

# **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**

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**Date completed**

**Declared competing interests of authors:** None

**Description of any pecuniary relationship with sponsors, both personal and of the TAR centre. If there are none, please state 'none':** None

### **Acknowledgements**

We would like to thank: Katie Cooper, Research Fellow in Health economics, ScHARR, for providing us information to model outcomes of long-term cancer patient management.

We would also like to acknowledge the help of Sue Whiffin and Jenny Lowe for their administrative support throughout the project.

### **Rider on responsibility for report**

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA programme. Any errors are the responsibility of the authors.

**This report should be referenced as follows:** Huxley N, Jones-Hughes T, Coelho H, Snowsill T, Meng Y, 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).

Please refer to the International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for manuscripts submitted to biomedical journals, see <http://icmje.org/>

### **Contributions of authors**

<b>Nicola Huxley</b>	Developed the short term model and adapted the long term model, executed the economic model and wrote the sections on the design and results of the economic model
<b>Yang Meng</b>	Co-authored the original long term economic model , advised on its adaptation to the analysis, and contributed to writing the report
<b>Ruben Mujica-Mota</b>	Contributed to developing the protocol. Led the systematic reviews of economic evaluations, contributed to the design of the analysis and writing and editing of the report. Overall lead for the project and final report.
<b>Tracey Jones-Hughes</b>	Assessed abstracts and titles for inclusion, led the systematic review of clinical effectiveness, and contributed to the writing and editing of the report
<b>Helen Coelho</b>	Assessed abstracts and titles for inclusion, and contributed to the writing and editing of the report
<b>Tristan Snowsill</b>	Performed statistical analysis and contributed to the writing of the report
<b>Chris Cooper</b>	Designed and carried out literature searches for the systematic reviews and identification of model parameters, and contributed to the writing and editing of the report
<b>Chris Hyde</b>	Developed the protocol. Contributed to the systematic review,

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design of the model, and to the writing and editing of the report.  
Director of TAR group at PenTAG and Guarantor of the report

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## Errata

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**List of Authors, Citation and Contributions of Authors has been revised. Katie Cooper, ScHARR is no longer an author; her contribution is acknowledged under Acknowledgements.**

### **Revision to Acknowledgments, p.2**

We would like to thank: Katie Cooper, Research Fellow in Health economics, ScHARR, for providing us information to model outcomes of long-term cancer patient management.

We would also like to acknowledge the help of Sue Whiffin and Jenny Lowe for their administrative support throughout the project.

### **Revision to citation in p.2**

**This report should be referenced as follows:** Huxley N, Jones-Hughes T, Coelho H, Snowsill T, 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).

### **Executive Summary,**

#### **Section 1.1 Background,**

#### **Section 1.4.1 Clinical effectiveness systematic review, p. 19,**

#### **fifth bullet point**

Original text: "Other quality concerns included lack of detail on patient recruitment. Minimal information on patient characteristics and unclear sampling methods, e.g., no evidence was given of sample replicates and reproducibility for molecular analysis."

Revised text: "Other quality concerns included unclear sampling methods, e.g., no evidence was given of sample replicates and reproducibility for molecular analysis."

#### **4.2.1.4 Study characteristics, 4.2.1.4.2 OSNA,**

##### **p.63 first paragraph,**

Missing reference number: 59

##### **p.63**

**Insert at end of paragraph starting:** “A multicentre single gate study reported by Feldman et al. ...”

Insert text: “This study used the RD110i system with a reagent kit different from that other included studies.”

#### **4.2.1.6 Assessment of study quality, 4.2.1.6.2 OSNA, p.73**

Original text: “Snook et al. reports a prospective study comparing OSNA with five-level histology... No financial contribution was received from any organisation; however, support in the form of training and advice was provided by Sysmex Life Science.”

Revised Text: “Snook et al. reports a prospective study comparing OSNA with five-level histology.....No financial contribution was received from any organisation; however, support in the form of training and advice and compensation for the additional workload due to the study protocol and all necessary material for OSNA analysis was provided by Sysmex Life Science.”

#### **5.1.3.3. Analysis and interpretation of results, p. 112, second paragraph, fourth sentence**

Original text: “The validity of results in both studies is uncertain by their lack of information on the way accuracy was measured.”

Revised text: “The results in both studies are likely to be biased due to the inherent limitations of observational studies, which commonly lack control for the effect of confounders on outcomes. The validity of these studies’ findings is further made uncertain

by their lack of reporting of information on methods used to measure diagnostic accuracy outcomes.”

### **5.3.2.3. The ScHARR model structure,**

#### **P.121, first paragraph**

Original text: “The model does not consider metastatic disease curable and therefore patients in this state may move to a death state, either from breast cancer or other causes. Patients in all states can die from other causes.”

Revised text: “The model does not consider metastatic disease curable and therefore patients in this state may only move to a death state, either from breast cancer or other causes. Patients in all states can die from other causes.”

#### **p.122, last sentence**

Original text: “During the course of our review process we have worked with two of the ScHARR model authors in adapting and updating their model for our purposes, and they have become co-author in this report (YM,KC).”

Revised text: “During the course of our review process we have worked with two of the ScHARR model authors in adapting and updating their model for our purposes, and they have become co-author in this report (YM) or been acknowledged (Katie Cooper).”

#### **Table 49, p.134**

##### **Cost per patient OSNA half node, under Analysis using costs based on YHEC model**

Original figure: £2,387

Corrected figure: £2,284

##### **Cost per patient Difference Histopathology vs. OSNA half node, under Analysis using costs based on YHEC model**

Original figure: £373

Corrected figure: -£56

**Table 51, p. 137**

**Incremental cost per QALY gained, Incremental results Difference OSNA half node vs. histopathology**

Insert word “extended” before “dominated”

**5.3.7.2 Long term analysis, p. 138, fourth sentence:**

Original text: “As this demonstrates, the QALY difference was small: less than 0.10.”

Corrected text: “As this demonstrates, the QALY difference was approximately equal to 0.10 (i.e. 5 weeks of full health life).”

**Table 53, p. 140**

Original Table:

**Table 1. Long term incremental outcomes comparing histopathology to intraoperative analysis (TAB adjusted)**

Measure	Incremental results					
	Frere Belda <sup>60</sup>		Snook <sup>63</sup>		Khaddage <sup>59</sup>	
	Difference OSNA half node vs. OSNA full node	Difference Histopathology vs. OSNA half node	Difference OSNA half node vs. OSNA full node	Difference Histopathology vs. OSNA half node	Difference OSNA half node vs. OSNA full node	Difference Histopathology vs. OSNA half node
NHS reference costs of ALND						
Cost per patient (discounted)	£395	£82	£408	£96	-£367* <sup>2</sup>	-£583* <sup>2</sup>
QALYs (discounted)	0.041	0.001	0.051	0.006	0.015* <sup>2</sup>	0.003* <sup>2</sup>
Incremental cost per QALY gained	OSNA half node extended dominated	£9,493*	£8,063	£14,967	OSNA half node dominated	Histopathology dominated* <sup>2</sup>
Analysis using costs based on YHEC model						
Costs per patient (discounted)	£356	-£94	£361	-£85	-£367* <sup>2</sup>	-£355* <sup>2</sup>
Incremental cost per QALY gained	OSNA half node extended dominated	£5,215*	OSNA half node extended dominated	£4,850*	OSNA half node dominated	Histopathology dominated* <sup>2</sup>

\* Comparison is Histopathology relative to full node OSNA due to the half node OSNA option being dominated or extended dominated. \*<sup>2</sup>OSNA full node has greater number of QALYs, therefore the order of comparison is switched here to compare OSNA full node vs. half node and then histopathology vs. OSNA full node. In both costing strategies, OSNA full node dominates OSNA half node i.e. has lower costs and greater benefits.

Revised Table:

**Table 2. Long term incremental outcomes comparing histopathology to intraoperative analysis (TAB adjusted)**

Measure	Incremental results					
	Frere Belda <sup>60</sup>		Snook <sup>63</sup>		Khaddage <sup>59</sup>	
	Difference OSNA half node vs. OSNA full node	Difference Histopathology vs. OSNA half node	Difference OSNA half node vs. OSNA full node	Difference Histopathology vs. OSNA half node	Difference OSNA half node vs. Histopathology <sup>*2</sup>	Difference OSNA full node vs. OSNA half node <sup>*2</sup>
NHS reference costs of ALND						
Cost per patient (discounted)	£395	£82	£408	£96	-£216	-£367
QALYs (discounted)	0.041	0.010	0.051	0.006	0.0025	0.0151
Incremental cost per QALY gained	OSNA half node extended dominated	£9,493*	£8,063	£14,967	Histopathology dominated	OSNA half node dominated
Analysis using costs based on YHEC model						
Costs per patient (discounted)	£356	-£94	£361	-£85	-£367	-£13
Incremental cost per QALY gained	OSNA half node extended dominated	£5,215*	OSNA half node extended dominated	£4,850*	Histopathology dominated	OSNA half node extended dominated

\* Comparison is Histopathology relative to full node OSNA due to the half node OSNA option being dominated or extended dominated. <sup>\*2</sup>OSNA strategies have a greater number of QALYs, therefore the order of comparison is switched. In both costing strategies, OSNA full node dominates OSNA half node i.e. has lower costs and greater benefits.

**p. 143**

Original text: “Long term results presented in **Error! Reference source not found.** show a similar finding to the accuracy results: as the sensitivity of OSNA increased, so did the ICER for cost per QALY gained by histopathology. These ranged from £2,199 per QALY gained when OSNA had sensitivity 70% to £14,193 per QALY gained when OSNA had 100% sensitivity. Unlike the accuracy results, the cost difference between histopathology and OSNA also increased each time the sensitivity increased. Again, as the sensitivity of OSNA

neared 100% the ICERs began to increase much faster, as demonstrated in **Error! Reference source not found.**

Revised text: “Long term results. presented in **Error! Reference source not found.**, show a similar finding to the accuracy results: as the sensitivity of OSNA increased, so did the ICER for cost per QALY gained by histopathology. These ranged from £2,119 per QALY gained when OSNA had sensitivity 70% to £14,193 per QALY gained when OSNA had 95% sensitivity. At 100% sensitivity OSNA dominated histopathology, having more QALYs and fewer costs. Unlike the accuracy results, the cost difference between histopathology and OSNA also increased each time the sensitivity increased. Again, as the sensitivity of OSNA neared 100% the ICERs began to increase much faster, as demonstrated in **Error! Reference source not found.**”

**Page 144, end of paragraph**

Original text “Error! Reference source not found”

Revised text ”Figure 19”

**Table 56 p. 144**

Original Table:

**Table 3: Accuracy results for threshold analysis for specificity**

Measure	Base case: 91.8%	Increase in accuracy Histopathology vs.OSNA <sup>1</sup> with sensitivity						
		70%	75%	80%	85%	90%	95%	100%
Accuracy <sup>a</sup>	0.0966	0.2710	0.2310	0.1910	0.1510	0.1110	0.0710	0.0310
Sensitivity*Prevalence <sup>1</sup>	0.0656	0.24	0.20	0.16	0.12	0.08	0.04	0
NHS reference costs of ALND								
Costs per patient	£590	£283	£353	£424	£494	£565	£635	£706
Incremental cost per additional patient correctly diagnosed	£6,108	£1,043	£1,529	£2,218	£3,272	£5,087	£8,945	£22,761
Incremental cost per additional node-negative case detected	£8,994	£2,671	£3,117	£3,787	£4,902	£7,133	£13,826	Histopathology dominated

<sup>1</sup> Node positive prevalence fixed at 20%. <sup>a</sup> Accuracy refers to the cost per case correctly identified. Here strategies that are dominated have the same detection rate, but are more expensive.

Revised Table:

**Table 4: Accuracy results for threshold analysis for specificity**

Measure	Increase in accuracy Histopathology vs.OSNA <sup>1</sup> with specificity							
	Base case: 91.8%	70%	75%	80%	85%	90%	95%	100%
Accuracy <sup>a</sup>	0.0966	0.2710	0.2310	0.1910	0.1510	0.1110	0.0710	0.0310
Specificity*(1-Prevalence) <sup>1</sup>	0.0656	0.24	0.20	0.16	0.12	0.08	0.04	0
NHS reference costs of ALND								
Costs per patient	£590	£283	£353	£424	£494	£565	£635	£706
Incremental cost per additional patient correctly diagnosed	£6,108	£1,043	£1,529	£2,218	£3,272	£5,087	£8,945	£22,761
Incremental cost per additional node-negative case detected	£8,994	£1,178	£1,766	£2,648	£4,118	£7,058	£15,878	Histo-pathology dominated

<sup>1</sup> Node positive prevalence fixed at 20%. <sup>a</sup> Accuracy refers to the cost per case correctly identified. Here strategies that are dominated have the same detection rate, but are more expensive.

### 5.3.8.2 Prevalence, p.147, second paragraph

Original text: “When prevalence was 10%, histopathology dominated OSNA half node and had ICERs under £20,000 per additional case correctly identified for histopathology versus OSNA full node, both overall and when split into node negative and node positive patients. Short term cost utility results remained the same, with full node OSNA dominating the rest. In the long term, histopathology dominated half node OSNA, and the ICER for histopathology compared to full node OSNA was £1,896 per QALY gained.”

Revised text: “When prevalence was 10%, histopathology dominated OSNA half node and had ICERs under £20,000 per additional case correctly identified for histopathology versus OSNA full node, both overall and when split into node negative and node positive patients. Short term cost utility results remained the same, with full node OSNA dominating the rest. In the long term, histopathology dominated half node OSNA, and the ICER for histopathology compared to full node OSNA was £2,626 per QALY gained.”

#### 5.3.8.4 Long term costs, p.148,

##### first paragraph

Original text: “Adjuvant therapy costs were altered by +/-10%. This only affected the long term results and did not greatly influence their results. High costs for patients undergoing hormonal adjuvant therapy (£1195) increased the ICERs most significantly, with histopathology compared to full node OSNA having an ICER of £11,532.”

Revised text: “Adjuvant therapy costs were altered by +/-10%. This only affected the long term results and did not greatly influence their results. High costs for patients undergoing hormonal adjuvant therapy (£1195) increased the ICERs most significantly, with histopathology compared to full node OSNA having an ICER of £4,353.”

##### end of second paragraph

Insert “Additional two-way sensitivity analyses showed that in order to be cost-effective (see Appendix 10) OSNA full node has to have a sensitivity and specificity estimates of 95% or above.”

**Table 5. Sensitivity analyses for short term and long term cost-effectiveness, p. 150**

Original entries:

Annual cost of adjuvant therapy (hormone therapy and follow up)	£1,087	£978	N/A	N/A	OSNA half node extended dominated	£6,424*
		£1,195	N/A	N/A	OSNA half node extended dominated	£11,646*

Revised entries:

Annual cost of adjuvant therapy (hormone therapy and follow up)	£1,087	£978	N/A	N/A	OSNA half node extended dominated	£4,311*
		£1,195	N/A	N/A	OSNA half node extended dominated	£4,353*

### 5.3.9 Metasin Results,

#### p. 152

Original text: “The ICER for node-negative cases comparing histopathology to full node Metasin was £30,453 per additional node negative case detected with NHS Reference costs and £22,848 with YHEC costs.”

Revised text: “The ICER for node-negative cases comparing histopathology to full node Metasin was £30,453 per additional node negative case detected with NHS Reference costs and £22,484 with YHEC costs.”

#### Table 62, p. 154

Original table:

Table 6. Long term costs and QALYs for Metasin

Measure	Mean estimates			Incremental results	
	Histopathology	Metasin half node	Metasin full node	Difference Metasin half node vs. Metasin full node	Difference Histopathology vs. Metasin half node
NHS reference costs of ALND					
Cost per patient	£20,530	£20,523	£20,099	£401	£427
QALYs	9.321	9.320	9.288	0.032	0.001
Incremental cost per QALY gained				£12,374	£467,113
<u>Analysis using costs based on YHEC model</u>					
Costs per patient	£18,771	£18,546	£18,179	£367	£225
Incremental cost per QALY gained				£11,329	£246,089

Revised table:

**Table 7. Long term costs and QALYs for Metasin**

Measure	Mean estimates			Incremental results	
	Histopathology	Metasin half node	Metasin full node	Difference Metasin half node vs. Metasin full node	Difference Histopathology vs. Metasin half node
NHS reference costs of ALND					
Cost per patient	£20,530	£20,103	£19,702	£401	£427
QALYs	9.321	9.320	9.288	0.032	0.001
Incremental cost per QALY gained				£12,374	£467,113
<u>Analysis using costs based on YHEC model</u>					
Costs per patient	£18,771	£18,546	£18,179	£367	£225
Incremental cost per QALY gained				£11,329	£246,089

## Addendum Appendix 10: Two-way threshold analysis of OSNA sensitivity and specificity

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The two way sensitivity analyses examine the effect of altering both the specificity and sensitivity while fixing other parameters at their base case values. . Here we present the long term ICERs comparing histopathology to full node OSNA, as this analysis accounts for all costs and benefits of the tests. As a guide, we chose a cost-effectiveness threshold of £30,000 per QALY gained.

To begin with, we present the results in Table 8, using the range of sensitivity and specificity as used in the one way threshold analyses (70%-100% for both sensitivity and specificity, see Section 5.3.8.1 pp. 142-147, Tables 54-57 of the Diagnostic Assessment Report). This demonstrates that histopathology was cost effective at a threshold of £30,000 per QALY gained for most values in the analysis. However, when the specificity is 90% and the sensitivity was 100%, the ICER increased to over £94,000 per QALY gained. Furthermore, when the sensitivity was 95% and the specificity 100%, the ICER increased to over £103,000. When the sensitivity was 100% and the specificity was 95% or above, OSNA dominated histopathology, having lower costs and larger QALY gains.

Table 9 narrows down the range of sensitivity and specificity values at which the ICER crossed the £30,000 threshold. The increments of specificity are shown in steps of 2%, purely to keep the table concise. As the table shows, if the sensitivity of OSNA was 100%, the specificity had to be above 88% for the ICER to be above £30,000 per QALY gained (at 87% specificity the ICER was £24,928 per QALY gained). When the specificity was 92% or above and the sensitivity 100%, OSNA dominated histopathology, having higher QALY gains and lower costs. If the specificity was 100% the sensitivity of OSNA had to be at least 93% to have an ICER above £30,000 per QALY gained (at 92% sensitivity the ICER was £24,683). In this case the sensitivity had to reach 96% before OSNA dominated histopathology. When neither sensitivity nor specificity was 100%, the ICERs decreased. When we looked at reducing both sensitivity and specificity, but keeping the ICER above £30,000 per QALY gained, the lowest values they could take were: specificity 95% and sensitivity 96% (the ICER was £34,639 per QALY gained compared to histopathology).

Though these results suggest there are values for sensitivity and specificity at which OSNA may be considered cost effective, there is little evidence in the clinical effectiveness review that suggests that these values are the true sensitivity and specificity of OSNA.

**Table 8. Two-way threshold analysis for sensitivity and specificity of OSNA**

		Incremental cost per QALY gained by Histopathology vs. OSNA full node							
		OSNA sensitivity							
		Base Case: 84.5%	70%	75%	80%	85%	90%	95%	100%
		NHS reference costs of ALND							
OSNA specificity	Base case: 91.8 %	£4,324	£2,119	£2,588	£3,294	£4,476	£6,862	£14,193	OSNA dominated histopathology
	70%	Histopathology dominates OSNA	Histopathology dominates OSNA	Histopathology dominates OSNA	Histopathology dominates OSNA	Histopathology dominates OSNA	Histopathology dominates OSNA	Histopathology dominates OSNA	Histopathology dominates OSNA
	75%	£156	£15	£49	£96	£164	£270	£460	£898
	80%	£1,068	£543	£667	£841	£1,099	£1,526	£2,366	£4,776
	85%	£2,210	£1,146	£1,389	£1,736	£2,277	£3,234	£5,386	£14,691
	90%	£3,683	£1,842	£2,242	£2,835	£3,807	£5,691	£10,899	£94,097
	95%	£5,655	£2,652	£3,266	£4,214	£5,875	£9,529	£24,166	OSNA dominates histopathology
	100%	£8,430	£3,608	£4,518	£5,997	£8,823	£16,367	£100,308	OSNA dominates histopathology

**Table 9. Two-way threshold analysis for sensitivity and specificity of OSNA at high levels of accuracy.**

		Incremental cost per QALY gained by Histopathology vs. OSNA full node								
		OSNA sensitivity								
		Base Case: 84.5%	93%	94%	95%	96%	97%	98%	99%	100%
		NHS reference costs of ALND								
OSNA specifi city	Base case: 91.8%	£4,324	£9,972	£11,720	£14,193	£17,958	£24,389	£37,867	£84,008	OSNA dominates histopatholog y
	88%	£3,046	£6,264	£7,115	£8,225	£9,730	£11,890	£15,248	£21,185	£34,527
	90%	£3,683	£8,001	£9,232	£10,899	£13,279	£16,957	£23,393	£37,547	£94,097
	92%	£4,399	£10,221	£12,041	£14,631	£18,608	£25,498	£40,345	£95,774	OSNA dominates histopatholog y
	94%	£5,209	£13,159	£15,947	£20,204	£27,506	£42,943	£97,181	OSNA dominates histopatholog y	OSNA dominates histopatholog y
	96%	£6,132	£17,228	£21,746	£29,425	£45,362	£98,379	OSNA dominates histopatholog y	OSNA dominates histopatholog y	OSNA dominates histopatholog y
	98%	£7,194	£23,238	£31,259	£47,620	£99,410	OSNA dominates histopatholog y	OSNA dominates histopatholog y	OSNA dominates histopatholog y	OSNA dominates histopatholog y
	100%	£8,430	£33,015	£49,733	£100,308	OSNA dominates histopatholog y	OSNA dominates histopatholog y	OSNA dominates histopatholog y	OSNA dominates histopatholog y	OSNA dominates histopatholog y