

Health Policy Advisory Committee on Technology

Technology Brief Update

SentiMag[®] and Sienna+[®] for sentinel lymph node
localisation in breast cancer

April 2016



Australian
Safety
and Efficacy
Register
of New
Interventional
Procedures –
Surgical



Royal Australasian
College of Surgeons

HealthPACT

emerging health technology

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This brief was prepared by Dr Thomas Vreugdenburg from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).

2016 Summary of findings

SentiMag[®] is a hand-held magnetic sensor used in conjunction with a magnetic tracer (Sienna+[®]), used to identify sentinel lymph nodes (SLNs) in patients with breast cancer. It is proposed to have equivalent efficacy to the standard radioisotope technique for detecting SLNs, but without the associated logistical issues. Since the initial Technology Brief was published in 2014, five additional non-randomised comparative trials (Level III-2) have been published. No significant safety issues were identified in the included trials beyond dark staining of skin at the injection site, which faded over time. There were no allergic reactions or adverse responses at the injection site. In terms of efficacy, SentiMag[®] demonstrated equivalence in detecting SLNs; however, the results of the included trials were biased by the concurrent use of both SentiMag[®] and the standard radioisotope technique during surgery. As a result, the extent to which the accuracy of each device was affected by the other is unclear. There are two ongoing trials (one RCT and one non-randomised trial) which aim to investigate the SLN detection rate of the SentiMag[®] system compared to the radioisotope technique in separate patient groups. These trials are due for completion in 2016, and will avoid the operator biases present in the existing evidence.

2016 HealthPACT assessment

SentiMag[®] and Sienna+[®] appear to demonstrate equivalent efficacy to the standard technique utilising ^{99m}Tc radioisotope and injectable blue dye, however there is potential of bias within the reported outcomes. Future planned randomised controlled trials may address this issue. There are no identified safety considerations, with the exception of transient skin discolouration, however it should be noted that the technology can cause subsequent magnetic resonance imaging artefacts. Although the technology is more expensive than the standard treatment, SentiMag[®] and Sienna+[®] may provide greater flexibility in surgical planning, and is not associated with the risks and logistics associated with radioisotope manufacture, transport and disposal.

Although HealthPACT does not support public investment in this technology in clinical practice at this time, it does recommend that the evidence from the ongoing randomised controlled trials be incorporated into this assessment once published.

Technology, Company and Licensing

Register ID	WP175
Technology name	SentiMag® handheld magnetometer and Sienna+® superparamagnetic iron oxide tracer
Patient indication	To identify the presence or absence of metastatic spread to the local lymph nodes, particularly the ‘sentinel’ lymph node(s), during breast cancer surgery

Reason for assessment

In 2014, a Technology Brief investigated the use of the SentiMag® handheld magnetometer and Sienna+® superparamagnetic iron oxide tracer (Figure 1) for detecting sentinel lymph nodes (SLNs) during breast cancer surgery. Based on the limited but growing body of evidence for this technology, and its potential impact on the investigation of SLN localisation in patients with breast cancer, it was recommended that this technology be monitored for 24 months. In line with this recommendation, the purpose of the current Update is to consider the evidence that has emerged since 2014, and to determine whether this new evidence may provide additional information to inform policy decisions.

Description of the technology

During breast cancer surgery, 2 mL of Sienna+® superparamagnetic iron oxide (SPIO) tracer (a dark brown liquid containing a solution of iron oxide particles) is injected into the breast following anaesthesia. The SentiMag® hand-held magnetic sensor (magnetometer) is then used to detect the Sienna+® SPIO tracer that has collected in the lymphatic system that drains the breast. This guides the surgeon to SLNs (those most likely to contain malignant cells) that require removal and histological analysis. SentiMag®, the only hand-held probe currently marketed, consists of the probe, a base unit, and a detachable air-operated footswitch.



Figure 1 The SentiMag® hand-held probe and Sienna+® magnetic tracer (printed with permission)

The SentiMag[®] probe detects the SPIO tracer by emitting an alternating magnetic field that is absorbed by the SPIO particles. The particles emit a magnetic field that is detected by the sensor, which guides the surgeon to the location of axillary (armpit) lymph nodes that are draining the affected breast. The surgeon identifies the SLNs via both visual and audio cues, that is, brown lymph node staining and increasing frequency and higher numbers on the SentiMag[®] display. The benefits of using SPIO as a tracer include an 18-month shelf-life (facilitating shipment outside urban centres), an absence of the special handling procedures required for conventional radioisotope tracers and an apparent lack of toxicity.^{1, 2} Sienna+[®] can be injected up to seven days prior to surgery, but no later than 20 minutes prior to SLN biopsy, depending on patient and clinician preference.³

2016 Stage of development in Australia

- | | |
|--|---|
| <input type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input checked="" type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

2016 Licensing, reimbursement and other approval

The SentiMag[®] and Sienna+[®] system received updated approval for marketing and sale in Europe in October 2015.⁴ It has not received approval for marketing in the United States, but was granted an investigational device exemption in December 2014 for use in clinical trials (clinical trial NCT02336737).⁵ The SentiMag[®] device and Sienna+[®] solution were registered as Class IIa medical devices on the Australian Register of Therapeutic Goods (ARTG) in January 2013 by the sponsor GRC Surgical Pty Ltd (Cheltenham, Australia). In June 2014, both devices were re-registered on the ARTG by a different sponsor, Emergo Australia (Sydney, Australia), with updated device descriptions.^{6, 7}

2016 Australian Therapeutic Goods Administration approval

- | | |
|---|--------------------------------|
| <input checked="" type="checkbox"/> Yes | ARTG number (s) 224067, 224054 |
| <input type="checkbox"/> No | |
| <input type="checkbox"/> Not applicable | |

2016 Diffusion of technology in Australia

The SentiMag[®] system is not currently used in Australian clinical practice. The manufacturer of SentiMag[®] and Sienna+[®], Endomagnetics Limited (Cambridge, United Kingdom), contracted EBOS Healthcare (Kingsgrove, Australia) to distribute the SentiMag[®] system in Australia and New Zealand in April 2016 (Personal communication, Endomagnetics Limited, 02 April 2016). Endomagnetics Limited also continues to market the product overseas.

2016 International Utilisation

Country	Level of Use		
	Trials underway or completed	Limited use	Widely Diffused
Algeria		✓	
Australia		✓	
ABC Islands (Aruba, Bonaire, Curacao)		✓	
Austria	✓	✓	
Belgium	✓	✓	
Bosnia-Herzegovina		✓	
Canada*			
Czech Republic	✓	✓	
Croatia		✓	
Denmark	✓	✓	
France	✓	✓	
Germany	✓	✓	
Hong Kong		✓	
Hungary	✓	✓	
Italy	✓		✓
Montenegro		✓	
Morocco		✓	
Netherlands		✓	
New Zealand		✓	
Norway	✓	✓	
Poland	✓		✓
Portugal	✓	✓	
Serbia	✓	✓	
Singapore		✓	
Slovakia	✓	✓	
Spain	✓		✓
Sweden	✓	✓	
Switzerland	✓		✓
Turkey	✓	✓	
Tunisia		✓	
United Kingdom	✓	✓	
United States	✓		

*Regulatory approval by Health Canada for distribution has been submitted.

2016 Economic evaluation

Cost-effectiveness

No economic literature on cost-effectiveness was identified.

Cost

The Australian list price of the SentiMag® device and re-usable probe is \$39,975. The Sienna+® tracer costs \$650 per vial.

With regards to comparator costs, a commonly utilised radioisotope within Australia is ^{99m}Tc antimony sulphur colloid, costing approximately \$100 per dose (personal communication, Royal Brisbane and Women's Hospital Department of Nuclear Medicine, 12 May 2016).

There are two dyes available. Patent Blue V (2.5%, 2ml) costs approximately \$105 per dose, and Methylene Blue (1%, 5ml) costs approximately \$35 per dose (personal communication, Royal Brisbane and Women's Hospital Central Pharmacy, 12 May 2016).

As such, the consumables cost of Sienna+® alone is greater, however this does not take into other costs associated with radioisotope use. A 2012 study reported that preoperative injection of ^{99m}Tc and lymphoscintigraphy incurred costs of USD\$1,267 per patient.¹⁸ Additional considerations would include costs of radioisotope handling, waste disposal, regulations, training, and licensing of operating theatre staff.

Medical Benefit Schedule (MBS) Reimbursement

The use of the SentiMag® system can be claimed against existing MBS items for SLN biopsy with lymphotropic dye (30302, 30303). Available reimbursements for item no. 30302 (dissection in a level I axilla) are fees of \$509.95 and benefit (75%) of \$382.50, and for item no. 30303 (dissection in a level II/III axilla) are fees of \$611.85 and benefit (75%) of \$458.90.

2016 Evidence and Policy

Safety and efficacy

Five prospective, non-randomised comparative trials (Level III-2) investigated the use of the SentiMag® and Sienna+® system for SLN detection during breast cancer surgery.⁸⁻¹² All of the included studies tested the Sienna+® tracer and a radioisotope in the same patients. The SentiMag® probe was typically used to identify SLNs prior to the reference test (gamma probe), but the extent to which confounding occurred was unclear.

Table 1 Profile of included studies

Authors; Country	Study design	Funding/conflict of interest	Recruitment period	No. of patients
Hopeau et al (2016) France (4 centres)	Prospective, non-randomised comparative trial (Level III-2)	Sysmex Europe GmbH (Norderstedt, Germany) provided financial support for this trial, but had no input into the study design, data collection, or analysis.	February 2013 to December 2013	115
Ghilli et al (2015) Italy (3 centres)	Prospective, non-randomised comparative trial (Level III-2)	Sysmex España S.L. (Barcelona, Spain) provided the device and contrast, but had no input into data collection or analysis.	October 2012 to January 2014	193
Piñero-Madronea et al (2015) Spain (9 centres)	Prospective, non-randomised comparative trial (Level III-2)	No financial support or conflict of interest was reported.	November 2015 to June 2014	181
Rubio et al (2015) Spain (single centre)	Prospective, non-randomised comparative trial (Level III-2)	Sysmex España S.L. provided the device and contrast, but had no input into study design or analysis or interpretation of data.	July 2013 to March 2014	120
Thill et al (2014) Germany, Switzerland, Poland (4 centres)	Prospective, non-randomised comparative trial (Level III-2)	The study was sponsored by Sysmex Europe GmbH, which had no involvement in the data collection or interpretation.	November 2012 to June 2013	150

SLN = sentinel lymph node

Hopeau et al (2016)

The aim of the study was to determine the safety and efficacy of intraoperative SLN identification using SentiMag[®] and Sienna+[®] compared to the standard technique (radioisotope ± blue dye).¹² In total, 115 patients were prospectively enrolled in a non-randomised method (Level III-2). Included patients had T0-T2 breast cancer proven by histology or cytology, were clinically node negative, and were scheduled for sentinel node biopsy. Patients received the radioisotope tracer either the day prior to surgery, or up to two hours before surgery. The Sienna+[®] tracer was administered intraoperatively following anaesthesia. SLN identification was conducted with the SentiMag[®] probe, followed by the gamma-probe. Nodes with a magnetic or radioactive signal of at least 10 per cent of the highest scoring node were removed. Excised nodes were assessed for malignancy using One Step Nucleic Acid Amplification (OSNA) or histology. The primary outcome measure of the study was the per-patient detection rate of SLNs with either technique.

Safety

There were no serious adverse events recorded for either tracer. Some darkened skin pigmentation due to the Sienna+[®] tracer was observed at the injection site at 30 days follow-up in 22 patients.

Efficacy

A total of 220 SLNs were identified in 106 patients (two patients had complete failure of SLN identification using all three tracers, five had insufficient intraoperative data). Identification

of at least one SLN with SentiMag® system and the standard technique was achieved in 97 per cent (105/108) and 95 per cent (103/108) of patients, respectively. Concordance rates were 96 per cent (104/108) per patient and 88 per cent (189/214) per node. For the 46 patients with nodal involvement, overall concordance was 94 per cent (43/46) per patient and 87 per cent (53/61) per node.

Ghilli et al (2015)

This non-inferiority trial (Level III-2) prospectively enrolled 193 consecutive women with breast cancer, who were scheduled for SLN biopsy on the basis of a negative axillary assessment. All three participating sites were specialist breast centres, of which two had access to nuclear medicine and one did not. Data were collected by the surgical staff after each procedure and analysed by an independent research team.

All patients were injected with a standard radioisotope tracer the day prior to operation, followed by the Sienna+® tracer on the day of the procedure. SLNs were localised at least 20 minutes after administration of Sienna+® using the SentiMag® probe, and confirmed using a gamma probe. SLN biopsy was conducted using the SentiMag® probe initially, with each step in the process confirmed using the gamma probe. Biopsy was performed on true SLNs marked with either tracer, which were then assessed for malignancy intraoperatively using OSNA or histology. The primary outcome measure of the study was the per-patient detection rate of SLNs with either technique.

Safety

None of the included patients experienced allergic or inflammatory reactions at the tracer injection site. Brown skin pigmentation at the inject site was noted in 71 patients (47%), but this had faded (70%) or vanished (21%) in the majority of patients within a mean follow-up period of 6 months. The area of enhanced pigmentation was enlarged in one patient, and remained unchanged in five patients at the end of follow-up.

Efficacy

In total, 380 nodes were removed during the study, with an average of two (range 0-4) nodes removed per patient. The SentiMag® system detected at least one SLN in 98 per cent (189/193) of patients, compared with 99 per cent (191/193) for the radioisotope technique (Table 2). The tracers demonstrated a concordance rate of 98 per cent (187/191), meaning that in four patients the SentiMag® system failed to identify the SLN identified by the gamma probe. The reverse concordance rate was 99 per cent (187/189), meaning that in two patients the gamma probe failed to identify the SLN identified by the SentiMag® system.

The SentiMag® system was able to identify 96 per cent (364/380) of individual nodes, compared with 95 per cent (360/380) for the gamma probe. The techniques showed good concordance, as SentiMag® identified 96 per cent (344/360) of nodes that were also

identified by radioisotope tracer, and the radioisotope tracer identified 95 per cent (344/364) of nodes identified by the SentiMag[®] system.

In total, 29 per cent (55/189) of patients with a SLN identified by SentiMag[®], and 29 per cent (56/191) of patients identified by the radioisotope method had signs of malignancy. A total of 57 patients had a malignant SLN, of which SentiMag[®] correctly identified 97 per cent (55/57), compared to 98 per cent (56/57) with the standard technique. None of the reported differences in this trial were statistically significant, demonstrating that SentiMag[®] was equivalent to the standard technique for identifying SLNs in breast cancer patients.

Table 2 Sentinel lymph node detection rate between SentiMag[®] and the standard technique (gamma probe)

Study	SentiMag [®] detection rate, per patient (n)	Gamma probe detection rate, per patient (n)	SentiMag [®] detection rate, per node (n)	Gamma probe detection rate, per node (n)
Hopeau et al (2016)	97% (105/108)	95% (103/108)	NR	NR
Ghilli et al (2015)	98% (189/193)	99% (191/193)	96% (364/380)	95% (360/380)
Piñero et al (2015)	97% (176/181)	98% (177/181)	93% (295/319)	89% (285/319)
Rubio et al (2015)	98% (116/118)	96% (113/118)	92%* (264/287)	80%* (230/287)
Thill et al (2014)	98% (147/150)	97% (146/150)	97%* (283/291)	92%* (267/291)

*SentiMag[®] had a significantly higher detection rate per node compared to the standard technique

Piñero-Madrona et al (2015)

This study assessed the non-inferiority of the SentiMag[®] and Sienna+[®] system for detecting SLNs compared with standard the gamma-probe technique, with or without blue dye (Level III-2). The study enrolled 181 consecutive patients who were scheduled for SLN biopsy and had a clinically and radiologically negative axillary assessment prior to surgery. Patients received a radioisotope tracer injection the day preceding surgery, followed by Sienna+[®] and an optional blue dye on the day of surgery. The injection site for the Sienna+[®] tracer was either periareolar (n=90) or peritumoral (n=91).

The ability of both methods to detect SLNs above the skin (transcutaneous), during surgery (intraoperatively), and postoperatively on the excised nodes was evaluated. Intraoperative detection was first conducted with SentiMag[®], with positive results confirmed by the gamma probe. All nodes that returned a SentiMag[®] score greater than 10 per cent of the highest node were excised. Once a magnetic signal was no longer detected, the gamma probe was used to identify any nodes that may have been missed. Excised nodes were tested again using both probes and evaluated for malignancy using either OSNA or histology. The primary endpoint of the study was the SLN detection rate per patient.

Safety

No safety issues were reported in this study.

Efficacy

In total, 319 nodes were examined during surgery, and 321 were excised for histopathological assessment. The reason for the discrepancy between the number of intraoperative and excised nodes was not explained by the authors.¹

Intraoperatively, SentiMag[®] identified at least one SLN in 97 per cent (176/181) of patients, which was equivalent to the standard technique (98%, 177/181). The techniques were also equivalent at detecting individual nodes: SentiMag[®] identified 93 per cent (295/319) of SLNs and the standard technique identified 89 per cent (285/319; *p* value not reported). In 60 patients with a confirmed malignancy, SentiMag[®] identified at least one SLN in 92 per cent (55/60) of patients, compared with 88 per cent (53/60) for the standard technique. Although SentiMag[®] had slightly higher SLN detection rates overall, these differences were not statistically significant. Based on these results, the authors concluded that the SentiMag[®] system demonstrated equivalent efficacy to the standard technique.

Rubio et al (2015)

The aim of this comparative trial (Level III-2) was to evaluate the relative SLN detection rate of the SentiMag[®] and Sienna+[®] system compared to the standard gamma probe technique. Between July 2013 and March 2014, 120 consecutive patients with a negative clinical and imaging axillary assessment were enrolled. All patients received a radioisotope tracer injection the day before surgery, followed by a subareolar Sienna+[®] injection during the procedure. During surgery, the SentiMag[®] probe was used initially to identify SLNs for removal. All nodes with a magnetic score greater than 10 per cent of the highest rated node were removed. The gamma probe was used after SentiMag[®], to identify nodes that were not detected using SentiMag[®]. Excised nodes were assessed for malignancy using OSNA or histology.

Safety

No allergic reactions to the Sienna+[®] tracer occurred in the sample population; however, 20 patients developed a darkened area of skin that began to fade within six months.

Efficacy

The SentiMag[®] system detected at least one SLN in patients at an equivalent rate (98%, 116/118) to the standard gamma probe technique (96%, 113/118; *p*=0.35). Five patients had SLNs identified by SentiMag[®] that were missed by the gamma probe, while the gamma probe identified SLNs in two patients that were missed by SentiMag[®]. Overall, 98 per cent (111/118) of patients had a SLN identified by both tests.

¹ It is possible that the two additional nodes were identified by blue dye staining and may have been missed by both the gamma and SentiMag[®] probes. These missing nodes were not accounted for in the intraoperative analysis.

In contrast, the SentiMag[®] detected more individual SLNs (92%, 264/287) compared with the standard technique (80%, 230/287), which led to a greater number of nodes being removed per patient (mean 2.2 versus 1.9; $p=0.001$). The authors suggested that the increased number of excised nodes was likely due to the learning curve associated with the SentiMag[®] probe, and that fewer nodes would be excised as the surgical team became more familiar with the technique.

In total, 31 per cent (36/118) of patients tested positive for malignancy, of which 44 per cent (16/36) had macrometastasis and 56 per cent (20/36) had micrometastasis. The tests showed good concordance, identifying 89 per cent (32/36) of positive nodes. Two positive nodes were only identified by SentiMag[®], and one was only identified by the standard technique. One positive node was missed by both tests, and was detected by physical examination. The results of this study demonstrated the non-inferiority of SentiMag[®] compared with the gamma probe technique.

Thill et al (2014)

This article was identified as a conference abstract in the original Technology Brief, and has since been published in full. The primary aim of this non-randomised comparative study (Level III-2) was to determine the relative SLN detection rate of the SentiMag[®] and Sienna+[®] system compared with the standard radioisotope technique. The study enrolled 150 patients with clinically and radiologically node-negative breast cancer, who were scheduled for SLN biopsy. All patients received a radioisotope injection one or two days prior to the procedure, followed by the Sienna+[®] tracer during the operation. During the procedure, the gamma and SentiMag[®] probes were used to identify SLNs above the skin, as well as during excision of SLNs. Nodes that recorded a reading of at least 10 per cent of the highest SLN score on either probe were removed and checked for malignancy with histopathology.

Safety

No injection site reactions, irritations or allergies were observed.

Efficacy

As reported in Table 2, SentiMag[®] identified at least one SLN in each patient at an equivalent rate to the standard technique. The techniques had good concordance (99%, 145/146) and reverse concordance (99%, 145/147) in detection rates per patient, meaning that the gamma probe identified a SLN in one patient that SentiMag[®] missed, and SentiMag[®] identified a SLN in two patients that the gamma probe missed. In contrast, SentiMag[®] identified significantly more individual SLNs (283/291; 97%, 95% confidence interval [CI] 94.9 to 98.7) than the gamma probe (267/291; 92%, 95% CI 88.2 to 94.5). The gamma probe identified four individual SLNs that SentiMag[®] missed, whereas SentiMag[®] identified 20 SLNs that were missed by the gamma probe. In patients with a confirmed malignancy, SentiMag[®] identified at least one SLN in 97 per cent (33/34) of patients, compared with 91 per cent (31/34) for the radioisotope method. For individual nodes,

SentiMag® identified 96 per cent (43/45) of malignant SLNs compared with 91 per cent (41/45) for the gamma probe.

The results presented demonstrated equivalent SLN detection rates per patient between the two systems, and a slightly better detection rate per node for the SentiMag® system.

Teshome et al (2016)

An additional meta-analysis was published in early 2016, after the initial search date.¹³ The study combined the results of four primary studies included in this Update, and one study reported in the original Tech Brief. The pooled results demonstrated the SentiMag to have non-inferior efficacy at detecting SLNs compared to the radioisotope technique. The authors had unrestricted educational grant support from the SentiMag manufacturer (Endomagnetics Inc, Austin, United States of America).

Karakatsanis et al (2016) Karankatsanis et al conducted a non-randomised comparative study (Level III-2) comparing SentiMag® and Sienna+® with the standard radioisotope technique. A meta-analysis was subsequently performed combining the results of this study and those of the other studies already included in this assessment.¹⁷

Study Results

Patients were injected with the radioactive tracer (^{99m}Tc), usually 40–60 mBq, either on the day of surgery or the day before. The blue dye (1–2 ml of Patent Blue V) and Sienna+® (two ml of Sienna+® diluted with 3 ml saline) was injected after the onset of anaesthesia. During the operation, SentiMag® was used to detect the area with the greatest uptake. The finding was confirmed with the gamma probe and the SLNs removed. All SLNs were excised until the counts were lower than 10 per cent of the highest count or a maximum of four nodes per patient were removed.

SLN detection rates were similar between standard technique and SentiMag® per patient (97.1 vs. 97.6 %, $p = 0.76$). Concordance rates were reported at 98 per cent per patient, with a reverse concordance of 97.5 per cent. Skin discolouration was present in 35.5 per cent of patients postoperatively, almost exclusively where breast conservation was employed. The discolouration faded over time, however was still detectable in 8.6 per cent of patients after 15 months.

Meta-analysis Results

The six other studies for meta-analysis included one study from the original technology brief, and the five studies reported in this technology brief update. The meta-analysis reported similar detection rates ($p = 0.71$) and concordance rates ($p = 0.82$) per patient. The authors concluded that SentiMag® and Sienna+® were comparable to the standard radioisotope technique.

2016 Ongoing research

Three ongoing trials were identified. Both trials are currently in the recruitment phase; one is scheduled for completion in December 2015 and the other in June 2016. NCT02336737 (SentiMagIC) is a comparative trial investigating the relative SLN detection rate of the new formulation of Sienna, called SiennaXP® (Endomagnetics Limited, Cambridge, United Kingdom). NCT02249208 (SENTINAC-01) is a randomised controlled trial which aims to investigate the SLN detection rate of Sienna+® after neoadjuvant chemotherapy. NCT02612870 (Sentimag02), which begins recruitment in February 2016, aims to investigate the impact of injection time on the effectiveness of the Sienna+® tracer.

Table 3 Ongoing clinical trials of SentiMag® and Sienna+® for detecting SLNs in breast cancer

Trial ID; location	Study design	Estimated enrolment	Intervention(s)	Outcome measure(s)	Status	Estimated completion
NCT02336737 (SentiMagIC) United States	Non-randomised comparative trial (6 centres)	180 patients	1. SiennaXP® 2. Blue dye 3. Radioisotope	Lymph node detection rate, adverse event rate	Recruitment complete	June 2016
NCT02249208 (SENTINAC-01) Spain	Randomised controlled trial (1 centre)	150 patients	1. Sienna+® 2. Sienna+® plus radioisotope 3. Radioisotope plus blue dye	False negative rate, lymph node detection rate	Recruiting	June 2016
NCT02612870 (Sentimag02) Switzerland	Randomised controlled trial (2 centres)	40 patients	1. Sienna+® retro 2. Sienna+® peri 3. Sienna+® retro 4-6 4. Sienna+® peri 4-6 5. Technetium 1	False negative rate, detection rate.	Not yet recruiting	June 2016

2016 Other issues

Conflicts of interest

Three of the included trials were sponsored by Sysmex Europe GmbH (Norderstedt, Germany), the distributors of SentiMag® and Sienna+® in Europe, the Middle East and Africa. In each of the three trials, Sysmex supplied the device but reportedly had no involvement in data collection, interpretation of results or writing of manuscripts. However, one of the principal authors from Thill et al (2014) received consultant and speaker honoraria from Sysmex, and two of the included studies received “organisational support” and assistance with data analysis from Sysmex consultants.^{10, 11}

Expanded indications for use

Since the original Tech Brief, researchers have begun investigating the utility of the SentiMag® and Sienna+® system for tumour localisation, and SLN detection in diseases other than breast cancer. In the MagSNOLL trial, investigators injected Sienna+® directly

into breast tumours for lesion localisation, and used a migrated tracer to detect SLNs.¹⁴ This method was effective for tumour localisation, but did not allow enough time for the tracer to migrate to the SLNs, leading to a SLN detection rate of 85 per cent (28/33). To overcome this, the manufacturer is developing a magnetic seed, called Magseed® (formerly SentiMark®). Magseed® is intended to be used for tumour localisation prior to lumpectomy, and can be used in conjunction with the Sienna+® tracer; however, there is no clinical data available for this device yet. One ongoing, non-comparative trial that aims to investigate the feasibility of using Magseed® to localise breast cancer (Trial ID NCT02635737). The trial will aim to enrol 25 patients, and is estimated for completion in October 2016.

A study published in 2014 investigated the feasibility of using the SentiMag® and Sienna+® system for SLN detection in patients with prostate cancer.¹⁵ In addition, one ongoing clinical trial (NCT02445456) is currently investigating the efficacy of the SentiMag® and Sienna+® system in identifying SLNs in patients with rectal cancer. The trial has yet to commence, but it aims to enrol 40 patients. It is scheduled for completion in April 2016, and the principal outcomes are rates of adverse events and intra-operative SLN detection.

MRI artefacts

A small study of six patients has demonstrated that residual magnetic tracer can be left in the breast after injection with the Sienna+ tracer, which can cause image artefacts on subsequent MRI.¹⁶ Observed artefacts were greater than 5mm in diameter, and could obscure clinically meaningful findings on MRI. In one patient, this effect was seen 25 months after injection. This was not identified as a safety issue in the identified clinical trials, as patients did not have a follow-up MRI during the study period. Image artefacts are an important consideration for the use of the SentiMag® system in patients that require MRI follow-up, at least until more data about the extent of artefacts are known.

Extra-axillary or Unanticipated Lymph Drainage An issue generally not addressed within reported studies to date relates to unanticipated or extra-axillary nodal drainage. With nuclear medicine-based localisation, lymphoscintigraphy is commonly utilised by surgeons prior to theatre to determine if there are clinically significant lymphatic flows to internal mammary, supraclavicular, in-transit or unusually placed nodes, which can then be included for biopsy. Additionally, where unusual node locations are discovered, SPECT/CT can also be employed to direct the surgeon to the exact anatomical location.

Most of the current studies to date do not specifically refer to the actual location of the SLNs located for biopsy. These studies employed a range of pre-surgical LN localisation methods, including either blinded or open lymphoscintigraphy, and clinical or ultrasound examination.

There was only a single study (Piñero-Madrona et al., 2015) that reported location of five extra-axillary LNs, associated with peri-tumour injection of radiotracer. Three were detected by gamma probe only, and were located within the internal mammary chain. The remaining

two were detected by both the gamma probe and SentiMag[®], and corresponded to the internal mammary chain and an intra-mammary LN.

The other studies are silent on the actual location of the excised SLN, and are therefore assumed to be axillary in origin. Further evidence on efficacy in locating non-axillary or unusually located SLN, against appropriate nuclear medicine comparators, would be beneficial.

2016 Number of studies included

All evidence included for assessment in this Technology Brief has been assessed according to the revised National Health and Medical Research Council (NHMRC) levels of evidence. A document summarising these levels may be accessed via the [HealthPACT web site](#).

Total number of studies 5

Total number of Level III-2 studies 5

Search criteria used (MeSH terms)

((((sentinel lymph node) OR biopsy, sentinel lymph node [MeSH Terms])) AND ((((((SPIO) OR superparamagnetic) OR sienna*) OR sienna+) OR sentimag*) OR magnet*); MeSH: biopsy, sentinel lymph node; text words: sentinel lymph node, SPIO, superparamagnetic, sienna*, sienna+, sentimag*, magnet*; Date limited from January 2014.

Date searched

10/11/2015

2016 References

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TECHNOLOGY BRIEF 2014

Technology, Company and Licensing

Register ID	WP175
Technology name	SentiMag® handheld magnetometer and Sienna+® superparamagnetic iron oxide tracer
Patient indication	To identify the presence or absence of metastatic spread to the local lymph nodes, particularly the 'sentinel' lymph node(s), during breast cancer surgery

Description of the technology

During breast cancer surgery, 2 mL of Sienna+® superparamagnetic iron oxide (SPIO) tracer (a dark brown liquid containing a solution of iron oxide particles) is injected into the breast once anaesthesia is established. The SentiMag® hand-held magnetic sensor (magnetometer) is then used to detect the Sienna+® SPIO tracer that has collected in the lymphatic system that drains the breast. This guides the surgeon to sentinel lymph nodes (SLNs) (those most likely to contain malignant cells) that require removal and histological analysis. SentiMag®, the only hand-held probe being marketed, consists of the probe, a base unit, and a detachable air-operated footswitch. The SentiMag® probe detects the SPIO tracer by emitting an alternating magnetic field that is absorbed by the SPIO particles. The particles emit a magnetic field that is detected by the sensor and this guides the surgeon to the location of axillary (armpit) lymph nodes that are draining the affected breast. The surgeon identifies the SLNs via both visual and audio cues, that is, brown lymph node staining and increasing frequency and higher numbers on the SentiMag® display. The benefits of SPIOs as tracers include an 18 month shelf-life (facilitating shipment outside urban centres), absence of special handling procedures otherwise required for conventional radioisotope tracer injections, and apparent lack of toxicity.(1, 2) SPIOs can also be injected after administration of general anaesthesia, up to 20 minutes prior to SLN biopsy, thereby avoiding any associated pain.(3)

Company or developer

SentiMag® was developed in 2007 and is being commercialised by Endomagnetics Limited (Cambridge, United Kingdom). Endomagnetics recently signed an agreement with the international diagnostic solutions company Sysmex Europe GmbH (Hamburg, Germany) to sell the device in Europe, the Middle East and Africa (EMEA).(4-6)

Reason for assessment

The current standard-of-care approach for SLN localisation and biopsy has significant technical and geographical limitations. It may be possible to overcome these through the

use of magnetic technologies such as a hand-held magnetometer and an injectable SPIO tracer.

Stage of development in Australia

- | | |
|--|---|
| <input type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input checked="" type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

Licensing, reimbursement and other approval

SentiMag® and Sienna+® are Class IIa devices that are CE-approved for marketing and sales in the EMEA region (SentiMag® in 2010 and Sienna+® in 2011).(7) The SentiMag® and Sienna+® system received Therapeutic Goods Administration (TGA) approval in January 2013:

- Metal detector, magnetic (205070): to be used in conjunction with an iron oxide nanoparticle magnetic tracer injected into interstitial tissue to locate SLNs for subsequent surgical removal.(8)
- Magnetic nanoparticle tracer (205069): a magnetic tracer intended and calibrated for use with the SentiMag® device only, as an overall system to mark and locate lymph nodes in cancer patients prior to their surgical removal.(9)

The devices do not appear to be approved for sale elsewhere, including in the United States.

Australian Therapeutic Goods Administration approval

- | | |
|---|-------------------------------|
| <input checked="" type="checkbox"/> Yes | ARTG number(s) 205070, 205069 |
| <input type="checkbox"/> No | |
| <input type="checkbox"/> Not applicable | |

Technology type **Diagnostic**

Technology use **Diagnostic**

Patient Indication and Setting

Disease description and associated mortality and morbidity

In breast cancer, abnormal breast tissue cells multiply and form tumours that can spread to other parts of the body. Risk factors for breast cancer include family history and genetics;

breast conditions such as ductal carcinoma *in situ* and increased breast density; hormonal factors such as early menarche, late menopause, and some hormone replacement therapies; child-bearing history such as no children or first birth at a later age; and personal and lifestyle factors such as increasing age, higher socioeconomic status, greater height, obesity, low physical activity, and alcohol consumption.(10)

When breast cancer spreads, its cells are carried through the lymphatic system; this makes knowledge of the regional lymph node status essential in order to plan local control and determine prognosis. SLNs are the first lymph nodes to receive drainage and are therefore the most likely to harbour metastatic cancer. Determining the local and distant spread of a malignant tumour ('cancer staging') is a key predictor of survival and is critical for establishing additional treatment.(1)

With respect to burden of disease, breast cancer was expected to be the sixth leading cause of death for Australian females in 2012 (61,300 disability-adjusted-life-years [DALYs]), accounting for about four per cent of all female burden of disease and almost one quarter (24%) of all female burden due to cancer.(10)

Number of patients

Australia

In 2008, 13,567 new invasive breast cancers were diagnosed in Australian women (affecting one in eight women at a rate of 37 per day). Breast cancer was the most common cancer in females, with 69 per cent of cases diagnosed in women aged 40 to 69 years. The number of new breast cancers diagnosed more than doubled over the 26 years between 1982 and 2008, although this increase is largely attributable to improved methods of detection due to the introduction of the national mammography screening program in 1991. The incidence rate of breast cancer has remained fairly stable since 1995. With an ageing population, the number of women diagnosed with invasive breast cancer is expected to increase to 17,120 diagnoses in 2020. However, mortality from breast cancer is decreasing, with 2,680 deaths in 2007 (the second most common cause of cancer death in women after lung cancer). From 1994 to 2007, the age-standardised mortality rate decreased by 29 per cent (from 31/100,000 in 1994 to 22/100,000 in 2007), possibly due to earlier diagnosis associated with screening and better treatments; however, some population subgroups have lower rates of survival, for example women in remote areas and those of Aboriginal and Torres Strait Islander descent.(10)

New Zealand

In 2010, breast cancer was the most common cancer in New Zealand women, accounting for 28 per cent of all cancers in this group: 2,791 patients with cancer were registered (2,415 non-Māori and 376 Māori). It was the second most common cause of cancer death in women at 16 per cent. With respect to trends between 2000 and 2010, the age-

standardised incidence of breast cancer in non-Māori women decreased by nine per cent and the mortality rate fell by 19 per cent; however, the age-standardised incidence for Māori women largely showed an upward trend. In 2010, this group had an incidence rate 1.6 times higher than the rate for non-Māoris and a mortality rate 1.9 times higher.(11)

Speciality

Surgery

Technology setting

Specialist and General Hospitals

Impact

Alternative and/or complementary technology

The SentiMag® and Sienna+® system would be a direct substitute for current techniques used to identify SLNs during breast cancer surgery, including blue dye and radioisotope injections.

Current technology

Introduced in the 1990s, SLN biopsy is a minimally invasive and highly accurate technique to track the possible spread of metastatic disease for patients with breast cancer without clinical or radiological evidence of axillary lymph node involvement.(12) It has been concluded that lack of metastases to SLNs means the remaining axillary nodes are not affected and do not require excision.(13) Compared with axillary node dissection (the previous approach), SLN biopsy reduces morbidity due to lymphedema, numbness, infection, reduced shoulder mobility, and chronic pain.(14)

The current standard of care for SLN identification is a combination of systemically injecting (some hours before surgery) and tracking a radioisotope, technetium-99m (Tc-99m), plus injecting and tracking blue dye locally once anaesthesia is established.(12-15) After allowing for the materials to localise in the lymphatic system, a hand-held scintillation counter (gamma probe) is used to locate the lymph nodes receiving primary drainage from the tumour. The blue dye also assists in node localisation. Lymph nodes that are radioactive, blue or both are judged to be SLNs. They are removed and sent for microscopic histological examination. The detection rate of the technique has been reported at 96 per cent.(1) Despite its advantages, SLN biopsy procedures are offered to only 60 per cent of eligible patients in the Western world and there is minimal access for patients in the rest of the world.(1)

This diagnostic approach has significant drawbacks. For radioisotopes these include: obtaining, managing and handling exposure to the radioisotope (which has a half-life of 6 hours and has significant limitations due to disruptions in supply and impractical distribution beyond large urban centres); and legislative issues related to staff training and management of radioactive waste.(1, 14) Small and medium-sized hospitals are unlikely to get involved with radioactive technologies, which further limits the availability of this procedure. The blue dye can obscure the surgical field, may leave a skin residue that can take months to

fade or be permanent ('tattoo stain'), and is associated with a 0.4 per cent risk of anaphylaxis.(14)

Diffusion of technology in Australia

SentiMag® and Sienna+® received approval from the Australian Register of Therapeutic Goods in January 2014. According to Endomagnetics, there are plans to launch first phase, multicentre clinical evaluations in Australia in April 2014. (Personal Correspondence, Endomagnetics Inc.)

International utilisation

Country	Level of Use		
	Trials underway or completed	Limited use	Widely diffused
Austria	✓	✓	
Belgium	✓		
Czech Republic	✓		
France	✓	✓	
Germany	✓	✓	
Hungary	✓		
Italy	✓		✓
Japan	✓		
Netherlands	✓		
Norway	✓		
Poland	✓		
Slovakia	✓		
Spain	✓	✓	
Switzerland	✓	✓	
United Kingdom	✓	✓	

Cost infrastructure and economic consequences

The Medicare Benefits Schedule includes surgical fees for four types of SLN biopsy for breast cancer (item numbers 30299, 30300, 30302, 30303).(14) The variation is due to the approach taken and the extent of the surgery, with fees ranging from \$510 to \$765. (These fees are listed as "interim" pending the outcome of clinical trials on the long-term outcomes of SLN biopsy compared with lymph node removal, and further consideration by the Medical Services Advisory Committee is imminent). For the calendar year 2012, the total number of surgical services provided across the four SLN biopsy item numbers was 7,217 at a cost of more than \$2.6 million.(16)

No specific economic information on SentiMag® or Sienna+® was available, although potential economic considerations were described in a EuroScan publication, that is, "*If the system allows the SLN biopsy procedure to be performed more widely this may in some cases*

avoid complete lymph node removal which is a more invasive procedure, takes longer and is associated with more complications, a longer hospital stay and long-term adverse effects. The above factors may result in savings for the health service if the SentiMag® and Sienna+® system is used but these would need to be balanced against the cost of the probe and ongoing costs of the tracer.”(7) As well as this, the potential widespread availability of the SentiMag® and Sienna+® system has the potential to reduce travelling costs for patients and hospital expenses may improve due to more flexible scheduling of lists.

Ethical, cultural or religious considerations

No specific ethical, cultural or religious considerations were identified in the published literature. However, the issues surrounding availability of radioisotopes (the current standard approach to SLN localisation) are significant, with very limited access beyond major urban or Western institutions.(17) Due to recent and ongoing disruptions in radioisotope supply and no obvious long-term plan to avoid these disruptions, non-radioactive solutions mean beneficial approaches to SLN localisation could be disseminated more widely, offering patients with breast cancer alternatives that are associated with lower morbidity.

Evidence and Policy

Safety and effectiveness

Two prospective, non-randomised comparative studies (Level III-2 intervention evidence) of SentiMag® and Sienna+® (‘magnetic technology’) were located; both examined SLN biopsy in patients with breast cancer, comparing contemporary use in each patient of the magnetic technology and the ‘reference standard’ (radioisotope with or without injected blue dye). (3, 14)

Table 4 Profile of included studies

Authors; country	Study name	Funder	Time span	No. of patients
Douek et al. (2013); UK & Netherlands (7 centres)	SentiMag® Multicentre Trial: a phase II paired equivalence trial	UK National Institute of Health Research & unrestricted educational grant from Endomagnetics, Ltd.	March to September 2013	160
Thill et al. (2013); Germany, Poland & Switzerland (4 centres) [Abstract only]	Central SentiMag® Study	Full text not available at time of brief production. Study now available on the Sysmex-Lifescience website (Sysmex 2014) ²	Ended June 2013	150

² Thill M, Kurylcio A, Welter R, van Haasteren V, Grosse B, Berclaz G, et al. The Central-European SentiMag study: Sentinel lymph node biopsy with superparamagnetic iron oxide (SPIO) vs. radioisotope. *Breast*. 2014 Jan 28.

Douek et al. 2013 (14)

The non-inferiority study recruited 160 women with breast cancer who were clinically and radiologically node negative, scheduled for SLN biopsy, and available for at least 12 months' follow-up. The seven participating centres in the United Kingdom and the Netherlands were high volume (>300 cases of newly diagnosed breast cancer per year) and experienced with SLN biopsy. The chief investigator, principal investigators, and members of the Trial Management Committee were blinded to all data until patient accrual was complete.

SLN biopsy was undertaken after administration of both the magnetic (SentiMag®/Sienna®) and standard (radioisotope with or without blue dye) tracers in the affected breast(s). Centres employed their standard technique: one used radioisotope alone, one used selective blue dye on some patients, and five used the combined technique on all patients.

Excision of nodes with SentiMag®/Sienna+® was undertaken using the same cut-off as for the radioisotope (gamma) probe. Any node with a count of 10 per cent or more of the node with the highest count was excised. Nodes were sent for evaluation according to local protocols and were reported as normal or containing macrometastases (>2 mm), micrometastases (from 0.2 to 2 mm) or isolated tumour cells (<0.2 mm); the latter were regarded as node negative. Trial end points were the proportion of SLNs detected with each technique and the mean number of nodes excised overall.

Safety

Three patients had a reaction to the dye/tracer injection, two of which were attributed to the blue dye. A third was indeterminate. The two related to blue dye were blue rash without systemic reaction and the third was a transient drop in blood pressure during surgery accompanied by rash. No other adverse events or safety concerns were reported.

Effectiveness

SLN identification rates were 94.4 per cent (151 of 160) and 95.0 per cent (152 of 160) with the magnetic and the standard techniques, respectively. The identification rate with the gamma probe (radioisotope) alone was 91 per cent (145 of 160). Of the nine patients in whom the need for SLN biopsy was not detected with the magnetic technique, two had macrometastases, only one of which was detected using the standard technique.

Of 35 patients (22%) with SLN involvement, 25 had at least one macrometastasis: 23 (92%) were identified with the magnetic technique and 24 (96%) with the standard technique. The remaining 10 patients had at least one micrometastasis as the largest metastatic deposit and all were identified by both techniques. The lymph node retrieval rates were 2.0 nodes per patient with the magnetic technique and 1.9 nodes per patient with the standard technique.

Of 404 lymph nodes removed, 297 (74%) were true SLNs (as detected by the standard technique) and 268 (67%) were also identified by the magnetic technique. Of 107 nodes not identified by the standard technique, 55 nodes (51%) were identified by the magnetic

technique and 24 were identified in 11 patients in whom the standard technique failed. The authors noted that the magnetic technique did not always identify the same nodes as the standard technique, which resulted in false-negative staging; however, they hypothesised that this could result from competition between the dyes for the same nodes and suggested that a randomised controlled trial is needed to confirm non-inferiority.

Thill et al. 2013 (3)

A prospective, multicentre European study is thus far only reported in abstract form.³ The study enrolled 150 patients with histologically verified breast carcinoma at four centres in Germany, Poland and Switzerland. The study arms compared SentiMag®/Sienna+® with radioisotope technology.

Safety

No safety issues were reported in the study abstract.

Effectiveness

The abstract reported an interim analysis of 96 patients. The detection rate for SLNs was 99 per cent for the magnetic system versus 92 per cent for the radioisotope technology. Means of 2.0 and 1.9 nodes were collected per patient via the magnetic and radioisotope systems, respectively. The proportion of pathologically positive lymph nodes was the same for both systems at 12 per cent.

Economic evaluation

No cost-effectiveness studies were identified in the literature.

Ongoing research

One additional trial assessing the performance of the SentiMag®/Sienna+® system was identified from ClinicalTrials.gov and the Australian and New Zealand Clinical Trials Register (Table 5). The trial is funded by the Oscar Lambret centre and Symec America Inc.

Table 5 Ongoing trial of SentiMag® and Sienna+® for detecting SLNs in breast cancer

Trial identifier; country	Study design	Status	Comparison	Primary outcome measure(s)	Follow-up	Completion date
NCT01790399 France (4 centres) n=115	Multi-centre comparative	Recruiting	SentiMag® and Sienna+® versus blue dye and radioisotope or radioisotope alone	Proportion of SLNs detected	Unknown	July 2014

³ Subsequent to the writing of this brief the full article has become available: Thill M, Kurylcio A, Welter R, van Haasteren V, Grosse B, Berclaz G, et al. The Central-European SentiMag study: Sentinel lymph node biopsy with superparamagnetic iron oxide (SPIO) vs. radioisotope. *Breast*. 2014 Jan 28.

Three additional trials were identified by Endomagnetics. They included one Italian trial of 200 patients, data of which was presented at the Italian Senology Congress in January 2014, a Spanish trial of 250 patients whose data is to be presented at the European Breast Cancer Congress in Glasgow in March 2014 and a trial which is currently recruiting 250 patients across 9 sites in Denmark, Sweden and Norway. (Personal Correspondence, Endomagnetics Inc.)

Other issues

Neither of the included studies addressed the learning curve associated with the use of the SentiMag® and Sienna+ system. Presumably as the operators of the system becomes more experienced their proficiency will be improved; as preliminary findings indicate equivalent effectiveness with radioisotope/blue dye for identifying SLNs, this is of importance. The studies also did not acknowledge what happened to women who were found to have pathology positive lymph nodes.

As well as this, the safety of future magnetic resonance imaging (MRI) in women who had previously been injected with the SPIO tracer is of interest. There does not appear to be any evidence published which discusses this.

Concurrent developments for SLN localisation

Due to the limitations in SLN localisation using radioisotope and blue dye combinations, a number of minimally invasive approaches are being explored including SPIO magnetic resonance imaging (15, 17, 18), fluorescent indocyanine green imaging (15), computed tomography lymphotropic tracers (15) and other technologies and approaches. It is anticipated that these techniques will become available for SLN localisation in the near future.

Safety information from Sienna+® product insert

There is no evidence of adverse reaction following the recommended route of administration, interstitial injection. When similar material is injected intravenously, the following undesirable effects have been reported:

- Common (<2%): pain at the injection site, vasodilation and paraesthesia.
- Uncommon (≥0.1% to <1%): asthenia, back pain, injection site reactions, chest pain, nausea, vomiting, headache, taste perversion, pruritus and rash.
- Rare (≥0.01% to <0.1%): hypersensitivity and anaphylaxis, hypertension, phlebitis, hyperaesthesia (abnormal sensitivity to stimuli of the senses), anxiety, dizziness, convulsion, parosmia (dysfunction of smell), shortness of breath, increased cough, rhinitis, eczema and hives. (3)

Additional study of interest

A study from Japan (13) was excluded for several reasons: the sensor/magnetometer was locally developed (Kyoushin, Tochigi) and information on the device is not available; a different SPIO tracer was used (Risovist[®], Bayer Schering Pharma AG, Leverkusen, Germany); and all patients underwent complete axillary node removal, a more aggressive surgery than SLN biopsy. This study was of relevance however because it compared the use of blue dye with a SPIO tracer.

Thirty women with clinically node-negative breast cancer were enrolled (mean age 58 years, range 39 to 76 years). The reference standard was blue dye, that is, radioisotopes were not used at this hospital for logistical and economic reasons. After induction of general anaesthesia, the SPIO tracer and blue dye were concurrently injected in the breast. Several minutes later the magnetic signal in the SLNs was sought using the sensor. The axillary node removal then commenced, guided by 'hot spots' detected by the sensor. All excised nodes were submitted for histology. SLNs were detected in 27 patients (90%) with SPIO and blue dye combined, 23 patients (77%) with SPIO alone and 24 patients (80%) with blue dye alone. On average, 11 nodes were excised (range 3 to 22) with a mean of 1.6 SLNs per patient (range 1 to 3). Eight of the 30 patients (27%) had node metastases.

Additional oncology applications for hand-held magnetometers

During the scoping exercise for this topic there was reference to use of the locally developed Japanese hand-held magnetometer with Resovist[®] as the SPIO tracer in patients with non-small cell lung cancer (19) although recent citations were not identified. There are also possible applications for SPIO tracers and magnetometers to identify SLNs in patients with melanoma.(20)

Summary of findings

When exploring the extent of disease and developing a treatment plan for patients with breast cancer, it is essential to determine the presence or absence of local lymphatic spread. For patients with no clinical or radiological evidence of spread to the axillary lymph nodes, the standard of care is localisation of the SLNs (the nodes most likely to be invaded by tumour cells) to make a decision about SLN biopsy. The current approach is a combination of systemically injected radioisotope plus locally injected blue dye; however, despite high rates of SLN identification, this approach has a number of drawbacks and limitations preventing its widespread use.

A recently developed non-invasive technology, locally injected SPIO detected by a hand-held magnetometer (the SentiMag[®]/Sienna+[®] system) has shown equivalence to the current approach without the drawbacks or limitations. The largest published study conducted in seven European centres (n=160 patients) reported performance that matched the radioisotope/blue dye system with about 95 per cent SLN identification. A similar European study reported thus far only in abstract form (n=150 patients) reported SLN detection rates of 99 per cent for the magnetic system and 92 per cent for the radioisotope technology. It has been suggested that further evidence from randomised controlled trials with separate

intervention arms for magnetic agents, radioisotopes, and blue dye injections would be useful in order to minimise the potential of confounding when all three are injected simultaneously.

HealthPACT assessment

Based on the scant but growing body of evidence for this technology, and its potentially significant potential impact on the investigation of SLN localisation in patients with breast cancer, it is recommended that this technology be monitored for a period of 24 months.

Number of studies included

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

Total number of studies	2
Total number of Level IIIb studies	2

Search criteria to be used (MeSH terms)

((((sentinel lymph node) OR biopsy, sentinel lymph node [MeSH Terms])) AND ((((((SPIO) OR superparamagnetic) OR sienna*) OR sienna+) OR sentimag*) OR magnet*); MeSH: biopsy, sentinel lymph node; text words: sentinel lymph node, SPIO, superparamagnetic, sienna*, sienna+, sentimag*, magnet*; no date limits

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1. Ahmed, M.&Douek, M. (2013). 'The role of magnetic nanoparticles in the localization and treatment of breast cancer'. *Biomed Res Int*, 2013, 281230.
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