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Australia and New Zealand Horizon Scanning Network

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Horizon Scanning Technology Prioritising Summary

Fermiscan®: The detection of breast cancer by the analysis of diffraction patterns of hair

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The production of this *Horizon scanning prioritising summary* was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

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PRIORITISING SUMMARY

REGISTER ID: **000298**

NAME OF TECHNOLOGY: **FERMISCAN**

PURPOSE AND TARGET GROUP: **THE DETECTION OF BREAST CANCER THROUGH THE ANALYSIS OF DIFFRACTION PATTERNS OF HUMAN HAIR**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☐	Yet to emerge	☐	Established
☐	Experimental	☐	Established *but* changed indication or modification of technique
☒	Investigational	☐	Should be taken out of use
☐	Nearly established		

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐	Yes	ARTG number
☐	No	
☒	Not applicable	

The TGA have taken the view that Fermiscan is developing *a service* not a product. Fermiscan is not considered to be a medical device as no medical device is employed either in the sampling of human hair or in the production of a diffraction pattern. Therefore Fermiscan is not considered a therapeutic good and the regulatory requirements for advertising therapeutic goods do not apply.

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Australia	✓		
Singapore	✓		

IMPACT SUMMARY:

Fermiscan Ltd provides the Fermiscan® Test with the aim of detecting the presence of breast cancer cells in human hair. The technology would only be made available through the private company, Fermiscan for asymptomatic women of any age.

The Evaluators are bringing this technology to the attention of HealthPACT as it satisfies the threshold criteria used to assess new technologies of being *"associated with obvious safety and ethical issues or controversies."*

BACKGROUND

Human hair is a dynamic structure the cells of which are regulated by several genes. Bone morphogenetic proteins (BMPs), their antagonists, and BMP receptors are involved in controlling a large number of biological functions including cell proliferation, differentiation, cell fate decision, and apoptosis in many different types of cells and tissues during embryonic development and postnatal life. Genetic studies have demonstrated a role for BMP signalling in the control of cell differentiation and apoptosis, as well as in the regulation of key steps of hair follicle development. BMP signalling plays an important role in controlling the initiation of the growth phase and is also involved in the regulation of apoptosis-driven hair follicle involution (Botchkarev & Sharov 2004). The BMPs have been studied in several cancers with contradictory results, especially in breast cancer. A systematic expression survey of BMPs and their receptors in breast cancer cell lines suggests BMP4 and BMP7 play an important role in functional cell signalling in breast cancer (Alarmo et al 2006). The Fermiscan technology relies on the same BMPs being expressed in hair and breast cancer and that differences in the molecular structure of hair will be observed in individuals who have breast cancer. It also has been suggested that hair growth may reflect an individual's state of health at the time it emerges from the skin (James 2006).

The molecular structure of hair can be determined using X-ray diffraction generated by a synchrotron. The diffraction pattern is produced by X-rays hitting the crystalline α-keratin component of hair at right angles. A synchrotron can produce high-intensity X-rays compared to conventional sources of X-rays. High-intensity X-rays reduce exposure times from hours to second and produce more refined diffraction patterns.

A synchrotron is a cyclic particle accelerator in which the magnetic field (to turn the particles so they circulate) and the electric field (to accelerate the particles) are synchronized with the travelling particle beam (Figure 1).

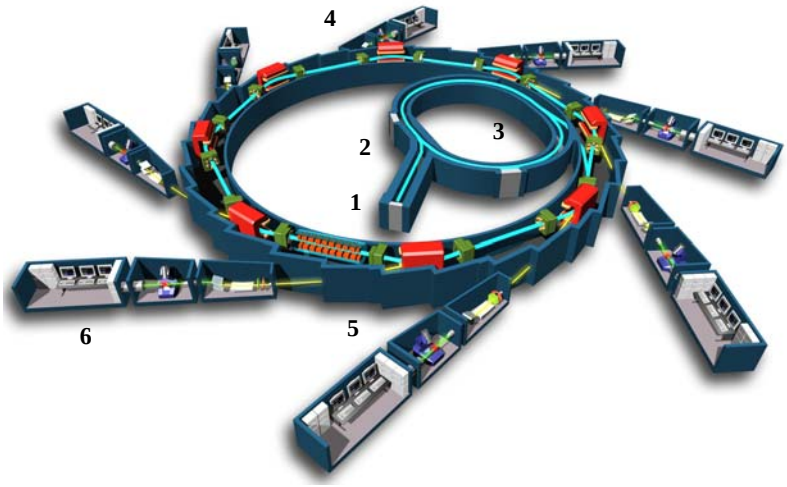

Figure 1 A synchrotron (Wikipedia 2007)

Electrons are produced and accelerated (1) into the linear accelerator (2). They are then injected into the booster ring (3) and further accelerated to 99.987% the speed of light. They are then injected and held in a circular orbit using a magnetic field where light is created with the use of bending magnets (4). The light is channelled down beam lines (5) and utilised at the work stations (6) (Fermiscan Ltd 2007; Wikipedia 2007).

Chemically treated (hair dyes), or exposure to radiation (UV) or mechanical (split ends or handling hair when wet) damage may alter the structure of normal hair. Therefore sample collection must be taken ≤ 3mm from the skin surface. The hair sample should also be as straight as possible, therefore sampling from close to the skin should ensure a straight section is obtained. Head or pubic hair may be utilised for the Fermiscan® test (James 2003a). Ten hair samples are collected from each woman (cut not plucked) and each hair sample must be at least 30mm long (Fermiscan Ltd 2007). It is unclear from any of the papers describing this test how the hair samples are stored prior to analysis. When loading samples into the analysis tube, the hairs should be kept taut but not stretched or twisted (low humidity will prevent stretching). Hairs should be examined before and after loading under a microscope for any mechanical damage that may have occurred from handing with tweezers and this is especially crucial if pubic hairs are being analysed. Figure 2 demonstrates the diffraction patterns obtained from normal hair (a) and hair from an individual with breast cancer (b). For hair diffraction patterns to be clinically useful in the diagnosis of disease, the diffraction pattern of normal hair must be fully understood (James 2003a).

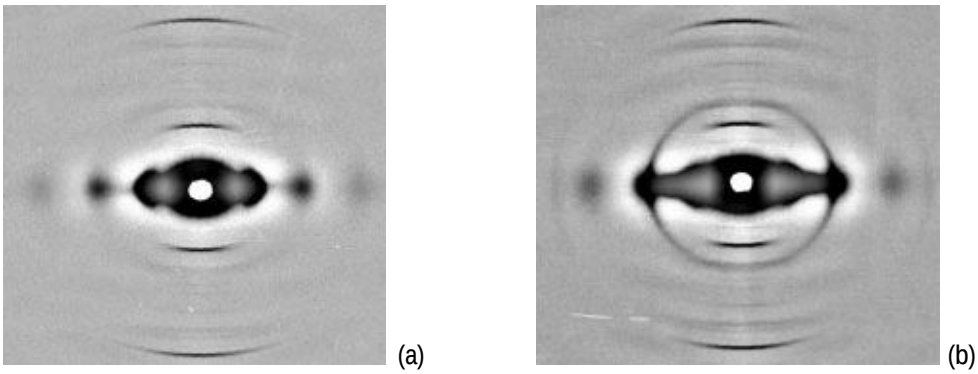

Figure 2 (a) X-ray diffraction pattern of hair from an individual without breast cancer
(b) X-ray diffraction pattern of hair from a woman with breast cancer (James et al 1999)

It has been proposed that the shorter exposure times of the synchrotron will make this technology ideal for the mass screening of hair samples, with the high cost of synchrotron beam time counterbalanced by a high throughput of samples (James 2006). Currently, due to the high demand for synchrotron time, researchers must book a block of beam time and process all samples in one session. This would prohibit the

screening of patients on an *ad hoc* basis and thus patients may experience delays getting the results of their test back.

CLINICAL NEED AND BURDEN OF DISEASE

In 1991 mammographic breast screening was introduced in Australia as a national program known as BreastScreen Australia. The program aims to provide mammographic screening at two-year intervals for asymptomatic women aged 50-69 years, however women aged 40-49 and over 70 years of age may attend free of charge (Forrest & Anderson 1999; National Breast Cancer Centre 2002). Mammographic examinations are available under the MBS (item numbers 59300 and 59303) for women with symptoms. In 2002-2003, more than 1.6 million Australian women aged between 50 and 69 years were screened as part of the BreastScreen Australia program. The participation rate for all Australian women in this target group was 56.1 per cent, slightly lower than the 56.9 per cent recorded in 2001-2002 (AIHW 2006). Current data suggests that screening 10,000 women aged 50-69 years of age, over 10 years, will prevent approximately 18 deaths, compared to preventing seven deaths in 10,000 women aged 40-49 years of age (National Breast Cancer Centre 2002). In Australia, the number of females diagnosed with breast cancer was estimated to be 13,261 in 2006 and is predicted to rise to 14,800 in 2011 (AIHW & NBCC 2006).

DIFFUSION

Fermiscan Ltd is currently undertaking clinical trials in Australia. Australian Therapeutic Goods Administration approval is not required for this service. Fermiscan Ltd is seeking approval from the Food and Drug Administration to market the Fermiscan® test in the United States.

COMPARATORS

The current gold standard in Australia for breast cancer detection is the mammogram, which consists of a set of two-dimensional X-rays of the breast. The patient's breasts are placed between two plates, which firmly compress the breast, flattening and pulling the breast tissue away from the chest wall. The standard mammographic examination includes two sets of low-dose X-rays, one taken from the side (medio-lateral oblique) and one from the top view (cranio-caudal) resulting in a two-dimensional radiographic representation of the breast. The procedure takes approximately 20 minutes. Double readings of screening mammograms is mandatory in Australia (Forrest & Anderson 1999; President and Fellows of Harvard College 2003). The use of ionising radiation limits the age of patients who can undergo a mammogram and the frequency with which mammograms can be used. The radiation dose used for a mammogram will depend on the breast size, thickness and density of the tissue (Warren 2001). The initial mammogram serves as a baseline reference to enable the radiologist and clinicians to track any changes in the breast that may occur over time. On a mammogram of normal breast tissue, fat will appear as grey and the

denser breast tissue as white. Abnormalities are easier to identify in older, post-menopausal women as their breasts have proportionally greater amounts of fat. Mammography may not be as sensitive in older women who are taking hormone replacement therapy which may lead to denser breast tissue. Mammographic screening can detect cancer of the breast in its preclinical phase, detecting abnormalities as small as 5mm, which would not be detectable by palpation. Mammograms will detect microcalcifications, of which 80 per cent are harmless and will not lead to cancer. On finding an abnormality, the radiologist may recommend a repeat mammogram, additional magnified X-rays or a biopsy (Forrest & Anderson 1999; President and Fellows of Harvard College 2003).

EFFECTIVENESS AND SAFETY ISSUES

The diagnosis of breast cancer by studying the diffraction patterns of human hair was first reported by James et al in 1999 (level III-1 diagnostic evidence). Blinded synchrotron analysis was conducted in the United States. The resultant small angle X-ray scatter (SAXS) patterns were analysed and the breast cancer status of the samples were determined. Of the 23 hair samples taken from women diagnosed with breast cancer, all (100%) returned a positive SAXS image for breast cancer. Of the women *not* diagnosed with breast cancer, 24/28 (86%) returned a SAXS image that was normal. No follow-up information was made available on the 4/28 women who were found to have a positive SAXS image for breast cancer. Five high-risk women (familial history of presence of BRCA1 mutation) were analysed and 3/5 (60%) returned a positive SAXS image indicating the presence of breast cancer (James et al 1999).

A number of studies attempted to replicate the results of this initial study without success. Howell et al (2000) conducted a double blind study on the diffraction hair patterns of 109 women: normal population (n=27), unaffected by breast cancer and are BRCA1 or BRCA2 negative (n=23), unaffected and are either BRCA1 or BRCA2 positive (n=10), known to have breast cancer and are BRCA1 or BRCA2 negative (n=21), known to have breast cancer and are BRCA1 or BRCA2 negative (n=25), and no family history (n=3) (level III-1 diagnostic evidence). A positive SAXS image was returned in 15/27 (56%) of the normal population, 15/23 (65%) of the unaffected (BRCA1/2 negative) and in 7/10 (70%) of the unaffected (BRCA1/2 positive) women. Of those women with breast cancer, there were 10/21 (48%) positive samples for those BRCA1/2 negative and 7/25 (28%) positive for those BRCA1/2 positive. The authors concluded that there is no measurable association between the diffraction patterns observed and breast cancer (Howell et al 2000). James has attributed the failings of these studies to poor sample preparation and analysis (James 2003a; James 2003b).

A total of 500 hair samples have been analysed using this technique in a number of small studies. A summary of these results were reported by James et al (2005) and

tabulated in Table 1. No false negatives were reported, however a number of false positives were, and these results would have implications for the women involved in terms of follow-up procedures (James et al 2005).

Table 1 Results of human breast cancer studies

Samples positive for breast cancer by surgery or mammography					
Sample origin	N	Synchrotron results		Sensitivity (%)	Specificity (%)
		False negative	False positive		
Australia	100	0		100	
Europe	58	0		100	
North America	52	0		100	
Samples negative for breast cancer by surgery or mammography					
Sample origin	N	Synchrotron results		Sensitivity	Specificity
Australia	118		13		89
Europe	88		13		85
North America	87		21		76

COST IMPACT

The Fermiscan® Test requires the use of a synchrotron. Currently beam time is booked on the Chicago synchrotron to process a large block of samples. The Victorian Government, in conjunction with funding partners, has constructed Australia's only synchrotron facility at a cost of $157 million. This facility is due to be opened and functional early 2007 (CSIRO 2006; State Government of Victoria 2007). It is unclear at this time what the cost of booking beam time on the Australian synchrotron would be and the number of samples which could be processed in that time span. However, it has been estimated that the cost per test would be $249 and that approximately 100,000 samples per year could be processed utilising one synchrotron beam line (personal communication Fermiscan Ltd).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

The Fermiscan® test does not require approval from the TGA and can therefore be offered to women of all ages regardless of need. Direct marketing to consumers may have social consequences, which may be reflected in an increased burden on the health care system, dealing with false positive or false negative results. For example a large number of false positive samples may result in an increase in the number of mammograms performed, especially in women younger than the specified mammographic screening target range of aged 50-69 years. Current BreastScreen mammography programs have a well-known track record for acknowledging and managing the sensitivities of women and the associated anxieties that may accompany a positive or equivocal result. Specific programs to support women being screened for breast cancer are unlikely to be in place in a private diagnostic firm such as Fermiscan Ltd. There is no ethically acceptable reason to expose women perceived to be at no

greater risk of breast cancer than the general population to potential harm by allowing them to be screened in an environment that does not acknowledge and address their specific issues.

OTHER ISSUES

A blinded clinical trial was conducted on in Singapore in 2006 on 330 hair samples. Samples were obtained from women who were attending the clinic for their yearly mammogram. These results have not yet been released. Fermiscan Ltd acknowledged that this clinical trial had "experienced technical issues in terms of the protocol and sample handling" (personal communication Fermiscan Ltd).

An Australian validation trial is currently being conducted by Fermiscan Ltd in conjunction with a number of private radiology clinics (11 in Sydney and 1 in Geelong). The trial will involve Australian women who have been referred to radiologists by their GP for a mammogram. These women will then be asked if they would like to participate in the Fermiscan® trial. Fermiscan Ltd aim to enrol 2,000 women in this trial and results will be unblinded in stages once the first 200 samples are analysed (Fermiscan Ltd 2007).

Fermiscan Ltd expects this service to be fully operational and available to the general public by November 2007 (Fermiscan Ltd 2007).

CONCLUSION:

It appears that this technique is not reproducible in the hands of a non-specialist. Sample preparation is the key to producing consistent and correct results and research groups other than Professor James do not appear able to replicate these ideal conditions, limiting the applicability of this technology as a diagnostic tool. There is limited and conflicting data available, and a lack of reported follow-up on false positive samples. However, it is likely that there would be a high demand for a non-invasive breast cancer diagnostic technique from women of all ages.

HEALTHPACT ACTION:

HealthPACT has recommended that further assessment of this technology is no longer warranted. However, in light of ethical concerns and the potential to do harm, HealthPACT have recommended that this summary be disseminated to the National Breast Cancer Centre and consumer groups.

SOURCES OF FURTHER INFORMATION:

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Mitchell, S. (2006b). *Oops, they shot the inventor*. In *Australian Financial Review* (Sydney) p 22, published 26th August 2006.

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Warren, R. (2001). 'Screening women at high risk of breast cancer on the basis of evidence', *European Journal of Radiology,* 39 (1), 50-59

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LIST OF STUDIES INCLUDED

Total number of studies	
Level III-1 diagnostic evidence	2

SEARCH CRITERIA TO BE USED:

Breast Neoplasms

Hair/*chemistry

Humans
Keratins/metabolism
Synchrotrons
Diagnostic Tests, Routine
Female
Mass Screening/*methods