NICE National Institute for Health and Care Excellence

The Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 test and BRAHMS sFlt-1 Kryptor / PlGF plus Kryptor PE ratio to aid the assessment of suspected pre-eclampsia

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EAG comments highlighted are either [redacted] or [redacted]

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Alere	1.	29	1.5	Each of the manufacturer's PlGF assays employ antibodies with different specificities to PlGF isoforms and to free and bound PlGF [PlGF complexes with sFlt-1]. Research is required to determine suitable cut-offs for each of the commercial PlGF assays because the concentration of PlGF measured by each assay is not correlated.	Despite the differences in antibody target affinities among the assays there is some evidence as noted on DAR page 75 that PlGF concentrations appear to correlate across assays, but (depending upon which assays/biomarkers are being compared) biomarker concentrations are systematically under-or over-estimated. The EAG agrees that these differences support a need for cutoffs which are assay specific.
	2.	34	1.8	We note that the capital cost is only included for the Alere Triage system, and not for the other tests in this assessment. Not all facilities will have access to, budget for, or skilled personnel required for a laboratory analyser required to run the other assays in this assessment.	This is incorrect. The Roche Elecsys sFlt-1/PlGF test has a listed price per test of £57.23; this cost was not used in the EAG model. [redacted] Likewise, the costs submitted by ThermoFisher Scientific for the BRAHMS Kryptor sFlt-1/PlGF test include capital and maintenance costs. The concern of Alere that not all facilities will have budget or skilled personnel seems to assume that central laboratories would not be an option for these locations. See Roche's comment 21.

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	3.	45	4.1	Incorrect statement. "The PETRA study, reported in a company submission to NICE provided by Alere (Sibai and colleagues6) and also reported in the Alere Triage PlGF test product insert." Please revise to: Studies on the Alere Triage PlGF test included in the review are: • The PETRA study, reported in a company submission to NICE provided by Alere (Sibai and colleagues6). • The PELICAN study, reported by Chappell and colleagues in an academic journal paper5, three meeting abstracts72-74 and also reported in the Alere Triage PlGF test product insert.40.	The EAG thanks Alere for spotting this error and acknowledges that the reference to the product insert should refer to PELICAN, not PETRA. The EAG agrees to the proposed rewording.
	4.	130	5.5.2.2	Cost-effectiveness is estimated for either central laboratory (base model) and near patient testing (sensitivity analysis). 1) The shorter turnaround time for near patient testing might influence the timeliness of	1. Turnaround time is implicitly the subject of the sensitivity analysis. If a patient is being assessed at a day-case unit, they may be admitted if turnaround time is too slow. Naturally this could lead to a slight delay in

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				clinical decision-making and the timing of interventions. Turnaround time has not been considered in the analysis. 2) The suitability of near patient testing for smaller midwife-led clinics might increase access to PlGF testing for this healthcare worker and either expedite or reduce the need for patient referral.	diagnosis, but it is unlikely that a few hours difference in a patient that has been properly managed will result in any additional adverse outcomes. 2. The EAG was informed that PlGF assessment was likely to be conducted at a midwife-led day-case unit. The EAG has assumed that this is the case. There is a need to better establish how the testing machines are used in practice; the EAG has had to use some observed and some theoretical usage data based on clinical advice.
Royal College of Nursing	5.			The Royal College of Nursing have no comments to submit to inform in the above consultation.	No EAG comment necessary.
Royal College of Pathologists	6.	14	Scientific summary Conclusions line 11	The report notes that investment in equipment and training will be required for any of the biomarkers tests to be employed in NHS practice. This should also include support costs for laboratories that will be required for the test including analytical verification for ISO15189 accreditation, reagent, quality control and maintenance costs.	The EAG agrees in principle with this statement. However, information on implementation was unavailable to the EAG. To ascertain the actual costs that would be involved it would be appropriate to consult finance departments at hospital trusts.
	7.	182	7 Conclusions	The report notes that investment in equipment and training will be required for any of the biomarkers tests to be employed in NHS practice. This should	Ditto.

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			7.1 Implications for service provision	also include support costs for laboratories that will be required for the test including analytical verification for ISO15189 accreditation, reagent, quality control and maintenance costs.	
Roche diagnostics	8.	11	Summary	Regarding the use of the sFlt-1/PlGF ratio to replace quantitative proteinuria (PU) testing - In clinical practice, clinicians currently using the Elecsys® immunoassay sFlt-1/PlGF ratio decide using quantitative PU on a case-by case basis. Data from the PreOs study suggest less quantitative PU testing for women with suspected PE when using the sFlt-1/PlGF ratio.	For 24-hour proteinuria testing, the PreOS study reported by Klein and colleagues (academic in confidence) showed that when using the biomarker test ratio [redacted]
	9.	12	Summary	The finding of the de-novo cost-effectiveness analysis that the tests are cost-saving compared to standard care seems very robust. It should be mentioned that all scenarios investigated resulted in cost savings when using the PlGF or sFlt-1/PlGF ratio tests in addition to current investigations. The EAG analysis results agree with our model (Ref. 266) that was based on a different data set (derived	The EAG agrees.

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				from the PROGNOSIS study, Ref. 51). In our view, this highlights the robustness of the results.	
	10.	13	Summary	We do not agree with there being uncertainty around data for women presenting before week 30: The PROGNOSIS study recruited women from gestational week 24 and 780 of 1273 enrolled patients presented before gestational week 30, representing a significant number of women. The PROGNOSIS study resulted in selection of a single cut-off for the short-term prediction of pre-eclampsia, irrespective of gestational age, i.e. there was no accuracy advantage in selecting gestational age specific cut-offs in the derivation cohort.	PROGNOSIS is not published, and the manuscript submitted to the EAG did not break down subgroups by gestational age beyond using the established definition of early pre-eclampsia. [redacted] However, even if we optimistically assume that [redacted] [numbers omitted] women developed pre-eclampsia before 30 weeks, [redacted] the EAG statement about uncertainty before 30 weeks still stands. There was some thought among clinicians that there is an additional subgroup of women for very early pre-eclampsia that has higher risk (both maternal

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					and fetal outcomes); hence, this is why we emphasize the lack of data on this group. From the manuscript the EAG received, it was unclear what the outcomes for this subgroup would be (i.e. when delivery would occur and by what method, and maternal and neonatal short and long-term outcomes) and what further costs would be associated with these outcomes.
	11.	32	Table 5	Although table 5 is correct, we suggest omitting it in favour of table 6 that link the different cut-offs to clinical interpretations.	The EAG agrees that it is reasonable to focus on Table 6.
	12.	45	4.1	We suggest describing the key characteristics of the identified studies (from table 8: location, design & cohort size) at this point in the report together with the citations.	The EAG feels that Table 8 is sufficient as it provides a concise summary of the key study characteristics which are readily accessible in one place – it's not clear that repeating this information earlier would improve interpretation, and it might possibly create confusion through duplicate reporting of information.
	13.	54	4.1	We appreciate the recognition that PROGNOSIS had a clear definition of pre-eclampsia. This, and the fact that the study was multicentre, including one UK	No action by EAG necessary.

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				site, results in transferability of the results to the UK.	
	14.	71	4.3	It is worth mentioning that the cut-off 23 is not in the pack-insert but only relates to a single study. We suggest referring the reader to table 6.	The EAG has reported all relevant evidence we could find for the decision problem and this is not limited to any particular cutoffs. Note that cutoffs in the pack insert are based on case-control studies on women who either had pre-eclampsia or were healthy, rather than studies on women with suspected pre-eclampsia, so it does not necessarily follow that a cutoff specified in the pack insert would be any more appropriate than one developed from an ad hoc academic study.
	15.	86	5.1.1	Hadker and colleagues 2010: This study was conducted for a general population of pregnant women, not for those with suspected pre-eclampsia and is therefore not directly relevant to the decision problem as stated by NICE. However, it is likely that higher savings would have resulted by restricting the analysis to women presenting with suspected pre-eclampsia only.	This is all correct.
	16.	120	5.5.1	Justification for week 35 regarding expectant management in the model is not entirely clear: the NICE guidance states “suggest offering women with	The previous guideline models in CG107 assumed immediate delivery management for women presenting after 34 weeks based on the HYPITAT study (reference 132). The EAG has used data from the PELICAN trial,

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				PE delivery from week 34 and recommend delivery to women from week 37."	wherein women diagnosed with pre-eclampsia after 35 weeks' gestation had a median time to delivery of four days and a median gestational week of just over 37 at delivery. Outcomes are based on patients between 35 and 37 weeks from PELICAN, HYPITAT, and HYPITAT II.
	17.	119	5.5.1	Use of rule-in and rule-out cut-offs for the Elecsys assay: using a single cut-off of 38 to rule-out PE within one week and to rule-in for a pre-eclampsia pathway can be considered a conservative assumption. According to Stepan et al. (Ref. 52 & DAR Table 6, p. 32) the high-risk group (sFlt-1/PlGF ratio > 38) can be further stratified using the higher diagnostic threshold (i.e. 85 for gestation <34 wk and 110 for gestation >=34 wk, respectively) for 'rule-in'.	Stepan et al. was an opinion piece that combined cut-offs from PROGNOSIS and Verlohren et al. (2014) (reference 49). PROGNOSIS, referenced in the product insert, used a single cut-off of 38. Verlohren had a case-control design; this design would likely have overestimated test accuracy. The EAG suggests that if additional cut-offs are to be used to manage women with a >38 sFlt-1/PlGF ratio, then the sensitivity and specificity should be based on PROGNOSIS to maintain consistent populations. The EAG model uses PROGNOSIS with a cut-off of 38.
	18.	124	5.5.2	We agree with the use of resource use data from the PELICAN study as relevant for the UK. The resources cited in this report seem also broadly in agreement with the data from the PROGNOSIS	No action by EAG necessary.

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				study.	
	19.	130	5.5.2.2	We assumed some re-testing to be more conservative. In our model, only women who tested negative but still re-presented with symptoms were re-tested (approximately 60% of all women presenting) according to PROGNOSIS data. However, we agree that re-testing would not happen to this extend in clinical practice.	We were advised by clinical experts and NICE that re-testing would not be appropriate in the EAG model. Re-testing would result in some additional cost for the test, but may also reduce costs for women falsely diagnosed with pre-eclampsia.
	20.	163	5.6.3	In addition to the sensitivity analysis on NICU stay, we like to comment that adding the Elecsys® immunoassay sFlt-1/PlGF ratio to current care is expected to result in cost-savings in antenatal care alone according to our analysis based on PROGNOSIS data (Ref. 266).	The EAG notes that the Strunz-McKendry model (reference 266 – poster presentation marked by the company as academic in confidence) would not be representative of UK practice, according to CG107. [redacted] NICE Guidance advises more intensive management of women with pre-eclampsia. The EAG model treats women

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					with suspected pre-eclampsia under the standard hypertension in pregnancy pathway before confirmation of pre-eclampsia diagnosis (diagnosis includes false positives), which means that women who are not confirmed with pre-eclampsia by standard assessment would be discharged and their monitoring adjusted accordingly. Additionally women with confirmed pre-eclampsia are hospitalised until delivery. [redacted] The EAG highlighted similar issues with the management strategies in the Roche submission model, which appears to be structurally similar or identical to the Strunz-McKendry model.
	21.	172	5.6.3	To assume near-patient testing in the absence of access to laboratory services with appropriate turn-around times seems reasonable. However, 24/7 laboratory access is now increasingly available in the NHS, in particular in larger hospitals, and turn around times similar to those for A&E samples are	This is a valid assessment, and something that the Committee could consider.

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				realistic for the Elecsys immunoassay test running on automated platforms. Another aspect of near patient testing or testing on non-automated platforms is higher staff costs to perform the test & QC.	
	22.	176	5.6.3	The assumption of equivalent accuracy made for the assay is difficult to justify without the relevant data and where the intended use does not include aid in diagnosis or short-term prediction of pre-eclampsia. For example, the source of the suggested 85 cut-off cited in section 1.5 for the BRAHMS assay is a study using the Roche Elecsys® immunoassay SFlt-1/PlGF ratio only. In regards to cost-comparison between different tests, it should be noted that in addition to consumables and equipment, staff time for training & QC is likely to be higher when running assays on a different analyser platform for a lab that otherwise has already access to the cobas platform.	The EAG agrees with this statement and has indicated in the DAR that this sensitivity analysis is highly uncertain with great need of better data.
	23.	181	6.3	Data on twin and multiple pregnancies is forthcoming: in PROGNOSIS there were 78 multiple pregnancies, in STEPS (Study of Early	The EAG does not have access to forthcoming analyses so is unable to make an informed comment here. The STEPS study was on women at high risk of (but not

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				Preeclampsia in Spain; see Perales A. et al. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 5, 2015, 216–218) there were 302 multiple pregnancies. Roche is planning to analyse the data of multiple pregnancies in these two studies.	suspected) pre-eclampsia; risk factors included abnormal uterine artery Doppler and antiphospholipid antibodies which the EAG understands are not part of a routine assessment for suspected pre-eclampsia. So this study might not strictly meet the NICE scope for this assessment.
	24.	181	6.3	The proportion of women developing PE before 30 may be small. However, the number of women presenting with suspected PE is not necessarily small – see our comments on the summary regarding the PROGNOSIS study. Our economic analysis (Ref. 266) also included the entire cohort of PROGNOSIS from week 24.	Because the tests' primary savings are through reducing overtreatment, the number of women with suspected pre-eclampsia is important, as Roche indicates. The EAG model does include women before 30 weeks, but does not include outcomes for neonates beyond admission to NICU. The EAG also notes that no economic models relevant to the scope of this assessment that have been published [redacted] include outcomes for neonates or mothers. These outcomes, as previously indicated, are expected to be worse for neonates and mothers with pre-eclampsia that develops before 30 weeks. Without more data on suspected and confirmed pre-eclampsia management before 30 weeks it is difficult to make any assumptions with regards to resource use by different test strategies,

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					PROGNOSIS did not provide these data in the manuscript submitted to the EAG.
	25.	182	6.3	Although some uncertainties regarding the health related quality for life (HRQoL) remain, the ERG as put considerable effort into deriving values. We also like to highlight that the test are still cost saving under the assumption that there would be no difference in quality adjusted life-years compared to current care.	No EAG response appears to be required here.
	26.	183		We do not see the need for further primary accuracy studies with the Elecsys® immunoassay sFlt-1/PlGF ratio: PROGNOSIS was a large, prospective, multi-centre primary study that addressed the need to derive robust cut-off values for the short-term prediction for pre-eclampsia in women with suspected pre-eclampsia. With a clear end-point definition, inclusion criteria that reflect clinical practice and centres in several countries, the study met its primary objectives with results transferable and relevant to the UK setting.	The EAG agrees that this comment by Roche seems reasonable - the DAR (page 187) does not specifically recommend further primary accuracy studies are required on the Elecsys sFlt-1/PlGF assay.
Thermo Fisher Scientific	27.	10	Number and quality of test accuracy	There are two publications which have recently appeared regarding BRAHMS sFlt-1/PLGF plus Kryptor PE ratio and the equivalent clinical and assay performance when compared to the Roche	

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			studies	Elecsys assay. We note that the EAG committee has identified the Andersen paper (48) - **Bjorkholt Andersen L, *et al.* Journal of the American Society of Hypertension 9(2) (2015) 86–96** – this study shows in our opinion • An equal or better performance of sFlt-1 and PlGF on KRYPTOR compared to Elecsys in diagnosing pre-eclampsia and also proves usefulness of both markers in a routine clinical setting • KRYPTOR sFlt-1/ PlGF ratio results in higher sensitivity at the cost of slightly lower specificity in diagnosing pre-eclampsia when compared to Elecsys • The same cut-offs published for the ELECSYS assay can be applied for KRYPTOR assays (85 in general as well as 33 and 110) • Complete description of assay characteristics and performance for KRYPTOR and Elecsys described in publication (page 3) We would also ask if the following paper was of assistance in estimating diagnostic accuracy - **van**	The study by Andersen and colleagues (reference 48) is outside the NICE scope since it did not include women with suspected pre-eclampsia. It has a case-control design with diagnostic accuracy based upon test results for two groups of women: those already diagnosed with pre-eclampsia and those with an uncomplicated pregnancy. This would not be reflective of the clinical setting being considered in the current diagnostic assessment. As noted in Appendix 3 of the DAR this study was excluded from the review of test accuracy by the EAG. The company's bullet points here therefore apply to the case-control study only, and an assumption would need to be made that the case-control study results would be applicable to women with suspected pre-eclampsia. The EAG is not aware of any support for such an assumption. The study by van Helden and Weiskirchen

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				Helden et al, Clin Biochem 2015 (Available online 27 June 2015) – this study shows in our opinion:
				• Confirmation of good correlation between the BRAHMS and Elecsys assays
				• Application of the established cut-off values for Elecsys yielded the same clinical performance in the diagnosis of pre-eclampsia
				• Calculation of optimal cut-off for diagnosing pre-eclampsia for this study cohort
				  ○ KRYPTOR ratio, optimal cut-off = 99.2 (sensitivity 92%, specificity 100%)
				  ○ Roche ELECSYS ratio: optimal cut-off = 70.3 (sensitivity 94%, specificity 96%)
				• Users are able to define their cut-offs according to their patient population and clinical needs, but they can safely start with the Roche ELECSYS cut-offs as there is no difference in clinical performance when using these with the BRAHMS assay.
					(reference 278) is also outside the NICE scope for the same reason as the study by Andersen and colleagues, i.e. it is another case-control study on women with diagnosed pre-eclampsia and those with uncomplicated pregnancies. This study, as indicated in Appendix 3 of the DAR, was also excluded from the review of test accuracy by the EAG. The same caveats apply to this study as those noted above for Andersen and colleagues. The company's bullet points here therefore apply to the case-control study only, and an assumption would need to be made that the case-control study results would be applicable to women with suspected pre-eclampsia. The EAG is not aware of any support for such an assumption.
					
					In addition, the EAG stresses that case-control studies are by their nature likely to overestimate diagnostic accuracy. However, it is unclear whether the degree of any overestimation would be the same for both tests.

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	28.	10	Test accuracy outcomes	We believe that the BRAHMS assay can be treated as equivalent to the Roche ELECSYS assay in terms of assay performance and clinical utility, based on the two recent comparator publications detailed above.	As noted above both these studies were outside the NICE scope and both were excluded from the review of test accuracy by the EAG.
	29.	63	4.3	van Helden et al, Clin Biochem 2015 (Available online 27 June 2015) could be considered as an example of head to head studies conducted in relevant clinical populations	As noted above this study is outside the NICE scope and was excluded from the review of test accuracy by the EAG.