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Horizon Scanning Technology Horizon Scanning Report

The role of scintimammography in the diagnosis of breast cancer

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Executive Summary

In Australia and New Zealand, breast cancer is the most common notifiable cancer in females. In Australia during 2006, the age-standardised incidence rate for breast cancer was 112.4 per 100,000 women and invasive ductal carcinoma accounted for the majority of these new cases. The five-year relative survival rate for Australian women diagnosed with breast cancer during the period 2000-2006 was 88 per cent. Survival is decreased for women diagnosed with large tumours but increased in women whose lymph nodes are found to be cancer free. During 2007 in New Zealand, cancer of the breast had the highest age-standardised registration rate among females with 90.3 cases per 100,000. This rate, and the age-standardised death rate, were markedly higher in the Māori population compared to the rates in the non-Māori population.

Scintimammography (SMM) has previously been assessed as a potential method for the first-line *screening* of asymptomatic women in the report "New and emerging technologies for breast cancer detection". In addition, two meta-analyses examined after the publication of this report, reported an approximate sensitivity and specificity of 85 and 86 per cent, respectively, for scintimammography for the *diagnosis* of breast cancer. It was concluded that scintimammography should be considered as an additional diagnostic test in cases where mammography gives equivocal results.

This report seeks to more fully assess the role of SMM in the diagnosis of breast cancer.

SMM involves the intravenous injection of ^{99m} technetium-sestamibi (^{99m}Tc-sestamibi), which crosses the cellular plasma membrane and adheres in the cytoplasm with the negatively charged mitochondria. Cancerous cells use high levels of energy in comparison to healthy cells and have highly active mitochondria and will therefore take up increased levels of ^{99m}Tc-sestamibi, which shows up as regions of brightness on captured images. The potential clinical indications for the use of SMM include women with: equivocal mammograms; dense breast tissue; palpable abnormalities that cannot be imaged with mammography; axillary lymph node metastases of an adenocarcinoma of unknown primary origin; breast implants; parenchymal distortions of the breast; breast iatrogenic architectural distortion; suspected recurrent breast cancer; and for the assessment or monitoring of doubtful micro-calcifications; of multi-centric disease; and response to neoadjuvant chemotherapy.

Although a number of facilities in Australia have experience with scintimammography, SMM is not routinely used. In Australia gamma imaging is mainly used for the identification of the sentinel node from primary cancers.

Mammography is the gold standard *screening* tool for the identification of breast cancer. Women found to be positive by mammography may be presented with a number of treatment options, including surgery, radiotherapy or chemotherapy. Before treatment the extent of disease spread must be ascertained using clinical examination and a number of imaging modalities, including mammography, magnetic resonance imaging, ultrasound and in some cases positron emission tomography. For women with palpable lesions, fine needle aspiration biopsy may be used to establish a pre-operative diagnosis, however a definitive histological diagnosis can only be obtained by a core biopsy.

Safety

None of the studies included in this assessment reported any specific safety outcomes associated with the scintimammography procedure. The obvious safety issue is the number of false positives and false negatives resulting from the procedure, and the harms associated with these diagnoses.

Effectiveness

Evaluation of disease and patient management

Four studies that explicitly reported the results of scintimammography in terms of a change in patient management were included for assessment. These studies indicated that SMM may provide additional information when decisions are made on the clinical and surgical management of women diagnosed with breast cancer, especially if used in conjunction with other imaging modalities such as ultrasound. However, the high number of false positive (9.2% to 15%) and negative (6.8% to 48.3%) diagnoses remain a concern.

Evaluation of women already diagnosed with breast cancer

Five studies reported the results of scintimammography when used to evaluate women already diagnosed with breast cancer, however, the impact of SMM results on patient management was not reported. Although these studies did not explicitly state the impact that SMM had on the surgical outcomes of patients, it was clear that the information gained, such as the presence of additional tumours, could be used to inform the surgical work-up and pre-surgical planning of these patients, and as such is a potentially good adjunctive tool for the assessment of women diagnosed with breast cancer. Diagnostic accuracy was significantly (p< 0.01) improved when SMM was used in conjunction with mammography, compared to either modality alone. Of importance is the reported increase in sensitivity from 85 per cent to 91 per

cent when a dual-head, rather than a single-head, gamma camera is employed. However, the number of false negatives reported by all studies remain a concern given this is a symptomatic population.

Evaluating disease recurrence

Both of the included studies indicated that SMM is a useful imaging modality for the evaluation of disease recurrence, especially in the chest wall. Diagnostic accuracy was higher with the use of SPECT alone compared to SMM alone, in women with suspected disease recurrence. The use of SPECT alone increased the sensitivity (89% vs 78%) and the negative predictive value (78% vs 64%) markedly compared to SMM.

Monitoring therapy with scintimammography

It would appear from the assessment of the two included studies that using SMM to predict response or resistance to neoadjuvant chemotherapy is not a reliable technique. Other studies, dated pre-2005 and not included in this assessment, reported conflicting results with some concluding that SMM could be a useful tool in the prediction of response to treatment or in the prediction of therapy resistance, whilst other studies reported the opposite finding.

One cost analysis was identified by the search strategy, however, as it was conducted in Taiwan, it may not be applicable to an Australasian population. In addition, the study, conducted in 2002, is dated, and therefore the estimated costs per procedure may have changed markedly. In a hypothetical cohort, ranging between 16,000 and 40,000, of women with an indeterminate mammogram, the number of unnecessary biopsies performed was estimated to be reduced. In addition, a total cost saving of between US$123,075 and US$307,776 would be gained if an excisional biopsy was only performed in women with an equivocal SMM, rather than on all women with an indeterminate mammogram.

In summary, the included studies indicate that SMM is a useful adjunct in the pre-surgical evaluation of women with biopsy-proven breast cancer. A number of studies indicated changes in the clinical management of some women as a consequence of SMM. However, SMM should be used with caution and in conjunction with other imaging modalities as the number of false negatives and false positives may lead to serious physical and mental consequences for patients. As the dual-head camera offers superior imaging for breast lesions of all sizes, the single-head camera should not be considered for the evaluation of women with breast cancer. In addition, consideration should be given to the role and use of single photon emission computed tomography (SPECT/CT) in the evaluation of women with breast cancer. Further evaluation of the prognostic value of SMM for the prediction of response or resistance to therapy may be warranted.

Scintimammography (SMM) was considered in a previous HealthPACT report as a method for screening women for breast cancer, but was not recommended as a screening test because of its invasive nature and its unacceptably high false positive and false negative rates in the asymptomatic population. The aim of this report is to examine the role of SMM in the diagnosis of breast cancer.

Generally mammography and breast biopsy are considered the gold standard for the diagnosis of breast cancer. However, the available studies used SPECT, combined SPECT/CT, MRI, ultrasound and PET as comparators for SMM.

The evidence indicates that SMM cannot be considered as a replacement for mammography and biopsy but may be a useful adjunct in surgical planning to evaluate the extent of diagnosed breast cancer (ie to detect multifocal disease). The use of a dual head gamma camera in conjunction with breast compression is superior to the use of a single head camera. The literature also suggests that SMM may also be useful for the post-surgical evaluation of suspected disease recurrence, especially in the chest wall, because diagnosis of recurrent breast cancer is often difficult due to scarring, calcifications and other skin changes.

The prospective studies have small cohorts and some of the larger studies are retrospective. Further prospective, preferably randomised, trials are needed to assess patient outcomes and costs associated with the use of this technology.

The National Horizon Scanning Unit, AHTA, School of Population Health and Clinical Practice, University of Adelaide has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the use of scintimammography (SMM), also known as breast-specific gamma imaging (BSGI) or molecular breast imaging (MBI), for the diagnosis of women with breast cancer (horizon scanning register ID number 000441).

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of scintimammography for the diagnosis of women with breast cancer, its present use, the potential future application of the technology, and its likely impact on the Australian health care system. It provides a preliminary evaluation of the safety, effectiveness, cost-effectiveness and ethical considerations associated with scintimammography for the evaluation of women already diagnosed with breast cancer.

A number of companies within Australia manufacture and/or distribute gamma cameras, however these may not be suitable for use for routine SMM:

- Philips Electronics Australia Ltd have two stationary gamma cameras listed on the Australian Register of Therapeutic Goods (ARTG 117642 and 125577) plus the application software (ARTG 158037);
- GE Healthcare Australia Pty Ltd has one stationary gamma camera listed (ARTG 128982);
- Siemens Ltd has a stationary gamma camera with application software (ARTG 141951 and 98947, respectively);
- Gammasonics Institute for Medical Research Pty Ltd has a mobile gamma camera capable of performing thyroid imaging, static bone scans, renography, hepatobiliary, gastric emptying, sentinel node imaging and scintimammography (ARTG 167380);
- Insight Oceania Pty Ltd has a mobile gamma camera capable of performing bedside imaging (ARTG 168583); and
- Global Medical Solutions Australia Pty Limited has a mobile gamma camera for the detection and imaging of radionuclide uptake during surgery (ARTG 146997).

InSight Oceania Pty Ltd are currently in discussions with Dilon Technologies (USA) with a view to distributing the only commercially available breast-specific gamma camera, the Dilon 6800, in Australia, after should they receive TGA approval.

SMM is likely to be offered through specialist, tertiary hospitals under the guidance of a multidisciplinary clinical team which may include a radiologist and surgeon. A number of facilities in Australia have experience with scintimammography, however it is not routinely used in Australia[1].

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[1] An Australia study was conducted in 2004 by Sultana et al (2004) from the Faculty of Medicine and Health Sciences, University of Newcastle. 110 women underwent SMM prior to surgery. Surgical outcomes were compared to a matched group (n=80) who did not undergo SMM. All attempts to locate this paper by the evaluators failed: the journal is not held by any institution in Australia, the researchers are no longer at the University of Newcastle and the authors do not appear to have published any further work.

In Australia and New Zealand, breast cancer is the most common notifiable cancer in females. The most common histological type of breast cancer is invasive ductal carcinoma (70-80%), where the abnormal cell growth begins in the ducts or lobes (invasive ductal or lobular carcinoma). 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 1). 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 may be difficult to treat (Avril & Adler 2007).
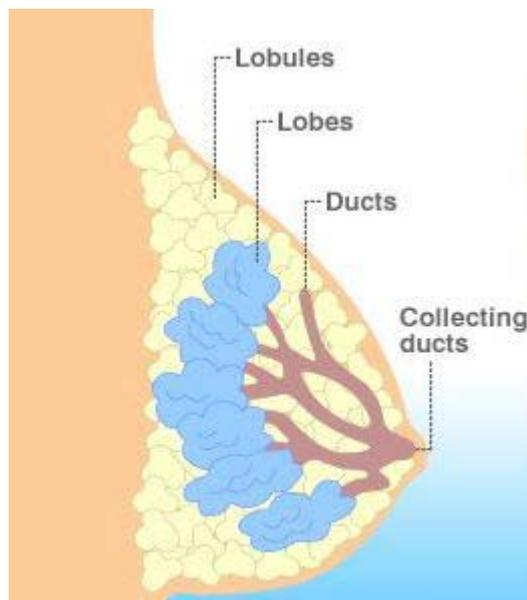
Figure 1   Anatomy of the breast

The extent or spread of disease is referred to as staging and a number of systems can be used to stage tumours. The TNM staging system uses information about the size of the primary tumour (T), lymph node involvement (N) and the presence or absence of distant metastases (M) to assign a value to invasive breast cancers which can range from stage I (early disease) to stage IV (advanced disease). The Surveillance Epidemiology End Results staging system, commonly used when reporting cancers to registries, has three categories that indicate the extent of spread of breast cancer at diagnosis: local (tumour is confined to the breast); regional (tumour has spread to surrounding tissue or nearby lymph nodes); and distant (tumour has spread to distant

organs). Staging is important when determining the most effective treatment and for the determination of patient prognosis (AIHW and NBOCC 2009).

Description of the technology

The procedure

Scintimammography was previously assessed as a potential method for *screening* asymptomatic women in the report "New and emerging technologies for breast cancer detection". When used as a diagnostic or screening tool in *asymptomatic*, albeit *high-risk*, women, SMM had a sensitivity of 76.9 per cent compared to a poor 23.1 per cent for mammography, as determined by excisional biopsy and histology. In *symptomatic* women, sensitivity was increased to 91.4 per cent when the newer dual-head gamma cameras, as opposed to single-head cameras, were used.

A meta-analysis of 64 studies (5,354 lesions) reported an overall sensitivity and specificity of 85 and 87 per cent, respectively, for scintimammography for the *diagnosis* of breast cancer. The sensitivity and specificity were both approximately 88 per cent for patients with a palpable mass, however the sensitivity was markedly reduced for patients with a non-palpable mass (67%) (Liberman et al 2003). These results were confirmed by a later meta-analysis which separated single site (n=2,424) and multi-site studies (n=3,049), and reported a sensitivity of 85 per cent and a specificity of approximately 84 per cent (Hussain & Buscombe 2006). It was concluded that scintimammography should be considered as an adjuvant test to mammography, adding sensitivity and specificity, especially in younger women with dense breasts (Schillaci et al 2005) and women with breast implants (Peng et al 2003), where mammography often gives equivocal results. Due to the low specificity of mammography a large number of unnecessary biopsies are conducted, therefore it has been suggested that the use of scintimammography in equivocal cases may decrease the number of biopsies performed (Schuster & Halkar 2004).

This report seeks to more fully assess the role of SMM in the diagnosis of breast cancer.

SMM is based on a technique initially developed in the early 1990s for the diagnosis of cardiac disease. Although this procedure is considered to be non-invasive, it does involve the intravenous injection of the radiopharmaceutical and perfusion imaging agent, ^{99m} technetium-sestamibi (^{99m}Tc-sestamibi), a cationic, lipophilic compound (Taillefer 2005; Schuster & Halkar 2004). ^{99m}Tc-sestamibi crosses the cellular plasma membrane and adheres in the cytoplasm with the negatively charged mitochondria, the cytoplasmic

organelles responsible for cellular energy production (Schuster & Halkar 2004). When used for the diagnosis of heart disease, it was noted that healthy cardiac cells consume more energy and concentrate a greater proportion of the ^{99m}Tc-sestamibi than diseased cardiac cells. In cancer, the opposite of this occurs as diseased, cancerous cells use high levels of energy and therefore have hyperactive mitochondria. Compared to the healthy surrounding cells, cancerous cells will take up increased levels of ^{99m}Tc-sestamibi and emit more gamma rays, and this will show up on the captured images as regions of brightness (Figure 2) (Schmidt 2008). The majority of studies on SMM have used ^{99m}Tc-sestamibi, however other radiopharmaceuticals have been successfully used or have potential to be used to perform SMM including ^{99m}Tc-tetrofosmin, ^{99m}Tc-labelled analogs of glucose (O'Connor et al 2009) and ^{99m}Tc-methionine (Sharma et al 2009).
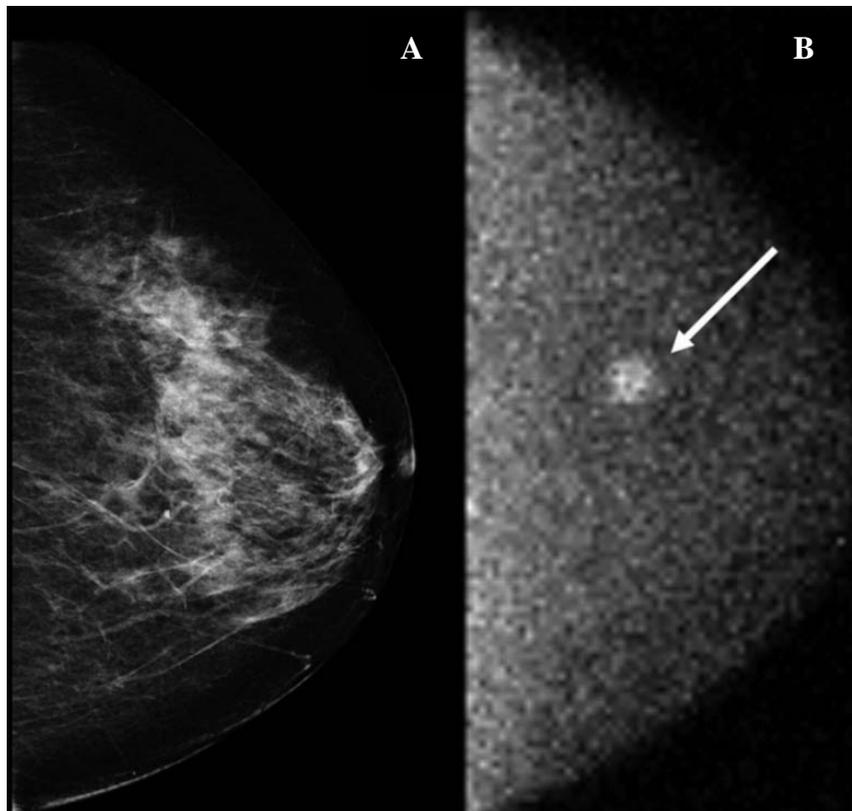
Figure 2   A) Negative image acquired using digital mammography and B) Positive 7mm cancer image acquired with MBI (Schmidt 2008)

The standard dose of ^{99m}Tc-sestamibi used in a SMM study (740-925 MBq[2]), is similar to the dose received in myocardial perfusion studies. Usually the ^{99m}Tc-sestamibi is delivered intravenously as a bolus, however 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

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

2005). Images are taken approximately 5-10 minutes after injection and the total time required for examination is 45-60 minutes (Prasad & Houserkova 2007). Studies have suggested that SMM should not be used in patients with acute inflammation of the breast, such as acute mastitis, as this may result in a high number of false positives (Pappo et al 2000).

Figure 3   Positioning of the gamma camera in the caudal, oblique and medial views (Dilon Diagnostics 2009)

The resolution of gamma cameras was limited in the past due to the amount of "dead" space between the camera and the patient, which required the patient to be imaged in a prone position with the camera placed laterally. More compact gamma cameras have been developed which have detectors made with multi-crystal arrays of caesium iodide or sodium iodide, or semi-conductor materials such as cadmium zinc telluride (CZT). These small field-of-view detectors (total active area 20x20cm or 20x15cm) are capable of capturing high-resolution images and also allow for greater flexibility in patient positioning (O'Connor et al 2009). With a breast-specific gamma camera, seated patients can be imaged comfortably with the detector placed against the chest wall. Compression of the breast increases the sensitivity of the device (Schillaci & Buscombe 2004) (Figure 3). To date, the only commercially available breast-specific gamma camera is the Dilon 6800 system (Dilon Technologies, USA) (O'Connor et al 2009). A dual-head SMM system has been developed in which the breast can be positioned between two opposing detectors in a similar fashion to mammography, resulting in improved resolution (Hruska et al 2008a).

The sensitivity of scintimammography can be limited due to Compton scattering contamination, which occurs when gamma rays pass through a body and the scattering of photons results in a decrease in energy. Compton scattering may be overcome by specialised image analysis, increasing sensitivity and reducing the number of false positives (Bonifazzi et al 2006).

Some studies have advocated combining planar scintimammography with SPECT (single photon emission computed tomography) to improve sensitivity through increased contrast resolution, however further studies are required to

establish the true value of combining these two technologies (Schillaci & Buscombe 2004). Some centres performing sentinel node scintigraphy use the combined SPECT/CT to gain additional anatomical information (personal communication Siemens Healthcare Australia). Some studies have also advocated the use of fused images obtained with MRI and SMM to evaluate tumour size (Duarte et al 2007).

Intended purpose

The potential clinical indications for the use of SMM include:
- women with suspected breast cancer who have:
  - equivocal mammograms;
  - dense breast tissue;
  - palpable abnormalities that cannot be imaged with mammography;
  - axillary lymph node metastases of an adenocarcinoma of unknown primary origin;
  - breast implants;
  - parenchymal distortions of the breast;
  - breast iatrogenic architectural distortion; or
- suspected recurrent breast cancer; and for the assessment or monitoring of
  - doubtful micro-calcifications;
  - of multi-centric disease; and
  - response to neoadjuvant chemotherapy (Schillaci & Buscombe 2004; Jones et al 2009).

A number of studies have proposed using SMM as a means of assessing the response or resistance to chemotherapy or endocrine therapy in breast cancer patients (Kim et al 2006; Van Den Bossche et al 2006).

A number of Medicare Benefits Schedule (MBS) numbers exist for lymphoscintigraphy, a method used for the assessment of axillary lymph node status and to identify the sentinel lymph node. Studies describing the identification of sentinel lymph nodes will not be considered in this assessment.

Clinical need and burden of disease

In Australia, the risk of females developing breast cancer up to the age of 75 years is one in 11 and one in nine up to the age of 85 years. However, the age-standardised incidence rate is expected to remain relatively the same from 2006-2010 with only a 0.1 projected increase per 100,000 women (AIHW and AACR 2008). Having said this, the actual number of women diagnosed with breast cancer is expected to increase in the future due to the ageing of the population. By 2015, an estimated 15,409 women are expected to be

diagnosed with breast cancer, 22 per cent higher than the number diagnosed in 2006.

In 2006, breast cancer was the most common cancer diagnosed in females with a total of 12,614 cases, accounting for 27.7 per cent of all cancer registrations in Australian women. The age-standardised incidence rate for breast cancer was 112.4 per 100,000 women. Invasive ductal carcinoma accounted for the majority of these cases with a total of 9,933 women diagnosed (78.7%), followed by invasive lobular carcinoma with 1,354 cases (10.7%). In the same year, breast cancer was the second most common cause of cancer death in women with a total of 2,618 deaths, representing a mortality rate of 22.1 per 100,000 women, a slight reduction compared to the previous year (23.6 per 100,000 in 2005) (AIHW and NBOCC 2009).

The one-year relative survival rate for Australian women diagnosed with breast cancer during the period 2000-2006 was 97 per cent. For the same period, the five-year relative survival rate was 88 per cent, that is, women five years after diagnosis were 88 per cent as likely to be alive as woman of a comparable age in the general population. Survival rates decrease with age (Figure 4), which may be due to less aggressive treatment options being offered to older women, a reduced likelihood of being diagnosed with early or stage I disease and an increased likelihood of having other co-morbidities. Survival is decreased for women diagnosed with large tumours compared to those with small tumours. The five-year survival rate for women with tumours 10mm in size was 98 per cent compared to 73 per cent with tumours of ≥30mm. Survival is also greater in women whose lymph nodes were found to be cancer free compared to those where the cancer has spread to the lymph nodes (AIHW and NBOCC 2009).
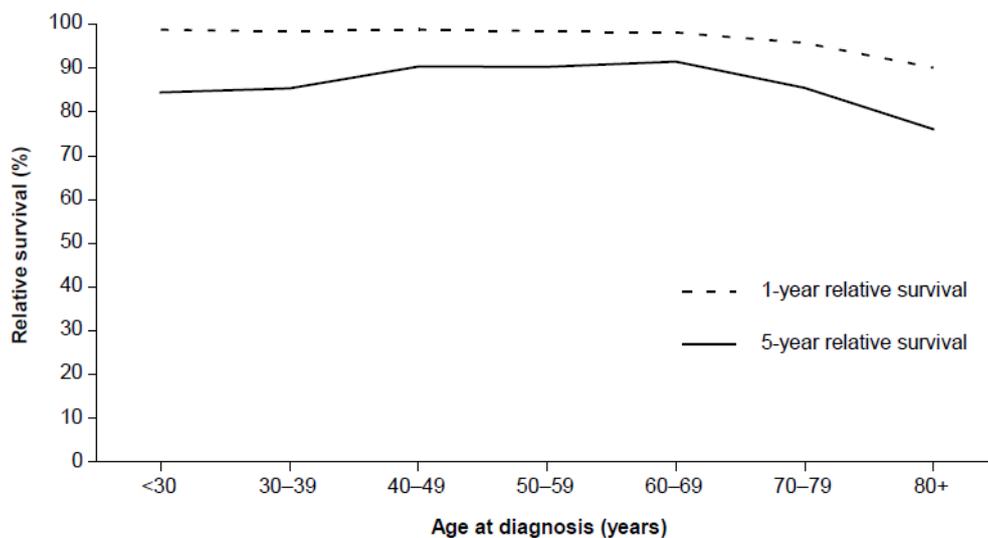
In Australia during 2007-08, there were 106,067 hospitalisations of female patients for breast cancer. Of these, 87,561 were same-day hospitalisations and 18,506 were of a longer duration (overall average length of stay 4.1 days, however the ALOS increased for women aged 70-79 years: 5.3 days and for those aged 80+ years: 6.8 days) (AIHW and NBOCC 2009).

In New Zealand, cancer of the breast was the most commonly registered cancer in 2007 with 2,575 registered cases, accounting for 27.9 per cent of all cancer registrations in females. Breast cancer had the highest age-standardised registration rate among females with 90.3 cases per 100,000. This rate was markedly higher in the Māori population compared to the rate in the non-Māori population (124.6 vs 87.2 registrations per 100,000). The majority of breast cancer registrations (85%) occurred in women aged >45 years. In addition, breast cancer was the leading cause of death from cancer among females in 2007, with 643 deaths or 17.1 per cent of all female cancer deaths. Of all cancers, breast cancer had the highest age-standardised death rate among females with 20.8 deaths per 100,000. This rate was markedly higher in the Māori population compared to the rate in the non-Māori population (29.9 vs 20.0 deaths per 100,000) (Ministry of Health 2010).

Registration rates for breast cancer in females remained stable between 1997 and 2007, however mortality rates trended downwards over the same period with a drop of 19.3 percent. Between 1997 and 2007, the age-standardised mortality rate for Māori women dropped by 18.0 percent. However, the rates have been highly variable over this time. A downward trend was observed for the mortality rate for breast cancer in non-Māori women, falling by 19.2 percent between 1997 and 2007 (Ministry of Health 2010).

Stage of development

A number of facilities in Australia have experience with scintimammography, however SMM is not routinely used in Australia (personal communication Peter MacCallum Cancer Centre, Melbourne). SMM may develop as an adjunct in the screening and diagnosis of breast cancer but may prove to be more useful when used for planning of treatment options for women already diagnosed with breast cancer. In Australia, gamma imaging is used for the identification of the sentinel node from a number primary cancers including cancers of the breast, cervical, vulva, penile, prostate and testes, as well as for melanomas. Most of these procedures would utilise a gamma probe (personal communication Siemens HealthCare Australia). There are many hundreds of gamma cameras installed nationally (at least 30 installed in South Australia) that would be capable of performing scintimammography, however they are

not currently used for this purpose (personal communication InSight Oceania Pty Ltd).

Treatment Alternatives

Existing comparators

Histology is the gold standard for the *diagnosis* of breast cancer, however its invasive nature means that there needs to be careful selection of women who are at risk of breast cancer. Both Australia and New Zealand have in place comprehensive population-based mammography screening programs, which target and triage for further testing *asymptomatic* women aged 50-69 years. Masses and calcifications are the most common abnormalities identified on mammograms. The density of a woman's breast tissue will impact on the ability of radiographers to identify abnormalities on a mammogram, with dense tissue (usually observed on younger women <50 years) reducing the sensitivity of mammography by obscuring abnormalities (Corsetti et al 2008). In cases where mammography may be considered of reduced value, including among women with dense breast tissue, digital mammography or MRI may be indicated (Jones et al 2009).

Women who are symptomatic for breast cancer also receive mammography as the first imaging component but will usually undergo more comprehensive and complementary imaging studies than asymptomatic women. After diagnosis, women may be presented with a number of treatment options, including surgery, radiotherapy or chemotherapy, however before treatment can commence the extent of disease spread must be ascertained. A full clinical history and physical examination should be conducted, examining the breasts and axillae for signs of primary cancer and local spread, and the rest of the body of signs of distant spread. A number of imaging modalities, including mammography, MRI, ultrasound and in some cases PET, may be used to pre-operatively assess women once they have been diagnosed with breast cancer. These modalities may be used alone or in conjunction with each other and is especially important in women diagnosed with DCIS. Mammography may underestimate the extent of disease in these women. Although ultrasound is not used as a screening tool, it is a useful tool in the assessment of women diagnosed with breast cancer, and can provide a reliable assessment of tumour size in cases of invasive breast cancer, particularly in women with dense breast in whom mammography performs poorly (NHMRC 2001b). In addition, MRI, which has been approved by the MBS for the screening of women at *high-risk* of developing breast cancer, may be used to accurately assess tumour size and spread. Although MRI is highly sensitive, it has a relatively low specificity which may result in high numbers of false positives. In addition, the use of

MRI for the assessment of disease spread in breast cancer patients is relatively new, therefore a learning curve for radiologists is likely to exist. In Australia, the high cost of and the limited number of MRI units, which are under extreme usage pressure, may prohibit assessments for breast cancer by MRI (Sakorafas & Safioleas 2010).

For women with palpable lesions, fine needle aspiration biopsy (FNAB) may be used to establish a pre-operative diagnosis. For non-palpable lesions, fine needle aspiration may be conducted under image guidance. This procedure provides a cytological not histological diagnosis, and imaging would be required to support the FNAB results prior to definitive surgery. A definitive histological diagnosis can be obtained by a core biopsy, which uses a wide bore needle to obtain a tissue sample (NHMRC 2001b).

Mammography and ultrasound are not useful in the assessment of some types of breast cancer such as invasive lobular carcinoma (NHMRC 2001b). The high rate of false positives that may arise from mammography remains a concern as suspicious or abnormal mammograms may result in women undergoing FNAB or core biopsy unnecessarily, with its associated high economic and psychological/emotional costs (Liberman et al 2003).

Safety

None of the studies included in this assessment reported any specific safety outcomes associated with the scintimammography procedure. The obvious safety issues associated with a procedure of this kind is the number of false positives and false negatives and the harms associated with these findings. Patients with a false positive result may be subjected to unnecessary and highly invasive surgical procedures, which may have long lasting physical and mental consequences for the patient in question. Similarly, a false negative result gives false reassurance to patients who believe they are disease free. The number of false positive and false negative rates are summarised in the effectiveness section.

Effectiveness

A total of 13 studies were included for assessment (see Appendix B for study profiles). There were four diagnostic level II (3 assessing disease and patient management and 1 disease recurrence), one diagnostic level III-1 (assessment of disease), six diagnostic level III-2 (2 assessing disease and patient management, 2 assessing disease, 1 disease recurrence and 1 patient management) and two level II prognostic level of evidence studies (response to therapy).

Diagnosis of disease and patient management

Four studies that explicitly reported the results of scintimammography in terms of changing patient management were included for assessment (Table 1). Two of these studies were conducted prospectively (Lumachi et al 2006b and Usmani et al 2008) and are therefore less liable to bias compared to the two retrospective studies (Zhou et al 2009 and Killelea 2009).

The larger of the two prospective studies reported on the use of SMM and ultrasound for the evaluation of women diagnosed with breast cancer (n=77) (level III-2 diagnostic evidence). No significant difference in the sensitivities of the two techniques was reported (78.4% and 67.6%, respectively), however using the two techniques combined increased sensitivity and accuracy markedly (91.9% and 92.2%, respectively, significance not reported). In addition the number of false positives and false negatives were markedly reduced when the two imaging modalities were used in combination. The SMM results in these women were used to inform clinical decision making with 49 women (64%) undergoing breast conserving surgery rather than all 77 women undergoing radical mastectomy (Lumachi et al 2006b).

The small (n=21) but good prospective study by Usmani et al (2008) reported on surgical decision making in 21 women undergoing SMM (level II diagnostic evidence). Although only 14 women were found to be positive by SMM (13 true and one false positive), 18 women underwent a surgical procedure: six radical mastectomies and 12 wide local excisions.

The two retrospective studies were both published in 2009 and reported on the surgical management of women with biopsy proven breast cancer who had undergone SMM (level III-2 diagnostic evidence). Although these studies were retrospective, and therefore more prone to bias, the results reported by them were more recent (SMM conducted from 2005-2008 and 2006-2007). The prospective studies which reported on SMM were conducted on women during 2004-2005. As such, these retrospective studies may reflect a maturation of the technology.

Of the 82 SMM scans performed by Killelea et al (2009), 77 detected the presence of a known malignancy (sensitivity 94%), however a false negative rate of seven per cent was reported. Two and three of the missed tumours were ductal carcinoma in situ and invasive ductal carcinoma, respectively with an average size of 10mm (range 8-12mm). SMM identified lesions in 18 patients which were not detected by other imaging modalities including mammography, ultrasound, positron emission tomography and MRI. SMM resulted in a change in management in these 18 (22%) patients, with one patient opting for mastectomy and 17 undergoing biopsy of the additional lesions. Eight of these patients were false positives, that is, they were biopsy negative despite being SMM positive and thus underwent this more invasive procedure unnecessarily. SMM resulted in a change in surgical management for 10 patients who underwent necessary additional or more extensive surgery to remove the new lesions.

Zhou et al (2009) reported retrospectively on 138 women, 25 (18.1%) of whom had a positive SMM in a position remote from the original biopsied lesion. False positive lesions were identified in ten of these women were and four of these patients underwent an additional biopsy which was found to be benign, five patients underwent additional ultrasound and one woman had a mastectomy. Fourteen women (10.1%) had a negative SMM scan but had residual tumour on surgical examination. However, 15 (10.9%) patients had a true positive SMM scan for a synchronous or more extensive malignancy in the same (n=8) or contralateral breast (n=7). The clinical management was changed in all eight women with additional cancer in the same breast, with six women undergoing mastectomy, one undergoing neoadjuvant chemotherapy and the remaining women undergoing a combination of mastectomy and neoadjuvant chemotherapy.

It should be noted that the type of gamma camera used in these studies varied. The two studies by Killelea et al and Zhou et al used the single-head breast-specific gamma camera, whilst the good study by Usmani et al used a dual head and Lumachi et al used a triple head camera. Differences in hardware make comparisons between studies difficult, however preliminary studies by Hruska et al (2008) (as summarised below in Table 2) have indicated that dual-head gamma cameras can increase the sensitivity of SMM.

It is clear from the above studies that the use of SMM may provide additional information when decisions are made in the clinical and surgical management of women diagnosed with breast cancer, especially if used in conjunction with other imaging modalities such as ultrasound. However, the high number of false positives and negatives remains a concern. Reported false negative rates were unacceptably high, ranging from 6.8 (Killelea et al) to 48.3 per cent (Zhou et al) indicating a large number of women received false reassurance that they were disease free after undergoing scintimammography. Although, by comparison, the false positive rates were lower (ranging from 9.2% to 15%) this still indicates that a large number of women received inappropriate and highly invasive treatment. Three out of the four studies reported good positive predictive values (82.9, 89.6 and 92.9%) indicating that out of 100 women who test positive by SMM, then 83-93 women were correctly identified as being positive. However the study by Zhou reported a positive predictive value of 60 per cent. Negative predictive values ranging from 81 to 88 per cent indicates that SMM is reasonably good at reassuring those patients who test negative that they do not have cancer.

Table 1   Scintimammography for the evaluation of confirmed breast cancer and subsequent change in patient management

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Killelea et al 2009	III-2	Retrospective cross-classification of patients on SMM compared to core-needle and/or excisional biopsy.	790 women at high-risk of breast cancer who underwent 942 SMM scans. Of these, 82 women with a biopsy-proven breast cancer underwent SMM, mean age 53 years (range 33-83 years). 55 IDC, 3 ILC, 14 DCIS, 9 mixture of IDC & ILC. SMM conducted using breast-specific Dilon 6800 single head gamma camera and ^{99m}Tc-sestamibi.	**Scintimammography** 77/82 (93.9%) confirmed presence of known malignancy, average tumour size 1.5cm (range 1-5cm) Sens 69/74 (93.2%) Spec PPV 69/77 (89.6%) NPV FP 8/8 (100%) FN 5/74 (6.8%) **False negative rate for SMM** 5/74 (6.8%), average tumour size 1.0cm (range 0.8-1.2 cm) Of these 2/5 (40%) DCIS 3/5 (60%) IDC **Change in patient management** 18/82 (22%) additional lesions identified by SMM. 17/18 (94.4%) underwent biopsy 5/18 (27.8%) invasive carcinoma 2/18 (11.1%) DCIS 1/18 (5.6%) LCIS 2/18 (11.1%) papilloma 8/18 (44.4%) benign **Change in surgical management** 10/82 (12.2%) underwent additional surgery to remove new lesions 1/10 (10%) underwent total mastectomy instead of breast conserving therapy

Lumachi et al 2006b	III-2	Prospective cross-classification of patients on SMM compared to histopathology.	77 consecutive women, median age 54 years (range 36-70 years) with primary breast cancer detected by CE, MRx or both and conformed by biopsy. All patients underwent axilla examination using US and SMM using a triple head gamma camera (Philips Irix) and ^{99m}Tc-sestamibi for initial staging prior to surgery.	66/77 (85.7%) IDC 4/77 (5.2%) ILC 2/77 (2.6%) medullary 5/77 (6.5%) mixed

	TP	FP	TN	FN
SMM	29	6	34	8
US	25	8	32	12
SMM + US	34	3	37	3

SMM
Sens	29/37 (78.4%)
Spec	34/40 (85.0%)
PPV	29/35 (82.9%)
NPV	34/42 (81.0%
FP	6/40 (15%)
FN	8/37 (21.6%)
Acc	63/77 (81.8%)

US
Sens	25/37 (67.6%)
Spec	32/40 (80.0%)
PPV	25/33 (75.8%)
NPV	32/44 (72.7%)
FP	8/40 (20%)
FN	12/37 (32.4%)
Acc	57/77 (74.0%)

SMM + US
Sens	34/37 (91.9%)
Spec	37/40 (92.5%)
PPV	34/37 (91.9%)
NPV	37/40 (92.5%)
FP	3/40 (7.5%)
FN	3/37 (8.1%)
Acc	71/77 (92.2%)

There was no significant difference between US and SMM

US + SMM gave increased accuracy

49/77 (63.6%) women underwent breast conserving surgery with axillary node dissection instead of radical mastectomy.

28/77 (36.4%) women underwent radical mastectomy.

Usmani et al 2008	II	Prospective cross-classification of patients on SMM compared to core-needle and/or excisional biopsy.	21 consecutive women, mean age 48 ± 14.3 years (range 26-77 years) with proven breast cancer who had undergone breast lump excision, referred for SMM. SMM conducted with dual head Toshiba GCA 7200A/PI using ^{99m}Tc-methoxy isobutyl isonitrile (MIBI).	All 21 women underwent biopsy to confirm breast cancer diagnosis. 18 women underwent further surgery 12/18 wide local excision 6/18 radical mastectomy **Positive SMM** 14/21 (66.7%)

	TP	TN	FP	FN
WLE	8	2	1	1
MRM	5	1	0	0
No surg		3		
Total	13	6	1	1

Sens	13/14 (92.9%)
Spec	6/7 (85.7%)
PPV	13/14 (92.9%)
NPV	6/7 (85.7%)
FP	1/7 (14.3%)
FN	1/14 (7.1%)
Acc	19/21 (90.5%)

Zhou et al 2009	III-2	Retrospective cross-classification of patients on SMM compared to core-needle and/or excisional biopsy.	138 women with biopsy-proven breast cancer, mean age 55 years (range 30-81 years): 69 IDC, 20 ILC, 32 DCIS, 17 mixture of IDC, ILC, DCIS. SMM conducted using breast-specific Dilon 6800 single head gamma camera and ^{99m}Tc-sestamibi.	**Positive SMM** 25/138 (18.1%) at a site remote from known cancer. 13/25 (18.8%) were IDC 4/25 (20%) were ILC 2/25 (6.25%) were DCIS 6/25 (35.3%) mix IDC, ILC, DCIS

	TP	TN	FP	FN
IDC	9		4	5
ILC	3		1	
DCIS	1		1	8
Mix	2		4	1
Total	15	99	10	14

Sens	15/29 (51.7%)
Spec	99/109 (90.8%)
PPV	15/25 (60.0%)
NPV	99/113 (87.6%)
FP	10/109 (9.2%)
FN	14/29 (48.3%)
Acc	114/138 (82.6%)

Of the 10 SMM false positives
10/138 (7.2%)
4/10 (40%) underwent additional biopsy found to be benign
5/10 (50%) underwent US found to be benign
1/10 (10%) underwent mastectomy found to be benign

Change in management of the 15 true positives(additional cancers)

7/15 (46.7%) converted to mastectomy
1/15 (6.6%) converted to neoadjuvant chemotherapy
7/15 (46.7%) contralateral cancer

SMM = scintimammography, ILC = invasive lobular carcinoma, IDC = invasive ductal carcinoma, DCIS = ductal carcinoma in situ, LCIS = lobular carcinoma in situ, US = ultrasound, MRx = mammography, CE = clinical examination, PPV = positive predictive value, NPV = negative predictive value, Sens = sensitivity, Spec = specificity, Acc = accuracy, FP = false positive, FN = false negative, TP = true positive, TN = true negative, WLE = wide local excision, MRM = radical mastectomy

Diagnosis of women with breast cancer

Five studies reported the results of scintimammography used to evaluate women already diagnosed with breast cancer, however, the impact of SMM results on patient management was not reported (Table 2). Three of these studies were conducted prospectively and two were retrospective studies. A further eight full text studies, published prior to 2005, were retrieved that described the extent of disease in women diagnosed with breast cancer, or the assessment of micro- calcifications or the assessment of multifocal or multicentric disease, however due to the time constraints placed on the writing of this report, the full results of these studies are not presented (Bagni et al 2003; Cayre et al 2004; Cwikla et al 2001; De Cicco et al 2004; Fondrinier et al 2004; Klaus et al 2000; Lumachi et al 2002; Marini et al 2001).

Two of the better large, cross comparative studies were conducted by Gommans et al (2007) and Grosso et al (2009) (level II diagnostic evidence) using a single-head gamma camera. The results as reported by Grosso, however, were difficult to interpret as women (n=283) with micro-calcifications were classified according to their high, low or intermediate risk of having a carcinoma. Of the 69 women with lesions that were operated on, 32 had a carcinoma confirmed by histology. Of these 32, mammography classified 26 (81.3%) as being at high or intermediate risk of carcinoma compared to 25/32 (78.1%) by SMM. By combining mammography and SMM, however, this number rose to 30/32 (93.8%). If only the women considered to be at high-risk of carcinoma were considered, then SMM, and the combination of SMM and mammography, was superior to mammography alone (56.3% and 71.9%, respectively, compared to 40.6%). In their analysis, Grosso et al considered the women classified as low and intermediate-risk as negative and only those classified as high-risk as positive, and thus they calculated the accuracy of the two methods. Due to the uncertainty of this classification system, these values were not summarised in Table 2. The diagnostic value of mammography alone compared to SMM or combined SMM and mammography was determined by calculating the receiver operating characteristic (ROC). There was a statistically significant difference between the areas under the ROC curves for mammography alone (0.72 ± 0.052) compared to SMM (0.84 ± 0.046) and mammography and SMM combined (0.86 ± 0.039) ($p < 0.01$).

Grosso et al also reported on the follow-up (median 8.7 years) of the 214 women found not to have lesions at time of diagnosis. Follow-up consisted of clinical examination, mammography, US and SMM where required. This follow-up aspect of the study was only discussed briefly in the paper and confirmed the initial findings of the study that combined imaging with mammography plus SMM was superior to either imaging modalities alone.

Gommans et al (2007) reported good values for the accuracy of SMM for the diagnosis of women with non-palpable breast lesions, however a false negative rate of 17.8 per cent is of concern. Of the 101 women initially evaluated, 37 were found to be true positive and of these 35 had lobular or ductal carcinomas. When SMM was used for the pre-surgical evaluation of axillary lymph node metastases in these women, the sensitivity was poor compared to histology (33%), however the high specificity (100%) indicates that SMM may be good at identifying those women who *do not* have axillary node metastases. The authors speculated that using SPECT rather than SMM would increase the sensitivity to 66 per cent and that the low sensitivity in this case was due to the high number of micro-metastases (n=10).

The small, cross-comparative study (n=26) by Brem et al (2009) compared the ability of mammography and SMM to evaluate the extent of disease in women with biopsy proven invasive lobular carcinoma (level III-2 diagnostic evidence). Lobular invasive carcinoma represents approximately 10 per cent of all breast cancers and may be difficult to detect. SMM was the most sensitive imaging modality, detecting 26 of the 28 lesions, compared to MRI, US and mammography. The size of lesion detected by SMM ranged from 2-77mm, with an average size of 20.3mm. The two lesions missed by SMM measured five and 90mm. SMM identified an additional six lesions that were occult on mammograms.

Additional tumours were also identified in the retrospective study by Zhou et al (2008), SMM was used to assess the presence of malignancies that were remote from the known cancer in 48 women. SMM was positive in six women but of these three were found to be benign on US or core biopsy (PPV = 50%).

The retrospective study by Hruska et al (2008) compared the use of single and dual-head SMM systems to investigate 100 and 150 women with suspicious breast lesions identified by mammography and/or US. SMM results were compared to pathology results from core needle biopsy or surgical excision (level III-1 diagnostic evidence). Of the 100 women in the single-head SMM study 53 women had 59 tumours identified by mammography and/or US. Although SMM identified eight tumours in seven patients not detected by mammography, it gave false negative results for 10 *tumours* in seven patients (false negative rate 15%). Possible reasons for the false negative results included five patients with small tumours (<5mm). In addition, all seven patients had large breasts and technical problems, including poor patient positioning (n=5) and low ^{99m}Tc-sestamibi uptake (n=5), may have had an impact on results. In the dual-head SMM study, 62 of the 150 women were benign for breast cancer. A total of 128 tumours were detected in the 88 women found to have breast cancer. Of these, 119 were identified with

mammography or ultrasound and a further nine were detected with SMM. The dual-head detector was more sensitive (91%) than the single-head, identifying 117 of the 128 tumours with eleven false negatives reported. SMM had the greatest sensitivity for detecting larger tumours (>10mm), however, sensitivity was greatly improved for the detection of smaller tumours (<10mm) when a dual-head detector was employed. The same results were presented in earlier papers by O'Connor et al (2007) (single-head gamma camera) and Hruska et al (2008b) (dual-head gamma camera).

As with the studies included in the above section, firm conclusions regarding the use of SMM for the diagnosis of breast cancer are difficult to draw due to differences in study design and the manner in which results were reported. Although these studies did not explicitly state the impact that SMM had on the surgical outcomes of patients, it was clear that the information gained could be used to inform the surgical work-up and pre-surgical planning of these patients. Of importance is the study by Hruska et al (2008a) that reported an increase in sensitivity when a dual-head gamma camera is employed. The number of false negative results remain a concern.

Table 2   Scintimammography for the evaluation of confirmed breast cancer

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Brem et al 2009	III-2	Retrospective cross-classification of patients on SMM (n=26), MRx (n=26), MRI (n=12) and sonography (n=25) compared to core-needle and/or excisional biopsy.	26 women with biopsy-proven invasive lobular carcinoma, mean age 63 years (range 46-82 years). SMM conducted using breast-specific Dilon 6800 single head gamma camera and ^{99m}Tc-sestamibi.	**Lesions imaged** 　　　　　Total　　+ve　　-ve SMM　　28　　　26　　　2 MRx　　28　　　22　　　6 Sono　　25　　　17　　　8 MRI　　12　　　10　　　2 **Sensitivity [95% CI] per lesion** SMM　　93% [76.5, 99.1] MRx　　79% [59.1, 91.7] Sono　　68% [46.5, 85.1] MRI　　83% [51.6, 97.9] **Differences in sensitivity** [$98\frac{1}{3}$% CI] per lesion of SMM compared to: MRx　　0.14 [-0.13, 0.42] 　　　　p = 0.29 Sono　　0.24 [-0.05, 0.53] 　　　　p = 0.07 MRI　　0.17 [-0.19, 0.53] 　　　　p = 0.50

| Gommans et al 2007 | II | Prospective cross-classification of patients on SMM compared to core-needle and/or excisional biopsy. | 101 consecutive women with non-palpable lesions detected by MRx. Mean age 61 ± 7.3 years (range 50-75 years). SMM conducted using GE-Millenium VG single head gamma camera and [99mTc]-sestamibi. | **SMM results for breast cancer**

41/101(40.6%) positive
    26/41 (63.4%) IDC
    5/41 (12.2%) ILC
    6/4114.6%) DCIS
    4/41 (9.8%) papilloma or mastophatic tissue
5/101 (5.0%) positive uptake in axilla

60/101 (59.4%) negative
19/60 (31.7%) no histopathology and clear of malignancies at follow-up
Of the 41/60 (68.3%) negative cases where histopathology was performed
    2/41 (4.9%) IDC
    2/41 (4.9%) ILC
    4/41 (9.8%) DCIS
    8/41(19.5%) cystic tissue
    7/41 (17.1%) mastophatic
    10/41 (24.4%) fibrotic tissue |

SMM results for breast cancer

	Disease	
	+ve	-ve
+ve SMM	37 (TP)	4 (FP)
-ve SMM	8 (FN)	52 (TN)

Sens	37/45 (82.2%)
Spec	52/56 (92.8%)
PPV	37/41 (90.2%)
NPV	52/60 (86.7%)
FP	4/56 (7.1%)
FN	8/45 (17.8%)

SMM results for axillary lymph node metastases

Of the 35 lobular or ductal carcinomas, histopathology confirmed axillary lymph node metastases in 15/35 (42.9%). Of these, 10/15 (66.7%) were micro metastases (<2mm).

	Disease	
	+ve	-ve
+ve SMM	5 (TP)	0 (FP)
-ve SMM	10 (FN)	20 (TN)

Sens	5/15 (33.3%)
Spec	20/20 (100%)
PPV	5/5 (100%)
NPV	20/30 (66.7%)
FP	0/20 (0%)
FN	10/15 (66.7%)

SMM compared to histopathology

SMM able to identify significantly more cases of IDC than ILC and DCIS, $p=0.001$

26/28 (92.9%) IDC +ve SMM
5/7 (71.4%) ILC +ve SMM
6/10 (60.0%) DCIS +ve SMM

98/101 (97%) agreement between two blinded assessors

Grosso et al 2009	II	Cross-classification of patients on SMM compared to core-needle and/or excisional biopsy.	283 consecutive women, mean age 53 ± 8.2 years (range 32-79 years) with micro-calcifications detected by screening MRx. SMM performed in all women within 2 weeks of MRx using 6800 single head gamma camera (GE Medical Systems) and ^{99m}Tc-sestamibi.	At time of diagnosis

At time of diagnosis

69/283 (24.4%) lesions operated on Suspicion of malignancy classified:

Carcinoma	32/69 (46.4%)
MRx	
Low	6/32 (18.8%)
Intermediate	13/32 (40.6%)
High	13/32 (40.6%)
SMM	
Low	7/32 (21.9%)
Intermediate	7/32 (21.9%)
High	18/32 (56.3%)
MRx + SMM	
Low	2/32 (6.3%)
Intermediate	7/32 (21.9%)
High	23/32 (71.9%)
Benign	37/69 (53.6%)
MRx	
Low	10/37 (27.0%)
Intermediate	18/37 (48.6%)
High	9/37 (24.3%)
SMM	
Low	26/37 (70.3%)
Intermediate	8/37 (21.6%)
High	3/37 (8.1%)
MRx + SMM	
Low	9/37 (24.3%)
Intermediate	19/37 (51.4%)
High	9/37 (24.3%)

It was not possible to calculate sens, spec, PPV and NPV due to the manner in which patients were classified.

Area under the ROC curve (AUC)

MRx	0.72 ± 0.052
SMM	0.84 ± 0.046
MRx + SMM	0.86 ± 0.039

Difference between AUCs

MRx and SMM	$p<0.01$
MRx and MRx + SMM	$p<0.01$

Of the 214 women followed-up for a median of 8.7 years

MRx	
Low	110/214 (51.4%)
Intermediate	95/214 (44.4%)
High	9/214 (4.2%)
SMM	
Low	181/214 (84.6%)
Intermediate	32/214 (15.0%)
High	1/214 (0.5%)
MRx + SMM	
Low	103/214 (48.1%)
Intermediate	101/214 (47.2%)
High	10/214 (4.7%)

| Hruska et al 2008a

The same results for patients imaged using the single-head gamma camera were also reported in O'Connor et al 2007, which built on a preliminary study (n=40) by Rhodes et al 2005

The same results for patients imaged using the dual head gamma camera were also reported in Hruska et al 2008b | III-1 | Prospective cross-classification of patients on SMM compared to core-needle and/or excisional biopsy. | 100 women with suspicious breast lesions determined by MRx or US imaged with SMM prior to surgery with single-head MBI system
and
150 women with suspicious breast lesions determined by MRx or US imaged with SMM prior to surgery with dual-head MBI system. Both used ^{99m}Tc-sestamibi | **Single-head SMM**
53/100 (53%) had confirmed breast cancer
59 tumours identified by Mx or US
8 additional tumours identified by SMM not detected by Mx and confirmed by MRI and surgery as true positives
Total of 67 tumours
SMM
57/67 (85.1%) tumours correctly identified **in 45/53 (84.9%) patients**
∴ 10/67 (14.9%) tumours negative by SMM in 8/53 (15.1%) patients (false negative)
SMM detected 26/35 (74.3%) of tumours ≤10mm

Histopathology
Identified 67 tumours in 53 patients
44/67 (65.7%) IDC
8/67 (11.9%) DCIS
7/67 (10.4%) ILC
7/67 (10.4%) mixture
1/67 (1.5%) papillary carcinoma

Dual-head SMM
88/150 (58.7%) had confirmed breast cancer
119 tumours identified by Mx or US
9 additional tumours identified by SMM not detected by Mx and confirmed by MRI and surgery as true positives
Total of 128 tumours
SMM detected 117/128 (91.4%)
∴ 11/128 (8.6%) false negative
SMM detected 52/61 (85.2%) of tumours ≤10mm

Sensitivity (%) of SMM according to tumour size (table below)

Sensitivity (%) of SMM according to pathology (table below) |

Sensitivity (%) of SMM according to tumour size

	Single-head	Dual-head
0-5mm	29	69
6-10mm	86	91
>10mm	97	97
All tumours	85	91

Sensitivity (%) of SMM according to pathology

	Single-head	Dual-head
IDC	84	91
ILC	71	81
DCIS	100	94
IDC + DCIS	67	100
Mix	100	91
Other	100	80

Zhou et al 2008	III-2	Retrospective cross-classification of patients on SMM compared to core-needle and/or excisional biopsy or US.	176 women underwent SMM however only 48 of these women had a known diagnosis of breast cancer. Mean age 57 years (range 27-86 years). SMM conducted using breast-specific Dilon 6800 single head gamma camera and ^{99m}Tc-sestamibi.	**Positive SMM** 6/48 (12.5%) at a site remote from known cancer. 4/6 (66.7%) contralateral breast 2/6 (33.3%) ipsilateral breast 1/6 (16.7%) US found to be benign 5/6 (83.3%) core biopsy Of these: 2/5 (40%) benign 3/5 (60%) additional cancer of which: IDC (n=2) and DCIS (n=1) Sens 3/3 (100%) Spec 42/45 (93.3%) PPV 3/6 (50%) NPV 42/42 (100%) FP 3/45 (6.7%) FN 0/0 (0%)

SMM = scintimammography, ILC = invasive lobular carcinoma, IDC = invasive ductal carcinoma, DCIS = ductal carcinoma in situ, LCIS = lobular carcinoma in situ, US = ultrasound, MRI = magnetic resonance imaging, MRx = mammography, Sono = sonography, MIBI = ^{99m}Tc-methoxy isobutyl isonitrile, ROC = receiver operator characteristic – Wilcoxon test, AUC = area under the curve, Sens = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value, Acc = accuracy, FP = false positive, FN = false negative, TP = true positive, TN = true negative

Evaluating disease recurrence

Only two studies were identified for inclusion in this assessment that reported on the results of scintimammography for the evaluation of breast cancer recurrence (Table 3). One additional study, published prior to 2005, was retrieved that described the use of SMM to evaluate women with suspected recurrence of breast cancer after treatment with radiotherapy or mastectomy (n=36) (Yildiz et al 2001). However due to the time constraints placed on the writing of this report, the full results of this study are not presented. The study by Spanu et al (2003) described the use of scintigraphy rather than scintimammography for the evaluation of disease occurrence and was therefore excluded.

The small prospective study by Usmani et al (2007) evaluated 26 women with suspected disease recurrence using both scintimammography and SPECT[3] (level II diagnostic evidence). Histopathology confirmed disease recurrence in 18 of the 26 women (69.2%) and of these SMM and SPECT detected 15 and 17, respectively. Both modalities detected only one false positive (12.5%), however twice as many false negatives were misdiagnosed using SMM (4/26, 22.2%) than SPECT (2/26, 11.1%). The use of SPECT improved the sensitivity (89%) and negative predictive value (78%) markedly (no significance stated). Both modalities had good positive predictive values (93 and 94%) indicating that out of 100 women who test positive by SMM, then approximately 94 women were correctly identified as being positive. Many studies have advocated the use of combined SPECT/CT to gain greater

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[3] SPECT = single photon emission computed tomography

contrast and therefore anatomical information. It should be noted that the good results reported by Usmani et al were conducted using a dual-head gamma camera, rather than the conventional single head camera.

These promising results were confirmed by an earlier retrospective study by Bongers et al (2004). Fifty-four women with suspected breast cancer recurrence had 55 SMM scans with a single-head gamma camera. SMM was diagnostic in fifty of these patients, with 30 women having a true positive scan and 21 having a true negative scan. One false negative scan was reported in a woman with an enlarged lymph node in the neck which was later proven by histology to be malignant. In addition three false positive cases were reported, with uptake of tracer occurring in inflamed scar tissue and lymph nodes. When looking for local recurrence in the breast, SMM was 100 per cent sensitive, 93 per cent sensitive when looking for chest wall recurrence and 93 per cent sensitive for regional recurrence. SMM also detected two unknown metastases, one in the lung and one in the sternum. By contrast, mammography and ultrasound, which were only used to assess a subset of women, was diagnostic in only 56 per cent of cases evaluated.

Diagnosis of disease recurrence in breast cancer is often difficult due to surgical and irradiation damage and changes including calcifications, scarring, skin modifications which mimic cancer recurrence, fibrosis and inflammatory changes (Usmani et al 2007). Both of the included studies indicated that SMM is a useful imaging modality for the evaluation of disease recurrence, especially in the chest wall. It is clear that the use of SPECT/CT[4] improves the diagnostic accuracy and therefore this may warrant further investigation.

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[4] MBS item number 61462 states: REPEAT PLANAR AND SINGLE PHOTON EMISSION TOMOGRAPHY IMAGING, OR REPEAT PLANAR IMAGING OR SINGLE PHOTON EMISSION TOMOGRAPHY IMAGING on an occasion subsequent to the performance of any one of items 61364, 61426, 61429, 61430, 61442, 61450, 61453, 61469, 61484 or 61485 where there is no additional administration of radiopharmaceutical and where the previous radionuclide scan was abnormal or equivocal. (R).
Use of a hybrid PET/CT or SPECT/CT machine: CT scans rendered on hybrid Positron Emission Tomography (PET)/CT or hybrid Single Photon Emission Computed Tomography (SPECT)/CT units are eligible for a Medicare benefit provided: the CT scan is not solely used for the purposes of attenuation correction and anatomical correlation of any associated PET or SPECT scan; and the CT scan is rendered under the same conditions as those applying to services rendered on stand-alone CT equipment. For example, the service would need to be properly requested and performed under the professional supervision of a specialist radiologist, including specialist radiologists with dual nuclear medicine qualifications.

Table 3   Scintimammography for the evaluation of disease recurrence

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Bongers et al 2004	III-2	Retrospective cross-classification of patients on SMM compared to core-needle and/or excisional biopsy.	54 women, mean age 55 years (range 31-90 years) with suspected recurrence of breast cancer. 55 SMM studies conducted with single head Toshiba 901 HG using ^{99m}Tc-tetrofosmin.	33/55 (60.0%) positive SMM scans TP TN FP FN SMM 30 21 3 1 Sens 96.8% Spec 87.5% PPV 90.9% NPV 95.4% Acc 92.7% **Local recurrence in breast** Sens 12/12 (100%) Spec 11/11(100%) PPV 100% NPV 100% Acc 100% **Chest wall recurrence** Sens 14/15 (93%) Spec 17/17 (100%) PPV 100% NPV 94.4% Acc 96.9% **Regional recurrence (lymph node)** Sens 14/15 (93%) Spec 36/40 (90%) PPV 77.8% NPV 97.3% FP 10% FN 6.7% Acc 90.9% **36/54 (66.7%) evaluated by MRx** Diagnostic in 20/36 (55.6%) Non-diagnostic in 12/36 (33.3%) Equivocal in 4/36 (11.1%) **18/54 (33.3%) evaluated by US** Diagnostic in 10/18 (55.6%) Non-diagnostic in 6/18 (33.3%) Equivocal in 2/18 (11.1%)

Usmani et al 2007	II	Prospective cross-classification of patients on SMM compared to core-needle and/or excisional biopsy.	26 consecutive women, mean age 47 ± 15.4 years (range 22-77 years) with suspected chest wall recurrence of breast cancer. SMM planar imaging conducted with dual head Toshiba GCA 7200A/PI using ^{99m}Tc-methoxy isobutyl isonitrile (MIBI) followed by SPECT imaging.	Positive histopathology for disease recurrence 18/26 (69.2%) Planar SMM positive 15/26 (57.7%) SPECT positive 17/26 (65.4%)

	TP	TN	FP	FN
SMM	14	7	1	4
SPECT	16	7	1	2

	SMM	SPECT
Sens (%)	78	89
Spec (%)	87.5	87.5
PPV (%)	93	94
NPV (%)	64	78
FP (%)	12.5	12.5
FN (%)	22.2	11.1
Acc (%)	81	88

SMM = scintimammography, SPECT = single photon emission computed tomography, Sens = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value, Acc = accuracy, FP = false positive, FN = false negative, TP = true positive, TN = true negative

Monitoring therapy with scintimammography

^{99m}Tc-labelled tracers accumulate in both normal and malignant cells by passive mechanisms driven by membrane potentials. It has been suggested that tracers such as ^{99m}Tc-methoxy isobutyl isonitrile (MIBI) may reflect metabolic changes in the cell, with increased uptake in malignant cells due to the increased metabolic activity, with a corresponding reduction in uptake reflecting a tumour response to chemotherapy (Marshall et al 2005). In addition, ^{99m}Tc-labelled tracers may also interact with P-glycoprotein (PgP), which transports the tracers into the extracellular compartment. PgP is encoded by the *MDR1* gene and over expression of PgP may result in resistance to a number of chemotherapeutic agents. Another multi-drug resistance protein, MRP1 uses ^{99m}Tc-methoxy isobutyl isonitrile (MIBI) as a substrate. It has been suggested that resistance to chemotherapy may be predicted with the initial use of SMM, in that resistance will result in ^{99m}Tc-MIBI being rapidly expelled from the cell rather than being taken up by the tumour (Travaini et al 2007).

The full text of two recent studies that evaluated the ability of a baseline SMM to predict the patient response or resistance to neoadjuvant chemotherapy were retrieved (Table 4). An additional nine studies were identified that reported on the use of SMM for the evaluation of the response, or resistance to therapy in women with breast cancer, however full text versions of these studies could not be obtained (Sergieva et al 2006; Baena-Canada et al 2005; Cayre et al 2002; Maseeh uz et al 2009; Maublant et al 2002; Mezi et al 2003; Spanu et al

2008; Takeuchi et al 2002; Tiling et al 2001). One study reported on the use of whole-body scintigraphy and SPECT to evaluate the response of patients to endocrine therapy. As this study did not report on the use of breast-specific SMM using a gamma camera it was also excluded (Van Den Bossche et al 2006).

The results of Travaini et al (2007) are difficult to interpret, however the premise of the study was that patients who are more likely to respond to chemotherapy could be predicted by obtaining a baseline SMM image with ^{99m}Tc-MIBI (level II prognostic evidence). A washout index[5] (WO%) for tumour area (T) and intense uptake of ^{99m}Tc-MIBI (I) was obtained for all SMM images taken at baseline. A logistic regression analysis was performed using an arbitrarily chosen washout threshold of 45 per cent and treatment (chemotherapy or hormonal therapy) as predictors for response to treatment (response or disease progression), using chemotherapy as the reference treatment. Response to therapy was not predicted by the tumour uptake/background tracer ratio (p=0.44), the washout threshold (p=0.83), treatment with combined chemotherapy plus hormonal therapy (p=0.24) or treatment with hormonal therapy (p=0.12). The authors concluded that baseline SMM should *not* be used to predict response to therapy in women with locally advanced breast cancer. Marshall et al (2005) reported on the use of SMM to monitor the response of locally advanced breast cancer to neoadjuvant chemotherapy. At the end of follow-up, 4/26 (15.4%) of women had a positive uptake of MIBI post-chemotherapy, all of whom had significant residual tumour confirmed by post-operative histology. However, of concern are the four women (15.4%) who were negative for MIBI uptake at the end of the course of chemotherapy but still had significant residual tumour. Although a positive MIBI scan is predictive of residual disease, a negative MIBI scan cannot rule out the presence of residual disease. The authors concluded that whilst ultrasound and clinical examination tended to underestimate the response therapy, SMM using MIBI tended to overestimate the response.

It would appear from these two studies that using SMM to predict response or resistance to neoadjuvant chemotherapy is not a reliable technique. A further seven full text studies were retrieved that described the response or resistance to neoadjuvant chemotherapy, however due to the time constraints placed on the writing of this report, the full results of these studies are not presented (Sun et al 2000; Alonso et al 2002; Fuster et al 2002; Liu et al 2003; Sciuto et al 2002; Takamura et al 2001; Wilczek et al 2003). Results from these studies varied greatly. The small (n=23) study by Wilczek et al (2003) reported that ^{99m}Tc-MIBI could *not* be used to predict therapy response after one round of

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[5] Washout index is calculated early tumour tracer uptake minus delayed tumour tracer uptake, divived by early tumour uptake.

chemotherapy. Liu et al (2003) reported that SMM *may* be useful in the prediction of the resistance proteins PgP and MRP1 but that further, larger studies were required. This finding was supported by the earlier, small study by Sun et al (2000) (n=24). The small prospective study (n=30) by Sciuto et al (2001) found that ^{99m}Tc-sestamibi washout, using the same cut-off level as Travaini et al (2007), was a reliable predictor for tumour response to neoadjuvant chemotherapy. The earlier studies by Fuster et al (2002) (n=25), Alonso et al (2002) (n=33) and Takamura et al (2001) (n=46) also agreed that SMM could be a useful tool in the prediction of response to treatment, however, the value of these results is unclear as these studies were all reported more than seven years ago. Further evaluation of this contentious area of SMM assessment may be warranted.

Table 4   Scintimammography for the evaluation and monitoring of therapy response

Study	Prognostic level of evidence	Study design	Population	Outcomes
Marshall et al 2005	II	Prospective cross-classification of patients on SMM compared to clinical assessment of response to treatment with US.	26 women with biopsy proven invasive breast carcinoma undergoing chemotherapy. SMM imaging conducted on an ADAC Argus gamma camera using ^{99m}Tc-MIBI. At study end all patients underwent surgery and histopathology was performed.	Complete clinical response (CR): tumour reduction >75% Partial response (PR): reduced <75% but >25% No response (NR): reduced by <25% or increased in size **Clinical response** CR PR NR +ve MIBI 0 3 1 -ve MIBI 18 2 1 **US response** **MIBI** CR PR NR +ve MIBI 0 2 1 -ve MIBI 9 8 4 Tumour (T): background ratio (B) Ultrasound Pre-chemotherapy 25/26 (96.2%) T:B >1.0 Post-chemotherapy 3/26 (11.5%) T:B >1.0 Clinical evaluation Pre-chemotherapy 25/26 (96.2%) T:B >1.0 Post-chemotherapy 4/26 (15.4%) T:B >1.0 Histology 4/26 (15.4%) significant residual tumour with +ve MIBI uptake 4/26 (15.4%) significant residual tumour with -ve MIBI uptake

Travaini et al 2007	II	Prospective cross-classification of patients on SMM compared to standard clinical assessment of response to treatment including US, MRx, MRI and physical examination. At study end all patients underwent surgery and histopathology was performed.	51 consecutive women with biopsy proven invasive breast carcinoma. Post-operative therapy: Chemotherapy (CT) n=14, mean age 47 years. Hormonal therapy (HT) n=23, mean age 47 years. CT + HT n=14, mean age 50 years. Baseline evaluation: MRx, MRI, US, SMM followed by 3-week cycles of CT or 2 months HT followed by 1st imaging evaluation (MRx, MRI, US, SMM). 3-week cycles of CT or 2 months HT followed by 2nd imaging evaluation (MRx, MRI, US, SMM). SMM imaging conducted using ^{99m}Tc-MIBI, followed by surgery.	**Washout threshold**

Washout threshold

	≤45% n (%)	>45% n (%)
CT		
Responder	7 (50)	4 (28.6)
Progressor	1 (7.1)	2 (14.3)
Total	8 (57.1)	6 (42.9)
HT		
Responder	13 (56.5)	9 (39.1)
Progressor	1 (4.3)	0 (0.0)
Total	14 (60.9)	9 (39.1)
CT + HT		
Responder	6 (42.9)	7 (50.0)
Progressor	1 (7.1)	0 (0.0)
Total	7 (50.0)	7 (50.0)

Logistic regression analysis: response to therapy was not predicted by tumour uptake/background tracer ratio (p=0.44), washout threshold (p=0.83), treatment with CT + HT (p=0.24), treatment with HT (p=0.12).

There was incomplete follow-up of patients who underwent the 2nd SMM (n=41) and 3rd SMM (n=27) and these results were not reported.

SMM = scintimammography, US = ultrasound, MRI = magnetic resonance imaging, MRI = magnetic resonance imaging, MRx = mammography, MIBI = ^{99m}Tc-methoxy isobutyl isonitrile

Two other studies also not included for complete assessment reported on the correlation of ^{99m}Tc-sestamibi uptake and histological grade of malignancy (Danielsson et al 2003) and tumour angiogenesis (Bekis et al 2005). Uptake of ^{99m}Tc-sestamibi was greater in high malignancy grade tumours which may provide information on the biologic characteristics of the tumour and hence guide therapeutic planning. No correlation, however, was found between ^{99m}Tc-sestamibi uptake and the angiogenic or invasive properties of the tumour.

A retrospective multivariate analysis of the relationship between ^{99m}Tc-sestamibi uptake (tumour: background ratio, TBR) and potential prognostic factors of breast cancer was conducted by Lumachi et al (2005) (prognostic level III-3 evidence). This study was undertaken to identify factors which may

be the cause of false negative SMM results, and did not report on the use of SMM to evaluate woman with breast cancer, therefore the results are not summarised in the above table. Prognostic factors analysed included levels of oestrogen and progesterone receptors, cancer antigen CA 15-3 serum levels, Ki-67 antigen, CEA (carcinoembryonic antigen) serum levels. TBR correlated with the size of tumour, however no pre-operative prognostic factors of breast cancer were identified which would be useful in increasing the sensitivity of SMM (Lumachi et al 2006a).

Cost analysis

Only one cost analysis was identified by the search strategy. Chen et al (2002) reported on the costs associated with using SMM in Taiwanese women with indeterminate, mammographically dense breasts, with a view to reducing the number of unnecessary biopsies performed. Hypothetical cohorts ranging from 16,000 to 40,000 were constructed. The diagnostic accuracy of SMM was estimated from previous studies: sensitivity and specificity of 83.3 and 87.5 per cent, respectively. The positive likelihood ratio (i.e. the odds for a positive result from SMM) was estimated to be 10.4 per cent and the negative likelihood ratio (i.e. the odds for a negative result from SMM) was estimated to be 19.0 per cent. The analysis compared two strategies: conventional excisional biopsy alone and screening with SMM prior to excisional biopsy after an indeterminate mammogram. If an indeterminate result was obtained with SMM, an excisional biopsy would be performed.

The estimated costs of an excisional biopsy and SMM were US$177.70 and US$137.10, respectively. In cohorts of women ranging from 16,000 to 40,000 it was estimated that SMM would produce indeterminate results in 2,963 to 7,407 women who would then go on to require an excisional biopsy. SMM would obtain definite results in 13,037 to 32,593 women. The total cost of strategy A, that is performing an excisional biopsy on all of the women with an indeterminate mammogram, ranged from US$2,843,200 (177.7 x16,000) to US$7,108,000 (177.7 x 40,000). The total cost of strategy B, that is performing SMM on all women followed by excisional biopsy in those with an indeterminate SMM result, ranged from US$2,720,125 (137.1 x 16,000 + 177.7 x 2,963) to US$6,800,224 (137.1 x 40,000 + 177.7 x 7,407). Strategy B resulted in a total cost saving of between US$123,075 and 307,776 when compared to strategy A (Chen et al 2002).

It is unclear whether these results would be applicable to an Australasian setting as the population structure in Taiwan is likely to be quite different to that found in Australia and New Zealand. Although, the study is dated, having been conducted in 2002, and therefore the estimated costs per procedure are likely to have changed markedly, the estimated diagnostic accuracies of SMM appear to have remained stable with similar sensitivities and specificities quoted in the recent literature. A cost-effectiveness analysis has not been conducted and so the value for money of SMM in terms of life years gained from use of the procedure is unknown. In addition, the benefits or harms to patients should be considered, with the impact on quality of life measured when an excisional biopsy is avoided or performed unnecessarily.

As previously stated, a number of companies within Australia manufacture and/or distribute TGA approved gamma cameras, which would be capable of performing scintimammography. To date, the only commercially available breast-specific gamma camera is the Dilon 6800 system which was approved for use by the United States FDA in 2004 (Dilon Technologies, USA) (O'Connor et al 2009). There are approximately 170 Dilon 6800 systems in use worldwide. The Dilon 6800 retails for US$336,000[6] in the United States, with the only consumable required being the cost of the ^{99m}Tc-Sestamibi. Other tracers including ^{99m}Tc-tetrofosmin and Thallium^{201} can be used with this system. The Dilon 6800 system is also capable of performing biopsy using either the Hologic or Ethicon vacuum-assisted biopsy systems, both of which would require the purchase of a biopsy gun kit in addition to consumables which include: the GammaLoc stereotactic biopsy-guidance apparatus which mounts to the Dilon 6800 to provide image guidance for vacuum-assisted needle biopsies (US$69,000 for the hardware and approximately US$3,000 for the pair of Cerium^{139} marker sources. The hardware can be used for several years, however the Cerium^{139} sources need to be replaced annually (personal communication Dilon Diagnostics).

InSight Oceania Pty Ltd are currently in discussions with Dilon Technologies with a view to distributing the Dilon 6800 in Australia, after gaining TGA approval. InSight expect these negotiations to be finalised within the next few months and that the Dilon 6800 will be available in Australia late 2010 or early 2011. InSight currently supply the Sentinella gamma camera manufactured by Oncovision (Spain), which is a small field-of-vision gamma camera designed for intra-operative imaging, one of which is currently in use at the Mater Hospital, Sydney. Although this unit is not designed for scintimammography it may be feasible to use it for this purpose and has been used for intra-operative lesion location (Paredes et al 2008). However, clinical advice has noted that intra-operative procedures can only be adequately performed by a gamma camera designed for nuclear medicine and performed in a nuclear medicine facility (personal communication NSW Health). The approximate cost of the InSight unit is A$200,000 (personal communication InSight Oceania Pty Ltd).

InSight also distribute the two gamma cameras manufactured by Philips Healthcare. There are two stationary gamma cameras listed on the Australian Register of Therapeutic Goods (ARTG 117642 and 125577) by Philips, both of which are dual head and capable of performing scintimammography. These cameras range in price from $450,000 to over $1m for high end SPECT/CT (personal communication InSight Oceania Pty Ltd).

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[6] On 14th July 2010 US$336,000 converts to A$380,032

Siemens Ltd manufacture a number of gamma cameras capable of performing scintimammography, ranging in price (excluding GST) from A\$420,000 for the Symbia E Dual Header to A\$500,000 for the Symbia S Dual Header. To perform scintimammography these standard systems would have to include a mammography pallet (personal communication Siemens HealthCare Australia).

Another Australian company distribute a gamma camera which costs approximately A\$400-500,000 depending on the number of inclusions (personal communication Gammasonics, Australia).

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).

Informed consent

Providers of diagnostic tests for breast cancer 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 a test to determine treatment options for breast cancer, confidence in the veracity of the test result is extremely important so that individual women can feel secure that the results of the test are valid. Women will want to be assured that a test result indicates whether disease is truly present or absent and that the recommended treatment is definitely the most. This is especially true in situations where the consequences of a positive result may result in a surgical procedure, which may be harmful to the woman both in a physical and psychological sense. Accurate information about the predictive value of all breast cancer diagnostic tests is essential, as is a concerted effort to help women understand the meaning of results. Information about breast cancer diagnostic 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 harms and benefits of SMM will vary according to the sensitivity and specificity of SMM. Some harms, such as discomfort during the procedure, are obvious; other harms, however, 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 (Couglin 2008). The benefit of avoiding an unnecessary excisional biopsy or other surgical procedure cannot be underestimated.

Access issues

Routine SMM as a clinical management tool is likely to become available in large public and private hospitals in Australia. However, women already diagnosed with breast cancer who live in rural and remote areas of Australia, who may benefit from SMM, would already be seeking treatment options in large, regional centres.

Training

Training in Nuclear Medicine is required to conduct SMM and is usually undertaken after completion of the Royal Australasian College of Physicians'(RACP) Part 1 exam, or after completion of the Royal Australian and New Zealand College of Radiologists' (RANZCR) Part II exam. Training is overseen by the Australian and New Zealand Association of Physicians in Nuclear Medicine on behalf of the Joint Specialist Advisory Committee of the RACP and RANZCR (personal communication NSW Health).

The RANZCR offer a more detailed syllabus for graduates of the Part II of the Fellow of the College (FRANZCR) examination for breast imaging. There are 16 components in the extended syllabus "Breast Imaging Learning Competencies" which encompasses all aspects of the diagnosis of breast conditions by the use of appropriate imaging techniques, as well as the reporting, interpreting and communication of these findings. It is expected that the competent (trainee) radiologist will be able to explain imaging findings in benign and malignant breast disease using Tc-sestamibi or Tc-tetrofosmin scintimammography (RANZCR 2009).

Clinical guidelines

In Australia, there are currently no clinical practice guidelines for the assessment of breast cancer using SMM. The National Health and Medical Research Council have two published clinical practice guideline documents: the management of early breast cancer (NHMRC 2001b) and the management of advanced breast cancer (NHMRC 2001a).

RANZCR promote and support population screening for breast cancer in asymptomatic women over the age of 40 using mammograms. In addition, the RANZCR advocate the use of MRI as a complementary imaging modality, which can provide additional information to standard imaging by mammography (RANZCR 2010).

The United States Department of Health's Agency for Healthcare Research and Quality (AHRQ) are currently asking for public comment on a draft analytical framework for the comparative effectiveness of non-invasive *diagnostic tests* for breast abnormalities, which includes scintimammography (AHRQ 2010).

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

An Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, an Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of SMM for the diagnosis of breast cancer, its present and potential use in the Australian public health system, and future implications for the use of this technology.

Search strategy used for the report

The medical literature (Table 6) was searched utilising the search terms outlined in Table 5 to identify relevant studies and reviews, from January 2000 until May 2010. In addition, major international health assessment databases were searched.

Table 5   Search terms utilised

Search terms
MeSH
Diagnostic imaging OR radionuclide imaging OR Gamma camera imaging OR Gamma Rays/diagnostic use OR Technetium Tc 99m Sestamibi
AND
Breast Neoplasms
Text words
Molecular breast imaging OR scintimammography OR breast specific gamma imaging
AND
Breast cancer
Limits
English, human, female

Table 6   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.mhra.gov.uk/index.htm
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	Dependent on technology topic area

Availability and level of evidence

A total of 11,630 potential studies were downloaded into Endnote. Once duplicates were removed, 6,880 references were assessed for relevance. Of these, 446 were considered to be germane to SMM and their abstracts were assessed accordingly. Many of these studies described the use of lymphoscintigraphy, an MBS approved method of sentinel node biopsy (MBS item numbers 30299, 30300, 61469), which were therefore not considered. In addition, a number of studies reported on the use of SMM for the *diagnosis* of breast cancer, rather than for the evaluation of disease spread. A total of 149 references had their abstracts appraised and of these, 66 had a full text version available and 13 studies were included for assessment (see Appendix B for study profiles). There were four diagnostic level II (3 assessing disease and patient management and 1 disease recurrence), one diagnostic level III-1 (assessment of disease), six diagnostic level III-2 (2 assessing disease and patient management, 2 assessing disease, 1 disease recurrence and 1 patient management) and two level II prognostic level of evidence studies (response to therapy).

Sources of further information

The Canadian Agency for Drugs and Technologies in Health (CADTH) will soon begin work on a project 'Optimizing Health System Use of Medical Isotopes and Other Imaging Modalities'. The project's objective is to develop and disseminate improved policies, protocols and standards to inform health system decisions with respect to the optimal use of Technetium (Tc)-99m, other isotopes and alternative types of medical imaging. Feedback is being sought on the three questions below, which will provide valuable information on how the Tc-99 shortages have impacted health systems internationally.

1)   What are future alternative technologies to Tc-99?

2)   What are the policy, practice guideline and protocols in place, for management of Tc-99m supplies during the isotope shortage?

3)   What was the impact of Tc-99 shortages in your country (including intended and unintended consequences)?

In Australia and New Zealand, breast cancer is the most common notifiable cancer in females. In Australia, the risk of females developing breast cancer up to the age of 75 years is one in 11 and one in nine up to age 85 years. The age-standardised incidence rate for breast cancer was 112.4 per 100,000 women and invasive ductal carcinoma accounted for the majority of these cases (78.7%), followed by invasive lobular (10.7%). The five-year relative survival rate for Australian women diagnosed with breast cancer during the period 2000-2006 was 88 per cent, that is, women five years after diagnosis were 88 per cent as likely to be alive as woman of a comparable age in the general population. Survival is decreased for women diagnosed with large tumours compared to those with small tumours. Survival is also greater in women whose lymph nodes were found to be cancer free compared to those where the cancer had spread to the lymph nodes (AIHW and NBOCC 2009).

In New Zealand, cancer of the breast was the most commonly registered cancer in 2007 with the highest age-standardised registration rate among females with 90.3 cases per 100,000. This rate was markedly higher in the Māori population compared to the rate in the non- Māori population (124.6 vs 87.2 registrations per 100,000). Of all cancers, breast cancer had the highest age-standardised death rate among females with 20.8 deaths per 100,000. This rate was markedly higher in the Māori population compared to the rate in the non- Māori population (29.9 vs 20.0 deaths per 100,000) (Ministry of Health 2010).

Mammography is the gold standard *screening* tool for the identification of breast cancer and histology is the gold standard for the *diagnosis* of breast cancer. Both Australia and New Zealand have comprehensive population-based mammography screening programs, which target and triage for further testing *asymptomatic* women aged 50-69 years. Masses and calcifications are the most common abnormalities identified on mammograms. After diagnosis, women may be presented with a number of treatment options, including surgery, radiotherapy or chemotherapy, however before treatment can commence the extent of disease spread must be ascertained. Clinical examination and a number of imaging modalities, including mammography, MRI, US and in some cases PET, may be used to pre-operatively assess women once they have been diagnosed with breast cancer. These modalities may be used alone or in conjunction with each other (NHMRC 2001b). For women with palpable lesions, fine needle aspiration biopsy (FNAB) may be used to establish a pre-operative diagnosis. For non-palpable lesions, fine needle aspiration may be conducted under image guidance. This procedure provides a cytological not histological diagnosis, and imaging would be

required to support the FNAB results prior to definitive surgery. A definitive histological diagnosis can be obtained by a core biopsy, which uses a wide bore needle to obtain a tissue sample (NHMRC 2001b). The extent or spread of disease is referred to as staging and a number of systems can be used to stage tumours, which is important when determining the most effective treatment and for the determination of a prognosis for the patient (AIHW and NBOCC 2009).

Scintimammography has previously been assessed as a potential method for *screening* asymptomatic women in the report "New and emerging technologies for breast cancer detection". Two meta-analyses reported an approximate sensitivity and specificity of 85 and 86 per cent, respectively, for SMM for the *diagnosis* of breast cancer (Hussain & Buscombe 2006; Liberman et al 2003). It was concluded that SMM should be considered as an additional diagnostic test to mammography, increasing diagnostic sensitivity, especially in younger women with dense breasts (Schillaci et al 2005) and women with breast implants (Peng et al 2003), where mammography often gives equivocal results. Due to the low specificity of mammography a large number of unnecessary biopsies are conducted, therefore it has been suggested that the use of SMM in equivocal cases may decrease the number of biopsies performed (Schuster & Halkar 2004).

SMM is considered to be non-invasive, however it does involve the intravenous injection of the radiopharmaceutical and perfusion imaging agent, ^{99m}technetium-sestamibi (^{99m}Tc-sestamibi) (Taillefer 2005; Schuster & Halkar 2004). ^{99m}Tc-sestamibi crosses the cellular plasma membrane and adheres in the cytoplasm with the negatively charged mitochondria (Schuster & Halkar 2004). Cancerous cells use high levels of energy in comparison to healthy cells and therefore have hyperactive mitochondria. Cancerous cells will take up increased levels of ^{99m}Tc-sestamibi and emit more gamma rays compared to healthy cells, which shows up as regions of brightness on the captured images (Schmidt 2008).

Small field-of-view detectors are capable of capturing high-resolution images being and also allow for greater flexibility in positioning of the patient (O'Connor et al 2009). With a breast-specific gamma camera, patients can be imaged seated comfortably with the detector placed against the chest wall and compression of the breast increases the sensitivity of the device (Schillaci & Buscombe 2004). A dual-head SMM system has been developed 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). Some studies have advocated combining planar scintimammography with SPECT (single photon emission computed tomography) or SPECT/CT to improve sensitivity to increase contrast resolution, however further studies are

required to establish the true value of combining these two technologies (Schillaci & Buscombe 2004).

The potential clinical indications for the use of SMM include women with: equivocal mammograms; dense breast tissue; palpable abnormalities that cannot be imaged with mammography; axillary lymph node metastases of an adenocarcinoma of unknown primary origin; breast implants; parenchymal distortions of the breast; breast iatrogenic architectural distortion; suspected recurrent breast cancer; and for the assessment or monitoring of doubtful micro-calcifications; of multi-centric disease; and response to neoadjuvant chemotherapy (Schillaci & Buscombe 2004; Jones et al 2009).

A number of facilities in Australia have experience with scintimammography, however SMM is not routinely used in Australia (personal communication Peter MacCallum Cancer Centre, Melbourne). SMM may develop as an adjunct in the screening and diagnosis of breast cancer but may prove to be more useful when used for planning of treatment options for women already diagnosed with breast cancer. In Australia, gamma imaging is used for the identification of the sentinel node from primary cancers. A number of companies within Australia manufacture and/or distribute gamma cameras that would be capable of performing SMM. In Australia, there are currently no clinical practice guidelines for the assessment of breast cancer using SMM.

Training in Nuclear Medicine is required to conduct SMM and is usually undertaken after completion of the Royal Australasian College of Physicians'(RACP) Part 1 exam, or after completion of the Royal Australian and New Zealand College of Radiologists' (RANZCR) Part II exam. Training is overseen by the Australian and New Zealand Association of Physicians in Nuclear Medicine on behalf of the Joint Specialist Advisory Committee of the RACP and RANZCR (personal communication NSW Health).

Safety

None of the studies included in this assessment reported any specific safety outcomes associated with the scintimammography procedure. The obvious safety issues associated with a procedure of this kind is the number of false positives and false negatives and the harms associated with these findings. The number of false positive and false negative diagnoses are summarised in the effectiveness section.

Effectiveness

A total of 14 studies were included for assessment There were four diagnostic level II (3 assessing disease and patient management and 1 disease recurrence), one diagnostic level III-1 (assessment of disease), seven diagnostic level III-2 (2 assessing disease and patient management, 3 assessing

disease, 1 disease recurrence and 1 patient management) and two level II prognostic level of evidence studies (response to therapy).

Diagnosis of breast cancer and patient management

Four studies that explicitly reported the results of scintimammography in terms of change in patient management were included for assessment. These studies indicated that SMM may provide additional information when decisions are made in the clinical and surgical management of women diagnosed with breast cancer, especially if used in conjunction with other imaging modalities such as ultrasound. However, the high number of false positive and false negative diagnoses remains a concern. Reported false negative rates were unacceptably high, ranging from 6.8 (Killelea et al) to 48.3 per cent (Zhou et al) indicating a large number of women received false reassurance that they were disease free after undergoing scintimammography. Although, by comparison, the false positive rates were lower (ranging from 9.2% to 15%) this still indicates a large number of women received unnecessary and highly invasive treatment or surgical procedures, which may have long lasting physical and mental consequences for the patient in question. Three out of the four studies reported good positive predictive values (82.9, 89.6 and 92.9%) indicating that out of 100 women who test positive by SMM, then 83-93 women were correctly identified as being positive. However the study by Zhou reported a low positive predictive value of 60 per cent. Negative predictive values ranging from 81 to 88 per cent indicates that SMM is reasonably good at reassuring those patients who test negative that they do not have cancer. It should be noted that the type of gamma camera used in these studies varied. The two studies by Killelea et al and Zhou et al used the single-head breast-specific gamma camera, whilst the good study by Usmani et al used a dual head and Lumachi et al used a triple head camera. Differences in hardware make comparisons between studies difficult, however preliminary studies by Hruska et al (2008a) have indicated that dual-head gamma cameras can increase the sensitivity of SMM.

Diagnosis of breast cancer

Five studies reported the results of scintimammography used to diagnose breast cancer, however, the impact of SMM results on patient management was not reported. Three of these studies were conducted prospectively and two were retrospective studies. As with the studies included in the above section, firm conclusions regarding the use of SMM in the evaluation of women already diagnosed with breast cancer are difficult to draw due to differences in study design and the manner in which results were reported. Although these studies did not explicitly state the impact that SMM had on the surgical outcomes of patients, it was clear that the information gained could be used to

inform the surgical work-up and pre-surgical planning of these patients, and as such is a potentially good adjunctive tool for the assessment of women diagnosed with breast cancer. A small cross-comparative study (n=26) identified six additional lesions with SMM in women with lobular carcinoma that were occult on mammography, which is of particular importance as lobular invasive carcinoma is difficult to detect (Brem et al 2009). Additional malignancies remote from the known cancer were also identified in another small comparative study (n=48), however of the six identified tumours, three were benign on biopsy and therefore false positives (PPV = 50%) (Zhou et al 2007). A large, cross comparative studies imaged 283 women with SMM and mammography and 69 women with lesions were operated on, with 32 having a carcinoma confirmed by histology (Grosso et al 2009). The diagnostic value of mammography alone compared to SMM or combined SMM plus mammography was determined by calculating the receiver operating characteristic (ROC). There was a statistically significant difference between the areas under the ROC curves for mammography alone (0.72 ± 0.052) compared to SMM (0.84 ± 0.046) and mammography and SMM combined (0.86 ± 0.039) ($p < 0.01$), suggesting that SMM should be used in conjunction with mammography for the evaluation of breast cancer. Of importance is the study by Hruska et al (2008a) that reported an increase in sensitivity from 85 per cent to 91 per cent when a dual-head gamma camera is employed. SMM had the greatest sensitivity for detecting larger tumours (>10mm), however, sensitivity was greatly improved for the detection of smaller tumours (<10mm) when a dual-head detector was employed. The number of false negatives reported by all studies remain a concern given this is a symptomatic population.

Evaluating disease recurrence

Only two studies were identified for inclusion in this assessment that reported on the results of scintimammography for the evaluation of breast cancer recurrence. Diagnosis of disease recurrence in breast cancer is often difficult due to surgical and irradiation damage and changes including calcifications, scarring, skin modifications which mimic cancer recurrence, fibrosis and inflammatory changes (Usmani et al 2007). Both of the included studies indicated that SMM is a useful imaging modality for the evaluation of disease recurrence, especially in the chest wall. The diagnostic accuracy was increased when SPECT was used alone compared to SMM in women with suspected disease recurrence. In a small comparative study (n=26) Usmani et al (2007) reported that twice as many false negatives were misdiagnosed using SMM (4/26, 22.2%) than SPECT (2/26, 11.1%). In addition, the use of SPECT alone increased the sensitivity (89% vs 78%) and the negative predictive value (78% vs 64%) markedly compared to SMM alone. Many studies have advocated the

use of combined SPECT/CT to gain greater contrast and therefore anatomical information and therefore this may warrant further investigation.

Monitoring therapy with scintimammography

[99m]Tc-labelled tracers accumulate in both normal and malignant cells by passive mechanisms driven by membrane potentials. It has been suggested that tracers such as ^{99m}Tc-methoxy isobutyl isonitrile (MIBI) may reflect metabolic changes in the cell, with increased uptake in malignant cells due to the increased metabolic activity, with a corresponding reduction in uptake reflecting a tumour response to chemotherapy (Marshall et al 2005). In addition, ^{99m}Tc-labelled tracers may also interact with P-glycoprotein (PgP), which transports the tracers into the extracellular compartment. PgP is encoded by the *MDR1* gene and over expression of PgP may result in resistance to a number of chemotherapeutic agents. Another multi-drug resistance protein, MRP1 uses ^{99m}Tc-methoxy isobutyl isonitrile (MIBI) as a substrate. It has been suggested that resistance to chemotherapy may be predicted with the initial use of SMM, in that resistance will result in ^{99m}Tc-MIBI being rapidly expelled from the cell rather than being taken up by the tumour (Travaini et al 2007).

The full text of two recent studies that evaluated the ability of a baseline SMM to predict the patient response or resistance to neoadjuvant chemotherapy were retrieved. It would appear from the assessment of these two studies that using SMM to predict response or resistance to neoadjuvant chemotherapy is not a reliable technique. Other studies, dated pre-2005 and not included in this assessment, reported conflicting results with some concluding that SMM could be a useful tool in the prediction of response to treatment or in the prediction of therapy resistance, whilst other studies reported the opposite finding. Further evaluation of this contentious use of SMM may be warranted.

Only one cost analysis was identified by the search strategy, however it is unclear whether these results would be applicable to an Australasian setting. In addition, the study is dated, having been conducted in 2002, and therefore the estimated costs per procedure are likely to have changed markedly. Chen et al (2002) reported on the costs associated with using SMM in Taiwanese women with indeterminate, mammographically dense breasts, with a view to reducing the number of unnecessary biopsies performed. Hypothetical cohorts ranging between 16,000 and 40,000 were constructed using an estimated sensitivity and specificity of 83.3 and 87.5 per cent, respectively. Conventional excisional biopsy alone was compared to screening with SMM prior to excisional biopsy after an indeterminate mammogram. The total cost (in US dollars) of performing an excisional biopsy on all of the women with an indeterminate mammogram, ranged from $2.8 to $7.1 million. The total cost performing SMM on all women followed by excisional biopsy in those with an

indeterminate SMM result, ranged from $2.7 to $6.8 million, which would result in a total cost saving between $123,075 and 307,776.

As previously stated, a number of companies within Australia manufacture and/or distribute TGA approved gamma cameras, which would be capable of performing of scintimammography. To date, the only commercially available breast-specific gamma camera is the Dilon 6800 system which was approved for use by the United States FDA in 2004, which retails for US$336,000 in the United States (Dilon Technologies, USA) (O'Connor et al 2009). The only consumable required is the ^{99m}Tc-sestamibi, which is manufactured locally as a sestamibi "cold kit" with the ^{99m}Technetium added later when required. A typical order for 2 GBq (a typical SMM study uses 740-925 MBq), which would cost approximately A$95 (personal communication, Lantheus Medical Imaging Pharmacy). Other gamma cameras are available on the market ranging in price from A$450,000 to over $1 million for high end SPECT/CT.

In summary, the included studies indicate that SMM may be a useful adjunct in the pre-surgical evaluation of women with biopsy-proven breast cancer. A number of studies indicated changes in the clinical management of some women. However, SMM should be used with caution and in conjunction with other imaging modalities as the number of false negatives and false positives may lead to serious consequences for patients. As the dual-head camera offers superior imaging for breast lesions of all sizes, the single-head camera should not be considered for the evaluation of women with breast cancer. In addition, consideration should be given to the role and use of SPECT/CT in the evaluation of women with breast cancer.

Appendix A: Levels of evidence (Merlin et al 2009)

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

1. *Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000).
2. The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the <u>effectiveness</u> of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (MSAC 2005; Sackett & 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 & 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: (Phillips et al 2001; NHMRC 1999; Lijmer et al 1999; Bandolier editorial 1999)

Appendix B: Profiles of studies

Diagnostic level of evidence	Study	Location	Study design	Study population	Outcome assessed	Length of follow-up
III-2	Bongers, V. Perre, C. de Hooge, P. (2004)	Utrecht, The Netherlands	Retrospective cross-classification of patients on SMM compared to core-needle and/or excisional biopsy.	54 women, mean age 55 years (range 31-90 years) with suspected recurrence of breast cancer. 55 SMM studies imaging conducted with single head Toshiba 901 HG using ^{99m}Tc-tetrofosmin.	Disease recurrence	Mean 41 months from primary treatment (range 3-168 months)
III-2	Brem, R.F. Ioffe, M. Rapelyea, J.A. Yost, K.G. Weigert, J.M. Bertrand, M.L. Stern, L.H. (2009)	Washington USA	Retrospective cross-classification of patients on SMM, MRx (n=26), MRI (n=12) and sonography (n=25) compared to core-needle and/or excisional biopsy.	26 women with biopsy-proven invasive lobular carcinoma, mean age 63 years (range 46-82 years). SMM conducted using breast-specific Dilon 6800 single head gamma camera and ^{99m}Tc-sestamibi.	Assessment of confirmed breast cancer.	N/A
II	Gommans, G.M.M. van der Zant, F.M. van Dongen, A. Boer, R.O. Teule, G.J.J. de Waard, J.W.D. (2006)	Hoorn, The Netherlands	Prospective cross-classification of patients on SMM compared to core-needle and/or excisional biopsy.	101 consecutive women with non-palpable lesions detected by MRx. Mean age 61 ± 7.3 years (range 50-75 years). SMM conducted using GE-Millenium VG single head gamma camera and ^{99m}Tc-sestamibi.	Assessment of confirmed breast cancer and patient (surgical) management	Surgery performed within 2 weeks of presentation. Mean follow-up of negative patients 64.4 months (range 28-88 months).

II	Grosso, M. Chiacchio, S. Bianchi, F. Traino, C. Marini, C. Cilotti, A. Manca, G. Volterrani, D. Roncella, M. Rampin, L. Marzola, M.C. Rubello, D. Mariani, G. (2009)	Pisa, Italy	Cross-classification of patients on SMM compared to core-needle and/or excisional biopsy.	283 consecutive women, mean age 53 ± 8.2 years (range 32-79 years) with micro-calcifications detected by screening MRx. SMM performed in all women within 2 weeks of MRx using 6800 single head gamma camera (GE Medical Systems) and ^{99m}Tc-sestamibi.	Assessment of confirmed breast cancer and patient management	5 years, median follow-up 8.7 years
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 SMM compared to core-needle and/or excisional biopsy.	100 women with suspicious breast lesions determined by MRx or US imaged with SMM prior to surgery with single-head MBI system and 150 women with suspicious breast lesions determined by MRx or US imaged with SMM prior to surgery with dual-head MBI system. Both used ^{99m}Tc-sestamibi.	Assessment of confirmed breast cancer.	N/A

III-2	Killelea, B.K. Gillego, A. Kirstein, L.J. Asad, J. Shpilko, M. Sha, A. Feldman, S. Boolbol, S.K. (2009)	New York, USA	Retrospective cross-classification of patients on SMM compared to core-needle and/or excisional biopsy.	790 women at high-risk of breast cancer who underwent 942 SMM scans. Of these, 82 women with a biopsy-proven breast cancer underwent SMM, mean age 53 years (range 33-83 years). 55 IDC, 3 ILC, 14 DCIS, 9 mixture of IDC & ILC. SMM conducted using breast-specific Dilon 6800 single head gamma camera and ^{99m}Tc-sestamibi.	Patient management	N/A
III-2	Lumachi, F. Tregnaghi, A. Ferretti, G. Povolato, M. Marzola, M.C. Zucchetta, P. Cecchin, D. Bui, F. (2006)	Padova, Italy	Prospective cross-classification of patients on SMM compared to histopathology.	77 consecutive women, median age 54 years (range 36-70 years) with primary breast cancer detected by CE, MRx or both and conformed by biopsy. All patients underwent axilla examination using US and SMM using a triple head gamma camera (Philips Irix) and ^{99m}Tc-sestamibi.	Assessment of confirmed breast cancer.	Patients underwent SMM 2-15 days (median 4 days) prior to surgery.
III-2	O'Connor, M.K. Phillips, S.W. Hruska, C.B. Rhodes, D.J. Collins, D.A. (2007)	Minnesota, USA	Prospective cross-classification of patients on SMM compared to histopathology.	100 women with a suspicious mass identified by MRx or US that measured <2 cm scheduled for biopsy. Mean age 59 years (range 18-86 years). SMM conducted using prototype CZT single head gamma camera and ^{99m}Tc-sestamibi.	Assessment of confirmed breast cancer.	Time interval between SMM and biopsy was one day.

II	Usmani, S. Khan, H.A. Niaz, K. Uz-Zaman, M. Niyaz, K. Javed, A. Mohannadi, S. al Huda, F.A. Kamal, S. (2008)	Karachi, Pakistan	Prospective cross-classification of patients on SMM compared to core-needle and/or excisional biopsy.	21 consecutive women, mean age 48 ± 14.3 years (range 26-77 years) with proven breast cancer who had undergone breast lump excision, referred for SMM. SMM conducted with dual head Toshiba GCA 7200A/PI using ^{99m}Tc-methoxy isobutyl isonitrile (MIBI).	Assessment of confirmed breast cancer and patient management	Median 3 months from primary treatment (range 1-6 months)
II	Usmani, S. Niaz, K. Uz-Zaman, M. Niyaz, K. Khan, H.A. Habib, S. Kamal, S. (2007)	Karachi, Pakistan	Prospective cross-classification of patients on SMM compared to core-needle and/or excisional biopsy.	26 consecutive women, mean age 47 ± 15.4 years (range 22-77 years) with suspected chest wall recurrence of breast cancer. SMM planar imaging conducted with dual head Toshiba GCA 7200A/PI using ^{99m}Tc-methoxy isobutyl isonitrile (MIBI) followed by SPECT imaging.	Disease recurrence	Median 24 months from primary treatment (range 6-144 months)
III-2	Zhou, M. Johnson, N. Gruner, S. Ecklund, G.W. Meunier, P. Bryn, S. Glissmeyer, M. Steinbock, K. (2009)	Oregon, USA	Retrospective cross-classification of patients on SMM compared to core-needle and/or excisional biopsy.	138 women with biopsy-proven breast cancer, mean age 55 years (range 30-81 years): 69 IDC, 20 ILC, 32 DCIS, 17 mixture of IDC, ILC, DCIS. SMM conducted using breast-specific Dilon 6800 single head gamma camera and ^{99m}Tc-sestamibi.	Assessment of confirmed breast cancer and patient management	N/A

III-2	Zhou, M. Johnson, N. Blanchard, D. Bryn, S Nelson, J. (2008)	Oregon, USA	Retrospective cross-classification of patients on SMM compared to core-needle and/or excisional biopsy or US.	176 women underwent SMM however only 48 of these women had a known diagnosis of breast cancer. Mean age57 years (range 27-86 years). SMM conducted using breast-specific Dilon 6800 single head gamma camera and ^{99m}Tc-sestamibi.	Assessment of confirmed breast cancer.	N/A
Prognostic level of evidence	**Study**	**Location**	**Study design**	**Study population**	**Outcome assessed**	**Length of follow-up**
II	Marshall, C. Eremin, J. El-Sheemy, M. Eremin, O. Griffiths, P.A. (2005)	Lincoln, England	Prospective cross-classification of patients on SMM compared to clinical assessment of response to treatment with US.	26 women with biopsy proven invasive breast carcinoma undergoing chemo-therapy. SMM imaging conducted on an ADAC Argus gamma camera using ^{99m}Tc-MIBI. At study end all patients underwent surgery and histopathology was performed.	Response to neoadjuvant therapy.	N/A
II	Travaini, L.L. Baio, S.M. Cremonesi, M. de Cicco, C. Ferrari, M. Trifirò, G. Prisco, G. Viale, G. Colleoni, M.A. Radice, D. Sivolapenko, G.B. Paganelli, G. (2007)	Milan, Italy	Prospective cross-classification of patients on SMM compared to standard clinical assessment of response to treatment including US, MRx, MRI and physical examination. At study end all patients underwent surgery and histopathology was performed.	51 consecutive women with biopsy proven invasive breast carcinoma. Post-operative therapy: Chemo-therapy (CT) n=14, mean age 47 years. Hormonal therapy (HT) n=23, mean age 47 years. CT + HT n=14, mean age 50 years. Baseline evaluation: MRx, MRI, US, SMM followed by 3-week cycles of CT or 2 months HT followed by 1st	Response to neoadjuvant therapy.	Not explicitly stated however CT was given in 2 blocks of 3 week cycles and HT was given in 2 blocks of 2-month cycles.

				imaging evaluation (MRx, MRI, US, SMM). 3-week cycles of CT or 2 months HT followed by 2nd imaging evaluation (MRx, MRI, US, SMM). SMM imaging conducted using ^{99m}Tc-MIBI. Followed by surgery.		

SMM = scintimammography, ILC = invasive lobular carcinoma, IDC = invasive ductal carcinoma, DCIS = ductal carcinoma in situ, LCIS = lobular carcinoma in situ, US = ultrasound, MRI = magnetic resonance imaging, MRx = mammography, CE = clinical examination, MIBI = ^{99m}Tc-methoxy isobutyl isonitrile, SPECT = single photon emission computed tomography, N/A = not available, CT = chemotherapy, HT = hormone therapy, CZT = cadmium zinc telluride

Ipsilateral: Situated or appearing on or affecting the same side of the body.

Contralateral: Occurring on, affecting, or acting in conjunction with a part on the opposite side of the body.

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.

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

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

False positive rate: complement of test specificity

False negative rate: complement of test sensitivity

Invasive cancer: cancerous cells that 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.

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.

SPECT: single photon emission computed tomography

Appendix D: HTA internet sites

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

- Health Economics Unit, Monash University
  http://www.buseco.monash.edu.au/centres/che/

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 Agency for Drugs and Technology in Health (CADTH)
  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/frz_about.htm

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

The role of scintimammography in the diagnosis of breast cancer
August 2010

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.gezondheidsraad.nl/en

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/?l=sv

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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