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Diagnostics Assessment Programme

PLGF-based testing to help diagnose suspected preterm pre-eclampsia

The following documents are made available to stakeholders:

1. **Stakeholder comments on the Diagnostics Consultation Document (DCD) and responses**

2. **Decision Support Unit report third addendum –** additional analysis

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DIAGNOSTICS ASSESSMENT PROGRAMME

PLGF-based testing to help diagnose suspected preterm pre-eclampsia (update of DG23)

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 26 April 2022
Theme: New evidence for the BRAHMS sFlt-1 Kryptor/PlGF plus Kryptor PE ratio

Comment number	Name and organisation	Section number	Comment	NICE Response
1	Thermofisher	1.6	We would like to submit further evidence to prove the clinical performance of the assays (see comments 2 and 3).	Thank you for your comment which the committee considered.
2	Thermofisher	3.6	Rule out cut-off will be included in the next version of the Instruction for Use of the B·R·A·H·M·S PLGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR. This version will be compliant with IVDR regulation and will be released when the IVDR certificate will be granted (expected late Q2/beginning Q3 2022). Below is the extract of the Clinical Performance Characteristics chapter from the IFUs. **Pre-eclampsia diagnosis and prognosis in pregnant women with suspected pre-eclampsia** In an external study, using the B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR assays in parallel on samples from 109 pregnant women with normal pregnancy outcome and 20 patients with preeclampsia ,the published cut-off [7] for the sFlt-1/PlGF ratio of 85 was applied to calculate sensitivity and specificity for this cohort. At a cut-off of 85 the sensitivity was calculated at 95 % and the specificity at 84%. In an external study, using the B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR assays in parallel on samples from 501 pregnant women with signs and symptoms of pre-eclampsia including 150 women that developed pre-eclampsia, the published cut-off [16] for the sFlt-1/PlGF ratio of 66 was applied to calculate sensitivity, specificity, PPV and NPV for this cohort. For the prediction of pre-eclampsia within 1 week, at a cut-off of 66, the sensitivity was calculated at 82%, the specificity at 91%, the PPV at 70% and NPV at 96%. For the prediction of pre-eclampsia within 4 weeks, at a cut-off of 66, the sensitivity was calculated at 72%, the specificity at 92%, the PPV at 75% and NPV at 90%. All pregnancies were singleton pregnancies. Pre-eclampsia was defined as new onset of hypertension and proteinuria after 20 weeks of gestation. A pre-eclamptic pregnancy was defined as early-onset if clinical signs appeared before 34 weeks of gestation.	Thank you for your comment which the committee considered. The committee noted that while the instructions for use did refer to these 2 thresholds they did not state whether they should be used as single thresholds or together, or whether they should be used to rule in or rule out pre-eclampsia. Clinical experts commented that this could lead to uncertainty in how to interpret test results. The committee concluded that, even based on the information from the updated instructions for use, it is not clear how to use the test. It also noted that the test's accuracy using the threshold of 66 had not been validated in a population independent from the one used to set this threshold. These considerations are in section 3.6 of the diagnostics guidance document. The committee acknowledged the new evidence from Andersen et al. but concluded that there was still too much uncertainty about the diagnostic performance of the BRAHMS ratio test to recommend routine

NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

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Comment number	Name and organisation	Section number	Comment	NICE Response
			In addition to the rule in cut-off of 85, a rule out cut-off of 66 is included. This cut-off is supported by the publication of Andersen (Andersen LLT, Helt A, Sperling L, Overgaard M. Decision Threshold for Kryptor sFlt-1/PlGF Ratio in Women With Suspected Preeclampsia: Retrospective Study in a Routine Clinical Setting. J Am Heart Assoc. 2021 Sep 7;10(17):e021376. doi:10.1161/JAHA.120.021376. Epub 2021 Aug 28. PMID: 34459248; PMCID: PMC8649230). The clinical performance of the tests at the cut-off of 66 is determined with a sensitivity at 0.82, a specificity at 0.91, PPV at 70% and NPV at 96% for predicting preeclampsia within 1 week. The clinical performance of the tests at the cut-off of 66 is determined with a sensitivity at 0.72, a specificity at 0.92, PPV at 75% and NPV at 90% for predicting preeclampsia within 4 weeks.	adoption. A study using a pre-specified threshold, or thresholds, done in a population not used to derive these thresholds (external validation) was needed to demonstrate performance. These considerations are in section 3.13 of the diagnostics guidance document. A recommendation for further research was made by the committee stating that a high quality test accuracy study is needed for the BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio test, using thresholds defined by the company, done in a population independent from that used to establish the test's thresholds, and with the test used as intended in the NHS (see section 4.1 of the diagnostics guidance document).
3	Thermofisher	4.1	We would like to submit to the committee the study from Andersen et al. published in September 2021: Andersen LLT, Helt A, Sperling L, Overgaard M. Decision Threshold for Kryptor sFlt-1/PlGF Ratio in Women With Suspected Preeclampsia: Retrospective Study in a Routine Clinical Setting. J Am Heart Assoc. 2021 Sep 7;10(17):e021376. doi: 10.1161/JAHA.120.021376. Epub 2021 Aug 28. PMID: 34459248; PMCID: PMC8649230. This observational retrospective study was performed in Denmark and was using B·R·A·H·M·S PLGF plus and B·R·A·H·M·S sFlt-1 KRYPTOR assays.	Thank you for your comment which the committee considered. The committee noted that the Andersen et al. study did not use a pre-specified threshold. The DSU did a quality assessment of this study using QUADAS-2, and concluded that this could have biased the study results. The committee highlighted the importance of using separate populations to establish test

NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

PLGF-based testing to help diagnose suspected preterm pre-eclampsia (update of DG23)

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Comment number	Name and organisation	Section number	Comment	NICE Response
			The study included a cohort of 501 pregnant women with suspected preeclampsia after week 20 from the first 18 months after the implementation of the sFlt-1/PlGF ratio in clinical routine. A total of 125 women developed preeclampsia during pregnancy. Among them, 32 women developed early onset preeclampsia (before 34 weeks) and 93 developed late onset preeclampsia (after week 34). Women were referred to the outpatient clinic or admitted at the maternity ward in suspicion of or observation for preeclampsia after GW 20. Preeclampsia was defined according to the Danish 2018 national clinical guideline for hypertensive disorders in pregnancy and preeclampsia, which relates to the international definitions of preeclampsia as provided by ISSHP. Diagnostic performance and predictive value of the sFlt-1/PlGF ratio have been assessed to rule in and rule out preeclampsia within 1 week and 4 weeks using 2 pre-specified cut-offs (33 and 85). From the retrospective analysis of the study, the optimal ratio threshold for preeclampsia within 1 and 4 weeks was determined at 66. We believe that this study is fitting the requirements of the committee and could be included as evidence of the clinical performance of the B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 assays as: - The population included is women with signs and symptoms of pre-eclampsia - The number of patients is significant with more than 500 women with signs and symptoms and one third developing preeclampsia - The setting is a clinical routine setting over 18 months which would be likely to be reproduced at any place - The criteria for defining suspicion of preeclampsia are comparable to the studies selected in the NICE evaluation	thresholds and assess accuracy at a given threshold, in order to obtain reliable estimates of performance. These considerations are described in section 3.13 of the diagnostics guidance document. The committee acknowledged the new evidence from Andersen et al. but concluded that there was still too much uncertainty about the diagnostic performance of the BRAHMS ratio test to recommend routine adoption. A study using a pre-specified threshold, or thresholds, done in a population not used to derive these thresholds (external validation) was needed to demonstrate performance. These considerations are in section 3.13 of the diagnostics guidance document. The committee also considered the UK NEQAS pilot scheme data provided. It concluded that setting well validated test specific thresholds for use, and demonstrating performance at these thresholds, was needed to recommend use in the NHS (as described above).

NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

PLGF-based testing to help diagnose suspected preterm pre-eclampsia (update of DG23)

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Theme: New evidence for the BRAHMS sFlt-1 Kryptor/PlGF plus Kryptor PE ratio

<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE Response</th></tr>
<tr><td></td><td></td><td></td><td>
- The criteria for the diagnosis of preeclampsia are following the international guidelines (ISSHP)

In addition to this clinical study, we would like to emphasize that all the methods selected for this evaluation measure the same molecules and give consistent results. As an evidence, we would like to submit the summary of the UK Neqas pilot scheme for PlGF and sFlt-1.
<table>
<tr><td>Distribution 74-86 Feb 2021-Feb 2022</td><td>KRYPTOR PlGF</td><td>Delfia Xpress PlGF</td><td>Roche Elecys PlGF</td></tr>
<tr><td>Mean number of laboratories</td><td>35</td><td>16</td><td>56</td></tr>
<tr><td>Mean bias (%)</td><td>1.8</td><td>-27.9</td><td>7.2</td></tr>
<tr><td>Mean Variance (%)</td><td>6.0</td><td>8.6</td><td>5</td></tr>
</table>
<table>
<tr><td>Distribution 76-86 Apr 2021-Feb 2022</td><td>KRYPTOR sFlt-1</td><td>Roche Elecys sFlt-1</td></tr>
<tr><td>Mean number of laboratories</td><td>8</td><td>45</td></tr>
<tr><td>Mean bias (%)</td><td>-21.3</td><td>5.0</td></tr>
<tr><td>Mean Variance (%)</td><td>6.0</td><td>2.7</td></tr>
</table>
Please note that the number of KRYPTOR laboratories reporting for the sFlt-1 scheme is growing (12 in the distribution 86) as the pilot scheme started to include sFlt-1 in 2021.

The number of laboratories reporting results for PlGF and sFlt-1 is significant demonstrating the routine use of the assays. The Variance representing the imprecision is at 6% for the KRYPTOR method and the bias is at 1.8% for PlGF and -21.3% for sFlt-1 confirming difference in the calibration of the reporting methods. This
</td><td></td></tr>
</table>

NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

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Comment number	Name and organisation	Section number	Comment	NICE Response
			demonstrates the good agreement of the respective methods albeit differences of calibration.	

NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

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Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 26 April 2022
Theme: Impact of test use on costs

Comment number	Name and organisation	Section number	Comment	NICE Response
4	AHSN Network	2.5 (the interventions)	The clinical evidence provided through NICE DG23 is accepted by most clinicians, however the financial case is currently developed from theoretical modelling which follows the clinical evidence and has received less support. It would be very useful to have a cost-impact model developed on real-world experience and cost savings. Across the AHSN network, we are seeing that assumptions made in the current DG23 resource impact model are not borne out in real-world situations. Suggestions of additional benefits to consider, which can provide a real-world cost saving, include reduction in clinical risk, reduction in avoidable costs (e.g. emergency deliveries and neo-natal costs) and the avoidance of never-events. It would also be extremely useful to have a financial model covering the breakdown local “on-costs” for delivering a PlGF-based testing service, including such variables as laboratory and transport overhead, etc	Thank you for your comment which the committee considered. The NICE resource impact assessment (RIA) team will be producing a resource impact report for the updated guidance, that will consider further data on the use of the tests available since DG23 published.

NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

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Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 26 April 2022
Theme: Consideration of further tests

Comment number	Name and organisation	Section number	Comment	NICE Response
5	AHSN Network	2.5 (the interventions)	We are particularly keen to ensure that inclusion of new tests is performance based, i.e. any new supplier meeting the specificity/ sensitivity PPV / NPV standards should be able to be included. Naming suppliers can be perceived as being anti-competitive in practice, works against rapid uptake of solutions and doesn't give credit to Quality Systems and professional expertise in place.	Thank you for your comment which the committee considered. In addition to performance, test cost also needs to be considered in deciding if a test is cost effective, which would not be considered if only minimal criteria for performance were set. After the guidance is published NICE may review and update diagnostics guidance at any time if significant new evidence becomes available. Stakeholders, including product sponsors, researchers and clinicians, can inform NICE of developments in the evidence base. Local decision makers can also compare the performance of new tests versus those recommended in NICE guidance, and also test costs, and make decisions about use.

NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

PLGF-based testing to help diagnose suspected preterm pre-eclampsia (update of DG23)

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 26 April 2022
Theme: Factual detail in guidance and published documents

Comment number	Name and organisation	Section number	Comment	NICE Response
6	Roche Diagnostics Ltd	All	As we have raised in previous rounds of consultation, we have concerns with the fact the DAR report is to be published in full. While the literature review from the DAR has not been superseded, all other elements of the report have, it's unclear why the superseded elements of the report cannot be removed or redacted. The inclusion of these sections, especially appearing before the main DSU report, we feel, could lead to unnecessary confusion and hesitancy in the tests efficacy from both commissioners and clinicians, in turn limiting access to patients. While we understand the need for transparency, the DSU includes an overview and critique of the DAR model structure, it's it still unclear exactly why the DAR needs to be published when it raises the possibility of misinterpretation to the lay reader.	Thank you for your comment which the committee considered. The DAR was released to stakeholders for comment and therefore formed part of the committee papers. Before release, all pages in the DAR that were superseded by the DSU's report were indicated as such, and further text has been added to the contents page to highlight this: "Economic analyses in the Diagnostics Assessment Report (DAR), and addendum and erratum to this document, are replaced by the NICE Decision Support Unit (DSU) report. The parts of these documents that are superseded by the DSU's report are indicated with a watermark." The final guidance document further describes the issues with EAG's model (section 3.8) and describes the cost effectiveness results from the DSU's work that were used for decision making (for example, in section 3.10). While the DSU's report does include a description of the EAG's model, this is in summary and for complete transparency the DAR (clearly marked where elements have been superseded) will be included, as submitted to committee and for stakeholder review, with the final guidance. The external

DIAGNOSTICS ASSESSMENT PROGRAMME

PLGF-based testing to help diagnose suspected preterm pre-eclampsia (update of DG23)

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Diagnostics Advisory Committee date: 26 April 2022
Theme: Factual detail in guidance and published documents

Comment number	Name and organisation	Section number	Comment	NICE Response
				assessment group informed the committee that their economic modelling work has been removed from their HTA monograph, and so will not be formally published,
7	AHSN Network	2.5 (the interventions)	Calculations of the cost of each test do not seem to be consistent. The whole cost breakdown is not available, but assuming the same lab costs are applied, the calculated Perkin Elmer Tests seem expensive pro-rate compared to the other tests (given their much lower cost per test based on stated price and number of tests) e.g. • Perkin Elmer: 96 tests for £944. Quoted price per test £37.42 (PlGF) or £71.41 (ratio) • Quidel: 24 tests for £1000. Quoted price per test £49.58 • Roche: 100 tests for £6,621. Quoted price per test £79.23	Thank you for your comment which the committee considered. A full breakdown of how the test costs per use were calculated for use in the economic model is in appendix 15 of the diagnostics assessment report (pages 293 to 301).
8	AHSN Network	2.10	Table 4: The stated 1- and 4-week rule-out thresholds are the same (would expect them to be different)	Thank you for your comment which the committee considered. The 1 week and 4 week rule out thresholds are reproduced from the DELFIA Xpress sFlt-1/PLGF ratio test instructions for use document.

NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

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Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 26 April 2022
Theme: No comments

Comment number	Name and organisation	Section number	Comment	NICE Response
9	PerkinElmer		Thank you for the opportunity to comment. No additional comments to • DAP53 PlGF (DG23 update) committee papers for consultation [redacted] DAP53 PlGF DCD for stakeholders 20220318 [no ACIC]	Thank you for your comment which the committee considered.
10	PerkinElmer		Thank you for the opportunity to comment. No additional comments to • DAP53 PlGF ScHARR model 20220128 [No ACIC] • ScHARR MASTER DAP53 PlGF Addendum 2_new test 20220221DB [No ACIC] ScHARR MASTER DAP53 PlGF new rule out_Addendum 2_new test 20220221DB [No ACIC]	Thank you for your comment which the committee considered.

PLGF-BASED TESTING TO HELP DIAGNOSE SUSPECTED PRE-ECLAMPSIA (UPDATE OF DG23): ADDENDUM 3

REPORT BY THE DECISION SUPPORT UNIT

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ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) External Assessment Centre is based at the University of Sheffield with members at York, Bristol, Leicester and the London School of Hygiene and Tropical Medicine. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Centre for Health Technology Evaluation Programmes. Please see our website for further information www.nicedsu.org.uk.

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This report should be referenced as follows:

Kearns B., Wailoo A., Abdullah P., PLGF-Based Testing to Help Diagnose Suspected Pre-Eclampsia (Update of DG23): Addendum 3. NICE DSU Report 2022.

CONTENTS

TABLES

1. ADDITIONAL ANALYSIS OF THE BRAHMS (KRYPTOR) RATIO TEST

1.1. INTRODUCTION AND METHODS

In the original DSU report, the BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus Kryptor PE ratio (hereafter 'BRAHMS') test used cut-off values of 38 and 85, with evidence on test performance (sensitivity and specificity) relative to the Elecsys test taken from Simon 2020[1]. During comments on the diagnostics consultation document, a commenter submitted the 2021 study by Andersen and colleagues[2]. This evaluated the performance of the BRAHMS test for diagnosing pre-eclampsia (PE) for differing thresholds: 33, 66, and 85. This new evidence means that it is possible to evaluate use of the BRAHMS test with a rule-out threshold of 66 and rule-in threshold of 85.

In the Andersen 2021 study, two different PE cohorts were considered: early-onset (before 34 weeks) and late-onset (34 weeks or later). Both were for women with a gestational age of at least 20 weeks. In addition, two timeframes for the diagnoses of PE were considered: within four weeks or within one week. The evidence used from Simon 2020 is based on women with a gestational age of 24 to 28 weeks and who had PE by 32 weeks[1]. Hence it was decided to use evidence for the early-onset PE cohort from Andersen 2021, with diagnosis within four weeks. For this sub-group, reported estimates of sensitivity were identical for the two thresholds of 66 and 85 (at 75%). Specificity was reported to be 94% (threshold 66) and 95% (threshold 85). Hence, for this exploratory analysis the two thresholds were assumed to have equivalent performance.

A quality assessment of the publication by Andersen and colleagues[2], is provided in Table 1 and Table 2. This publication reported the results of a retrospective observational study conducted at a Danish University Hospital. Included women had a gestational age of at least 20 weeks. The threshold of 66 was identified as part of the study.

Table 1: Quality assessment of Andersen study: risk of bias

Patient selection	
1. Was a consecutive or random sample of patients enrolled?	Yes
2. Was a case-control design avoided?	Yes
3. Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low
Index test	
1. Were the index test results interpreted without knowledge of the results of the reference standard?	N/A
2. If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High
Reference standard	
1. Is the reference standard likely to correctly classify the target condition?	Yes
2. Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear*
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Flow and Timing	
1. Was there an appropriate interval between index test(s) and reference standard?	Yes
2. Did all patients receive a reference standard?	Yes
3. Did patients receive the same reference standard?	Yes
4. Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low

* Whilst this is unclear, this is not judged to lead to bias.

Table 2: Quality assessment of Andersen study: applicability

Patient selection	
Is there concern that the included patients and settings do not match the review question?	Low
Index test	
Is there concern that the index test, its conduct, or interpretation differ from the review question? i.e. used/followed decision tool	Low
Reference standard	
Is there concern that the target condition as defined by the reference standard does not match the review question?	Low

Results for both types of standard assessment, and all other PLGF-based tests previously assessed, remain unchanged. To aid in comparisons, results for BRAHMS (based on the original inputs) and standard assessment from both DG23 and INSPIRE are also provided.

1.2. RESULTS

1.2.1. Rule-out testing: base-case analysis

Deterministic results for the base-case used in the DSU report (hypertension distribution and baseline test performance both from PARROT UK, true positives do not cost more than false negatives, PLGF-based tests used to rule-out PE) are provided in Table 3, with corresponding incremental values in Table 4. Full results are provided in the Appendix Table 9.

Table 3: Deterministic results, PLGF-based tests to rule-out PE

Rule-out testing	SA: DG23	SA: INSPIRE	BRAHMS (original)	BRAHMS (updated)
Total cost	£10,215	£10,223	£10,230	£10,227
Test	£0	£0	£52	£52
Clinical management	£620	£615	£600	£598
Delivery	£3,781	£3,781	£3,781	£3,781
Maternal short-term	£364	£365	£362	£362
Neonatal short-term	£4,373	£4,377	£4,357	£4,357
Neonatal long-term	£1,077	£1,084	£1,077	£1,077
Total QALYs	17.6110	17.6093	17.6151	17.6151
Clinical management	-1.41E-05	-9.18E-06	-9.05E-06	-8.68E-06
Delivery	0.035	0.035	0.035	0.035
Maternal short-term	0.384	0.384	0.384	0.384
Neonatal short-term	-0.001	-0.001	-0.001	-0.001
Maternal long-term	17.363	17.363	17.364	17.364
Neonatal long-term	-0.171	-0.172	-0.168	-0.168
True Positives	9.5%	8.0%	9.2%	9.2%
True negatives	62.7%	65.9%	66.0%	66.2%
False positives	9.2%	6.0%	5.9%	5.7%
False negatives	18.6%	20.1%	18.9%	19/0%

Table 4: Incremental base-case results, PLGF-based tests to rule-out PE

	Total costs		Total QALYs			
	DG23	**INSPIRE**	**DG23**	**INSPIRE**		
Standard assessment	£10,215	£10,223	17.6110	17.6093		
	Incremental costs vs		**Incremental QALYs vs**		**Incremental cost-effectiveness ratio**	
	DG23	**INSPIRE**	**DG23**	**INSPIRE**	**DG23**	**INSPIRE**
BRAHMS (original)	£14.6	£6.9	0.0042	0.0058	£3,508	£1,183
BRAHMS (updated)	£12.3	£4.6	0.0042	0.0058	£2,963	£794

Use of the updated inputs led to a slight decrease in overall costs (from £10,230 to £10,227), driven by a decrease in clinical management costs. There was a corresponding decrease in QALYs lost due to clinical management with the updated inputs, but the impact of this was minor, with overall QALYs being the same to four decimal places. The improved cost-effectiveness results are reflected by slight improvements in the ICERs for BRAMS relative to both types of standard assessment.

Table 5: Impact on base-case results of excluding neonatal outcomes

Including neonatal outcomes	**BRAHMS (original)**	**BRAHMS (updated)**
ICER vs SA (DG23)	£3,508	£2,963
ICER vs SA (INSPIRE)	£1,183	£794
Excluding long-term neonatal outcomes		
ICER vs SA (DG23)	£14,797	£12,115
ICER vs SA (INSPIRE)	£10,518	£8,584
Excluding all neonatal outcomes		
ICER vs SA (DG23)	£31,593	£28,992
ICER vs SA (INSPIRE)	£25,553	£23,682

ICER: Incremental cost-effectiveness ratio. SA: Standard assessment

Cost-effectiveness results with neonatal outcomes excluded are provided in Table 5. As with the original analyses, their exclusion leads to an increase in ICER relative to both types of standard assessment. For all scenarios, use of the updated inputs led to lower ICERs than the original inputs, with all updated ICERs below £30,000. Due to the very minimal impact of using the updated results, probabilistic analyses were not re-run.

1.2.1. Rule-out testing: applying PLGF-based tests to the outcomes of standard assessment

The additional results of the first addendum (dated 16th February 2022), in which PLGF-based tests were applied to the outcomes of standard assessment to rule-out PE, are replicated for the BRAHMS test with the updated inputs, with results provided in Table 6, and full results available in the Appendix Table 9.

As with the original inputs, applying the BRAHMS ratio to the results of standard assessment to rule-out PE leads to a cost-saving and increased QALYs, and hence is dominant. This occurs for both types of standard assessment. When comparing the original and updated inputs, there is little change. The updated inputs lead to a slight decrease in true positivise but also a slight increase in true negatives. For standard assessment from DG23, the updated inputs lead to a minor reduction in costs and increase in QALYs gained. For standard assessment from INSPIRE the converse occurs.

Table 6: Deterministic results, PLGF-based tests to rule-out PE compared with standard assessment

	Standard assessment (SA) from DG23			**SA from INSPIRE**		
Rule-out testing	**SA: DG23**	**BRAHMS (original)**	**BRAHMS (updated)**	**SA: INSPIRE**	**BRAHMS (original)**	**BRAHMS (updated)**
Total cost	£10,724	£10,394	£10,389	£10,239	£10,101	£10,102
Test	£0	£52	£52	£0	£52	£52
Clinical management	£1,238	£1,015	£1,014	£844	£711	£710
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
Maternal short-term	£361	£345	£344	£349	£343	£343
Neonatal short-term	£4,357	£4,220	£4,216	£4,257	£4,207	£4,207
Neonatal long-term	£987	£980	£981	£1,007	£1,007	£1,008
Total QALYs	17.6217	17.6583	17.6591	17.6461	17.6594	17.6593
Clinical management	-0.00109	-0.00005	-0.00004	-0.00041	-0.00002	-0.00002
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
Neonatal short-term	-0.0006	-0.0005	-0.0005	-0.0005	-0.0005	-0.0005
Maternal long-term	17.3660	17.3743	17.3745	17.3715	17.3746	17.3746
Neonatal long-term	-0.1618	-0.1347	-0.1341	-0.1437	-0.1339	-0.1340
True Positives	27.6%	26.5%	26.2%	21.7%	20.8%	20.7%
True negatives	17.1%	42.3%	43.5%	49.0%	59.5%	60.0%
False positives	54.8%	29.6%	28.4%	22.9%	12.4%	11.8%
False negatives	0.6%	1.7%	1.9%	6.5%	7.3%	7.5%

1.2.2. Rule-out and rule-in tests

Results of using PLGF-based tests to both rule-out and rule-in PE are (based on survey responses) are provided in Table 7. Use of the original inputs led to the BRAHMS test dominating both types of standard assessment. The updated inputs led to a slight reduction in total costs and increase in total QALYs, and hence still

dominated standard assessment. Similar results were observed for the other types of rule-out and rule-in (results not displayed for brevity).

Table 7: Deterministic base-case results, PLGF-based tests to rule-out and rule-in PE

Rule-out and rule-in testing based on survey responses			ICER vs standard assessment	
	Total cost	Total QALYs	DG23	INSPIRE
Standard assessment (DG23)	£10,734	17.510		
Standard assessment (INSPIRE)	£10,251	17.544		
BRAHMS (original)	£10,162	17.572	Dominates	Dominates
BRAHMS (updated)	£10,098	17.673	Dominates	Dominates

1.2.3. Scenario analyses

Table 8 provides incremental results of scenario analyses when PLGF-based tests are used to rule-out PE. Results were robust to the choice of baseline test performance, and do if true positives could cost more than false negatives. Results were more sensitive to the choice of hypertension distribution. As with the original analyses, the highest ICERs were observed when the hypertension distribution was taken from PARROT Ireland, although these ICERs remained below £15,000 for both types of standard assessment. Use of a hypertension distribution from either PELICAN or the EAG led to the BRAHMS test dominating both types of standard assessment.

Table 8: Scenario results for BRAHMS (updated), rule-out testing

Incremental cost-effectiveness ratios	**Vs SA (DG23)**	**Vs SA (INSPIRE)**
Base-case	£2,963	£794
INSPIRE for baseline test performance	£3,027	£14,726
True positive test results cost more than false negative results	£2,721	£1,368
Hypertension distribution from PARROT Ireland	£14,153	£8,780
Hypertension distribution from PELICAN	Dominates	Dominates

Hypertension distribution from EAG DAR (Triage, PE)	Dominates	Dominates

APPENDIX

A.1 ADDITIONAL COST-EFFECTIVENESS RESULTS

Table 9: Deterministic results: BRAHMS (updated results)

	Rule out (base-case)	Rule out applied to SA (DG23)	Rule out applied to SA (INSPIRE)	Rule out and standard rule-in	Rule out and cautious rule-in	Rule out and rule-in based on PreOS
Total cost	£10,227	£10,389	£10,102	£10,098	£10,162	£10,221
Test	£52	£52	£52	£52	£52	£52
Clinical management	£598	£1,014	£710	£787	£693	£633
PE: True positive	£89	£255	£201	£244	£167	£117
PE: False negative	£173	£18	£67	£18	£95	£145
No PE: True negative	£261	£366	£286	£212	£236	£225
No PE: False positive	£75	£374	£156	£314	£194	£145
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
PE: True positive	£383	£1,096	£861	£1,095	£739	£511
PE: False negative	£793	£80	£315	£80	£436	£665
No PE: True negative	£2,400	£1,576	£2,176	£1,894	£2,147	£2,231
No PE: False positive	£205	£1,029	£430	£712	£459	£374
Maternal short-term	£362	£344	£343	£338	£350	£359
PE: True positive	£34	£98	£77	£98	£66	£46
PE: False negative	£110	£11	£44	£11	£60	£92
No PE: True negative	£197	£129	£178	£155	£176	£183
No PE: False positive	£21	£106	£44	£73	£47	£38
Neonatal short-term	£4,357	£4,216	£4,207	£4,162	£4,260	£4,335
PE: True positive	£663	£1,896	£1,490	£1,895	£1,279	£883
PE: False negative	£1,684	£170	£668	£171	£927	£1,413
No PE: True negative	£1,820	£1,195	£1,650	£1,436	£1,628	£1,692
No PE: False positive	£191	£956	£399	£661	£426	£348
Neonatal long-term	£1,077	£981	£1,008	£977	£1,027	£1,060
PE: True positive	£255	£729	£573	£728	£492	£340
PE: False negative	£647	£65	£257	£66	£356	£543
No PE: True negative	£158	£104	£144	£125	£142	£147
No PE: False positive	£17	£83	£35	£58	£37	£30
Total QALYs	17.6151	17.6591	17.6593	17.6730	17.6440	17.6220
Clinical management	-8.68E-06	-4.35E-05	-1.82E-05	-3.39E-04	-1.74E-04	-6.74E-05
PE: True positive	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0
No PE: False positive	-8.68E-06	-4.35E-05	-1.82E-05	-3.39E-04	-1.74E-04	-6.74E-05
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
PE: True positive	0.003	0.009	0.007	0.009	0.006	0.004
PE: False negative	0.006	0.001	0.003	0.001	0.004	0.005

No PE: True negative	0.024	0.016	0.021	0.019	0.021	0.022
No PE: False positive	0.002	0.010	0.004	0.007	0.005	0.004
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.035	0.101	0.079	0.101	0.068	0.047
PE: False negative	0.073	0.007	0.029	0.007	0.040	0.061
No PE: True negative	0.254	0.167	0.231	0.201	0.228	0.236
No PE: False positive	0.022	0.109	0.046	0.075	0.049	0.040
Neonatal short-term	-0.0006	-0.0005	-0.0005	-0.0004	-0.0005	-0.0006
PE: True positive	-4.48E-05	-1.28E-04	-1.01E-04	-1.28E-04	-8.65E-05	-5.98E-05
PE: False negative	-3.95E-04	-3.98E-05	-1.57E-04	-4.01E-05	-2.18E-04	-3.32E-04
No PE: True negative	-1.19E-04	-7.80E-05	-1.08E-04	-9.37E-05	-1.06E-04	-1.10E-04
No PE: False positive	-4.58E-05	-2.30E-04	-9.60E-05	-1.59E-04	-1.02E-04	-8.36E-05
Maternal long-term	17.3642	17.3745	17.3746	17.3778	17.3710	17.3658
PE: True positive	1.591	4.551	3.576	4.548	3.070	2.120
PE: False negative	3.270	0.329	1.298	0.331	1.801	2.744
No PE: True negative	11.521	7.565	10.444	9.089	10.305	10.709
No PE: False positive	0.983	4.929	2.057	3.409	2.196	1.792
Neonatal long-term	-0.1677	-0.1341	-0.1340	-0.1233	-0.1455	-0.1624
PE: True positive	-0.017	-0.047	-0.037	-0.047	-0.032	-0.022
PE: False negative	-0.103	-0.010	-0.041	-0.010	-0.057	-0.086
No PE: True negative	-0.038	-0.025	-0.034	-0.030	-0.034	-0.035
No PE: False positive	-0.010	-0.051	-0.021	-0.036	-0.023	-0.019
True Positives	9.2%	26.2%	20.6%	26.2%	17.7%	12.2%
True negatives	66.2%	43.5%	60.0%	52.2%	59.2%	61.6%
False positives	5.7%	28.4%	11.8%	19.6%	12.6%	10.3%
False negatives	19.0%	1.9%	7.5%	1.9%	10.4%	15.9%

SA: Standard assessment

2. REFERENCES

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