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New and emerging technologies for breast cancer detection

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Executive Summary

A comprehensive evaluation of the BreastScreen Australia Program has been conducted, under the direction of the Australian Health Ministers Advisory Council (AHMAC) and managed by the Department of Health and Ageing. To inform this evaluation, the Department of Health and Ageing requested that the Health Policy Advisory Committee on Technology (Health PACT) undertake a Horizon Scan on new and emerging technologies for the screening of breast cancer.

The aim of this *Emerging Technology Bulletin* was to identify any new and emerging technologies for the early detection of breast cancer, not previously examined in horizon scanning summaries or reports[1] and to give a brief but *non-systematic* overview on the current available evidence on these techniques.

Direct evidence of a reduction in breast cancer mortality due to screening can only be generated by large scale, long-term (5-10 years) prospective randomised controlled trials with mortality as an outcome or endpoint. Trials such as this as are expensive and require substantial infrastructure. Surrogate endpoints such as diagnostic accuracy of a screening modality and cancer detection rate are often used, and inferences are made in respect to the impact that such endpoints may have on mortality in a screening environment.

Mammography is considered an imperfect screening tool, as it is neither highly sensitive nor highly specific. The 2006 Cochrane review by Gotzsche and Nielsen reported mammography to have a sensitivity ranging between 71-79 per cent, meaning that between 21 and 29 per cent of breast cancers are false negatives and are missed at screening. Although mammography has its limitations, there is no doubt that, with the introduction of the universal mammography program offered by BreastScreen Australia for women aged 50-69 years, that the mortality associated with breast cancer has declined over time and with increased community participation.

This *Emerging Technology Bulletin* identifies seven technologies used for the detection of breast cancer: computed tomography (CT), positron emission tomography (PET), ultrasonography, thermography, electrical impedance, scintimammography and ductoscopy. In addition this *Bulletin* gives a brief description of three future technologies which may not be of any clinical value within a five-year time frame: volatile organic compound breath tests, radar-based microwave imaging and optical coherence tomography; two of which are being investigated by researchers in Western Australia. Finally, the use of prognostic indicators or risk assessment tools for breast cancer are described.

Few studies reported on the use of technologies in a truly *asymptomatic* population. By screening a *symptomatic* population, the "prevalence" of the disease is artificially increased, the number of true positives detected by the test

[1] See www.horizonscanning.gov.au

will increase as will the positive predictive value, giving a false impression of the accuracy of the test in a screening population. Screening programs can be conducted in high-risk populations to maximise yield, however for breast cancer detection in Australia this should occur in women in the age group 50-69 years rather than symptomatic women.

A total of eight studies reported the results of new diagnostic technologies on *asymptomatic* women, however of these studies four were conducted on women with highly dense breast tissue or women considered to be at high-risk (BRCA mutation, personal or family history of breast cancer). Of the remaining four studies, three were case series (one PET study and two which used electrical impedance) and only diagnostic yields were reported. Only one study, by Ohlinger et al (2006) described results obtained with ultrasound in a truly *asymptomatic* population. In this population, ultrasound achieved a sensitivity and specificity of 100 and 55 per cent, however mammography performed as well, if not better with a sensitivity and specificity of 100 and 73 per cent, respectively, in the same population. When U/S was used in conjunction with mammography specificity was reduced to 36 per cent.

Of concern are technologies that are available in Australia on a direct-to-market basis which do not require regulatory control by the TGA and can therefore be offered to women of all ages. Currently thermography and electrical impedance are offered to Australian women on a user pays basis. Direct marketing to consumers may have social consequences, such as increasing the burden on the health care system to cope with false positive or false negative test results. For example a large number of false positive tests 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. There is no ethically acceptable reason to expose healthy women to potential harm by allowing self-testing of products, that have poorer performance than mainstay screening tests, without prominent informed consent regarding the potential harms.

Extensive research is currently being conducted to identify factors, biomarkers or genetic markers that may be of potential use for the assessment of a woman's risk of developing breast cancer. This may in turn enable medical practitioners to provide suitable medical, psychological or surgical management appropriate to a woman's needs. However, it should be stressed that these factors are surrogate markers that are *associated* with an increased *risk* of developing disease, and as such results of marker studies are *not diagnostic* and should be treated with caution. The results of prognostic tests may result in increased surveillance of women considered to be at elevated risk, which may in turn lead to earlier detection of disease.

In summary, it is clear from the studies included for assessment in this *Bulletin*, that to draw any meaningful conclusions regarding the potential of new breast cancer diagnostic technologies, larger, long-term studies of appropriate study design need to be conducted in *asymptomatic* women. Mammography may be considered an imperfect screening modality, however the addition of MRI for

high risk women and the roll out of digital mammography have increased the options available to women in Australia. Only a brief snap shot of the diagnostic capabilities of the new technologies included in this *Bulletin* have been presented. An in-depth analysis of the level of training, infrastructure and financial support required to become proficient at conducting diagnostic testing and interpreting the results of these new technologies was considered to be beyond the scope of this Bulletin, but remains an important concern.

Introduction

A comprehensive evaluation of the BreastScreen Australia Program has recently been conducted, under the direction of the Australian Health Ministers Advisory Council (AHMAC) and managed by the Department of Health and Ageing. To inform this evaluation, the Department of Health and Ageing requested that the Health Policy Advisory Committee on Technology (Health PACT) undertake a Horizon Scan on new and emerging technologies for the screening of breast cancer.

The National Horizon Scanning Unit within Adelaide Health Technology Assessment (AHTA), Discipline of Public Health, University of Adelaide has prepared an *Emerging Technology Bulletin* to provide advice to HealthPACT on the state of play of new and emerging technologies for breast cancer screening.

In recent years, several new technologies for the detection of breast cancer have been identified by the National Horizon Scanning Unit and these technologies have been published on the Horizon Scanning web site[2] (see Appendix B). In addition the MSAC have recently completed two assessments concerning breast cancer screening. In November 2006, the MSAC recommended *interim* public funding for the use of magnetic resonance imaging (MRI) in the diagnosis of breast cancer in asymptomatic women at high risk[3] of developing breast cancer when used as part of an organised surveillance program. Evidence suggested that breast MRI in combination with mammography may be cost-effective when compared with mammography alone in high risk women aged less than 50 years. This evidence is due for review in 2009 at the earliest. In November 2007 the MSAC recommended public funding for digital mammography as a screening test for breast cancer in asymptomatic women aged over 40 years or women at high risk and for the investigation of women with symptoms of breast cancer, acknowledging that film will be superseded by digital technology. These breast cancer screening technologies previously assessed both by the National Horizon Scanning Unit and the MSAC will *not* be considered further in this *Emerging Technology Bulletin*.

Most of the technologies addressed in this Emerging Technology Bulletin are still in the early stages of clinical investigation. Thus, assessments of diagnostic accuracy of these technologies have been undertaken in both symptomatic and asymptomatic populations. Consideration of their use as part of a screening program would be premature.

[2] Horizon Scanning web site: http://www.horizonscanning.gov.au/
[3] A definition of women considered to be at high-risk can be found in Appendix C

Criteria for the implementation of a population screening program

The accepted criteria for the appraisal of the viability, effectiveness and appropriateness of population screening, as outlined by the UK Screening Committee, include, amongst others, the following points:

- the condition should be an important health problem;
- the natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage;
- there should be a simple, safe, precise and validated screening test;
- the test should be acceptable to the population;
- there should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals;
- there should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment;
- there should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public;
- the benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment) (NSC 2003).

Recommendations for or against a screening program are provided after considering the available evidence of the potential benefits of identifying and treating a health problem against that of the cost and potential harms associated with the screening program, according to the above principles.

Current Australian breast cancer screening program

The Australia National Program for the Early Detection of Breast Cancer, known as BreastScreen Australia, was introduced by the Commonwealth and the states and territories in 1991 (AIHW 2008). It is now recognised as one of the most comprehensive population-based mammography screening programs in the world. BreastScreen Australia is a free biennial service targeting asymptomatic women aged 50-69 years, however the service is accessible to all women aged 40 or above on request.

A mammogram is 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. Independent double readings of screening mammograms by accredited radiologists is mandatory in Australia (Forrest & Anderson 1999; President and Fellows of Harvard College 2003).

Images obtained via a mammogram are characterised by radiologists into categories known as BI-RADS (breast imaging reporting and data system) which are defined in Box 1 (Avril & Adler 2007).

Box 1 BI-RADS categories and definitions (Avril & Adler 2007)

0:	More information is needed to give a final mammogram report
1:	Mammogram is normal
2:	Mammogram shows benign finding
3:	Probably benign finding – short interval follow-up suggested
4:	Suspicious abnormality- biopsy should be considered
5:	Highly suggestive of malignancy- appropriate action should be considered

Masses and calcifications are the most common abnormalities identified on mammograms. The density of a woman's breast tissue will have an effect on the ability of mammography to identify abnormalities, with dense tissue (usually observed on younger women <50 years) reducing the sensitivity of mammography by obscuring abnormalities (Figure 1) (Corsetti et al 2008).

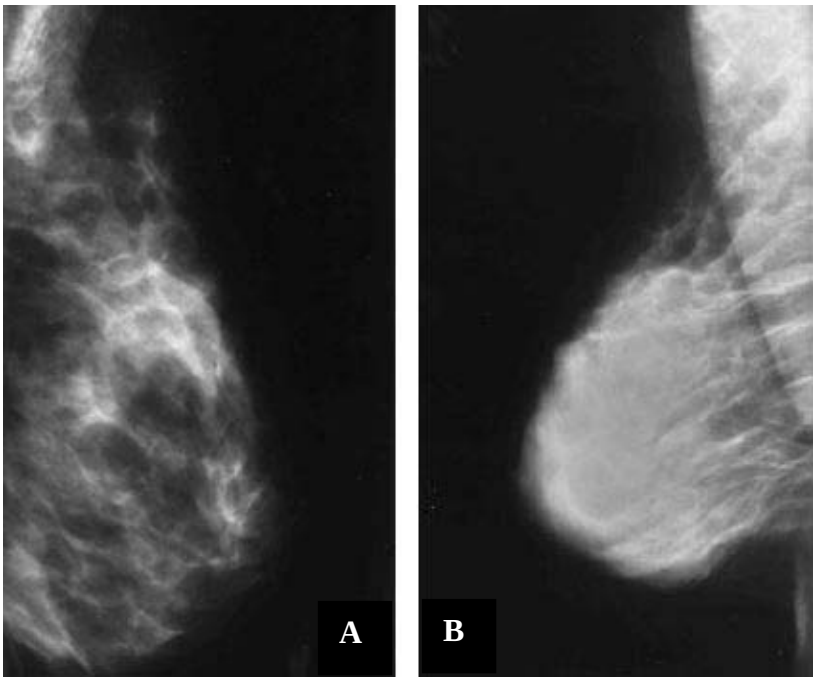

Figure 1 A: Mammogram is more sensitive when imaging breasts with a high proportion of fatty tissue compared to B: extremely dense breast tissue which may obscure abnormalities, reducing the sensitivity of mammography (Prasad & Houserkova 2007)

A high participation rate by women in the target age group (50-69 years) is recognised as being essential to increase the levels of detection of, and therefore maximise the reduction in mortality from, breast cancer. The performance objective of BreastScreen Australia is to have 70 per cent of eligible women (50-69 years) participating in the screening program in a two-year period. Although during the period 2004-05, 1.6 million women were screened by BreastScreen Australia, the participation rate of eligible women was 56.2 per cent, a figure which has remained largely unchanged since 2001-2002 (Figure 2) (AIHW 2008).

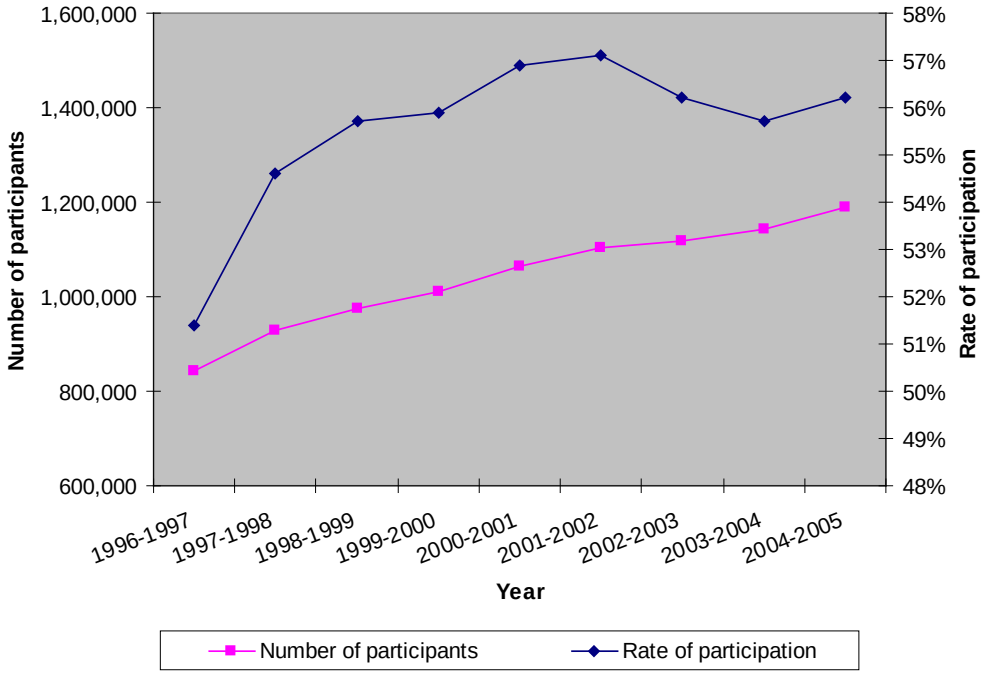

Figure 2 **Participation of women aged 50-69 years in the BreastScreen Australia program, adapted from AIHW 2008.**

In Australia, breast cancer is the most common notifiable cancer in females (AIHW 2007b). The most common histological type of breast cancer is invasive ductal carcinoma (70-80%). There are two types of non-invasive breast cancer: ductal (DCIS) and lobular (LCIS) in-situ carcinoma, which are confined within the terminal duct lobular unit and the adjacent ducts but have not invaded through the basement membrane (Figure 3). LCIS is usually not identified via a mammogram but is an incidental finding during biopsy. DCIS is usually diagnosed due to microcalcifications appearing on mammograms. Patients with locally advanced breast cancer develop distant metastases which are difficult to treat (Avril & Adler 2007).

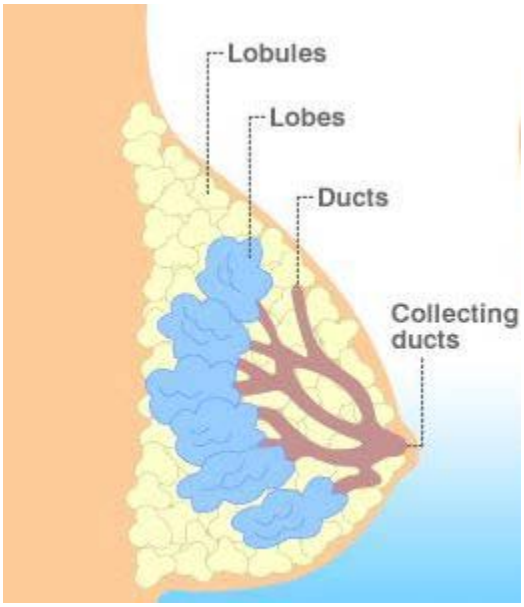

Figure 3 Anatomy of the breast

Burden of disease

During 2004 in Australia, there were 12,126 *new* cases of breast cancer diagnosed in women, with an approximate lifetime risk of one in eleven of developing breast cancer before the age of 75 years. In 2002, the risk of a first diagnosis before the age of 85 years was estimated to be 1:8. Breast cancer is also the most common cause of death among all registrable cancers in Australian women, with 2,664 deaths reported during the same period. One- and five-year survival rates for the period 1998-2002 were 94.5 and 79.7 per cent, respectively (AIHW 2007a; AIHW & NBCC 2006).

The age-specific incidence rates of breast cancer in Australian demonstrate a clear positive correlation between the incidence of breast cancer and age (Figure 4). Women aged 70 years or above are approximately six times more likely to develop breast cancer than those below 50 years. From 1988 to 2002 incidence rates for both the 50 to 69 years age group and the 70 years or above age group have fluctuated. The greatest change was observed in women aged 50 to 69 years between the year 1990 and 1995, with the incidence of breast cancer increasing from approximately 200 new cases per 100,000 women in 1990 to 280 per 100,000 women in 1995 (AIHW & NBCC 2006). However, this large increase has been attributed to the introduction of the BreastScreen Australia Program in 1991, reflecting an increase in the number of early detected cancers that would otherwise not have been identified until later (McDermid 2005). There had been very little change in the incidence rates of breast cancer among women under 50 years of age between 1988 and 2002.

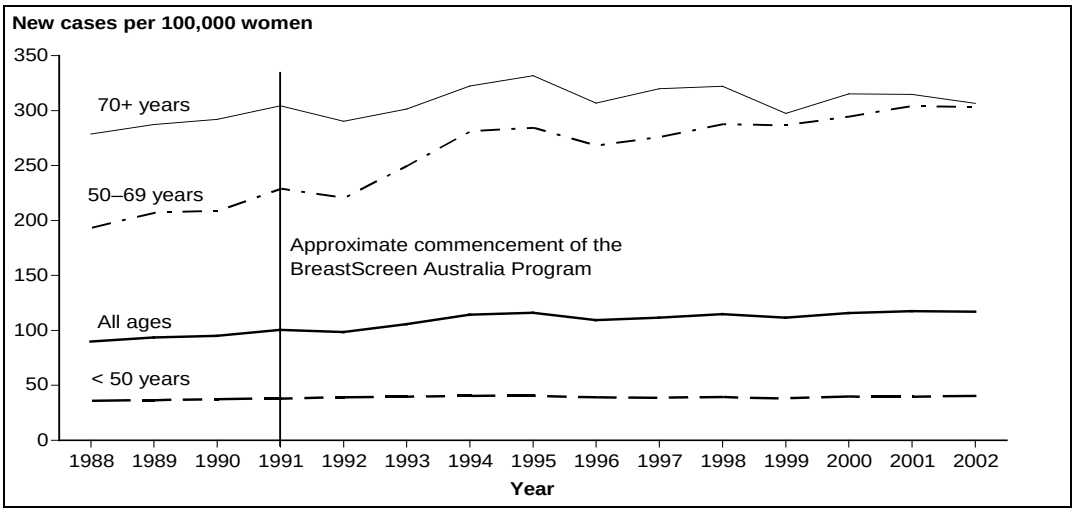

Figure 4 Age-specific incidence rates of breast cancer in Australia (AIHW & NBCC 2006)

Since the introduction of screening mammography, the age-standardised mortality rate of breast cancer for Australian women aged between 50 and 69 years, in contrast to the incidence rate, has decreased significantly, from 65 deaths per 100,000 women in 1993 to 52 deaths per 100,000 women in 2005. A similar declining trend in mortality over time has been observed in women aged 70 years and above, although the mortality rate for this group of women is roughly double that of those aged 50-69 years. The mortality rate for women aged less than 50 years has remained consistently below 10 deaths per 100,000 women from the year 1990 to 2004. Despite a lower incidence rate for breast cancer Aboriginal and Torres Strait Islander women had nine per cent higher age-adjusted breast cancer mortality when compared to the Australian female population as a whole (Figure 5) (AIHW & NBCC 2006).

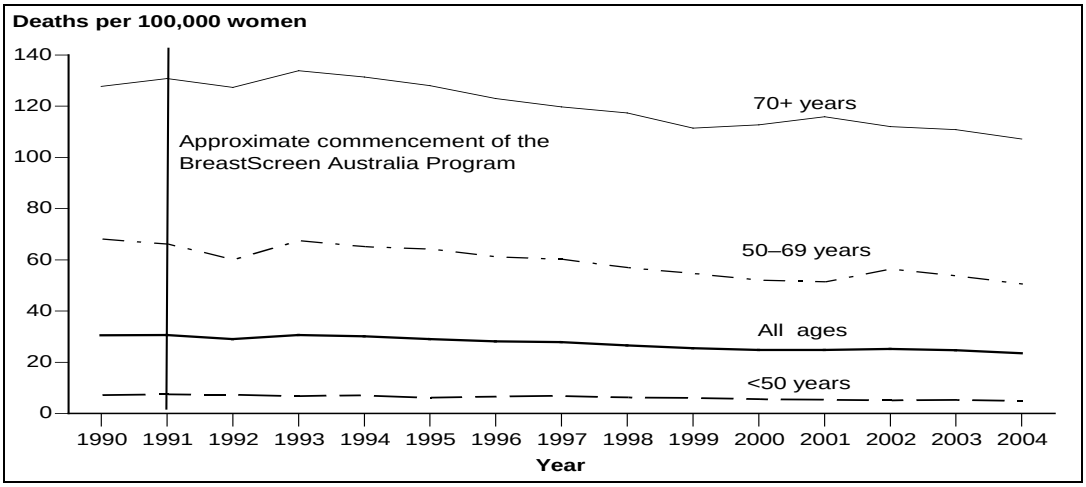

Figure 5 Age-specific mortality rates of breast cancer in Australia (AIHW & NBCC 2006)

In addition, there is evidence of reduced morbidity with the *early* detection of small-diameter cancers and ductal carcinoma in situ (DCIS), which may in turn

result in reduced morbidity from the radical treatment associated with more advanced disease (AIHW & NBCC 2006).

The success of the BreastScreen Australia Program may be viewed in terms of the sensitivity of detecting breast cancer with the use of a mammogram and the recall rate of women who have undergone screening in the program. The sensitivity of the program may be defined as the ability of a mammogram to correctly identify those women with breast cancer, or in other words, the proportion of women who have breast cancer who also returned a positive or suspicious mammogram result. The sensitivity of the BreastScreen Program is defined as the proportion of invasive breast cancers that are detected within the program, out of the total of all breast cancers (interval cancers plus screen-detected cancers) diagnosed in program-screened women in the two year screening interval (AIHW 2008). For women aged 40 years or over there were 11,304 screen-detected cancers and 4,515 interval cancers during the period 2001-03, a sensitivity of 71.5 per cent. During the same period there were 7,943 screen-detected cancers and 3,156 interval cancers in women in the target age group (50–69 years), a sensitivity of 71.6 per cent. During 2001–2003, the sensitivity rate for women in the target age group 24 months after their *first* screen was 79.2 per cent compared to 71 per cent for women attending subsequent screening rounds (AIHW 2008).

High recall rates in a breast screening program are of particular concern. A suspicious or equivocal finding from a routine mammogram will result in the woman being recalled for further assessment, which may include additional mammography, ultrasound, fine needle aspiration or a biopsy, and as a consequence she may experience high levels of emotional stress and anxiety (Kavanagh et al 2006). A false positive screen is defined as one which results in a recall for assessment which is subsequently found not to be breast cancer. Factors which may affect the false positive rate include the woman's age, use of hormone replacement therapy, family history of breast cancer, symptomatic status and whether previous mammograms are available for comparison. Recall rates may also vary with the radiologists examining the film (Kavanagh et al 2006).

The National Accreditation Standards require that among woman aged 50-69 years, *less than 10 per cent* who attend for their *first* screen and *less than five per cent* who attend for their *second or subsequent* screen, are recalled for assessment. Women attending the BreastScreen Australia Program for the first time have a significantly higher all-size cancer detection rate than those who have previously been screened. This is reflected in a higher recall rate for women who attend for their first screening round compared with those who attend for a subsequent round. In 2005, the proportion of women aged 50–69 years recalled for assessment was significantly higher for women being screened for the first time (9.8%) compared to women attending for a subsequent round of screening (4.0%), both figures being less than those required by National Accreditation Standards (AIHW 2008).

The use of mammography for the systematic population screening of women is associated with both benefits and harms. A recent Cochrane review reported a

reduction in breast cancer mortality in the target age group of 50-69 years of 20 per cent, however when only high quality studies were assessed this rate was reduced to 15 per cent (Gotzsche & Nielsen 2006). Mammography is an imperfect screening tool which is neither highly sensitive nor specific, with stated sensitivities ranging from 71-79 per cent indicating that between 21 and 29 per cent of breast cancers are missed at screening. In addition, factors such as over diagnosis could be considered as a potential harm. Mammography is more likely to detect in situ carcinoma, with approximately only half of these cases progressing to invasive cancers. However these women will all be treated, some unnecessarily, with surgery, chemotherapy and/or radiation (Gotzsche & Nielsen 2006) Another major limitation of conventional mammography is that malignant and benign breast lesions will often appear to be similar (Avril & Adler 2007). In light of these concerns new modalities are currently being researched and assessed for the diagnosis of primary breast cancer, which may, in the future, be used in conjunction with standard mammography or digital mammography, or as stand alone diagnostic techniques. These techniques include positron emission tomography (PET), computed tomography (CT), electrical impedance tomography (EIT), thermography and scintimammography amongst others (Prasad & Houserkova 2007). The aim of this *Emerging Technology Bulletin* is to give a brief but not systematic overview of the current available evidence on these new diagnostic techniques, and to provide a preliminary assessment of their suitability as a potential breast cancer screening tool.

Computed tomography

Background

The concept of a breast computed tomography (CT) scanner is not new: a dedicated breast CT system was built in the mid 1970s in the early years of CT technology development (Reese et al 1976). Although early clinical studies indicated breast CT be a sensitive imaging examination for the detection of malignancies, dedicated breast CT as a potential cancer screening and diagnostic tool was suspended in the late 1970s due to concerns over high radiation dose, relatively low specificity, expensive equipment, and lack of spatial resolution (Chang et al 1978; Gisvold et al 1979; Glick 2007). With developments in digital flat-panel detectors for mammography and other imaging examinations, and improvements in temporal resolution (128 images/second) as well as in spatial resolution (0.4mm in-plane and 0.5mm in the z-direction), dedicated breast CT has regained academic and commercial interest. Several prototype breast CT systems are currently being designed, fabricated, and tested in various university laboratories and by companies (Boone et al 2006; Gupta et al 2006).

During a breast CT examination, the women lies prone on a table with her breasts in the pendant position through a hole in the table (Figure 6). Each breast is scanned individually without compression. In order to image all of the breast tissue, especially the ductal and glandular breast tissue near the chest wall, a depression is designed in the centre of the tabletop. This allows the women's chest wall to slump into the scan plane, such that the chest wall can be imaged by dedicated breast CT (Boone et al 2006).

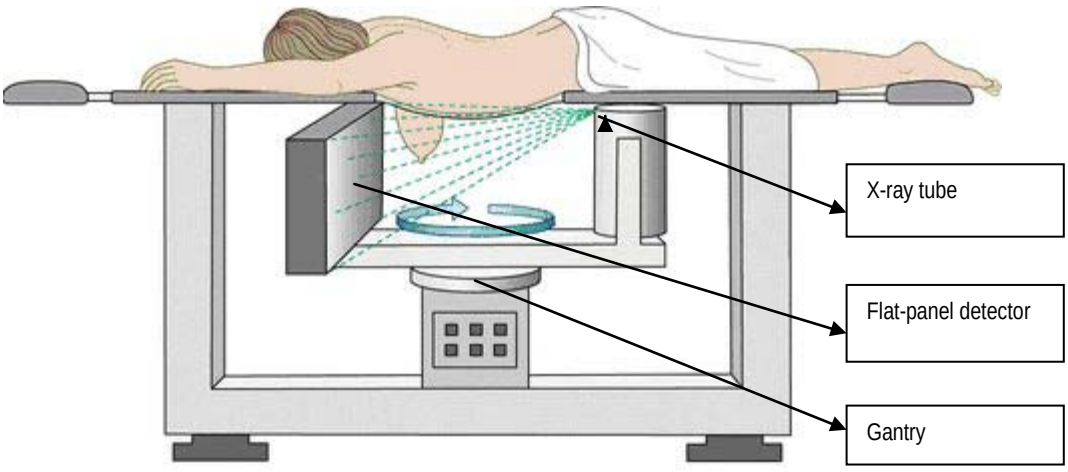

Figure 6 Illustration of a dedicated breast CT (Glick 2007)

Under the table, an X-ray tube and a flat-panel detector are installed on a mechanical gantry, with a distance of about 90cm. In order to insure coverage of the posterior of the breast, the X-ray tube and the detector are positioned

immediately below the tabletop to minimise the distance between the bottom of the table and the X-ray focal spot. X-ray tubes currently being investigated are end-windowed, water-cooled X-ray tube and carbon nanotube X-ray tube (Boone et al 2006; Zhang et al 2005). Although different in X-ray source, these two X-ray tubes have similar characteristics: 1) a small but powerful X-ray source to produce many breast images in a limited time period; 2) a large cone angle (16 degrees) to image the entire breast and 3) a small focal size (about 0.5mm) to minimize the penumbra effect. (Boone et al 2006; Glick 2007; Gupta et al 2006; Zhang et al 2005). An X-ray filter is inserted into the X-ray tube to remove photons with very low energy which can be absorbed by the breast tissue, therefore impairing the quality of the obtained image (Glick 2007; Gupta et al 2006).

The flat-panel detector for dedicated breast CT provides a field of view of 25 x 25 x 18cm^3, which is slightly smaller than the field-of-view in film mammography. Cesium-iodine (Cs-I) is usually used as the scintillator and is coupled to thin film transistors and photodiodes. The detector consists of a native pixel matrix of 2,048 x 1,536 elements, each with a pixel dimension of 194 x 194μm^2. Therefore, a breast CT is capable of spanning 18cm (z-direction) and producing 1,536 slices in one rotation. A readout speed of 30 frames per second (fps) is usually recommended, although the flat-panel detector has a potential maximum readout rate of 100 fps (Boone et al 2006; Glick 2007; Gupta et al 2006). In front of the flat-panel, an anti-scatter grid is often positioned with the purpose of preventing the generated scatter radiation from reaching the detector (Glick 2007; Gupta et al 2006).

As the X-ray tube and the flat-panel detector rotate around the examined breast, a number of cone-beam projection images are collected (Boone et al 2006). In order to improve imaging of the breast tissue near the chest wall, a breast CT gantry has been designed to allow the X-ray tube and detector to be tilted at various angles (Figure 7) (Glick 2007). The raw data from projection images are used to set up a three-dimensional representation of the breast using a CT reconstruction algorithm. In addition, a number of data correction algorithms, such as scatter correction, offset subtraction and adaptive filter mask are also required to compensate for system imperfection (Gupta et al 2006).

Compared with conventional mammography, dedicated breast CT has two advantages: 1) breast CT provides true three-dimensional images with isotropic resolution, which overcomes tissue superposition problems with conventional mammography and 2) examined women feel more comfortable, since painful breast compression is avoided during the examination (Glick 2007; Lindfors et al 2008).

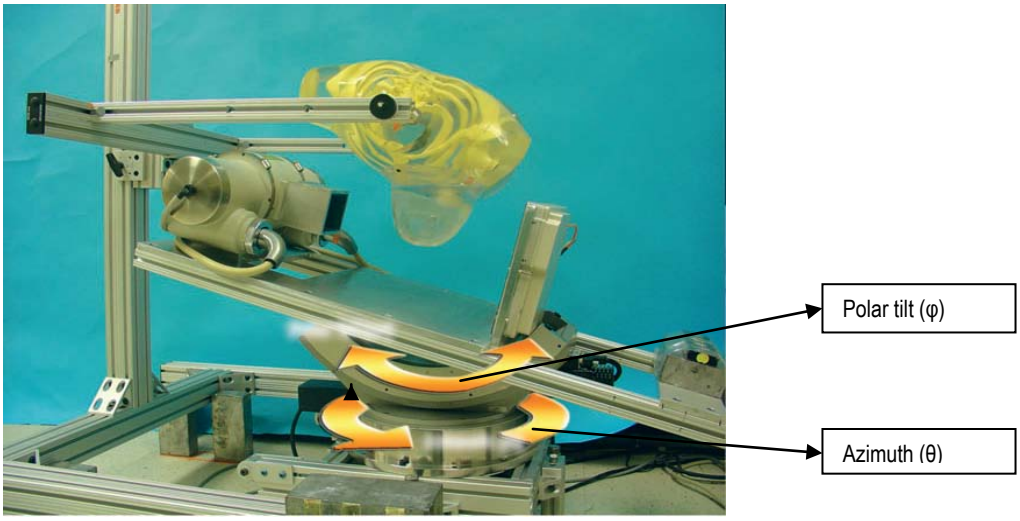

Figure 7 Dedicated breast CT gantry (developed at Duke University) (Glick 2007)

Safety

Radiation dose is a major safety consideration when evaluating the feasibility of dedicated breast CT. Compared to whole body CT, lower X-ray tube voltage and current settings are possible in breast CT. During dedicated breast CT only the examined breast is exposed to radiation, thus avoiding the need for higher energy radiation to penetrate the whole thorax (Glick 2007; Kalender & Kyriakou 2007). Experimental and Monte Carlo simulation studies have suggested that the radiation dose levels needed to produce adequate image quality during dedicated breast CT are approximately equal to those during two-view mammography (Boone et al 2005; Glick 2007; Gong et al 2006). Due to the relative uniform entrance of X-ray fluence in breast CT imaging, a more homogenous distribution of radiation dose through the breast was also observed for dedicated breast CT than for conventional mammography. Therefore, breast CT would have a lower maximum radiation dose to the breast than conventional mammography (Boone et al 2004; Thacker & Glick 2004). The clinical study included this *Emerging Technology Bulletin* did not report any adverse events associated with the use of dedicated breast CT. The mean glandular doses for patients with smaller, moderate or larger sized breasts (breast diameter at the chest wall of 12, 14 and 16cm, respectively) were 2.5mGy, 6.0mGy, and 10.3mGy, respectively (Lindfors et al 2008).

Effectiveness

Only one study, which investigated the use of dedicated breast CT for detecting breast lesions was identified (Lindfors et al 2008) (Table 1). Lindfors et al (2008) examined 69 *symptomatic* women (mean age 54.4 years) with BI-RADS category 4 and 5 lesions (see Box 1) with dedicated breast CT prior to core biopsy. Two patients were excluded due to movement during the CT, another two were excluded because the lesions detected by screen-film mammography were not in

the breast CT scan field of view. Therefore, the detection of breast lesions with dedicated breast CT was compared against those detected by mammography in a total of 65 patients (with 67 breast lesions).

Of these breast lesions, 38 (56.7%) were BI-RADS category 4 lesions; 28 (41.8%) were category 5 lesions; and one (1.5%) was a category 3 lesion. More than three quarters (77.6%, 52/67) of the breast lesions were masses; micro-calcification lesions accounted for 17.9 per cent (12) of all breast lesions; and the remaining 4.5 per cent (3) were lesions of other types. The breast density types as described in the mammography reports were: fatty replaced (1.5%), scattered fibro-glandular densities (40.3%), heterogeneously dense (38.3%), and dense (19.4%). Post-breast CT histology showed that, of the 67 breast lesions identified by mammography, 37 (55.2%) were malignancies; 28 (41.8%) were benign lesions; the other two (3.0%) were later proved to be summation artefacts and, therefore, biopsy was not carried out.

In assessing the conspicuity of breast lesions on breast CT relative to screen-film mammography, an experienced mammographer was asked to compared breast CT against screen-film mammography on a continuous scale of 1 to 10, where 1 indicated much better visualisation with breast CT than with mammography; 5.5 indicated equal visualisation between breast CT and mammography; and 10 indicated much better visualisation with mammography than with breast CT. No significant difference was reported in the overall visualisation of breast lesions between the two imaging modalities, with a mean lesion conspicuity score of 5.4 (p=0.48). Dedicated breast CT offered advantage over screen-film mammography in providing better visualisation of breast masses (4.9, p=0.002); whilst screen-film mammography was better than breast CT for micro-calcification visualisation (7.8, p=0.006). Breast CT was equal to screen-film mammography in distinguishing between benign breast lesions and malignancies or for the effect of breast density on lesion visualisation (p>0.05). The two false positives (summation artefacts) detected by mammography were not identified on dedicated breast CT. In the remaining 65 true breast lesions seen at mammography, seven lesions (10.8%) were not revealed by breast CT, including two malignant micro-calcification lesions, one subtle malignant mass (15mm), two benign micro-calcifications, one diabetic mastropathy, and one cyst (4mm). Dedicated breast CT detected one small satellite breast cancer which was not identified by mammography.

This study has limitations as only one individual scored both modalities and so it is unclear whether these results would be replicated by other radiologists. Further, the study is likely to have been affected by partial verification bias as only those women with a positive mammogram received a biopsy to ascertain true disease status.

A patient comfort survey was also carried out in this study. Ten additional healthy volunteers (mean age: 52 years) receiving breast CT examinations as well as three women with BI-RADS category 5 lesions who underwent contrast-enhanced breast CT were also required to complete patient comfort questionnaires. These 82 women were asked to compare their comfort levels during breast CT and

mammography on a continuous scale of 1 to 10: score 1: much more comfort with mammography than with breast CT; 5.5: equal comfort with breast CT and mammography; 10: much more comfort with breast CT. It was discovered that although position discomfort was expressed by many women during breast CT, subjects found it a more comfortable examination than screen-film mammography (p<0.001).

Table 1 Comparison of dedicated breast CT to mammography

Study	Diagnostic level of evidence	Study design	Population	Outcomes (Mean±SD)
Lindfors et al (2008)	III-2	Cross-classification of patients on CT and MX, compared to excisional biopsy.	69 *symptomatic* with BI-RADS category 4 and 5 lesions, mean age 54 years (range: 36-82 years) 10 healthy volunteers, mean age 52 year (range: 40-67 years) 4 women with BI-RADS category 5 lesions who were randomly selected	MX (*symptomatic* women only) Of the 67 lesions detected by MX 37/67 (55.2%) were malignant on biopsy 28/67 (41.8%) were benign on biopsy 2/67 (3.0%) artefacts CT (*symptomatic* women only) Of the 67 lesions detected by MX, CT detected 58/67 (86.6%) Of the true lesions (not artefacts) CT detected 58/65 (89.2%) Of the 7 lesions identified by MX but missed by CT 3/7 (42.9%) were malignant Conspicuity of lesions compared to MX* Overall (n=67): 5.4±1.9, p= 0.48 Lesion type: Masses or other findings (n=55): 4.9±1.5, p=0.002 Micro-calcifications (n=12): 7.8±1.9, p= 0.006 Lesion diagnosis: Malignant (n=37): 5.7±1.9, p= 0.81 Benign (n=28): 5.3±2.0, p= 0.35 Breast density type: Fatty replaced (n=1): 9.0 Scattered fibro-glandular (n=27): 5.1±1.4, p= 0.06 Heterogeneously dense (n=26): 5.3±1.8, p= 0.42 Dense (n=13): 6.4±2.8, p= 0.26 Patient comfort (all women) Overall (n=82): 7.9±2.1, p< 0.001 Position (n=82): 6.7±2.6, p< 0.001 Breath hold (n=82): 7.7±2.3, p< 0.001 Comfort during examination (n=82): 8.9±1.9, p< 0.001

MX = mammography, * A value of 5.5 indicates equal visualisation with breast CT and MX, a score <5.5 indicates superior visualisation with breast CT and a score of >5.5 indicates superior visualisation with MX, *p*-value calculated by using a Wilcoxon signed rank test with 5.5 subtracted, SD = standard deviation

Potential cost impact

As prototype dedicated breast CT systems are currently manufactured in academic or company laboratories and not marketed worldwide, the costs of capital equipment as well as medical services for dedicated breast CT are undetermined. It is hypothesised that the professional fee for breast CT would be more expensive than that for mammography (screen-film or digital), since dedicated breast CT is likely to require longer interpretation time for radiologists. However, the higher professional fee for breast CT might be offset by the reduced number of women who will be recalled for re-evaluation of suggestive breast lesions which are actually summation artefacts (Lindfors et al 2008).

In summary, little evidence on the safety and effectiveness of dedicated breast CT is currently available. The clinical performance of this technology as a diagnostic and screening tool still awaits further study and replication of the results by a larger group of blinded radiologists assessing an unselected population. However, limited evidence suggests that breast CT may be more comfortable for women than mammography.

Positron emission tomography

Background

The MSAC has completed several systematic reviews on the use of positron emission tomography (PET) for the detection of various cancers including solitary pulmonary nodules and non-small-cell lung cancer (approved for public funding) and for the assessment of patients with primary cancer of the oesophagus or the gastro-oesophageal junction (some indications approved for public funding). In addition, the MSAC are currently conducting two systematic reviews on the use of PET for lymphoma and head and neck cancer. Two references are waiting to be assigned to an evaluator group for the assessment of the use of PET for glioma and sarcoma, and breast and cervical cancer (MSAC 2008). As the projected time line for this review is suggested to be 12-24 months, a brief overview of the use of PET for the detection of primary breast cancer is merited.

PET is a minimally invasive procedure, which utilises the radionucleotide 2-[^{18}F] fluoro-2-deoxy-D-glucose (^{18}F-FDG) tracer, a radio-analogue of glucose with a half-life of approximately two hours, to produce diagnostic images. PET is useful in oncology imaging due to the tendency of tumours to utilise increased levels of glucose compared to surrounding normal tissue or benign neoplasms. Prior to imaging, patients must fast for at least 4-6 hours to ensure low plasma glucose levels (ideally <150mg/100ml). Sixty minutes after injection of the ^{18}F-FDG tracer (approximately 300-400 MBq[4]) into the bloodstream, a scanner detects and generates images of areas of high FDG uptake. Increased breast cancer detection rates have been observed with high doses (750 MBq) of ^{18}F-FDG (Avril & Adler 2007; Bristow et al 2003; Phelps 2000). There is, however considerable variation in the uptake of FDG by breast cancers, with invasive ductal carcinomas having a significantly higher uptake when compared to invasive lobular carcinomas. Uptake is higher in regions where the density of blood vessels is lower and in regions of high tumour cell proliferation (Avril & Adler 2007).

Many studies examining the use of PET for the diagnosis of breast cancer have used whole-body PET, which has a limited resolution (4.8-7.1 mm in plane resolution). It is unlikely that whole-body PET would be able to detect the small carcinomas that are easily detectable with mammography or MRI because of the loss of contrast due to scatter (Avril & Adler 2007). However, companies such as Naviscan Incorporated have developed a dedicated PET or positron emission mammography (PEM) system, the PEM Flex® Solo II, which was approved by the USA Food and Drug Administration (FDA) in 2003[5]. Although the PEM Flex® Solo II may be used for imaging small body parts that are capable of fitting into the gantry, its primary clinical use is as an adjunct to conventional imaging of the

[4] MBq = megabecquerels, a measure of radiation activity
[5] The PEM Flex® Solo II is not registered on the Australian Register of Therapeutic Goods

breast (Figure 8), specifically the detection, staging and management of primary breast cancer (Naviscan 2008).

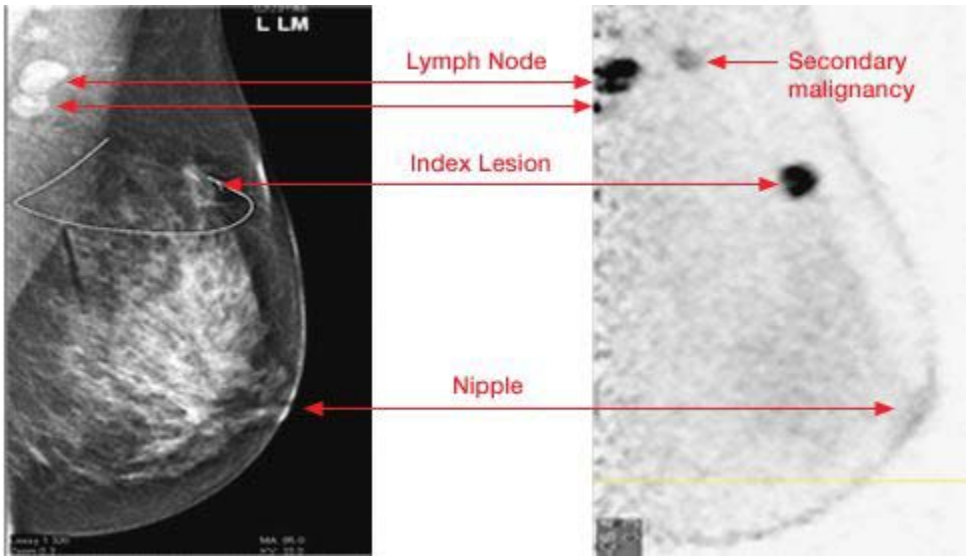

Figure 8 Mammography (LHS) identified index lesion but missed secondary malignancy identified by PEM (RHS) (Naviscan 2008) (printed with permission)

The PEM Flex® device consists of two detector heads which are mounted in compression paddles that are applied to the breast and images are processed by an on-board computer (Figure 9). Analysis allows for cross-correlation of images if digital X-rays are available, producing a fusion image (Weinberg et al 2005).

Figure 9 The Naviscan PEM Flex® Solo II imaging the breast (Naviscan 2008) (printed with permission)

Dedicated units such as these have improved resolution (1.5-2 mm) in comparison to whole-body PET and are seen as a means of improving the detection rate of small lesions (Figure 10). Conventional PET imaging of the breast requires the

patient to lie prone with the breast hanging free. The PEM Flex® compresses the breast tissue in a similar manner to a conventional mammogram, to reduce the mean path of gamma emissions, resulting in reduced scatter (Avril & Adler 2007).

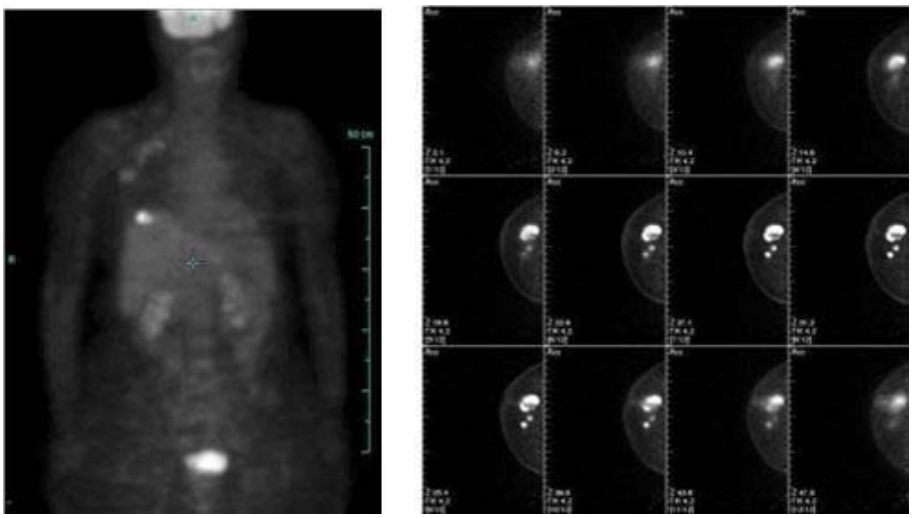

Figure 10 Comparison of whole-body PET (LHS), which identified 1 large lesion and PEM which identified 2 additional satellite lesions (Naviscan 2008) (printed with permission)

Safety

It is generally accepted that PET is a non-invasive and safe diagnostic procedure. It has been estimated that the dose of ionising radiation received by a patient undergoing a FDG-PET scan is equivalent to that received during a diagnostic CT scan (less than 10 millisieverts) (Marinovich et al 2004). None of the studies included for assessment reported any adverse events associated with the use of PET, however as with any diagnostic test, the potential harms of PET arise from the number of false positives (patients receiving unnecessary treatment) and false negatives (patients receiving no treatment).

Effectiveness

It should be stressed that the success of a diagnostic test for screening purposes relies on the prevalence of the disease within the population being screened. In a population with a high prevalence, ie a group of *symptomatic* women with suspicious lesions, as described in several studies included in this assessment, the diagnostic test will perform well and positive predictive value will increase. These results may be misleading if extrapolated to a screening environment with *asymptomatic* women. For an correct ascertainment of the accuracy of a diagnostic test which may be potentially used for screening, the test should be conducted in an *asymptomatic* population and be compared to the current gold or reference standard.

Two studies reported on the use of PET for the diagnosis of breast cancer among *symptomatic* women (Table 2). There is a reasonably large body of evidence on the use of whole-body PET for breast cancer, however the majority of these

studies lay outside the search period for this assessment. It would appear from the included studies that a dedicated breast PET scan is more effective at diagnosing breast cancer than whole-body PET. Although the three comparative studies included for assessment were of a high level of evidence, the generalisability of the results is poor as these studies were conducted on a small number of *symptomatic* women, rather than in an asymptomatic population.

A large case series screened *asymptomatic* women (n=660) who underwent PET imaging of the isolated breast (women imaged in the prone position with the breast held in a positioning device) and compared it to diagnosis with whole-body PET (level IV diagnostic evidence). Although the study stated that PET was compared to other imaging modalities, it was unclear whether *all* women enrolled in the study underwent this comparison, or if only those found to be PET-positive for cancer, therefore this study had to be considered a case series. Mammographic results were not presented, therefore a comparison of diagnostic accuracy could not be made. Of the 660 women, 62 (9.4%) were found to have an abnormality, however only 54 of these women were available for biopsy follow-up. Although seven women were correctly identified as having breast cancer (positive predictive value 13%), 47/54 (87%) were incorrectly diagnosed with an abnormality based on subsequent mammography or histopathology. Whole-body PET incorrectly classified as negative two of the women identified as positive by breast PET. So although a dedicated breast PET out performed whole-body PET, it still had a very high false positive rate (Kaida et al 2008b). A study conducted by the same author examined the use of whole-body PET and breast PET in *symptomatic* women with known lesions suspected of having breast cancer. Dedicated breast PET again performed better than whole-body PET (Kaida et al 2008a).

A pilot study examined 94 women with suspected or proven breast cancer (Tafra et al 2005). Of these women, 44 had biopsy confirmed breast cancer and were recruited for examination with a dedicated PEM unit. Eight readers were recruited to evaluate and review PEM images and the results of patient mammograms were made available. Some patients had also undergone ultrasound (27/44, 61%) and MRI (22/44, 50%). Readers were blinded to both surgical planning and outcome for the women (level III-I diagnostic evidence). PEM imaging was used to detect the primary lesion, determine the presence of multifocal disease or non-index lesions and to predict the status of the margins of patients undergoing mastectomy.

PEM detected 39/44 (89%) of the index lesions. Of the five missed lesions, one was posterior and could not be visualised with the PEM device. The four remaining PEM missed lesions, visible by mammography, were: a 3mm intermediate grade infiltrating ductal carcinoma, a 6mm low grade tubular carcinoma, a 10mm low grade infiltrating ductal carcinoma and a 1mm breast lymphoma. However, PEM detected four out of five (80%) incidental breast cancers, three of which were cases of extensive DCIS *not* detected by other imaging modalities. Of interest was that PEM was able to detect all index lesions of the women with dense breast tissue (n=23) (Tafra et al 2005). Other reports

have expressed concern that the uptake of ^{18}F-FDG varies considerably with breast density. It has been suggested that the standardised uptake values between 1-1.4 are well below the value of 2.5 regarded as the threshold for malignancy (Franc & Hawkins 2007). Although this study demonstrated a reasonable correlation with mammography, it is limited in that PEM was not used to screen or diagnose *asymptomatic* women and therefore gives no information as to the specificity or negative predictive value of the PEM device.

Berg et al (2006) later reported on the same group of 94 women but included *all* women with either confirmed breast cancer or a suspicious lesion, not just those with biopsy-confirmed breast cancer (level III-I diagnostic evidence). After excluding women with either type I or poorly controlled type II diabetes, 77 women were included in the study. Suspicious findings were reported in 33 (42.9%) of these women by core biopsy prior to PEM, 38 (49.3%) had an abnormal or suspicious mammogram and six (7.8%) had suspicious findings upon clinical breast examination. However, all results were reported in the context of identifying suspicious lesions, rather than in terms of the number of women diagnosed with cancer by each imaging modality. As a consequence the results of this study are not included in Table 2.

The recent review by Avril and Adler (2008) states that the low sensitivity of FDG-PET, due to its inability to detect small breast carcinomas, micrometastases, and small tumour-infiltrated lymph nodes, currently makes PET an unsuitable imaging modality for the routine screening of asymptomatic women. However, with the further development of dedicated positron emission mammographic units, this situation may alter (Avril & Adler 2007). It has also been suggested that the combination imaging modality of PET-CT, which gives more anatomical information, may be more useful in the diagnosis of breast cancer (Franc & Hawkins 2007). Most authors agree that the greatest advantage of PEM is in the planning of breast surgery and that it has promise for the axillary staging of breast cancer. For the true value of PEM or breast PET to be evaluated, large studies need to be conducted on asymptomatic women.

Potential cost impact

No economic studies were identified which have examined the use of PET for the *diagnosis* of breast cancer in comparison to mammography. A 2005 cost-effectiveness analysis examined the use of PET for the *staging and management* of breast cancer patients in Canada. Using the PET strategy, a cost saving of C$695 per person is expected with an increase in life expectancy of 7.4 days, when compared with the non-PET strategy. This cost-saving robust to a sensitivity analysis.

The Medicare Benefits Schedule (MBS) currently limits the use of FDG-PET. Item number 61559 allows for a FDG-PET study of the brain for the evaluation of refractory epilepsy (fee: $918) and item number 61529 allows for a whole-body FDG-PET study for the staging of proven non-small cell lung cancer (fee $953).

The MBS lists item number 59300 (fee $89.50) for the mammographic investigation of both breasts for a clinical abnormality (not routine screening of asymptomatic women) (Medicare Benefits Schedule 2009). During the period 2004-05, the BreastScreen Australia program screened 1.6 million women (AIHW 2008). If all these women underwent a FDG-PET scan the cost (MBS fees only, downstream costs/cost savings not included) would be approximately $1.5 billion, a substantial increase over the cost of conducting a mammogram (approximately $144 million).

A Naviscan PEM Flex® unit is estimated to cost between US$750-850,000 (personal communication, Naviscan).

Table 2 PET as a breast cancer diagnostic tool

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Kaida et al (2008a)	III-I	Cross-classification of patients on breast PET and whole-body PET, compared to histopathology/ biopsy.	118 *symptomatic* women with lesions suspected to have breast cancer as diagnosed by MX or clinical examination. Mean age 58 years (range 28-91 years)	Of 118 women with 122 lesions, 112 patients with 114 lesions were diagnosed as having breast cancer by histopathology. Breast PET Sensitivity 95.6% Specificity 50% PPV 96.5% NPV 44.4% Diag accuracy 92.6% 4/8 (50%) lesions false positive 5/114 (4.4%) lesions false negative Whole-body PET Sensitivity 83% Specificity 50% PPV 96% NPV 80%
Kaida et al (2008b)	IV	Case series	660 *asymptomatic* women, mean age 59.9 years (range 27-85 years) underwent whole-body and dedicated breast PET	Breast PET and whole-body PET Detected 62/660 (9.4%) women with abnormalities, of these 54 were available for follow-up Breast PET 7/54 (13%) were correctly identified as having breast cancer (PPV) 47/54 (87%) were incorrectly identified as having breast cancer Whole-body PET 5/54 (9.3%) were correctly identified as having breast cancer (PPV) 47/54 (87%) were incorrectly identified as having BC 2/54 (3.7%) were incorrectly identified as *not* having BC
Tafra et al (2005)	III-I	Cross-classification of patients on PEM and MX, compared to excisional biopsy.	44 *symptomatic* women with biopsy confirmed breast cancer, mean age 57 years (range 25-88 years), 31/44 (70%) post-menopausal, 19/44 (43%) on HRT	PEM detected 39/44 (89%) of index lesions PEM detected 4/5 (80%) of incidental breast cancers, 3/5 (60%) of these were not detected by other imaging modalities

MX = mammography, PEM = positron emission mammogram, HRT = hormone replacement therapy, PPV = positive predictive value, NPV = negative predictive value, BC = breast cancer

Ultrasonography

Background

A previous Horizon Scanning summary reported on the use of ultrasound elasticity imaging (USEI), a modification of ultrasound, which incorporates tissue compression and elasticity measurements (see Appendix B). USEI exploits the property that malignant masses are 'stiffer' than normal tissue. This Emerging Technology Bulletin will not consider USEI further, but will concentrate on the use of conventional ultrasound (U/S) for the diagnosis of breast cancer.

U/S is frequently used to guide interventional procedures, such as core-needle biopsy, in women with suspicious findings on a mammogram. In addition, ultrasonography has been used as an adjunct imaging modality, especially in cases of equivocal mammograms. U/S may be used to differentiate solid masses from cysts, which may constitute 25 per cent of breast lesions (Figure 11). The majority of cysts are benign fluid-filled sacs (Prasad & Houserkova 2007). Advances in transducer technology and signal processing have improved image quality to the point that ultrasonography may be considered as a diagnostic imaging modality for breast cancer, especially in younger women with dense breast tissue (Corsetti et al 2006; Karellas & Vedantham 2008).

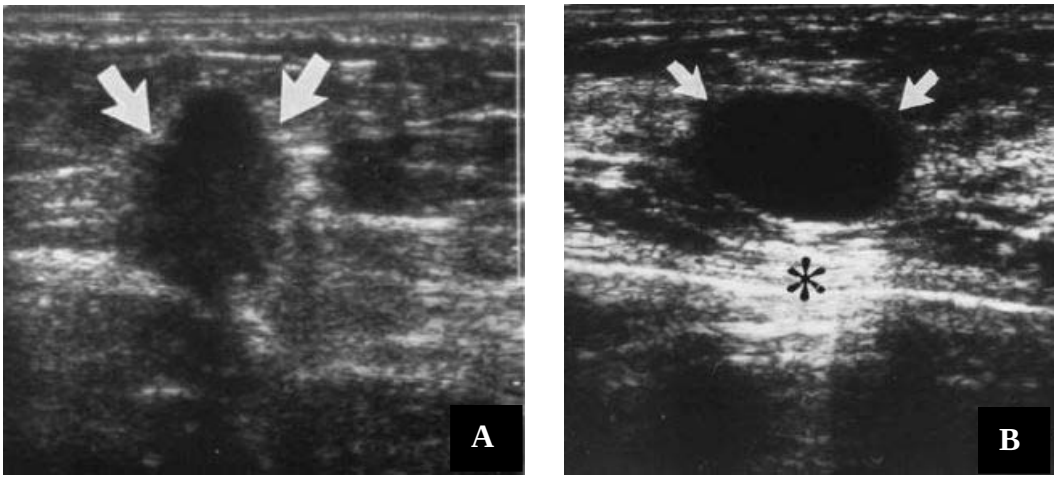

Figure 11 A: Ultrasonogram of a breast carcinoma, with arrows indicating ill-defined margins and low-level heterogeneous internal echoes
B: Ultrasonogram of a cyst (arrows) which is characterised by an oval or round shape, absence of internal echoes, clearly defined posterior wall and enhancement of distal echoes (Prasad & Houserkova 2007)

A useful addition to breast imaging with U/S is Doppler U/S, which is commonly used to assess blood flow and may be useful in the characterisation of solid masses such as malignancies which may have an increased blood flow (Prasad & Houserkova 2007). Breasts should be scanned in vertical and horizontal stripes,

covering the areola and axillary tail, ensuring that the entire breast volume is scanned (Figure 12) (Corsetti et al 2008).

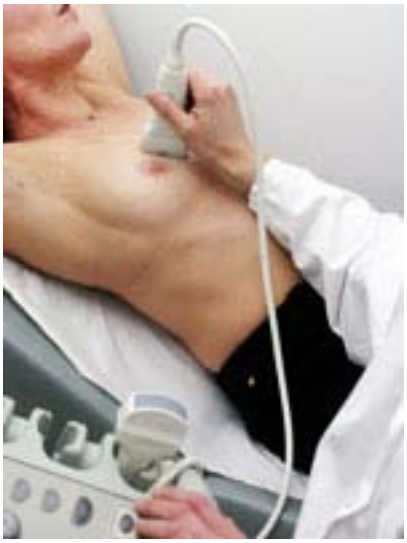

Figure 12 Woman undergoing breast ultrasound (Health Media Ventures Inc 2009)

Safety

Ultrasound is considered a safe procedure as it does not use ionising radiation and therefore it can be used on a more regular basis than mammography. No adverse events associated with the use of U/S for the diagnosis of breast cancer were reported by any of the included studies.

Effectiveness

Three studies that used U/S as a tool for diagnosis of breast cancer were identified for inclusion in this assessment (Table 3) (Berg et al 2008; Corsetti et al 2008; Ohlinger et al 2006).

The cross classification study conducted by Corsetti et al (2008) reported on the ability of U/S to detect breast cancer in *asymptomatic* women with a breast density greater than 50 per cent who had previously been found to be negative for breast cancer by mammography (level III-1 diagnostic evidence). Suspicious findings were reported in 449 women, 50 of whom subsequently had biopsy-confirmed breast cancer. The positive predictive[6] value for U/S was therefore 11.13 per cent. It was interesting to note, however, that U/S detected breast cancers at a significantly earlier stage than mammography (p=0.001) (data not shown). An earlier 2006 study by the same author reported findings on 17,883 consecutive women undergoing mammography (Corsetti et al 2006). Similar rates of breast cancer detection were reported for mammography and U/S as those described by Corsetti et al (2008). It has been assumed that the patient population

[6] Positive predictive value = the proportion of women who tested positive for breast cancer who actually had the disease

is the same, with the 2006 study reporting preliminary findings, and therefore this study is not presented in Table 3.

Although the study by Berg et al (2008) reported on the sensitivity and specificity of the use of U/S alone, the study was not designed to allow a direct comparison of mammography with U/S alone, rather the study reported on the use of U/S as an adjunct to mammography (level III-1 diagnostic evidence). The diagnostic accuracy of using U/S alone was similar to that achieved with mammography alone (0.80 vs 0.78) relative to the gold standard of biopsy-confirmed breast cancer. The positive predictive value of U/S alone was low at 8.6 per cent, meaning that of all suspicious findings found by U/S, 91.4 per cent were benign. The positive predictive value of mammography alone was higher (14.7%), however, the PPV for U/S plus mammography was between these two values (10.1%). U/S, used in conjunction with mammography, resulted in a 55 per cent increase in the number of breast cancers diagnosed per 1,000 women compared to mammography alone (11.8/1000 vs 7.6/1000). So although the addition of U/S to mammography increases the number of cancers detected per 1,000 women, it also has the effect of increasing the number of false positives. However it does substantially reduce the number of false negatives, suggesting that U/S as an adjunct to mammography may have some benefit. There were statistically significant differences in sensitivity, specificity and diagnostic accuracy of U/S combined with mammography when compared to mammography alone.

Ohlinger et al (2006) conducted a similar but much smaller (n=448) study to that conducted by Berg et al (2008) with the exception that the asymptomatic study population did not consist of women at high-risk of breast cancer. The results obtained varied greatly from those obtained by Berg et al. This may be an indication that the smaller study may be underpowered to detect a meaningful result, particularly given the lower risk of cancer in this population. The results may also reflect a difference in either U/S technique or interpretation of the U/S images, as the value obtained for diagnostic accuracy of mammography was similar in both studies (Berg = 78%, Ohlinger = 78.6%) with diagnostic accuracy quite different between the two studies for U/S alone (Berg = 80%, Ohlinger = 64.3%) and U/S plus mammography (Berg = 91%, Ohlinger = 50%).

Table 3 Ultrasound as a breast cancer diagnostic tool

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Berg et al (2008)	III-1	Cross-classification of patients on U/S and MX, versus U/S or MX alone, compared to excisional biopsy	2,725 *asymptomatic* women with dense breast tissue and/or a *high risk* of BC (personal history of BC, family history of either a 1st or 2nd degree relative with BC or a known BRCA mutation) presenting for routine MX. Mean age 55 years (range 25-91 years)	2,637 women available for follow-up **U/S alone [95% CI]** Diagnosed BC 20/2636 (0.75%) Sensitivity 20/40 (50%) [33.8, 66.2] Specificity 2383/2596 (91.8%) [90.7, 98.8] PPV 20/233 (8.6%) [5.3, 13.0] NPV 2383/2403 (99.2%) [98.7, 99.5] FP 8.2% FN 50% DA 0.80 [0.70, 0.88] **MX alone [95% CI]** Diagnosed BC 20/2637 (0.76%) Sensitivity 20/40 (50%) [33.8, 66.2] Specificity 2481/2597 (95.5%) [94.7, 96.3] PPV 20/136 (14.7%) [9.2, 21.8] NPV 2481/2501 (99.2%) [98.8, 99.5] FP 4.5% FN 50% DA 0.78 [0.67, 0.87] **U/S + MX [95% CI]** Diagnosed BC 31/2637 (1.18%) Sensitivity 31/40 (77.5%) [61.6, 89.2] Specificity 2322/2597 (89.4%) [98.2, 90.6] PPV 31/306 (10.1%) [7.0, 14.1] NPV 2322/2331 (99.6%) [99.3, 99.8] FP 10.6% FN 22.5% DA 0.91 [0.84, 0.96]

				U/S + MX compared to MX alone Difference, p value Sensitivity 27.5 % [9.5, 45.5] p=0.003 Specificity -6.12% [-7.24, -5] p <0.001 DA 0.23 [0.10, 0.35] p <0.001 Odds ratio PPV 0.65, p = 0.03 NPV 2.08, p = 0.004
Corsetti et al (2008)	III-1	Cross-classification of patients on U/S and MX, compared to excisional biopsy	26,047 consecutive *asymptomatic* women presenting for MX. 25,572 women negative on MX, of these 9,157 had >50% breast density. These women were assessed by U/S. Suspicious U/S followed by MX and biopsy.	475/26047 (1.8%) suspect MX PPV for MX recall to assessment 166/475 (34.9%) 9157/25572 (35.8%) classified as having breast density >50% and classified as negative for BC by MX U/S detected 449/9157 (4.9%) positive 50/9157 (0.55%) additional BC PPV 11.13% 13/50 (26%) were symptomatic or had other clinical findings and were excluded. Relative incremental BC detection at U/S in *asymptomatic* women, over MX detected All cancers 37/179 (20.6%) >50 years 18/133 (13.5%) <50 years 19/46 (41.3%)
Ohlinger et al (2006)	III-1	Cross-classification of patients on U/S and MX, compared to excisional biopsy	448 *asymptomatic* women underwent U/S followed by MX. Mean age 49.1 years (range 21-89 years)	U/S alone Diagnosed BC 3/448 (0.67%) Sensitivity 3/3 (100%) Specificity 6/11 (54.5%) PPV 3/8 (37.5%) NPV 6/6 (100%) FP 5/11 (45.5%) FN 0/3 (0%) DA 9/14 (64.3%) MX alone [95% CI] Diagnosed BC 3/448 (0.67%) Sensitivity 3/3 (100%) Specificity 8/11 (72.7%) PPV 3/6 (50%) NPV 8/8 (100%) FP 3/11 (27.3%)

				FN	0/3 (0%)
				DA	11/14 (78.6%)
				U/S + MX [95% CI]	
				Diagnosed BC	3/448 (0.67%)
				Sensitivity	3/3 (100%)
				Specificity	4/11 (36.4%)
				PPV	3/10 (30%)
				NPV	4/4 (100%)
				FP	7/11 (63.6%)
				FN	0/3 (0%)
				DA	7/14 (50%)

MX = mammography, BC = breast cancer, U/S = ultrasound, PPV = positive predictive value, NPV = negative predictive value, FP = false positive, FN = false negative, DA = diagnostic accuracy

Potential cost impact

The cross classification study conducted by Corsetti et al (2008) calculated the additional cost per woman of an ultrasound examination and the cost per additional cancer detected by ultrasound. The cost per ultrasound-scanned women was estimated to be €59-62. The standard cost for the detection of one cancer by conventional mammography screening was estimated to be €5,000 compared to the cost per ultrasound-detected cancer which ranged between €14,618-15,234, taking into account costs of all additional testing. Interestingly, the earlier 2006 study by Corsetti et al reported a reduced cost per women examined with U/S of €22 but a much higher cost per additional breast cancer detected of €25,847. This was primarily due to the lower rate of cancer detection by U/S alone in the study's earlier findings, which may be due to technique learning curve. The rate of breast cancer detection by U/S in the mammography negative *asymptomatic* women was 2008: 0.40% vs 2006: 0.23%. Therefore the cost per U/S-only detected breast cancer was much higher in the 2006 study. The cost per U/S scanned woman was also much higher in the 2008 study and the reason for this difference is unclear. The authors state that they do not advocate the use of ultrasound for routine screening of *asymptomatic* women, however it may be of use in cases of equivocal mammography findings.

There are two MBS item numbers for diagnostic U/S of the breast. Item number 55070 allows the U/S of one breast where the patient is referred by a medical practitioner; and the service is not associated with a service to which an item in Subgroup 2 or 3 of this group applies; and the referring medical practitioner is not a member of a group of practitioners of which the providing practitioner is a member (fee $98.25). Item number 55073 allows the U/S of one breast where the patient is not referred by a medical practitioner; and the service is not associated with a service to which an item in Subgroup 2 or 3 of this group applies (fee $34.05) (Medicare Benefits Schedule 2009).

Thermography

Background

Thermography is non-invasive diagnostic tool which uses infrared imaging to detect changes in skin temperature. The use of thermography for the detection of cancers exploits the principle that tumours are areas of high cell growth and metabolism. To fuel the increase in cell growth and cell turnover, tumours enlarge existing blood vessels and recruit new vessels via angiogenesis. The increase in blood flow and metabolic rate may be reflected in an increase in the temperature of the tumour relative to normal tissue, which is then captured by the infrared camera. Intense red regions indicate heat and therefore possible tumours and blue indicate cooler regions correlating to normal tissue (Figure 13) (Ng & Kee 2008; Prasad & Houserkova 2007).

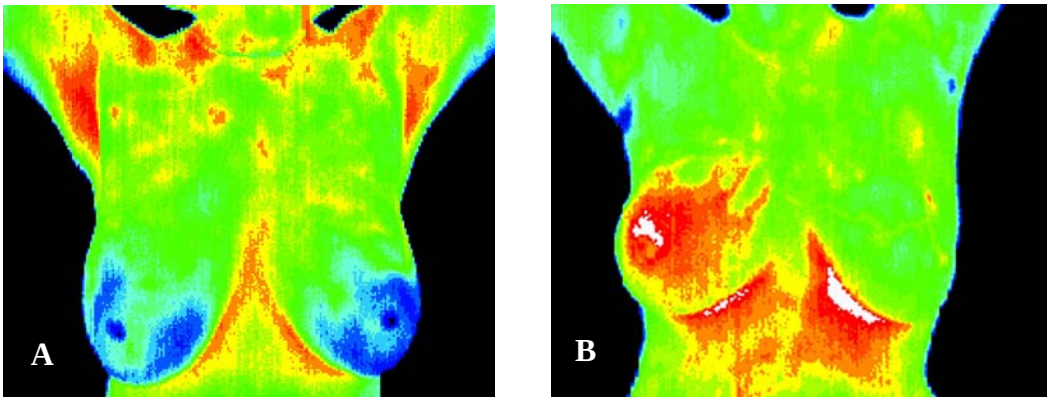

Figure 13 Images acquired by thermography. A: indicating normal breast tissue (blue) and B: indicating invasive breast cancer (red) (Meditherm 2008) (printed with permission)

The majority of thermographic systems are referred to as static thermography. These systems consist of an infrared camera for image acquisition which is connected to a computer or work station where the image can be viewed and digitally stored. The imager converts the thermal energy into electrical signals and displays this information as a temperature profile. Specialised software enables images to be manipulated for interpretation by specialised readers. The infrared camera should be located greater than 0.5m, but less than 6m, away from the subject and the ambient temperature of the imaging room should be between 20-25°C (Figure 14). Women are advised to abstain from any physical activity 20 minutes prior to imaging to reduce their metabolic rate. In addition subjects are advised to avoid alcohol and cigarettes prior to imaging as they may affect the body's temperature. Pre-menopausal women should also be within the 5th to the 12th and 21st days of their menstrual cycle to ensure vascularisation is at a basal level. Three images are taken during the process: one frontal and two lateral. Imaging takes approximately 15 minutes (Ng & Kee 2008).

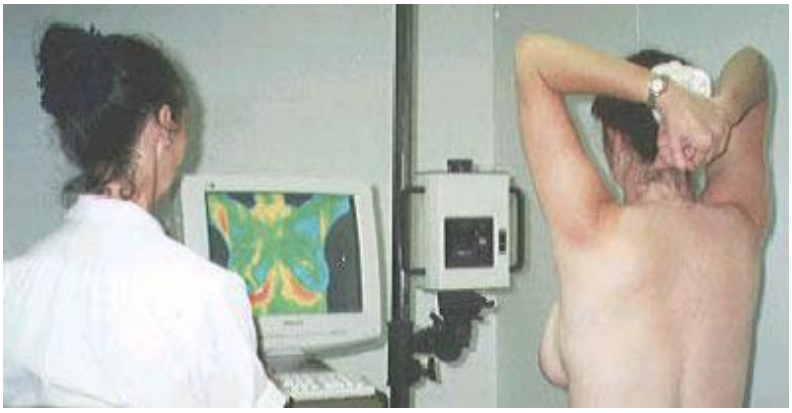

Figure 14 Woman undergoing thermography (Meditherm 2008) (printed with permission)

An alternative method to static thermography is dynamic thermography. During dynamic thermography, eight sensors are attached to each breast and microprocessors record temperature variations of the skin over a 48-hour period, during which time women are advised to maintain their normal daily activities. Approximately 9,000 data points are collected from each sensor during this time period and plotted against each other to form a thermal motion picture. Algorithms are applied to categorise these images (Salhab et al 2005).

In 1982, the FDA approved thermography for the adjunctive detection of temperature change in breast cancer patients (Arora et al 2008). The Australian Therapeutic Goods Administration (TGA) has one thermography system listed on the therapeutic goods register (July 2007, ARTG number 145067, sponsored by Surgical Synergies Pty Ltd) (TGA 2009).

Safety

Thermography is non-invasive and appears to be a safe diagnostic procedure. None of the studies included for assessment reported any adverse events associated with the use of thermography, however as previously stated, the potential harms of thermography when used for breast cancer diagnosis arise from the number of false positives (patients receiving unnecessary treatment) and false negatives (patients receiving no treatment).

Effectiveness

A 2004 review written by New Zealand Health Technology Assessment (NZHTA) assessed the use of thermography as a diagnostic and adjunctive diagnostic tool for breast cancer (Kerr 2004). This review identified one prospective cohort study (Williams et al 1990), which satisfied the inclusion criteria for thermography as a diagnostic tool. This poor quality study reported on a population consisting of both asymptomatic and symptomatic women. Statements on the generalisability of thermography for breast cancer diagnosis could not be made as the results of these two groups were not presented separately. In addition, clinical effectiveness could not be measured as there was

no blinded application of the reference standard to enrolled subjects. Two studies, a case-control (Keyserlingk et al 1998) and a non-controlled clinical trial (Parisky et al 2003), were identified which investigated the use of thermography as an adjunctive diagnostic tool. Both of these studies were considered to be of poor quality with flaws in their study design and reporting of data. The NZHTA review did not identify any randomised controlled trials comparing the use of thermography to mammography. This review found that most of the current thermography literature was in the form of narrative review or opinion articles. In addition, no economic studies on the use of thermography were identified (Kerr 2004).

Only two new studies were identified for inclusion in this bulletin (Table 4). As with previous studies discussed in this report, although the cross-classification studies were a reasonable level of evidence, the generalisability of results is poor as thermography was conducted on a *symptomatic* population, limiting the generalisability of the findings. The study by Arora et al (2008) used three modes of post-imaging analysis to generate three different scores: an overall risk score (screening mode), a clinical score (based on patient information) and an artificial neural network score (based on an algorithm). Good sensitivity and poor specificity was reported for all modes (Table 4). The poor specificity (11.8%) obtained in the screening mode would be mean that the number of false positives obtained in an *asymptomatic* population would be unacceptably high. However, the negative predictive value of 82 per cent (figures not shown) indicates that thermography is reasonably good at reassuring those patients who test negative that they do not have cancer. Results obtained with the use of *dynamic* thermography demonstrated an improved specificity compared to the study by Arora et al, however of concern is the reduced sensitivity and positive predictive value considering the population tested was symptomatic (Salhab et al 2006).

A third small study was identified which investigated the applicability of a new algorithm using the amplitude of localised temperature increases in breast tissue. The use of this algorithm is in the initial stages of development and not in routine clinical use (Tang et al 2008).

Potential cost impact

In Australia, there are many private companies offering thermography as a direct-to-market service. One company offers an initial or yearly routine thermography scan for $150, and a follow-up scan (within 6 months) for $99 (Sunstate Thermal Imaging 2008). The Australian distributing company for the only ARTG listed infrared thermography imaging system was contacted in regard to pricing structure, however no response was received. Meditherm Inc manufactures a number of thermography imaging units with prices ranging from US$22,500-34,850 (Meditherm 2008).

Table 4 Thermography as a breast cancer diagnostic tool

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Arora et al (2008)	III-2	Cross-classification of patients on infrared thermography compared to histopathology/ biopsy.	92 *symptomatic* women with lesions suspected as BC and detected by MX or U/S. Mean age 51 years (range 23-85 years)	94 biopsies were performed in 92 women. Of these, 60/94 (63.8%) were malignant on biopsy Screening mode Sensitivity 96.7% Specificity 11.8% Clinical mode Sensitivity 90.0% Specificity 44.1% Artificial neural network Sensitivity 96.7% Specificity 26.5%
Salhab et al (2006)	III-2	Cross-classification of patients on dynamic thermography and MX compared to histopathology/ biopsy.	173 *symptomatic* women with suspicious findings on a MX; thermography imaged prior to biopsy. Mean age 56 years (range 17-85 years)	Thermal data analysed from only 160 women. Sensitivity 72% Specificity 33% PPV 67% NPV 38.3% Diagnostic Accuracy 58.8%

MX = mammography, U/S = ultrasound, PPV = positive predictive value, NPV = negative predictive value, BC = breast cancer

In summary, there is little evidence to support the use of thermography for the diagnosis of breast cancer in asymptomatic women. The majority of authors of the included studies stated that thermography may have a role as an adjunct to conventional mammography or MRI in young, pre-menopausal women with dense breast tissue. There is a need for high quality randomised controlled trials to be conducted comparing the use of thermography and mammography to detect breast cancer in an asymptomatic population.

The National Advisory Committee to the BreastScreen Australia Program does not recommend the use of thermography for the early detection of breast cancer (National Breast and Ovarian Cancer Centre 2003).

Electrical impedance

Background

Electrical impedance (EI), also known as EI tomography, is a measure of how fast electricity travels through a given material. EI is a non-invasive, radiation-free, imaging technique that assesses the electrical conductivity[7] of the breast. The electrical conductivity of many tumours may significantly differ from that of the surrounding normal tissue due to changes in cell structure and pathology. Biological alterations within cancerous cells including alterations in the intra- and extra-cellular fluid compartments, cell membrane surface area and ionic permeability, affect the electrical impedance of the cell. The electrical conductivity of breast cancer cells is higher, and therefore will have a lower electrical impedance, compared to the surrounding normal tissue. During EI, an electrode is either placed on, or held by the subject. A small alternating electric current (between 1-1.25 volts) is applied and the electrical current on the surface of the breast is measured by a hand held transducer or scanning probe placed over the breast (Figure 15) (Prasad & Houserkova 2007; Prasad et al 2008).

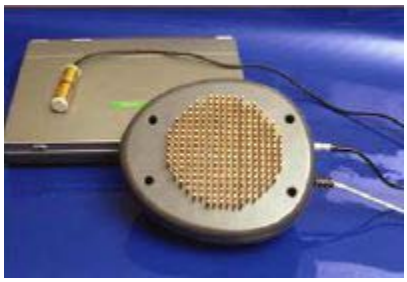

Figure 15 An EI unit with hand held transducer (Prasad et al 2008)

If a cancerous lesion is present, the electric field is distorted by the increase in capacitance[8] and electrical conductivity within the breast. Voltage measurement data are recorded on a computer and specialised algorithms construct a low resolution image of the impedance distribution. EI is limited by the low resolution of the images (Figure 16), variations in electrode-skin contact and poor signal-to-noise ratio (Prasad & Houserkova 2007; Prasad et al 2008).

EI is proposed as an adjunctive breast cancer diagnostic tool in young, pre-menopausal women, as it is thought that impedance is affected by hormonal alterations brought about by menopause (Stojadinovic et al 2008). It therefore may have little relevance for a breast screening program which is targeted at an older population.

In 1999, the FDA approved the T-Scan 2000 EI scanner, manufactured by TransScan Medical Inc, to be used in cases of an ambiguous mammogram, to determine whether or not a woman should be evaluated further. The device was not approved for use in patients with clear mammographic or non-mammographic indications for biopsy (FDA 1999). There is only one EI scanner listed on the ARTG (May 2008, ARTG number 152697, sponsored by Health Screening

[7] Electrical conductivity is a measure of a material's ability to conduct an electric current
[8] Capacitance is the ability of a body to hold an electrical charge

Technologies Pty Ltd). This multi-frequency EI imaging device is intended to be used to detect differences in capacitance and resistance between neoplastic and surrounding normal tissue (TGA 2009).

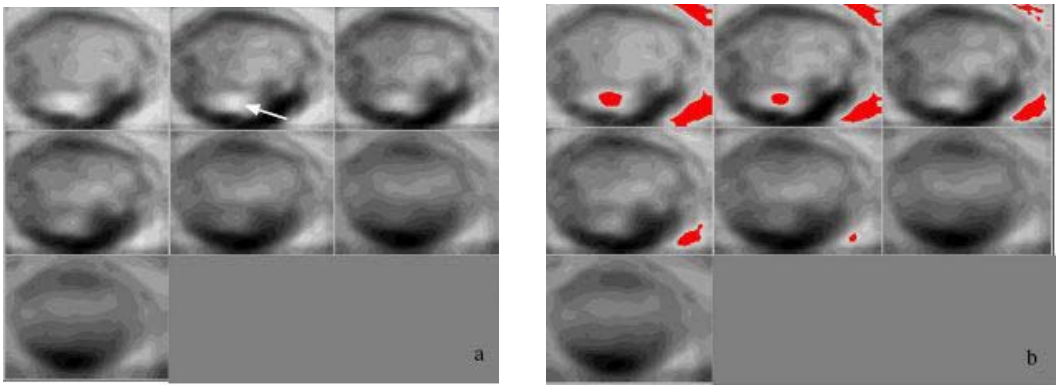

Figure 16 a) The white arrow indicates a region of hyper-impedance, suggestive of breast cancer, which is highlighted in red in b) (Prasad et al 2008)

Safety

Electrical impedance is non-invasive and does not use radiation. EI appears to be a safe diagnostic procedure. None of the studies included for assessment reported any adverse events associated with the use of EI. However of concern is potential harm resulting from the high number of false negatives (62 and 74%) as reported by Stojadinovic et al (2006 and 2008), and thus potentially delayed treatment.

Effectiveness

Four studies which assessed the use of EI as a diagnostic tool for breast cancer were identified (Table 5). However, three of these studies were progressive reports on the same group of women, with incremental recruitment (Stojadinovic et al 2006; Stojadinovic et al 2005; Stojadinovic et al 2008). Only the results of the 2006 and 2008 studies are presented. These studies were divided into two arms, described by the authors as a specificity arm (level IV diagnostic) and a sensitivity arm (level III-1 diagnostic evidence). In the specificity arm, *asymptomatic* women were screened with EI during routine clinical visits. A small number of women were found to be positive using EI (4.9 and 5.3%), however, the authors did not conduct follow-up clinical or breast pathology testing on these patients, despite an ethical imperative to do so. All EI positive women were assumed to be false positives due to the small likelihood of breast cancer being present in young, pre-menopausal women. The authors erroneously reported a specificity value using this assumption. In the sensitivity arm, *symptomatic* women were examined with EI prior to biopsy. The diagnostic accuracy of EI was calculated by the evaluators to be 69 per cent.

The remaining study (level III-2 diagnostic evidence) compared the diagnostic ability of EI to that of mammography and ultrasound in symptomatic women (Prasad et al 2008). The performance of EI was comparable to these two modalities, with no significant difference between modalities (mammography vs

U/S p=0.219, mammography vs EIT p=0.779, U/S vs EI p= 0.169). However, sample size calculations were not reported and the study may be underpowered to detect meaningful differences. It is also apparent that EI performed poorly at detecting carcinoma when compared with mammography and U/S and thus would appear to be less successful at detecting the targe condition (Prasad 2008).

Table 5 Electrical impedance as a breast cancer diagnostic tool

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Prasad et al (2008)	III-2	Cross-classification of patients on electrical impedance and MX and/or U/S compared to histopathology/ biopsy.	88 *symptomatic* women with suspicious findings on MX or US, imaged prior to biopsy. Age and menopausal status not stated.	59/88 (67%) confirmed abnormality by biopsy MX detection rate [95% CI] Total 50/59 (84.7%) [77.1, 92.3] Cyst 17/21 (81.0%) [58.1, 94.6%] Fibroadenoma 14/16 (87.5%) [61.7, 98.5] Carcinoma 4/4 (100%) [39.8, 100] Fibrocystic mastitis 15/18 (83.3%) [58.6, 96.4] U/S detection rate [95% CI] Total 54/59 (91.5%) [85.6, 97.4] Cyst 21/21 (100%) [83.9, 100] Fibroadenoma 12/16 (75.0%) [57.2, 92.7] Carcinoma 4/4 (100%) [39.8, 100] Fibrocystic mastitis 17/18 (94.4%) [72.7, 99.9%] EI detection rate [95% CI] Total 49/59 (83.1%) [75.1, 91.0] Cyst 21/21 (100%) [83.9, 100] Fibroadenoma 11/16 (68.8%) [41.3, 88.9] Carcinoma 3/4 (75.0%) [19.4, 99.4] Fibrocystic mastitis 14/18 (77.8%) [52.4, 93.4]

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Stojadinovic et al (2008)	III-1	This study is a continuation of the 2006 study. Prospective cohort, cross-classification of patients on electrical impedance and/or MX, CBE, U/S compared to histopathology/ biopsy. Blinded.	Sensitivity arm 390 *symptomatic* women with suspicious findings on CBE, MX, U/S or MRI, aged between 30-45 years, assessed with EI prior to biopsy. Post-menopausal or pregnant women were excluded from the study.	87/390 (22.3%) found to be positive on biopsy Electrical impedance* Sensitivity 23/87 (26.4%) Specificity 245/303 (80.9%) NPV 245/309 (79.3%) PPV 23/81 (28.4%) FP 58/303 (19.1%) FN 64/87 (73.6%) Diagnostic accuracy 268/390 (68.7%)
Stojadinovic et al (2008)	IV	This study is a continuation of the 2006 study. Case series	Specificity arm 1,751 *asymptomatic* women aged between 30-39 years. Post-menopausal or pregnant women were excluded from the study.	93/1751 (5.3%) found to be positive on EI. No follow-up breast pathology on these women was conducted.
Stojadinovic et al (2006)	III-1	Prospective cohort, cross-classification of patients on electrical impedance and/or MX, CBE, U/S compared to histopathology/ biopsy. Blinded.	Sensitivity arm 189 *symptomatic* women with suspicious findings on CBE, MX, U/S or MRI, mean age 39.3 ± 4.3 years, assessed with EI prior to biopsy. Post-menopausal or pregnant women were excluded from the study.	50/189 (26.5%) found to be positive on biopsy Electrical impedance* Sensitivity 19/50 (38.0%) Specificity 112/139 (80.6%) NPV 112/143 (78.3%) PPV 19/46 (41.3%) FP 27/139 (19.4%) FN 31/50 (62.0%) Diagnostic accuracy 131/189 (69.3%)

Stojadinovic et al (2006)	IV	Case series	<u>Specificity arm</u> 1,361 *asymptomatic* women. Mean age 34.6 ± 3.1 years. Post-menopausal or pregnant women were excluded from the study.	67/1361 (4.9%) found to be positive on EI. No follow-up breast pathology on these women was conducted.

MX = mammography, EI = electrical impedance, PPV = positive predictive value, NPV = negative predictive value, FN = false negative, FP = false positive, CBE = clinical breast examination, U/S = ultrasound, MRI = magnetic resonance imaging

* All values apart from sensitivity and false positive calculated by evaluator

Potential cost impact

In Australia, there are many private companies offering electrical impedance as a direct-to-market service. One such company offers a routine EI scan for $145, with some health insurance companies offering rebates. The EI system costs less than $50,000 (personal communication Health Screening Technologies).

Scintimammography

Background

Scintimammography or molecular breast imaging (MBI) is an invasive procedure which was first developed in the early 1990s for the diagnosis of cardiac disease. MBI of the breast uses the radiopharmaceutical and perfusion imaging agent, ^{99m} technetium-sestamibi (^{99m}Tc-sestamibi), which was approved by the FDA for use in breast radionuclide imaging in 1997 (Taillefer 2005). The mechanism of ^{99m}Tc-sestamibi uptake in cancerous cells is thought to occur via the mitochondria, the cytoplasmic organelles responsible for cellular energy production. When used for the diagnosis of heart disease, it was noted that healthy cardiac cells that consume more energy will concentrate a greater proportion of the ^{99m}Tc-sestamibi compared to diseased cardiac cells. When applied to the diagnosis of cancer, the opposite occurs. As previously noted, cancerous cells use high levels of energy and will therefore have hyperactive mitochondria in comparison to the healthy surrounding cells. As a result, any cancerous cells will take up increased levels of ^{99m}Tc-sestamibi and emit more gamma rays, which can then be recorded and images can be acquired (Figure 17) (Schmidt 2008).

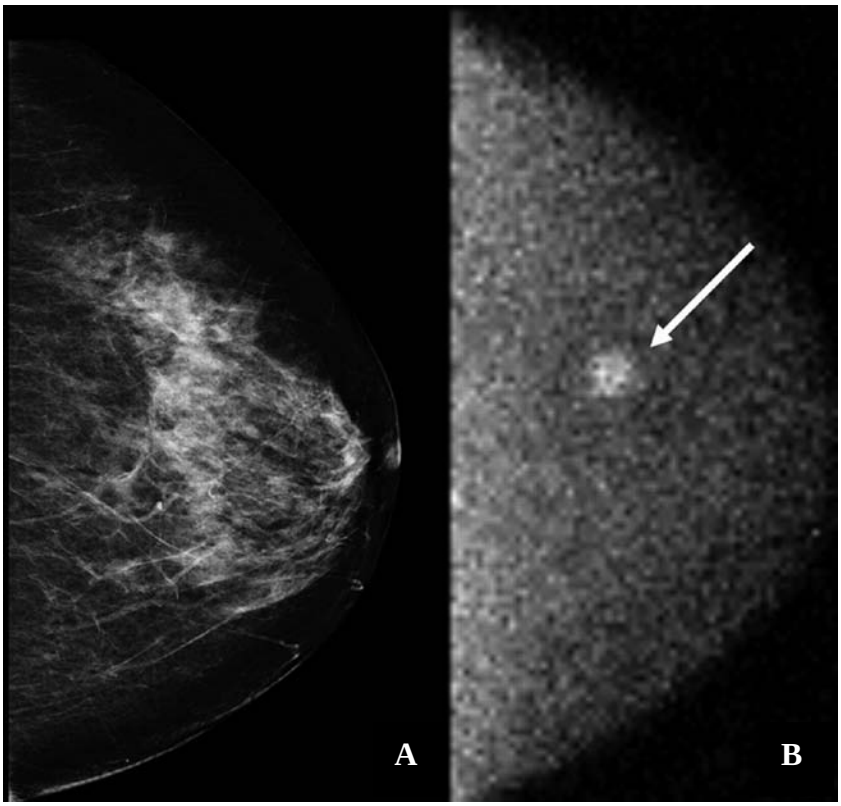

Figure 17 A) Negative image acquired using digital mammography and
B) Positive 7mm cancer image acquired with MBI (Schmidt 2008)

MBI has been proposed as an adjunct to mammography, especially with indeterminate cases. The standard dose of ^{99m}Tc-sestamibi (740-925 MBq[9]), is similar to the dose received in myocardial perfusion studies. ^{99m}Tc-sestamibi is delivered intravenously as a bolus. If the patient has a known lesion, the injection should be delivered via the vein in the opposite arm to avoid false positive uptake by the lymph nodes. If bilateral lesions are suspected, the dorsal pedal vein in the foot may be used (Taillefer 2005). Prone, rather than supine imaging, on a specialised table, that allows the breast to fall through a cut out, is recommended to avoid erroneous imaging of the heart or liver, as both of these organs have a tendency to uptake high levels of ^{99m}Tc-sestamibi. A double-headed gamma camera may be used with the breasts separated by a lead divider so that both breasts can be imaged simultaneously (Hussain & Buscombe 2006). Some research groups have developed a dual-head MBI system, in which the breast can be positioned between two opposing detectors in a similar fashion as mammography, resulting in improved resolution (Hruska et al 2008a). Images are taken approximately 5-10 minutes after injection and the total time required for examination is 45-60 minutes. MBI may be of particular use in the detection of breast cancer in women with dense breast tissue and may be used to check for metastases in the axillary lymph nodes or to determine multifocal breast cancers (Prasad & Houserkova 2007).

Safety

None of the included studies reported any adverse events associated with the use of molecular breast imaging or scintimammography. This technique is invasive and due to the use of radiopharmaceuticals would not be suitable for use in pregnant women.

Effectiveness

In 2006, Hussain and Buscombe conducted a meta-analysis of the use of MBI for the diagnosis of primary breast cancer. Usually a meta-analysis would be afforded the highest level of evidence, however this depends on the strength of the evidence of the included studies. This meta-analysis presented the results of both prospective (2) and retrospective (10) single-centre trials separately to those from prospective multi-site trials (5). The results of either mammography or ultrasound were not blinded to the MBI reader in the single-centre trials (level III-2 diagnostic evidence), however readers in the multi-centre trials were blinded to the results of other modalities (level III-1). The meta-analysis must therefore be classified as the lowest level of evidence of the studies it assessed (level III-2 diagnostic evidence). The multi-centre and single-centre trials yielded similar sensitivity and specificity (Table 6) regardless of blinding status. These values did not appear to differ with maturity of technique (comparing studies conducted in 1997 to those conducted in 2005) or with increasing patient numbers. Three of the higher evidence multi-centre studies recorded the ability of MBI to detect palpable and non-palpable lesions and values differed markedly. Reported

[9] MBq = megabecquerels, a measure of radiation activity

sensitivity for detecting non-palpable lesions were 30, 75 and 47 per cent in Palmedo et al (1998), Prats et al (1999) and Khalkhali et al (2000), respectively, compared to 83, 94 and 76 per cent reported for palpable lesions in the same studies. Reported specificity for non-palpable lesions were 50, 81 and 93 per cent in Palmedo et al (1998), Prats et al (1999) and Khalkhali et al (2000), respectively, compared to 75, 61 and 85 per cent reported for palpable lesions in the same studies.

Hruska et al (2008a) reported the initial results of a study using the dual-head MBI system. Although the authors intend to test 2,000 *asymptomatic* but *high-risk* women, they reported the initial results of 650 women, comparing MBI to mammography (level III-1 diagnostic evidence). MBI performed well, detecting 7/9 (77.8%) of the biopsy-confirmed tumours with a false negative rate of 22 per cent. Mammography detected only 3/9 (33.3%) of the tumours. Similar results were presented at the 2008 Breast Cancer Symposium on 940 *asymptomatic high-risk* women, a follow-up to the 2008a study (Hruska et al 2008c).

The cross classification study by Hruska et al (2008b) investigated the use of a single versus a dual-head MBI system (level III-2 diagnostic evidence). The two systems performed comparably for tumours larger than 5mm, however the dual-head system had increased sensitivity when detecting tumours and lesions less than 5mm in size (68.8% dual vs 28.6% single). In addition, the number of false negatives was markedly reduced when the dual-head system was used (8.6% dual vs 47.9% single). The same patient group[10] and results were reported in a separate paper, and are therefore not presented in Table 6. This paper did state, however, that the increase in sensitivity with the dual-head system for the detection of all tumour sizes was highly significant ($p<0.0005$) (Hruska et al 2008b). The results of using the single-head MBI system on 100 symptomatic patients were also reported in a separate paper, again not summarised in Table 6 (O'Connor et al 2007).

Change to patient management

The study by Spanu et al (2008) investigated the ability of MBI to detect multi-focal and bilateral breast cancer compared to mammography (level II diagnostic evidence). This study evaluated a subset (n=44) of patients with suspicious findings on a mammogram (n=264) who were confirmed to have multi-focal and bilateral breast cancer at biopsy. In this study, mammography was as sensitive at detecting *cancer* in this subgroup of patients as MBI (90.1% mammography vs 93.2% MBI). However MBI was significantly more sensitive at the detection of multiple invasive and multi-focal breast cancer (35/40, 87.5%) than mammography (20/40, 50%), $p< 0.005$. The authors state that the addition of MBI to the pre-operative work-up in this patient group correctly altered the proposed surgical management in 7/44 (16%) of cases (Spanu et al 2008).

[10] Hruska 2008a only reported the results of the 150 symptomatic women imaged with the dual-head MBI. Hruska 2008b reported the results of the same 150 symptomatic women imaged with both the single- and dual-head MBI systems.

In summary, scintimammography or MBI appears to be a promising, maturing technique for the detection of primary breast cancer. When used as a diagnostic tool in *asymptomatic*, albeit *high-risk*, women, MBI had a sensitivity of 76.9 per cent compared to a poor 23.1 per cent for mammography. The trade-off in cancer detection versus test invasiveness would, however, have to be considered when assessing MBI's role as a screening tool in the general population. Advances in the hardware used for MBI (dual-head as opposed to single-head systems) appear to improve sensitivity (91.4%), however this was obtained in a *symptomatic* population. The results from the completed Hruska et al study (n=2,000) may provide greater information as to the effectiveness of MBI as a diagnostic tool.

Table 6 Scintimammography as a breast cancer diagnostic tool

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Hussain & Buscombe (2006)	III-2	Meta-analysis	Included studies had >100 patients enrolled. Results compared to pathology. Single-centre trials (12), total of 2,424 women. 10/12 studies retrospective. (Blinding status of studies not ascertained. Multi-centre trials (5), total of 3,049 women enrolled. All studies prospective. Readers blinded to results of other imaging modalities.	Single-centre studies n= 2,424 Enrolled patient numbers ranged from 105 to 353 women Overall sensitivity 85% Overall specificity 84% Overall PPV 79% Overall NPV 80% Sensitivity range 69-90% Specificity range 71-94% PPV range 69-99% NPV range 55-93% Multi-centre trials n= 3,049 Enrolled patient numbers ranged from 246 to 1,243 women Overall sensitivity 85% Overall specificity 83% Overall PPV 71% Overall NPV 85% Sensitivity range 71-93% Specificity range 69-90% PPV range 58-97% NPV range 10-98%

Hruska et al (2008a)	III-1	Cross-classification of patients on MBI and MX, compared to excisional biopsy.	650 *asymptomatic* women with dense breast tissue and/or a high risk of BC (personal history of BC, family history of either a 1st or 2nd degree relative with BC or a known BRCA mutation) imaged with dual-head MBI.	9/650 (1.4%) had cancer detected 5/9 (55.6%) detected by MBI alone 1/9 (11.1%) detected by MX alone 2/9 (22.2%) detected by MBI+ MX 1/9 (11.1%) not detected by either modality (found 6 months later by biopsy) <u>MBI detected</u> 7/9 (77.8%) of all tumours FN of MBI 2/9 (22.2%) 0/1 (0%) tumours 0-5mm 3/3 (100%) tumours 6-10 mm 4/5 (80.0%) tumours >10 mm FN of MX 6/9 (66.7%)
Hruska et al (2008b)	III-1	Cross-classification of patients on MBI and MX and/or U/S compared to histopathology/ biopsy.	100 *symptomatic* women with suspicious findings on MX or U/S, imaged with single-head MBI system prior to biopsy. and 150 *symptomatic* women with suspicious findings on MX or U/S, imaged with dual-head MBI system prior to biopsy. Age and menopausal status not stated.	Single-head MBI system (n=100) 53/100 (53%) had breast cancer confirmed at biopsy. In the 53 breast cancer patients, MX and/or U/S identified 59 tumours 8 additional tumours were identified by MBI alone <u>MBI detected</u> TP 57/67 (85.1%) FN 10/67 (47.9%) 2/7 (28.6%) tumours 0-5mm 24/28 (85.7%) tumours 6-10 mm 31/32 (96.9%) tumours >10 mm Dual-head MBI system (n=150) 88/150 (58.7%) had breast cancer confirmed at biopsy. In the 88 breast cancer patients, MX and/or U/S identified 119 tumours 9 additional tumours were identified by MBI alone <u>MBI detected</u> TP 117/128 (91.4%) FN 11/128 (8.6%) 11/16 (68.8%) tumours 0-5mm 41/45 (91.1%) tumours 6-10 mm 65/67 (97.0%) tumours >10 mm

Hruska et al (2008c) Abstract	III-1	Cross-classification of patients on MBI and MX, compared to excisional biopsy. This study presents further incremental results from the Hruska et al (2008a) screening study.	940 *asymptomatic* women with dense breast tissue and/or a high risk of BC (personal history of BC, family history of either a 1st or 2nd degree relative with BC or a known BRCA mutation) imaged with dual-head MBI.	12/940 (1.3%) had 13 tumours detected 8/13 (61.5%) detected by MBI alone 1/13 (7.7%) detected by MX alone 2/13 (15.4%) detected by MBI + MX 2/13 (15.4%) not detected by either modality (found 6 months later by biopsy) False negative of MBI 3/13 (23.1%) Therefore sensitivity MBI = 76.9% False negative of MX 10/13 (76.9%) Therefore sensitivity MX = 23.1%
Spanu et al (2008)	II	Cross-classification of patients on MBI and MX and/or U/S compared to histopathology/ biopsy. The detection of multi-focal, multi-centric and bilateral breast cancer and the impact of MBI on surgical planning.	264 consecutive *symptomatic* women with suspicious findings on MX or U/S, imaged with single-head MBI system prior to biopsy. Median age 56 years (range 26-81 years).	At surgery/ biopsy 32/264 (12.1%) had benign lesions 44/232 (19.0%) patients diagnosed with multi-focal, multi-centric and bilateral breast cancer <u>Overall specificity in multi-focal BC</u> MBI 88.2% MX 52.9% MBI correctly changed surgical management in 7/44 (16%) cases <u>Multiple invasive loci (MLI) (n=24)</u> 23/24 (95.8%) BC detected by MBI 22/24 (91.7%) MLI detected by MBI 23/24 (95.8%) BC detected by MX 11/24 (45.8%) MLI detected by MX $p<0.0005$ <u>Multi-focal primary BC (MF) (n=16)</u> 14/16 (87.5%) BC detected by MBI 13/16 (81.3%) MF detected by MBI 13/16 (81.3%) BC detected by MX 9/16 (56.3%) MF detected by MX <u>Bilateral primary BC (n=4)</u> 4/4 (100%) detected by MBI 3/4 (75%) detected by MX

MX = mammography, U/S = ultrasound, PPV = positive predictive value, NPV = negative predictive value, U/S = ultrasound, MBI = molecular breast imaging or scintimammography, BC = breast cancer, FN = false negative, TP = true positive

Potential cost impact

The MBS does not list any item numbers which use ^{99m}Technetium-sestamibi, however several item numbers exist which utilise labelled technetium:

- Item number 61433, whole body study using cells labelled with technetium, fee $496.95;

- Item number 61434, whole body study using cells labelled with technetium, with single photon emission tomography, fee $615.40;
- Item number 61441, bone marrow study, whole body study using technetium labelled bone marrow agents, fee $489.70;
- Item number 61445, bone marrow study, localised using technetium labelled agent, fee $286.80;
- Item number 61454, localised study using cells labelled with technetium, fee $348.10;
- Item number 61457, localised study using cells labelled with technetium, with single photon emission tomography, fee $470.45.

^{99m}Technetium-sestamibi is also used in myocardial perfusion studies (MBS item numbers 61302, 61303, 6106 & 6107) with fees ranging from $448.85 to $834.90 (Medicare Benefits Schedule 2009).

Currently sestamibi is manufactured locally in Australia as a “cold kit” and the ^{99m}Technetium is added when required. A typical order would be for 2 GBq which would cost approximately A$95 (personal communication, Lantheus Medical Imaging Pharmacy).

Ductoscopy

Background

It is unlikely that ductoscopy would ever be used as a routine tool for the diagnosis of breast cancer in *asymptomatic* women as it is an invasive and labour intensive procedure. Therefore only a brief overview of this technology will be provided. Ductoscopy is, however, emerging as diagnostic procedure for the following indications: the evaluation of women with nipple discharge, patients with a normal breast examination who are at *high-risk* of developing breast cancer (BRCA mutation, family history of breast cancer) or women with breast cancer who are undergoing lumpectomy (Denewer et al 2008). It has been estimated that approximately 85 per cent of breast cancers begin in the ductal epithelium with normal cells becoming atypical and progressing to carcinoma. By visualising the appearance of cells in the duct and sampling these cells for pathology analysis, it has been suggested that ductoscopy may be able to identify precursor lesions to breast cancer several years before they become visible by mammography (Sarakbi et al 2005). There are approximately 11-48 central ducts in the papilla of the nipple, however only 13-18 of these ducts open at, or just below the nipple surface, which may mean that a large proportion of the ducts are not accessible to examination by ductoscopy (Mokbel et al 2005).

Ductoscopy can be performed in a doctor's office setting under local anaesthesia (topical local anaesthetic cream plus intradermal local anaesthetic injection at the areolar margin). A microendoscope (0.9 – 1.2mm external diameter) is inserted through the ductal opening on the surface of the nipple after the duct has been dilated with a suitable probe such as lacrimal dilators (Figure 18) (Escobar et al 2006; Mokbel et al 2005).

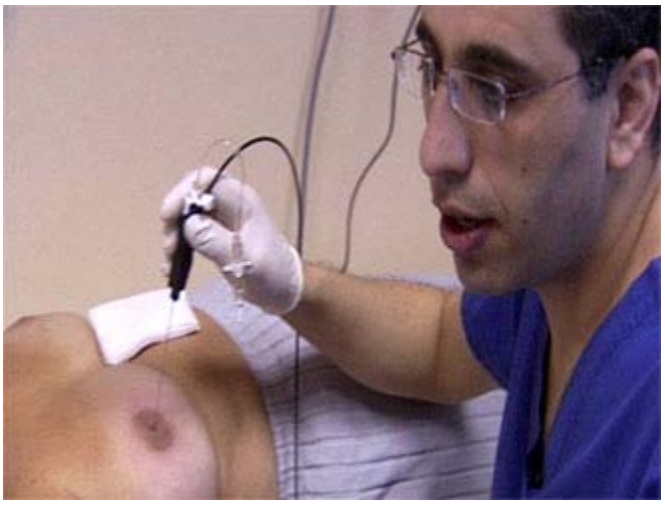

Figure 18 Woman undergoing ductoscopy, printed with permission (Mokbel)

The endoscope may be rigid or flexible. Saline is injected into the duct to widen the channel and to allow easy passage of the endoscope into the intraductal space. The endoscope allows up to 60 times magnification and may be able to visualise small lesions located in peripheral sites (Figure 19) (Escobar et al 2006; Mokbel et al 2005).

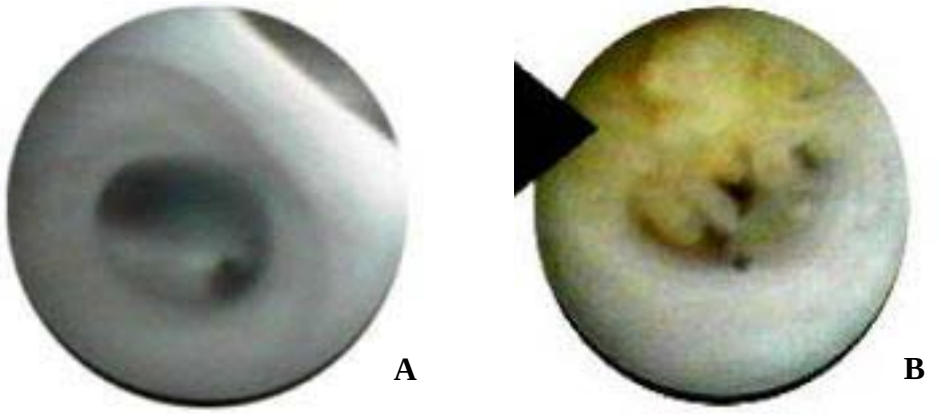

Figure 19 Nipple endoscopy showing a normal milk duct (A) and a milk duct showing the early signs of papillary DCIS (B), printed with permission (Mokbel)

The recent development of autofluoresence ductoscopy aims to improve visualisation with the possibility of visual semi-quantitative histological evaluation of intraductal lesions. Endoscopes used in autofluoresence have a dual light source of standard white light and excitation light from the blue-violet spectrum. This innovation is in the early stages of development (Jacobs et al 2007).

Ductal lavage is a similar technique. As with ductoscopy, the breast is anaesthetised with topical anaesthesia. A breast pump is applied to the nipple and gentle suction is employed to identify secreting ducts. A micro-cannula is then inserted into the secreting ducts and 30ml of saline is used to lavage the ducts. The ductal lavage fluid is then sent off for cytologic analysis, checking for the presence of atypical cells (Carruthers et al 2007).

Safety

Despite the invasive nature of the ductoscopy procedure there were no intra- or post-operative complications reported.

Effectiveness

Only two studies, by the same author, were identified which compared the diagnostic ability of ductoscopy to mammography in women with biopsy-confirmed breast cancer (Grunwald et al 2007; Grunwald et al 2006). It is likely that the 2007 study followed on from the 2006 study and reported on the same patient group, therefore only the results from the 2007 study are summarised. Although this study reported on the use of additional modalities including MRI

and galactography, not all patients received these examination methods. Therefore only the results of ductoscopy and mammography are presented in Table 7. The study only reported the sensitivity and specificity values for mammography plus ductoscopy but provided enough raw data for the evaluator to calculate all other values for ductoscopy only. A positive predictive value of 86.5 per cent for ductoscopy indicates that of all suspicious findings only 13.5 per cent were benign. Ductoscopy appears to be a promising technique for this group of high-risk women. Whether it has merit for other groups of women remains to be seen. The authors indicate that they are currently undertaking a prospective, multi-centre study in order to identify the indications for ductoscopy.

Table 7 Ductoscopy as a breast cancer diagnostic tool in high-risk women

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Grunwald et al (2008)	III-2	Cross-classification of patients on ductoscopy, and MX compared to histopathology/ biopsy.	64 *symptomatic* women with nipple discharge. 71 breasts examined. Mean age 52.3 years (range 21-77).	Ductoscopy Sensitivity 32/58 (55%) Specificity 8/13 (62%) NPV 8/34 (24%)) PPV 32/37 (87% FP 5/13 (39%) FN 26/58 (45%) Diagnostic accuracy 40/71 (56%) Mammography Sensitivity 38% Specificity 92% FP 8% FN 62%

PPV = positive predictive value, NPV = negative predictive value, FN = false negative, TP = true positive

Breath test

One study was identified which evaluated the detection of volatile organic compounds (VOCs) in breath samples as a means of identifying women at risk of developing breast cancer. Samples were collected after an overnight fast from 51 women with an abnormal mammogram and biopsy-confirmed breast cancer and compared to samples collected from 42 age matched healthy women (level III-3 diagnostic evidence). Samples were analysed by gas chromatography, mass spectroscopy and thermal desorption. Candidate breath VOCs were established using a training set of samples, which identified five breath biomarkers. These biomarkers were then tested on a prediction set of samples. The authors reported a sensitivity of 94 er cent , a specificity of 85 per cent and an accuracy of prediction (area under the curve) of 0.90 but conclude that larger, more highly powered, prospective studies should be conducted to establish the usefulness of a VOC breath test in the prediction of breast cancer risk (Phillips et al 2006). A research group from the University of Western Australia are investigating the use of detecting VOCs in breath samples (personal communication).

Of interest is preliminary work which applies the same principles as that of the VOC breath test but uses trained dogs to detect VOCs exhaled in cancer patient's breath. The canine olfactory system is capable of detection thresholds as ow as parts per trillion. In an initial study, dogs were trained on a reward basis on a set of 31 breast cancer patients and 83 healthy controls (level III-3 diagnostic evidence), with the correct identification of a cancer sample being indicated by the dog sitting or lying in front of the sample or ignoring the control sample. Once trained, dogs were tested on 125 samples from women with breast cancer and 266 samples from healthy controls which had not previously been encountered by the animal. Dog handlers and experimental observers were blinded to the status of the samples. A sensitivity of 88 per cent (95%CI [75, 100]) and specificity of 98 per cent (95%CI [90, 99]) was reported. When breast cancer patients were stratified according to stage of disease, the sensitivity and specificity remained largely unchanged. The authors conclude that this pilot study warrants further investigation (McCulloch et al 2006).

Radar based microwave imaging

Microwave imaging for breast cancer is a new technology being developed in the United Kingdom. It is based on the contrast in electrical properties of healthy fatty breast tissue and malignant tumours. Microwaves are reflected from tumours embedded in normal tissue, and variations in these microwave reflections are detected by changes in antennae location, creating a three dimensional image of the breast. The radar breast imaging system consists of a ceramic cup in which the breast sits and radar transmitters and receivers are arranged around the cup. Microwave technology does not expose the women to ionising radiation and it is

estimated that an examination will take only six minutes. This technology is in the early stages of development and patient studies are planned for 2009 (Kurrant & Fear 2009; Kurrant et al 2008; ScienceDaily 2008).

Optical coherence tomography

Researchers in the University of Western Australia are investigating the use of optical coherence tomography (OCT), which is an imaging modality which will complement CT, MRI, ultrasound and PET. OCT uses near infrared light to measure the thickness of structures and is therefore is capable of high resolution structural imaging (5-20μm resolution[11]) and provides histology-scale imaging. OCT is in the early stages of development and may be five years away from clinical use in breast cancer detection (personal communication, University of Western Australia).

[11] 1μm = one thousandth of a millimeter

Prognosis or risk assessment

An accurate assessment of a woman's risk of developing breast cancer may enable medical practitioners to provide suitable medical, psychological or surgical management appropriate to the woman's needs. Extensive research is currently being conducted to identify factors, biomarkers or genetic markers to be used for assessing such risk. However, it should be stressed that these factors are surrogate markers that are *associated* with an increased *risk* of developing disease, and as such results of marker studies are *not diagnostic* and should be treated with caution. The results of prognostic tests may results in increased surveillance of women considered to be at elevated risk, which may in turn lead to earlier detection of disease. In time, research may show that these biomarkers have a diagnostic capability which may in turn be developed into screening assays (Levenson 2007).

As the body of prognostic breast cancer literature is large and speculative, only a brief overview has been provided.

Statistical model

Much of the breast cancer risk assessment literature, as well as the United States National Cancer Institute (NCI), cite and use the Gail Model as the tool used to estimate a woman's risk of developing invasive breast cancer (see Appendix C) (National Cancer Institute 2009). The Gail Model uses a series of questions about a woman's personal medical history (number of previous breast biopsies and the presence of atypical hyperplasia in any previous breast biopsy specimen), reproductive history (age at menarche and age at the first (if any) live birth of a child), and the history of breast cancer among first-degree relatives to estimate her *risk* of developing invasive breast cancer over time. These questions were formulated from data obtained from a case control study of 2,852 Caucasian women whose breast cancer was incident (not prevalent at first screening) between 1973 and 1980. These women were compared to 3,146 disease-free Caucasian women (controls). Although this model has been validated in Caucasian women, it still needs to be validated in other racial subgroups (Gail et al 1989; National Cancer Institute 2009).

Models and questionnaires such as the Gail Model should be used with caution however as they may under or overestimate a woman's risk of developing cancer, as demonstrated by the retrospective cohort study conducted by Pankratz et al (2008) (level III-3 prognostic evidence). Of 9,376 women who underwent biopsy after a suspicious mammogram, 331 were found to be benign with atypia. The Gail Model predicted an average 5-year cancer risk of 4.2 per cent (± 2.7%, range 0.3 to 18.8%), equating to a predicted total of 13.9 breast cancers within five years. During this period, eight women developed invasive breast cancer, with a ratio of observed to predicted events of 0.58 (95%CI [0.29, 1.15], p=0.12). At mean follow-up of 13.7 years 58 women (17.5%) developed invasive breast

cancer, which was significantly (1.66 times) more than the 34.9 predicted by the Gail Model (95%CI [1.29, 2.15], $p<0.001$) (Pankratz et al 2008).

Mammographic density

Mammographic images will vary according to the make-up or composition of the breast tissue. The breast is composed of two types of tissue: fat and fibroglandular, which consists of the stroma and epithelium. The fibroglandular tissue attenuates X-rays more than fat, as fat is more transparent to X-rays. Therefore on a mammogram, fat will appear darker and the fibroglandular tissue will appear lighter, and is referred to as a region of "mammographic density" (see Figure 1). Density is influenced by age, parity, body mass index, and menopause and may possibly have a genetic component. The sensitivity of a mammogram decreases with increased breast density as abnormalities may be obscured (Yaffe 2008; Boyd et al 2009). Several methods of measuring breast density have been described including quantitative density measurement from digitised mammograms, volumetric density assessment using computed tomography or tomosynthesis, or other imaging modalities including ultrasound and MRI, which may be more suitable for use in young patients as neither requires the use of ionising radiation (Yaffe 2008).

There is a great deal of literature describing the possible use of mammographic density as a risk factor for developing breast cancer. A recent meta-analysis reviewed 42 studies which described the association between breast density and the development of breast cancer. It has been suggested that women should be classified into four categories of breast density: <25, 25-49, 50-75 and >75 per cent density. The results of the meta-analysis, which indicated that a high breast density was associated with breast cancer, were consistent in the general, *asymptomatic* population but were highly heterogeneous in *symptomatic* populations. The combined relative risks of incident breast cancer in the general population were 1.79, 95% CI [1.48, 2.16], 2.11 [1.70, 2.63], 2.92 [2.49, 3.42], and 4.64 [3.64, 5.91] for categories 5-24, 25-49, 50-75 and >75 per cent density. These values were calculated relative to "baseline" women with less than five per cent breast density (McCormack & dos Santos Silva 2006).

Nipple aspirate fluid

Nipple aspirate fluid (NAF), as opposed to nipple secretions or discharges, is fluid that is extracted from the breasts of *asymptomatic* women for cytomorphic examination of exfoliated epithelial cells (Levenson 2007). NAF may be obtained by manual nipple aspiration, which may require the successive application of heat and massage to the breast. A suction cap is placed over the nipple and nipple fluid is extracted by a syringe attached to the suction cap (Figure 20). This method does not require the application of anaesthesia. Once fluid has been extracted, the sample is placed into a liquid cytology vial and transported to a cytology laboratory for processing. Thin layered slides are prepared for visual inspection by a trained pathologist for the presence of atypical epithelial cells (see Figure 23 in glossary). Limitations and disadvantages of NAF is that many women do not

produce fluid (non-yielders) and the low cellular yield as many samples are acellular. It has been estimated that between 0.7 to 2.7 per cent of asymptomatic women will have atypical cells in their NAF (Bentz 2008).

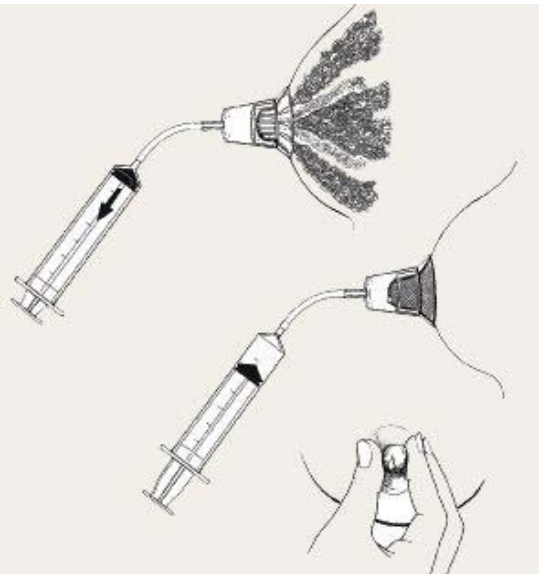

Figure 20 Extraction of NAF (Love 2009)

A United States company, NeoMatrix, markets an FDA approved (2002) complete NAF system called the HALO Breast Pap Test™ which has not yet entered the Australian market. General practitioners purchase or lease the HALO system, which massages the breast and provides suction to extract the NAF. The HALO kit contains an alcohol prep pad, a disposable cup and collection swab for each breast. Prior to starting the HALO cycle, both nipples are cleansed with the alcohol swab to dissolve any keratin plugs that may be sealing the ducts. The "sample collection cups" do not actually collect the sample as their primary purpose is to prevent contact between the patient and the HALO system. As the NAF sample is usually small and will adhere to the nipple, the collection swab is used to collect it. The swabs are immediately placed into liquid based cytology vials provided by the cytology laboratory, and then are transported to the laboratory. The procedure takes approximately five minutes. The kit cost US$21 and the cost for processing and evaluation by a pathologist is paid by the patient (personal communication, NeoMatrix).

Ductal lavage (see section on ductoscopy) has also been proposed as a method of obtaining NAF containing epithelial cells, however this technique is invasive, time consuming, labour intensive, requires the cannulation of individual ducts and is not well tolerated by women. Studies have suggested that ductal lavage has a limited role in the early detection of breast cancer due to inconsistent NAF production, difficulties in duct cannulation, lack of consistent cytologic interpretation of NAF samples and inadequate NAF samples (Khan 2004; Patil et al 2008; Visvanathan et al 2007).

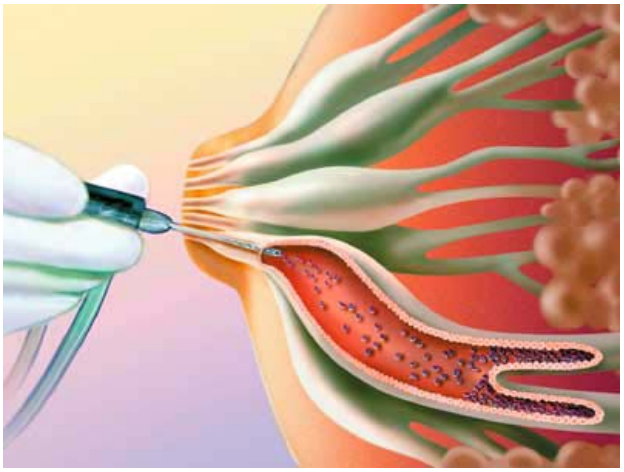

Figure 21 Ductal lavage demonstrating the cannulation of a duct (Davidson 2004)

Proteomics

Cytological examination of exfoliated epithelial cells in NAF is thought to be too subjective and samples may contain large amounts of protein rather than cells of interest. Therefore a great deal of research is currently being conducted on the identification of proteins or protein expression patterns in NAF that may be associated with breast cancer. One technique used to assess protein profiles is surface-enhanced laser desorption ionisation time-of-flight mass spectroscopy (SELDI-TOF). SELDI-TOF is capable of identifying proteins over a large size range and is sensitive down to the femtomolar[12] level. This technology combined with ProteinChip® arrays, allows high sample throughput while using only a small amount of biological sample (1µl). The surface of the ProteinChip® can be modified to selectively bind different protein subsets with specific chemical properties (anionic or cationic for negatively or positively charged proteins, metal affinity for capturing Histidine-tagged proteins, hydrophobic or hydrophilic proteins) (He et al 2007; Noble et al 2007; Pawlik et al 2005; Sauter et al 2005). The ProteinChip® captures the protein and by using a combination of arrays up to 2,000 protein species can be detected and then presented directly to the mass spectrometer. An advantage of this technology is that samples may be frozen at -80°C and analysed at a later date (Bertucci et al 2006).

Several studies have compared the protein profiles of NAF samples obtained from women with breast cancer to those obtained from women without breast cancer. The largest of these recruited 114 women suspected of having breast cancer, prior to biopsy. NAF samples were collected from the 27 women with biopsy confirmed breast cancer and the remaining healthy 87 women (level III-3 diagnostic evidence). Three different types of ProteinChip were used for SELDI-TOF NAF analysis and samples were run in duplicate. The overall coefficient of variation for the internal standard was ≤0.17 per cent for each chip and ≤0.29 per cent for the unknown proteins. An example of a SELDI-TOF-MS NAF profile is

[12] Millimole = 10^{-3}, micromole = 10^{-6}, nanomole = 10^{-9}, picomole = 10^{-12}, femtomole = 10^{-15}

illustrated in Figure 22. These profiles are simply comparing the presence or absence of a particular size of protein, measured in Daltons. Peaks measured in the 10,000, 11,800 and 13,880 (arrows) Dalton regions were identified in women with breast cancer but were absent in the healthy women (Sauter et al 2005).

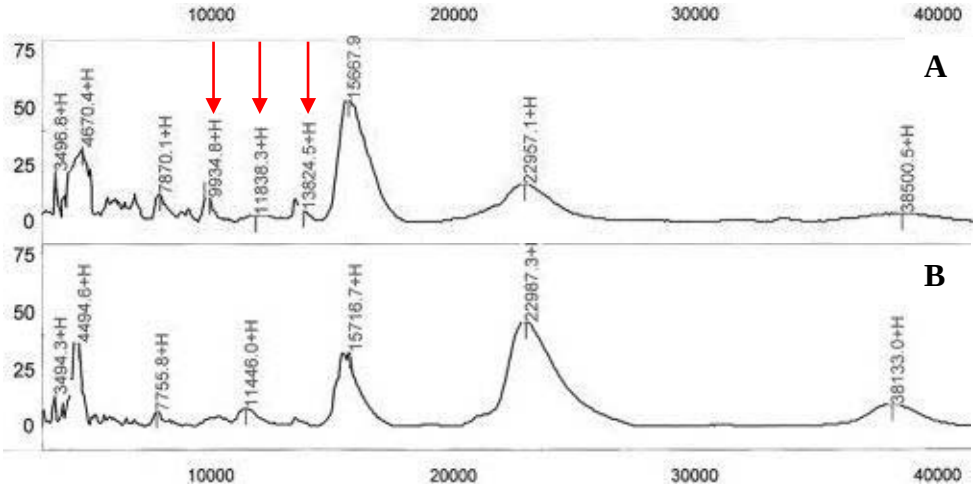

Figure 22 Comparison of SELDI-TOF spectrum of NAF fluid in a woman with breast cancer (A) and a woman without breast cancer (B)

The study by Noble et al (2007) recruited 21 women who were diagnosed with unilateral breast cancer and compared the SELDI-TOF NAF protein profiles obtained from the affected and the unaffected breast, as well as comparing it to the profiles of 44 healthy women (level III-3 diagnostic evidence). There was no difference in the profiles obtained from either breast in the women diagnosed with breast cancer, however there were significant differences in nine protein peaks when the cancer patients were compared to the healthy controls. The author concluded that proteomic profiling of NAF is not suitable as a diagnostic tool but may have more value for risk assessment.

A new technique developed subsequent to the SELDI-TOF is a matrix-assisted laser desorption/ionisation (MALDI) source with a time-of-flight mass analyser. This is capable of higher throughput analysis by allowing for a profiling approach of multiple protein species (Laronga & Drake 2007).

Other techniques to identify differences in the expression of proteins between women with and without breast cancer include:

- two-dimensional electrophoresis, which separates proteins according to their size and allows visualisation on a gel. Separated proteins can be further analysed using mass spectroscopy and the spectra can be used to search protein sequence databases;
- yeast two-hybrid system, which is capable of generating large volumes of data but is highly time consuming;
- tissue microarrays, where a tissue sample is taken (biopsy). Hundreds of small (0.6-2.0mm) tissue sections are arrayed on a glass slide for immunohistochemistry (Baak et al 2005).

Several studies have used techniques such as those described above, or gene expression studies, to identify candidate proteins associated with breast cancer. Sauter et al (2007) evaluated 208 NAF samples from 191 women collected prior to biopsy for the following proteins: two human glandular kallikreins, hK2 and hK3, also known as prostate-specific antigen (PSA). Lower levels of hK2 and hK3 and a lower ratio of hK2/PSA are associated with breast cancer. These are co-expressed in breast tumours and NAF, as is basic fibroblast growth factor (bFGF), which is an important angiogenic factor found to be elevated in body fluids of cancer patients. When all samples were compared to biopsy findings, bFGF was found to be associated with breast cancer (p= 0.005) (Table 8). When women with nipple discharge were excluded, independent predictors foe breast cancer included increased age, post-menopause (both p<0.01), elevated bFGF (p=0.004) and low PSA (p=0.05). Sensitivity and specificity was 100 and 41 per cent, respectively, when women were stratified for menopausal status, using NAF levels of hK2 or PSA and age as predictors in pre-menopausal women. Sensitivity and specificity was 93 and 12 per cent respectively for the same predictors in post-menopausal women (Sauter et al 2007). Large, prospective cohort studies, with long-term follow-up, are required to be conducted to ascertain whether these biomarkers are associated with the development of breast cancer in *asymptomatic* women.

Table 8 Biomarker expression

Marker (ng/g)		N	Mean ± SEM	Median	p value
PSA	Cancer	37	1477.4 ± 898.6	19.0	0.180
	No cancer	84	1464.6 ± 655.2	57.6	
hK2	Cancer	36	37.4 ± 22.5	0.0	0.463
	No cancer	70	42.1 ± 17.2	0.0	
bFGF	Cancer	34	41.6 ±17.4	3.5	0.005
	No cancer	67	4.8 ±2.3	0.0	
Women without nipple discharge					
Marker (ng/g)		N	Mean ± SEM	Median	p value
PSA	Cancer	35	1562 ± 949	20.0	0.05
	No cancer	46	2411 ± 1181	197.5	
hK2	Cancer	35	38.5 ± 23.1	0.0	0.59
	No cancer	40	59.4 ± 29.3	3.5	
bFGF	Cancer	32	39.2 ± 18.1	3.5	0.004
	No cancer	40	3.3 ± 1.8	0.0	

SEM = standard error of the mean, PSA = prostate-specific antigen, bFGF = basic fibroblast growth factor

Studies have also assessed circulating protein biomarkers in blood and plasma, with many being used to monitor the progress of breast cancer and having a role in patient management (CA 15-3, CA125, CEA, RS/DJ-1, HER-2, TPS, TPA).[13]

[13] CA = cancer antigen, CEA = carcinoembryonic antigen, RS/DJ-1 = protein that regulates RNA-protein interaction, HER-2 = human epidermal growth factor receptor 2, TPS = tissue polypeptide specific antigen, TPA = tissue plasminogen activator

However, not all of these markers are elevated in all breast cancer patients and are therefore of little value for the detection of early breast cancer (Duffy 2007). Other research has suggested that cytoplasmic serine hydroxylmethyltransferase (cSHMT), Tbx3 and utrophin may be candidate plasma proteins for the early detection of breast cancer (Souchelnytskyi et al 2006). It remains to be seen whether any of these proteins will routinely predict susceptibility to breast cancer.

Genomics

The incidence of breast cancer has been correlated to clustering in families and first degree relatives. During the 1990s the search for a genetic component or susceptibility gene identified mutations in the BRCA1 and BRCA2 genes as well as the TP53 gene (Miki et al 1994; Wooster et al 1995). The BRCA1 gene is mapped to chromosome 17q21 and encodes for a protein with several functional domains including a transcriptional co-activator. The BRCA2 gene maps to chromosome 13q12 and encodes for a protein that is twice the size of that produced by BRCA1, but has no well-defined functional domains. The roles of BRCA1 and 2 are unclear, however, it is thought that they play a role in DNA repair, the regulation of gene expression and embryogenesis. The BRCA genes are highly heterogeneous and by 2002 the National Human Genome Research Institute had identified 864 distinct nucleotide variants in BRCA1 and 882 in BRCA2. The TP53 gene is one of the most common mutations and is associated with malignancies such as soft tissue and bone sarcomas, brain tumours, leukaemias, adrenocortical tumours, breast cancer and Li-Fraumeni syndrome. TP53 gene products have many biological functions, including checking the control of the cell cycle after DNA damage (Marsh et al 2001). Several methods are available to identify mutations, however, precise characterisation requires direct sequencing, which makes screening for these mutations a difficult and expensive task (NHMRC 1999; Radice 2002). Mutations in these genes account for only 5-10 per cent of *all* breast cancers and for only 65 per cent of all *inherited* breast cancers. Even though the numbers associated with carrying the BRCA1 and 2 genes are small, those carrying mutations of these genes have a lifetime risk of developing breast cancer of 55-87 per cent. Other genes have been identified in family linkage studies including PTEN, CHEK2, ATM, NBS1, RAD50, BRIP1 and PALB2, however these genes in conjunction with the BRCA 1 and 2 genes still account for only 50 per cent of familial or inherited breast cancer. Further research is being conducted to identify other possible genetic candidates (Dimri 2008; Stemke-Hale et al 2006).

Sequence variation studies are being conducted in an effort to identify single nucleotide polymorphisms (SNPs), where the insertion or deletion of nucleotides into an individual's DNA may result in breast cancer. The Breast Cancer Association Consortium has been conducting studies searching for SNPs of candidate genes. However, results have been mixed with comparisons made difficult due to the different populations studied. In addition, sample sizes may be too small to give any meaningful results. Many of these studies have found that a large number of SNPs previously thought to be associated with breast cancer are not associated with breast cancer risk. Weak associations were found for SNPs in

those genes involved in the cell-cycle control pathway, steroid hormone metabolism and signalling, however studies with much larger sample sizes are required to clarify these possible associations. Genome-wide association studies utilise rapid SNP screening technologies which are capable of scanning the 1,000s of genes in large numbers of individuals to find SNPs associated with breast cancer. In addition, researchers can access large volumes of genetic information from the International HapMap Project, which is a catalogue of common genetic variants (SNPs) that occur in the human genome[14]. A number of candidate SNPs have been identified, however further large scale studies need to be conducted to test whether these correlations are true associations (Dimri 2008).

Two commercial tests are currently on the market to assess the susceptibility or risk of women developing breast cancer.

deCODE genetics, a firm based in Iceland, have developed the deCODE BreastCancer™ test, for assessing individual risk of the common forms of breast cancer (deCODE genetics 2007). The deCODE BreastCancer™ test is based on familial cluster studies conducted in Iceland, which genotyped 300,000 SNPs in 1,600 women with breast cancer and 11,563 women without breast cancer. Candidate SNPs were then tested in five replication populations, totalling 4,554 women with breast cancer and 17,577 controls (Stacey et al 2007; Stacey et al 2008). Seven SNPs are tested for by deCODE BreastCancer™, all of which were detected by genome-wide association studies and are associated with an increased risk of breast cancer. The test does not check for the BRCA 1 or 2 mutations, which are protected by patent. It has been suggested that only five per cent of women using the test will have a 20 per cent risk of breast cancer, compared to the average risk of 12 per cent. United States guidelines recommend additional MRI screening for women with a 20 per cent risk of developing breast cancer. The cost of the test is estimated to be US$1,625. Doubts have been raised as to the value of conducting tests such as these. A woman who may test positive to several of the SNPs detected by the tests may have an increased risk of 100 per cent, or a doubling of risk, which would be the equivalent risk of having one family member with breast cancer. However, the absolute risk may be small depending on the age and other characteristics of the women. The small number of variants tested for is also of concern, especially when considering the large number of potential variants as described above (Couzin 2008).

DiaGenic ASA, a firm based in Norway, launched their BCtect™ test in India in 2008. The test searches for a gene expression signature using TaqMan® Arrays, a system of performing large scale real time polymerase chain reactions (DiaGenic ASA 2009). Limited information is available on this product, however BCtect™ is based on research conducted by Sharma et al (2005). Gene expression patterns of 37 candidate genes from 60 blood samples from 56 women were analysed. Of these samples, 24 were from women with breast cancer, 19 were from women with an abnormal first mammogram and 17 were from women with no reported

[14] HapMap project: http://www.hapmap.org/whatishapmap.html

breast abnormality. The test claims that the set of 37 genes with correctly predict the diagnostic class in 82 per cent of women (Sharma et al 2005).

The difficulty with genomic tests is that women who test negative for these tests may be given false reassurance that they will not go on to develop breast cancer (Couzin 2008).

In summary, caution should be used when interpreting factors association with an *increased risk* of developing breast cancer. The presence of a genetic variant or a biomarker may be significant but the effect at an individual level may be small. It is unknown what effect environment has on these variants, or whether these variations may act in a synergistic or additive manner.

Ethical considerations

Informed consent

Providers of screening programs face particular challenges with informed consent. Those providing tests must provide information about the procedure, any likely harms or discomfort that may arise, and the implications of a positive or negative result. Just as importantly, they must also ensure that women understand the information they provide. For all women undergoing screening for breast cancer, confidence in the veracity of the test result is extremely important, not only so that individual women can feel secure that the results of the test are valid, but also to maintain trust in the screening program in the community. Two issues are of particular concern here. First, women will want to be sure that a test result indicates whether disease is truly present or absent. Accurate information about the predictive value of all breast screening tests is essential, as is a concerted effort to help women understand the meaning of results. It is of particular concern that for a number of these tests, there is insufficient evidence to provide this accurate information.

Second, information about screening tests needs to be provided in an environment which can attend to the sensitivities of women and the associated anxieties that may accompany a positive or equivocal result. The current BreastScreen Australia mammography program has a well-known track record in this regard. Given the newness of these tests, specific programs to support women being screened for breast cancer may not be available. Any alternative breast screening tests should ensure that best practice standards for the delivery of breast cancer screening services are adopted.

The appropriateness of the test environment is particularly important for those tests which are marketed direct to consumers. Women may self-refer for these tests with little understanding of the likely psychological impact of the test result. In some instances, there is little evidence that these tests are of value, and yet they are readily available to Australian women. There is a view that "consumers should have the right to spend their own funds to purchase medical services, even if those services have uncertain clinical value" (Lee & Brennan 2002). While this view gives weight to the important principle of respect for patient autonomy, it does not pay enough attention to the need to minimise the risk of harm to patients and the subsequent impact on the health system.

Harms and Benefits

The tests described in this Bulletin span a wide range of screening, diagnostic and prognostic tests for symptomatic, asymptomatic, and high-risk populations and of varying test sensitivity and specificity. Because of this variability, the balance between risks or harms and benefits will be different for each test. Some harms (such as discomfort during the procedure) will be relatively obvious; others, such

as the anxiety invoked unnecessarily by a false positive result, or the false sense of security provided by a false negative result, will also need to be taken into account (Lee & Brennan 2002; Couglin 2008). For a number of the tests reported in this Bulletin the test sensitivity and specificity is not acceptable, or it has not been possible to calculate. This suggests that some degree of caution needs to be exercised before these tests are regarded as ethically acceptable.

Access Issues

Some of the tests reported in the Bulletin are only available in, or likely to become available in, large public and private hospitals in Australia. This will limit the access to screening for women who live in rural areas.

Sources of information

The medical literature (Table 9) was searched utilising the search terms outlined in Table 10 to identify relevant studies and reviews, from January 2005 until October 2008. In addition, major international health assessment databases were searched.

Table 9 Literature sources utilised in assessment

Source	Location
Electronic databases	
AustHealth	University library
Australian Medical Index	University library
Australian Public Affairs Information Service (APAIS) - Health	University library
Cinahl	University library
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	University library
Current Contents	University library
Embase	Personal subscription
Pre-Medline and Medline	University library
ProceedingsFirst	University library
PsycInfo	University library
Web of Science – Science Citation Index Expanded	University library
Internet	
Australian Clinical Trials Registry	http://www.actr.org.au/default.aspx
Current Controlled Trials metaRegister	http://controlled-trials.com/
Health Technology Assessment international	http://www.htai.org
International Network for Agencies for Health Technology Assessment	http://www.inahta.org/
Medicines and Healthcare products Regulatory Agency (UK).	http://www.medical-devices.gov.uk/
National Library of Medicine Health Services/Technology Assessment Text	http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat
National Library of Medicine Locator Plus database	http://locatorplus.gov
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/grey.shtml
Trip database	http://www.tripdatabase.com
U.K. National Research Register	https://portal.nihr.ac.uk/Pages/NRRArchive.aspx
US Food and Drug Administration, Center for Devices and Radiological Health.	http://www.fda.gov/cdrh/databases.html
Websites of Specialty Organisations	
National Breast Cancer Foundation	http://www.nbcf.org.au/

Table 10 Search terms utilised

Search terms
MeSH
Breast Neoplasms and Mass Screening
Limits
English, Human

Journals of interest: Table of contents searched January 2006-September 2008

Journal of the National Institute of Cancer
http://jnci.oxfordjournals.org/

Breast Cancer Research
http://breast-cancer-research.com/

Breast Cancer Online
http://www.bco.org/

Clinical Breast Cancer
http://cigjournals.metapress.com/content/121019/

Breast Cancer: Basic and Clinical Research
http://www.la-press.com/journal.php?journal_id=84

BMC Cancer
http://www.biomedcentral.com/bmccancer/

The Breast Journal
http://www.blackwellpublishing.com/journal.asp?ref=1075-122X

Cancer
http://www3.interscience.wiley.com/journal/28741/home?CRETRY=1&SRETRY=0

New England Journal of Medicine
http://content.nejm.org/

Nature Reviews: Cancer
http://www.nature.com/nrc/archive/index.html

Science
http://www.sciencemag.org/

Conclusions

Screening programs directed at the early detection of breast cancer must satisfy a number of essential criteria, in that the disease is an important health problem and effective, acceptable interventions are available to patients identified through the program of early detection. An ideal screening program would have a 100 per cent sensitivity and specificity, with no false positives or false negatives. However, sensitivity and specificity are usually inversely related. If the specificity is increased, the false positive rate is decreased and vice a versa for a decrease in specificity. If the sensitivity is increased, the false negative rate is decreased, and vice a versa for a decrease in sensitivity. There is a fine balance between sensitivity and specificity, and thus when screening for breast cancer in an asymptomatic population it may be preferable to reduce the number of false negatives (increase the sensitivity of a test) at the expense of increasing the number of false positives.

Whether or not mammography is the best means of early detection for breast cancer has been a matter of considerable debate, as it is associated with both benefits and harms. Mammography is considered an imperfect screening tool, as it is neither highly sensitive nor highly specific. The 2006 Cochrane review by Gotzsche and Nielsen reported mammography to have a sensitivity ranging between 71-79 per cent, meaning that between 21 and 29 per cent of breast cancers are false negatives and are missed at screening. Although mammography has its limitations, there is no doubt that, with the introduction of the universal mammography program offered by BreastScreen Australia for women aged 50-69 years that the morbidity and mortality associated with breast cancer has declined over time and with increased participation.

The aim of this *Emerging Technology Bulletin* was to identify any new and emerging technologies for the early detection of breast cancer, and to give a brief but *non-systematic* overview on the current available evidence on these techniques. Direct evidence of a reduction in breast cancer mortality due to screening can only be generated by large scale, long-term (5-10 years) prospective randomised controlled trials with mortality as an outcome or endpoint. Trials such as this as are expensive and require substantial infrastructure. Surrogate endpoints such as diagnostic accuracy of a screening modality are often used instead, and inferences are made in respect to the impact that this may have on mortality. It is essential, however, that new testing modalities are undertaken in the appropriate population. Many of the studies included in this *Emerging Technology Bulletin* compared the results of a new diagnostic technology in *symptomatic* women who had a suspicious finding on a mammogram, rather than truly asymptomatic women. By screening a *symptomatic* population, the "prevalence" of the disease is artificially increased, the number of true positives detected by the test will increase as will the positive predictive value, giving a false impression of the accuracy of the diagnostic test. Screening programs should be conducted in high-risk populations to maximise yield, however when referring to breast cancer this

should refer to women in the age group 50-69 years rather than symptomatic women.

This *Emerging Technology Bulletin* identified seven technologies used for the detection of breast cancer: computed tomography (CT), positron emission tomography (PET), ultrasonography, thermography, electrical impedance, scintimammography and ductoscopy. In addition this *Bulletin* gave a brief description of three future technologies which may not be of any clinical value within a five-year time frame: volatile organic compound breath tests, radar-based microwave imaging and optical coherence tomography two of which are being investigated by researchers in Western Australia. Finally, the use of prognostic indicators or risk assessment tools are described.

Only one study which described the use of a dedicated CT scanner for the detection of breast lesions. This small study (n=60) by Lindfors et al (2008) was poorly reported and simply described the ability of CT to identify the same lesions as mammography in symptomatic women, rather than the diagnostic accuracy of CT compared to the gold standard of biopsy. The clinical relevance of using CT for the detection of breast cancer remains to be evaluated.

Three studies described the use of PET for the detection of breast cancer, however two of these studies, although comparative, were conducted on a symptomatic population and therefore the generalisability of the results is poor. Although the largest study (n=660) was conducted on an *asymptomatic* population, it had to be considered a case series as it was unclear from the methods section whether all women enrolled in the study underwent imaging with mammography as well as PET, or only those found to be positive by PET. Although this study reported that dedicated breast PET (or positron emission mammography, PEM) outperformed whole-body PET, PEM did in fact perform poorly with a positive predictive value of only 13 per cent, meaning that 87 per cent of cases were incorrectly diagnosed with an abnormality based on subsequent mammography or histopathology. The low sensitivity of PET currently makes it an unsuitable imaging modality for the routine screening of asymptomatic women.

Three large cross classification studies reported on the use of ultrasonography (U/S) for the detection of breast cancer in *asymptomatic* women. The study by Corsetti et al (2008) reported on the use of U/S in women who were found to be negative by mammography but who had greater than 50 per cent breast density (n=9,157). This study reported a poor positive predictive value for U/S alone (11%), however U/S did detect breast cancer at a significantly earlier stage than mammography (p=0.001). The study by Berg et al (2008) reported on the use of U/S in women who were considered to be at high-risk or had dense breast tissue (n=2,725). The positive predictive value of U/S alone was again poor (8.6%) and only slightly improved when combined with the use of mammography (10%). Finally the study by Ohlinger et al (2006) reported a sensitivity and specificity of 100 and 55 per cent when U/S was used on 448 *asymptomatic* women. The results of this study varied greatly from those reported by Berg et al perhaps as a consequence of the smaller study size and the study being too underpowered to report a meaningful result.

The use of thermography, a non-invasive diagnostic tool which uses infrared imaging to detect changes in skin temperature, was reported by two cross classification studies and also the subject of a 2004 review conducted by New Zealand Health Technology Assessment. A sensitivity greater than 72 per cent was reported by both studies, however the enrolled population was *symptomatic*. There was no evidence to support the use of thermography for the detection of breast cancer in *asymptomatic* women.

Electrical impedance (EI) is a non-invasive, radiation-free, imaging technique used to scan the electrical conductivity of the breast. Three studies reported on the use of EI to detect breast cancer, however two of these studies reported on two different populations (asymptomatic and symptomatic) and should therefore be considered as distinct studies. The two "specificity" arms of the 2006 and 2008 studies by Stojadinovic et al reported a small number of women found to be positive by EI and reported them as false positives due to the small likelihood of breast cancer being present in young, pre-menopausal women. No further clinical follow-up or breast pathology was conducted on these women. Poor test sensitivity was reported in the studies (26% and 38%) conducted on *symptomatic* women. The remaining small (n=88) cross classification study by Prasad et al (2008) in *symptomatic* women reported much higher test sensitivity (83%).

Both thermography and electrical impedance are available in Australia on a direct-to-market basis and do not require regulatory control by the TGA and can therefore be offered to women of all ages. Direct marketing to consumers may have social consequences, such as increasing the burden on the health care system to cope with false positive or false negative test results. For example a large number of false positive tests 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. There is no ethically acceptable reason to expose healthy women to potential harm by allowing self-testing of products, that have poorer performance than mainstay screening tests, without prominent informed consent regarding the potential harms.

Four cross classification studies and a meta-analysis reported on the use of scintimammography or molecule breast imaging (MBI) for the detection of breast cancer. MBI is an invasive procedure whereby ^{99m}Tc-sestamibi is infused and emits higher levels of gamma rays from cancerous cells, that can then be recorded and images produced. Two of these studies enrolled *symptomatic* women. The remaining two studies reported the incremental results of the same study in *asymptomatic* women (n=650 and n=940) who were considered to be at high-risk or had dense breast tissue. MBI appears to be a promising, maturing technique for the detection of primary breast cancer. When used as a diagnostic tool in *asymptomatic*, albeit *high-risk*, women, MBI had a sensitivity of 77 per cent compared to only 23 per cent for mammography. Advances in the hardware used for MBI (dual-head as opposed to single-head systems) also appear to improve sensitivity (91.4%), however this was obtained in a *symptomatic* population. The results from the completed Hruska et al study (n=2,000) may provide greater information as to the effectiveness of MBI as a diagnostic tool.

One small (n=64) cross-classification study reported on the use of ductoscopy for the detection of breast cancer in *symptomatic* women with nipple discharge. It is unlikely that ductoscopy would ever be used as a routine tool for the diagnosis of breast cancer in *asymptomatic* women as it is an invasive and labour intensive procedure. Ductoscopy is, however, emerging as diagnostic procedure for the evaluation of women with nipple discharge or patients with a normal breast examination who at *high-risk* of developing breast cancer. In women with nipple discharge, ductoscopy was more sensitive than mammography (55 vs 38%) and had a positive predictive value of 86.5%, indicating that of all suspicious findings only 13.5 per cent were benign.

In summary, few studies reported on the use of technologies in a truly *asymptomatic* population. A total of eight studies reported the results of new diagnostic technologies on asymptomatic women, however of these studies four were conducted on women with highly dense breast tissue or women considered to be at high-risk (BRCA mutation, personal or family history of breast cancer). Of the remaining four studies, three were case series (one PET study and two which used electrical impedance) and only diagnostic yields were reported. Only one study, by Ohlinger et al (2006) described results obtained with ultrasound in a truly asymptomatic population. In this population, ultrasound achieved a sensitivity and specificity of 100 and 55 per cent, however mammography performed as well, if not better with a sensitivity and specificity of 100 and 73 per cent, respectively. When U/S was used in conjunction with mammography specificity was reduced to 36 per cent. This study may be too underpowered to report a meaningful result due to the small study size.

Extensive research is currently being conducted to identify factors, biomarkers or genetic markers that may be of potential use for the assessment of a woman's risk of developing breast cancer. This may in turn enable medical practitioners to provide suitable medical, psychological or surgical management appropriate to a woman's needs. However, it should be stressed that these factors are surrogate markers that are *associated* with an increased *risk* of developing disease, and as such results of marker studies are *not diagnostic* and should be treated with caution. The results of prognostic tests may result in increased surveillance of women considered to be at elevated risk, which may in turn lead to earlier detection of disease.

It is clear from the included studies, that to draw any meaningful conclusions regarding the potential of new breast cancer diagnostic technologies, larger, long-term studies of appropriate study design need to be conducted in *asymptomatic* women. Mammography may be considered an imperfect screening modality, however the addition of MRI for high risk women and the roll out of digital mammography have increased the options available to women in Australia. Only a brief snap shot of the diagnostic capabilities of the new technologies included in this *Bulletin* have been presented. An in-depth analysis of the level of training, infrastructure and financial support required to become proficient at conducting diagnostic testing and interpreting the results of these new technologies was

considered to be beyond the scope of this Bulletin, but remains an important concern.

Glossary of terms

Atypia: cells appear to be visually different from normal cells but do not have all the features of cancer cells (Figure 23).

Bias: A deviation of results or inferences from the truth, or processes leading to such a deviation. Bias in a clinical trial may result in a erroneous conclusion when a researcher or a patient knows what treatment is being given. To avoid bias a blinded study should be conducted. Bias can result from poor study design, flawed data or flawed data collection.

Blinded study: For diagnostic studies, researchers interpreting results are unaware of the patient's disease status.

Carcinoma: A malignant tumour made up of epithelial cells that may infiltrate surrounding tissues, spreading to other parts of the body via the blood or lymph (Figure 23).

Case-control study: The observation of cases (those with the disease) and controls (those without disease) to ascertain the relationship of an attribute or factor to the disease by comparing, retrospectively, the past history and exposure of both groups with regard to how frequently the attribute is present. A study in which the risk factors of people with a disease are compared with those without a disease.

Cohort: A group that has been exposed to a factor is compared to a group not exposed to factor. May be retrospective or prospective. Cohorts are usually large groups of individuals followed over a long period of time.

Confidence interval: eg 95%CI is a 95% probability that the true value of a variable (mean, rate etc) is contained within the interval. The 95%CI is the range of values in which it is 95% certain that the true value lies for the entire population.

Ductal carcinoma in situ (DCIS): a non-invasive tumour of the mammary gland (breast) arising from cells lining the ducts (Figure 23). May appear as micro-calcifications on a mammogram.

False positive rate: complement of test specificity

False negative rate: complement of test sensitivity

Hyperplasia: there are more cells than you would normally expect to see in the walls of the ducts or lobules of the breast, but they still appear normal (Figure 23).

Invasive cancer: cancerous cells have spread outside the duct into other areas of the breast.

Positive predictive value (PPV): The proportion of patients with a positive test result who are correctly diagnosed ie the number of true positives divided by the total number who tested positive.

Negative predictive value (NPV): The proportion of patients with a negative test result who are correctly diagnosed ie the number of true negatives divided by the total number who tested negative.

Recall to assessment: The recall to assessment indicator measures the rate of women who are recalled for assessment following attendance for a routine screening at a BreastScreen Australia service. In most cases, the recall is made because a woman's screening mammogram shows signs that there may be breast cancer.

Reference standard: an independently applied test that is compared to the diagnostic test being evaluated in order to ascertain the accuracy of the new diagnostic test. Required for the verification of true negatives and true positives.

Screening: the performance of tests on asymptomatic individuals in order to detect a disease or medical condition at an earlier stage than would otherwise be the case. A screening test is not intended to be diagnostic, an individual with a positive or suspicious result must be referred for diagnosis and treatment.

Sensitivity: the ability of a test to correctly identify those individuals with the disease or the proportion of individuals who have the disease who also returned a positive test result for the disease.

Specificity: the ability of a test to correctly identify those individuals who do not have the disease or the proportion of individuals who do not have the disease who also returned a negative test result for the disease.

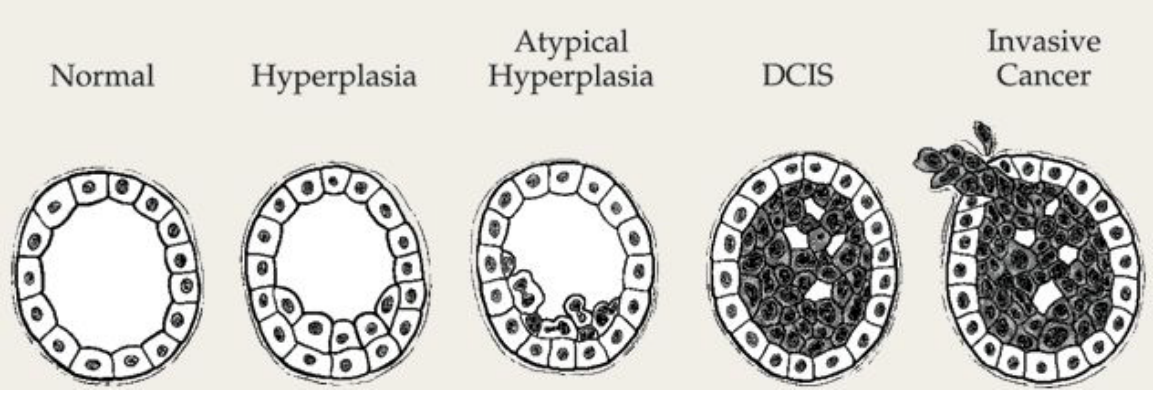

Figure 23 Breast cancer development (Love 2009)

(AIHW 2008; Kerr 2004)

Appendix A: Levels of evidence

Level	Intervention [1]	Diagnostic accuracy [2]	Prognosis	Aetiology [3]	Screening Intervention
I [4]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among consecutive persons with a defined clinical presentation[6]	A prospective cohort study[7]	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation[6]	All or none[8]	All or none[8]	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial[9] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study[10] ▪ Interrupted time series without a parallel control group	Diagnostic case-control study[6]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[11]	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Tablenotes

[*1] Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

[2] The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

[3] If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

[4] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

[5] The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

[6] Well-designed population based case-control studies (eg. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

[7] At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.

[8] All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

[9] This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).

[10] Comparing single arm studies ie. case series from two studies. This would also include unadjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

[11] Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Source: Hierarchies adapted and modified from: (Bandolier editorial 1999; Lijmer et al 1999; NHMRC 1999; Phillips et al 2001)

Appendix B: Previous HS assessments for breast cancer diagnosis

MRI targeted screening for breast cancer in genetically high-risk women.
Horizon Scanning Report May 2004
http://www.horizonscanning.gov.au/internet/horizon/publishing.nsf/Content/30948B2D5B54C4BDCA25715C000223DE/$File/MRI%20breast%20cancer%20Final%20Report.pdf

Computer aided detection systems in mammography.
Horizon Scanning Report July 2004
http://www.horizonscanning.gov.au/internet/horizon/publishing.nsf/Content/30948B2D5B54C4BDCA25715C000223DE/$File/CAD%20HS%20Report%20Final.pdf

Digital Mammography: a screening modality for breast cancer.
Prioritising summary, December 2005
http://www.horizonscanning.gov.au/internet/horizon/publishing.nsf/Content/38A7076E82346B63CA25714D008383CD/$File/Digital%20Mammography%20December2005.pdf

MR Spectroscopy for breast cancer diagnosis.
Prioritising summary, September 2006, updated 2007
http://www.horizonscanning.gov.au/internet/horizon/publishing.nsf/Content/C0C2B288C566A9B2CA2574C800098BA1/$File/Magnetic%20resonance%20spectroscopy%20Vol%2014%20No%203%20Sept2006.pdf

Fermiscan®: Hair diffraction for the diagnosis of breast cancer.
Prioritising summary, May 2007
http://www.horizonscanning.gov.au/internet/horizon/publishing.nsf/Content/D7C4AF89B5854F3BCA2572AC0083A970/$File/May%20Vol%2016%20No%208%20-%20Fermiscan.pdf

Breast cancer diagnosis using ultrasound elasticity imaging.
Prioritising summary, October 2007, updated November 2008
http://www.horizonscanning.gov.au/internet/horizon/publishing.nsf/Content/D7C4AF89B5854F3BCA2572AC0083A970/$File/Vol%2018%20-%20breast%20cancer.pdf

Breast tomosynthesis: A breast cancer screening tool.
Prioritising summary, August 2008
http://www.horizonscanning.gov.au/internet/horizon/publishing.nsf/Content/874217A91463AE97CA25741D007F026E/$File/Volume_21_Aug_2008_Breast%20Tomosynthesis.pdf

Appendix C: Indicators of high-risk of breast cancer

Women at potentially high risk of breast cancer (<1% of the female population) are defined as follows:

- women who are at potentially high risk of ovarian cancer;
- two 1º or 2º relatives on one side of the family diagnosed with breast or ovarian cancer plus one or more of the following features on the same side of the family:
    - additional relative(s) with breast or ovarian cancer;
    - breast cancer diagnosed before the age of 40;
    - bilateral breast cancer;
    - breast and ovarian cancer in the same woman;
    - Ashkenazi Jewish ancestry; or
    - breast cancer in a male relative.
- one 1º or 2º relative diagnosed with breast cancer at age 45 or younger plus another 1º or 2º relative on the same side of the family with sarcoma (bone/soft tissue) at age 45 or younger;
- member of a family in which the presence of a high risk breast cancer gene mutation has been established eg *BRCA1*, *BRCA2*, *Tp53*;
- personal history of breast cancer; or
- pre-malignant conditions: lobal carcinoma *in situ* or atypical ductal hyperplasia.

(MSAC 2007; NBCC 2006)

The Gail Model

The United States National Cancer Institute use the following questionnaire, based on the Gail Model. The Breast Cancer Risk Assessment Tool will estimate a woman's risk of developing invasive breast cancer during the next 5-year period and up to age 90 (lifetime risk) based on the woman's age and the risk factor information provided. For comparison, the tool will then calculate 5-year and lifetime risk estimates for a woman of the same age who is at average risk for developing breast cancer. Lifetime risk estimates are higher than 5-year estimates because breast cancer risk increases with years at risk (National Cancer Institute 2009).

Question 1: *Does the woman have a medical history of any breast cancer or of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS)?*
Explanation: A medical history of DCIS or LCIS increases the risk of developing invasive breast cancer. The method used by the Breast Cancer Risk Assessment Tool to calculate the risk of invasive breast cancer is not accurate for women with a history of DCIS or LCIS. In addition, the tool cannot accurately predict the risk of another breast cancer for women who have a medical history of breast cancer.

Question 2: *What is the woman's age?*

Explanation: The risk of developing breast cancer increases with age. The great majority of breast cancer cases occur in women older than age 50. Most cancers develop slowly over time. For this reason, breast cancer is more common among older women. **Note:** *Tool only calculates risk for women 35 years of age or older.*

Question 3: *What was the woman's age at time of her first menstrual period?*
Explanation: Women who had their first menstrual period before age 12 have a slightly increased risk of breast cancer. The levels of the female hormone estrogen change with the menstrual cycle. Women who start menstruating at a very young age have a slight increase in breast cancer risk that may be linked to their longer lifetime exposure to estrogen.

Question 4: *What was the woman's age at her first live birth of a child?*
Explanation: Risk depends on many factors, including age at first live birth and family history of breast cancer. The relationship of these two factors is shown in the following table of relative risks. For women with 0 or 1 affected relative, risks increase with age at first live birth. For women with 2 or more first degree relatives, risks decrease with age at first live birth.

Relative risk of developing breast cancer

Age at first birth	Number of affected relatives		
	0	1	2 or more
< 20 years	1	2.6	6.8
20-24	1.2	2.7	5.8
25-29 or no child	1.5	2.8	4.9
>30 years	1.9	2.8	4.2

Question 5: *How many of the woman's first-degree relatives - mother, sisters, daughters have had breast cancer?*
Explanation: Having one or more first-degree relatives (mother, sisters, daughters) who have had breast cancer increases a woman's chances of developing this disease.

Question 6: *Has the woman ever had a breast biopsy?*
6a: How many previous breast biopsies (positive or negative) has the woman had?
6b: Has the woman had at least one breast biopsy with atypical hyperplasia?
Explanation: Women who have had breast biopsies have an increased risk of breast cancer, especially if their biopsy specimens showed atypical hyperplasia. Women who have a history of breast biopsies are at increased risk because of whatever breast changes prompted the biopsies. Breast biopsies themselves do not cause cancer.

Question 7: *If known, please indicate the woman's race/ethnicity.*
Explanation: While race/ethnicity is included in the calculation, it does not influence breast cancer risk as much as other factors. **Note:** *If the woman's race/ethnicity is unknown, the tool will use data for white females to estimate the predicted risk.*

Appendix D: Profiles of included studies

Profiles of the studies included for assessment for the safety and effectiveness of new breast screening technologies.

Diagnostic level of evidence	Study	Location	Study design	Study population	Outcome assessed	Length of follow-up
Computed tomography						
III-2	Lindfors, K.K. Boone, J.M. Nelson, T.R. Yang, K. Kwan, A.L. Miller, D.F. (2008)	California, the United States	Prospective and intra-individual comparison between dedicated breast CT and MX	10 healthy volunteers, mean age 52 year (range: 40-67 years) 69 symptomatic and asymptomatic women with BI-RADS category 4 and 5 lesions, mean age 54 years (range: 36-82 years)	Detection of breast lesions Patient comfort	N/A
Positron emission tomography/ mammography						
III-1	Kaida, H. Ishibashi, M. Fujii, T. Kurata, S. Uchida, M. Baba, K. Miyagawa, T. Kaibara, H. Kawamura, S. Ogo, E. Hayabuchi, H. (2008)	Fukuoka, Japan	Cross-classification of patients on breast PET and whole-body PET, compared to histopathology.	118 *symptomatic* women with lesions suspected to have breast cancer as diagnosed by MX or CBE. Mean age 58 years (range 28-91 years)	Detection of index cancers and lesions Diagnostic accuracy Specificity Sensitivity PPV NPV	N/A
IV	Kaida, H. Ishibashi, M. Fujii, T. Kurata, S. Ogo, E. Tanaka, M. Hayabuchi, N. (2008)	Fukuoka, Japan	Case series	660 *asymptomatic* women, mean age 59.9 years (range 27-85 years) underwent whole-body and dedicated breast PET	Breast cancer detection	N/A

Diagnostic level of evidence	Study	Location	Study design	Study population	Outcome assessed	Length of follow-up
III-1	Tafra, L. Cheng, Z. Uddo, J. Lobrano, M.B. Stein, W. Berg, W.A. Levine, E. Weinberg, I.N. Narayanan, D. Ross, E. Beylin, D. Yarnell, S. Keen, R. Sawyer, K. van Geffen, J. Freimanis, R.L. Staab, E. Adler, L.P. Lovelace, J. Shen, P. Stewart, J. Dolinsky, S. (2005)	Multi-centre study, United States	Cross-classification of patients on PEM and MX, compared to excisional biopsy	44 *symptomatic* women with biopsy confirmed breast cancer, mean age 57 years (range 25-88 years), 31/44 (70%) post-menopausal, 19/44 (43%) on HRT	The ability of PEM to detect the primary lesion, the presence of multifocal disease, the presence of non-index lesions and to predict the status of the margins of patients undergoing mastectomy.	N/A
Ultrasonography						
III-1	Berg, W.A. Blume, J.D. Cormack, J.B. Mendelson, E.B. Lehrer, D. Böhm-Vélez, M. Pisano, E.D. Jong, R.A. Evans, W.P. Morton, M.J. Mahoney, M.C. Hovanessian-Laresen, L. Barr, R.G. Farria, D.M. Marques, H.S. Boparai, K. ACRIN 6666 Investigators (2008)	Multi-centre, United States	Cross-classification of patients on U/S and MX, versus U/S or MX alone, compared to excisional biopsy	2,725 *asymptomatic* women with dense breast tissue and/or a *high risk* of BC (personal history of BC, family history of either a 1st or 2nd degree relative with BC or a known BRCA mutation) presenting for routine MX. Mean age 55 years (range 25-91 years)	Specificity Sensitivity PPV NPV	12 months
III-1	Corsetti, V. Houssami, N. Ferrari, A. Ghirardi, M. Bellarosa, S. Angelini, O. Bani, C. Sardo, P. Remida, G. Galligioni, E. Ciatto, S. (2008)	Calcinato, Italy	Cross-classification of patients on U/S and MX, compared to excisional biopsy	26,047 consecutive *asymptomatic* women presenting for MX. 25,572 women negative on MX, of these 9,157 had >50% breast	Breast cancer detection PPV	N/A

				density. These women were assessed by U/S. Suspicious U/S followed by MX and biopsy.		
III-1	Ohlinger,R. Heyer, H. Thomas, A. Paepke, S. Warm, H. Klug, U. Frese, H. Schulz, K. Schimming, A. Schwesinger, G. Köhler, G. Wodny, M. Kohlmann, T.H. Grunwald, S. (2006)	Multi-centre, Germany	Cross-classification of patients on U/S and MX, compared to excisional biopsy	448 *asymptomatic* women underwent U/S followed by MX. Mean age 49.1 years (range 21-89 years)	Specificity Sensitivity PPV NPV Diagnostic accuracy Image interpretability	N/A
Thermography						
III-2	Arora, N. Martins, D. Ruggerio, D. Tousimis, E. Swistel, A.J. Osborne, M.P. Simmons, R.M. (2008)	New York, USA	Cross-classification of patients on digital thermography compared to histopathology/ biopsy.	92 *symptomatic* women with lesions suspected to have breast cancer as diagnosed by MX or U/S. Mean age 51 years (range 23-85 years)	Ability of thermography to confirm breast cancer diagnosis Specificity Sensitivity	N/A
III-2	Salhab, M. Keith, L.G. Laguens, M. Reeves, W. Mokbel, K. (2006)	Chicago, USA	Cross-classification of patients on dynamic thermography and MX compared to histopathology/ biopsy.	173 *symptomatic* women with suspicious findings on a MX, imaged prior to biopsy. Mean age 56 years (range 17-85 years)	Ability of thermography to confirm breast cancer diagnosis Diagnostic accuracy Specificity Sensitivity PPV NPV	N/A

Diagnostic level of evidence	Study	Location	Study design	Study population	Outcome assessed	Length of follow-up
Electrical impedance						
III-2	Prasad, S. Houserkova, D. Campbell, J. (2008)	Olomouc, Czech Republic	Cross-classification of patients on electrical impedance and MX and/or U/S compared to histopathology/ biopsy.	88 *symptomatic* women with suspicious findings on a MX or U/S, imaged prior to biopsy. Age and menopausal status not stated.	Correlation of diagnosis with other imaging modalities and final biopsy result.	N/A
IV	Stojadinovic, A. Moskovitz, O. Gallimidi, Z. Fields, S. Brooks, A.D. Brem, R. Mucciola, R.N. Singh, M. Maniscalco-Theberge, M. Rockette, H.E. Gur, D. Shriver, C.D. (2006)	Multi-centre study, United States and Israel	Case series	<u>Specificity arm</u> 1,361 *asymptomatic* women. Mean age 34.6 ± 3.1 years. Post-menopausal or pregnant women were excluded from the study.	Diagnostic yield	N/A
III-1	Stojadinovic, A. Moskovitz, O. Gallimidi, Z. Fields, S. Brooks, A.D. Brem, R. Mucciola, R.N. Singh, M. Maniscalco-Theberge, M. Rockette, H.E. Gur, D. Shriver, C.D. (2006)	Multi-centre study, United States and Israel	Prospective cohort, cross-classification of patients on electrical impedance and/or MX, CBE, U/S compared to histopathology/ biopsy. Blinded.	<u>Sensitivity arm</u> 189 *symptomatic* women with suspicious findings on CBE, MX, U/S or MRI. Mean age 39.3 ± 4.3 years. Assessed with EI prior to biopsy. Post-menopausal or pregnant women were excluded from the study.	Diagnostic accuracy Specificity Sensitivity PPV NPV FN FP	

Diagnostic level of evidence	Study	Location	Study design	Study population	Outcome assessed	Length of follow-up
IV	Stojadinovic, A. Nissan, A. Shriver, C.D. Mittendorf, E.A. Akin, M.D. Dickerson, V. Lenington, S. Platt, L.D. Stavros, T. Goldstein, S.R. Moskovitz, O. Gallimidi, Z. Fields, S. Yeshaya, A. Allweis, T. Manassa, R. Pappo, I. Ginor, R.X. Agostino, R.B. Gur, D. (2008)	Multi-centre study, United States and Israel	This study is a continuation of the 2006 study. Case series	<u>Specificity arm</u> 1,751 *asymptomatic* women aged between 30-39 years. Post-menopausal or pregnant women were excluded from the study.	Diagnostic yield	N/A
III-1	Stojadinovic, A. Nissan, A. Shriver, C.D. Mittendorf, E.A. Akin, M.D. Dickerson, V. Lenington, S. Platt, L.D. Stavros, T. Goldstein, S.R. Moskovitz, O. Gallimidi, Z. Fields, S. Yeshaya, A. Allweis, T. Manassa, R. Pappo, I. Ginor, R.X. Agostino, R.B. Gur, D. (2008)	Multi-centre study, United States and Israel	This study is a continuation of the 2006 study. Prospective cohort, cross-classification of patients on electrical impedance and/or MX, CBE, U/S compared to histopathology/ biopsy. Blinded.	<u>Sensitivity arm</u> 390 *symptomatic* women with suspicious findings on CBE, MX, U/S or MRI Aged between 30-45 years. Assessed with EI prior to biopsy. Post-menopausal or pregnant women were excluded from the study.	Diagnostic accuracy Specificity Sensitivity PPV NPV FP FN	N/A

Diagnostic level of evidence	Study	Location	Study design	Study population	Outcome assessed	Length of follow-up
Scintimammography or Molecular Breast imaging						
III-2	Hussain, R. Buscombe, J.R. (2006)	Bangladesh and United Kingdom	Meta-analysis	Included studies ≥100 patients enrolled. Results compared to pathology. Single-centre trials (12), total of 2,424 women. Majority of studies retrospective (10/12). Blinding status of studies not ascertained. Multi-centre trials (5), total of 3,049 women enrolled. All studies prospective. Readers blinded to results of other imaging modalities.	Diagnosis of primary breast cancer. Specificity Sensitivity PPV NPV	N/A
III-1	Hruska, C.B. Boughey, J.C. Phillips, S.W. Rhodes, D.J. Wahner-Roedler, D.L. Whaley, D.H. Degnim, A.C. O'Connor, M.K. (2008)	Minnesota, USA	Cross-classification of patients on MBI and MX and/or U/S compared to histopathology/ biopsy.	100 *symptomatic* women with suspicious findings on MX or U/S, imaged with single-head MBI system prior to biopsy. and 150 *symptomatic* women with suspicious findings on MX or U/S, imaged with dual-head MBI system prior to biopsy. Age and menopausal status not stated.	Diagnosis of primary breast cancer	N/A

Diagnostic level of evidence	Study	Location	Study design	Study population	Outcome assessed	Length of follow-up
III-1	Hruska, C.B. Boughey, J.C. Phillips, S.W. Rhodes, D.J. Wahner-Roedler, D.L. Whaley, D.H. Degnim, A.C. O'Connor, M.K. (2008)	Minnesota, USA	Cross-classification of patients on MBI and MX, compared to excisional biopsy.	650 *asymptomatic* women with dense breast tissue and/or a high risk of BC (personal history of BC, family history of either a 1st or 2nd degree relative with BC or a known BRCA mutation) imaged with dual-head MBI.	Diagnosis of primary breast cancer	N/A
III-1 Abstract	Hruska, C.B. Rhodes, D.J. Phillips, S.W. Whaley, D.H. Alabin, T.T. O'Connor, M.K. (2008)	Minnesota, USA	Cross-classification of patients on MBI and MX, compared to excisional biopsy. This study presents further incremental results from the Hruska et al (2008a) screening study.	940 *asymptomatic* women with dense breast tissue and/or a high risk of BC (personal history of BC, family history of either a 1st or 2nd degree relative with BC or a known BRCA mutation) imaged with dual-head MBI.	Diagnosis of primary breast cancer	N/A
II	Spanu, A. Chessa, F. Battista Meloni, G. Sanna, D. Cottu, P. Manca, A. Nuvoli, S. Madeddu, G. (2008)	Sassari, Italy	Cross-classification of patients on MBI and MX and/or U/S compared to histopathology/ biopsy.	264 consecutive *symptomatic* women with suspicious findings on MX or U/S, imaged with single-head MBI system prior to biopsy. Median age 56 years (range 26-81 years).	Change to patient management. The detection of multi-focal, multi-centric and bilateral breast cancer and the impact of MBI on surgical planning.	N/A

Diagnostic level of evidence	Study	Location	Study design	Study population	Outcome assessed	Length of follow-up
Ductoscopy						
III-2	Grunwald, S. Heyer, H. Paepke, S. Schwesinger, G. Schimming, A. Hahn, M. Thomas, A. Jacobs, V.R. Ohlinger, R. (2007)	Multi-centre, Germany	Cross-classification of patients on ductoscopy, and MX compared to histopathology/ biopsy.	64 *symptomatic* women with nipple discharge. 71 breasts examined. Mean age 52.3 years (range 21-77).	Sensitivity Specificity PPV NPV FP FN	N/A

BI-RADS = Breast Imaging Reporting and Data System, CT = computed tomography, MX = mammography, PEM = positron emission mammogram, HRT = hormone replacement therapy, CBE = clinical breast examination, U/S = ultrasound, MRI = magnetic resonance imaging, MBI = molecular breast imaging or scintimammography, BC = breast cancer, FP = false positive, FN = false negative, PPV = positive predictive value, NPV = negative predictive value

Appendix E: HTA internet sites

AUSTRALIA

- Centre for Clinical Effectiveness, Monash University
  http://www.mihsr.monash.org/cce/

- Health Economics Unit, Monash University
  http://chpe.buseco.monash.edu.au

AUSTRIA

- Institute of Technology Assessment / HTA unit
  http://www.oeaw.ac.at/ita/welcome.htm

CANADA

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/site/index.php?accueil

- Alberta Heritage Foundation for Medical Research (AHFMR)
  http://www.ahfmr.ab.ca/publications.html

- Canadian Coordinating Office for Health Technology Assessment (CCHOTA) http://www.cadth.ca/index.php/en/

- Canadian Health Services Research Foundation
  http://www.chsrf.ca/about/index_e.php

- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org

- Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca

- Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm

- Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca

DENMARK

- Danish Institute for Health Technology Assessment (DIHTA)
  http://www.dihta.dk/publikationer/index_uk.asp

- Danish Institute for Health Services Research (DSI)
  http://www.dsi.dk/engelsk.html

FINLAND

- FINOHTA http://www.stakes.fi/finohta/e/

FRANCE

- L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) http://www.anaes.fr/

GERMANY

- German Institute for Medical Documentation and Information (DIMDI) / HTA http://www.dimdi.de/dynamic/en/

THE NETHERLANDS

- Health Council of the Netherlands Gezondheidsraad http://www.gr.nl/adviezen.php

NEW ZEALAND

- New Zealand Health Technology Assessment (NZHTA) http://nzhta.chmeds.ac.nz/

NORWAY

- Norwegian Centre for Health Technology Assessment (SMM) http://www.kunnskapssenteret.no/

SPAIN

- Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology Assessment Agency (AETS) http://www.juntadeandalucia.es/salud/orgdep/aetsa/default.asp

- Catalan Agency for Health Technology Assessment (CAHTA) http://www.gencat.net/salut/depsan/units/aatrm/html/en/Du8/index.html

SWEDEN

- Swedish Council on Technology Assessment in Health Care (SBU) http://www.sbu.se/en/

- Center for Medical Health Technology Assessment http://www.cmt.liu.se/

SWITZERLAND

- Swiss Network on Health Technology Assessment (SNHTA)
  http://www.snhta.ch/

UNITED KINGDOM

- NHS Quality Improvement Scotland
  http://www.nhshealthquality.org/nhsqis/qis_display_home.jsp?pContentID=43&p_applic=CCC&pElementID=140&pMenuID=140&p_service=Content.show&

- National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA)
  http://www.ncchta.org/

- University of York NHS Centre for Reviews and Dissemination (NHS CRD)
  http://www.york.ac.uk/inst/crd/

- National Institute for Clinical Excellence (NICE)
  http://www.nice.org.uk/

UNITED STATES

- Agency for Healthcare Research and Quality (AHRQ)
  http://www.ahrq.gov/clinic/techix.htm

- Harvard School of Public Health – Cost-Utility Analysis Registry
  http://www.tufts-nemc.org/cearegistry/index.html

- U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (TEC) http://www.bcbs.com/tec/index.html

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