NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Biomarker tests to help diagnose preterm labour in women with intact membranes

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 10 April 2018

THEME: Comments on overview document

Comment number	Name and organisation	Section number	Comment	NICE response
1	RCOG Guidelines Committee	Page 5 (of the 36 page overview document)	Diagnostic accuracy studies – most studies did not state if tocolytics were used. Does this not defeat the purpose of analysing the tests? Results may be due to (unstated) tocolytic use and not a reflection on the accuracy of the test in these cases.	Thank you for your comment which the committee considered. Section 5.5 of the diagnostics guidance outlines the committee's considerations on the limitations in the research evidence, including the variation in reporting of the use of tocolytics. Section 5.14 of the diagnostics guidance document has been changed to note that future studies should collect and report data on the use of tocolytics.
2	RCOG Guidelines Committee	Page 20 (of the 36 page overview document)	Why has atosiban been chosen as the tocolytic to evaluate cost effectiveness when nifedipine is recommended in NICE preterm labour guidance (and is much cheaper)?	Thank you for your comment which the committee considered. Section 5.10 of the diagnostics guidance document has been changed to note the committee considerations on the price of tocolytics used in the economic model. The ERG was advised by a clinical expert that atosiban and nifedipine were used routinely in

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				current practice. They also noted that a study (Parisei et al., 2016) indicated that atosiban was routine practice at the University College London Hospital in 2009. The committee were aware that the NICE guideline recommends using nifedipine as a first line treatment and agreed that it would have been preferable to include this. It noted that the cost savings observed in the model would have been overestimated as a result of using the cost for atosiban. However, this only impacted on one of the scenario analyses, and did not change the committee's overall conclusions.
3	RCOG Guidelines Committee	Page 25 (of the 36 page overview document)	Why are sections on this page blacked out?? The Abbot unpublished study makes no sense as a result	Thank you for your comment which the committee considered. The results on page 25 of the overview document have been redacted because the Abbot study is unpublished and the results were provided as Academic-in-confidence. The results of the study were available to the committee and were taken into consideration when the committee made its draft recommendations.

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4	RCOG Guidelines Committee	Page 28 (of the 36 page overview document)	Fig 5 Typo. “Sesitivity” should read “Sensitivity”	Thank you for your comment which the committee considered.

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THEME: Comparative accuracy data

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5	Hologic		We have no comments to make specifically regarding the DCD. We are in broad agreement with the DCD. However we would like to highlight some new evidence that supports the conclusions in the DCD and the assessment of the Wing et al study by the analysts working on behalf of NICE who found that in the Wing study the sensitivity of PAMG-1 test was low for a rule out test (although we believe that the Wing study analysis was not included as part of the DCD analysis due to late timing of whichever company submitted it).	Thank you for your comment which the committee considered. The Wing study was included in the EAGs analysis as part of an addendum, further details can be found in section 4.37 of the diagnostics guidance. The committee decided that no changes to the guidance were needed.
6	Hologic		This data (attached) was presented at a recent congress in Australia it is in line with the DCD and the NICE analysis of the Wing study in showing the low sensitivity of PAMG-1 when compared with fFN. This data shows the sensitivity of PAMG-1 was low (20%) in detecting sPTB. This is a significant problem for a rule out test where the aim of performing the test is to send patients away as a negative (normal) test result means that sPTB is unlikely. Low sensitivity means that sPTB is missed with potentially serious consequences.	Thank you for your comment which the committee considered. The committee heard that the Dawes study would not have been eligible for inclusion in the EAGs systematic review as it is in abstract form and noted that the results reported fall within the ranges reported in the diagnostics assessment report. The committee decided that no changes to the guidance were needed.

DIAGNOSTICS ASSESSMENT PROGRAMME

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7	Hologic		We support the DCD conclusion that we should not be using tests where there is no evidence to suggest that these tests are effective in ruling out PTD, and indeed we feel that the recent evidence (Wing and the Dawes study) proves without doubt that PAMG-1 does not have the sensitivity required to safely rule out PTD. The slide below shows* PAMG-1 failed to detect 4 of the 5 patients in this study that delivered sPTB within 7 days! This is also what was seen in the Wing study. We find it hard to believe that a test like this is even being considered for use by the NHS.	Thank you for your comment which the committee considered. The committee noted that it had previously considered the results of the Wing study which were reported in an addendum to the diagnostics assessment report.

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THEME: General comments

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8	RCOG Guidelines Committee	General	Thank you for inviting us to review this well conducted and thorough review. The authors highlight the uncertainties due to the heterogeneity and quality of the studies. We believe that the documents provide a reasonable summary of the evidence for the effectiveness and cost effectiveness of the three biomarkers. We agree that there is currently insufficient evidence to recommend replacing the current fetal fibronectin test with any of these other tests. We are unclear whether these documents are intended for, and will be available to, 'every day clinicians'. If so, it would be helpful to include clear recommendations regarding the value of the biomarkers, and we would suggest: It is / is not clinically / cost effect to use the specific biomarker tests because: • *There are fewer / more hospital admissions, compared to the current fetal fibronectin test* • *There are fewer / more steroids (+/- tocolytics) given* • *The gestation of delivery is etc.*	Thank you for your comment which the committee considered. The final guidance will be published on the NICE website. Recommendations on the use of the technologies are included in section 1 of the guidance document. The committee concluded that there was insufficient evidence to recommend the use of the technologies (Actim Partus, Partosure and Rapid fetal fibronectin10Q Cassette Kit (using thresholds other than 50 ng/ml to guide clinical management) in the NHS. Fetal fibronectin at a cut-off of 50ng/ml (as described in NICE's guidance on preterm labour and birth) remains the standard of care for assessing pre-term labour in women with intact membranes. The committee heard from the EAG that it did not find any data on clinical outcomes in its systematic review and the results of the economic modelling were highly uncertain. Therefore the committee was not able to advise on the likely impact of the tests on hospital admissions, use of

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				steroids and the gestation of delivery (see section 5.5 of the diagnostics guidance).
9	Parsagen	General	we have no further comments	Thank you for your comment which the committee considered.
10	Department of Health and Social Care	General	No comments	Thank you for your comment which the committee considered.