DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Advisory Committee date: 10 April 2013

Diagnostics Consultation Document – Themed Comments

THEME: EVIDENCE - METASIN TEST

Comment number	Name and organisation	Section number	Comment	Response
1	Consultee 6: NHS Professional (Developer of Metasin test)	1	I concede that Metasin has not been published. The data we have garnered is being consolidated towards reaching this goal. The index manuscript describing the methodology is now in submission format to an on-line journal, primarily in the hope that reviewers will be able to respond sooner. The main validation data as submitted to NICE statistical approval is now undergoing major re-drafting. It will be submitted before the 10th of April meeting. The greatest advantage(s) of the Metasin assay is: 1. gives good consistent results of very low discordant rates and 2 centres have been monitoring the data assiduously. 2. The costing is predicated on having a	Thank you for your comment which the Committee considered The Committee concluded that the test appeared promising but that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice. The Committee concluded that a consequence of the uncertainty in the evidence base was that there was too much uncertainty in the cost-effectiveness analyses to form conclusions about the cost-effectiveness of the Metasin test.

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			technical member at PAH carrying out appropriate QCs and despatching test kits bought in from TiBMoL Biol. To protect the PAH NHS Trust, there is in addition a premium of Â£25 to cover for NHS indemnity. This costing is predicated on an initial volume of 1000 patients. If it gets NICE approval, the number of tests carried out will increase substantially, bring the price of Â£80 per test down to the order of Â£50 per patient. Personal financial gain is NOT the motivator here. It is the perceived win for the NHS.	
2	Consultee 6: NHS Professional (Developer of Metasin test)	1	**1. Metasin Assay not recommended** We have developed this assay at Harlow initially as an in-house reagent. The assay has shown to be very robust with discordance rates under 4%. The data has taken a considerable length of time to collate. At the time of the start of the NICE approval process (?) April 2012 the assay was very much an in-house assay.	Thank you for your comment which the Committee considered. The Committee concluded that the test appeared promising but that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice.

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			Since then we have: 1. collated the data and sent a preliminary draft manuscript to NICE in time for the October 2012 deadline for submissions. The incomplete nature of the manuscript relates to 2 gaps. i. The lack of the write up of the methodology-now completed and in submission to Journal of Molecular Sciences-Copy of paper submitted to Dr Sara Byron today-after submission ii. The analysis of discordant nodes by an independently validatable assay. This has now been largely completed as part of an MSc project for a member of a BMS member in our Department (SB): we have used an RT-PCR approach with another series of markers (CK7, CK20, Pip1, B726 GABA and B305D). This analysis conclusively shows that over 40% of the false positives show expression of these epithelial/breast specific markers, indicating that the false positive nodes are truly positive and the discordance relates to tissue allocation bias. A improved but still should be considered a	

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Comment number	Name and organisation	Section number	Comment	Response
			manuscript in preparation. I have forwarded a copy of this to Dr Sarah Byron today. I anticipate that the methodology paper will be in press by the time the committee meet in April 2013. The validation paper will be submitted soon and ther again would hope that the peer review process will be completed by June this year since the data is all completed.	
3	Consultee 2: NHS Professional	2	The metasin test has been extensively validated at Queen Alexandra Hospital in Portsmouth.	Thank you for your comment which the Committee considered. The Committee concluded that the test appeared promising but that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice.
4	Consultee 3:	4	Modern primers and probes sequencing design	Thank you for your comment which the

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	NHS Professional		software use the same selection criteria and algorithms rank them as best. Metasin is similar to the discontinued Genesearch Veridex Assay, you would expect to get similar detection rates even though using different primers and probes. After 5 years of testing, we have found this to be the case; as we have tested over 700 cases using Veridex in the first 2 years of testing and more than 800 cases in the preceding 3 years with Metasin. Just taking the first 700 cases tested by Metasin we found similar detection rates, sensitivity and specificity.	Committee considered. The in-house Metasin test differs from the discontinued commercial test by using different primer-probe combinations to detect the CK19 and mammaglobin genes so any data showing the diagnostic accuracy of the GeneSearch assay was not considered transferable to the Metasin test.
5	Consultee 1: NHS Professional	5	The study by Sundaresan et al is criticised for not reporting details of patient recruitment but it states that the patients are all breast cancer patients undergoing sentinel node biopsy. No patient exclusion grounds are detailed because there are none so there is no hidden risk of bias The study Cutress et al assesses the cost effectiveness of the now withdrawn GeneSearch	Thank you for your comment which the Committee considered. The Committee concluded that the test appeared promising but that there was too much uncertainty associated with the evidence to recommend use of the test in

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			Assay. There is a criticism that this is not directly relevant to Metasin as both assays would be expected to perform differently. However both GeneSearch and Metasin assays use the same equipment, take the same time to perform and are performed by users with the same level of expertise using the same type of RNA extraction kit the only difference in a cost effectiveness analysis is that primers and probes used in the Metasin Assay are a good deal cheaper than GeneSearch kits. I would therefore consider this study to be relevant.	routine clinical practice. The in-house Metasin test differs from the discontinued commercial test by using different primer-probe combinations to detect the CK19 and mammaglobin genes so any data showing the diagnostic accuracy of the GeneSearch assay was not considered transferable to the Metasin test..
6	Consultee 6: NHS Professional (Developer of Metasin test)	5	The data presented and on Metasin is stated incorrectly. Would ALL STATISTICS NEED TO REWORKED IN THE LIGHT OF THIS? See Table 3 (UNPUBLISHED DATA). The discordance rate is 4.4% before formal discordance analysis.	Thank you for your comment which the Committee considered. The External Assessment Group is not aware of any incorrectly stated data. The data reported in the assessment report were presented as stated in the unpublished literature.

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			After formal discordance analysis the numer drops to 4.2% and after cases are excluded on the basis of macro-mets or micro-mets in axillary clearance samples the discordance level drops to 3.96%. The delay in submitting the manuscript rest on incompleteness of teh study. We have since examined the homogenates (n=25 only) of cases that were discordant and show over 50% to show expression of CK7 and PIP1 markers in these smaples, implying in the Histology negative metasin positive group that this supports the contention of metastatic disease. Conversely, apart from 2 cases, all Histology positive Metasin negative cases were negative for these markers. The 2 cases that came up with PIP1 and CK7 were GeneSearch positive. I suppose this implies that Metasin missed these in diagnsotic terms!	The Committee concluded that the test appeared promising but that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice.
7	Consultee 2: NHS	7	All data on metasin should be published as soon as possible.	Thank you for your comment which the Committee considered.

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Comment number	Name and organisation	Section number	Comment	Response
	Professional			The Committee concluded that the test appeared promising but that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice.
8	Consultee 6: NHS Professional (Developer of Metasin test)	10	This preliminary consultation document states that Metasin is not to be recommended, on the grounds that there is NO peer reviewed publications. At the start of this process, to a great extent, the emphasis was of the absence of CE-marking, not completed and to a great extent, I was personally focussing on this goal. The data exists and I have shared (no longer in academic confidence) all of the data re. the validation study. I am actively pursuing the publications of the Metasin assay. I concede, delays were partly due to incomplete data sets which have now mainly been addressed. The amended but still far from complete manuscript in revised form, but still	Thank you for your comment which the Committee considered. The Committee concluded that the test appeared promising but that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice.

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Comment number	Name and organisation	Section number	Comment	Response
			needing more rewording includes some of the STARD data requested. I will be confident that the manuscripts will be successfully peer reviewed before the end of June/July. I hope the committee considers this likely possibility.	
9	Consultee 6: NHS Professional (Developer of Metasin test)	General	I hope the manuscript in submission now gets to 'in-press status' by the time of the meeting on the 10th of April meeting: ikewise the validation paper by the end of June 2013.	Thank you for your comment which the Committee considered. The Committee concluded that the test appeared promising but that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice.

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THEME: ACCURACY - METASIN TEST

Comment number	Name and organisation	Section number	Comment	Response
10	Consultee 3: NHS Professional	4	Using both Veridex and Metasin assays we have found that patients with just Mammaglobin only positive nodes accounted for 8% of our positive patients. Over 5 years that means over 30 patients would have been missed.	Thank you for your comment which the Committee considered. The Committee acknowledged that the Metasin test includes a marker for mammaglobin, however, it concluded that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice.
11	Consultee 1: NHS Professional	3	The Metasin assay tests for 2 tumour markers, Mammaglobin as well as CK19. During the 5 years the assay has been running at Portsmouth 8% of the positive patients have had nodes positive for Mammaglobin only. That means that 33 patients would have been missed if we had tested for just the one tumour marker.	Thank you for your comment which the Committee considered. The Committee acknowledged that the Metasin test includes a marker for mammaglobin, however, it concluded that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice.
12	Consultee 7:	All	The Metasin test has been developed based on	Thank you for your comment which the

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THEME: ACCURACY - METASIN TEST

Comment number	Name and organisation	Section number	Comment	Response
	Manufacturer (TIB MOLBIOL)		the Veridex BLNA which has been withdrawn from the market. In the early phase of the development the results were aligned against the Veridex kit. The Metasin test provides similar or better results compared with Veridex. • The number of discordant results of about 4% is lower than published for Veridex. This can be due to the high accuracy work performed at the test site and we expect • that the average results from other laboratories might arrive in the range known for the Veridex test (7%) or below. • Both false-negative and false-positive results obtained compared to histopathology are most likely due to the sampling bias..	Committee considered. The in-house Metasin test differs from the discontinued commercial test by using different and primer-probe combinations to detect the CK19 and mammaglobin genes so any data showing the diagnostic accuracy of the GeneSearch assay was not considered transferable to the Metasin test.

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THEME: PRE-SCREENING TUMOURS

Comment number	Name and organisation	Section number	Comment	Response
13	Consultee 2: NHS Professional	4	Using a test which looks at two rather than one markers is better. In our series using genesearch and then metasin, we have had over 30 patients with SLNs testing positive for mammaglobin and negative for CK-19. Pre-screening of tumours for expression of the two markers would be expensive and time-consuming at a time that the NHS and in particular histopathology departments are struggling to keep up with the workload and save money.	Thank you for your comment. The Committee considered this comment and agreed that pre-screening for expression of CK19 and mammaglobin was not likely to take place in routine clinical practice. (see section 6.9 of the guidance). The Committee acknowledged that the Metasin test includes a marker for mammaglobin, however, it concluded that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice.
14	Consultee 6: NHS Professional (Developer of Metasin test)	4	4. There is no need to screen for tumours with CK19 immunohistochmemistry as advocated above for METASIN. The issue is that there are about 10% of CK19 negative nodes. If we (Metasin) were to drop the Mammaglobin marker in our assay then we would fail to detect these cases. Our recent publication, clearly states that the leap from protein expression data to RNA is a big leap of faith, especially without any evidence	Thank you for your comment. The Committee considered this comment and agreed that pre-screening for expression of CK19 and mammaglobin was not likely to take place in routine clinical practice. (see section 6.9 of the guidance). The Committee acknowledged that the Metasin test includes a marker for

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THEME: PRE-SCREENING TUMOURS

Comment number	Name and organisation	Section number	Comment	Response
			to substantiate this. Our current paoer illustrates 2 cases which are K19 immuno positive in the tumour but are negative in the mammaglobin positive sentinel node immunohistochemistry to RNA. 5. The MGB staining is seen in 56% of breast tumours, consiedrably less than that seen with CK19 (see Al-Ramadhani et al-in submission).	mammaglobin, however, it concluded that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice.
15	Consultee 3: NHS Professional	6	4. Re: pre-screening for the tumour expression of two markers- I cannot see how this would add anything and it would be time consuming and costly. Tumour heterogeneity is well known and gene expression can be variable at any given moment.	Thank you for your comment. The Committee considered this comment and agreed that pre-screening for expression of CK19 and mammaglobin was not likely to take place in routine clinical practice (see section 6.9 of the guidance).

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THEME: ACCURACY OF HISTOPATHOLOGY

Comment number	Name and organisation	Section number	Comment	Response
16	Consultee 1: NHS Professional	4	The Metasin tests for Mammaglobin, this is rarely available as an immuno stain in Histology labs as the antibody is notoriously difficult to work with. Tissue allocation bias is inevitable when assessing half a node. The nodes have to be sliced into a workable size during the limited time taken for the assay, in practice it is virtually impossible to cut slices smaller than 2mm in the londitudinal plane. A micromets can easily sit between these slices and even a macromets is possible when taking the width of the node into account. I fail to see how this can be tested for. The only way to avoid tissue allocation bias is to put the whole node through the assay.	Thank you for your comment. The Committee considered this comment and agreed that pre-screening for expression of CK19 and mammaglobin was not likely to take place in routine clinical practice because of the resource restraints on pathology services (see section 6.9 of the guidance). The Committee heard that the main source of inaccuracy in histopathology is tissue allocation bias, but that other sources of inaccuracy are possible, including user variability. The Committee noted that it was unlikely that a macrometastasis would be missed if the current histopathology guidelines were followed but that it was possible that micrometastases could be missed (see section 6.6). Furthermore the Committee concluded that whole-node OSNA analysis should be fully implemented in local clinical practice to reduce the risk of tissue allocation bias (see section 6.8).

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THEME: EVIDENCE - OSNA TEST

Comment number	Name and organisation	Section number	Comment	Response
17	Consultee 2: NHS Professional	5	I am concerned that the sensitivity and specificity values reported in different publications on the OSNA method vary significantly.	Thank you for your comment which the Committee considered. The external assessment group reported that when sample type and adjustment for tissue allocation bias are taken into account, there is a small amount of variation between the values for sensitivity and specificity which is consistent with chance alone.
18	Consultee 4: Manufacturer (Sysmex UK)	5	Sysmex would like to comment on section 5.12 regarding OSNA technology which utilises RT-LAMP rather than PCR.	Thank you for your comment. The guidance now reflects this (see section 5.12 of the guidance).

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THEME: TECHNOLOGY – METASIN TEST

Comment number	Name and organisation	Section number	Comment	Response
19	Consultee 6: NHS Professional (Developer of Metasin test)	2	2. CE Marked the Metasin Assay in collaboration with TiBMOL BIOL. We are in the process of evaluating a new series of pre-mixes. Here the risk of each hospital being a manufacturer of it own reagents are eliminated. The need for any significant expertise of scientists and back up are no longer necessary. This is on the background that when we at PAH established the assay, the FY2 Trainee (Dr Salma Al Ramadhani) very junior at the time, had, with no previous molecular expertise., nor laboratory experience. She established the assay and has moved on to The Barts and the Royal London as an ST2 trainee in Histopathology. Currently all of the pre-mixes are prepared in-house and we go through a detailed process of QC of the reagents. We look forward to the use of the CE marked reagents which to a great extent overcome the risk of the in house reagents. 3. Below I append a study evaluating the new CE marked reagents. This work is very preliminary at	Thank you for your comment. The Committee considered this comment and decided to add section 6.2 and change section 6.3 of the guidance.

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THEME: TECHNOLOGY – METASIN TEST

Comment number	Name and organisation	Section number	Comment	Response
			present and shows that there is significant correlation with the data obtained from in-house reagents. The advantages are: 1. No need for local QC with associated risks of faulty preparationor bathc variability. 2. Much simpler protocol for the assay and require some basic competency in handling a pipettor and general laboratory skills, equivalent to a BMS band 6. The BMS staff carrying this task now are of this grade at PAH. The BMS member carrying out he reagent preparation is a band 7. Nevertheless, she has no previous experience of nucleic acid chemistry. She has a BSc and MSC based on an immunohistochemistry project.	
20	Consultee 6: NHS Professional (Developer of Metasin test)	4	1. The Metasin BLNA runs in the current format of result in under 26 mins ONLY on the CEPHEID SAMARTCYCLER. 2. The assay can detect upto 500 cells which is	Thank you for your comment which the Committee considered. The Committee concluded that the Metasin test appeared promising but that there was too much uncertainty associated with the

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THEME: TECHNOLOGY – METASIN TEST

Comment number	Name and organisation	Section number	Comment	Response
			in the hinterland of ITCs/negative. The assay easily picks up 500 to 1000 cells which is in the beiginings of hte micro-mets arena. As for the macro-mets there are no issues. 3. We at PAH have considerable experience of the Metasin asay and have a discordant level of under 4%.	evidence to recommend use of the test in routine clinical practice.
21	Consultee 6: NHS Professional (Developer of Metasin test)	4	5. Our considerable experience since 2008 when we implemented the GeneSearch assay after evaluating both technologies (OSNA inclusive) is that we are now ready to consider using the whole node in the assay. This is pertinent now, as our tier 2 assay is coming to readiness and we now a have a robust assay to evaluate cases that may be 'assay fails'.	Thank you for your comment which the Committee considered. The Committee concluded that the Metasin test appeared promising but that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice.
22	Consultee 1: NHS Professional	6	The Metasin Assay is portable and very robust. The SmartCycler can be transported anywhere. It takes up very little space.	Thank you for your comment. The Committee considered this comment and decided to add section 6.2 to the guidance.
23	Consultee 6:	6	3. Whole node analysis: Our experience at PAH	Thank you for your comment which the

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THEME: TECHNOLOGY – METASIN TEST

Comment number	Name and organisation	Section number	Comment	Response
	NHS Professional (Developer of Metasin test)		in Harlow is substantial and we are of teh opinion that we consider this assay to eb very robust, such that we would now consider submitting the whole node for Metasin. The one difficulty is if the assay fails, we need a fail-safe. The new CK7 and PiP1 (GCFP) markers developed as a the 'Tier 2 assay' overcomes this potential limitation. Clear guidelines should be established for this eventuality.	Committee considered. The Committee concluded that the Metasin test appeared promising but that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice.
24	Consultee 7: Manufacturer (TIB MOLBIOL)	All	• We recommend to use a half-node technique and to run histopathology for all negative samples to prevent to oversee any metastasis by the molecular assay. Samples rated as positive shall be collected and archived to enable a verification of the molecular test results, in particular for quality assurance purposes. • The instrument required to run the Metasin test are moderate. Many laboratories are equipped with a SmartCycler system while laboratories	Thank you for your comment which the Committee considered. The Committee concluded that the Metasin test appeared promising but that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice.

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Comment number	Name and organisation	Section number	Comment	Response
			purchasing a new instrument • can use it to run also other tests (from different suppliers). • The discussion regarding the amplification and detection of pseudogenes is theoretical. Primers and probes are positioned in a way to exclude an amplification of other genes or transcripts. Neither human genomic DNA nor mRNA from non-tumour tissues yield any positive signals for CK19 and MGB. • We use a reference gene transcript to verifying that extraction, reverse transcription and amplification and to quantify the extend of over-expression of CK19 and MGB in order to classify positive samples as micro-metastasis or macro- metastasis. The cut-off values have been verified by parallel histopathology studies. Tests which rely on amplification of CK19 only miss a	

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THEME: TECHNOLOGY – METASIN TEST

Comment number	Name and organisation	Section number	Comment	Response
			sample and inhibition control.	

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THEME: TECHNOLOGY – OSNA TEST

Comment number	Name and organisation	Section number	Comment	Response
25	Consultee 3: NHS Professional	2	2. OSNA technology uses turbidity as an indication of PCR amplification and is therefore only capable of detecting a single marker in a reaction tube. Real time PCR technology used by Metasin can detect multiple targets (currently two markers and a housekeeping gene) in a reaction tube using a different coloured fluorophore for each target. More targets can be added to the assay, work is currently underway to include PiP1. 3. Quantitative Reverse Transcription Real time polymerase chain reaction qRT-PCR using TaqMan/hydrolysis probes technology is well established and has been in widespread use for nearly two decades with thousands of applications. The probe technology allows instant confirmation of the sequence of amplified product.	Thank you for your comment which the Committee considered. The Committee concluded that the Metasin test appeared promising but that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice.
26	Consultee 4: Manufacturer	2	OSNA can be used both intra-operatively and post-operatively for lymph node analysis. In	Thank you for your comment which the

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THEME: TECHNOLOGY – OSNA TEST

Comment number	Name and organisation	Section number	Comment	Response
	(Sysmex UK)		addition the OSNA system is also CE marked for colon cancer and gastric cancer.	Committee considered. The Committee acknowledged that the OSNA system could be used intra-operatively or post-operatively but, concluded that the intra-operative use of the OSNA system during breast surgery offered significant benefits to patients and the NHS, above those of current practice (post-operative histopathological analysis) or post-operative use of the OSNA system. Using the OSNA system for colon cancer and gastric cancer is outside the scope of this guidance.

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THEME: PREVALENCE

Comment number	Name and organisation	Section number	Comment	Response
27	Consultee 2: NHS Professional	6	I do not accept the comment that the prevalence of SLN metastases is likely to be around 30%. The accuracy of pre-operative tests is improving and axillary lymph node metastases are increasingly detected pre-operatively, therefore, the prevalence of SLN metastases is decreasing.	Thank you for your comment. The Committee heard that the sentinel lymph node metastases prevalence was likely to be higher than 20% and it considered that it was appropriate to assume a higher prevalence than that used in the base case (see section 6.5 and 6.13)..

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THEME: COSTS

Comment number	Name and organisation	Section number	Comment	Response
28	Consultee 5: NHS Professional	3	3.13- Not all centres will currently perform an axillary lymph node dissection for micrometastatic disease. THis needs to be added in the cost evaluation.	Thank you for your comment. The Committee considered this comment and decided to change section 6.15 of the guidance.
29	Consultee 5: NHS Professional	4	4.5: same comment as for 3.13 about micrometastatic disease and ALND	Thank you for your comment. The Committee considered this comment and decided to change section 6.15 of the guidance.
30	Consultee 5: NHS Professional	5	5.23: the cost for histology given in this comparator is ABSURD and TOO HIGH! This has been mentioned in the last consultation too and has been completely ignored by the committee. £472 is higher than the total costs for histology examination of a mastectomy with node clearance (lab + consultant costs) in my dept even for a specimen from the private sector. Costs for NHS specimens are significantly cheaper. This MUST NOT be ignored by the committee as	Thank you for your comment. The Committee considered this comment and considered that if the economic model used a more realistic cost for histopathology, it would indicate that the RD-100i OSNA system was less cost effective than the base-case ICERs presented in the diagnostics assessment report. However, given all of the uncertainty in the cost-effectiveness analyses, the Committee concluded that the RD-100i OSNA system was still likely to be a cost-effective use of NHS resources (see

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Advisory Committee date: 10 April 2013

Diagnostics Consultation Document – Themed Comments

THEME: COSTS

Comment number	Name and organisation	Section number	Comment	Response
			these costs have been used for all calculations.	section 6.14 of the guidance)..
31	Consultee 6: NHS Professional (Developer of Metasin test)	10	The impact of getting NICE approval would have a further significant cost benefit. The pricing of £80+£25 (latter for indemnity) is predicated on a 1000 test per year and running costs of £45k+£25k per annum. For instance the requirement was for 5000 tests then the cost would be £50. A win for the NHS.	Thank you for your comment which the Committee considered. The Committee concluded that the Metasin test appeared promising but that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice. The Committee concluded that a consequence of the uncertainty in the evidence base was that there was too much uncertainty in the cost-effectiveness analyses to form conclusions about the cost-effectiveness of the Metasin test.
32	Consultee 7: Manufacturer (TIB MOLBIOL)	All	Costs per sample are moderate. The intention to introduce the Metasin test was not to save costs but to give the patient a fast and reliable diagnosis and to prevent a second surgery for the 25%-35% metastasis-positive patients. A	Thank you for your comment which the Committee considered. The Committee concluded that the test appeared promising but that there was too

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			second surgery increases the risk for the patient and causes additional costs.	much uncertainty associated with the evidence to recommend use of the test in routine clinical practice. The Committee concluded that a consequence of the uncertainty in the evidence base was that there was too much uncertainty in the cost-effectiveness analyses to form conclusions about the cost-effectiveness of the Metasin test.

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THEME: IMPLEMENTATION

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33	Consultee 6: NHS Professional (Developer of Metasin test)	4	4. The assay has the capability of being run remotely in a non-pathology setting. eg. In Queen Alexandra Hospital, Portsmouth, the assay is run by a non-BMS member in theatre (AMcD). The surgeons are now adept at interpreting the data (safely) even before the machine 'calls the result'. There is a lead –in period of learning which institutions who adopt this technology will gain over time.	Thank you for your comment. The Committee considered this comment and decided to add section 6.2 to the guidance.
34	Consultee 4: Manufacturer (Sysmex UK)	6	Sysmex are currently supporting scientists in France who are working on the creation of suitable samples for an EQA Scheme.	Thank you for your comment..
35	Consultee 6: NHS Professional (Developer of Metasin test)	6	2.Expertise to run Metasin: It is a mistake to imply and state that you need to have a deeper understanding of nucleic acid chemistry to run the Metasin assay. The gap here is when it was run as an in-house reagent, when the local Depatment had to manufacture the reagents and run their own QC. The pre-mixes in the CE-marked Metasin are brilliant, since they are lyophillised reagents: just add water, enzyme and	Thank you for your comment. The Committee considered this comment and decided to add section 6.2 and change section 6.3 of the guidance.

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			RNA and run. Controls are included.	
36	Consultee 7: Manufacturer (TIB MOLBIOL)	All	• We agree that performing the Metasin test requires skilled and particular trained staff, but common laboratory technician can be trained to run the assay with the required performance. • The Metasin test can not be applied in a surgery theatre but needs a standard molecular biology laboratory environment. The average run time of the test allows to cover an additional (short) transportation of the tissue to the laboratory.	Thank you for your comment. The Committee considered this comment and decided to add section 6.2 and change section 6.3 of the guidance.

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THEME: RESEARCH

Comment number	Name and organisation	Section number	Comment	Response
37	Consultee 4: Manufacturer (Sysmex UK)	7	Sysmex would like to comment that a database has been developed by existing OSNA users across Europe lead by a multidisciplinary working group of expert clinicians.	Thank you for your comment. The Committee considered this comment and decided to change section 7.1 of the guidance.

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THEME: CURRENT PRACTICE

Comment number	Name and organisation	Section number	Comment	Response
38	Consultee 5: NHS Professional	6	6.10: While the comments made on robustness of the Z11 trial are reasonable, its impact on Breast cancer surgical practice worldwide (including the UK) is not to be underestimated. This has also in part led to the reason why micromets are not being treated by ALND in many centres. The Committee's views therefore are somewhat naive and potentially biased by the advisors views.	Thank you for your comment. The Committee considered this comment and decided to change section 6.15 of the guidance.

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THEME: TIMING OF GUIDANCE

Comment number	Name and organisation	Section number	Comment	Response
39	Consultee 1: NHS Professional	1	A number of papers are due to be submitted for publication. I am involved in 4 myself. The timing of this report is most unfortunate	Thank you for your comment which the Committee considered. The Committee concluded that the Metasin test appeared promising but that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice. NICE will update the literature search at least every 3 years to ensure that relevant new evidence is identified. NICE will contact product sponsors and other stakeholders about issues that may affect the value of the diagnostic technology. NICE may review and update the guidance at any time if significant new evidence becomes available.
40	Consultee 3: NHS Professional	1	1. It is unfortunate that the assessment is happening now rather than in 6 months time when there are due to be a number of peer reviewed papers on Metasin.	Thank you for your comment which the Committee considered. NICE will update the literature search at least

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THEME: TIMING OF GUIDANCE

Comment number	Name and organisation	Section number	Comment	Response
				every 3 years to ensure that relevant new evidence is identified. NICE will contact product sponsors and other stakeholders about issues that may affect the value of the diagnostic technology. NICE may review and update the guidance at any time if significant new evidence becomes available.
41	Consultee 2: NHS Professional	10	Peer-reviewed data and paper on metasin will be published very soon, therefore, an early review and update of the guidance should be considered.	Thank you for your comment which the Committee considered. NICE will update the literature search at least every 3 years to ensure that relevant new evidence is identified. NICE will contact product sponsors and other stakeholders about issues that may affect the value of the diagnostic technology. NICE may review and update the guidance at any time if significant new evidence becomes available.

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THEME: OTHER

Comment number	Name and organisation	Section number	Comment	Response
42	Consultee 4: Manufacturer (Sysmex UK)	1	Sysmex have no additional comments to make in relation to the provisional recommendations.	Thank you for your comment
43	Consultee 4: Manufacturer (Sysmex UK)	3	Sysmex have no additional comments to make in relation to clinical need and practice.	Thank you for your comment
44	Consultee 4: Manufacturer (Sysmex UK)	4	Sysmex have no additional comments to make in relation to the diagnostic tests.	Thank you for your comment
45	Consultee 4: Manufacturer (Sysmex UK)	8	Sysmex have no additional comments to make in relation to this but support this concept.	Thank you for your comment
46	Consultee 4: Manufacturer (Sysmex UK)	9	Sysmex have no additional comments to make in relation to this.	Thank you for your comment
47	Consultee 4: Manufacturer	10	Sysmex have no additional comments to make in relation to this.	Thank you for your comment

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THEME: OTHER

Comment number	Name and organisation	Section number	Comment	Response
	(Sysmex UK)			

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THEME: PART II - RECOMMENDATIONS

Comment number	Name and organisation	Section number	Comment	Response
48	Consultee 2: NHS Professional	1	I agree that peer-reviewed publications on metasin are required. We are in the process of finalising papers based on our experience with this method (over 1000 cases in a single centre). We have already shared some of our results through abstracts and presentations. This guidance should recommend that institutions already successfully using metasin should continue to do so in order to produce publications based on their results which will add to the debate on this topic and help introduce this method into routine NHS practice in the near future.	Thank you for your comment. The Committee considered this comment and decided to change section 1.2 of the guidance. The Committee concluded that the Metasin test appeared promising but that there was too much uncertainty associated with the evidence to recommend use of the test in routine clinical practice.
49	Consultee 5: NHS Professional	1	Should 1.1 state "intra-operative use"? Surely it is superior only when used in an intra-op setting to histology	Thank you for your comment. The Committee considered this comment and decided to change section 1.1 of the guidance.