CONFIDENTIAL UNTIL PUBLISHED

Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Placental growth factor (alone or in combination with soluble fms-like tyrosine kinase 1) as an aid to the assessment of women with suspected pre-eclampsia: systematic review and economic analysis

Second addendum (27 November 2015) covering the EAG's response to consultation on the Diagnostics Consultation Document

Produced by Southampton Health Technology Assessments Centre

Authors Geoff Frampton, Senior Research Fellow, SHTAC
Jeremy Jones, Principal Research Fellow, SHTAC
Liz Payne, Research Fellow, SHTAC
Micah Rose, Research Fellow, SHTAC

Correspondence to Corresponding author:
Dr Geoff Frampton
Southampton Health Technology Assessments Centre (SHTAC)
University of Southampton
First Floor, Epsilon House
Enterprise Road, Southampton Science Park
Southampton, SO16 7NS, UK.
Tel: +44(0)23 8059 XXXX
Fax:+44(0)23 8059 5639
email: G.K.Frampton@soton.ac.uk

Date completed: 27th November 2015

Confidential information
This addendum does not contain any information considered at the time of writing to be confidential. However, the main Diagnostic Assessment Report to which this document refers does contain confidential information and this is clearly identified in the main report.

Source of funding: This report was commissioned by the NIHR HTA Programme as project number **14/169/05** and will be published in full in *Health Technology Assessment* (http://www.journalslibrary.nihr.ac.uk/hta).

Declared competing interests of authors

None

All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare 1) no financial support for the submitted work from anyone other than their employer; 2) no financial relationships with commercial entities that might have an interest in the submitted work; 3) no spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; and 4) no non-financial interests that may be relevant to the submitted work.

Rider on responsibility for the report

The views and opinions expressed in this report are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health. Any errors are the responsibility of the authors.

EAG ADDITIONAL ANALYSES

In response to stakeholders' comments on the Diagnostics Consultation Document (DCD), NICE requested the EAG to investigate the effect on cost-effectiveness of the Alere Triage test for rule-in of pre-eclampsia in early gestation using a cutoff PlGF <12 pg/mL (DCD comment 1).

A further stakeholder comment in the DCD (comment 15) highlights data from the PELICAN study for rule-out of pre-eclampsia in late gestation which the EAG had not included in its analyses. The EAG has therefore investigated the impact of this cutoff on the cost-effectiveness of the Alere Triage test.

Results of these two analyses are presented below.

1. Alere Triage test for rule-in of pre-eclampsia during gestation weeks 20-34 using a cutoff of PlGF <12 pg/mL

In response to Alere's comments on the DCD, NICE requested the EAG to investigate the effect on cost-effectiveness of including the Triage test with a cutoff PlGF <12 pg/mL (using test accuracy data as reported in DCD Table 7). The EAG would like to clarify that the diagnostic accuracy results available for this cutoff refer to the endpoint 'preterm delivery', not specifically preterm delivery resulting from pre-eclampsia as interpreted by Alere in their DCD comments. It is possible that a number of women who have a PlGF concentration <12 pg/mL will deliver preterm for reasons other than pre-eclampsia; however, since this cutoff identifies a high-risk group, the majority of preterm deliveries would be expected to be related to pre-eclampsia. In the base case analysis, total costs for the Alere Triage PlGF test were £6,048 and QALYs were 0.39445. As shown in Table 1, using this rule-in endpoint ('preterm delivery') increases the dominance of the Alere Triage test by decreasing costs by £468 and increasing QALYs by 0.00016 relative to the base case. The difference between the Alere Triage and Roche Elecsys tests more than doubles with this alternative rule-in endpoint for the Alere test, but there remain concerns that not all of the women identified by this test would have pre-eclampsia, which may exaggerate test accuracy, and inappropriately reduce costs.

Table 1 Cost-effectiveness of the Alere Triage test for rule-in of pre-eclampsia for women presenting before 35 weeks' gestation (Pre-term delivery, PlGF<12 pg/mL: sensitivity = 0.44, specificity = 0.97)

Strategy	**Costs**		**QALYs**		**ICER**
	Total	Increment	Total	Increment	
Triage PlGF test	£5,580		0.39461		

Elecsys sFlt-1/PlGF ratio test	£6,456	£876	0.39434	-0.00027	Dominated
Standard assessment	£8,945	£2,489	0.39368	-0.00066	Dominated

2. Alere Triage test for rule-out of pre-eclampsia during gestation weeks 35^{+0} to 36^{+6} using a cutoff of PlGF<100 pg/mL

In response to comment 15 in the DCD, the EAG acknowledges that data from the PELICAN study for the endpoint "pre-eclampsia requiring pre-term delivery" with a specific cutoff of PlGF<100 pg/mL for rule-out of pre-eclampsia in late gestation, reported as 'exploratory analyses' in a paper by Chappell and colleagues, were not included in the Diagnostic Assessment Report (DAR). These data are reproduced below in Table 2. They provide an additional table (G) to be included alongside the existing Tables A-F of the data extraction form for the PELICAN study (Appendix 5 in the DAR).

Table 2 Addendum to Appendix 5 in the DAR
(G) Presentation 35^{+0} to 36^{+6} weeks: Prediction of pre-eclampsia requiring delivery before week 37

PlGF cutoff <100 pg/mL ('exploratory analysis')	**Population with PE**	**Population without PE**	**Total**
PlGF test positive	(a) 37	(c) 67	104
PlGF test negative	(b) 2	(d) 31	33
Total	39	98	137
Test accuracy statistics	**Parameter value**	**95% CI**	
Sensitivity *a / (a + b)*	0.95	0.83 to 0.99	
Specificity *d / (c + d)*	0.32	0.22 to 0.42	
Positive predictive value *a / (a + c)*	0.36	0.26 to 0.44	
Negative predictive value *d / (b + d)*	0.94	0.80 to 0.99	
Positive likelihood ratio *sensitivity/(100-specificity)*	1.4	1.2 to 1.6	
Negative likelihood ratio *(100-sensitivity)/specificity*	0.16	0.04 to 0.64	
Disease prevalence* *a + b / (a + b + c + d)*	28.47%	21.09% to 36.80%	

* calculated by reviewer

Using these test accuracy data, the EAG has investigated the influence on cost-effectiveness outcomes of the PlGF<100 pg/mL cutoff for rule-out of pre-eclampsia in late gestation. In the base case, the cost

of the Alere Triage test in women presenting between 35 and 36^{+6} weeks' gestation was £3,393. As shown in Table 3, this alternative rule-out endpoint based on the diagnostic accuracy reported in Table 2 has no discernible impact on the cost-effectiveness of the Alere Triage test.

Table 3 Cost-effectiveness of Alere Triage test for rule-out of pre-eclampsia for women presenting between 35 weeks and 36^{+6} weeks' gestation (pre-eclampsia requiring pre-term delivery, PlGF <100 pg/mL: sensitivity = 0.95, specificity = 0.32)

Strategy	Costs		QALYs		ICER
	Total	Increment	Total	Increment	
Triage PlGF test	£3,393		0.39541		
Elecsys sFlt-1/PlGF ratio test	£3,584	£191	0.39541	0	Dominated
Standard assessment	£3,758	£174	0.39541	0	Dominated