NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Tests for rapidly identifying bloodstream bacteria and fungi (LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay)

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 4 November 2015

THEME: Diagnostic accuracy data

Comment number	Name and organisation	Section number	Comment	Response
1	Royal College of Pathologists	4.6	Diagnostic accuracy reported from the systematic review appeared quite disappointing. Sensitivity for the IRIDICA, Septifast and Sepsitets were 81%, 65% and 48% respectively and one study which evaluated the Sepsitest reported a sensitivity of only 11% in comparison with blood culture and MALDI-TOF (Loonen et al. 2014). The recent RADICAL study (Vincent et al 2015) which was not properly considered within this NICE assessment reported sensitivity of 81% for the IRIDICA system but demonstrated a significant increase in the detection rate compared to blood culture. The authors report however that most of the patients in the study were exposed to antibiotic combinations prior to recruitment which would preclude culture detection. Although the NICE assessment comments that the number of false positive results (i.e. additional	Thank you for your comment which the Committee considered. Data from the RADICAL study (Vincent et al. 2015) was used in the diagnostic accuracy meta-analysis for the IRIDICA BAC BSI assay and is therefore included in the pooled sensitivity and specificity estimates in section 4.12 of the guidance. Data on change in antimicrobial treatment plan and mortality were also taken from the RADICAL study and are reported in sections 4.28 and 4.29 of the guidance document. The Committee considered that the absolute number of false positive results that would be expected in clinical practice is driven by the specificity of the tests and the low prevalence of positive blood cultures. This consideration is described in section 5.5 of the guidance. The Committee also discussed the likely reasons for

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			positives identified buy the rapid test compared to blood culture) is likely to be high (section 5.5) this was not demonstrated in the systematic analyses where overall sensitivity was disappointing. This may reflect the poor quality of the studies but clearly better evidence is needed. Sensitivity of the rapid test would need to high to enable treatment to be altered as the consequence of changing antimicrobial therapy in this group would be high. It is therefore unlikely a negative rapid test would impact on clinical management.	false positive results with the rapid molecular tests when compared to blood culture. This is described in section 5.4 of the guidance. The Committee noted that although the absolute number of false-negative rapid molecular test results was likely to be low in practice, the consequences of changing antimicrobial therapy on the basis of a negative rapid molecular test result could be severe. This consideration is noted in section 5.5 of the guidance.

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THEME: Costs

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2	Royal College of Pathologists	4.37	Overall costs to the laboratory were not considered comprehensively and did not include additional staff costs and other overheads. This is critical in implementing such a service as currently the majority of clinical microbiology laboratories could not provide a timely result 7 days a week.	Thank you for your comment which the Committee considered. The Committee noted that laboratory overheads and additional staff costs had been excluded from the External Assessment Group's analyses, and that their inclusion would likely increase the cost of the rapid molecular tests as is described on page 127 of the diagnostics assessment report where a formula for calculating the cost of service reconfiguration is given. Further, the Committee noted that the different models of service delivery and variation in test throughputs would have made estimating these costs difficult within the timeframe of the assessment. The Committee considered that in view of the clinical uncertainties, the omission of these costs from the analyses is unlikely to have had a substantial effect on its conclusions. This Committee consideration is described in section 5.13 of the guidance document.

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3	Royal College of Pathologists		The cost of the rapid test is considerable and its uptake by clinicians for diagnosis in less critically ill patients needs to be considered. The clinician has to balance the additional cost of the test against persisting with a relatively cheap antibiotic regime with an improving patient.	Thank you for your comment which the Committee considered. The Committee noted that improvements in antimicrobial stewardship are dependent on behavioural and cultural changes towards using rapid molecular test results as a basis for treatment changes. This Committee consideration is described in section 5.20 of the guidance document.

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THEME: Further research

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4	Royal College of Pathologists		The overall conclusion was that there is currently insufficient evidence to recommend adoption of these tests into routine use within the NHS. The majority of the reported studies were not sufficiently robust to provide adequate evidence to inform on the clinical and cost effectiveness of these tests. There is therefore a need for future research to inform on the impact of such rapid tests in assessment of the impact on antibiotic use, clinical outcome, cost benefit and benefits in antibiotic stewardship.	Thank you for your comment which the Committee considered. The Committee noted that further research is needed in the UK to determine the clinical scenarios in which the tests may offer most benefit in clinical decision making and to quantify their clinical utility. This Committee consideration is described in section 5.18 – 5.22 of the guidance document.
5	Royal College of Pathologists	4.37	There is need for a robust prospective study that can assess the impact of the rapid result, real-time clinical decision on antibiotic prescribing, clinical outcomes and cost benefit.	Thank you for your comment which the Committee considered. The Committee noted that further research is need in the UK to establish the clinical utility of tests. This Committee consideration is described in sections 5.18 – 5.22 of the guidance document.

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THEME: General comments

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6	Abbott Laboratories	General	We don't have any specific comments on the report itself, which was consistent with the earlier report that was reviewed on September 1. Thank you for checking.	Thank you for your comment which the Committee considered.
7	Molzym	General	I do not have specific comments on the diagnostic consultation document	Thank you for your comment which the Committee considered.
8	Roche Diagnostics	General	Roche have no additional comments to make relating to the above consultation	Thank you for your comment which the Committee considered.
10	Royal College of Pathologists		This assessment consisted of a systematic review of published evidence on test performance and clinical-effectiveness data for the LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI and with blood culture or blood culture with MALDI-TOF	Thank you for your comment which the Committee considered.
11	Royal College of Pathologists		The aim of the rapid tests is to identify an infectious cause for a patient presenting with sepsis, and where identified the information can be used to modify the prescribed antibiotics for an improved patient outcome with reduced hospital stay and reduced costs. Narrowing the antimicrobial coverage is desirable in reducing the risk of a superinfection, the likelihood of	Thank you for your comment which the Committee considered.

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			developing resistance and reducing side effects of broad spectrum agents.	
12	Department of Health	General	We welcome this report but the clarity of the text could be improved, and it may be useful to include information on current NHS practice, such as an estimate of laboratories already using MALDI-TOF MS.	Thank you for your comment which the Committee considered. Current NHS practice for processing and reporting blood cultures is described in sections 2.10 to 2.13 of the guidance document. The Committee heard from clinical specialists that MALDI-TOF mass spectrometry is currently being adopted in the NHS, and that consequently it would be difficult to provide an accurate estimate of the number of laboratories using MALDI-TOF mass spectrometry at present.
13	Department of Health	2.19	A sentence to explain the importance of carbapenem resistance should be added. At the moment, it is not clear why this section is included.	Thank you for your comment which the Committee considered. Further details have been added to section 2.19 of the guidance document.
14	Department of Health	4.50	It is not clear what is meant by “the LightCycler SeptiFast dominates MALDI-TOF MS”, especially given 5.3 which states that there was insufficient evidence to establish either the diagnostic accuracy or the clinical utility of the rapid molecular test against MALDI-TOF. This is significant, given the research recommendation that new tests be compared to	Thank you for your comment which the Committee considered. Further details have been added to sections 4.50 and 5.3 of the guidance document.

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Comment number	Name and organisation	Section number	Comment	Response
			MALDI-TOF MS in future studies.	