USA	United States of America

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