NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation document

Magtrace and Sentimag for locating sentinel lymph nodes for breast cancer

How medical technology guidance supports innovation

NICE medical technologies guidance addresses specific technologies notified to NICE by companies. The 'case for adoption' is based on the claimed advantages of introducing the specific technology compared with current management of the condition. This case is reviewed against the evidence submitted and expert advice.

If the case for adopting the technology is supported, the specific recommendations are not intended to limit use of other relevant technologies that may offer similar advantages. If the technology is recommended for use in research, the recommendations are not intended to preclude the use of the technology but to identify further evidence which, after evaluation, could support a recommendation for wider adoption.

1 Recommendations

1.1 Magtrace and Sentimag is recommended as an option to locate sentinel lymph nodes for breast cancer in hospitals with limited or no access to radiopharmacy.

1.2 Further data collection is recommended to monitor the number of additional sentinel lymph node biopsies done in each hospital after the technology is adopted in clinical practice.

Why the committee made these recommendations

Evidence shows that Magtrace and Sentimag is likely to be as effective at detecting sentinel lymph nodes as the radioactive isotope tracer and blue dye dual technique

used in standard practice. Standard practice requires nuclear medicine safety procedures and facilities.

Clinical expert advice suggested that hospitals with limited or no access to radiopharmacy are more likely to realise the opportunity costs that make this technology a cost saving option. These hospitals are likely to be able to do more procedures because scheduling is less dependent on external supply chain and staffing resources.

Because the potential cost saving depends on the opportunity costs, and the economic evidence is limited, data collection is recommended to understand if cost savings are made once the technology is adopted in clinical practice.

2 The technology

Technology

2.1 The Magtrace and Sentimag system (Endomag) comprises a magnetic liquid tracer (Magtrace) and a handheld magnetic sensing probe (Sentimag). Magtrace is intended for use only with the Sentimag system. Magtrace is a non-radioactive dark brown liquid containing superparamagnetic iron oxide with a carboxydextran coating. It is both a magnetic marker and a visual dye. Magtrace is injected into the tissue beneath the areola or interstitial tissue around a tumour. The particles are then absorbed into lymphatics and become trapped in sentinel lymph nodes that can then be detected by the magnetic sensing probe and visualisation to assist with biopsy.

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

Care pathway

2.3 A sentinel lymph node biopsy helps to stage cancer that has spread to the lymph nodes and is followed by a surgical procedure to remove 1 or more of the nodes. NICE's guideline on early and locally advanced breast cancer recommends sentinel lymph node biopsy as the preferred technique to stage the axilla for people with invasive breast cancer and no evidence of lymph involvement on ultrasound or a negative ultrasound-guided needle biopsy. The guideline also recommends that sentinel lymph node biopsy should be offered to people who are having a mastectomy for ductal carcinoma in-situ breast cancer and people with a preoperative diagnosis of ductal carcinoma in-situ who are considered to be at high risk of invasive disease.

2.4 The recommended treatment option for locating sentinel lymph nodes during biopsy is a dual technique combination of a tracer containing a radioactive isotope, and blue dye. When the radioactive isotope is not available, some centres report using blue dye on its own, but this can reduce the detection rate of sentinel lymph nodes.

Innovative aspects

2.5 The key innovative feature of the Magtrace and Sentimag system is its magnetic mechanism of action. This means that unlike the dual technique, the system can be used without the need for nuclear medicine safety procedures and facilities. Magtrace can also be injected up to 30 days before surgery, whereas the radioactive tracers can be given no more than 24 hours before the sentinel lymph node biopsy procedure.

Intended use

2.6 Magtrace and Sentimag are intended to help locate sentinel lymph nodes during biopsy procedures for cancer staging. Magtrace can be injected by a nurse or surgeon up to 30 days before a biopsy or in the operating theatre 20 minutes before surgery. Sentimag is then used by the surgeon

during the biopsy procedure to detect the tracer trapped in the lymph nodes.

Contraindications

2.7 Known contraindications to Magtrace include people with known hypersensitivity to iron oxide or dextran compounds, people with iron overload disease and people with a metal implant in the axilla or in the chest. Sentimag is contraindicated for use within 15 mm of a working pacemaker.

Costs

2.8 Magtrace costs £226 per unit (excluding VAT). The Sentimag probe costs £24,900 to purchase. However, NHS trusts entering a consumable commitment of 100 to 120 units per annum receive the Sentimag system free of charge.

For more details, see the website for Magtrace and Sentimag.

3 Evidence

NICE commissioned an external assessment centre (EAC) to review the evidence submitted by the company. This section summarises that review. Full details of all the evidence are in the project documents on the NICE website.

Clinical evidence

The main clinical evidence comprises 36 studies

3.1 The EAC included a total of 36 studies which included 18 non-randomised controlled trials, 16 cohort studies, 1 prospective paired comparison study and 1 validation study. The 36 studies include a total of 4,202 people who had procedures in which Magtrace and Sentimag was used. Nine studies were reported in conference abstracts only. For full details of the clinical evidence, see section 4 of the assessment report.

Studies comparing Magtrace and Sentimag with the dual technique are considered most relevant

3.2 The published clinical evidence on Magtrace and Sentimag included several comparators. Five studies compared the dual technique radioisotope with Magtrace and Sentimag and were considered most relevant to the decision problem. These studies were powered to show non-inferiority compared with the dual technique. Eleven studies compared Magtrace and Sentimag with radioisotope alone. Six studies included both the dual technique and radioisotope only but did not report outcomes separately for each comparator. Fourteen non-comparative studies were included for patient reported outcome measures and adverse events only. Studies comparing Magtrace with blue dye alone were not included because of high false negative rates and known inferiority of blue dye when compared with the dual technique.

The evidence supports the non-inferiority of Magtrace and Sentimag compared with standard care for detection of sentinel and malignant lymph nodes

3.3 The published evidence for the detection rates of Magtrace and Sentimag compared with standard care is based on non-inferiority trials. Twelve studies were statistically powered to show non-inferiority, only 1 of which reported dual technique outcomes exclusively. The detection rates per patient for Magtrace ranged from 89.7% to 100% compared with 83.3% to 100% for radioactive isotope with and without blue dye. Detection rates per patient for malignant lymph nodes for Magtrace and Tc-99m with and without blue dye were also comparable, with ranges of 91.7% to 100% and 90.8 to 100% respectively.

Future imaging studies may be effected by artefacts after Magtrace administration

3.4 Six studies noted future MRI of the injection and drainage sites being affected by artefacts for up to 5 years after Magtrace administration. Chapman et al. (2021) reported the outcome of MRI in 16 people after Magtrace injection. MRI image quality was impaired in all studies and

5 people had non-diagnostic MRI results. Krischer et al. (2017) evaluated MRI done 42 months after Magtrace injection in a sample of 25 people. Imaging interpretation was not restricted in 12 cases, impaired in 10 cases and not possible in 3 cases because of Magtrace residues. There is no longitudinal evidence to determine the effect of this on future diagnoses or treatment.

The main adverse event associated with using Magtrace is the incidence of skin staining

3.5 Warnberg et al. (2019) assessed skin staining up to 36 months postoperatively. People who had retro-areolar Magtrace injections were more likely to experience skin staining compared with those who had peritumoral Magtrace injection with 67.3% and 37.8% incidence reported at 3 weeks respectively. These figures decreased to 46.2% and 9.4% at 36 months. Karakatsanis et al. (2018) and Karakatsanis et al. (2016) reported that 97% and 95.6% of people having breast conserving surgery presented with skin staining. People having mastectomy rarely experienced skin staining. No evidence was identified which directly compared skin staining outcomes of Magtrace with blue dye. A small number of studies that investigated patient reported outcomes did not identify skin staining as a significant problem for patients. For full details of the adverse events, see section 5.3 of the assessment report.

Most studies reported intraoperative administration of Magtrace

3.6 Of the 36 included studies, 18 administered Magtrace intraoperatively or on the day of surgery, 7 injected Magtrace within 1 to 3 days of surgery, 5 included people injected more than 3 days before surgery and 6 did not report injection timing. Clinical experts report that Magtrace is usually injected at a routine clinical visit within 30 days of surgery rather than intraoperatively because this gives an improved visual and magnetic signal during surgery. Karakatsanis et al. (2017) note a higher tracer-specific sentinel lymph node detection rate with preoperative administration of Magtrace compared with perioperative administration,

with 95.3% and 86.0% respectively (p=0.031). From the available studies, there is no evidence to support significantly improved detection rate with earlier Magtrace administration.

Cost evidence

The company's cost modelling finds Magtrace and Sentimag to be cost saving compared with the dual technique

3.7 The company developed a de-novo cost-minimisation analysis from an NHS perspective, which compared Magtrace and Sentimag with the dual technique. The time horizon of the model is from the time the person attends the hospital for sentinel lymph node biopsy to the end of the procedure. The company received resource use data from 3 NHS trusts without on-site access to radiopharmacy or nuclear medicine. The data stated that 30 minutes of theatre time was lost for 20% of all sentinel lymph node biopsies because of delays in surgery or staff shortages. The company model also assumed that 1 additional sentinel lymph node biopsy procedure could be done each week with Magtrace. These 2 factors were included as opportunity costs in the model by measuring the number of sentinel lymph node biopsy procedures foregone, with only 50% of potential additional procedures being realised. The company's base case showed a cost saving of £105 per person using Magtrace and Sentimag. For full details of the cost evidence, see section 9 of the assessment report.

The company's cost model is appropriate, but the EAC made changes to the structure and parameters of the model

3.8 Although the EAC accepted most of the assumptions and parameters in the company's base-case analysis, the model was reformulated into a decision tree to improve the clarity of the clinical pathway and allow probabilistic sensitivity analysis. The EAC included 3 arms to represent the different timings and settings of the tracer injections. This included 1 arm for administration of the radioisotope and blue dye, 1 arm for

intraoperative Magtrace injection and 1 arm for Magtrace injected at a separate clinic. The model assumes that intraoperative Magtrace injection needs 20 minutes additional theatre time to allow drainage to the axilla. The EAC did not include opportunity costs associated with a lack of availability of radioisotope but did include an opportunity cost for 1 additional sentinel lymph node biopsy procedure each week was included. The EAC assumes that the opportunity costs are achieved in 50% of hospitals.

Magtrace and Sentimag is still cost saving compared with the dual technique with the EAC's changes to the model

3.9 When using the EAC's base-case model, Magtrace and Sentimag remains cost saving by £78.90 per person compared with the dual technique. The EAC did a sensitivity analysis to determine the effect of Magtrace injection timing on the cost of the sentinel lymph node biopsy procedure. When time for intraoperative Magtrace injection was more than 29 minutes, Magtrace was cost incurring. The EAC included additional scenario analyses that explored the cost impact of contraindications for Magtrace and effect on future MRI. Assuming 1% of people cannot have Magtrace because of contraindications and need the dual technique instead, Magtrace remains cost saving by £78.11 per person. If 1% of people in both arms need future MRI and 5% of those who have had Magtrace then have uninterpretable MRI and need gadolinium-enhanced MRI, Magtrace remains cost saving by £78.82.

Opportunity costs are the key cost driver

3.10 The key cost driver in the model was the opportunity cost associated with being able to do more sentinel lymph node biopsy procedures each week. Cost savings were dependent on the number of centres that can realise these opportunity costs in clinical practice. It was assumed that using Magtrace would lead to 1 additional sentinel lymph node biopsy per week because of improved management of operating lists. Based on centres performing 400 biopsies annually and 50% of centres realising the

opportunity costs, the threshold at which Magtrace became cost incurring was 0.42 additional procedures each week. If no additional procedures are realised, Magtrace would be cost incurring by £58.17 per procedure. If less than 21% of hospitals using Magtrace can do 1 additional sentinel lymph node biopsy procedure each week, Magtrace would be cost incurring.

4 Committee discussion

Clinical-effectiveness overview

Magtrace and Sentimag is as effective as standard care for locating sentinel lymph nodes for breast cancer

4.1 The committee noted that the clinical evidence showed Magtrace and Sentimag to be as effective as the dual technique for detecting sentinel lymph nodes, including malignant nodes. Other clinically relevant outcome measures such as the number of nodes retrieved per procedure and pain scores were deemed to be equivalent when compared with standard care. The committee considered the non-inferiority studies to be well conducted. The evidence base includes studies that have been done in a UK and NHS context. The committee concluded that the clinical evidence supports non-inferiority of Magtrace and Sentimag compared with current standard care.

Magtrace can be injected much earlier than the radioisotope used in standard care

4.2 The committee was advised that although Magtrace can be injected in the theatre 20 minutes before the start of a sentinel lymph node biopsy procedure, injection is more commonly done at a standard clinical appointment up to 30 days before surgery to give a better detection signal. The clinical experts highlighted the advantages of earlier injection in terms of improved theatre scheduling and convenience. The company explained that the longest published time period for injection before the

procedure is 46 days. An ongoing study is exploring the earliest appropriate time point for Magtrace injection before sentinel lymph node biopsy. The committee accepted the maximum time period for injecting Magtrace of 30 days stated in the manufacturer's information for use and concluded that Magtrace allows for significantly earlier injection than the radioisotope used in standard practice.

Side effects and adverse events

Future MRI can be affected after using Magtrace, so Magtrace should be carefully considered for people who are likely to need follow-up MRI studies

4.3 The committee acknowledged that future MRI of the breast could be affected by residual Magtrace that remains in the body after a sentinel lymph node biopsy procedure. The EAC explained that the clinical evidence shows that follow-up MRI can be impaired for as long as 5 years after the procedure. There is 1 study that shows that a mammography was also affected after an injection of Magtrace. The clinical experts highlighted that follow-up MRI studies are becoming more common, particularly in the following groups: young women under the age of 40, people with occult cancers and people with dense breasts. Consensus from clinical experts is that Magtrace would not be advised for people who are likely to need MRI within 3 months after sentinel lymph node biopsy. Contrast enhanced digital mammography or gadolinium-enhanced MRI could be used as alternative imaging techniques for these people, but they are associated with higher radiation or higher costs. The committee queried whether residual Magtrace would remain localised in lymph nodes in the breasts or whether it would spread throughout the body over time and affect imaging of other areas. The company clarified that this would remain residually in the breast tissue and that any particles outside of this would be engulfed by macrophages and excreted. The clinical experts stated that issues with mammography had not been identified after 3 years of using Magtrace. The committee concluded that future imaging is an important issue for clinicians to consider, so Magtrace should be

carefully considered for people who are likely to need follow-up MRI studies after having a sentinel lymph node biopsy procedure.

Magtrace and Sentimag is safe to use, but skin staining is a common adverse event

4.4 The committee noted that the clinical evidence identified skin staining as the most common adverse event associated with Magtrace. The patient expert commented that skin staining was not a key issue, and that people find the brown staining is preferable to the blue staining associated with blue dye. The company provided data on patient experience, stating that 90% of people did not worry about skin staining caused by Magtrace. The clinical experts commented that from their experience, the size of the breasts and method of injection affects the rate of staining. A deeper peritumoral breast injection causes less staining, and this has been adopted by clinicians in practice. The committee concluded that skin staining is also an issue with the dual technique comparator and is not a significant concern for people having the injection.

Other patient benefits or issues

People should have information made available to them before having sentinel lymph node biopsy with Magtrace and Sentimag

4.5 The patient expert explained that people can be quite worried before having a sentinel lymph node biopsy procedure because of the need for radioactive material to be injected into the body and the risk of anaphylaxis associated with blue dye. The patient expert highlighted that these risks do not exist with Magtrace, but there are other considerations which are important for people having the procedure. Some people with breast cancer will have yearly follow-up imaging, and these could be affected by artefacts because of residual Magtrace. People may also experience skin staining and pass darker coloured urine after having Magtrace injected. Therefore, the patient expert suggested that people would prefer to have information before having sentinel lymph node

biopsy with Magtrace and Sentimag. The committee agreed with the patient expert and concluded that it is important for people to be appropriately informed of the adverse events associated with the technology before the procedure.

Cost modelling

If the opportunity costs are realised, Magtrace and Sentimag is cost saving compared with standard care

4.6 The committee considered that the EAC base-case model was appropriate for decision making. They agreed with the parameters included in the model but were uncertain about whether the opportunity costs associated with additional sentinel lymph node biopsy procedures would be realised in practice. Opportunity costs were identified as the key cost driver for Magtrace and Sentimag. In the EAC's base-case analysis, Magtrace and Sentimag is cost saving by £78.90 per procedure, but cost incurring by £58.16 per procedure when opportunity costs are excluded from the model.

NHS considerations overview

The efficiency gains from using Magtrace will depend on where the procedure is done

4.7 The EAC highlighted that there are currently 3 scenarios to consider when looking at the different hospitals in which sentinel lymph node biopsies are done. The differentiating factor is whether radiopharmacy and nuclear medicine facilities exist on the same site as where the sentinel lymph node biopsy is being done. Some hospitals can produce the radioisotope injection on the same site as the procedure, whereas other hospitals need the radioisotope to be transported to their site for injection before the procedures. The third scenario needs people to travel to 1 site for the radioisotope injection, then a different site where the biopsy is done. Clinical experts work at centres with and without access to radiopharmacy and explained there was general agreement that hospitals with limited or

no access to radiopharmacy and nuclear medicine would be most likely to realise the opportunity costs which make Magtrace and Sentimag cost saving. The EAC highlighted that 55.9% of centres performing SLNB procedures have radiopharmacy and nuclear medicine facilities on site or are already using Magtrace and Sentimag, and would therefore be less likely to realise the opportunity costs included in the economic model. The committee concluded that hospitals without access to on-site radiopharmacy and nuclear medicine are likely to benefit from Magtrace because of the efficiency gains related to theatre scheduling and reduced supply chain issues. The committee acknowledged that Magtrace and Sentimag could also be an option for some hospitals with on-site radiopharmacy, who still have challenges with theatre scheduling or experience delays.

Device compatibility

The Sentimag probe needs regular recalibration and is similar to the gamma probes used in current practice

4.8 The company explained that the Sentimag probe has a 5-year lifespan and is supplied with a calibration cap which is used to calibrate the device each day before starting surgery. This takes about 20 seconds and is logged. During the procedure, the probe also needs to be reset each time it is moved out of the operation field which takes around 3 seconds. In the event of an issue with the Sentimag probe, there is a contact procedure in place to report this to the company. The committee was advised that the gamma probes used in current practice needs similar calibration. The lifespan of a gamma probe is around 2 years. The clinical experts did not consider calibration of the Sentimag probe to cause any inconvenience to clinicians. They also noted that the gamma probe was smaller and had a softer feel than the Sentimag probe. The committee concluded that the Sentimag probe is broadly similar to the gamma probes used in current practice.

Training

There is a learning curve associated with using Magtrace and Sentimag

4.9 The company commented that a minimum of 5 procedures were needed to build familiarity with Magtrace and Sentimag. The company suggested that representatives from the manufacturer are usually present for the first few procedures to support clinicians. Online resources and surgical footage are also available, as well as an annual retraining session for sites who regularly use the technology. The clinical experts stated that a learning curve of 50 procedures or 2 years is associated with Magtrace. The committee concluded that a learning curve is associated with using Magtrace and Sentimag, and the company has processes in place to support clinicians during this time period.

Further research

Further data collection on the number of sentinel lymph node biopsies being done would help to understand the efficiency gains associated with Magtrace and Sentimag

4.10 The committee stated that further data collection was needed to monitor the difference in the number of sentinel lymph node biopsies being done in each hospital once Magtrace and Sentimag have been adopted into clinical practice. The realisation of the efficiency gains and opportunity costs is defined as being able to do additional procedures each week with Magtrace. Adverse events should also be reported and impact on future imaging should be monitored.

5 Committee members and NICE project team

Committee members

This topic was considered by NICE's medical technologies advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of the medical technologies advisory committee, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each medical technologies guidance topic is assigned to a team consisting of 1 or more health technology assessment analysts (who act as technical leads for the topic), a health technology assessment adviser and a project manager.

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