National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

PlGF testing (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

This overview summarises the key issues for the Diagnostics Advisory Committee's consideration. This document is intended to be read in conjunction with the final scope issued by NICE for the assessment and the diagnostics assessment report. A glossary of terms can be found in Appendix B.

1 Background

1.1 Introduction

The purpose of this assessment is to evaluate the clinical and cost effectiveness of 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 for the diagnosis of pre-eclampsia in the second and third trimesters of pregnancy. The tests are intended for use in conjunction with clinical judgement and other existing diagnostic tests, to aid the diagnosis of pre-eclampsia.

Pre-eclampsia is a potentially serious complication of some pregnancies which, when identified, requires referral to a specialist and hospital admission for both maternal and fetal monitoring. Pre-eclampsia is characterised in the mother by high blood pressure (hypertension) and proteinuria which occurs

when the kidneys leak protein into the urine. The presence of either hypertension or proteinuria alone during pregnancy can also indicate a risk of developing pre-eclampsia. It is thought to be related to problems with the development of the placenta. Other symptoms include headache, visual disturbances, epigastric or right upper quadrant pain, oedema (swelling of the hands, face or feet) and oliguria (low output of urine). If pre-eclampsia is not diagnosed and closely monitored, it can lead to potentially life-threatening complications for the mother including eclampsia, HELLP syndrome, disseminated intravascular coagulation, stroke, or organ dysfunction. It can also affect the fetus, increasing the risk of intrauterine growth restriction and intrauterine death.

The PlGF tests measure the amount of placental growth factor (PlGF) in blood plasma. PlGF is a protein involved in placental angiogenesis (the development of new blood vessels) and in pre-eclampsia, levels of PlGF can be abnormally low. In normal pregnancy, PlGF levels rise and peak at 26 to 30 weeks gestation so the failure of PlGF levels to rise during pregnancy may be an indicator of placental dysfunction. In addition, some PlGF tests also measure soluble FMS-like tyrosine kinase-1 (sFlt-1), a protein which is thought to disable those proteins associated with blood vessel formation, such as PlGF. In women who develop pre-eclampsia, the levels of sFlt-1 are thought to be higher than those seen in normal pregnancy.

Provisional recommendations on the use of these technologies will be formulated by the Diagnostics Advisory Committee at the Committee meeting on 30 September 2015.

1.2 Scope of the evaluation

Table 1: Scope of the evaluation

Decision questions	What is the clinical and cost-effectiveness of 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: • in addition to clinical assessment for the diagnosis of pre-eclampsia in the second and third trimesters of pregnancy? • as a replacement for quantitative proteinuria tests in the diagnosis of pre-eclampsia in the second and third trimesters of pregnancy?
Populations	Women presenting with suspected pre-eclampsia between 20 weeks, and 36 weeks and 6 days of pregnancy who have received blood pressure assessment and qualitative assessment of proteinuria. Potential subgroups include: • Women with chronic hypertension • Women with pre-existing or gestational diabetes • Women with renal disease • Women with an autoimmune disease
Interventions	1. Clinical assessment (as defined for the comparator) in conjunction with: • Triage PlGF test • Elecsys immunoassay sFlt-1/PlGF ratio • DELFIA Xpress PlGF 1-2-3 test • BRAHMS sFlt-1 Kryptor / PlGF plus Kryptor PE ratio 2. Clinical assessment (as defined for the comparator but **without** quantitative proteinuria testing) in conjunction with the PlGF tests listed above in 1.
Comparator	Clinical assessment guided by a combination of the following clinical information: • maternal hypertension (based on 3 blood pressure measurements) • proteinuria test (qualitative and quantitative) • clinical symptoms suggestive of pre-eclampsia • ultrasound fetal growth measurements Maternal hypertension, proteinuria or clinical symptoms alone may be sufficient to diagnose pre-eclampsia, or they may also occur in combination with fetal growth restriction and/or signs of biochemical or haematological impairment.
Healthcare setting	Secondary care
Outcomes	Intermediate measures for consideration may include:

	• Diagnostic accuracy • Prognostic accuracy • Time to test result • Test failure rate • Time to diagnosis • Proportion of women diagnosed with pre-eclampsia • Time to onset of pre-eclampsia and/or eclampsia • Proportion of women returned to less intensive follow-up • Length of in-patient hospital stay • Time to delivery
	Clinical outcomes for consideration may include: • Maternal morbidity and mortality • Fetal morbidity and mortality • Emergency admission for hypertensive disease • Health related quality of life including anxiety
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Costs of equipment, reagents and consumables • Cost of staff and associated training • Medical costs arising from testing and care such as hospital stay • Medical costs arising from adverse events including those associated with false test results and inappropriate treatment
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life years (QALYs).
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

Further details including descriptions of the interventions, comparators, care pathway and outcomes can be found in the final scope.

2 The evidence

This section summarises data from the diagnostics assessment report compiled by the External Assessment Group (EAG).

2.1 Clinical effectiveness

The EAG conducted a systematic review of the evidence on the diagnostic accuracy of the 4 index tests for the diagnosis of pre-eclampsia in the second and third trimesters of pregnancy. Details of the review can be found starting on page 39 of the diagnostics assessment report. Studies were included if they contained information on the following:

- Women with suspected pre-eclampsia between 20 weeks, and 36 weeks plus 6 days of pregnancy who have received blood pressure assessment and qualitative assessment of proteinuria.
- Triage PlGF; Elecsys immunoassay sFlt-1/PlGF ratio; DELFIA Xpress PlGF 1-2-3; and BRAHMS sFlt-1 Kryptor/PlGF plus Kryptor PE ratio, in conjunction with usual clinical assessment, or in conjunction with usual clinical assessment excluding quantitative determination of proteinuria.
- A reference standard of clinical assessment guided by maternal hypertension, proteinuria, symptoms suggestive of pre-eclampsia, and ultrasound fetal growth measurements.
- Test performance outcomes, including diagnostic and prognostic test accuracy (sensitivity, specificity, incidence and related outcome measures) for pre-eclampsia.

Overview of included studies

Following searches and inclusion screening, 13 publications of 4 studies were included in the review. Two of these studies were on the Alere Triage PlGF test and 2 studies were on the Roche Elecsys sFlt-1/PlGF ratio. None of the studies included more than one test; therefore no head-to-head comparisons of the index tests were available. Further, none of the included studies were

on the Perkin Elmer DELFIA Xpress PlGF test or the ThermoFisher Scientific BRAHMS Kryptor sFlt-1/PlGF ratio.

An overview of the studies is given in table 1. Studies were done in various locations, with only the PELICAN study done fully in the UK and Ireland. Most studies covered a large proportion of the period of pregnancy specified in the scope (20^{+0} to 36^{+6} weeks). The studies also differed in the amount of detail they provided about why pre-eclampsia was suspected (table 2).

Table 1: Overview of included studies

Study	Location	Design	Number of patients	Timing of tests
Alere Triage PlGF test				
PETRA study (2015)	24 centres in USA and [redacted]	[redacted]	[redacted]	[redacted]
PELICAN study (2013)	7 centres in UK and Ireland	Prospective, single cohort	424	20^{+0} to 34^{+6} weeks (n=287) and 35^{+0} to 36^{+6} weeks (n=137)
Roche Elecsys sFlt-1/PlGF ratio test				
PROGNOSIS study (2015)	[redacted] across 14 countries, including UK	Prospective, two cohorts (feasibility, validation)	1050	24^{+0} to 36^{+6} weeks
Alvarez-Fernandez et al. (2014)	Spain	Retrospective, single cohort	62	20 to 34 weeks

Table 2: Reasons for suspecting pre-eclampsia

Study	Reasons for suspecting pre-eclampsia
PETRA study (2015)	[redacted]
PELICAN study (2013)	Headache, visual disturbances, epigastric or right upper quadrant pain, hypertension, dipstick proteinuria, or suspected fetal growth restriction.
PROGNOSIS study (2015)	New onset raised blood pressure, aggravation of pre-existing hypertension, new onset proteinuria, aggravation of pre-existing proteinuria, or one or more from the following: epigastric pain, excessive oedema (face, hands, feet), headache, visual disturbance, sudden weight gain, low platelets, elevated liver transaminases, suspected intrauterine growth restriction, abnormal uterine perfusion.
Alvarez-Fernandez et al. (2014)	High blood pressure, proteinuria, abnormal uterine artery Doppler, headache not responding to analgesic, visual symptoms, and/or severe oedema affecting hands, feet or face.

Because studies had different patient baseline characteristics, and the outcome data used different test cut-offs and different gestation timings, the EAG considered it inappropriate to conduct meta-analyses. Full details of the baseline characteristics can be found starting on page 47 of the diagnostics assessment report.

Critical appraisal of included studies

The studies were critically appraised using the QUADAS criteria and the EAG also did an assessment of the generalisability of the studies to clinical practice in the UK. Full details of the critical appraisal can be found starting on page 55 of the diagnostics assessment report. The results of the critical appraisal using the QUADAS criteria are presented in table 3. Overall, studies were judged to be at [redacted] risk of bias. However, the risk of clinical review bias, that is, where the information used when interpreting the index test does not reflect that which would be available in clinical practice, was judged to be [redacted]

[redacted]

In terms of generalisability, only 2 studies included centres in the UK (PELICAN study and PROGNOSIS study); however, it is unclear how the geographical location of a study would influence generalisability of the study outcome to clinical practice in the UK. The definitions of pre-eclampsia used in the studies tended to be broader than the definitions used in the NICE clinical guideline on hypertension in pregnancy (2010), which may limit the generalisability of the studies.

Table 3. Overview of QUADAS assessment

QUADAS question	Alere Triage PlGF test		Roche Elecsys immunoassay sFlt-1/PLGF ratio	
	PETRA study	PELICAN study	PROGNOSIS study	Alvarez-Fernandez et al.
Was the spectrum of patients representative of the patients who will receive the test in practice?	[redacted]	Yes	[redacted]	Yes
Is the reference standard likely to classify the target condition correctly?	[redacted]	Yes	[redacted]	Yes
Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	[redacted]	Yes	[redacted]	Yes
Did the whole sample or a random selection of the sample, receive verification using the intended reference standard?	[redacted]	Yes	[redacted]	Yes
Did patients receive the same reference standard irrespective of the index test result?	[redacted]	Yes	[redacted]	Yes
Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	[redacted]	Yes	[redacted]	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	[redacted]	Yes	[redacted]	Yes
Were the index test results interpreted without knowledge of the results of the reference standard?	[redacted]	Yes	[redacted]	Yes
Were the same clinical data available when test results were interpreted as would be	[redacted]	No	[redacted]	No

available when the test is used in practice?				
Were uninterpretable/ intermediate test results reported?	[redacted]	Yes	[redacted]	No
Were withdrawals from the study explained?	[redacted]	Yes	[redacted]	Yes

Results for the Alere Triage PlGF test

Diagnostic accuracy outcomes for the Alere Triage PlGF test are available for three test cut-offs: 100 picogram/ml, the 5th centile of PlGF concentration for gestational age, and 12 picogram/ml. PlGF concentrations above 100 picogram/ml are considered normal and would be unlikely to progress to delivery within 14 days. As such, a result of 100 picogram/ml or greater is used to rule out pre-eclampsia.

The cut-offs of 100 picogram/ml and 5th centile of PlGF concentration for gestational age both gave [redacted] for identifying women likely to develop pre-eclampsia requiring delivery within [redacted] days of testing, when presenting with suspected pre-eclampsia up to 35 weeks of gestation ([redacted] to 96%; table 4). The cut-off of 12 picogram/ml yielded lower sensitivity for identifying women likely to develop pre-eclampsia requiring delivery within 14 days of testing, when presenting with suspected pre-eclampsia up to 35 weeks of gestation (63%; table 3).

Table 4: Alere Triage PlGF test accuracy for predicting pre-eclampsia requiring delivery within [redacted] days during weeks 20^{+0} to 34^{+6} of gestation

Study and test cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
PETRA 100 pg/ml	[redacted]	[redacted]	[redacted]	[redacted]
PELICAN <100 pg/ml	0.96 (0.89 to 0.99)	0.56 (0.49 to 0.63)	0.44 (0.36 to 0.52)	0.98 (0.93 to 1.00)
PELICAN ≥100 pg/ml	0.96 (0.89 to 0.99)	0.56 (0.49 to 0.63)	0.43 (0.36 to 0.51)	0.98 (0.93 to 1.00)
PELICAN <5th centile	0.96 (0.89 to 0.99)	0.55 (0.48 to 0.61)	0.43 (0.36 to 0.51)	0.98 (0.93 to 1.00)
PELICAN <12 pg/ml	0.63 (0.51 to 0.74)	0.90 (0.85 to 0.94)	0.70 (0.57 to 0.80)	0.87 (0.82 to 0.91)

The cut-off of 100 picogram/ml was not tested for women presenting later than 34^{+6} weeks. But in the PELICAN study, both the 5th centile of PlGF for gestational age and the 12 picogram/ml cut-offs had poor diagnostic accuracy for predicting pre-eclampsia requiring delivery within 14 days when women presented after week 34^{+6} (70% and 22%; table 5).

Table 5: Alere Triage PlGF test accuracy for predicting pre-eclampsia requiring delivery within 14 days during weeks 35^{+0} to 36^{+6} of gestation

Study and test cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
PELICAN <5th centile	0.70 (0.58 to 0.81)	0.64 (0.52 to 0.75)	0.65 (0.53 to 0.76)	0.69 (0.57 to 0.80)
PELICAN <12 pg/ml	0.22 (0.13 to 0.34)	0.91 (0.82 to 0.97)	0.71 (0.48 to 0.89)	0.55 (0.46 to 0.64)

Only the PETRA study reported the accuracy of the Alere Triage PlGF test for predicting pre-eclampsia requiring delivery within [redacted] days of testing, for women presenting with suspected pre-eclampsia up to 35 weeks of gestation. The

test had [redacted] sensitivity with [redacted] precision using a cut-off of 100 picogram/ml ([redacted]% [95% CI [redacted]]; table 6).

Table 6: Alere Triage PlGF test accuracy for predicting pre-eclampsia requiring delivery within [redacted] days during weeks 20^{+0} to 35^{+0} of gestation

Study and test cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
PETRA 100 pg/ml	[redacted]	[redacted]	[redacted]	[redacted]

A range of other outcomes were also reported. The Alere Triage PlGF test with a cut-off of 100 picogram/ml had [redacted] sensitivity at predicting delivery within [redacted] days (or [redacted] days) of testing independent of the pre-eclampsia diagnosis ([redacted] [95% CI [redacted]] to 94% [95% CI 87% to 98%]; table 7). A cut-off of 12 picogram/ml had poor sensitivity (44%) but good specificity (97%) for predicting preterm delivery, independent of the pre-eclampsia diagnosis.

Table 7: Other test accuracy outcomes for the Alere Triage PlGF test during weeks 20^{+0} to 34^{+6} of gestation

Study and test cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Preterm pre-eclampsia				
PELICAN <100 pg/ml	0.90 (0.83 to 0.95)	0.65 (0.58 to 0.73)	0.65 (0.57 to 0.72)	0.90 (0.83 to 0.95)
Delivery within [redacted] days of testing				
PETRA 100 pg/ml	[redacted]	[redacted]	[redacted]	[redacted]
PELICAN ≥100 pg/ml	0.94 (0.87 to 0.98)	0.57 (0.50 to 0.64)	0.47 (0.39 to 0.55)	0.96 (0.91 to 0.99)
Delivery within [redacted] days of testing				
PETRA 100 pg/ml	[redacted]	[redacted]	[redacted]	[redacted]
Preterm delivery				
PELICAN <12 pg/ml	0.44 (0.36 to 0.52)	0.97 (0.93 to 0.99)	0.94 (0.86 to 0.98)	0.62 (0.55 to 0.68)

Area under curve estimates from ROC analyses suggest that the optimal predictive ability of the Alere Triage PlGF test was for pre-eclampsia requiring delivery within 14 days of testing, and for predicting preterm pre-eclampsia (table 8). The predictive accuracy of the test for all outcomes was greater when women presented with suspected pre-eclampsia before week 35 of gestation, compared to presentation after week 35.

Table 8: ROC analysis area under curve values for the Alere Triage PlGF test

Study	Outcome	Area under curve (95% CI or SE)
PETRA	**Presentation 20^{+0} to 35^{+0} weeks**	
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	Presentation 35^{+0} to 36^{+6} weeks	
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
PELICAN	**Presentation 20^{+0} to 34^{+6} weeks**	
	PE requiring delivery ≤ 14 days	0.87 (0.03)
	Preterm PE	0.862 (0.818 to 0.907)

Results for the Roche Elecsys sFlt-1/PlGF ratio test

Diagnostic and prognostic accuracy outcomes for the Roche Elecsys sFlt-1/ PlGF ratio test are available in two studies which assessed three test cutoffs: 23 picograms/ml, 38 picograms/ml, and 85 picograms/ml. The studies are not directly comparable because they differed in the cut-offs used and the time periods during which the rule-in or rule-out of pre-eclampsia was applied.

The PROGNOSIS study analysed two cohorts. The feasibility cohort (n=500) aimed to derive a cut-off-based prediction model for the sFlt-1/PlGF ratio and the validation cohort (n=550) aimed to test the model. The cut-off derived from the model was 38 picograms/ml. Values below 38 picograms/ml were considered negative and were used to rule out pre-eclampsia within 1 week. Sensitivity for ruling out pre-eclampsia within 1 week was relatively high ([redacted] [95% CI [redacted]] to [redacted] [95% CI [redacted]]) with relatively [redacted] confidence intervals. Specificity ranged from [redacted] (95% CI [redacted]) to [redacted] (95% CI

[redacted]) with [redacted] confidence intervals suggesting [redacted] precision of the estimates (table 9). Values above 38 picogram/ml were used to rule in pre-eclampsia within 4 weeks. Sensitivity for ruling in pre-eclampsia within 4 weeks was [redacted] than for the rule-out algorithm, ranging from [redacted] (95% CI [redacted]) to [redacted] (95% CI [redacted]), with relatively [redacted] confidence intervals. Specificity was relatively [redacted] ([redacted] [95% CI [redacted]) with [redacted] precision; however the positive predictive value was only 38.6% (combined cohort), indicating nearly two-thirds of patients diagnosed would be false positives (table 9).

Table 9. Test accuracy outcomes for the Roche Elecsys sFlt-1/PlGF ratio; presentation 24^{+0} to 36^{+6} weeks; cut-off 38 picograms/ml (PROGNOSIS study)

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Rule out of pre-eclampsia within 1 week				
Feasibility cohort (n=500)	[redacted]	[redacted]	NR	[redacted]
Validation cohort (n=550)	[redacted]	[redacted]	NR	[redacted]
Combined cohorts (n=1050)	0.857 (0.728 to 0.941)	0.791 (0.765 to 0.816)	[redacted]	0.991 (0.982 to 0.996)
Rule in of pre-eclampsia within 4 weeks				
Feasibility cohort (n=500)	[redacted]	[redacted]	[redacted]	NR
Validation cohort (n=550)	[redacted]	[redacted]	[redacted]	NR
Combined cohorts (n=1050)	0.703 (0.619 to 0.778)	0.831 (0.805 to 0.855)	0.386 (0.326 to 0.450)	[redacted]

The study by Alvarez-Fernandez et al. analysed Roche Elecsys sFlt-1/PlGF ratio cut-offs of 23 picogram/ml and 85 picogram/ml for predicting pre-eclampsia (table 10). The cut-off of 23 picogram/ml had considerably higher sensitivity than the cut-off of 85 picogram/ml (92% [95% CI 73% to 99%] compared with 56% [95% CI 35% to 75%]). Specificity was lower for the 23

picogram/ml cut-off than the cut-off of 85 picogram/ml (81% compared with 97%).

Table 10. Test accuracy outcomes for the Roche Elecsys sFlt-1/PlGF ratio; presentation 20 to 34 weeks; cut-offs 23 picograms/ml and 85 picograms/ml (Alvarez-Fernandez et al.)

	Sensitivity (95% CI)	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
Rule out of pre-eclampsia within 3 weeks				
Cut-off: 23 picograms/ml	0.920 (0.725 to 0.986) [a]	0.811 (0.643 to 0.914) [a]	0.767 (0.573 to 0.894) [a]	0.938 (0.778 to 0.989) [a]
Cut-off: 85 picograms/ml	0.560 (0.353 to 0.750)	0.973 (0.842 to 0.999)	0.933 (0.660 to 0.997)	0.766 (0.616 to 0.872)
[a] 95% CI values reported by the authors and those calculated by the reviewer differ (by less than ±1.5%): the authors' data are presented here.				

Area under the curve estimates from ROC analyses suggest that, for the PROGNOSIS study, the sFlt-1/PlGF ratio test tended to have [redacted] accuracy than clinical information alone for ruling in or ruling out pre-eclampsia (range [redacted] compared with [redacted]), however, the confidence intervals for the estimates [redacted] (table 11) . Adding clinical information to the test result (range [redacted]) [redacted].

Table 11. ROC analysis area under curve values for the Roche Elecsys sFlt-1/PlGF ratio

Study	Outcome, cohort		Area under curve (95% CI)
PROGNOSIS (24^{+0} to 36^{+6} weeks)	**Rule out of pre-eclampsia within 1 week**		
	sFlt-1/PlGF ratio	Feasibility cohort	[redacted]
		Validation cohort	[redacted]
		Combined cohorts	[redacted]
	sFlt-1/PlGF ratio plus clinical data	Feasibility cohort	[redacted]
		Validation cohort	[redacted]
	Clinical data without sFlt-1/PlGF ratio	Feasibility cohort	[redacted]
		Validation cohort	[redacted]
	Rule in of pre-eclampsia within 4 weeks		
	sFlt-1/PlGF ratio	Feasibility cohort	[redacted]
		Validation cohort	[redacted]
		Combined cohorts	[redacted]
	sFlt-1/PlGF ratio plus clinical data	Feasibility cohort	[redacted]
		Validation cohort	[redacted]
	Clinical data without sFlt-1/PlGF ratio	Feasibility cohort	[redacted]
		Validation cohort	[redacted]
Alvarez-Fernandez et al. (20 to 34 weeks)	**Pre-eclampsia**		
	All women		0.903 (0.815 to 0.991)
	Women with single gestation only		0.907 (0.798 to 1.000)

2.2 Costs and cost effectiveness

Systematic review of cost effectiveness evidence

The External Assessment Group (EAG) conducted a search to identify existing studies investigating the cost effectiveness of 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 for the diagnosis of pre-eclampsia in the second and third trimesters of pregnancy. Full details of the review of cost-effectiveness evidence start on page 81 of the diagnostics assessment report.

Four studies described in 4 full text articles (1 unpublished) were included in the review. All studies were cost analyses; that is they focused on potential savings and did not formally evaluate health outcomes of the mother or baby. An overview of the characteristics of the included economic studies and a brief summary of their base case results is provided in table 12.

Table 12. Characteristics of economic studies

Author	Hadker et al.	Hadker et al.	Schnettler et al.	Hunter et al.
Year	2010	2013	2013	[redacted]
Country	UK	Germany	USA	[redacted]
Study type	Cost analysis	Cost analysis	Cost analysis	[redacted]
Population	Women >20 weeks' gestation receiving obstetric care	Women >20 weeks' gestation receiving obstetric care	Women < 34 weeks' gestation with suspected pre-eclampsia	[redacted]
Intervention(s)	Intervention: standard care + sFlt-1/PlGF (Elescsys) test [diagnostic threshold was sFlt1/PlGF ≥ 85] Comparator: standard care	Intervention: standard care + sFlt1/PlGF (Elescsys) test [diagnostic threshold was sFlt1/PlGF ≥ 85] Comparator: standard care	Intervention: standard care + sFlt1/PlGF (Elescsys) test [diagnostic threshold was sFlt1/PlGF ≥ 85] Comparator: standard care	[redacted]
Model type	Decision tree	Decision tree	Not clear	[redacted]
Intervention effect	Intervention: sensitivity=0.82 Specificity =0.95 Comparator: sensitivity=0.46 specificity=0.83	Intervention: sensitivity=0.82 specificity=0.95 Comparator: sensitivity=0.46 specificity=0.83	Intervention: sensitivity =0.76 specificity =0.94 Comparator: sensitivity =0.94 Specificity =0.36	[redacted]
Base case results	Overall cost reduction of £945 per patient, from £2,726 to £1,781	Overall cost reduction of €637 per patient, from €1,579 to €942	Overall cost reduction of $1,215 per patient, from $3,022 to $1,807	[redacted]

Economic analysis

The EAG developed a de novo economic model designed to assess the cost effectiveness of diagnostic tests based on PlGF or sFlt-1/PlGF ratio test results when used in addition to usual clinical assessment compared to usual clinical assessment alone.

Model structure

The model developed for this assessment was a decision tree, incorporating 4 structural components:

- **Risk stratification** (high, intermediate or low risk of pre-eclampsia) of women with suspected pre-eclampsia, determined on the basis of clinical signs, symptoms or findings with or without the addition of a PlGF based test. Clinical signs symptoms and findings were:
  - new onset hypertension or aggravation of pre-existing hypertension
  - new onset proteinuria or aggravation of pre-existing proteinuria
  - abnormal uterine perfusion
  - suspected intrauterine growth restriction
  - headache
  - oedema
  - epigastric pain
  - visual disturbance
  - sudden weight gain
  - low platelets
  - elevated liver transaminases
- **Management** (expectant management or immediate delivery) based on key symptoms of pre-eclampsia or emergent eclampsia. Expectant management involves monitoring of clinical signs, symptoms and findings, active management of conditions such as hypertension and planned delivery at 37 weeks of gestation. Immediate delivery involves delivery within 24 hours irrespective of gestational age due to clinical findings

indicating severe risk to a pregnant woman or fetus. Immediate delivery is the assumed treatment for pre-eclampsia detected after 35 weeks' gestation

- **Maternal outcomes** (admission to intensive care, extended hospital stay, and morbidity associated with pre-eclampsia)
- **Fetal and neonatal outcomes** (admission to intensive care, extended hospital stay, and morbidity and mortality associated with fetal conditions that may be associated with the underlying cause of maternal pre-eclampsia and/or with early delivery).

An outline of the model is presented in figure 1, which is also presented on page 121 of the diagnostics assessment report.

The probability of patients with suspected pre-eclampsia being identified as high, intermediate or low risk of pre-eclampsia is based on disease prevalence and the reported sensitivity and specificity of each diagnostic strategy.

Women with a low risk of pre-eclampsia are managed on the gestational hypertension pathway (expectant management). Women with an intermediate risk of pre-eclampsia are managed on a modified version of the gestational hypertension pathway which has an increased frequency of surveillance (expectant monitoring). Women with a high risk of pre-eclampsia presenting before 35 weeks gestation are managed using expectant monitoring when there are no signs of increased risk for the mother or neonate. Women with a high risk of pre-eclampsia presenting from 35 weeks gestation are managed by immediate delivery. These assumptions are in line with the NICE guideline on hypertension in pregnancy (2010).

Figure 1. Outline of the economic model

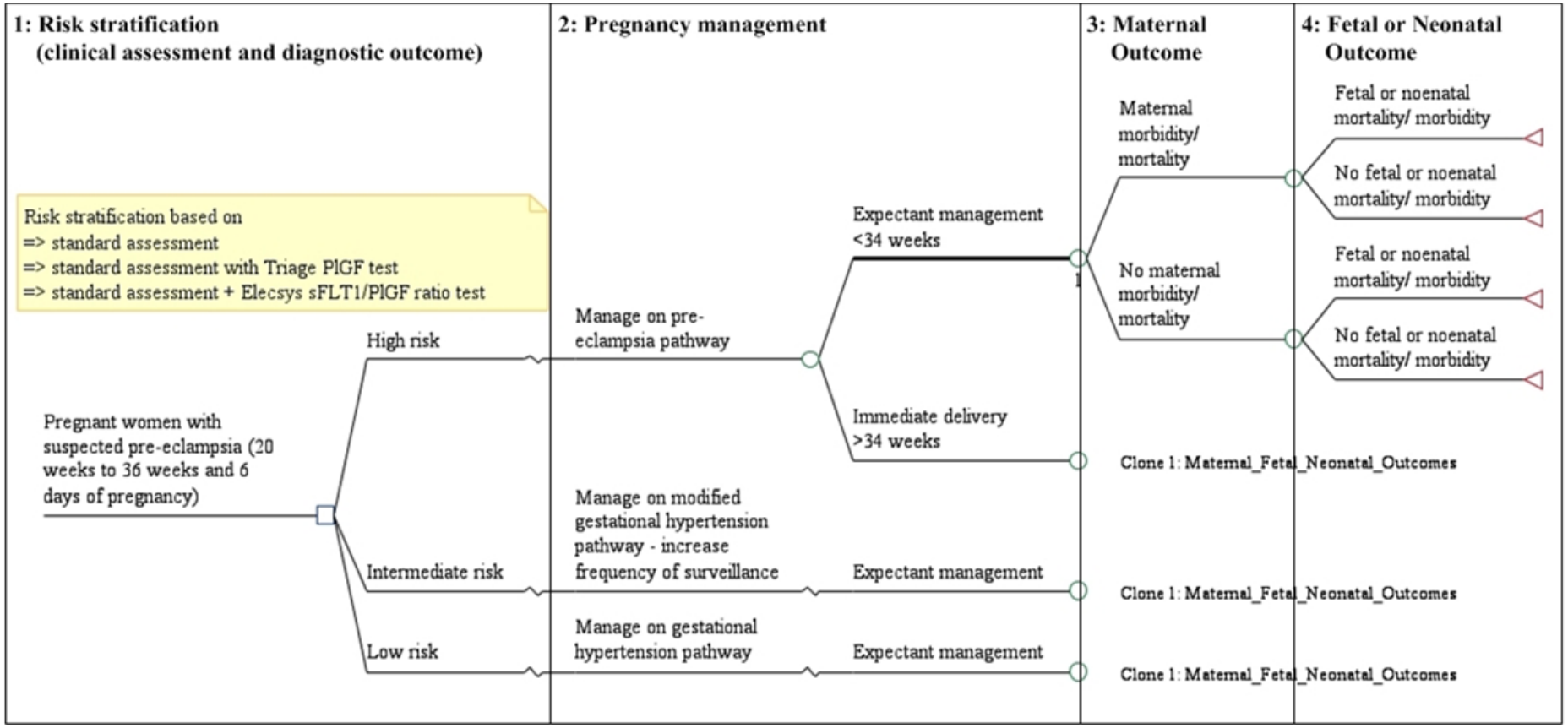


Figure 2. Maternal outcomes subtree

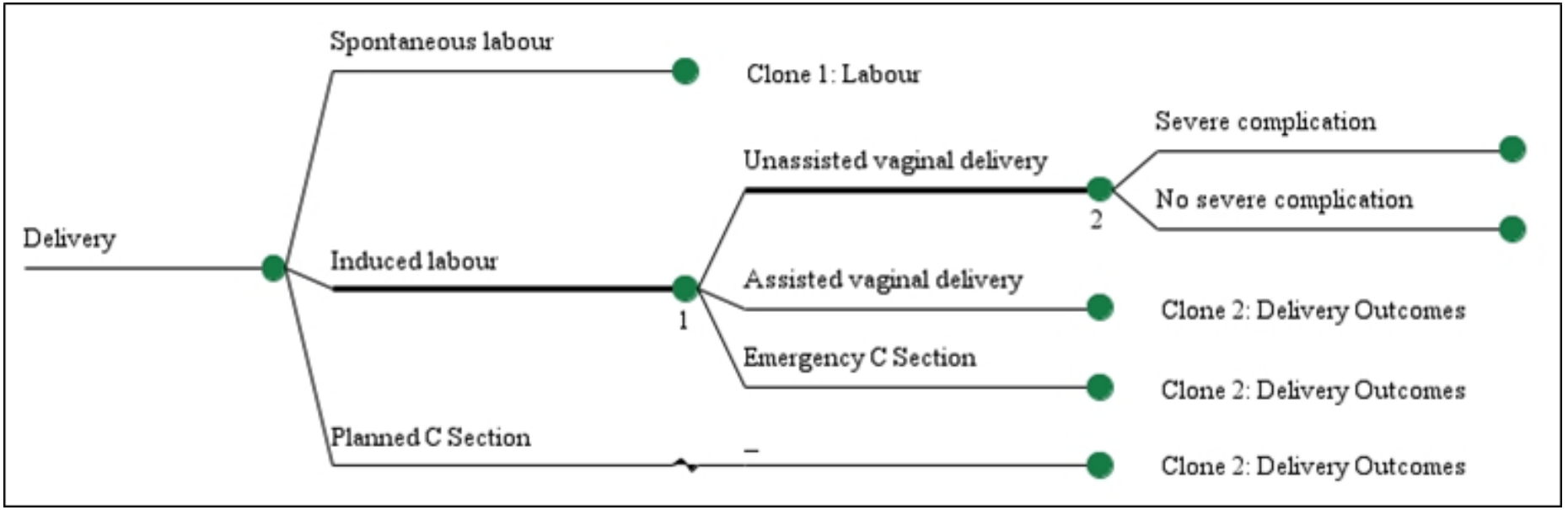
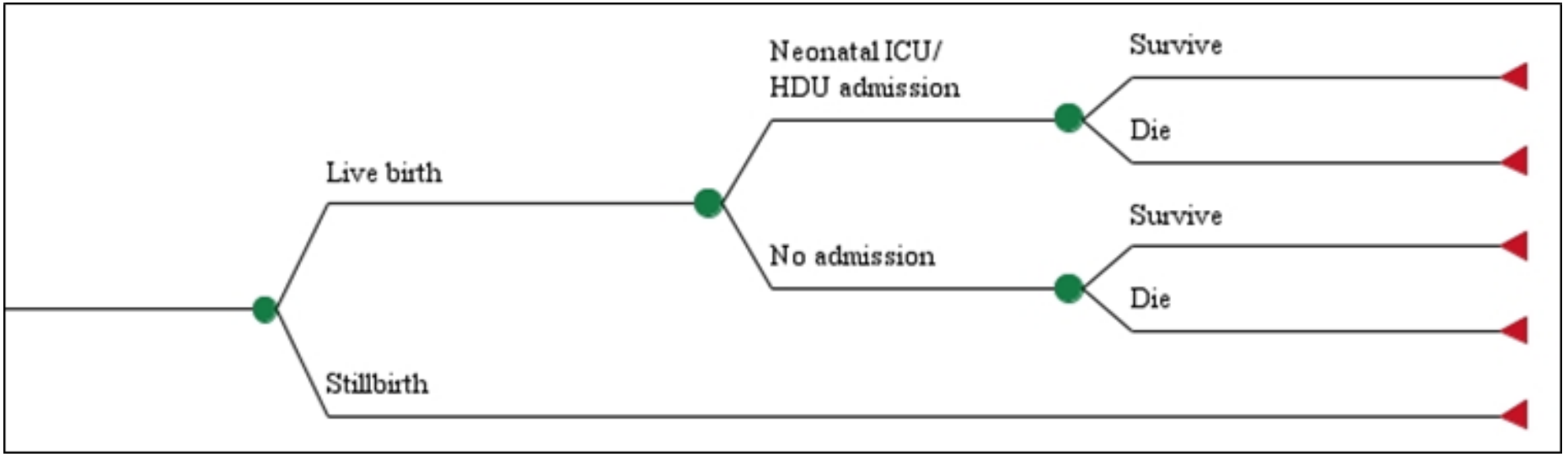


Figure 3. Fetal and neonatal outcomes subtree



Maternal and fetal outcomes in the model are assumed to be related to the presence or absence of pre-eclampsia. As a result, the outcome components of the model are preceded by an evaluation of true disease status. This is the probability of pre-eclampsia in women in each of the risk categories. It is calculated from disease prevalence, the reported sensitivity and specificity of each diagnostic strategy, and the probability of risk.

Maternal outcomes are modelled using the subtree presented in figure 2. Delivery results from either spontaneous labour, induced labour or planned caesarean section. Spontaneous and induced labour are associated with a risk of conversion to assisted vaginal delivery or emergency caesarean section. Each mode of delivery is associated with a risk of progression of pre-eclampsia to eclampsia during the delivery, which results in convulsions. Convulsions are associated with a higher maternal risk, admission to intensive or high dependency care, and a requirement for administration of anti-convulsive therapy. Women who do not experience convulsions are transferred to the ward following delivery and those who do not experience any further adverse events have a normal length of stay for the given mode of delivery.

Fetal and neonatal outcomes are modelled using the subtree presented in figure 3. Labour may result in a live birth or a still birth. A neonate from a live birth may or may not need admission to a neonatal intensive care unit or high dependency unit. The probability of admission to neonatal intensive or high dependency care is related to gestational age, presence or absence of pre-eclampsia, principal cause of early delivery (maternal condition or fetal distress), mode of delivery and the presence or absence of complications during delivery. The neonate may then survive or die.

Model inputs

Summaries of the model inputs are presented in the tables below. Further details on the identification of the model inputs and their sources are given starting on page 127 of the diagnostics assessment report.

Table 13 and 14 present the prevalence of pre-eclampsia, the distribution of women by the degree of hypertension, and the diagnostic test accuracy. The data on prevalence of pre-eclampsia are taken from the PELICAN study, which was conducted in the UK. The hypertension data were reported in Duckworth et al. as being derived from Anumba et al. The EAG was unable to verify the data from Anumba et al. but has used it in the absence of any better data. Test accuracy for the Triage PlGF test and the Elecsys sFlt-1/PlGF ratio test are taken from studies included in the systematic review of diagnostic test accuracy (PELICAN study and PROGNOSIS study). Test accuracy for standard clinical assessment is taken from a study included in the systematic review of economic evaluations (Schnettler et al.).

Table 13. Inputs used in the model - prevalence and distribution of pre-eclampsia

Prevalence of pre-eclampia				
Up to 35 weeks' gestation		0.265	0.215 to 0.320	PELICAN study
Between 35 and 37 weeks' gestation		0.489	0.403 to 0.576	
Distribution of women by degree of hypertension				
With pre-eclampsia	Severe	[redacted]	[redacted]	Anumba et al. as reported by Duckworth et al.
	Moderate	[redacted]	[redacted]	
	Mild or no hypertension	[redacted]	[redacted]	
Without pre-eclampsia	Severe	[redacted]	[redacted]	
	Moderate	[redacted]	[redacted]	
	Mild or no hypertension	[redacted]	[redacted]	

Table 14. Inputs used in the model - diagnostic test accuracy

Input		Value	Range	Source
Standard clinical assessment				
Sensitivity		0.941	0.838 to 0.988	Schnettler et al.
Specificity		0.357	0.263 to 0.460	
Alere Triage PlGF test				
20^{+0} to 34^{+6} weeks Rule-in	Sensitivity	0.632	0.513 to 0.739	PELICAN study
	Specificity	0.900	0.852 to 0.937	
20^{+0} to 34^{+6} weeks Rule-out	Sensitivity	0.960	0.888 to 0.992	
	Specificity	0.557	0.487 to 0.625	
35^{+0} to 36^{+6} weeks Rule-in	Sensitivity	0.224	0.131 to 0.342	
	Specificity	0.914	0.823 to 0.968	
35^{+0} to 36^{+6} weeks Rule-out	Sensitivity	0.701	0.577 to 0.807	
	Specificity	0.643	0.519 to 0.754	
Roche Elecsys sFlt-1/PlGF ratio test				
20^{+0} to 36^{+6} weeks Rule-in	Sensitivity	0.703	0.619 to 0.778	PROGNOSIS study and product insert
	Specificity	0.831	0.805 to 0.855	
20^{+0} to 36^{+6} weeks Rule-out	Sensitivity	0.857	0.728 to 0.941	
	Specificity	0.791	0.765 to 0.816	

Table 15 presents median times to delivery and probabilities of each type of delivery in women presenting with suspected pre-eclampsia up to 35 weeks of gestation. Table 16 presents this data for women presenting with suspected pre-eclampsia between 35 and 37 weeks of gestation. Table 17 reports the probabilities of fetal death, neonatal intensive care and the length of stay in the neonatal intensive care unit if admitted.

Table 15. Inputs used in the model – delivery characteristics for suspected pre-eclampsia presenting up to 35 weeks of gestation

Input		Value	Range	Source
Testing positive/rule-in for pre-eclampsia (delivery within 7 to 14 days)				
Median time to delivery (days)		9	3 to 16	PELICAN study
Onset of labour (probability)	Spontaneous	0.000		Assumption
	Induction	0.402		
	Planned caesarean section	0.598		EPIPAGE study
Mode of delivery (probability)	Non-assisted vaginal delivery	0.522		PELICAN study (assumed the same as for all deliveries before 35 weeks)
	Assisted vaginal delivery	0.225		
	Emergency caesarean section	0.254		
Testing negative/rule-out for pre-eclampsia				
Median time to delivery	Pre-eclampsia (days)	14	7 to 42	PELICAN study
	No pre-eclampsia (days)	62	14 to 63	
Onset of labour (probability)	Spontaneous	0.148		PELICAN study
	Induction	0.380		
	Planned caesarean section	0.472		
Mode of delivery (probability)	Non-assisted vaginal delivery	0.522		PELICAN study
	Assisted vaginal delivery	0.225		
	Emergency caesarean section	0.254		
Pregnancies with pre-eclampsia (true positive and false negative)				
Probability of severe complication of delivery due to pre-eclampsia		0.064	0.041 to 0.093	HYPITAT

Table 16. Inputs used in the model – delivery characteristics for suspected pre-eclampsia presenting between 35 and 37 weeks gestation

Input		Value	Range	Source
Testing positive/rule-in for pre-eclampsia (delivery within 7 days)				
Median time to delivery (days)		4	2 to 9	PELICAN study
Onset of labour (probability)	Spontaneous	0.184		PELICAN study
	Induction	0.551		
	Planned caesarean section	0.265		
Mode of delivery (probability)	Non-assisted vaginal delivery	0.568		PELICAN study
	Assisted vaginal delivery	0.137		
	Emergency caesarean section	0.295		
Testing negative/rule-out for pre-eclampsia				
Median time to delivery	Pre-eclampsia (days)	4	4 to 16	PELICAN study
	No pre-eclampsia (days)	16	6 to 23	
Onset of labour (probability)	Spontaneous	0.184		PELICAN study
	Induction	0.551		
	Planned caesarean section	0.265		
Mode of delivery (probability)	Non-assisted vaginal delivery	0.568		PELICAN study
	Assisted vaginal delivery	0.137		
	Emergency caesarean section	0.295		
Pregnancies with pre-eclampsia (true positive and false negative)				
Probability of severe complication of delivery due to pre-eclampsia		0.064	0.041 to 0.093	HYPITAT

Table 17. Inputs used in the model – fetal and neonatal outcomes

Input		Value	Range	Source
Up to 35 weeks gestation, testing positive/rule-in for pre-eclampsia (delivering within 7 to 14 days)				
Probability of adverse fetal outcome	Antepartum/ intrapartum fetal death	0.023	0.009 to 0.048	PELICAN study
	In-hospital neonatal death	0.007	0.001 to 0.025	
	Admission to neonatal intensive care	0.667	0.272 to 0.848	EPIPAGE study
Duration of stay in neonatal intensive care (days)		8.46	6.60 to 10.31	
Up to 35 weeks gestation, testing negative/rule-out for pre-eclampsia				
Probability of adverse fetal outcome	Antepartum/ intrapartum fetal death	0.023	0.009 to 0.048	PELICAN study
	In-hospital neonatal death	0.007	0.001 to 0.025	
	Admission to neonatal intensive care	0.074	0.049 to 0.106	HYPITAT II
Duration of stay in neonatal intensive care (days)		3.0	2.0 to 6.0	HYPITAT
Between 35 and 37 weeks gestation, testing positive/rule-in for pre-eclampsia (delivering within 7 days)				
Probability of adverse fetal outcome	Antepartum/ intrapartum fetal death	0.000		PELICAN study
	In-hospital neonatal death	0.000		
	Admission to neonatal intensive care	0.074	0.049 to 0.106	HYPITAT II
Duration of stay in neonatal intensive care (days)		3.0	2.0 to 6.0	HYPITAT
Between 35 and 37 weeks gestation, testing negative/rule-out for pre-eclampsia				
Probability of adverse fetal outcome	Antepartum/ intrapartum fetal death	0.000		PELICAN study
	In-hospital neonatal death	0.000		
	Admission to neonatal intensive care	0.037	0.020 to 0.063	HYPITAT II
Duration of stay in neonatal intensive care (days)		3.0	2.0 to 6.0	HYPITAT

Costs

The costs of the tests were taken from information submitted by the companies. Other costs were taken from NHS reference costs, the British National Formulary and published literature. A summary of the costs is presented in tables 18 and 19.

Table 18. Costs included in the economic model – management of suspected pre-eclampsia

Input		Value
Up to 35 weeks gestation – women testing negative for pre-eclampsia		
Mild or no hypertension	With pre-eclampsia	£103.30
	Without pre-eclampsia	£413.20
Moderate hypertension	With pre-eclampsia	£225.08
	Without pre-eclampsia	£900.32
Severe hypertension	With pre-eclampsia	£867.08
	Without pre-eclampsia	£1500.38
Up to 35 weeks gestation – women testing positive for pre-eclampsia		
Mild or no hypertension	With or without pre-eclampsia	£2315.95
Moderate hypertension	With or without pre-eclampsia	£2322.94
Severe hypertension	With or without pre-eclampsia	£2322.94
Between 35 and 37 weeks of gestation – women testing negative for pre-eclampsia		
Mild or no hypertension	With pre-eclampsia	£51.65
	Without pre-eclampsia	£103.30
Moderate hypertension	With pre-eclampsia	£112.54
	Without pre-eclampsia	£218.09
Severe hypertension	With pre-eclampsia	£754.54
	Without pre-eclampsia	£860.09
Between 35 and 37 weeks of gestation – women testing positive for pre-eclampsia		
Mild or no hypertension	With or without pre-eclampsia	£770.20
Moderate hypertension	With or without pre-eclampsia	£777.19
Severe hypertension	With or without pre-eclampsia	£777.19

Table 19. Costs included in the economic model – tests, delivery and critical care

Test costs		
Alere Triage PlGF test		[redacted]
Roche Elecsys sFlt-1/PlGF ratio test		[redacted]
Cost of delivery		
Spontaneous onset of labour	Normal delivery	£1506
	Assisted delivery	£1988
Induced labour	Normal delivery	£2133
	Assisted delivery	£3033
Caesarean delivery	Planned	£3182
	Emergency	£4013
Cost of critical care		
Maternal critical care		£1449
Neonatal intensive care unit		£978.50

Health related quality of life and QALY decrements

The External assessment group did a series of systematic searches to identify health related quality of life data in women with gestational hypertension, pre-eclampsia or outcomes of pregnancy that are related to gestational hypertension and pre-eclampsia. Utility values were taken from the published literature, however, many values had to be mapped from SF-36 to EQ-5D. A summary of the utility values is presented in table 20.

Table 20. Utility values used in the economic model

Parameter		**Value**
Baseline QALYs from (vaginal) delivery to six months post-partum	Birth to 3 weeks post-partum	0.0389
	3 weeks to 12 weeks post-partum	0.1496
	12 weeks to 6 months post-partum	0.2171
Decrement for caesarean delivery (birth to three weeks post-partum)	Non-emergency caesarean section	0.0050
	Emergency caesarean section	0.0092
Decrement for non-spontaneous delivery	3 weeks to 6 months post-partum	0.0084

Base-case results

The following assumptions were applied in the base case analysis:

- UK guidelines for management of suspected pre-eclampsia, gestational hypertension, and pre-eclampsia are followed
- Women presenting with pre-eclampsia before 35 weeks' gestation will be managed using expectant monitoring and women presenting from 35 weeks' gestation to 37 weeks' gestation will be managed using the immediate delivery strategy
- The Triage PlGF test has sensitivity and specificity values for detecting pre-eclampsia requiring delivery within 14 days, whilst the Elecsys sFlt-1/PlGF ratio test has sensitivity and specificity for detecting pre-eclampsia within 4 weeks (irrespective of delivery time); the 2 different outcomes are compared as if they were the same
- Costs of neonatal intensive care unit stay capture the effects of neonatal morbidity for deliveries occurring between 35 and 37 weeks' gestation
- Tests are conducted in a central laboratory
- The cost of proteinuria dipstick testing and blood pressure measurement is subsumed in the cost of a standard antenatal appointment
- The cost of blood pressure monitoring and quantitative proteinuria testing are subsumed in the cost of hospitalisation
- The length of stay for women with severe gestational hypertension is assumed to be 3 days.
- Women managed on the gestational hypertension pathway were assumed to receive 2 oral labetalol prescriptions.
- Women managed on the pre-eclampsia pathway receive 1 prescription for oral labetalol
- The unit costs associated with birth are not dependent on whether the mother has hypertension or pre-eclampsia
- Utility scores for birth were assumed to last for 3 weeks

- Utility scores and decrements for other periods had assumed lengths of exposure
- All utilities are assumed constant over the period in which they occur
- Differences in utility scores for diagnostic tests are determined by differences in modes of delivery

The cost effectiveness results for women presenting for assessment of suspected pre-eclampsia prior to 35 weeks' gestation, using each diagnostic strategy, are presented in Table 21. In the base case, total costs vary between £6,048 for the Triage test to £8,945 for standard clinical assessment. Both strategies including biomarker tests are cost-saving compared with standard clinical assessment, with the cost reductions per patient varying between £2,896 for the Alere Triage PlGF test and £2,488 for the Roche Elecsys sFLt-1/PlGF ratio test. Total QALYs for each diagnostic strategy were similar, with no more than 0.00076 QALYs separating the most clinically effective diagnostic strategy and the least clinically effective diagnostic strategy for women suspected of pre-eclampsia before 35 weeks' gestation. Therefore, the PlGF based tests dominate standard assessment. However, given that the differences in QALYs are so small they could be considered equivalent, the ICERs are probably meaningless.

Table 21. Base case results for women presenting with suspected pre-eclampsia before 35 weeks gestation.

Strategy	Costs		QALYs	
	Total	Increment	Total	Increment
Triage PlGF test	£6,048		0.39445	
Elecsys sFlt-1/PlGF ratio test	£6,456	£408	0.39434	-0.00011
Standard assessment	£8,945	£2,896	0.39368	-0.00076

The cost-effectiveness results for women with suspected pre-eclampsia presenting between 35 and 37 weeks are presented in table 22. The cost differences are much smaller than in women with suspected pre-eclampsia presenting before 35 weeks, and there is no difference in QALYs between any of the strategies. This is because health related quality of life is dependent on the type of delivery in the model, and there are no differences between the strategies after 35 weeks. Therefore, ICERs could not be calculated in this analysis.

Table 22. Base case results for women presenting with suspected pre-eclampsia between 35 and 37 weeks of gestation

Strategy	Costs		QALYs	
	Total	Increment	Total	Increment
Triage PlGF test	£3,393		0.3954	
Elecsys sFlt-1/PlGF ratio test	£3,584	£191	0.3954	0
Standard assessment	£3,758	£365	0.3954	0

Analysis of alternative scenarios

The external assessment group did a scenario analysis looking at using PlGF based tests as an alternative to quantitative proteinuria testing. This was included because quantitative proteinuria testing was identified by clinical experts as a possible factor that was leading to delays in diagnostic assessment of women with suspected pre-eclampsia, with a proportion being unnecessarily admitted for overnight stays awaiting results of the quantitative proteinuria test. As no evidence was found relating to this question in the review of diagnostic test accuracy, a simple cost-based analysis was performed. Results show that cost savings increased slightly if PlGF based tests replace quantitative proteinuria (table 23).

Table 23. Cost impact of replacing quantitative proteinuria test with a PlGF based test for assessment of suspected pre-eclampsia

Strategy	Proportion of women admitted overnight awaiting test results	Presenting before 35 weeks gestation		Presenting between 35 and 37 weeks gestation	
		Total	Difference from base case	Total	Difference from base case
Triage PlGF	0.0	£6,048 [a]	£0	£3,393	£0
		£6,223 [b]	£175	£3,396	£3
Elecsys sFlt-1/ PlGF ratio	0.0	£6,456 [a]	£0	£3,584	£0
		£6,540 [b]	£83	£3,567	£-17
Standard	0.1	£8,965	£21	£3,778	£21
	0.2	£8,986	£41	£3,799	£41
	0.3	£9,007	£62	£3,820	£62
	0.4	£9,028	£83	£3,841	£83
	0.5	£9,048	£104	£3,861	£104

[a] sensitivity and specificity of strategy including biomarker test at values used in the base case

[b] sensitivity and specificity of strategy including biomarker test set at lower limit of 95% confidence interval (to consider robustness of cost estimates to diagnostic accuracy of test strategy)

The external assessment group also did a sensitivity analysis looking as the cost impact of performing the Triage PlGF test in a near patient setting (a midwifery day unit) rather than in a laboratory. The same unit cost of the test was assumed as in the base case. It was also assumed that due to the adoption of near-patient testing in the midwifery day unit, no women are required to be admitted overnight while awaiting the return of test results. For the Elecsys sFlt-1/PlGF ratio test it was assumed that 10% of women being assessed for suspected pre-eclampsia requiring overnight stay while awaiting test results, and for standard clinical assessment a range of 10% to 50% was

assumed. Result show that cost savings increased very slightly as a result of performing near patient testing rather than laboratory test (table 24).

Table 24. Cost impact of performing the Triage PlGF test in a near patient setting rather than a laboratory

Strategy	Proportion of women admitted overnight	Presenting before 35 weeks' gestation		Presenting between 35 and 37 weeks' gestation	
		Total	Difference from base case	Total	Difference from base case
Triage PlGF Test	0.0	£6,048	£0	£3,393	£0
Elecsys sFlt-1/ PlGF ratio	0.1	£6,477	£21	£3,604	£21
Standard Assessment	0.1	£8,965	£21	£3,778	£21
	0.2	£8,986	£41	£3,799	£41
	0.3	£9,007	£62	£3,820	£62
	0.4	£9,028	£83	£3,841	£83
	0.5	£9,048	£104	£3,861	£104

Sensitivity analyses

Deterministic sensitivity analyses were performed on the following model inputs: test sensitivity and specificity, prevalence of pre-eclampsia in women suspected of pre-eclampsia, test cost, probability of admission and length of stay in neonatal intensive care, and distribution of hypertension across women included in the model. Only changes in costs were included in the sensitivity analyses. Full details of the deterministic sensitivity analyses can be found starting on page 168 of the diagnostics assessment report.

- **Prevalence:** In women with suspected pre-eclampsia presenting before 35 weeks gestation, if prevalence of pre-eclampsia is reduced, cost savings are reduced compared with the base case (range £127 to £281 for presentation before 35 weeks gestation; range £28 to £49 for presentation

between 35 and 37 weeks gestation). If prevalence of pre-eclampsia is increased, cost savings increase compared with the base case (range £139 to £309 for presentation before 35 weeks gestation; range £34 to £50 for presentation between 35 to 37 weeks gestation).

- **Test accuracy:** Increased sensitivity is associated with increased costs compared with the base case (range £27 to £62 for presentation before 35 weeks gestation; range £14 to £36 for presentation between 35 and 37 weeks gestation). Increased specificity is associated with lower costs compared with base case (range £122 to £525 for presentation before 35 weeks gestation; range £8 to £36 for presentation between 35 and 37 weeks gestation).
- **Test costs:** If the test costs are doubled or trebled, strategies involving a PlGF based test remain cost-saving compared with clinical assessment alone. If the list price test costs provided by the manufacturer are used in the analysis, (£40 for the Alere PlGF test and £57.23 for the Roche Elecsys sFlt-1/PlGF ratio test), there is very little change from the base case results.
- **Neonatal intensive care:** In women presenting with suspected pre-eclampsia before 35 weeks gestation with a true negative test results, changing the assumptions around neonatal intensive care has an impact on the cost, but strategies involving a PlGF based test remain cost saving compared with standard clinical assessment. If the probability of neonatal intensive care unit admission decreases to 27.2%, the cost savings compared with base case are reduced (range £1081 to £2356), whereas if the probability increases to 84.8%, the cost savings compared with base case are increased (range £496 to £1080). If the number of days spent in the neonatal intensive care unit is decreased to 2 days, the cost savings compared with base case are reduced (range £1394 to £3038), whereas if the number of days is increased to 15, the cost savings increase compared with base case (range £1412 to £3076). Changes in costs were much smaller in women presenting with suspected pre-eclampsia between 35 and 37 weeks gestation (range -£66 to £197).

- **Distribution of hypertension severity:** If the distribution of hypertension severity was changed to the upper or lower 95% confidence limit the maximum change from base case was plus or minus £33.

Analysis of index tests not included in the base case model

Two tests were not included in the base-case economic analysis due to insufficient data: the Thermo Fisher Scientific BRAHMS Kryptor sFlt-1/PlGF ratio test and the Perkin Elmer Delfia XPRESS 1-2-3 PlGF test.

The only sensitivity and specificity data for the BRAHMS Kryptor test were from a small study containing only 39 patients with confirmed pre-eclampsia and 76 with normotensive pregnancies. The study was not in a population of suspected pre-eclampsia patients and therefore, sensitivity and specificity may be exaggerated. The study compared the BRAHMS Kryptor test with the Roche Elecsys PlGF/sFlt-1 ratio test. In order to perform an analysis, the EAG assumed that the BRAHMS Kryptor sFlt-1/PlGF ratio test has equivalent diagnostic accuracy to the Roche Elecsys sFlt-1/PlGF ratio test.

No relevant information on the sensitivity and specificity of the Perkin Elmer Delfia XPRESS 1-2-3 PlGF test was available. The product insert indicates that each laboratory should establish their own diagnostic cut-off values. This would lead to different sensitivity and specificity in different laboratories.

The cost of the BRAHMS test is [redacted] for [redacted] patients ([redacted]) or [redacted] for [redacted] patients ([redacted]), including the instrument, reagents and consumables. The EAG estimated there would be 10,410 cases of suspected pre-eclampsia that occur between 20 and 37 weeks gestation annually in England and Wales. Therefore, pricing for [redacted] patients and [redacted] patients would apply and would mean that only 1 or 2 locations in the UK would have a BRAHMS Kryptor testing unit and would serve all of the UK.

As this scenario is unlikely, the EAG used regression analysis in order to estimate at which point the BRAHMS Kryptor test would cost [redacted], the same as

the Roche Elecsys sFlt-1/PlGF ratio test, assuming equivalent sensitivity and specificity. Results suggest that each BRAHMS Kryptor machine would need to run [redacted] tests annually, or [redacted] of all expected tests for suspected pre-eclampsia in the UK (table 25). This would be equivalent to having 17 testing machines for the entire UK, although there is a large amount of uncertainty in this analysis.

Table 25. Annual and per patient costs for alternative throughput thresholds for BRAHMS Kryptor sflt-1/PlGF ratio test

Patients (n)	Annual cost (£)	Cost/patient
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

3 Summary of the main findings from the assessment

Clinical effectiveness

Four studies met the inclusion criteria for the systematic review of test accuracy; 2 studies assessed the Alere Triage PlGF test and 2 studies assessed the Roche Elecsys sFlt-1/PlGF ratio. Critical appraisal of the studies suggests that they were probably at low risk of bias.

Based on the available evidence:

- the Alere Triage PlGF test has [redacted] prognostic sensitivity for predicting pre-eclampsia requiring delivery within 14 days of testing

- the Roche Elecsys sFlt-1/PlGF ratio has [redacted] diagnostic sensitivity for rule-out of pre-eclampsia within 1 week of testing and [redacted] specificity for rule-in of pre-eclampsia within 4 weeks [redacted] with a [redacted] false positive rate.
- When results were analysed by weeks of gestation, the Alere Triage PlGF test accuracy was greater when women presented with suspected pre-eclampsia before 35 weeks gestation, compared with presentation between 35 and 37 weeks.

Cost effectiveness

The cost-effectiveness model found that both the Alere Triage PlGF test and the Roche Elecsys sFlt-1/PlGF ratio test were cost saving compared to standard clinical assessment. The differences in QALYs were very small, requiring 4 decimal places to show a difference for presentation of suspected pre-eclampsia before 35 weeks gestation, and finding no difference in QALY for presentation of suspected pre-eclampsia between 35 and 37 weeks gestation.

Sensitivity and scenario analyses performed did not result in big changes to the base case analyses results, with PlGF-based testing always remaining cost saving compared with standard assessment. The most influential parameters in the model were associated with the probability and cost of stay for neonates in the neonatal intensive care unit.

One of the key drivers in the model is the false positive rates of the PlGF based tests. False positive results result in over-treatment of women with suspected pre-eclampsia and could result in immediate delivery of the fetus; the earlier the delivery, the higher the risk of the neonate requiring time in a neonatal intensive care unit. As the cost of neonatal intensive care is high, changes in the false positive rate lead to changes in the cost savings resulting from the model. This was investigated by the EAG in a sensitivity analysis on test accuracy. When specificity of the PlGF based tests was reduced - that is,

the false positive rate increased - the costs increased; however, PlGFbased test strategies still remained cost effective compared with standard assessment.

The external validity of the model is supported by previously published economic models identified in the systematic review of cost effectiveness evidence. These published studies all show cost savings associated with PlGF based test strategies compared with standard assessment.

4 Issues for consideration

Clinical effectiveness

- The systematic review of diagnostic accuracy identified only 4 studies, 2 of which are unpublished manuscripts which were provided in confidence by companies. There were 2 studies on the Triage PlGF test and 2 studies on the Elecsys immunoassay sFlt-1/PlGF ratio. No evidence on the diagnostic accuracy was identified for 2 of the tests included in the scope (the DELFIA Xpress PlGF 1-2-3 test and the BRAHMS sFlt-1 Kryptor / PlGF plus Kryptor PE ratio). The Committee should consider the similarities and differences between the different tests included in the scope to aid the assessment of suspected pre-eclampsia and whether the diagnostic accuracy results of the tests with evidence could be applied to the tests without evidence.
- The studies included in the review of diagnostic accuracy tended to use a broader definition of pre-eclampsia than that used in the NICE guideline on hypertension in pregnancy (2010). The Committee should consider if this affects the generalisability of the studies to clinical practice in the NHS. Further, the included studies based clinical decision making on the results of the PlGF based test, however, in clinical practice in the NHS it is likely that PlGF based test results would be used in combination with other clinical findings in order to inform clinical decision making. The Committee should consider if this difference also affects the generalisability of the studies.

- The studies included in the review of diagnostic accuracy reported on different outcomes; prognostic accuracy for the Alere Triage PlGF test; diagnostic accuracy for the Roche Elecsys sFlt-1/PlGF ratio test. This makes comparisons of the 2 tests difficult.
- No evidence was found on the use of PlGF based tests as an alternative to quantitative proteinuria testing. Quantitative proteinuria testing was identified by clinical experts as a possible factor that was leading to delays in the diagnostic assessment of suspected pre-eclampsia, with a proportion of women being unnecessarily admitted for overnight stays awaiting results of the quantitative proteinuria test. The External Assessment Group did a cost-based scenario analysis which looked at replacing quantitative proteinuria with PlGF based tests. Results showed a very small increase in cost savings compared with the base case results that include both quantitative proteinuria and a PlGF based test.

Cost effectiveness

- The availability of health related quality of life data for women with pre-eclampsia was poor. Therefore, EQ-5D data for the model had to be mapped from SF-36 data. It is possible that EQ-5D is overestimated, because it may be over sensitive to changes in quality of life during and after pregnancy, for example, a new baby significantly affects activities of daily living of the parents, but there are also some benefits from having a new baby that may not be captured by EQ-5D, . This was not investigated in sensitivity analyses; however, it is not expected that this uncertainty would change the base case results substantially as the difference in QALYs is so small.
- Base case results show that including a PlGF based test in the assessment of suspected pre-eclampsia is cost-saving compared with standard clinical assessment alone. The total QALYs for PlGF based testing strategies and standard clinical assessment were similar. For pre-eclampsia presenting before 35 weeks gestation, PlGF based testing strategies had very slightly

higher QALYs than clinical assessment alone, therefore PlGF based test strategies could be said to dominate clinical assessment alone. However, given the very small QALY differences, the Committee should consider whether PlGF based strategies and clinical assessment alone should be considered equivalent in terms of QALYs, which would then focus further considerations on the cost savings. For women presenting between 35 and 37 weeks gestation, there was no difference in QALYs.

- There was no information on some intermediate outcomes (time to test result, test failure rate, time to diagnosis, time to onset of pre-eclampsia, proportion of women returned to less intensive follow-up, length of inpatient stay, time to delivery). Therefore, the impact of the PlGF based tests on these outcomes could not be assessed in the economic model.
- The cost-savings seen in the base case are mainly due to a decrease in the number false positives and therefore a decrease in the number of women admitted to hospital for monitoring or immediate delivery. Therefore for these cost-savings to be realised in clinical practice it will be important for the test results to be correctly interpreted and applied.

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

No potential equality issues were identified in the diagnostics assessment report.

6 Implementation

Triage PlGF may be used in a laboratory or in a near patient setting. Scenario analyses suggest the setting of use would have little impact on cost savings, however, to use the test in a near patient setting may require changes to the

existing infrastructure in antenatal clinics and maternity units. The feasibility of centrifuging blood in a near patient setting would also need to be considered.

Where PlGF based tests are used in a laboratory setting, changes to laboratory infrastructure may be required to ensure that test turnaround times facilitate same day assessment of women presenting with suspected pre-eclampsia.

Antenatal services would need to develop local protocols to facilitate the introduction of PlGF based testing into the care pathway for women presenting with suspected pre-eclampsia.

7 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A. The diagnostics assessment report for this assessment was prepared by Southampton Health Technology Assessments Centre:

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. Southampton Health Technology Assessments Centre (SHTAC), 2015.

The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Companies providing technologies included in the final scope:

- Alere International Ltd
- Perkin Elmer LAS UK
- Roche Diagnostics Ltd
- Thermo Fisher Scientific

Other commercial organisations:

- Siemens

Professional groups and patient/carer groups:

- Action on Pre-eclampsia (APEC)
- Birth Trauma Association
- British Maternal and Fetal Medicine Society
- Institute of Biomedical Science
- National Childbirth Trust (NCT)
- Royal College of Nursing

- Royal College of Physicians
- Sands (Stillbirth and neonatal death charity)
- The Multiple Births Foundation
- The Royal College of Pathologists

Research groups:

None

Associated guideline groups:

None

Others:

- Department of Health
- Healthcare Improvement Scotland
- NHS England
- Welsh Government

Appendix B: Glossary of terms

Eclampsia
A convulsive condition arising in pregnancy, associated with pre-eclampsia.

Placental growth factor (PlGF)
A biomarker from the vascular endothelial growth factor (VEGF) family of proteins. It is emitted by the placenta and is involved in the development of new placental blood vessels (placental angiogenesis).

Pre-eclampsia
A hypertensive condition arising in pregnancy, which is defined by new hypertension presenting after 20 weeks of pregnancy and proteinuria in the NICE clinical guideline on hypertension in pregnancy (2010). Other guidelines, for example, those from the American College of Obstetricians and Gynaecologists (ACOG) and International Society for the study of Hypertension (ISSHP) have a broader definition of pre-eclampsia. Broader definitions state that the presence of either hypertension or proteinuria alone during pregnancy can indicate a risk of developing pre-eclampsia.

Proteinuria
The presence of a detectable level of protein in the urine. Initially, this is determined by an automated reagent-strip reading device and confirmed, and quantified, by either a spot urinary protein:creatinine ratio or 24 hour urine collection. A significant level of proteinuria is considered to be more than 300 milligrams per day or a protein:creatinine ratio of 30 milligrams/millimole.

Soluble FMS-like tyrosine kinase-1 (sFlt-1)
A protein which is thought to disable proteins that aid the development of new blood vessels. It is produced by variety of tissues and binds to circulating vascular endothelial growth factor and PlGF, reducing the effects of these proteins on the developing placenta.

Umbilical artery doppler velocimetry

A measure of blood flow in the umbilical artery via ultrasound.