National Institute for Health and Clinical Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

Intraoperative tests (RD-100i OSNA system and Metasin test) for detecting sentinel lymph node metastases in breast cancer

This overview summarises the key issues for the Diagnostics Advisory Committee's consideration. It includes a brief description of the topic, a description of the analytical structure and model, a discussion of the analytical difficulties, and a brief summary of the results. It is not a complete summary of the diagnostics assessment report, and it is assumed that the reader is familiar with that document. This overview contains sections from the original scope and the diagnostics assessment report, as well as referring to specific sections of these documents.

1 Background

1.1 Introduction

The RD-100I OSNA system (Sysmex UK Ltd.) was selected by the Medical Technologies Advisory Committee (MTAC) for the Diagnostics Assessment Programme to develop recommendations on its use in the NHS. One other intraoperative test, the Metasin test (Princess Alexandra Hospital, Harlow), was identified during the scoping phase and included in the assessment as an alternative technology.

The purpose of this assessment is to evaluate the clinical and cost effectiveness of using these two intraoperative tests to detect metastases in the sentinel lymph nodes of patients undergoing breast cancer surgery. Provisional recommendations on the use of these technologies in the NHS will

be formulated by the Diagnostics Advisory Committee at the Committee meeting on 6 February 2013.

1.2 The Condition(s)

Breast cancer is one of the most common cancers for women in England and Wales, with about 46,000 new cases diagnosed and 10,900 deaths recorded each year. Around one in nine women develop breast cancer at some stage in their life. Most breast cancers develop in women over the age of 50, but they can also occur in younger women, and in rare cases, men. In men, there are around 260 cases of breast cancer diagnosed and 68 deaths in England and Wales each year. Of new cases in women, around 11,000 require additional surgery each year to manage the spread of breast cancer to the lymph nodes. A small proportion of new cases in women and men are diagnosed in the advanced stages, when the tumour has spread significantly within the breast or to other organs of the body. In addition, a number of women who have been previously treated with curative intent subsequently develop either a local recurrence or metastases.

The main ways in which breast cancer can spread are by local spread to nearby tissues, or by regional or distant spread through the circulatory system or through the lymphatic system. Of particular relevance for this evaluation is the spread of breast cancer through the lymphatic system, which occurs when cancer cells become detached from the main breast tumour and are usually carried in the lymph to the axillary (armpit) lymph nodes. The first lymph nodes to which cancer is likely to spread from the primary breast tumour are known as the sentinel lymph nodes. The cancer cells can grow in the lymph node(s) and cause swelling, although not all metastatic lymph nodes are morphologically abnormal. Lymph nodes are often used to stage cancer (extent of disease) because their biological function is to monitor lymph which carries waste products from cells such as bacteria and viruses. Lymph nodes contain various immune system cells which trigger an immune response if a foreign substance detected and therefore, they are one of the earliest sites of spread for cancer.

The treatment of breast cancer can cause many side-effects including significant pain, persistent fatigue, a reduction in fertility and osteoporosis. Emotionally, a diagnosis of breast cancer and subsequent treatment can cause long-term anxiety, depression and isolation in both the individual and their relatives. Hair loss from cancer chemotherapy and radiotherapy and changes to the body from a mastectomy for example, are associated with social stigma, and can significantly impact on quality of life and reduce self-esteem.

One side-effect of lymph node surgery is lymphoedema, which is more likely after axillary lymph node dissection than sentinel lymph node biopsy. The most common symptom is swelling of the arm, hands and fingers on the side of the body that was operated on, which can persist for months or years. Swelling can also affect the breast, chest and shoulder. Lymphoedema does not affect all individuals who undergo lymph node surgery but in some individuals it can develop soon after treatment or years later precipitated by inflammation, infection and scarring.

Axillary lymph node dissections result in minor and major complications for 80% of women. Major complications include a 21% incidence of arm lymphoedema (general swelling), a 22% incidence of seromas (pockets of fluid under the skin) and a 14% infection rate. Other complications can include pain, limited mobility, numbness and sensory loss. Sentinel lymph node biopsy is associated with a 7% incidence of lymphoedema, a 7% incidence of seroma and a 2% infection rate.

1.3 Diagnostic and care pathways

NICE Clinical Guideline 80 ‘Early and locally advanced breast cancer: Diagnosis and treatment’ outlines the current care pathway.

This guideline recommends that ultrasound evaluation of the axilla (armpit) is performed for all patients being investigated for early invasive breast cancer. If

morphologically abnormal lymph nodes are identified, ultrasound-guided needle sampling is offered pre-operatively.

For patients who have no evidence of abnormal lymph nodes on ultrasound images or aspiration cytodiagnosis, minimal surgery is performed to stage the axilla at the same time as breast surgery to confirm that the cancer has not spread. Sentinel lymph node biopsy (SLNB) is the preferred technique in which the first lymph node(s) is removed to see if the cancer has spread from the original site. A radioactive solution and a blue dye are injected into the breast before surgery to help identify the sentinel lymph node(s) during surgery. Identifying the sentinel lymph node(s) during surgery can be difficult and there is a widely-recognised learning curve for performing SLNB. The Royal College of Surgeons, Cardiff university and the Department of Health established a surgical training programme (New Start) for performing SNLB and set standards for surgeons to achieve; greater than 90% localisation rate (ability to locate sentinel node(s)) and less than 10% false negative rate. One study reported that the localisation rate achieved for SNLB was around 98%.

The fresh biopsy tissue from SLNB is currently analysed by post-operative histopathology, which involves slicing the lymph node into very thin sections. These tissue sections are then stained and viewed by a consultant histopathologist to identify any abnormalities in the tissue. There is a risk of tissue allocation bias (TAB) in histopathology because only a few sections of the lymph node are examined and metastatic foci are not evenly distributed through a lymph node so the examined sections of the lymph node may not be the parts of the lymph node that contain the metastatic foci. It is not clear how many sections from a lymph node are currently analysed in routine NHS practice. The time to receive results from histopathology is usually between 5 and 15 working days in the NHS. If the results are positive, the patient will undergo a second operation to remove the remaining lymph nodes which may be technically more challenging than performing the axillary dissection as part of the initial surgery.

Two pathological methods that can be used intraoperatively are frozen section and touch imprint cytology. Frozen section involves a section of the lymph node being snap-frozen, stained and sliced before being viewed by a consultant histopathologist. Touch imprint cytology involves the lymph node being sliced and the cut surface of the node imprinted on to a slide, which is then stained and viewed by a consultant histopathologist or cytopathologist. Both intraoperative pathological methods can be used to help determine if axillary lymph node dissection is to be performed at the same time as the first surgery. Post-operative histopathology analysis is usually carried out on the remaining tissue to reduce the risk of a false negative result. However, in practice, these intraoperative methods are rarely used because they have low accuracy and pathology resources are very limited within the NHS.

The RD100i OSNA system and the Metasin test can analyse the whole lymph node so there is no risk of tissue allocation bias and post-operative analysis using histopathology may not be necessary. This is decided by clinical judgement because no histopathology can be performed if the whole lymph node is used.

Individuals who have macrometastases or micrometastases detected in their sentinel lymph node are regarded as lymph node-positive, and axillary lymph node dissection is usually performed. Individuals who have isolated tumour cells in their sentinel lymph node are regarded as lymph node-negative and will not receive axillary lymph node dissection.

All information on the sentinel nodes, axillary nodes and primary breast tumour is typically discussed at a multidisciplinary team (MDT) meeting to determine the appropriate systemic adjuvant therapy. NICE Clinical guideline 80 states that adjuvant chemotherapy and radiotherapy should be started as soon as clinically possible within 31 days of completion of surgery in patients with early breast cancer having these treatments. The use of intraoperative molecular tests and a potential consequent reduction in the number of second surgeries performed may result in patients starting adjuvant therapy earlier.

1.4 The population

The population considered in this assessment is individuals with invasive breast cancer who undergo a sentinel lymph node biopsy.

2 The technologies

2.1 RD-100i OSNA system

The RD-100i OSNA system analyses and amplifies mRNA from solubilised biopsy samples of sentinel lymph node tissue. It detects the level of expression of the CK19 gene, an epithelial marker associated with breast cancer. CK19 is normally not present in healthy lymph node tissue. The OSNA technology involves the homogenisation of sentinel lymph node tissue followed by analysis of the CK19 mRNA using the process of reverse transcription loop mediated isothermal amplification (RT-LAMP) on the automated analyser, RD100i. OSNA does not require the mRNA to be extracted and purified from the tissue before being analysed. The expression level of CK19 mRNA correlates with the size of the metastatic foci. Since the metastatic foci may not be evenly distributed throughout the node, the system provides more accurate results if more of the node is analysed because there is less risk of tissue allocation bias (sample bias). The result is most accurate if the entire node is used, but then no follow-up histopathology is possible. The system can be used with half of the lymph node (one piece or alternate slices), allowing for the possibility of follow-up histopathology but potentially decreasing the accuracy of the results due to the increased risk of tissue allocation bias. The time to results is dependent on the number of lymph nodes analysed, but the test takes approximately 30 - 45 minutes. The OSNA test result is expressed both quantitatively and qualitatively; - for lymph node negative test results, + (> 250 copies of CK19 m RNA / µl) for lymph nodes with a micro-metastatic tumour burden and ++ (>5000 copies of CK19 m RNA / µl) for lymph nodes with a macro-metastatic tumour burden. The analyser amplifies and detects the CK19 mRNA by using 6 different primers which have been specifically designed to avoid the amplification of CK19

pseudogenes or their transcripts; amplification of these would lead to false positive results. Undesired amplification of genomic DNA is avoided by precipitation of DNA at low pH during sample preparation and the isothermal reaction temperature of 65°C.

The manufacturer estimates that 1% of breast tumours do not express CK19 mRNA and therefore, if cancer spreads to the lymph nodes from these tumours, CK19 mRNA will not be detected even though the lymph nodes are metastatic. Pre-screening of tumour biopsies for CK19 expression could be carried out before using the RD100i OSNA test to reduce the small risk of false negative results for metastatic sentinel lymph nodes.

2.2 Metasin test

The Metasin test is an intraoperative molecular test developed within the NHS at the Princess Alexandra Hospital in Harlow, Essex. The test has similarities to a discontinued commercial test (Veridex GeneSearch BLNA assay) and uses the technique of quantitative reverse transcriptase PCR (qRT-PCR) to detect 2 predictive markers of metastases, CK19 and mammaglobin. Mammaglobin is expressed mainly by breast epithelial cells and high levels of mammaglobin are associated with breast cancer. A reference gene, PBGD, is used to confirm the validity of the mRNA used in the test and two other controls, positive and negative, are also included. The test uses reagents that can be purchased from Roche and Qiagen and can be used on any platform (PCR machine). This in-house test differs from the discontinued commercial test by using distinctly different and unique primer-probe combinations to detect the CK19 and mammaglobin genes. The test is reported to take 26 minutes to results after 6-10 minutes for extracting and purifying mRNA from the tissue. This Metasin test is currently used in the NHS as an in-house test to analyse half of the lymph node. The results are confirmed by follow-up histopathology. The Metasin test could also be used as a replacement test for

postoperative histopathology. Recently, the Metasin test received a CE mark and will be available from the manufacturer, TIB MOLBIOL (Berlin).

Pre-screening of tumour biopsies for CK19 mRNA and mammaglobin mRNA expression may be carried out before using the Metasin test because like the CK19 biomarker, mammaglobin is not expressed in all breast tumours. The proportion of breast cancer tumours that do not express mammaglobin mRNA is not known.

2.3 The Comparator

The comparator used in this assessment is post-operative histopathology alone.

This is the usual approach currently used in the NHS where the sentinel lymph node(s) is fixed in paraffin blocks, sliced very thinly to produce sections which are mounted on slides, stained and then examined under a microscope by a consultant histopathologist. The time to receive results from histopathology is usually between 5 and 15 working days in the NHS. Individuals who have macrometastases (defined as tumour deposits where at least one dimension is above 2mm) or micrometastases (tumour deposits which are only discernible microscopically, measure greater than 0.2 mm but no dimension greater than 2mm) detected in their sentinel lymph node are regarded as lymph node- positive, and axillary lymph node dissection will be performed on them. Individuals who have isolated tumour cells in their sentinel lymph node are regarded as lymph node-negative and will not receive axillary lymph node dissection.

The wait for histopathology test results can cause anxiety for patients and can also lead to the patient undergoing a second surgery to remove all of the axillary lymph nodes if the test result is positive. This second surgery can be more difficult and result in a higher risk of complications because the second surgery will involve operating on the same area of the breast and armpit as in the first surgery to remove the breast tumour and take a lymph node biopsy.

For this reason, intraoperative tests that avoid the need to wait for results have been developed.

There are a number of levels of histopathology that can be performed. One level histopathology involves the examination of one section of the lymph node and five level histopathology involves the examination of five sections of the lymph node. The level of histopathology used may affect the accuracy of histopathology because of risk of tissue allocation bias, in which the metastases may be missed because it is not situated in the section of the lymph node which is examined. There is also uncertainty in the accuracy of histopathology associated with the different staining techniques used, the thickness of the section examined and the experience of the pathologist reading the section slides.

3 The evidence

3.1 Clinical effectiveness

The External Assessment Group conducted a systematic review of the evidence on the clinical effectiveness of the two intraoperative tests for sentinel lymph node metastases. Supplementary evidence provided by the sponsors of the technologies is also included in the diagnostics assessment report.

Details of the systematic review can be found starting on page 49 of the diagnostics assessment report. Studies were included if they appeared relevant to the outcomes listed in the decision problem:

- Diagnostic test accuracy
- Test failure rate
- Discordant test results
- Time to test result
- Duration of anaesthesia/time in operating theatre

Clinical outcomes:

- Patient anxiety associated with waiting time for result and not knowing the extent of surgery prior to operation
- Number of repeat operations (except for re-excision of positive margins)
- Time to start and nature of adjuvant therapy
- Morbidity and mortality from biopsies, axillary dissections, first and second operations and treatment of cancer
- Adverse events from false test results including patient distress and sequelae

No study was excluded on the basis of intervention, population, comparator or outcome, provided it appeared relevant to the scope of the evaluation.

3.2 RD100i OSNA system

Sixteen studies that investigated the performance of the RD-100i OSNA system in detecting metastases in the sentinel or axillary lymph nodes were included in the systematic review although two of these studies reported the same trial. Fourteen of these sixteen studies reported test accuracy as an outcome and two of these fourteen studies also reported time to analysis. An additional observational study reported time to analysis as an outcome alone. One other study reported time in operating theatre, days in hospital, costs and post-operative complications. No data were found for the clinical outcomes, patient anxiety and number of repeat operations.

Eleven of the sixteen studies were a single-gate design in which individuals with unknown disease status were assessed by both the intraoperative test and the reference standard, histopathology, in order to compare the results of the two tests and confirm diagnosis. The remaining studies comprised four cohort studies and one observational study. In the cohort studies, different patient samples were utilised for each test which enabled whole node analysis by the RD-100i OSNA test.

There is heterogeneity across studies in their definitions of reference standard, histopathology. Three studies reported using five level

histopathological analysis (examining five sections of node) to detect metastases in the node. Two other studies used five level histopathological analysis during the validation phase of the study and one level histopathological analysis (examines one section of node) during routine use. Five studies reported using three level histopathological analysis (examine three sections of node) and one other study reported using one level histopathological analysis. The level of histopathological analysis used in the remaining studies is unclear. These varying levels of histopathological analyses may impact the accuracy of histopathology because the five level analysis may be more likely to detect micrometastases than one level analysis. In addition, some studies will not reflect current NHS practice for histopathological analysis depending on the level of analysis that is used.

In all of the studies there was a lack of detail on patient recruitment and patient characteristics so the risk of bias in the studies is unclear. Spectrum bias may occur if the severity of the cancer is greater in one study population than another because it is more likely that a test will detect metastases in individuals with severe disease and therefore, will appear to have a higher sensitivity. In addition, study populations may vary depending on the upstream diagnostic pathway because some clinics may be better at detecting metastases with fine needle aspiration cytology (FNAC) so an SLNB would not be needed in some cases. This could result in a patient population with higher levels of micrometastases than macrometastases receiving SLNB and therefore, the sensitivity of the intraoperative test or histopathology may appear lower in this population. There was also a lack of information on sampling methods so there was no evidence of sample replicates and reproducibility for molecular analysis.

The assessment of test accuracy for the RD-100i OSNA system was hindered by tissue allocation bias (TAB) and, by comparison with an inconsistent reference standard (different levels of histopathology). In some studies, discordant samples were further analysed (by extensive histopathology, molecular analysis or Western blotting) and attributed to TAB. In these cases,

the test accuracy analyses could be adjusted by excluding the data from the discordant samples. No adjustment could be made for the varying levels of histopathology used in the studies.

The test accuracy and level of histopathology used in each study are presented in tables 1 – 6. The tables enable an assessment of the number of discordant samples. Often, more than one sentinel node is removed from a patient so the results from some of the studies can be presented by patient, by individual node or both. Some of the results are also adjusted for TAB.

Table 1. Results for patients before TAB

First author	Patient (n)	Histology	H+/O+	H-/O-	H+/O-	H-/O+	% Sensitivity (95% CI) OSNA	% Specificity (95% CI) OSNA
OSNA								
Choi (SLN)[55]	199	3 level	27	157	9	6	77.8 (60-90)	96.3 (92-99)
Frere Belda (SLN)[60]	233	5 level	33	168	9	23	78.6 (63.1–89.7)	88.0 (82.4–92.3)
Khaddage (SLN)[59]	46	5 level	8	35	2	1	80.0 (44.4-97.5)[a]	97.2 (85.5-99.9)[a]
Khaddage (SLN)[59]	197	1 level	25	155	0	17	100 (88.7-100)[b]	90.1 (84.6-94.1)[b]
Tamaki (SLN) [65]	417	1 level	58	315	8	36	87.9 (77.5-94.6)[b]	89.7 (86.1-92.7)[b]
Bernet Vegue (Non SLN)[53]	55	1 level	6	26	0	23	100 (41.4-100)[b]	53.1 (38.3-67.5)[b]

NR – not reported. H+ and H- refer to positive and negative results for histology, O+ and O- refer to positive and negative results for OSNA, [a]CI calculated by PenTAG . [b] CI, sensitivity and specificity calculated by PenTAG

Table 2. Results for patients after TAB (SLN only)

First author	Patient (n)	Histology	H+/O+	H-/O-	H+/O-	H-/O+	% Sensitivity (95% CI) OSNA	% Specificity (95% CI) OSNA
OSNA								
Frere Belda [60]	215	5 level	32	168	3	12	91.4 (76.9–98.2)	93.3 (88.6–96.6)
Khaddage[59]	46	5 level	NR	NR	NR	NR	100	97.2
Snook[63]	194	5 level	44	137	5	8	89.8 (77.8-96.6)[a]	94.5 (89.4-97.6)[a]

NR – not reported. H+ and H- refer to positive and negative results for histology, O+ and O- refer to positive and negative results for OSNA, [a]CI calculated by PenTAG . [b] CI, sensitivity and specificity calculated by PenTAG

Table 3. Results for SLN before TAB

First author	Sample no	Histology	H+/O+	H-/O-	H+/O-	H-/O+	% Sensitivity (95% CI) OSNA	% Specificity (95% CI) OSNA
OSNA								
Feldman[56]	1044	3 level	107	868	31	38	77.5 (69.7-84.2)	95.8 (94.3-97.0)
Frere Belda[60]	503	5 level	51	413	12	27	80.9 (69.0–89.8)	93.9 (91.2–96.0)
Khaddage[59]	80	5 level	15	62	2	1	88.2 (63.6-98.5)[a]	98.4 (91.5-100)[a]
Tsujimoto[66]	81	3 level	14	64	2	1	87.5 (61.7-98.4)[b]	98.5 (91.7-100)[b]

NR – not reported. H+ and H- refer to positive and negative results for histology, O+ and O- refer to positive and negative results for OSNA, [a]CI calculated by PenTAG . [b] CI, sensitivity and specificity calculated by PenTAG

Table 4. Results for SLN after TAB

First author	Sample no	Histology level	H+/O+	H-/O-	H+/O-	H-/O+	% Sensitivity (95% CI) OSNA	% Specificity (95% CI) OSNA
OSNA								
Feldman	1018	3 level	NR	NR	NR	NR	82.7	97.7
Frere Belda	481	5 level	51	413	5	12	91.1 (80.3–97.1)	97.2 (95.1–98.6)
Khaddage	78	5 level	NR	NR	NR	NR	100	98.4
Snook	395	5 level	66	313	6	10	91.7 (82.7-96.9)[a]	96.9 (94.4-98.5)[a]

NR – not reported. H+ and H- refer to positive and negative results for histology, O+ and O- refer to positive and negative results for OSNA, [a]CI calculated by PenTAG . [b] CI, sensitivity and specificity calculated by PenTAG

Table 5. Results for ALN before TAB

Reference	Sample no	Histology level	H+/O+	H-/O-	H+/O-	H-/O+	% Sensitivity (95% CI) OSNA	% Specificity (95% CI) OSNA
OSNA								
Schem	343 ALN	5 level	104	211	2	26	98.1 (93.4-99.8)[a]	91.7 (84.3-92.7)[c]
Tamaki 2009 a	124 ALN	Sectioned at 0.2mm intervals	19	101	1	3	95 (75.1-99.9)	97.1 (91.8-99.4)
Tamaki 2009 b	450 ALN	3 level	70	348	10	22	87.5 (78.2-93.8)	94.1 (91.0-96.3)
Tsujimoto 2007	325 ALN/SLN	3 level	43	276	2	4	95.6 (84.9-99.5)[b]	98.6 (96.4-99.6)[b]
Vegue	567 ALN	1 level	6	522	0	39	100 (60.7-100)[b]	93.0 (90.6-95.0)[b]
Visser	346 ALN	3 level	61	267	3	15	95.3 (84.9 – 99.5)[a]	94.7 (96.4-99.6)[a]

NR – not reported. H+ and H- refer to positive and negative results for histology, O+ and O- refer to positive and negative results for OSNA, [a]CI calculated by PenTAG . [b] CI, sensitivity and specificity calculated by PenTAG

Table 6. Results for ALN after TAB

Reference	Sample no	Histology level	H+/O+	H-/O-	H+/O-	H-/O+	% Sensitivity (95% CI) OSNA	% Specificity (95% CI) OSNA
OSNA								
Schem	330 ALN	5 level	NR	NR	NR	NR	100	95.6
Tamaki 2009	450 ALN	Sectioned at 0.2mm intervals	71	348	10	21	87.7 (78.5-93.9)	94.3% (95.3 – 98.8)
Visser	339 ALN	3 level	NR	NR	NR	NR	95.3	97.1

NR – not reported. H+ and H- refer to positive and negative results for histology, O+ and O- refer to positive and negative results for OSNA, [a]CI calculated by PenTAG, [b] CI, sensitivity and specificity calculated by PenTAG

The range of estimates for sensitivity and specificity from the studies are shown in table 7 and are presented by patient or by individual node and, before or after TAB adjustment.

Table 7. Overall range of central estimates for sensitivity and specificity

	Sensitivity (%)	Specificity (%)
Patients before TAB (OSNA - SLN)	77.8 - 80.0	88.0 - 97.2
Patients after TAB (OSNA-SLN)	89.8 - 100	93.3 - 97.2
SLN before TAB (OSNA)	77.5 - 88.2	93.9 - 98.4
SLN after TAB (OSNA)	82.7 - 100	96.9 - 98.4
ALN before TAB (OSNA)	87.5 - 98.1	91.7 - 97.1
ALN after TAB (OSNA)	87.7 - 100	94.3 – 97.1

The EAG performed meta-analysis (bivariate method) of diagnostic test accuracy from studies which investigated the performance of the RD-100i OSNA. Only studies which reported the numbers of true positives, true negatives, false negatives and false positives in the text (or sufficient data for these test statistics to be calculated) were included in the meta-analysis. The results of this meta-analysis are shown in table 8.

Table 8. Meta-analysis of OSNA test accuracy

Sample type	Adjustment for TAB	Number of studies	Sensitivity (95% CI)	Specificity (95% CI)
Patient	No	5	0.845 (0.747–0.910)	0.918 (0.878-0.946)
Patient	Yes	3	0.913 (0.836–0.956)	0.942 (0.912-0.962)
SLN	No	4	0.799 (0.742–0.846)	0.955 (0.941-0.965)
SLN	Yes	5	0.890 (0.821–0.934)	0.975 (0.966-0.982)
ALN	No	6	0.951 (0.900–0.976)	0.949 (0.912-0.969)
ALN	Yes	4	0.965 (0.873–0.991)	0.962 (0.934-0.978)

The time taken for analysis of the lymph node by the RD-100i OSNA system across the studies is presented in table 9.

Table 9. Time to analysis

Nodes (n)	Median time to analysis, min							
	OSNA							
	Bernet [a,b] (range)	Choi [a,c]	Feldman [d]	Frere Belda [e]	Godey [a,f] (std)	Khadd -age [g]	Snook [h] (range)	Tsujimoto [i]
1	39.6 (26-70)	35.2	33.0	33	32.9 (4.9)		32 (22-97)	<30 min
2		44.8	39.6	40	36.4 (4.5)	37	42 (30-73)	
3		50.4	45.2	48	41.6 (5.2)		51 (38-73)	
4		50.0		54	48.5 (8.7)		62 (46-90)	

[a] mean, [b] time from receipt of node to report, [c]turnaround time, [d] interquartile mean from homogenisation to analyser output, [e] time needed for OSNA assay, [f] time required for results, [g] time from receipt of node to the result, [h] from node preparation to end of analysis, [i] all OSNA assays completed in under 30 min.

The estimates for time to analysis from the studies ranged from less than 30 minutes to 39.6 minutes for one node and, increased by 5–10 minutes per additional node analysed. One study reported that the longest and most variable time period corresponded to transporting the node from the operating room to the pathology department. The least variable time period corresponded to the homogenisation of tissue, preparation of the diluted sample and PCR amplification.

One other study compared the difference in operating time, days in hospital and number of post-operative complications between the use of histopathology and the use of RD-100i OSNA to analyse lymph node samples. The aim of this study was to analyse the economic costs of intraoperative OSNA testing compared to postoperative histopathology. The results are presented in tables 10 and 11.

Table 10. Effect of lymph node testing using OSNA on time in operating theatre and mean days in hospital.

	Mean Intervention Time, mins (sd)			Mean Days in Hospital (sd)		
	1st	2nd	Total	1st	2nd	Total
Histolog	57.11	78.33	78 (48.02)	1.8 (2.04)	2.41	2.44(0.78
OSNA	62.14	NA	62.14(21.93	1.54(0.78)	NA	1.54(0.78
	Absolute no. Intervention Time			Absolute no. Days in Hospital		
	1st	2nd	Total	1st	2nd	Total
Histolog	2570	940	3510	81	29	110
OSNA	2175	NA	2175	54	NA	54

Table 11. Effect of lymph node testing using OSNA on the number of post-operative complications.

	Complications in 1st intervention			Complications in 2nd intervention		
	None	Minor	Major	None	Minor	Major
Histology	28	17	0	4	8	0
OSNA	24	10	1	N/A	N/A	N/A

Overall, the patients undergoing intraoperative lymph node testing using the OSNA system experienced fewer post operative complications than those undergoing post-operative histopathology analysis, although the only major complication occurred in the OSNA group (no further details of the major complication were reported). These results should be interpreted with caution because this study was conducted in Spain and the findings may not be generalisable to the UK owing to differences in clinical practice.

3.3 Metasin test

Two draft unpublished studies which investigated the performance of the Metasin test in detecting metastases in the lymph nodes of breast cancer patients, were included in the systematic review.

[redacted] and one of the studies also reported time to analysis.

[redacted] One study reported using three level histopathological analysis (examining three sections of node) as the reference standard, to detect metastases in the nodes. [redacted]

[redacted] Similar to the studies investigating the performance of the RD-100i OSNA system, one of the main issues with assessing the test accuracy of the Metasin test was TAB. [redacted]. A study by Sundaresan et al. reported that 56 patients out of a total of 1265 patients received discordant results; 36 patients received a positive Metasin test and negative histopathology and, 20 patients received a negative Metasin test and positive histopathology. The authors considered that TAB was responsible for the discordant results although no evidence or analysis was presented in the study.

The test accuracy, level of histopathology and number of discordant samples in each study are presented by patient in table 12 and by node in table 13. These results are taken from unpublished, non-peer reviewed papers in draft form and therefore, should be interpreted with caution.

Table 12. Results by patient with no TAB adjustment

First author	Patient (n)	Histology	H+/O+	H-/O-	H+/O-	H-/O+	% Sensitivity (95% CI)	% Specificity (95% CI)
Metasin								
[redacted]								
Sundaresan[41]	1265	3 level	249	940	20	36	92 (89-95)[a]	97 (95-97)[a]

NR – not reported. H+ and H- refer to positive and negative results for histology, O+ and O- refer to positive and negative results for OSNA, [a]CI calculated by PenTAG . [b] CI, sensitivity and specificity calculated by PenTAG

Table 13. Results by node with no TAB adjustment

First author	Sample no	Histology	H+/O+	H-/O-	H+/O-	H-/O+	% Sensitivity (95% CI)	% Specificity (95% CI)
Metasin								
[redacted]								
Sundaresan[41]	2279	3 level	341	1770	35	60	93 (87.3-93.4)[a,c]	97 (95.8-97.5)[a]

NR – not reported. H+ and H- refer to positive and negative results for histology, O+ and O- refer to positive and negative results for OSNA, [a]CI calculated by PenTAG . [b] CI, sensitivity and specificity calculated by PenTAG

[redacted]

[redacted] No meta-analysis was performed by the EAG for the two studies investigating the performance of the Metasin test because at least four studies are needed in order to use the bivariate method of meta-analysis. The accuracy values from Sundaresan et al. (unpublished) were used in the cost-effectiveness analyses.

3.4 Costs and cost effectiveness

3.4.1 Systematic review of cost effectiveness evidence

Two studies were identified that were considered relevant for the systematic review on the cost effectiveness of intraoperative tests for the detection of sentinel lymph node metastases. Both studies were single centre observational studies that compared an intraoperative test with histopathology for assessing SLNB. One of the studies was based in the UK and assessed the GeneSearch BLNA assay and, the other study was conducted in Spain and evaluated the RD-100i OSNA system. Both studies found their respective intraoperative tests to be cost-effective compared to histopathology, with both assays being cost-saving whilst reducing theatre time and length of hospital stay. Neither study considered outcomes beyond the diagnostic phase. The UK study provided evidence on resource use and costs of intraoperative testing in the UK but evaluated the GeneSearch BLNA assay which has been withdrawn from the market. The Metasin test uses the same markers as the GeneSearch BLNA assay, CK19 and Mammaglobin, but different primer-probe combinations so, it is expected that it will perform differently to the GeneSearch BLNA assay. Therefore, this UK study is not directly relevant to this evaluation. The study conducted in Spain also provided evidence on resource use and costs but was limited in the extent to which it was generalisable to the UK. Therefore, this study was also considered not directly relevant to this evaluation.

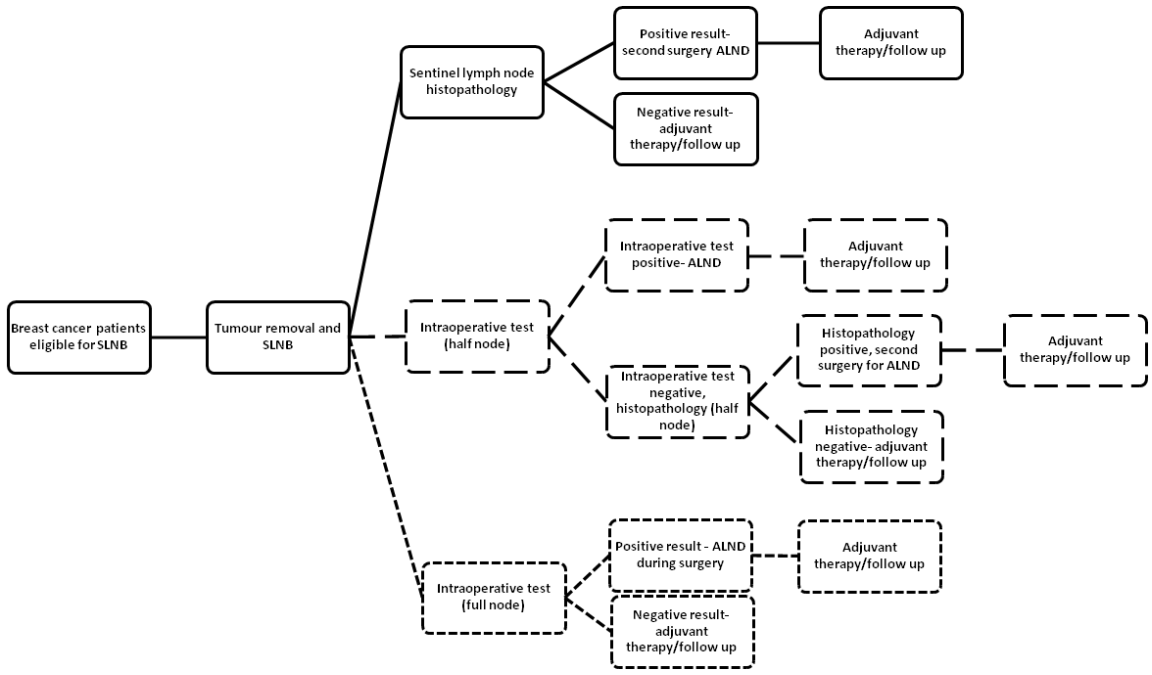
3.4.2 Economic analysis

The EAG performed an economic analysis to assess the cost effectiveness of using intraoperative tests to detect sentinel node metastases compared with using histopathology. The economic model was divided into two separate sections (diagnostic and management) to encompass both the short-term and long-term outcomes of intraoperative testing. The costs were evaluated from the perspective of the NHS and personal social services. Outcomes were expressed as quality-adjusted life years (QALYs). Both costs and outcomes were discounted using a 3.5% annual discount rate.

3.4.3 Modelling approach

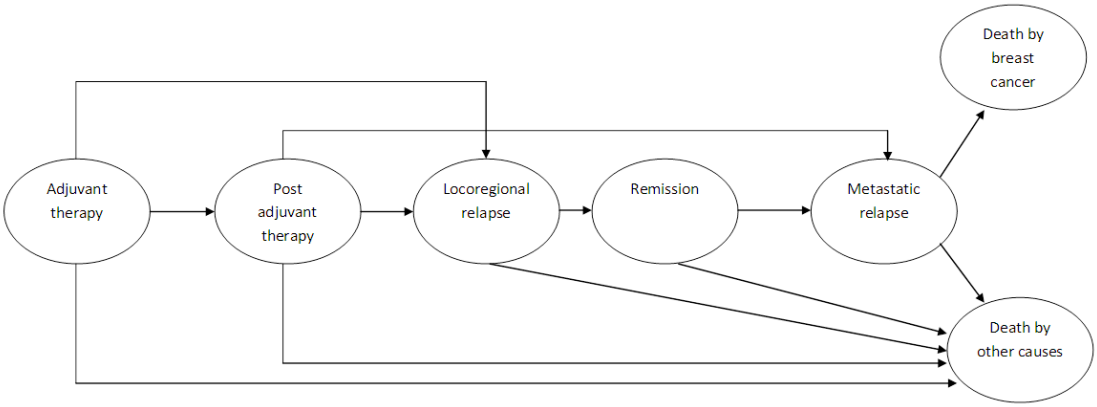
The EAG developed a decision tree to model the short-term diagnostic outcomes outlined in the decision problem. Patients entered the model as those who had SLNB performed during their initial tumour removal. The model then split into the three different diagnostic strategies (figure 1): post-operative histopathology (current practice) alone, intraoperative testing alone and intraoperative testing combined with post-operative histopathology confirmation. Patients who were diagnosed with sentinel lymph node metastases received axillary lymph node dissection, either during the same surgery as their SLNB if intraoperative testing was used or during a second surgery if post-operative histopathology was used.

Figure 1. Diagnostic pathway for lymph node metastases



Once the diagnostic sub groups had been identified (true positive SLN, false positive SLN, true negative SLN and false negative SLN), the model moved into the management pathway and the sub-groups were separated based on whether they received an axillary lymph node dissection. This section of the model calculated the long term outcomes for each sub-group and at this point, a discrete event simulation model, previously developed at the University of Sheffield (ScHARR-TAG), was used to model the natural disease history of the patients once their outcome from the diagnostic decision tree had been determined. After surgery, patients received adjuvant therapy. This involved chemotherapy and hormonal therapy (where appropriate) for those diagnosed with metastases and hormonal therapy alone (where appropriate) for those diagnosed without. After adjuvant therapy, patients can move into a disease free state or, experience locoregional or metastatic relapse. Patients can also move between these states. The basic layout of the ScHARR model is shown below in figure 2.

Figure 2. Basic layout of the ScHARR model (management pathway)



3.4.4 Model inputs

Details of the model inputs can be found on pages 122-131 of the diagnostics assessment report.

3.4.5 Diagnostic accuracy

The sensitivities and specificities of the intraoperative tests were provided by the patient level results of the clinical systematic review (Table 14). Histopathology was assumed to be the 'gold standard' and therefore, was given an accuracy of 100%.

Table 14. Accuracy of tests in the base case.

Test	Sensitivity	Specificity	Source
Histopathology	100%	100%	Assumed (used as 'gold standard' in studies)
OSNA	84.5%	91.8%	No adjustment for TAB: Meta-analysis results Section **Error! Reference source not found.**, page **Error! Bookmark not defined.** of DAR
OSNA	i)91.4% ii) 100% iii) 89.8%	i) 93.3% ii) 97.2% iii) 94.5%	Adjustment for TAB i)Frere Belda[60] ii) Khaddage[59] iii)Snook[63]
Metasin			No adjustment for TAB

	92.6%	96.3%	Sundaresan[80]

The meta-analysed accuracy values without adjustment for TAB for the RD-100i OSNA test and the accuracy values from Sundaresan et al. without adjustment for TAB for the Metasin test were used in the base case. The other accuracy values from the studies investigating the OSNA test were used in sensitivity analyses.

The node positive prevalence was set at 20% in the base case, in line with the norm of studies in the clinical systematic review.

3.4.6 Short term model (Diagnostic pathway)

3.4.6.1 Costs

Unit costs for the intraoperative tests were taken from the sponsors of the technologies and the cost of histopathology was based on data provided by the NHS Technology Adoption Centre. The surgery costs were mainly based on NHS reference costs and the costs of short term adverse events were taken from Jeruss et al. The costs associated with lymphoedema were obtained from the Sheffield Lymphoedema Service and the length of additional hospital stay was calculated from a study by the York Health Economics Consortium (YHEC). The costs of additional time in surgery were estimated from a study by Ng et al. and from the report by YHEC. The unit costs used in the base case analysis are presented in Table 15. All costs have been updated to 2010 levels.

Table 15. Unit costs of diagnostic and primary surgery services.

Test or surgery	Costs	Source
Histopathology	£472	Cutress et al., (2010)[3]
OSNA	£350	Manufacturer Information Submitted to NICE[76]
Metasin	£74	Sundaresan (2012)[80]
Breast surgery with SLNB	£2584	NHS Reference costs (2010-2011)[84] updated using same method as ScHARR using Pandharipande et al. (2008)[85]
With intraoperative test	£12	Additional time cost calculated: 3 minutes for 54% patients, Ng et al. (2010)[86] Extra cost updated to 2010, Burke and Patton (2010)[5]
With ALND	£3855	Breast surgery adjusted using Cooper et al, (2011) technique[4]
Secondary operation for ALND	£3569	NHS Reference costs (2010-2011)[84]
Additional hospital stay for surgery with ALND	£106	Burke and Patton (2010), updated to 2010 costs[5]
Additional hospital stay for second surgery for ALND	£512	Burke and Patton (2010), updated to 2010 costs[5]
Short term adverse event	£333	Jeruss et al., (2006), updated to 2010 prices[87]
Mild lymphoedema	£71	ScHARR updated to 2010 prices[4]
Moderate/severe lymphoedema	£1269	ScHARR updated to 2010 prices[4]

A report from YHEC considered the cost impact of implementing intraoperative testing and provided unit costs and resource use, and is a widely known report. Therefore, the EAG examined the impact of using surgery costs based on the YHEC report in addition to using surgery costs based on NHS Reference costs. Table 16 shows the surgery costs based on the YHEC report.

Table 16. Surgery costs based on the YHEC report

Surgery	Costs
Cost of operation with SLNB (with ward costs, MDT)	£1,282.06
Operation with SLNB and ALND	£1,579.55
ALND only	£1,284.45

Source: Burke M, Patton T. The Cost Impact of Implementing Intra-Operative Testing for the Diagnosis of Patients with Metastatic Breast Cancer in England. York Health Economics Consortium NHS Technology Adoption Centre (2010)

3.4.6.2 Health-related quality of life and QALY decrements

The QALY decrement associated with a two week wait for histopathology results was calculated by the EAG to be 0.019 (undiscounted). For patients undergoing a separate second surgery, the disutility was estimated as 0.03.

3.4.7 Long term model (management pathway)

3.4.7.1 Health state costs

The health state costs were calculated from NHS costs and relevant studies. The health state costs are based on the assumptions that:

- patients who have no further metastases detected in the axillary nodes will receive hormonal therapy for 5 years (where appropriate)
- patients who have metastases detected in the axillary nodes will receive chemotherapy for half a year followed by hormonal therapy for four and a half years
- 81% of patients are oestrogen receptor positive and will therefore respond to hormonal therapy
- Each patient will have an annual outpatient follow up appointment and a mammogram.

A summary of the health state costs is provided in Table 16.

Table 16. Health state costs

State	Cost	Parameter	Source
Cost adjuvant therapy (TN,FP, FN)	£1086.75	Annual cost	NHS reference cost outpatient follow up 10/11 [84] + mammogram NHS reference cost 02/03 [96] updated + Ward et al., (2007) hormone therapy updated [93]
Cost adjuvant therapy TP	£9447.15 first year	Cost for 6 months	Cooper et al., (2011) cost updated[4]
	£1086.75 After 1st year	Annual cost after first 6 months	NHS reference cost outpatient follow up 10/11 [84] + mammogram NHS reference cost 02/03 [96] updated + Ward et al., 2007 hormone therapy updated [93]
Cost post adjuvant therapy	0	Annual cost	Cooper et al., (2011) assumption[4]
Cost of locoregional recurrence	£13745	Annual cost	Karnon et al., (2008)[95]; 2005 prices reflated to 2010 using the Hospital and Community Health Services Index, Curtis et al., (2011) [97]
Cost of remission	£108	Annual cost	Karnon et al., (2008)[95]; 2005 prices reflated to 2010 using the Hospital and Community Health Services Index, Curtis et al., (2011) [97]
Cost of metastatic relapse	£10443	Annual cost	Karnon et al., (2008)[95]; 2005 prices reflated to 2010 using the Hospital and Community Health Services Index, Curtis et al., (2011) [97]
Cost of end-of-life care	£5713	Cost of event	Karnon et al., (2008)[95]; 2005 prices reflated to 2010 using the Hospital and Community Health Services Index, Curtis et al., (2011) [97]

3.4.7.2 Health state utilities

All health state utilities were based on the Tengs and Wallace study and used the same parameters and standard errors as ScHARR in the original model. The utilities of the health states were adjusted to take into account the general population change in utility that occurs with age. Lifetime utility decrements of 9.9% for mild/moderate lymphoedema and 12.3% for severe lymphoedema were included in the treatment phase. A summary of the health state utilities is provided in table 17.

Table 17. Health state utilities from Tengs and Wallace (2000)

State	Utility	Standard error
Adjuvant therapy TN FP FN	0.82	0.18
Adjuvant therapy TP	0.74	0.26
Post therapy	0.94	0.11
Locoregional recurrence	0.7	0.19
Remission	0.85	0.19
Metastatic relapse	0.4	0.19
Death	0	

3.4.7.3 Health state transition probabilities

The probabilities of annual transitions between health states in the management phase of the model are found in page 129 of the diagnostics assessment report.

3.4.8 Results of cost effectiveness analyses

For the purposes of decision making, the ICERs per QALY gained will be considered. The EAG consider the results of the cost effectiveness analyses for the Metasin test to be illustrative because of the high levels of uncertainty associated with the unpublished evidence base relating to the diagnostic accuracy of the test.

3.4.8.1 Short term analysis

The cost effectiveness analyses of the short term outcomes examined the diagnostic accuracy of the intraoperative tests compared to post-operative histopathology, and the disutility of waiting for histopathology results and undergoing a second operation. For strategies that did not involve histopathology the utility was 1 because there was no wait for test results or any second operations directly resulting from the intraoperative test. Results were presented for the three diagnostic strategies and used both NHS Reference costs and the costs based on the YHEC model (Table 18). Only short term QALY gains were included in these analyses. (Please note: The costs per patient for intraoperative analysis of the half node included the costs of the follow up histopathology).

Table 18. Cost effectiveness of intraoperative testing compared with standard histopathology (short term).

		Half-node	Full node	Full node vs half node	Half node	Full node	Full node vs half node
	Histopathology	**Metasin**	**Metasin**	**Metasin**	**OSNA**	**OSNA**	**OSNA**
Sensitivity	1.0000	1.0000	0.9260		1.0000	0.8450	
Specificity	1.0000	0.9630	0.9630		0.9180	0.9180	
Accuracy	1.0000	0.9704	0.9556		0.9344	0.9034	
Sensitivity*Prevelance	0.2000	0.2000	0.1852		0.2000	0.1690	
Specificity*(1-Prevalence)	0.8000	0.7704	0.7704		0.7344	0.7344	
NHS reference costs of ALND							
Costs (£) per patient	£3,987	£3,523	£3,086		£3,897	£3,397	
Utility	0.9739	0.9849	1.0000		0.9854	1.0000	
Incremental cost (£)		-465	-901	-437	-90	-590	-£500
Incremental QALYs		0.0110	0.0261	0.0151	0.0115	0.0261	0.0146
ICER (£/QALY gained)		**-42350**	**-34550**	**-28891**	**-7846**	**-22615**	**-£34,253**
		Metasin dominates	**Metasin dominates**	**Full node Metasin dominates**	**OSNA dominates**	**OSNA dominates**	**Full node OSNA dominates**
YHEC costs							
Costs (£) per patient	£2,228	£1,966	£1,562		£2,284	£1,855	
Utility	0.9739	0.9849	1.0000		0.9854	1.0000	
Incremental cost (£)		-263	-666	-403	56	-373	-429
Incremental QALYs		0.0110	0.0261	0.0151	0.0115	0.0261	0.0146
ICER (£/QALY gained)		**-23931**	**-25510**	**-26655**	**4832**	**-14313**	**-29400**
		Metasin dominates	**Metasin dominates**	**Full node Metasin dominates**		**OSNA dominates**	**Full node OSNA dominates**

Using the NHS reference costs, full node OSNA analysis and half node OSNA analysis dominated histopathology analysis because they were less costly and provided more QALY gains. Full node OSNA analysis also dominated half node OSNA analysis. Using the YHEC costs, full node OSNA analysis continued to dominate half node OSNA analysis and histopathology analysis. Half node OSNA analysis provided a small QALY gain over histopathology analysis, with an ICER of £4832 per QALY gained. It was estimated that 4.1% of the 76.5% of patients who received a negative test result from half node OSNA analysis would end up with a positive result upon waiting for a histopathology result. This compares to 20% of patients who would receive a positive result using post-operative histopathology analysis.

Regardless of the costing strategy, half node and full node Metasin analysis dominated histopathology analysis because they were less costly and more effective. Full node Metasin also dominated half node Metasin analysis. It was estimated that of the 78.5% of patients who received a negative result by half node Metasin analysis, 1.9% would receive a positive result upon waiting for confirmation by histopathology analysis. Again, this compares to 20% of patients who would receive a positive result using post-operative histopathology analysis.

3.4.8.2 Long term analysis

The cost effectiveness analyses of the long term outcomes examined all the costs and benefits of accurate diagnosis through to improved patient management. In these analyses, the diagnostic strategies were ordered by the number of QALYs, with full node OSNA analysis producing the lowest number of QALYs (9.22) and postoperative histopathology producing the most QALYs (9.32). The QALY difference is equal to 0.1 (i.e. 5 weeks of full health equivalent life) and this difference occurs as a direct consequence of the accuracies of the tests because higher accuracies lead to more correct diagnoses and subsequent treatment.

Using the NHS Reference costs, the ICER for full node OSNA analysis was £4324 saved per QALY lost compared to histopathology analysis and £24,863 saved per QALY lost for full node Metasin analysis compared to histopathology analysis (Table 19). Using the YHEC costs, the ICER for full node OSNA analysis was £2150 saved per QALY lost compared to histopathology analysis and £17,777 saved per QALY lost for full node Metasin analysis compared to histopathology analysis. Histopathology analysis dominated half node OSNA analysis because the OSNA analysis had higher costs and produced fewer QALYs. The ICERs for full node analysis analysis compared to histopathology analysis suggest histopathology analysis is cost effective but it is important to note, that there is a gain of approximately 0.1 QALY (i.e. 5 weeks of full health equivalent life) for the additional cost, compared to the intraoperative testing strategies. In addition, histopathology analysis was assumed to be the 'gold standard' and was given an accuracy of 100% sensitivity and 100% specificity in the modelling. The level of uncertainty in this assumption is unclear and therefore, the estimated ICERs may change depending on the assumed absolute accuracy of histopathology.

Table 19. Cost effectiveness of intraoperative testing compared with standard histopathology (long term).

		Half-node	Full node	Half node vs full node	Half node	Full node	Half node vs full node
	Histopathology	**Metasin**	**Metasin**	**Metasin**	**OSNA**	**OSNA**	**OSNA**
NHS reference costs							
Costs (£) per patient	20530	20103	19702		20523	20099	
Utility	9.3213	9.3204	9.2880		9.3066	9.2217	
Incremental cost (£)		-427	-828	-401	-7	-431	-424
Incremental QALYs		-0.0009	-0.0333	-0.0324	-0.0148	-0.0996	-0.0849
ICER (£ saved/QALY lost)		**467113***	**24863***	**12374***	**473***	**4324***	**4993***
YHEC costs							
Costs (£) per patient	18771	18546	18179		18910	18556	
Utility	9.321	9.320	9.2880		9.3066	9.2217	
Incremental cost (£)		-225	-592	-367	139	-214	-353
Incremental QALYs		-0.0009	-0.0333	-0.0324	-0.0148	-0.0996	-0.0849
ICER (£ saved/QALY lost)		**246089***	**17777***	**11329***	**-9401***	**2150***	**4160***
					Histopathology dominates		

* Please note: The ICERs in this table are £ saved per QALY lost because both intraoperative tests are cheaper and have fewer QALYs than the comparator, histopathology.

The sensitivity and specificity of OSNA analysis were changed to use values from studies that adjusted for TAB (Frere Belda et al., Snook et al. and Khaddage et al.). Using NHS Reference costs, the ICER for full node OSNA analysis was £9493 saved per QALY lost compared to histopathology analysis using accuracy values from the Frere Belda et al. study and £8840 saved per QALY lost for full node OSNA analysis compared to histopathology analysis using values from the Snook et al. study (Table 20). However, using the higher accuracy values from the Khaddage et al. study resulted in ICERs for full node OSNA analysis that dominated both half node OSNA analysis and histopathology analysis. Details of the ICERS resulting from using the YHEC costing strategy after TAB adjustment are on page 140 of the DAR.

Table 20. Cost effectiveness of intraoperative testing compared with standard histopathology (long term, TAB adjusted).

		Frere Belda			Snook			Khaddage		
		Half node	Full node	Half node vs full node	Half node	Full node	Half node vs full node	Half node	Full node	Half node vs full node
	Histopathology	OSNA	OSNA	OSNA	OSNA	OSNA	OSNA	OSNA	OSNA	OSNA
Sensitivity	1.000	1.000	0.914		1.000	0.898		1.000	1.000	
Specificity	1.000	0.933	0.933		0.945	0.945		0.972	0.972	
Accuracy	1.000	0.946	0.929		0.956	0.936		0.978	0.978	
NHS reference costs										
Costs (£) per patient	20530	20448	20053		20434	20026		20314	19947	
Utility	9.3213	9.3116	9.2711		9.3149	9.2644		9.3228	9.3389	
Incremental cost		-82	-477	-395	-96	-504	-408	-216	-583	-367
Incremental QALYs		-0.0097	-0.0502	-0.0405	-0.0064	-0.0569	-0.0505	0.0025	0.0176	0.0151
ICER (£ saved/QALY lost)		**8399***	**9493***	**9755***	**14967***	**8840***	**8063***	**-87585***	**-33189***	**-24309***
								OSNA dominates	**OSNA dominates**	**Full node OSNA dominates**

*Please note: The ICERs in this table are £ saved/QALY lost because both intraoperative tests are cheaper and have fewer QALYs than the comparator, histopathology.

3.4.8.3 Sensitivity analysis

The change in ICERs when accuracy values adjusted for TAB were used indicated that test accuracy has a direct impact on the cost-effectiveness of the tests. Threshold analysis was used to investigate sensitivity by increasing sensitivity over a range of 70-100% as specificity was held constant. The opposite was also performed to investigate specificity. These analyses were conducted on the results for the full node OSNA analysis. Short term utility results were not reported as the utility of OSNA was not affected by the accuracy of the test. Only the NHS referencing costing strategy was used in the sensitivity analyses.

The results of the threshold analysis for the long term results are presented in tables 21 and 22. As the sensitivity of OSNA increased (and specificity was kept at the 91.8% base case value), the ICER per QALY gained for histopathology analysis also increased compared to full node OSNA analysis. The ICERs for histopathology analysis ranged from £2,119 per QALY gained when OSNA had a sensitivity of 70% to £14,193 per QALY gained when OSNA had 95% sensitivity. At 100% sensitivity, OSNA dominated histopathology, having more QALYs gained and lower costs (the ICER is -£398,023). The cost difference between histopathology analysis and full node OSNA analysis also increased each time the sensitivity increased.

For specificity, the long term cost of OSNA decreased and the QALY gain increased as the specificity increased. At a specificity of 70%, full node OSNA analysis was dominated by histopathology analysis because it was more expensive and had fewer QALYs. The largest ICER for histopathology analysis was £8,430 per QALY gained when full node OSNA analysis had 100% specificity (and sensitivity was kept at the base case value of 94.5%).

Overall, the threshold analyses suggest that if the true values of sensitivity and specificity for full node OSNA analysis lie within the range of 90-100%, close to those of the sensitivity and specificity for histopathology analysis, the cost effectiveness of full node OSNA analysis may increase greatly. The

results also imply that changes to specificity may have more of an impact in the short term than the long term, but that changes to sensitivity may have a much greater impact on the long term cost effectiveness.

Table 21. Long term results for threshold analysis for sensitivity

	Increase in accuracy							
Measure	**OSNA[1] with sensitivity vs. Histopathology**							
	Base Case: 84.5%	**70%**	**75%**	**80%**	**85%**	**90%**	**95%**	**100%**
Incremental QALYs (discounted)	-0.0997	-0.1939	-0.1614	-0.1289	-0.0964	-0.0639	-0.0314	0.0011
		NHS reference costs of ALND						
Incremental costs per patient (discounted)	-£431	-£411	-£418	-£425	-£431	-£438	-£445	-£452
ICER (£ saving/QALY lost)	£4,324	£2,119	£2,588	£3,294	£4,476	£6,862	£14,193	OSNA dominates

Table 22. Long term results for threshold analysis for specificity

	Increase in accuracy							
Measure	**OSNA[1] with specificity vs. Histopathology**							
	Base case: 91.8%	**70%**	**75%**	**80%**	**85%**	**90%**	**95%**	**100%**
Incremental QALYs (discounted)	-0.0097	-0.1660	-0.1508	-0.1356	-0.1203	-0.1051	-0.0899	-0.0747
	NHS reference costs of ALND							
Incremental costs per patient (discounted)	-£431	£98	-£24	-£145	-£266	-£387	-£508	-£630
ICER (£ saving/QALY lost)	£4,324	Histopathology dominates	£156	£1,068	£2,210	£3,683	£5,655	£8,430

Sensitivity analysis was also conducted on the effect of prevalence of sentinel lymph node metastases in the patient population. When the prevalence was reduced to 10%, histopathology analysis dominated half node OSNA analysis and had an ICER of £2,626 per QALY gained compared to full node OSNA analysis. When the prevalence was increased to 40%, half node OSNA analysis dominated histopathology analysis and had an ICER of £2208 per QALY gained compared to full node OSNA analysis.

Changing individual costs and utility parameter values in the short term or long term sections of the model had very little impact on the overall cost-effectiveness results. This highlighted the importance of the diagnostic accuracy of the tests because this was the most influential parameter.

4 Issues for consideration

The existing evidence base for the RD-100i OSNA system and Metasin test compares the test accuracy of these tests with the reference standard, histopathology. All other conclusions have been based on the health economic model in a linked-evidence approach. The results of the quality assessment carried out by the EAG showed that the evidence base for the Metasin test was generally considered to be illustrative and required validation because it comprised two unpublished, non-peer reviewed studies of test accuracy. The evidence base for the OSNA test comprised 16 studies and was considered more robust and more generalisable than the evidence for the Metasin test. However, there is an assumption in all of the accuracy studies that the reference standard, histopathology, is a true measure of sentinel node metastases.

For all studies, there was variance in the level of histopathology used and it is uncertain which level of histopathology represents current NHS practice. Discordant results were not adjusted in all studies but in those studies that did adjust for discordant results, a conservative approach of sample exclusion was generally used. The EAG considered this adjustment to be reasonable in the studies. There is also uncertainty in the accuracy of histopathology associated with the processing and staining of the tissue, and with the clinical judgement of different pathologists, particularly regarding the detection of micrometastases, Both of the intraoperative tests appear to be effective in reducing the number of second separate ALND operations, which leads to cost savings and benefits for patients. However, both tests appear to be less accurate than histopathology so these short term gains are at the expense of diagnostic errors, both false negatives and false positives. The mean per patient loss in QALYs is 0.1 (i.e. 5 weeks of full health equivalent life) and all of these conclusions are based on the assumption that the accuracy of the reference standard, histopathology, is 100% accurate. The EAG considered there was uncertainty in the real costs of the technologies.

The changes in test accuracy after adjustment for TAB suggest that the accuracy of the OSNA test may have been underestimated in the studies which did not adjust for TAB and therefore, also the meta-analysis. The level of confidence in the accuracy of the OSNA test should be considered because when the higher accuracy values from the Khaddage et al. study were used, full node OSNA analysis dominated half node OSNA analysis and histopathology analysis. However, this particular study was small in size and therefore, produced larger sampling uncertainty in its accuracy estimates than the other two available studies that adjusted for TAB. Nevertheless, the OSNA test appears to save costs over current practice in the long term.

Following the publication of the Z0011 trial which reported no improvement in survival after ALND surgery in women who received a positive result for lymph node metastases, there has been widespread clinical debate about the benefits of ALND surgery. During scoping, it was concluded that there is a great deal of uncertainty about stopping ALND which would need to be addressed before any changes in clinical practice and therefore, as long as ALND surgery is being performed, this evaluation and subsequent guidance is still very relevant for patient care in the NHS.

5 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.

The prevalence of breast cancer is significantly more common in women than in men. People with a diagnosis of cancer are protected under the Equality Act 2010 from the point of diagnosis.

6 Implementation

Biomedical scientists can carry out the molecular intraoperative tests although a level of molecular biology expertise may be needed. This expertise may not be available in all hospitals performing breast surgery.

For efficient use of intraoperative testing, surgical theatre lists need to be carefully scheduled and multiple analysers may be needed for sentinel lymph node testing if breast operations occur in parallel.

7 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A The diagnostics assessment report for this assessment was prepared by Peninsula Technology Assessment Group (PenTAG):

Huxley N, Jones-Hughes T, Coelho H, Snowsill T, Cooper C, Meng Y, Cooper K, Hyde C, Mujica-Mota R. A systematic review and economic evaluation of intraoperative tests (RD-100i OSNA system and Metasin test) for detecting sentinel lymph node metastases in breast cancer. (2012) University of Exeter (Report).

B The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

I Manufacturers/sponsors:

Technologies under consideration

- Sysmex UK
- TIB MOLBIOL
- Princess Alexandra Hospital Trust

II Professional/specialist and patient/carer groups:

- Beatson West of Scotland Cancer Care
- Breakthrough Breast Cancer
- Breast Unit, Royal Surrey County Hospital
- Breast Cancer Care
- Department of Health
- Leeds and Wakefield NHS Trust
- NCRI Breast Clinical Studies Group
- NHS Bristol
- NHS Technology Adoption Centre
- Peony Breast Care Unit
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- The Royal Marsden NHS Foundation Trust