Health Policy Advisory Committee on Technology

Technology Brief

An assay to identify biopsy-negative prostate cancer

February 2013
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This brief was commissioned by Queensland Department of Health, in its role as the Secretariat of the Health Policy Advisory Committee on Technology (HealthPACT). The production of this brief was overseen by HealthPACT. HealthPACT comprises representatives from health departments in all States and Territories, the Australian and New Zealand governments and MSAC. It is a sub-committee of the Australian Health Ministers’ Advisory Council (AHMAC), reporting to AHMAC’s Hospital Principal Committee (HPC). AHMAC supports HealthPACT through funding.

This brief was prepared by Dr. Vicki Foerster, Dr. Merrîc Edgar-Hughes, Deanne Forel and Ben Hoggan for the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).
Technology, Company and Licensing

Register ID          WP 147
Technology name      Assay to identify biopsy-negative prostate cancer: ConfirmMDx™ for Prostate Cancer
Patient indication   Intended for use to assess tissue obtained from prostate biopsies, primarily to rule out false-negative results.

Description of the technology

Prostate biopsy procedures generally collect 10 to 12 needle biopsy cores, sampling less than one per cent of a prostate. This leads to a high rate of false negative results (25-30%)\(^1\) and can lead to many repeat biopsies, often on men who are free of prostate cancer. ConfirmMDx™ for Prostate Cancer is an epigenetic assay to help distinguish patients who have true-negative biopsies from those at risk for occult cancer. Epigenetics is the study of genome alterations that do not involve a change in the nucleotide sequence but rather changes such as DNA methylation. The ConfirmMDx™ assay tests the DNA methylation status of several genes associated with prostate cancer via a quantitative methylation-specific polymerase chain reaction (PCR) assay. Included in the assay are glutathione S-transferase P1 (GSTP1), adenomatous polyposis coli (APC) and retinoic acid receptor B2.

The assay, commercially available as of May 2012 in the United States of America, helps urologists to identify prostate-cancer-free men to avoid unnecessary repeat biopsies and also helps to identify high risk patients who may require repeat biopsies and potential treatment. The test is able to detect an epigenetic field effect or halo associated with the ‘cancerisation’ process at the DNA level in cells adjacent to cancer foci (Figure 1). This molecular halo around a cancer lesion can be present despite a normal microscopic appearance.\(^2\) Currently, prostate biopsy specimens are submitted to the vendor’s laboratories in the United States (US) or Belgium for DNA extraction and analysis.

Figure 1  The halo effect of a tumour of the prostate and the possibility of missing tumour cells on biopsy (used with permission of MDxHealth)
Company or developer
MDxHealth Inc., Belgium and US (California).

Reason for assessment
A technology with the potential to reduce the number of false-positive results related to biopsy for prostate cancer.

Stage of development in Australia
☐ Yet to emerge
☐ Experimental
☐ Investigational
☐ Established
☐ Established but changed indication or modification of technique
☐ Should be taken out of use
☐ Nearly established

Licensing, reimbursement and other approval
In Australia, the ConfirmMDx™ assay would most likely be classified as an in vitro diagnostic and therefore would require inclusion on the Australian Register of Therapeutic Goods (ARTG) before marketing. No evidence of its presence on the ARTG was located.

In the US, individual laboratory tests do not require US Food & Drug Administration approval. In a related process, the US Centers for Medicare & Medicaid Services regulates laboratory testing performed on humans through the Clinical Laboratory Improvement Amendments (CLIA) which cover 225,000 laboratory entities. The MDxHealth California laboratory received CLIA certification in January 2012. The laboratory is also accredited by the College of American Pathologists.

Australian Therapeutic Goods Administration approval
☐ Yes
☒ No
☐ Not applicable

Technology type
Diagnostics

Technology use
Diagnostic

Patient Indication and Setting

Disease description and associated mortality and morbidity
The causes of prostate cancer have not been established; however, the major risk factors for prostate cancer include age and family history.
In 2010, prostate cancer was the most common cancer in Australian men, with a five-year prevalence of 72,582 (39% of males with cancer) followed by melanoma and bowel cancer. It was the second highest cause of cancer death after lung cancer at 3,235 deaths; mean age at death was 80 years. Prostate cancer was associated with 16,935 overnight hospitalisations in 2010–11, eight per cent of all those for cancer. It was also associated with 18,241 same-day admissions, the highest of all cancers except non-melanoma skin cancer.

The overall benefits of screening for prostate cancer are currently uncertain, and there is no organised population screening program for prostate cancer in Australia or anywhere in the world. As to why there is no national screening program for prostate cancer in Australia:

While prostate cancer is also an important health condition, current evidence is that the commonly used PSA test, either alone or combined with digital rectal examination, is not suitable for use in a population-based screening program, and the harms of such screening outweigh the benefits. 

**Number of patients**

In Australia in 2012, prostate cancer was expected to be the most common cancer with an estimated incidence of 18,560 cases (age-standardised rate [ASR] of 147.9 per 100,000); the mean age at diagnosis was 67.4 years. Fluctuations in incidence occur year to year and are thought to be due mainly to methods of diagnosis. For example, prostate-specific antigen (PSA) testing was listed in the Medicare Benefits Schedule (MBS) in 1989 and a diagnostic peak in the early 1990s reflected the large pool of undiagnosed cases identified using the PSA test (and subsequent biopsy). A second rise in incidence in 2008 (ASR peaked at 191) may have been due to changes in diagnostic procedures, including lowering the investigation threshold, that led to an increase in the use of biopsy. In a 2008 international comparison, Australia had the highest incidence rate of prostate cancer among all countries considered.

**Speciality**

Men’s health / Surgery / Urology

**Technology setting**

Specialist hospital / general hospital

**Impact**

**Alternative and/or complementary technology**

ConfirmMDx™ would be used in combination with current diagnostic modalities, and would not replace them. A competitor test, the Prostate Core Mitomic Test™ (Mitomics, Ontario, Canada), is described as a highly advanced, proprietary test based on the science of mitochondrial DNA. Using existing prostate biopsy tissue, the test can determine the presence of malignant cells by detecting underlying molecular alterations in normal appearing tissue.
Another emerging technology to detect malignant disease in patients with false-negative biopsies of prostate tissue involves various new hematologic biomarkers such as PSA isoforms.\(^7\)

**Current technology**

Currently, the most common methods of identifying prostate cancer are the PSA blood test, with or without digital rectal examination (DRE), and needle biopsy of the prostate with histopathological analysis of the samples.\(^8\)

The two former tests may be conducted as a screening manoeuvre or case-finding as a result of symptoms. However, DRE and PSA have limited specificity (up to 75 per cent of men with elevated PSA levels do not have cancer),\(^8\) and PSA screening has a high rate of false-positive results.\(^9\) This results in large numbers of men with elevated PSA and/or other high-risk features, but a negative prostate biopsy. In this situation it is recommended that anterior zone biopsies also be taken.\(^10\) Many patients undergo subsequent biopsy procedures, although only 10–36 per cent of second biopsies detect cancer; this proportion decreases after each subsequent negative biopsy. Improved methods are needed to identify men who can forgo a repeat biopsy. The ideal test would have a high negative predictive value (NPV) and a low false-negative rate.\(^11\)

**Diffusion of technology in Australia**

Not yet available in Australia.

**International utilisation**

<table>
<thead>
<tr>
<th>Country</th>
<th>Trials underway or completed</th>
<th>Limited use</th>
<th>Widely diffused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>✓</td>
<td></td>
<td>Likely: ‘MDxHealth says it is only targeting urologists in the US, given the size of the market...sales were US$2.6 million in the first half of 2012.’(^12)</td>
</tr>
</tbody>
</table>

**Cost infrastructure and economic consequences**

The cost of prostate biopsy (i.e. as a repeat procedure to follow up) was estimated to be approximately US$2,500 (approx. A$2,411). In contrast, the price of the ConfirmMDx\(^\text{TM}\) test was reported as US$146 (approx. A$141) per tissue sample.\(^12\) If 10 to 12 biopsy samples are generally obtained per patient, and all are tested, the cost of testing per patient would be US$1,500 to US$1,800 (approx. A$1,447 to A$1,736). However, clinical expert opinion suggests that many urologists will take between 16 and 30 cores for repeat or saturation
biopsies prior to placing someone on active surveillance, which would increase the cost of testing to anywhere between US$2,300 and US$4,400 (approx. A$2218 to A$4244).

MBS costs associated with current tests for needle biopsy and PSA are listed in Table 1.

### Table 1 MBS fees and benefits associated with current tests for prostate cancer

<table>
<thead>
<tr>
<th>Item number</th>
<th>Description</th>
<th>Fee</th>
<th>Benefit 75%</th>
<th>Benefit 85%</th>
</tr>
</thead>
<tbody>
<tr>
<td>37218</td>
<td>PROSTATE, needle biopsy of, or injection into, excluding for insertion of radiopaque markers (anaes.)</td>
<td>$138.30</td>
<td>$103.75</td>
<td>$117.60</td>
</tr>
<tr>
<td>37219</td>
<td>PROSTATE, needle biopsy of, using prostatic ultrasound techniques and obtaining 1 or more prostatic specimens, being a service associated with a service to which item 55600 or 55603 applies (anaes.) (assist.)</td>
<td>$280.85</td>
<td>$210.65</td>
<td>$234.75</td>
</tr>
<tr>
<td>66655</td>
<td>Prostate specific antigen - quantitation - 1 of this item in a 12-month period. (Item is subject to rule 25.)</td>
<td>$20.15</td>
<td>$15.15</td>
<td>$17.15</td>
</tr>
<tr>
<td>66656</td>
<td>Prostate specific antigen - quantitation in the monitoring of previously diagnosed prostatic disease (including a test described in item 66655)</td>
<td>$20.15</td>
<td>$15.15</td>
<td>$17.15</td>
</tr>
<tr>
<td>66659</td>
<td>Prostate specific antigen - 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 that lies at or above the age-related median but below the age-related, method specific 97.5% reference limit - 1 of this item in a 12-month period. (Item is subject to rule 25.)</td>
<td>$37.30</td>
<td>$28.00</td>
<td>$31.75</td>
</tr>
<tr>
<td>66660</td>
<td>Prostate specific antigen - 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 that lies at or above the age-related, method specific 97.5% reference limit, but below a value of 10 ug/L - 4 of this item in a 12-month period. (Item is subject to rule 25.)</td>
<td>$37.30</td>
<td>$28.00</td>
<td>$31.75</td>
</tr>
</tbody>
</table>

MBS: Medicare Benefits Schedule; PSA: prostate-specific antigen.

### Ethical, cultural or religious considerations

Men in rural and regional Australia have a 21 per cent higher prostate cancer mortality rate than men in capital cities. This is attributed to a combination of lack of awareness and education about prostate cancer, distance from testing and treatment, poor primary care provider awareness, and limited access to urologists and other specialists.

### Evidence and Policy

### Safety and effectiveness

Evidence for this brief comes from three diagnostic accuracy studies, one prospective and two retrospective.

Trock et al

An industry-funded, prospective, three-site study in the US (level II diagnostic accuracy study) enrolled consecutive men whose initial prostate biopsy was negative but who were at high risk for a missed cancer (based on suspicious DRE, high-risk PSA level, or atypical cells...
on initial biopsy). Of 162 enrolled men, 86 (53%) met inclusion criteria and had adequate testing samples (mean age 60 years, 80% white). These men were stratified into three subgroups:

- Group 1 (n=21) had suspicious DRE or high-risk PSA level (PSA ≥ 8.0ng/ml and prostate volume < 50.0ml, PSA density ≥ 0.2ng/ml/cm³ or % free PSA ≤ 10.0)
- Group 2 (n=39) had high-grade prostatic intraepithelial neoplasia
- Group 3 (n=26) had atypical small acinar proliferation on initial biopsy.

The men in these subgroups were estimated to have a 20–60 per cent probability of prostate cancer detection on repeat biopsy, and it was hypothesised a priori that their prostate samples would exhibit different biomarker performance characteristics.

The aim of the study was to provide a preliminary estimate of the NPV of two DNA methylation markers, APC and GSTP1. Slides from initial and repeat biopsies were read by a single blinded reader at an academic centre. Tissue sections were sent to the commercial laboratory for quantitative methylation testing, blinded to pathology outcome; this laboratory was owned by a company that provided some funding for the study.

Safety
Not applicable.

Effectiveness

Twenty-four per cent (n=21) of the 86 men, with initial negative biopsy, included in this study had prostate cancer on repeat biopsy. Cancer incidence, on repeat biopsy, was 14%, 21% and 39% within subgroups 1, 2 and 3, respectively. For the three subgroups combined, the NPV (with methylation ratios below a pre-defined threshold, predicting no cancer) was 0.96 for the APC marker and 0.80 for the GSTP1 marker. The sensitivity of methylation testing (with methylation ratios above the threshold) was 0.95 and 0.43 for the two markers, respectively, which indicates a significant advantage for the APC marker (p<0.0001). The false-positive rate using APC methylation however was also significantly higher (0.60 vs. 0.25; p<0.001). This means that APC methylation was able to correctly identify more men with prostate cancer on repeat biopsy at the cost of wrongly diagnosing healthy men with a positive cancer finding. The sensitivity and NPV of the assay when both methylation markers were combined was similar to that of APC alone. APC methylation patterns were consistent with a possible field effect or occurrence early in carcinogenesis.

Trock et al also compared the performance of APC methylation/GSTP1 methylation with the use of per cent free PSA (%fPSA), which is a measure of the proportion of ‘free’ PSA in the bloodstream compared with PSA bound to other proteins. In general, men with prostate cancer have a lower percentage of ‘free’ PSA in their bloodstream; therefore, this measure
is often used to determine the need for biopsy. Of the patients included in this study, %fPSA was available for 37 patients (Table 2).

Table 2 Performance characteristics for %fPSA compared with APC methylation and GSTP1 methylation

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%fPSA*</td>
<td>0.63</td>
<td>0.54</td>
<td>0.83</td>
</tr>
<tr>
<td>APC</td>
<td>1.0</td>
<td>0.38</td>
<td>1.0</td>
</tr>
<tr>
<td>GSTP1</td>
<td>0.38</td>
<td>0.76</td>
<td>0.82</td>
</tr>
</tbody>
</table>

* using a threshold of 15%

Overall the authors concluded:

Methylation markers could have the potential to avoid up to 30% of re-biopsies after an initial negative biopsy.

And:

APC methylation provided a very high NPV with a low percentage of false negatives... The potential of APC methylation to reduce unnecessary repeat biopsies warrants validation in a larger prospective cohort.

Stewart et al\[8\]

The industry-funded, retrospective MATLOC (Methylation Analysis To Locate Occult Cancer) study (level III-1 diagnostic accuracy study) was conducted on archived prostate biopsy samples from patients in Scotland and Belgium (n=483; mean age 63). Using an epigenetic marker panel including APC, GSTP1 and RASSF1, researchers blindly tested histology-negative prostate biopsy samples that were followed by either a positive repeat biopsy (cases) or negative repeat biopsy (controls) within 30 months. Median time between biopsies was 7.3 months. The clinical performance of the marker panel was assessed and cross-validated; NPV was of particular interest (to reduce unnecessary biopsies). Samples from test subjects were assayed randomly and blinded for subsequent cancer detection. Methylation ratios were determined for all three genes.

Safety

Not applicable.

Effectiveness

The assay performed on the initial negative biopsies resulted in an NPV of 90 per cent (95% CI [87, 93]), sensitivity of 68 per cent, and specificity of 64 per cent. In a multivariate model corrected for age, PSA, DRE and histopathological characteristics of the first biopsy, the
assay was a significant independent predictor of patient outcome with an odds ratio of 3.2 (95% CI [1.8, 5.5]). The assay identified 68 per cent of the cases that were false negatives based on histology alone. Negative methylation status also confirmed the negative diagnosis for 64 per cent of the men who had undergone two serial, cancer-negative biopsies. Furthermore, of the 53 cases with benign histology in the first biopsy, 20 (38%) had confirmed significant cancer upon re-biopsy; 13 (65%) were detected by the assay, resulting in a sensitivity of 65 per cent.

The authors noted that their results were consistent with those of the smaller prospective study of Trock et al, commenting that their own use of three markers rather than two (APC and GSTP1) resulted in a stable overall performance with a high NPV. They concluded that:

*Such a test could be a valuable addition to the current [prostate cancer] diagnostic process, reducing the unnecessary repeat biopsies by 64%. Cancer-related epigenetic abnormalities can be detected up to 30 months prior to histopathological manifestation of [prostate cancer], using the initial, cancer-negative biopsy tissue.*

**Troyer et al**

In an earlier industry-funded, retrospective, multicentre study in the US (level III-1 diagnostic accuracy study), testing was completed on 971 archived paraffin-embedded tissue blocks from 264 men screened for prostate cancer and considered to be at risk. Core biopsy tissue from men with serial negative biopsies (defined as three negative results or two negatives separated by ≥ 24 months) served as negative controls, whereas tissue from men diagnosed with prostate cancer within 24 months served as positive controls. All biopsy specimens were submitted to the manufacturer’s laboratory in Belgium for quantitative methylation-specific PCR assay (including GSTP1, APC, and others) and were also reinterpreted by blinded experts in the US. The goal of the study was to evaluate the ability to detect prostate cancer in histopathologically negative biopsy samples from men who were positively diagnosed during follow-up biopsy.

**Safety**

Not applicable.

**Effectiveness**

The sensitivity and specificity of the assay used to test the initially negative biopsy tissue, in men who were later diagnosed with prostate cancer, was 52 per cent and 85 per cent, respectively. When the assay was used to test tissue biopsies containing histopathologically confirmed prostate cancer, sensitivity was 95 per cent.

**Economic evaluation**

Economic analyses were not available.
Ongoing research
No ongoing or planned studies of ConfirmMDx™ for Prostate Cancer were identified.

Other issues
MDxHealth is currently developing a version of ConfirmMDx™ for lung cancer. An additional test under development aims to distinguish between aggressive and slow-growing cancers.12

On 1 December 2012, MDxHealth commenced a collaboration with Ghent University in Belgium to establish NXTGNT, a new ‘Center in Pharmaco (Epi)genomics’ within the laboratory of Pharmaceutical Biotechnology. The Centre’s mission is ‘to accelerate innovation in personalized medicine by using advanced technology, knowledge and expertise in epigenetics’. The Center will bring together scientific expertise from basic researchers, clinical validation teams, informaticians and cutting edge epigenomic technology.4

Summary of findings
Prostate cancer is common, yet the methods currently used to diagnose it have limitations. In particular, only a small proportion of the prostate is sampled via needle biopsy and the rate of false-negative results is high. Many men are therefore subjected to additional, potentially unnecessary biopsy. The ConfirmMDx assay tests the DNA methylation status of several genes associated with prostate cancer in an attempt to lower the false-negative rate of biopsy results.

Evidence came from three fairly rigorous studies of diagnostic accuracy:

- A prospective study compared findings from quantitative methylation testing to the reference standard, blinded histology interpretation. NPVs of 96 and 80 per cent were obtained and the authors estimated that 30 per cent of re-biopsies could be avoided with use of the testing.

- The retrospective MATLOC study was conducted using a DNA methylation assay on archived initial prostate biopsy samples, with results from subsequent repeat biopsies available. The NPV was 90 per cent; the assay identified 68 per cent of the cases that were false negatives; and negative assay results confirmed the negative diagnosis for 64 per cent of the men who had undergone two serial, cancer-negative biopsies.

- An earlier study used a methylation assay to test archived prostate biopsy tissue blocks from at-risk men screened for prostate cancer. Follow-up biopsy samples were available and the histology was reinterpreted by blinded experts. Results showed that gene methylation showed promise as a tool for querying false negative results.
HealthPACT assessment

From the evidence base available, prostate cancer detection using DNA methylation assays appears to offer some benefit over existing methods of diagnosis. In particular, the high NPVs and the low rates of false-negatives observed indicate that DNA methylation assays may provide a means of reducing the number of healthy men incorrectly diagnosed and subjected to unnecessary biopsy; although, high-quality comparative studies are needed before this can be truly determined. Further studies investigating the effects of prostate cancer detection using DNA methylation compared with conventional techniques on overall patient survival are also required.

Despite these initial promising results, the need for ongoing monitoring of patients at high-risk of prostate cancer will remain and current patient management is unlikely to change; therefore, this technology will be archived.

Number of studies included

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

Total number of studies 3
Total number of Level II diagnostic accuracy studies 1
Total number of Level III-1 diagnostic accuracy studies 2

References


**Search criteria to be used (MeSH terms)**

MeSH: prostatic neoplasms, polymerase chain reaction, sensitivity and specificity
Keywords: prostate cancer, polymerase chain reaction, PCR, false negative