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

Diagnostics Assessment Report (DAR) - Comments

Responder reference no.	Comment no.	Page no.	Section no.	Comment	Response
RR1.	1.	111	-	Re: Table 38 one might have anticipated that the cost savings of averting the need for a second operation would have been considerably higher than was actually evidenced.	On a per patient basis, the cost saving due to avoidance of a second operation amounts to 28% (the node positive rate in the patient population) times the cost of a second operation (£2296), that is £643, but intra-operative testing increases the cost of the initial operation by £388 for all patients and the extended surgery required by immediate axillary clearance increases LOS by 0.6 days and theatre time by 40 minutes, adding £703 for the 28% with immediate axillary clearance, that is £197 per patient; £643-£585=$58
	2.	-	-	Was there an intention that a specific age group would benefit most from the Intraoperative tests in terms of cost effectiveness?	We conducted our analyses assuming an average age of 56. While the cost-effectiveness is likely to be affected by the remaining life expectancy of the individual we did not aim to differentiate by age in our analyses to avoid issues of equity that are expressly of no relevance to NICE decision-making process.
	3.	-	-	Will the tests be available to all patients regardless of age?	Yes.

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	4.	-	-	Clearer comparison tables showing sample age and grade of tumour.	Unable to respond without more details about table causing difficulty. In any case, please note that we are restricted by the presentation of this information in the studies. In many cases patient characteristics were not fully reported.
	5.	-	-	Provision of a summarised synopsis report, together with recommendations for stakeholders without the advantage of a scientific research background.	Agree that this may useful in future reports. Currently no provision for this in the EAG report. Overview prepared by NICE technical team is we understand designed to identify key information and express this in as accessible language as possible
RR2.	-	-	-	No comments made.	
RR3.	1.	-	-	We question the assumptions taken for this model: histopathology analysis is set with accuracy at 1 (100%). Therefore by definition quality of biomolecular analysis can only be inferior. We dispute this. Only cost effectiveness can be accurately assessed. This should be reflected in the conclusion.	We are sympathetic to this view-point. However, we identified no evidence to support the view that the errors suggested by the test accuracy studies were other than real and that OSNA was indeed inferior to research standard histopathology used in the accuracy studies we reviewed. The question as to whether research standard histopathology significantly overstates routine histopathology is a separate issue and not one we were able to answer. We

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					certainly identified no evidence which would allow us to quantify what the relative accuracy of routine histopathology for SLNB is. We felt this was essential before amending the model in the way the commentator seems to imply and we propose no changes to the conclusion. We understand some evidence on relative accuracy of routine practice may be forthcoming at the appraisal committee meeting. PS post AC meeting – although clinical opinion was advanced to support the equivalence/superiority of the accuracy of OSNA to routine histopathology, no research evidence was forthcoming)
	2.	118 44	5.3.2.2.1 2.3.6	Histopathology never analyses all of the material and therefore the accuracy is dependent on the number of levels and skip ribbons applied. It is necessary that both methods; histopathological and biomolecular analysis, should have the same accuracy for comparative purposes. NHS BSP 58 Guidelines state routine analysis should be done at least at 3mm intervals or less. Viale et al. clearly shows a pathology sensitivity of 76.4 % at 2mm intervals. In comparison OSNA studies are compared to 250 µm cutting intervals. Histopathology	This observation would need to be substantiated in systematic evidence of relative accuracy (i.e. histopathology vs. OSNA as opposed to histopathoplogy alone). In the absence of it, the reference standard would be a priori expected to be the more accurate technology until the weight of evidence suggests the index test is more accurate. Such evidence is not currently available. We are unclear about the purpose of para 1.

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				at this level would show a sensitivity of 94.4%. Weaver et al. emphasise such limitations due to the cutting protocol as well. Therefore this would strongly suggest that UK guideline routine pathology cannot be 100% sensitive. In addition we question whether routine histopathological analysis is done in a standardised way. Viale G et al., Comparative Evaluation of an Extensive Histopathologic Examination and a Real-Time Reverse-Transcription-Polymerase Chain Reaction Assay for Mammaglobin and Cytokeratin 19 on Axillary Sentinel Lymph Nodes of Breast Carcinoma Patients, *Annals of Surgery* 2008; 247:136-142 (table 4) & Weaver D, Pathology evaluation of sentinel lymph nodes in breast cancer: protocol recommendations and rationale, *Modern Pathology* 2010, 23:26-32 (figure 1&3)	The meaning of " It is necessary that both methods; histopathological and biomolecular analysis, should have the same accuracy for comparative purposes." is not clear Thank you for drawing our attention to the interesting study by Viale et al. We had not reviewed it because it considers the accuracy of the GeneSearch BLN, an intraoperative molecular test which has been withdrawn commercially and as a result was not a technology included in the appraisal. The primary purpose of the study was thus not to consider the accuracy of routine histopathology for SLNB as implied. The findings referred to by the commentator are not supported by a description of the methods used to achieve the estimation and do not directly relate to the primary purpose of the study which was to measure the accuracy of GeneSearch BLN, for which full methods were given. The study was unique in performing histology on very numerous closely spaced tissue sections, but this had to be achieved on frozen sections, so it is likely the accuracy estimates obtained are atypical. The accuracy obtained for the

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					GeneSearch BLN test (sensitivity 78%, specificity 95%) was much lower than other accuracy evaluations of this test and accuracy claims for similar tests such as Metasin. On both grounds we think it is unlikely that this study provides a valid estimate of the relative accuracy of routine histopathology in comparison to OSNA and we do not intend to include it in our report
	3.	122	5.3.3.1.1	We don´t quite understand why studies with TAB adjustment are excluded from base case. Using a study design with different tissue slices going into different methods a 100% concordance cannot be achieved. Test result quality was increased by TAB analysis. Daniele et al. concludes “that the sampling procedures of the tissue to be submitted to RT-PCR or conventional histopathological processes are the main reason for discrepancies between molecular and morphological analysis.” Daniele L et al., Technical limits of comparison of step-sectioning, immunohistochemistry and RT-PCR on breast cancer sentinel nodes: a study on methacarn fixed tissue, *J Cell Mol Med* 2009;	They are separately considered as they would be expected to be measuring a different population parameter from that measured by studies without TAB adjustment. In essence the two types of study measure a different outcome measure. We agree with this concern and have acknowledged the limitation of evidence on relative effectiveness based on studies without adjustment for TAB. The studies that report such adjustment were analysed separately and result in a reduced gap between the index test (OSNA) and the reference standard relative to studies without TAB adjustment. We are satisfied that the studies that adjusted for TAB did so in a plausible, sensible manner and that any

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				13(9B):4042-50	residual TAB that may remain is insignificant to our analyses.
	4.	85 161	4.2.2.3 7.1	One main outcome of the study is that with OSNA there is the risk of false positive results. However, the specificity study in Tsujimoto et al [66] shows that all tested pN0 patients also tested negative with OSNA. The cut-off is designed in a way that the CK19 mRNA copy number is set at 250 and not at 0 in order to compensate for any unspecific amplification if present. ITC`s are classified in the OSNA negative population. Also see the following study that underlines that epithelial cell inclusion in SLN which would lead to a false positive OSNA result is very unlikely: Iken S. et al., Breast Cancer Res Treat. Absence of ectopic epithelial inclusions in 3,904 axillary lymph nodes examined in sentinel technique. 2012,132(2):621-4. This should be reflected in conclusion as well.	? This is an included study. Although this study shows that specificity is perfect, other evaluations do not. The purpose of the systematic review is to put all the studies addressing a particular question (here specificity of OSNA) in context. This is the appropriate basis of the conclusions and so we propose no changes to the report in response to this comment.
	5.	59	4.2.1.3	The study from Feldman S. was conducted using a different analytical system (RD-110i) with a different reagent kit which was used for a study in the US only. It therefore in our opinion should not be considered in the analysis as data cannot be compared directly with	Thank you. It remains an included study by our pre-specified inclusion criteria. However we will add a note with the additional information. We do not believe it materially affects the results

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				the data from studies where RD-100i was used.	
	6.	125	5.3.3.2.1	Price for OSNA includes all, reagents & consumables as well as instrument, ancillary equipment and service contract. This might not be comparable to prices given by Metasin.	Metasin sponsors were required to and did provide cost information in the same format as that used by OSNA sponsors to provide information for their own test, including the information referred to (Personal communication 31 October 2012). However, more important for the assessment was the lack of robust evidence on clinical effectiveness/test accuracy for Metasin. We therefore treat the quality of the evidence received from Metasin as inferior to that available from OSNA and only use it as illustrative of what sponsors of the former test claim but have yet to document with peer reviewed evidence. This is all made clear in the DAR report.
	7.	73	4.2.1.6.2	Sysmex compensated the additional workload due to the study protocol and all necessary material for OSNA analysis for the study published by Snook et al.	Thank you for this additional information. We will add a note to this effect
	8.	144	5.3.8.1	Source not found.	Sorry. Formatting became corrupted. It was meant to be 'Figure 19'

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