Institution: Newcastle University

Unit of Assessment: UoA5

Title of case study: The *Prostate Core Mitomic Test*: a commercial diagnostic to improve the efficiency of prostate cancer diagnosis.

1. Summary of the impact

A novel test for prostate cancer was developed from research in mitochondrial genetics conducted at Newcastle University. The *Prostate Core Mitomic Test* was the first of its kind and is now commercially available in North America. It provides molecular evidence to confirm conventional pathology results showing that men identified as being at risk of prostate cancer are, at the time of examination, free of disease. This is an important patient benefit, as conventional pathology has a 30% chance of missing prostate cancer. The *Mitomic* test obviates the short-term need for a follow-up biopsy, which is an invasive and very uncomfortable procedure. It is also capable of identifying some men at high risk of having prostate cancer that conventional pathology would miss. The test was introduced to the American market in June 2011 and has generated a multi-million dollar investment and turnover.

2. Underpinning research

Researchers

Professor Mark Birch-Machin is a dermatologist with a background in mitochondrial genetics research at Newcastle University, and is a co-founder and a director of *Genesis Genomics Inc.* (since renamed *Mitomics Inc.*), together with Drs Ryan Parr and Robert Thayer, who are based in Canada. Birch-Machin was Principal Investigator on a Cancer Research UK study, and Dr Andrew Harbottle was the Research Associate (Harbottle joined *Mitomics* in 2005).

Background: prostate cancer

Prostate cancer is the second most common cancer in males worldwide, and the fifth most common cancer overall. Incidence rates vary depending on country and ethnicity, but the American Cancer Society reports a rate of 192,280 new cases per year and it is estimated that more than 2,600,000 men are living with the disease in the USA. The symptoms of prostate cancer are often similar to less serious conditions such as benign prostate enlargement; hence reliable diagnosis of malignant disease is important. The current best practice for reliable diagnosis is needle biopsy at 12 different locations in the prostate for microscopic examination by a pathologist (see Figure 1). However, this method relies on at least one of the biopsies taken hitting the tumour and prostate cancer often presents as multiple small tumours, rather than a single large mass. Consequently a negative result may be false. If blood tests and other indications still suggest a high risk of disease being present then a second biopsy procedure would be undertaken after a short time.

Background: mitochondria

Mitochondria are cellular structures that provide 90% of the body's energy requirements. They have their own DNA (the mitochondrial genome), which is highly susceptible to damage compared to nuclear DNA. This is because mitochondrial DNA lacks protective proteins and it is continually exposed to reactive oxygen species generated by cell respiration. It also has limited capacity for repair, unlike nuclear DNA. There are many different mitochondrial genomes in a cell, typically more than a thousand. This redundancy means that mitochondrial genomes can tolerate high levels (up to 90%) of damaged DNA. This can lead to the accumulation of genetic damage without cell function being compromised. One source of DNA damage is a so-called 'field effect' that surrounds malignant tumours; this concept was developed by D.P. Slaughter in 1953 (*Cancer*, PMID: 13094644). Tumour field effects are molecular changes in apparently benign cells located at a distance from a tumour.

Research

In 2003, Newcastle published the first detailed study of the distribution of multiple forms of mitochondrial DNA damage in non-melanoma skin cancer (R1). As well as identifying point mutations in the mitochondrial genome, this work provided quantitative data of the incidence of a common deletion of part of the mitochondrial DNA. Later work (R2) refined the methodology, and identified a practical application related to skin cancer and exposure to sunlight.

This research suggested that such mitochondrial DNA deletions may also be found in other cancers elsewhere in the body. By sequencing the whole mitochondrial genome from prostate cells taken from patients who had advanced prostate cancer, and comparing the results with those from patients who were free of disease, the researchers in Newcastle and Canada showed that deletions in the mitochondrial genome were not restricted to overtly cancerous tissue (R3, R4). Cells located at a distance, in healthy looking tissue, as well as those adjacent to tumours, carried the mitochondrial DNA changes that were also found in the cancer; this field effect is the basis of the Prostate Core Mitomics Test.

3. References to the research

(Newcastle researchers in bold. Citation count from Scopus, July 2013)

R1. Durham SE, Krishnan KJ, Betts J and **Birch-Machin MA** (2003) Mitochondrial DNA Damage in Non-Melanoma Skin Cancer. *British Journal of Cancer* 88:90-5. doi:10.1038/sj.bjc.6600773 **Cited by 54.**

R2. **Harbottle A** and **Birch-Machin MA** (2006) Real-time PCR analysis of a 3895 bp mitochondrial DNA deletion in nonmelanoma skin cancer and its use as a quantitative marker for sunlight exposure in human skin. *British Journal of Cancer* 94:1887-93. doi:10.1038/sj.bjc.6603178 **Cited by 17.**

R3. Parr RL, Dakubo GD, Crandall KA, Maki J, Reguly B, Aguirre A, Wittock R, Robinson K, Alexander JS, **Birch-Machin MA**, Abdel-Malak M, Froberg MK, Diamandis EP and Thayer RE (2006) Somatic Mitochondrial DNA Mutations in Prostate Cancer and Normal Appearing Adjacent Glands in Comparison to Age-Matched Prostate Samples without Malignant Histology. *The Journal of Molecular Diagnostics* 8(3):312-9. http://dx.doi.org/10.2353/jmoldx.2006.050112 **Cited by 36.**

R4. Parr RL, Dakubo GD, Thayer RE, McKenney K and **Birch-Machin MA** (2006) Mitochondrial DNA as a potential tool for early cancer detection. *Human Genomics*, 2(4):252-7. doi:10.1186/1479-7364-2-4-252 **Cited by 19.**

Funding

Cancer Research Campaign: 2001-2003 *Mutations and deletions of the mitochondrial genome in non-melanoma skin cancer.* Dr MA Birch-Machin, Dermatology, University of Newcastle, £82,400 (including £7,800 supplementation May 2002).

4. Details of the impact

The identification of a tumour field effect on mitochondrial DNA in prostate tissue resulted in the development of a commercially available test (launched in the USA in March 2011) that has benefitted men at risk of prostate cancer. This test works by: (i) reducing the need to have a second prostate biopsy by confirming their disease-free status, and (ii) identifying malignant disease in biopsy samples that appear healthy visually (www.mitomicsinc.com/prostate-core-mitomic-test/). A further impact is the expansion of a private company co-founded by Birch-Machin, in which Newcastle University is a shareholder.

Pathway to impact: Newcastle influence on product development

The chief executive officer of *Mitomics* says of Birch-Machin's contribution that:

> *In his role as chair of the company's Science Advisory Board and the science management committee, Birch-Machin was able to advise the background development of the science*

> *that eventually led to the prostate cancer test, drawing on his work on skin cancers and the correlation with mitochondrial DNA deletions.* (Ev a)

The design of both the mitochondrial DNA sequencing and analysis strategies was led by researchers at Newcastle University and based on Birch-Machin's approaches in skin cancer research. Birch-Machin also provided specialist advice on the review of mitochondrial DNA data that led to the final version of the diagnostic test (Ev a). The test was validated by the US National Institute of Standards and Technology under the Early Detection Research Network of the National Cancer Institute, following an external study conducted by them on 108 prostate biopsy samples in 2008 (Ev b & Ev c).

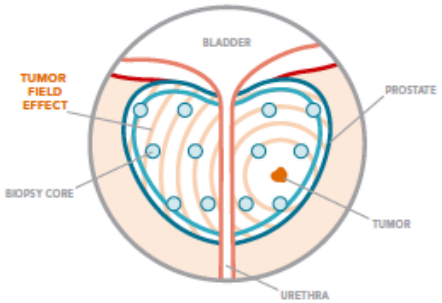
Patents

The technology underlying the final test has been protected by patents, on which Birch-Machin and Harbottle are named co-inventors. Filed in 2006 and granted in 2010, European patent number EP1877559B1 '*Mitochondrial mutations and rearrangements as a diagnostic tool for the detection of sun exposure, prostate cancer and other cancers*' protects the technology behind the methods and kits used to reveal mitochondrial DNA deletions and permit the early detection, diagnosis and progression of prostate cancer, sun exposure and non-melanoma skin cancer (Ev d). A patent (US8008008B2) filed in 2007 covering the specific mitochondrial biomarker and its application for the detection of prostate cancer was granted in the USA in 2011 (Ev e).

The Prostate Core Mitomic Test and patient benefit

As noted earlier, confirming a diagnosis of prostate cancer relies on a pathologist identifying the disease in one or more of 12 needle biopsies as shown in Figure 1. It is estimated that in 2011 there were 1,498,000 prostate biopsies performed in North America. On average, 70% of biopsies (around 1 million) show a negative result, and around 30% of these will be false negatives (Ev f).

Figure 1. Schematic of the prostate gland, needle biopsy strategy and the tumour field effect.



Using the same samples taken for pathology examination, The *Prostate Core Mitomic Test* makes use of the tumour field effect (shown in Figure 1) by identifying a particular mitochondrial DNA deletion in visually benign cells (Ev c).

It is sometimes the case that men whose cells appear disease-free on pathological examination still have raised levels of prostate-specific antigen (a protein in the blood associated with prostate cancer). However, in a clinical study involving 101 patients, the *Prostate Core Mitomic Test* identified those men who were truly free of disease with a negative predictive value of 91% by confirming the lack of a tumour field effect, and identified patients at high risk for undiagnosed prostate cancer at a sensitivity of 84% (Ev g). As the test is successful in identifying men at low risk who would otherwise require a follow-up biopsy procedure in the short term, there is an important patient benefit. The test's use of existing samples reduces stress and the risk of infection as no further biopsies are required to confirm the diagnosis. The test also identifies high risk patients undiagnosed with conventional biopsy; it identified 17 of 20 patients who were later diagnosed with prostate cancer.

Financial investment and commercial impact following product launch in 2011

The chief executive officer of Mitomics has confirmed in July 2013 that:

> *As a private company, we do not disclose financial information publicly. However, Mitomics has invested significant sums into the development of Prostate Core Mitomic Test… The launch of the product required the hiring of a sales and marketing team, as well as the*

establishment of a commercial laboratory for test processing. The combined peak staffing of the USA team is fifteen people. (Ev a)

The product development phase was funded by multi-million dollar investment from existing shareholders and private equity management companies. Following the launch of the test onto the American market, sales of the *Prostate Core Mitomics Test* have grown in line with forecasts and have reached several million dollars (Ev h).

Mitomics has entered into licence agreements with six companies with established networks of urologists in private and public healthcare (Ev i). These include LabCorp (one of the world's largest clinical laboratory providers, which has an annual revenue of $5.7 billion) and CML HealthCare (recently the subject of a takeover, in which the company was valued at $917 million).

Mitomics has twice (in 2007/8 and 2010/11) been selected as one of Canada's top 10 private companies in the life sciences sector. Winners of this competition are chosen by an independent expert panel of leading Canadian and US venture capitalists. Competition winners participate in a series of investment forums across the USA, providing access to potential strategic partners (Ev j).

5. Sources to corroborate the impact

Ev a. Letter from the chief executive officer of Mitomics Inc. Contact details are available on request should corroboration of evidence be required.

Ev b. Maki et al. (2008) Mitochondrial Genome Deletion Aids in the Identification of False- and True-Negative Prostate Needle Core Biopsy Specimens. American Journal of Clinical Pathology 129:57-66. DOI: 10.1309/UJJTH4HFEPWAQ78Q.

Ev c. Study data is shown at http://www.mitomicsinc.com/prostate-core-mitomic-test/ and can be found in the downloadable 'white paper'.

Ev d. The EU patent can be viewed at: http://www.google.com/patents/EP1877559B1?cl=en

Ev e. The USA patent can be viewed at https://www.google.com/patents/US8008008

Ev f. American data on prostate cancer screening is available at http://www.cancer.org/acs/groups/content/@nho/documents/document/500809webpdf.pdf

Ev g. Robinson et al (2010) Accurate prediction of repeat prostate cancer biopsy outcomes by a mitochondrial DNA deletion assay. Prostate Cancer and Prostatic Diseases 13:126-31. DOI: 10.1038/pcan.2009.64

Ev h. Mitomics Inc is a private company and as such does not disclose detailed financial information. However, the Chief Executive Officer may be contacted should confirmation of the multi-million dollar nature of investment and sales be required. Shareholder information is routinely available to Newcastle University but is commercially sensitive. Newcastle University is a minority shareholder and as such is unable to influence the commercial decision not to make financial details available in this impact case, but the University as a shareholder does have access to company financial statements that can be accessed on request, but not copied or otherwise shared.

Ev i. Press releases confirming the licensing agreements reached with six large distribution companies are available at http://www.mitomicsinc.com/media-center/press-releases.php

Ev j. The competition website, listing Mitomics among the winners, is available at http://www.topcanadiancompanies.com/winning_companies.html