Summary

- The technology described in this briefing is the Magtrace and Sentimag system. It comprises Magtrace, a magnetic liquid tracer that is injected into the body, and Sentimag, a probe that detects the tracer in the lymphatic system during sentinel lymph node biopsy (SLNB).

- The innovative aspects are the non-radioactive mechanism of action and increased timeframe during which the tracer can be injected (30 days to 20 minutes before the SLNB).

- The intended place in therapy is as an alternative to other methods of locating sentinel lymph nodes (SLNs) in people with cancer who are having SLNBs. The experts noted that the system has been used in people with breast cancer and there is evidence on the use of the system in other cancers such as melanoma. Currently, liquids containing radioactive isotopes, blue dye, or a combination of both are used.
• The **main points from the evidence** summarised in this briefing are from 6 publications including 3 non-inferiority trials, 1 non-randomised trial, 1 cohort study and 1 systematic review that reported pooled results based on 6 non-inferiority trials plus 1 cohort study. These include 1,854 people with breast cancer and 129 people with melanoma who had SLNBs. Evidence showed that the detection rate of people with SLNs were similar using the magnetic tracer and Sentimag system and the standard techniques.

• **Key uncertainties** around the evidence are there is no evidence from randomised controlled trials on the Magtrace and Sentimag system. The evidence would benefit from trials to capture clinical benefits.

• The **cost** of the Magtrace and Sentimag system is estimated at £226 per procedure. The cost of standard care using isotope and blue dye in combination is £194 per procedure.

## The technology

The Magtrace and Sentimag system (Endomag) is intended to help locate sentinel lymph nodes (SLNs) during SLN biopsy (SLNB) procedures for cancer staging.

The system comprises a tracer (Magtrace) and a handheld magnetic sensing probe (Sentimag). Magtrace (previously called Sienna+) is a dark brown liquid containing superparamagnetic iron oxide (SPIO) with a carboxydextran coating. It is injected into subareolar or peritumoral interstitial tissues. The magnetic particles are then absorbed into lymphatics and become trapped in SLNs. Magtrace serves as both a magnetic marker and a visual dye (because of the dark colour of the particles).

During surgery, the Sentimag probe detects the tracer trapped in the lymph nodes and guides the surgeon to remove them for biopsy. Sentimag uses sounds of different pitches and a visual reading to indicate how close the surgeon is to the tracer. The nodes often appear dark brown or black in colour, which also helps identification.

Magtrace can be injected in the operating theatre 20 minutes before an SLNB or up to 30 days before surgery at an outpatient clinic.

Magtrace may leave a brown bruise-like colouration around the area of injection in some people, which may fade over time.
Innovations

The key innovative feature of the Magtrace and Sentimag system is its magnetic mechanism of action. This means that unlike other similar interventions used in current practice, the system can be used without the need for nuclear medicine safety procedures and facilities. The Magtrace can also be injected up to 30 days before surgery, whereas the tracers used in current practice can be given no more than a day before.

Current care pathway

SLNBs help to diagnose cancer that has spread to the lymph nodes. An SLN is defined as the first lymph node to which cancer cells are most likely to spread from a primary cancer. Sometimes there can be more than 1 SLN. SLNB is a surgical procedure to remove 1 or more of the nodes. It is used in people who have already been diagnosed with cancer.

NICE has published guidance on the use of SLNB for the management of breast, skin and early oral cavity cancer. Specifically, SLNB is recommended by NICE for the following groups:

- people with invasive breast cancer who had no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle biopsy
- people with stage 1B to 2C melanoma with a Breslow thickness of more than 1 mm
- people with early oral cavity cancer (T1 to T2, N0), unless cervical access is needed at the same time.

In current practice, a tracer containing a radioactive isotope, technetium-99m, and blue dye are commonly used in combination to mark SLNs during SLNB. This aligns to the NICE guideline on early and locally advanced breast cancer, which recommends that the dual technique with isotope and blue dye should be used when performing SLNB. The NICE guidelines on melanoma and cancer of the upper aerodigestive tract do not include any recommendations on the type of tracer or dye that should be used during SLNB.

The following publications have been identified as relevant to this care pathway:

- NICE guideline on early and locally advanced breast cancer: diagnosis and management
Population, setting and intended user

The Magtrace and Sentimag system is intended to be used in people with cancer, during the SLNB procedure.

The company notes that Magtrace has been used in SLNB for breast cancer and other cancers such as melanoma, endometrial, cervical, prostate and oral cancer.

Magtrace can be injected by healthcare professionals such as surgeons or nurses before an SLNB procedure. On the day of the procedure, the surgeon uses Sentimag to identify the lymph nodes that are mapped by the tracer.

Costs

Technology costs

The cost of Magtrace is £226 per vial and the reusable Sentimag probe costs £25,000 per unit. The company states that the cost for using the system is £226 per Magtrace (the cost of the Sentimag unit has been deducted).

Costs of standard care

The company states that the cost of using the combination of a radioactive tracer (technetium-99m) and blue dye is £194.75 per procedure and this is based on 1 vial of radioactive tracer used for each person. This does not include the costs associated with handling nuclear medicines and radioactive waste disposal.

Resource consequences

The Magtrace and Sentimag system is currently being used in 50 NHS trusts. The technology is more expensive than using technetium-99m and blue dye in combination, but the company believe it could be resource releasing if it improves accessibility (no need
for a nuclear medicine facility) and efficiency in clinic scheduling and capacity.

An expert considered training would be needed to understand injection technique and use of the Sentimag probe. The company notes all training is included in the cost and provided free of charge. Training can be provided in person with product specialists to support surgical cases. There is also online material for users.

Regulatory information

Both Magtrace and Sentimag are CE-marked IIa medical devices under the Medical Device Directive.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

People with cancer are protected under the Equality Act from the point of diagnosis.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement for medtech innovation briefings. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

There is a wider body of evidence for the Magtrace and Sentimag system. The most up-to-date studies that provided comparative evidence were prioritised. Evidence from 1 systematic review that included a meta-analysis and 5 primary studies are summarised in this briefing.

The systematic review included 7 studies and the meta-analysis is based on results of
1,122 sentinel lymph node biopsy (SLNB) procedures undertaken in 1,118 people.

The primary studies in the briefing included a non-randomised trial, a cohort study and 3 non-inferiority trials in which all people received magnetic tracers and a comparator intervention simultaneously. The sample sizes of the other studies ranged from 59 to 193.

One study investigated the use of Magtrace and Sentimag in people with melanoma (Anninga et al. 2016). All of the other evidence relates to its use in patients with invasive breast cancer.

In 2 of the more recent publications (Shams et al. 2020 and Alvarado et al. 2019) the intervention is referred to by its current name, 'Magtrace and Sentimag'. In the studies by Anninga et al., Ghilli et al., Karakatsanis et al., and Zada et al., the intervention is referred to by the technology's previous name 'Sienna+ and Sentimag'.

The clinical evidence with its strengths and limitations are summarised in the overall assessment of the evidence.

**Overall assessment of the evidence**

Most of the evidence for Magtrace and Sentimag is in people with invasive breast cancer.

One systematic review of studies (Zada et al. 2016) compared the use of the magnetic tracer in detecting lymph nodes with the standard technique (isotope with blue dye) in detecting lymph nodes in people with breast cancer. One of the included studies in the systematic review involved UK sites.

One, small non-randomised study done in Germany found that Magtrace and Sentimag reduced time spent in preoperative care. The equipment used in this study was provided free of charge by the manufacturer. Outcomes reported in the other 4 primary studies relate to sentinel lymph node detection and excision rates, and adverse events. Most of the studies were done in European countries such as Sweden, Germany and Italy. The manufacturer fully or partly funded 4 studies.
Shams et al. (2020)

Study size, design and location

A non-randomised trial in 59 people with invasive breast cancer in Germany.

Intervention and comparator

People in the intervention group received Magtrace (n=30). People in the control group had technetium-99m (n=29).

Key outcomes

The average time spent in preoperative care in the Magtrace group was 5.4 minutes (standard deviation [SD] 1.3 minutes) compared with 82 minutes (SD 20 minutes) in the technetium-99 group.

Interoperatively, the median time to sentinel extraction was 5 minutes (interquartile range [IQR] 3 to 15 minutes) in the Magtrace group and 10 minutes (IQR 7 to 15 minutes) in the technetium-99m group.

The duration of the whole SLNB procedure including removal of all marked lymph nodes was similar in both groups. The median duration was 9 minutes (IQR 4 to 15 minutes) in the Magtrace group compared with 10 minutes (IQR 7 to 15 minutes) in the technetium-99m group. There was no difference in the overall time for the SLNB procedure. The median duration in the Magtrace group was 74 minutes (IQR 58 to 99 minutes) and in the technetium-99m group it was 71 minutes (IQR 56 to 87 minutes).

Self-reported pain scores were measured using the quality improvement in postoperative pain management questionnaire before and after the localisation procedure. The scores were almost identical in the Magtrace and technetium-99m groups. However, only 73% of patients in the Magtrace arm completed the questionnaire compared with 97% in the technetium-99m group.

Strengths and limitations

The study compared Magtrace with technetium-99m alone. The allocation was not randomised. The manufacturer provided the material and equipment free of charge. The
study author noted that the sample size in each treatment group was small and detailed patient-reported experience measurement was limited.

Alvarado et al. (2019)

Study size, design and location

A non-inferiority trial in 146 people with invasive breast cancer or ductal carcinoma in situ (DCIS) and no clinical signs of metastases in 6 US centres.

Intervention and comparator

All people had technetium-99m injections either the day before or on the day of surgery, and isosulfan blue dye per institutional protocol. All people also had interoperative Magtrace injections.

Once the incision was made, sentinel lymph nodes were first identified using Sentimag, either by the magnetic signal detected by the probe or by visual confirmation of the black/brown colour of the tracer in the node. A radioisotope count was taken using the gamma probe.

Key outcomes

The Magtrace and Sentimag system detected sentinel lymph nodes (SLNs) in 145 out of 146 people (99.3%; 95% confidence interval [CI] 98 to 100). The technetium-99m plus isosulfan blue dye (dual tracer) identified SLNs in 144 of 146 people (98.6%; 95% CI 96.7 to 100).

A total of 22 people had SLNs detected that were confirmed to be malignant (that is, had micro or macro metastases). In 21 of the 22 people, malignant nodes were identified by both Magtrace and the dual tracer. One person had a node that was confirmed to be positive for cancer that was not identified by either tracer. In this case, the surgeon identified the node intraoperatively as 'highly clinically suspicious'.

The Magtrace and Sentimag system detected 348 out of 369 SLNs (94.3%; 95% CI 91.9 to 96.7). The dual tracer detected 345 of 369 SLNs (93.5%; 95% CI 91.0 to 96.0). The difference in the number of nodes detected with each technique was 0.8%. Overall, 326 nodes were detected by both methods.
The dual tracer detected 19 nodes (5.1%) that were not detected by Magtrace and Sentimag, and 22 nodes (6.0%) were detected by Magtrace and Sentimag but not by the dual tracer. None of the discordant nodes were malignant.

Adverse events related to Magtrace were reported by 25 people. The most common event reported was breast discolouration or hyperpigmentation, which occurred in 23 (15.6%) people.

**Strengths and limitations**

This is a multisite study. All participants were injected with both tracing systems. The study was funded by the manufacturer.

**Ghilli et al. (2017)**

**Study size, design and location**

A noninferiority trial in 193 people who had a diagnosis of breast cancer with no sign of metastases, in 3 Italian breast centres.

**Intervention and comparator**

All participants were injected with both the magnetic tracer (Sienna+) and radioisotope (technetium-99). Sentinel lymph nodes were detected initially using the Sentimag probe for magnetic tracer and then confirmed by using a gamma probe to determine the presence of the radioisotope.

**Key outcomes**

Eleven people had ductal carcinoma in situ (6%) and the other 182 people were diagnosed with invasive cancer.

Magtrace and Sentimag identified SLNs in 189 out of 193 people (97.9%, 95% CI 95.9 to 99.9). The technetium-99m tracer identified SLNs in 191 of 193 people (99.0%, 95% CI 97.5 to 100).

SLNs that were confirmed to be malignant were identified in 57 people (that is, they had micro or macro metastases). The Magtrace and Sentimag system identified the malignant
nodes in 55 out of 57 people (96.5%, 95% CI 91.7 to 100). The technetium-99m identified the malignant nodes in 56 out of 57 people (98.3%, 95% CI 94.8 to 100). Malignancy was detected by both tracers in 54 people.

Magtrace and Sentimag detected 364 out of 380 SLNs (95.8%, 95% CI 93.8 to 97.8). The technetium-99m detected 360 of 380 SLNs (94.7%, 95% CI 92.5 to 97.0). Both tracers detected 344 nodes (95.6%, 95% CI 93.4 to 97.7).

No allergic or inflammatory reaction was reported. Side effects of the procedure included the appearance of slightly brown skin pigmentation at the site of injection in 71 (47.3%) people. The study followed up 150 people for an average of 5.9 months, and the skin pigmentation was attenuated in 70.4% and vanished in 21.1%. An enlargement of the pigmentation area was recorded in 1 person (1.4%) and the skin pigmentation unchanged in 5 people (7.1%).

**Strengths and limitations**

The manufacturer provided the Sentimag device and the Sienna+ for free for the period of the study. The study excluded 6 people because their injection of the magnetic tracer was not consistent with the protocol.

**Karakatsanis et al. (2017)**

**Study size, design and location**


**Intervention and comparator**

People in the study arm had the magnetic tracer (Sienna+, n=183) and blue dye was administered interstitially 10 minutes before skin incision if the transcutaneous magnetic signal was inadequate. The control arm had technetium-99m (n=155) on the morning of surgery or the day before and blue dye was injected routinely.

**Key outcomes**

In the magnetic tracer group, 182 people had 183 SLNBs and in the technetium-99m group 155 people had 159 SLNBs. The SLN detection rate per procedure was 95.6% in the
magnetic tracer arm and 96.9% in the technetium-99m group.

In the magnetic tracer group, the mean number of SLNs retrieved per procedure was 1.35 (95% CI 1.24 to 1.46) and the tracer-specific mean was 1.26 (95% CI 1.15 to 1.37). In the radioisotope arm, the mean number of SLNs retrieved was 1.89 (95% CI 1.74 to 2.03) nodes per procedure and the tracer-specific mean was 1.70 (95% CI 1.56 to 1.85) nodes.

Median follow up in the magnetic tracer group was 398 days. Around 40% people presented with skin staining that faded slowly in size and colour.

**Strengths and limitations**

People were recruited from 2 hospitals (1 hospital used the magnetic tracer and the other used technetium-99m). The study had a prospective design. The allocation was not randomised.

**Anninga et al. (2016)**

**Study size, design and location**

A non-inferiority trial in 129 people with melanoma and no sign of lymph node metastases who were scheduled for SLNB in the UK and Netherlands.

**Intervention and comparator**

All participants had (Sienna+), technetium-99m and blue dye.

Surgeons were needed to initially identify SLNs using the magnetic technique, and then confirmed this with the gamma probe.

**Key outcomes**

The magnetic tracer and Sentimag identified SLNs in 123 out of 129 people (95.3%). The standard technique using technetium-99m plus blue dye identified SLNs in 126 of 129 people (97.7%). The difference in the number of people was 2.3% (95% upper confidence limit [CL] 6.4, for non-inferiority, the upper 95% CL was expected not to exceed 5%).

The most common complications experienced within 30 days of receiving the magnetic
tracer were black staining (20.9 %) and blue staining (10.9 %).

Strengths and limitations

The study did not reach the predefined non-inferiority margin in the comparison of the detection rate with the standard technique. The study author noted that the trial did not reach the targeted number of people (n=160) because of lack of funding and insufficient magnetometers. The study was partly funded by the manufacturer.

Zada et al. (2016)

Study size, design and location

A systematic review and meta-analysis including 6 non-inferiority studies and 1 prospective cohort study in 1,118 people and 1,122 SLNB procedures.

Intervention and comparator

The magnetic technique (Sienna+) and Sentimag system was compared with the standard techniques using either radiolabelled tracer (technetium-99m and its parent isotope, molybdenum-99), blue dye alone, or a combination of both.

Key outcomes

Using the magnetic tracer and Sentimag detected SLNs in 1,089 of 1,122 SLNB procedures (97.1%, range 94.4 to 98.0). The dual tracer detected SLNs in 1,086 of 1,122 SLNB procedures (96.8%, range 94.2 to 99.0). The pooled data showed no significant difference between the 2 techniques (risk difference [RD] 0.00, 95% CI -0.01 to 0.01; p=0.690). The total number of lymph nodes retrieved was significantly higher (which is undesirable) using the magnetic technique and Sentimag than the standard technique (RD 0.05, 95% CI 0.03 to 0.06; p=0.003).

A total of 323 out of 1,118 people (28.9%) had malignant SLNs (metastasis). The total number of malignant SLNs was 430, which is 18.7% of all SLNs (n=2,298). Out of 2,298 SLNs, 36 (1.6%) were not detected by the magnetic technique and Sentimag and 47 (2.0%) were not detected by the standard technique. Mean false-negative rates were 8.4% for the magnetic technique and Sentimag, and 10.9% for the standard technique (RD 0.03, 95% CI 0.00 to 0.06; p=0.551).
Complications and adverse reactions were reported in all studies. Brown and grey skin colouration at the magnetic tracer injection site was reported by 5 studies (179 of 549 people). The following disadvantages of the magnetic technique and Sentimag were discussed in 6 studies:

- the relatively large diameter of the Sentimag handheld probe means larger surgical incisions are needed,
- the time-consuming frequent balancing of the magnetic baseline level needed for a correct localisation,
- the need for plastic alternatives instead of standard surgical retractors, and
- the role of lymphoscintigraphy (a special type of nuclear medicine imaging) in successful SLN localisation.

**Strengths and limitations**

The review searched databases including the MEDLINE, PubMed, Embase and Cochrane. The inclusion and exclusion criteria were defined in the study. The characteristics and the quality of the included studies were described in the study. The review authors evaluated the quality of the included studies using the modified CONSORT checklist for non-inferiority studies and classified all 6 non-inferiority studies as high quality. They noted that the prospective cohort study failed to meet all the CONSORT criteria and was therefore not considered high quality, but they did not exclude it from the review.

**Sustainability benefits**

Magtrace is for single-use and the Sentimag probe is reusable and designed to be used on multiple individuals. The company noted that the use of the Magtrace and Sentimag system could lower the environmental impact of SLNB procedures and reduce greenhouse gas emissions. This is primarily because people will not need to travel to hospitals with nuclear medicine departments that handle radioisotopes. Also, the injection of Magtrace can be done in the operating theatre 20 minutes before an SLNB or up to 30 days before surgery at an outpatient clinic. This would lead to a more efficient use of NHS resources such scheduled theatre time.
Recent and ongoing studies


Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

All of 4 experts were familiar with or had used this technology before.

Level of innovation

All of the experts considered the Magtrace and Sentimag system is based on the same principle of current techniques for identifying sentinel nodes. It is a minor variation on existing techniques, a non-radioactive tracer, avoids disadvantages of the dye techniques (allergic reactions) or complex logistics of using a radioactive tracer (technetium-99m).

Potential patient impact

All of the experts mentioned that using Magtrace and Sentimag could potentially avoid the need for travelling to hospitals with a nuclear medicine department for the radioisotopes, which may not be available in many small and medium size hospitals. They also mentioned
the fact that Magtrace is well tolerated and is likely to have fewer side effects compared with standard care; for instance blue dye has been known to cause severe anaphylaxis in a minority of people.

Skin staining was mentioned by 3 experts and discolouration of the breast skin was common. One expert suggested that this was observed immediately in one third of people who had the injection. Discolouration may fade over the time. But 1 expert thought an audit may be needed to monitor skin staining and its long-term effect. Two experts said that skin discolouration may also be seen with other dying methods, such as blue dye.

Three experts thought that all people with invasive breast cancer who need SLNB procedures would benefit from the Magtrace and Sentimag system.

**Potential system impact**

The potential to improve the logistics of sentinel lymph node biopsy (SLNB) procedures is a main system benefit. The experts mentioned that Magtrace is non-radioactive so there is no need for the special precautions needed for when using radioactive material. There are also likely to be fewer delays in sending the sample specimen to the lab.

The benefits of a reduced cost related to the nuclear medicine facilities, including staff, complex legislation, radiation protection and the administration of radioactive substances advisory committee (ARSAC) licences were highlighted. One expert considered that the Magtrace and Sentimag system would improve flexibility and efficiency in theatre capacity. The expert also noted that axillary incisions may be slightly longer when using the Magtrace and Sentimag system, because the Sentimag probe has a larger diameter than the probe used to detect technetium-99m.

**General comments**

Three experts thought the Magtrace and Sentimag system could potentially be used as an alternative to standard care. The experts agreed that no changes are needed to existing facilities except the initial purchase of Sentimag. Two experts considered the technology to be safe, but the presence of any metal instruments may alter the Magtrace signal. So standard surgical retractors cannot be used in surgery and plastic alternatives are needed. Another expert noted that Magtrace would not be suitable for people with iron metabolic disorders. One expert mentioned that the use of Magtrace may interfere with MRI
interpretation and the presence of artefacts may mask recurrence during MRI follow up. Training would be needed and the experts thought that any breast surgeon who is familiar with technetium-99m and blue dye used in SLNB would be able to adapt to the use of the Magtrace and Sentimag system.

**Expert commentators**

The following clinicians contributed to this briefing:

- Tomasz Graja, consultant breast oncoplastic and general surgeon, Dorset County Hospital NHS Trust. Did not declare any interests.
- Caroline Osborne, consultant general surgeon specialising in breast surgery, Yeovil District Hospital NHS Foundation Trust. Did not declare any interests.
- Sunita Shrotria, consultant breast oncoplastic surgeon, Ashford and St Peters Hospital NHS Trust. She is involved in a feasibility study for Magtrace.
- Kate Williams, consultant oncoplastic breast and chest wall surgeon, North Manchester Hospital. Did not declare any interests.

**Development of this briefing**

This briefing was developed by NICE. The [interim process and methods statement for medtech innovation briefings](https://www.nice.org.uk/terms-and-conditions#notice-of-rights) sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.