

Assessment of Prostate Disease

The latest advances in pathology testing



Following significant changes made to PSA reporting in July 2009, two new tests have been added to enhance the assessment of prostate disease. These are the “prostate health index” (*phi*) and urinary PCA3.

This article reviews the 2009 changes for PSA testing which introduced revised age-related reference intervals for total PSA* in five rather than ten year increments together with median PSA values. Medicare rebate rules for PSA and free PSA testing also were revised in 2009. Overall, these changes improve the risk assessment for prostate cancer to ensure that fewer older men are unnecessarily investigated and to improve diagnosis of early disease in younger men.

The *phi* offers further refinement to the free/total PSA ratio (FTR) in risk assessment and biopsy decision-making. Urinary PCA3 provides an aid to urologists in decision-making concerning repeat biopsy.

* Reference intervals based on Australian population data.

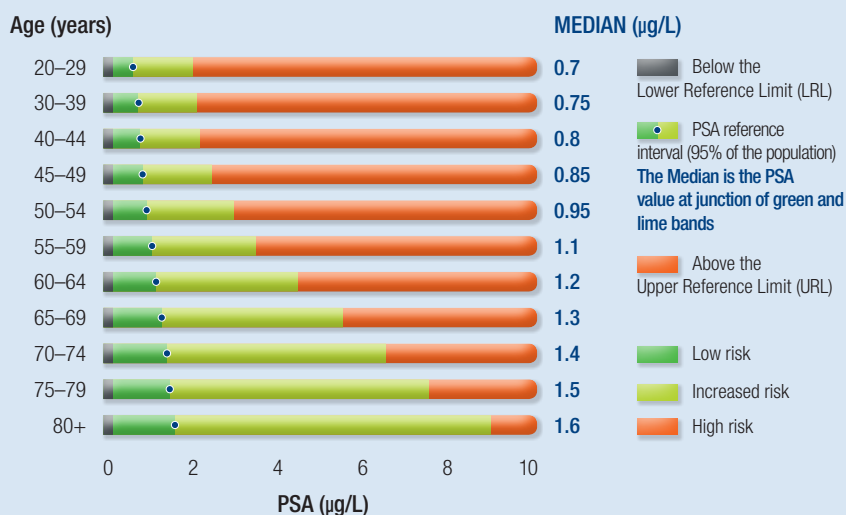
PSA chart

This colour chart has been devised to assist with explaining results to patients.

Age-related PSA reference intervals are shown in dark green and lime, separated by the age-related median value (shown as a black dot). Results below the median value and lower reference limit (LRL) are shown in green and indicate “below average risk” of prostate cancer. Results between the median and the URL (shown in lime) are associated with “above average risk”. Results above the upper reference limit (URL) but less than 10ug/L (shown in orange) are associated with “increased risk” of prostate cancer. Results of 10ug/L or above have “significantly increased risk” of prostate cancer.

PSA reports include:

1. The relevant age-specific reference interval for total PSA in 5-year increments
2. Median total PSA for age, where relevant
3. If performed, the free PSA with age-related median
4. Comments concerning follow-up



Medicare rebate and PSA

PSA test (total serum PSA) is rebated by Medicare:

- One PSA test in a 12-month period if no history of prostate disease
- For monitoring previously diagnosed prostate disease; no restrictions on total PSA ordering.

Free PSA test (free to total PSA ratio, FTR) is rebated by Medicare:

- If total PSA is at, or above the age-related median, but below the age-related method-specific upper reference limit, one episode FTR in a 12-month period.
- If total PSA is at or above the age-related method-specific upper reference limit, but below 10ug/L; four episodes of FTR in a 12-month period.

Medicare will NOT rebate free PSA (FTR) ordered in the following situations:**

- Total PSA result is below median for age (green and grey regions)
- PSA result is 10ug/L or higher
- Number of free PSA tests already exceeded for a 12-month period.

** If free PSA is still required, the patient will be charged for the test.

What if my patient is a known prostate cancer patient?

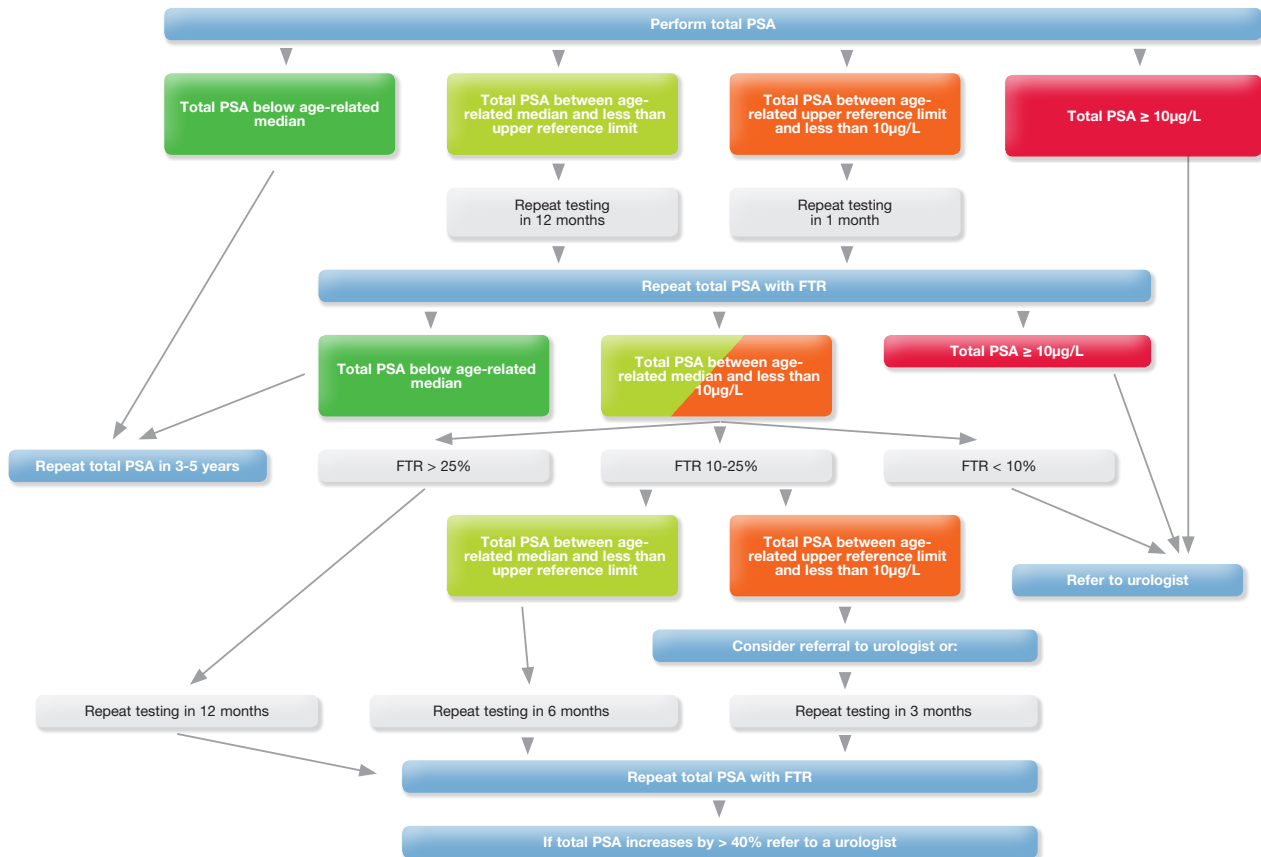
Total PSA testing is unrestricted and can be ordered as considered clinically appropriate. Free PSA (FTR) is not indicated after prostate cancer has been diagnosed.

A valid measurement of free PSA requires analysis without delay (within 24 hours). For measurement of free PSA on eligible patients on the same episode, please specify "total PSA with free PSA if indicated" on the request form.

Please contact Dr Michael Metz on 83662000 for further information, or to discuss a specific patient's results.

Assessment of Prostate Disease

Pathway for Management



The Gleason Score

Prognosis in Prostate Carcinoma

The Gleason Score is a simple system masked in complexity. It provides strong prognostic information in prostate carcinoma.

Tissue examination (histopathology) of prostatic tissue is initially focused on the identification of the presence of carcinoma. However, additional information can give guidance as to the behaviour of the carcinoma and therefore the patient's prognosis. This information relates to stage (spread or extent of tumour) and grade (degree of differentiation).

In regards to stage in TURP specimens, these prognostic features relate primarily to the volume of cancer. In core biopsy specimens, features relate to the volume of carcinoma, the number of cores involved, and the presence of perineural infiltration and vascular infiltration. In radical prostatectomy specimens, prognostic information is in the presence or absence of extraprostatic extension, seminal vesicle infiltration, nodal spread and positive margins.

However, in all specimen types, strong prognostic information relates to the Gleason Grade and Gleason Score.

The grade of a carcinoma indicates how different the carcinoma is in appearance compared to the tissue in which it arises: well-differentiated cancers have a similar appearance to the tissue of origin and can have a good prognosis; poorly-differentiated carcinomas have an appearance different from the tissue of origin and can have a bad prognosis. The Gleason Score is a marker of differentiation in prostate carcinoma. It is assessed by noting the pattern of carcinoma and allocating a grade number. There are 5 Gleason Grades (numbered 1 to 5) (Figure), 1 being very well-differentiated tumours and 5 being very poorly-differentiated tumours. The two most dominant grades are then added to give a Gleason Score (from 2 to 10) expressed as a formula (with the most dominant grade first) such as 3+4=7. Most tumours are between 6 and 10.

Patients with a Gleason Score 6 generally have a good prognosis. Patients with a Gleason Score of 8, 9 or 10 generally have a poorer prognosis.

Prof. Warick Delprado (2011)

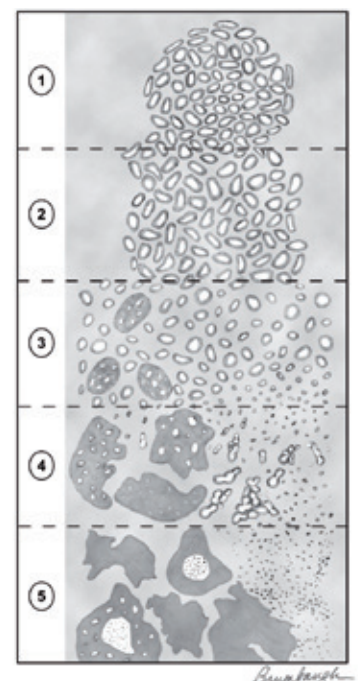


Fig: Am J Pathol. 2005 Sep;29(9):1228-42 The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Epstein JI et al.

New Tests in the Assessment of Prostate Disease

Two new tests are now available through Clinpath Laboratories:

1. *phi* (also known as prostate health index)
2. urinary PCA3 test

phi

Recently an assay for a new marker for prostate cancer has become available — truncated proPSA (p2PSA). This molecule circulates as part of the free PSA fraction, and is present as a higher proportion of the free PSA fraction in patients with prostate cancer. Enhanced sensitivity and specificity for prostate cancer were found when proPSA was combined with free PSA and total PSA, as a calculation known as the Prostate Health Index (*phi*).

The *phi* is reported as a single value (or index) and is interpreted according to the table, which gives a probability of prostate cancer according to *phi*.

<i>phi</i>	0-24	25-34	34-54	55+
Probability of prostate cancer (95%CI*)	11% (6.5-15.8%)	18.1% (13.7-22.6%)	32.7% (27.3-38.0%)	52.1% (42-62.1%)
*Confidence Interval				

Men with higher *phi* values had a higher risk of prostate cancer (study population n, 892 with serum PSA 2–10ug/L). A man with *phi* greater than 55 had a 52% probability of positive prostate biopsy, whereas a man with *phi* less than 25 had an 11% probability of prostate cancer.

What is the benefit of the *phi* result?

1. *phi* has been found to be more accurate than PSA and free PSA (FTR)¹.

The study indicated a *phi* result can give confidence about whether to proceed to prostate biopsy.

PSA	has ~55% diagnostic accuracy for prostate cancer***
Free/Total PSA Ratio	has ~65% diagnostic accuracy for prostate cancer
<i>phi</i>	has ~75% diagnostic accuracy for prostate cancer

***based on Area Under Curve analysis of Receiver Operator Characteristic Curves

2. Because the proPSA is expressed in malignant cells, the *phi* can preferentially detect more aggressive cancers which are likely to grow and spread more rapidly.
3. *phi* is minimally influenced by the age of an individual (hence no problem with reference intervals).

¹ A Multi-Center study of [-2] Pro-Prostate-Specific Antigen (PSA) in combination with PSA and free PSA for Prostate Cancer Detection in the 2.0 to 10.0 ng/ml PSA Range William J. Catalona, et al

When is *phi* indicated?

The *phi* is likely to be most useful in men where the total PSA lies **between 2 and 10ug/L**¹. Determining the cancer risk in this range can be difficult, as up to 25% of new prostate cancer patients have a total PSA < 4 ug/L and 60-70% of men with a PSA value > 4 ug/L have a benign biopsy result. Because of this uncertainty, a prostate biopsy is often considered necessary to establish the diagnosis.

It is envisaged that this test may assist in reducing the number of unnecessary biopsies in these patients. The role of *phi* in other clinical situations, such as follow-up of radical prostatectomy has yet to be established.

Prostate Health Index (*phi*)

At present *phi* is non-rebatable from Medicare and patients will receive an account for \$95.

Urinary PCA3

PCA3 is a unique messenger RNA molecule produced only by prostate cancer cells. PCA3 is shed into the urine following a prerequisite digital rectal prostate massage. Quantitation of urinary PCA3 is a test that was previously performed in Europe, but is now performed in Australia through DHMP and BSP.

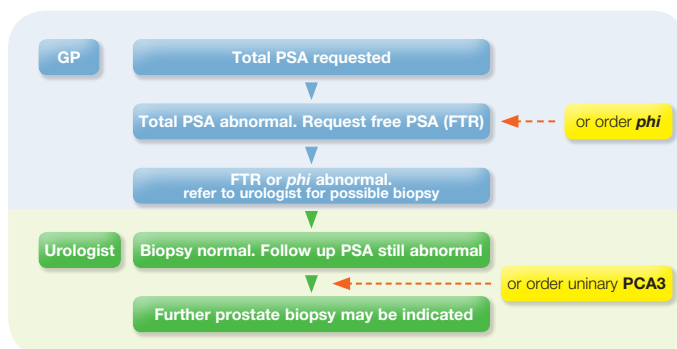
Analysis for PCA3 is labour-intensive and requires specialised RNA technologies for amplification and quantitation. There is no Medicare rebate for PCA3 and the cost of the test is \$495.

Initially PCA3 testing will only be performed via Urologist request, and only for patients with previous negative prostate biopsy but persistent risk indicators.

The current evidence supports use of PCA3 in this scenario only. The literature is mixed when PCA3 is used as a general test for cancer detection, or post prostatectomy testing for recurrence, so we do not advocate PCA3 testing at present in these circumstances.

We recommend discussing PCA3 testing with a urologist if repeat biopsy is contemplated for a man with previous negative results.

When to order *phi* & PCA3:



Please contact Dr Michael Metz on 83662000 for further information, or to discuss a specific patient's results.