Beyond PSA testing for prostate cancer

Better biomarkers are needed to ensure early and accurate detection and prognosis of prostate cancer

Prostate cancer is now the most common cancer diagnosed in men in Australia, and Australia has one of the highest incidence rates of prostate cancer in the world, with an estimated age-standardised rate of 119.2 per 100 000 men. Before 1960, the primary diagnostic test for prostate cancer was the prostatic acid phosphatase test. This was eventually replaced in the 1980s by the prostate-specific antigen (PSA) test.

PSA, a glycoprotein enzyme encoded in humans by the KLK3 gene, was discovered by Flocks and colleagues in 1960. Although a few small studies in the early 1980s suggested that PSA might be useful in the diagnosis of prostate cancer, other studies found that its primary benefit was for monitoring cancer progression and the impact of treatment. As a result, in 1986 the United States Food and Drug Administration (FDA) approved PSA testing for monitoring the progression of prostate cancer. However, in 1994, despite scant evidence for its accuracy as a diagnostic test, the FDA succumbed to pressure from biotechnology companies, clinicians and men’s lobby groups and approved the PSA test for screening; but only when combined with a digital rectal examination and in men aged 50 years and older.

Problems with PSA testing

The standard PSA total blood test has a sensitivity range of 78–100%, with a specificity range of 6–66%. Sensitivity may be improved by combining total PSA with other isoforms; however, at the expense of specificity. Notably, in an attempt to avoid biopsy, measuring the free PSA percentage for patients with total PSA levels in the grey area of 4–10 ng/mL, although more accurate than total PSA alone, still results in missed cancers.

Unfortunately, elevated serum PSA concentrations are not specific to prostate cancer, being also associated with benign prostatic hyperplasia, prostatitis, other inflammatory conditions, recent sexual intercourse and even bicycle riding. Indeed, less than 50% of men who have undergone a biopsy in response to a PSA reading > 4.0 ng/mL are diagnosed with prostate cancer. Further, about 15% of men with a “negative” PSA reading have prostate cancer.

Thus, PSA testing does not effectively meet any of the major requirements for pathological assessment, and PSA is only useful as a biomarker for detection, prognosis and monitoring in patients who have cancers that secrete it in high concentrations. The biology of PSA, including its secretion during inflammatory reactions and its control of the fluidity of ejaculate, limits its use in defining prostate cancer pathology. Moreover, PSA immunohistochemistry does not provide a reliable system for detecting and visualising prostate cancer in biopsy samples. These limitations result in missed cancer diagnoses, unnecessary biopsies on patients, over-treatment with surgery, and inaccurate information on which to base a clinical decision for patients with a Gleason score between 6 and 10 or accurate prognosis.

There are two main clinical pathology objectives that need to be met by biomarker technology.

- Early, accurate detection of the cancer: PSA testing fails to achieve this because of the large number of false positives. A PSA reading > 4 ng/mL has a positive predictive value of 30%, meaning that less than one-third will have prostate cancer, and if ≤ 4 ng/mL, a negative predictive value of 85%, meaning that 15% will have prostate cancer. Both of these problems result in poor patient management and less than optimal outcomes.

- Early, accurate prognosis: although PSA testing has been used to help predict disease progression, its lack of expression in many aggressive cancers leads to problems with reliability for early, accurate prognosis.

Clearly, PSA is not an optimal biomarker for accurate prostate cancer diagnosis and prognosis, but it is the current standard that clinicians are generally expected to use.

Clear identification of the core of the tumour is ideal, including its leading edges and invasive fronts, to achieve an accurate Gleason grade and prognosis. However, PSA immunohistochemistry does not currently enable reproducible, if any, visualisation of the cancer in some tissue biopsies or prostatectomy samples. It therefore adds minimally to Gleason grading. The lack of effective biomarkers for visualising prostate cancer and the reliance on standard haematoxylin and eosin stains contributes to unreliable Gleason grading.

PSA screening: evidence and controversies

Two large randomised studies designed to determine the benefit of PSA screening yielded apparently conflicting results. In the US, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, which randomised 76 693 men aged 55–74 years between PSA screening with digital rectal examination and usual care, showed that up to 15 years median follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups. The European Randomized Study of Screening for Prostate Cancer randomised 182 160 men aged 50–74 years to PSA screening compared with a control group who were not screened. The study showed a mortality advantage at 13 years of 21% in the 162 243 participants aged 55–69 years. However, a recent combined analysis of the two trials concluded that after accounting for differences in implementation and settings, the trials provide comparable evidence that screening reduces prostate cancer mortality.
Notably, a mortality benefit takes many years to become apparent, but the harms in a large group subject to over-diagnosis and subsequent over-treatment can affect quality of life immediately. The two most prominent harms resulting from treatment for prostate cancer are impotence and incontinence. This is why the Australian Government Standing Committee on Screening has recommended against population-based PSA screening, and has suggested that better tests are needed.\(^{14}\)

### The search for alternative biomarkers

A biomarker is any biological molecule found in blood, other body fluids or tissues that can be objectively measured and evaluated as a sign of a normal or abnormal biological process and a pathogenic condition or disease. Unfortunately, this broad definition has contributed to many of the problems in biomarker research, with attempts to fit biomarkers to a purpose rather than recognising that each biomarker has a place in the pathological process. Once we fully understand the biology of the disease, it should be easier to assign a biomarker to a particular functional role. This might then meet the need for diagnosis, prognosis, predictive biomarkers and surrogate biomarkers, instead of pushing PSA into different categories and trying to adapt it for multiple purposes. We believe we are at the point of needing to return to the cell biology of the disease and develop biomarkers that accurately reflect different aspects of the pathogenesis. A recently commissioned report provides a detailed review of the appropriate use and implementation of cancer biomarkers.\(^{15}\)

In the search for new prostate cancer biomarkers, a number of technologies and approaches have been employed. These include proteomics, secretomics, lipidomics, metabolomics, detailed analysis of the cell biology of the cancer, and systems biology. New technologies together with the evaluation of combinations of existing biomarkers are providing some promising avenues for the identification of effective prostate cancer biomarkers. For example, prostate cancer antigen 3 and the TMPRSS2:ERG fusion transcript have been shown to have higher specificity, which could potentially reduce false-positive results.\(^{16}\) Other potential approaches combine markers — for example, the Stockholm-3 model combines protein biomarkers with genetic polymorphisms and clinical characteristics — and have been shown to outperform PSA in high risk disease.\(^{17}\) The use of circulating tumour cells is also being investigated.\(^{18}\)

However, these approaches do not distinguish primary pathology from secondary downstream biology; consequently, they rely on associations to provide an indicator of outcome. This has been a major limitation, as investigators use their test cohorts to develop a set of biomarkers or an algorithm. The problem with this approach is that secondary cohort testing often fails, as the biomarker panel is specific to certain patients or sample groups.

We believe that prostate cancer biomarker development should first recognise the critical cell biology and only then use the technology to develop the biomarkers, and finally, test the biomarkers on independent highly annotated cohorts of patient samples with accurate longitudinal information. The recent identification of altered endosome biology in prostate cancer is a step towards such an alternative approach.\(^{19}\) Interestingly, PSA and many of the other biomarkers under current investigation have direct biology associated with this pathway and, for example, like PSA, are secreted from endosomal organelles. Endosome control secretion is a logical first choice for biomarker investigation to identify a candidate biomarker that is consistently secreted from cancer cells and reliably detected in circulation. We are at a point where biomarker discovery needs to be linked to critical cancer cell biology, so that we can identify biomarkers that reflect the primary pathology, provide optimal detection, enable visualisation of the pathogenesis in biopsies, and facilitate early, accurate prognosis.

### Conclusion

Current PSA-based diagnostic tests cannot accurately detect prostate cancer. After the cancer has been identified, the histopathological grading is less than reliable; and current pathology tests are not able to effectively distinguish between indolent and aggressive life-threatening cancer. These major problems with prostate cancer pathology testing result in poor patient management — the solution lies in the development and appropriate validation of new prostate cancer biomarkers.

**Competing interests:** Doug Brooks is developing cancer biomarkers for commercialisation with Envision Sciences Pty Ltd.

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