NICE National Institute for Health and Care Excellence

DAP36 - Tests in secondary care to identify people at high risk of ovarian cancer

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
Roche Diagnostics	1	34-35	2.3.3	We are concerned that the ultrasound variables in the ADNEX model would not be easy to measure for generalist sonographers. Further to the publication of the final scope, we sought advice from a clinical expert: the following advice was provided by [redacted], who granted permission to share their views with the Committee: 'As a sonographer, I do not think the ultrasound variables would be easy to measure and interpret. I do not understand exactly how the proportion of solid tissue should be interpreted. This is more than subjective. How did you choose the cut-off of 10 locules? The more important number will be the number of papillary projections (but you should define it as at least 3mm height) and distinguish between cystic lesions and solid ones (at least 80% solid tissue). I will use here the IOTA (*simple rules*) criteria that are for me the simplest and less subjective. I would consider that a specialist will be needed to take the measurements. Generalists wouldn't be that familiar and it varies depending on the experience of the sonographer. Additionally, the exclusion of the HE4 measurement leaves out clinically relevant information, especially	Comment only – No response required These are comments/queries about the development of the ADNEX model and are really questions to the IOTA group and not something that the EAG can address. As above.

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				for premenopausal patients, where HE4 is normal and CA125 is more often a false positive due to benign conditions. This is something that should be reconsidered.' We would bring to the Committee's attention the "Berlin model", which takes into account HE4, CA125 and ultrasound variables and demonstrated an increase in sensitivity and specificity in premenopausal women in the Berlin study.[1] Reference: 1) Braicu EI, et al. Oral presentation (ICGS-1279) at the 16th Biennial Meeting of the International Gynecologic Cancer Society. HE4 performs better than CA125 as a diagnostic biomarker in premenopausal pelvic mass patients. Final results from a prospective, multicentric study. The Berlin study. International Journal of Gynecological Cancer, 2016; 26 (Suppl. 3): 21-22 doi: 10.1097/01.IGC.0000503327.50238.5c1	The "Berlin model" is not included in the scope for this assessment and hence cannot be considered by the committee.
Roche Diagnostics	2	34-35	2.3.3	We are concerned that the ADNEX model includes a more complex ultrasound procedure that requires sonographers to receive specialist training and to pass a test before being qualified to assess the	Comment only – No response required. Training and implementation issues are considered in the discussion section of the report.

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				ultrasound features required for the model. This could lead to an increase in waiting times. To this point, we wish to bring to the Committee's attention the current volume of non-obstetric ultrasound workload and waiting times, as reported by the NHS England's National Statistics on Monthly Diagnostics Waiting Times and Activity. As of March 2017, the number of non-obstetric ultrasounds being carried out on patients on a waiting list was 494,397; however, 330,184 remained on the waiting list at month-end. Furthermore, 1078 patients were on the waiting list for longer than six weeks. As a proportion of these patients will be in the population of interest for this Guidance, i.e. patients with suspected ovarian cancer, any new requirement that may place an additional burden on the system should be fully investigated. According to the IOTA group website, training is run at infrequent intervals. Whilst we understand from the final scope that "an online training tool specifically for NHS practitioners is being developed, and will be available in the near future", we seek confirmation that the tool will be available on publication of the Guidance. Lastly, given this additional requirement for NHS practitioners to pass a test in order to be qualified to	Implementation issue. IOTA stated that there will be a freely accessible online training tool available to NHS practitioners. In addition, we were unable to estimate the average training costs per tests. For these reasons, training costs were not included in the base-case analysis. However, we explored increasing the costs of the IOTA risk scores by 20%

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				assess the ultrasound measurements for ADNEX model, we believe that that any costs associated with this training should be included in the Ovarian Cancer Screening model that informed the Diagnostic Assessment report.	(arbitrarily selected) to reflect potential training costs in a scenario analysis.
Roche Diagnostics	3	295-296	Appendix 6	We wish to provide feedback on the costs reported in the DAR. In the absence of information, the evidence review group have assumed some costs provided by other manufacturers can be applied to our instruments. We wish to provide some clarity on our costs. [redacted] We have also looked again at the calibration and wish to correct this for HE4 as it would typically be four times a year and not six. [redacted]	At this stage, we are not able to incorporate new data/evidence in our report. However, to inform the committee and aid decision making, these newly submitted data are briefly considered below. [redacted] [redacted] [redacted] [redacted]

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					[redacted]
IOTA Group	4	55-56		"*Eighteen (35%) studies were rated as having 'high' concerns regarding the applicability of the reference standard, because malignancy was defined as 'any malignant tumour', which could include non-ovarian cancers and metastases, whereas the scope of this assessment defined the target condition as ovarian cancer. However, it should be noted that, in order for a study to report risk score performance data for the specific target condition of ovarian cancer, study participants found to have non-ovarian cancers and metastases would need to be excluded from the analysis. Studies that excluded patients with nonovarian cancers and metastases were rated as having a 'high' risk of bias on the flow and timing domain, because post-hoc exclusion of these*	The applicability rating is determined by the pre-defined review question/scope. However, in this instance, it became apparent during the assessment that there was an inconsistency between studies which could be considered the target condition defined in the review question/scope and those studies which were representative of the 'real world' clinical situation. The quoted text is intended to highlight this issue.

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				patients may result in over estimation of test performance." **Comment:** (p55-56): this quote is confusing, it is unclear why these eighteen studies were rated as having high concerns given that they include the patients that one would be faced with in clinical reality. E.g. Van Calster (ref 17) is labeled high risk, Moore (ref 102) as low risk although Moore focuses on a selected subset of epithelial malignancies which can only be selected afterwards on the basis of surgery and histological examination of removed tissues. Excluding other types of cancer is simply not representative of clinical reality. Later, e.g. on p96 and 138-139, this is indeed acknowledged by the authors: **"***the population in which risk scoring would be applied in practice is likely to include some women who will ultimately be found to have a nonovarian primary and some who will have cancers which fall outside the scope of conditions covered in NICE CG1221 (e.g. germ cell tumours and sex cord stromal tumours of the ovary); we therefore consider that studies which include all participants in their analysis, irrespective of final histological diagnosis, are more likely to produce estimates of risk score performance which are representative of what might be expected in clinical practice***".**	

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IOTA Group	5	141		"*For both the IOTA simple ultrasound rules and the ADNEX model, there was evidence that specificity can be significantly decreased in post-menopausal women in comparison to overall populations or premenopausal women. Neither of these risk score incorporates menopausal status; preliminary evidence suggests that menopausal status should be taken into account when applying these tools in practice.*" (p141): **Comment:** ADNEX includes age, which largely covers menopausal status.	Comment for discussion by committee
IOTA Group	6	144		"*We are not aware of any previous systematic review that has considered the performance of both ultrasound-based risk scores such as IOTA simple rules and biomarker-based scores such as ROMA and Overa (MIA2G).*" **Comment:** (p144): the systematic review from **Kaijser (Hum Reprod Update, 2014)** is not considered in this report, but it does address ultrasound-based scores and ROMA.	This systematic review was identified by our searches and should have been cited in the opening paragraph of section 5.2.1 of the discussion. This omission will be corrected ahead of publication.
IOTA Group	7	147		P147, line 3: ref 42 should be ref 46 perhaps? 42 involves a Polish and Spanish center, 46 involves two UK centers and one Italian center.	This reference will be corrected ahead of publication.