National Institute for Health and Care Excellence

Diagnostics consultation document

PlGF-based testing to help diagnose suspected pre-eclampsia

The National Institute for Health and Care Excellence (NICE) is producing guidance on using PlGF-based testing in the NHS in England. The Diagnostics Advisory Committee has considered the evidence submitted and the views of expert advisers.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence base (the diagnostics assessment report and the diagnostics assessment report addendum), which is available from http://www.nice.org.uk/guidance/indevelopment?type=dg.

The Advisory Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?

Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between women with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different impact on women protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology
- could have any adverse impact on women with a particular disability or disabilities.

Note that this document is not NICE's final guidance on PlGF-based testing to help assess suspected pre-eclampsia. The recommendations in section 1 may change after consultation.

After consultation, the Committee will meet again to consider the evidence, this document and comments from the consultation. After considering these comments, the Committee will prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the Diagnostics assessment programme manual (available at https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-diagnostics-guidance).

Key dates:

Closing date for comments: 19 November 2015

Second Diagnostics Advisory Committee meeting: 1 December 2015

1 Provisional recommendations

1.1 The Triage PlGF test and the Elecsys immunoassay sFlt-1/PlGF ratio show promise in helping to diagnose pre-eclampsia in women of 20 weeks to 34 weeks plus 6 days of gestation. However, there is currently insufficient evidence to recommend their routine adoption in the NHS. Further research is recommended on using these tests in women with suspected pre-eclampsia (see section 6):

- to rule-in pre-eclampsia based on a positive test result and
- for repeat PlGF (placental growth factor)-based testing after a negative test result.

1.2 The DELFIA Xpress PlGF 1-2-3 test and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio are not recommended for routine adoption in the NHS. Further research is needed to show the clinical effectiveness of these tests, including diagnostic accuracy and analytical validity.

2 Clinical need and practice

The problem addressed

2.1 Placental growth factor (PlGF)-based tests are intended to be used with clinical judgement and other diagnostic tests, to help diagnose suspected pre-eclampsia. This assessment focuses on diagnosing pre-eclampsia in the second and third trimesters of pregnancy. Using PlGF-based tests in addition to standard clinical assessment could result in a faster and more accurate diagnosis of pre-eclampsia, and better risk assessment for adverse outcomes in women with suspected pre-eclampsia. It could also allow women in whom pre-eclampsia has been ruled out with a PlGF-based test to return to community care instead of being admitted to hospital for observation.

2.2 PlGF-based tests measure the amount of PlGF in blood plasma. PlGF is a protein involved in placental angiogenesis (the development of new blood vessels). In pre-eclampsia, levels of PlGF can be abnormally low. In normal pregnancy, PlGF levels rise and peak at 26–30 weeks, so when PlGF levels do not rise during pregnancy there may be placental dysfunction.

2.3 In addition, some PlGF-based tests measure soluble FMS-like tyrosine kinase-1 (sFlt-1), a protein that is thought to disable other 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.

2.4 Four PlGF-based tests were identified during scoping as relevant to this assessment: The Triage PlGF test (Alere International), Elecsys immunoassay sFlt-1/PlGF ratio (Roche Diagnostics), DELFIA Xpress PlGF 1-2-3 test (Perkin Elmer) and BRAHMS sFlt-1

Kryptor/BRAHMS PlGF plus Kryptor PE ratio (Thermo Fisher Scientific).

The condition

2.5 Pre-eclampsia is a potentially serious complication of some pregnancies, which when identified, needs referral to a specialist and hospital admission for both maternal and fetal monitoring. It is thought to be related to problems with the development of the placenta. Pre-eclampsia is characterised 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. Other symptoms include headache, visual disturbances, right upper quadrant abdominal (epigastric) pain, oedema (swelling of the hands, face or feet) and oliguria (low output of urine).

2.6 If pre-eclampsia is not diagnosed and closely monitored, it can lead to potentially life-threatening complications including eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes and low platelets), disseminated intravascular coagulation, stroke, or organ dysfunction. Women who have hypertension or pre-eclampsia during pregnancy may have a higher risk of placental abruption. Women who develop pre-eclampsia during pregnancy may also be at greater risk of cardiovascular disease in later life.

2.7 Gestational hypertension and pre-eclampsia may also affect the fetus, placing it at increased risk of intrauterine growth restriction, prematurity and intrauterine death.

The diagnostic and care pathways

2.8 The NICE guideline on antenatal care recommends measuring blood pressure and testing urine for proteinuria to screen for pre-eclampsia at each routine antenatal visit.

2.9 The NICE pathway on pre-eclampsia describes the assessment and treatment of women at risk of pre-eclampsia or with pre-eclampsia. The NICE guideline on hypertension in pregnancy was used to create the pathway.

Identifying and managing the risk of developing pre-eclampsia

2.10 The NICE guideline on hypertension in pregnancy states that women who are classified as being at high risk of pre-eclampsia are those who have any of the following risk factors identified during the booking appointment:

- hypertensive disease during a previous pregnancy
- chronic kidney disease
- autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
- type 1 or type 2 diabetes
- chronic hypertension.

2.11 Women who are classified as being at moderate risk of pre-eclampsia are those who have any of the following risk factors identified during the booking appointment:

- first pregnancy
- age 40 years or older
- pregnancy interval of more than 10 years
- BMI of 35 kg/m^2 or more at first visit
- family history of pre-eclampsia
- multiple pregnancy.

2.12 Women with either 1 high risk factor, or more than 1 moderate risk factor for pre-eclampsia, are advised to take 75 mg of aspirin daily from 12 weeks' gestation until the birth of the baby. They are also considered for more frequent blood pressure monitoring, and assessment for proteinuria. Women who have significant hypertension (diastolic pressure of 90-110 mmHg) or a proteinuria result of 1+ on urinalysis reagent strips need increased surveillance.

Management of pregnancy with gestational hypertension

2.13 The NICE guideline on hypertension in pregnancy defines gestational hypertension as new hypertension presenting after 20 weeks' gestation without significant proteinuria. Increased surveillance is needed to confirm a diagnosis of gestational hypertension, because some women may present with transient hypertension. Women with gestational hypertension are recommended to have assessment for proteinuria at each visit to detect the onset of suspected pre-eclampsia (see table 1).

Table 1 Management of pregnancy with gestational hypertension

Degree of hypertension	Mild (140/90 mmHg to 149/99 mmHg)	Moderate (150/100 mmHg to 159/109 mmHg)	Severe (160/110 mmHg or higher)
Admit to hospital	No	No	Yes (until blood pressure is 159/109 mmHg or lower)
Treat	No	With oral labetalol as first-line treatment	With oral labetalol as first-line treatment
Measure blood pressure	Not more than once a week	At least twice a week	At least 4 times a day
Test for proteinuria	At each visit	At each visit	Daily
Blood tests	Only those for routine antenatal care	Test kidney function, electrolytes, full blood count, transaminases, bilirubin	Test at presentation and then monitor weekly: kidney function, electrolytes, full blood count, transaminases, bilirubin
Birth before 37 weeks should not be offered to women with gestational hypertension whose blood pressure is lower than 160/110 mmHg with or without antihypertensive treatment.			

Management of pregnancy with pre-eclampsia

2.14 The NICE guideline on hypertension in pregnancy defines pre-eclampsia as new hypertension with significant proteinuria after 20 weeks' gestation. Women diagnosed with pre-eclampsia should be assessed at each consultation by a healthcare professional trained in the management of hypertensive disorders of pregnancy and offered an integrated package of care that includes admission, testing and treatment that relates to the severity of hypertension (see table 2).

Table 2. Management of pregnancy with pre-eclampsia

Degree of hypertension	Mild (140/90 mmHg to 149/99 mmHg)	Moderate (150/100 mmHg to 159/109 mmHg)	Severe (160/110 mmHg or higher)
Admit to hospital	Yes	Yes	Yes
Treat	No	With oral labetalol as first-line treatment	With oral labetalol as first-line treatment
Measure blood pressure	At least 4 times a day	At least 4 times a day	More than 4 times a day
Test for proteinuria	Do not repeat quantification of proteinuria	Do not repeat quantification of proteinuria	Do not repeat quantification of proteinuria
Blood tests	Monitor the following twice a week: kidney function, bilirubin, electrolytes, full blood count, transaminases	Monitor the following 3 times a week: kidney function, bilirubin, electrolytes, full blood count, transaminases	Monitor the following 3 times a week: kidney function, bilirubin, electrolytes, full blood count, transaminases,

3 The diagnostic tests

The interventions

Triage PlGF test

3.1 The Triage PlGF test (Alere International) is a CE-marked, single-use, fluorescence immunoassay device, which is used with the Triage MeterPro point-of-care analyser for the quantitative determination of placental growth factor (PlGF) in blood plasma samples. The test is intended for use with clinical judgement and other diagnostic tests, to help diagnose suspected pre-eclampsia and the level of risk for delivery arising from pre-eclampsia within 14 days of testing. It is recommended for use in pregnant women between 20 weeks and 34 weeks plus 6 days of gestation.

3.2 The test has a limit of detection of 9 picograms/ml and a measurable range of 12 to 3000 picograms/ml. The test turnaround time is about 15 minutes. The test cut-off values recommended by the company are shown in table 3.

Table 3 Recommended cut-off values for the Triage PlGF test

Result	Classification	Interpretation
PlGF <12 pg/ml	Test positive – highly abnormal	Highly abnormal and suggestive of patients with severe placental dysfunction and at increased risk for preterm delivery.
PlGF ≥12 pg/ml and <100 pg/ml	Test positive – abnormal	Abnormal and suggestive of patients with placental dysfunction and at increased risk for preterm delivery.
PlGF ≥100 pg/ml	Test negative – normal	Normal and suggestive of patients without placental dysfunction and unlikely to progress to delivery within 14 days of the test.
Abbreviation: PIGF, placental growth factor.		

Elecsys immunoassay sFlt-1/PlGF ratio

3.3 The Elecsys immunoassay sFlt-1/PlGF ratio (Roche Diagnostics) measures the amounts of PlGF relative to soluble FMS-like tyrosine kinase-1 (sFlt-1; also known as VEGFR1) in serum samples from women with suspected pre-eclampsia. The ratio is formed by combining the results from 2 CE-marked sandwich electrochemiluminescence immunoassays (Elecsys PlGF and Elecsys sFlt-1 assays), which are compatible with both the Roche Elecsys and the Cobas e automated analysers. The laboratory information system calculates and reports the sFlt-1/PlGF ratio and the individual assay values. The Elecsys immunoassay sFlt-1/PlGF ratio is intended to be used with clinical judgement and other diagnostic tests to diagnose pre-eclampsia. The ratio may also be used to help predict pre-eclampsia, eclampsia and HELLP syndrome in the short term. It may be used for testing pregnant women from 20 weeks' gestation up until the time of delivery.

3.4 The Elecsys sFlt-1 assay has a limit of detection of 10 picograms/ml (measuring range 10 to 85,000 picograms/ml) and a limit of quantitation of 15 picograms/ml. The Elecsys PlGF assay has a limit of detection of 3 picograms/ml (measuring range 3 to 10,000 picograms/ml) and a limit of quantitation of 10 picograms/ml. The turnaround time of the Elecsys immunoassay sFlt-1/PlGF ratio is about 18 minutes. The test cut-off values recommended by the company are shown in table 4.

Table 4 Recommended cut-off values for the Elecsys immunoassay sFlt-1/PlGF ratio

			sFlt-1/PlGF ratio
Aid in diagnosis of pre-eclampsia	20 weeks to 33 weeks plus 6 days	Rule-out cut-off	33
		Rule-in cut-off	85
	34 weeks to delivery	Rule-out cut-off	33
		Rule-in cut-off	110
Short-term prediction of pre-eclampsia (24 weeks to 36 weeks plus 6 days)		Rule-out*	<38
		Rule-in**	>38
* rule-out pre-eclampsia for 1 week ** rule-in pre-eclampsia within 4 weeks.			

DELFIA Xpress PlGF 1-2-3 test

3.5 The DELFIA Xpress PlGF 1-2-3 test (Perkin Elmer) is a CE-marked solid-phase, 2-site fluoroimmunometric sandwich assay for the quantitative determination of PlGF in serum samples. The assay is compatible with the 6000 DELFIA Xpress random access analyser. The test is intended to help diagnose pre-eclampsia during the second and third trimesters of pregnancy, and is used with clinical assessment.

3.6 The assay has a limit of detection of 1.9 picograms/ml (measuring range 1.9 to 4000 picograms/ml) and a limit of quantitation of 3.3 picograms/ml. The test has a turnaround time of about 30 minutes. The cut-off values for PlGF measurements obtained during the second trimester are highly dependent on gestational

day and the company suggests that cut-off values should be established by individual laboratories. In the third trimester, in addition to laboratory-calculated cut-off values based on gestational day, the company suggests that a fixed cut-off value of 184 picograms/ml can be used. Levels of PlGF lower than 184 picograms/ml indicate an increased probability of pre-eclampsia developing.

BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio

3.7 The BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio (Thermo Fisher Scientific) is formed by combining the results from 2 automated immunofluorescent sandwich assays, the BRAHMS sFlt-1 Kryptor assay and the BRAHMS PlGF plus Kryptor assay. They are indicated for the quantitative determination of sFlt-1 and PlGF in serum samples and are compatible with the BRAHMS Kryptor compact plus analyser. The assays are intended to be run at the same time, with the analyser reporting both the concentrations for each assay and the sFlt-1/PlGF ratio. The BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus KRYPTOR PE ratio is intended to be used with clinical assessment to help diagnose pre-eclampsia.

3.8 The BRAHMS sFlt-1 Kryptor assay has a limit of detection of 22 picograms/ml (measuring range 22 to 90,000 picograms/ml) and a limit of quantitation of 34 picograms/ml. The BRAHMS PlGF plus Kryptor assay has a limit of detection of 3.6 picograms/ml (measuring range 3.6 to 7000 picograms/ml) and a limit of quantitation of 6.9 picograms/ml. Reference ranges for each of the assays and the sFlt-1/PlGF ratio are given in the company instructions, and the company recommends that individual laboratories should validate these ranges or establish their own reference ranges before use. The turnaround time for the BRAHMS

sFlt-1 Kryptor assay is 9 minutes and the turnaround time for the BRAHMS PlGF plus Kryptor assay is 29 minutes.

The comparator

3.9 The comparator used in this assessment is standard clinical assessment to help diagnose suspected pre-eclampsia, guided by a combination of the following clinical information:

- maternal hypertension (categorised as mild, moderate or severe)
- quantitative proteinuria test
- clinical symptoms suggestive of pre-eclampsia (for example, headache, oedema, visual disturbances)
- fetal growth restriction.

4 Outcomes

The Diagnostics Advisory Committee (section 11) considered evidence from a number of sources (section 12).

How outcomes were assessed

4.1 The assessment consisted of:

- A systematic review of the evidence on the diagnostic accuracy of the 4 index tests for the assessment of suspected pre-eclampsia in the second and third trimesters of pregnancy.
- A review of cost-effectiveness evidence on the 4 index tests for the assessment of suspected pre-eclampsia in the second and third trimesters of pregnancy.
- A de novo economic model designed to assess the cost effectiveness of placental growth factor (PlGF)-based tests when used with standard clinical assessment compared with standard clinical assessment alone for the assessment of suspected pre-eclampsia in the second and third trimesters of pregnancy.

Assessment of test accuracy

4.2 Studies were included in the systematic review if they contained information on:

- Women with suspected pre-eclampsia between 20 weeks and 36 weeks plus 6 days of pregnancy who had blood pressure assessment and qualitative assessment of proteinuria.
- Triage PlGF test; Elecsys immunoassay sFlt-1/PlGF ratio; DELFIA Xpress PlGF 1-2-3 test; or BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio, with standard clinical assessment, or with standard 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

4.3 After searches and inclusion screening, 12 publications of 4 studies were included in the review. Two of these studies were on the Triage PlGF test and 2 studies were on the Elecsys immunoassay sFlt-1/PlGF ratio. None of the studies included more than 1 test; so no head-to-head comparisons of the index tests were available. None of the included studies were on the Perkin Elmer DELFIA Xpress PlGF 1-2-3 test or the Thermo Fisher Scientific BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor ratio.

4.4 The PETRA study was a multicentre study of the Triage PlGF test. The details of this study are academic in confidence at the time of writing this diagnostics consultation document.

4.5 The PELICAN study (2013) was a prospective, single cohort study of the Triage PlGF test done in 7 centres in the UK and Ireland. It included 287 women with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation, and 137 women with suspected pre-eclampsia between 35 weeks and 36 weeks plus 6 days of gestation.

4.6 The PROGNOSIS study was an international multicentre study of the Elecsys immunoassay sFlt-1/PlGF ratio, with 1 study centre in the UK. The study had 2 cohorts: a 'feasibility' cohort with 500 patients to derive a cut-off value based prediction model for the sFlt-1/PlGF ratio, and a 'validation' cohort with 550 patients to test the model. It included women with suspected pre-eclampsia between 24 weeks and 36 weeks and 6 days of gestation. The remaining details of this study publication are academic in confidence at the time of writing this diagnostics consultation document.

4.7 The study by Alvarez-Fernandez et al. (2014) was a retrospective study of the Elecsys sFlt-1/PlGF ratio in a single cohort of patients. The study was done in Spain and included 62 women with suspected pre-eclampsia between 20 weeks and 34 weeks of gestation.

4.8 The PELICAN study and the PROGNOSIS study defined hypertensive disorders according to the American College of Obstetrics and Gynecology practice bulletin (2002). This gives a broader definition of pre-eclampsia than the NICE guideline on hypertension in pregnancy, because it includes superimposed pre-eclampsia and atypical pre-eclampsia. The definition of pre-eclampsia used in the PETRA study is academic in confidence at the time of writing this diagnostics consultation document. The study by Alvarez-Fernandez et al. (2014) used a simple definition of

pre-eclampsia, which expands on the definition in the NICE guideline on hypertension in pregnancy by including pre-existing proteinuria with superimposed pre-eclampsia.

4.9 The PELICAN study (2013) and the study by Alvarez-Fernandez et al. (2014) were judged to be at low risk of bias using the using the Cochrane Collaboration adaptation of the QUADAS tool. However, both studies were judged to be at high risk of clinical review bias because the diagnosis of pre-eclampsia was based solely on whether index-test results were above or below the cut-off value, whereas in clinical practice index-test results would likely be interpreted alongside clinical signs and symptoms such as information about hypertension and proteinuria. The risk of bias of the PETRA study and the PROGNOSIS study is academic in confidence at the time of writing this diagnostics consultation document.

Diagnostic-accuracy results for the Triage PlGF test

4.10 Diagnostic-accuracy results for the Alere Triage PlGF test are available for 3 test cut-off values: 100 picograms/ml, the fifth centile of PlGF concentration for gestational age, and 12 picograms/ml. PlGF concentrations above 100 picograms/ml are considered normal and would be used to identify women unlikely to develop pre-eclampsia needing delivery within 14 days. As such, a result of 100 picograms/ml or greater is used to rule-out pre-eclampsia.

4.11 Results from the PELICAN study (2013) show that the Triage PlGF test at cut-off value of 100 picograms/ml and the fifth centile of PlGF concentration for gestational age gave high sensitivity with good precision for identifying women likely to develop pre-eclampsia needing delivery within 14 days of testing, when presenting with suspected pre-eclampsia before 35 weeks' gestation. The cut-off value of 12 picograms/ml yielded lower

sensitivity for identifying women likely to develop pre-eclampsia needing delivery within 14 days of testing, when presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation (see table 5).

Table 5 PELICAN study results – Triage PlGF test accuracy for predicting pre-eclampsia needing delivery within 14 days for women presenting between 20 weeks and 34 weeks plus 6 days of gestation

Test cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
<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)
≥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)
<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)
<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)

Abbreviations: CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; pg/ml, picograms per millilitre.

4.12 Results from the PELICAN study (2013) also show that for the cut-off values of fifth centile of PlGF for gestational age and 12 picograms/ml, the Triage PlGF test had poor diagnostic accuracy for predicting pre-eclampsia needing delivery within 14 days in women presenting with suspected pre-eclampsia between 35 weeks and 36 weeks plus 6 days gestation (see table 6).

Table 6 PELICAN study results – Triage PlGF test accuracy for predicting pre-eclampsia needing delivery within 14 days for women presenting between 35 weeks and 36 weeks plus 6 days of gestation

Test cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
<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)
<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)
Abbreviations: CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; pg/ml, picograms per millilitre.				

4.13 The PELICAN study (2013) also reported that the Triage PlGF test at a cut-off value of 100 picograms/ml had high sensitivity at predicting preterm pre-eclampsia and delivery within 14 days of testing independent of the pre-eclampsia diagnosis. A cut-off value of 12 picograms/ml had poor sensitivity but good specificity for predicting preterm delivery independent of the pre-eclampsia diagnosis (see table 7).

Table 7 PELICAN study results – Triage PlGF test accuracy for other outcomes for women presenting between 20 weeks and 34 weeks plus 6 days of gestation

Test cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Preterm pre-eclampsia				
<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 14 days of testing				
≥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)
Preterm delivery				
<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)
Abbreviations: CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; pg/ml, picograms per millilitre.				

Diagnostic-accuracy results for the Elecsys immunoassay sFlt-1/PlGF ratio

4.14 The PROGNOSIS study derived a cut-off value of 38; values below 38 were considered negative and were used to rule-out pre-eclampsia within 1 week; values above 38 were considered positive and used to rule-in pre-eclampsia within 4 weeks. Results from the combined cohort show that for women with suspected pre-eclampsia between 24 weeks and 36 weeks and 6 days of gestation, sensitivity and specificity for ruling out pre-eclampsia within 1 week was relatively high. Sensitivity for ruling in pre-eclampsia within 4 weeks was lower than for ruling out pre-eclampsia within 1 week, but specificity was relatively high (see table 8). Other results are academic in confidence.

Table 8 PROGNOSIS study results – Elecsys immunoassay sFlt-1/PlGF ratio accuracy for women presenting between 24 weeks and 36 weeks plus 6 days of gestation; cut-off value 38

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Rule-out of pre-eclampsia within 1 week	0.86 (0.73 to 0.94)	0.79 (0.77 to 0.82)		0.99 (0.98 to 1.00)
Rule-in of pre-eclampsia within 4 weeks	0.70 (0.62 to 0.78)	0.83 (0.81 to 0.86)	0.39 (0.33 to 0.45)	
Abbreviations: CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; pg/ml, picograms per millilitre.				

4.15 The study by Alvarez-Fernandez et al. (2014) analysed the Elecsys immunoassay sFlt-1/PlGF ratio at cut-off values of 23 and 85 (see table 9). Results show that for women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks of gestation, the cut-off value of 23 had higher sensitivity than the cut-off value of 85 for rule-out of pre-eclampsia within 3 weeks (92% compared with 56%). Specificity was lower for the 23 cut-off value than the 85 cut-off value for the rule-out of pre-eclampsia within 3 weeks (81% compared with 97%).

Table 9 Alvarez-Fernandez et al. (2014) study results – Elecsys immunoassay sFlt-1/PlGF ratio accuracy for rule-out of pre-eclampsia within 3 weeks for women presenting between 20 weeks and 34 weeks of gestation

Test cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
23	0.92 (0.73 to 0.99)	0.81 (0.64 to 0.91)	0.77 (0.57 to 0.89)	0.94 (0.78 to 0.99)
85	0.56 (0.35 to 0.75)	0.97 (0.84 to 1.00)	0.93 (0.66 to 1.00)	0.77 (0.62 to 0.87)
Abbreviations: CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.				

Review of cost-effectiveness evidence

4.16 Searches were done 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/BRAHMS PlGF plus Kryptor PE ratio for the diagnosis of pre-eclampsia in the second and third trimesters of pregnancy.

4.17 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.

4.18 Two studies by Hadker et al. (2010 and 2013) used the same model, populated with identical clinical inputs, to address UK and German healthcare payer perspectives. The study population was all women assessed for pre-eclampsia after 20 weeks' gestation. The intervention used was standard assessment plus Elescsys immunoassay sFlt-1/PlGF ratio (cut-off value of 85) compared with standard assessment alone. Base-case results from a UK healthcare payer perspective show that there was an overall reduction in cost of £945 per patient from £2726 to £1781 associated with the use of the Elecsys immunoassay sFlt-1/PlGF

ratio. From a German healthcare payer perspective, base-case results show an overall cost reduction of €637 per patient from €1579 to €942 associated with the use of the Elecsys immunoassay sFlt-1/PlGF ratio.

4.19 A study by Schnettler et al (2013) included women before 34 weeks' gestation with suspected pre-eclampsia. The intervention used was standard assessment plus Elescsys immunoassay sFlt-1/PlGF ratio (cut-off value of 85) compared with standard assessment alone. The perspective was that of a US healthcare payer. Base-case results show an overall cost reduction of $1215 per patient, from $3022 to $1807 associated with the use of the Elecsys immunoassay sFlt-1/PlGF ratio.

4.20 The fourth study was by Hunter et al. (2013) and is unpublished and commercial in confidence.

Economic evaluation

4.21 A decision tree model was developed to assess the cost effectiveness of PlGF-based tests used with standard clinical assessment compared with standard clinical assessment alone in women with suspected pre-eclampsia in 2 groups:

- those presenting between 20 weeks and 33 weeks plus 6 days of gestation
- those presenting between 34 weeks and 36 weeks plus 6 days of gestation.

Model structure

4.22 The model used a linked evidence approach in which maternal, fetal and neonatal outcomes were modelled from diagnostic test accuracy and prevalence of pre-eclampsia data. The model had 4 components: risk stratification, management, maternal outcomes, and fetal and neonatal outcomes.

4.23 Women with suspected pre-eclampsia were classified as being at high, intermediate or low risk of pre-eclampsia. This was based on clinical signs, symptoms or findings with or without the addition of a PlGF-based test. The probability of pre-eclampsia in women with suspected pre-eclampsia was based on the prevalence of pre-eclampsia and the reported sensitivity and specificity of each diagnostic strategy.

4.24 Suspected pre-eclampsia could be managed using expectant management or immediate delivery, dependent on the risk of pre-eclampsia (high, intermediate or low) and the number of weeks' gestation. Expectant management involves monitoring clinical signs, symptoms and findings, active management of conditions such as hypertension, and planned delivery at 37 weeks of gestation. Immediate delivery involves delivery much sooner, irrespective of gestational age because of clinical findings indicating severe risk to a pregnant woman or fetus. 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 fetus. Women with a high risk of pre-eclampsia presenting from 35 weeks' gestation are managed by immediate delivery when there are signs of increased risk for the mother or fetus. These assumptions are in line with the NICE guideline on hypertension in pregnancy.

4.25 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 (high, intermediate, low) assigned in the first stage of the model.

4.26 The maternal outcome component begins with delivery, resulting either from spontaneous labour, induced labour, or planned caesarean section. Each of these modes of delivery may be associated with a risk of conversion to assisted or instrumental vaginal delivery, or to emergency caesarean section. Each mode of delivery is associated with a risk of a severe adverse event associated with the progression of severity of pre-eclampsia during the delivery, which can result in convulsions. These adverse events may result in admission to an intensive or high-dependency care unit and the need for anti-convulsive therapy. The model assumes that women who do not have convulsions are transferred to the ward after delivery and those who do not have any further adverse events have a normal length of stay for the given mode of delivery.

4.27 The fetal and neonatal outcome component of the model first establishes whether the labour results in a live birth or stillbirth. After a live birth, a neonate may or may not need to be admitted to a neonatal intensive care unit or high dependency unit, the probability of which 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

4.28 Test accuracy data for the Triage PlGF test were taken from the PELICAN (2013) study and test accuracy data for the Elecsys immunoassay sFlt-1/PlGF ratio were taken from the PROGNOSIS study. Test accuracy for standard clinical assessment was taken

from a study included in the systematic review of economic evaluations (Schnettler et al. 2013). The data on prevalence of pre-eclampsia were taken from the PELICAN study, which was done in the UK. Other clinical and resource use inputs were taken from a variety of published studies.

4.29 Test costs used in the base-case model were taken from economic models produced by the companies. These were slightly different from the list price test costs submitted by the companies. The list price for a single Triage PlGF test is £40. The list price for a single Elecsys immunoassay sFlt-1/PlGF ratio is £57.23. Other costs were taken from NHS reference costs, the British national formulary and published literature.

4.30 Utility values were taken from the published literature, however, many values had to be mapped from SF-36 to EQ-5D (see table 10).

Table 10 Utility values used in the economic model

Parameter		Value	Source
Baseline quality-adjusted life years (QALYs) from (vaginal) delivery to 6 months post-partum	Birth to 3 weeks post-partum	0.0389	Jansen et al. 2007
	3–12 weeks post-partum	0.1496	Bijlenga et al. 2011
	12–6 months post-partum	0.2171	Bijlenga et al. 2011
Decrement for caesarean delivery (birth to 3 weeks post-partum)	Non-emergency caesarean section	0.0050	Jansen et al. 2007
	Emergency caesarean section	0.0092	Jansen et al. 2007
Decrement for non-spontaneous delivery (induced)	3–6 months post-partum	0.0084	Petrou et al. 2009
Abbreviation: QALYs, quality-adjusted life years.			

Base-case results

4.31 Key assumptions made in the model include:

- UK guidelines for management of suspected pre-eclampsia, gestational hypertension and pre-eclampsia are followed.
- The 2 different outcomes, pre-eclampsia needing delivery within 14 days (Triage PlGF test) and pre-eclampsia within 4 weeks irrespective of delivery time (Elecsys immunoassay sFlt-1/PlGF ratio) 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 done in a central laboratory.
- 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.

4.32 For women with suspected pre-eclampsia presenting before 35 weeks’ gestation, in the base case, total costs varied between £6048 for the Triage PlGF test to £8945 for standard clinical assessment. Both the Triage PlGF test and the Elecsys immunoassay sFlt-1/PlGF ratio were cost-saving compared with standard clinical assessment. Cost reductions per patient compared with standard clinical assessment were £2896 for the Triage PlGF test and £2488 for the Elecsys immunoassay sFlt-1/PlGF ratio. Total quality-adjusted life years (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 (see table 11). Although the PlGF-based tests dominated standard assessment, the differences in QALYs were so small that they could be considered comparable and so the calculation of incremental cost-effectiveness ratios (ICERs) was not appropriate.

Table 11 Base-case results for women presenting with suspected pre-eclampsia before 35 weeks' gestation

Strategy	Costs		QALYs	
	Total	Increment compared with standard assessment	Total	Increment compared with standard assessment
Triage PlGF test	£6048	−£2896	0.39445	−0.00076
Elecsys sFlt-1/PlGF ratio	£6456	−£2488	0.39434	−0.00066
Standard assessment	£8945		0.39368	
Abbreviation: QALYs, quality-adjusted life years.				

4.33 For women with suspected pre-eclampsia presenting between 35 and 37 weeks' gestation, the cost differences were much smaller than in women with suspected pre-eclampsia presenting before 35 weeks. In the base case, total costs varied between £3393 for the Triage PlGF test and £3758 for standard clinical assessment. Both strategies including PlGF-based tests were cost-saving compared with standard clinical assessment. Cost reductions per patient compared with standard assessment were £365 for the Triage PlGF test and £174 for the Elecsys immunoassay sFlt-1/PlGF ratio. There was no difference in QALYs between any of the strategies (see table 12). Therefore, ICERs could not be calculated in this analysis.

Table 12 Base-case results for women presenting with suspected pre-eclampsia between 35 and 37 weeks' gestation

Strategy	Costs		QALYs	
	Total	Increment compared with standard assessment	Total	Increment compared with standard assessment
Triage PlGF test	£3393	−£365	0.3954	0
Elecsys sFlt-1/PlGF ratio	£3584	−£174	0.3954	0
Standard assessment	£3758		0.3954	
Abbreviation: QALYs, quality-adjusted life years.				

Scenario and sensitivity analyses

4.34 A scenario analysis looking at using PlGF-based tests as an alternative to quantitative proteinuria testing was done. Quantitative proteinuria testing may delay the diagnostic assessment of women with suspected pre-eclampsia, leading to some being unnecessarily admitted for overnight stays to await results of the quantitative proteinuria test. No evidence was found relating to this question, so a simple cost-based analysis was done. Results suggested that cost savings could increase slightly if PlGF-based tests replace quantitative proteinuria.

4.35 A scenario analysis looking at the effect on costs of doing the Triage PlGF test in a near-patient setting (a midwifery day unit) rather than in a hospital laboratory was also done. The same unit cost of the test was assumed as in the base case. It was also assumed that because of the adoption of near-patient testing in the midwifery day unit, no women need to be admitted overnight while waiting for test results. For the Elecsys immunoassay sFlt-1/PlGF ratio it was assumed that 10% of women being assessed for suspected pre-eclampsia need an overnight stay while waiting for test results, and for standard clinical assessment a range of 10–

50% was assumed. Results suggested that cost savings could increase slightly as a result of doing near-patient testing rather than hospital laboratory testing.

4.36 Deterministic sensitivity analyses were done 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
- distribution of hypertension across women included in the model.

PlGF-based test strategies remained cost saving compared with standard clinical assessment in all sensitivity analyses. Changing the assumptions around neonatal intensive care had the biggest impact on costs, but strategies involving a PlGF-based test remained cost saving compared with standard clinical assessment.

Analysis of index tests not included in the base-case model

4.37 The BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio and the DELFIA Xpress 1-2-3 PlGF test were included in the scope for the assessment but were not included in the base-case economic analysis because there were insufficient data. One study comparing the diagnostic accuracy of the BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio with the Elecsys immunoassay sFlt-1/PlGF ratio was identified, but it did not meet the inclusion criteria for the systematic review of diagnostic test accuracy (Anderson et al. 2015). However, a threshold cost analysis was done for the BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio by assuming that it has equivalent diagnostic accuracy to the Elecsys immunoassay sFlt-1/PlGF ratio.

4.38 The study by Andersen et al. (2015) compared the diagnostic accuracy of the BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio with the Elecsys immunoassay PlGF/sFlt-1 ratio. It had 39 patients with confirmed pre-eclampsia and 76 with normotensive pregnancies. The study was not done in a population of patients with suspected pre-eclampsia, so sensitivity and specificity may be exaggerated. The BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio has a cost based on throughput, therefore the threshold analysis used regression analysis to estimate the point at which the BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio would cost the same as the Elecsys immunoassay sFlt-1/PlGF ratio, assuming equivalent sensitivity and specificity. The results of this analysis are commercial in confidence.

4.39 No relevant information on the diagnostic accuracy of the DELFIA Xpress 1-2-3 PlGF test was available, so no cost-analysis was done.

5 Considerations

5.1 The Committee considered the potential effects of pre-eclampsia on a pregnant woman's life and on the life of her partner. The Committee heard from a patient expert that women who have had pre-eclampsia fear that they will get pre-eclampsia again if they have another baby. It heard further that a few women decide not to complete their family due to the experience of pre-eclampsia in a previous pregnancy. The Committee also heard that there are currently no tests that can be used to confidently rule-out the presence of pre-eclampsia. Therefore pregnant women with suspected pre-eclampsia often need increased monitoring or admission to hospital, which can be inconvenient and can cause anxiety. The Committee concluded that tests that could help to

assess suspected pre-eclampsia could help to reduce anxiety and unnecessary monitoring, in women with suspected pre-eclampsia or pre-eclampsia.

5.2 The Committee considered the definitions of pre-eclampsia used in the studies compared with the definition of pre-eclampsia used in the NICE guideline on hypertension in pregnancy. It noted that the definition in the NICE guideline is narrower than the definitions used in the studies. It heard from clinical experts on the Committee that the decision on whether to deliver the baby in a woman with pre-eclampsia is based on clinical symptoms suggesting risk to the mother or baby, which aligns with the expanded definitions of pre-eclampsia used in the studies. The Committee concluded that the expanded definitions of pre-eclampsia used in the studies do not affect the generalisability of the studies to UK clinical practice.

5.3 The Committee further considered the generalisability of the studies included in the systematic review of diagnostic accuracy to clinical practice in the NHS. The Committee noted that 3 of the 4 studies were done mainly outside the UK. It heard from clinical experts on the Committee that in the NHS, women with suspected pre-eclampsia would be referred from community care to a day unit for further assessment before a decision on whether to admit them to hospital is made. It heard further that unlike in the NHS, some countries do not have day units so suspected pre-eclampsia would be managed differently. In countries where there are no day units, women with suspected pre-eclampsia would be referred from community care directly to hospital for further assessment. This results in suspected pre-eclampsia being managed for longer in the community than in the NHS, but if symptoms of suspected pre-eclampsia become worse, admission to hospital would happen earlier. The Committee concluded that this may affect the

generalisability of some of the studies to clinical practice in the NHS.

5.4 The Committee considered the test accuracy reported in the studies. It noted that test accuracy of the Triage PlGF test was better in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation than in women presenting with suspected pre-eclampsia between 35 weeks and 36 weeks plus 6 days of gestation. It heard from clinical experts on the Committee that decisions on the management of suspected pre-eclampsia are more difficult in women at earlier gestations. For example, in women with pre-eclampsia between 35 weeks and 36 weeks plus 6 days of gestation, the average time to delivery is about 4–5 days from diagnosis of pre-eclampsia. However, in women at earlier gestations the risk to the baby from premature delivery is higher than in women at later gestation, so the average time to delivery of a woman at 28 weeks' gestation is about 13 days. The Committee heard from a clinical expert that the reason for delaying delivery at early gestations is to reduce the risk of adverse neonatal outcomes. For a woman at 26 weeks' gestation, every day that the pregnancy can be extended leads to a 3% improvement in neonatal outcomes. The Committee concluded that PlGF-based tests would be more clinically useful in women presenting before 35 weeks' gestation.

5.5 The Committee considered the 2 tests that were not included in the base-case economic evaluation (the DELFIA Xpress PlGF 1-2-3 test and the BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio). It noted that the DELFIA Xpress PlGF 1-2-3 test does not have validated cut-off values, and neither test has diagnostic accuracy data for a population of women presenting with suspected pre-eclampsia between 20 weeks and 36 weeks and 6 days of gestation. The Committee concluded that the diagnostic accuracy

of the DELFIA Xpress PlGF 1-2-3 test and the BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio could not be assumed to be equivalent to the diagnostic accuracy of the Triage PlGF test and the Elecsys immunoassay sFlt-1/PlGF ratio.

5.6 The Committee considered the use of placental growth factor (PlGF)-based tests to rule-out pre-eclampsia. The Committee noted that the negative predictive value for the Triage PlGF test for the rule-out of pre-eclampsia needing delivery within 14 days in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation, using a cut-off value of 100 picograms/ml, was 98% (PELICAN study 2013). It also noted that the negative predictive value for the Elecsys immunoassay sFlt-1/PlGF ratio for the rule-out of pre-eclampsia within 1 week in women presenting with suspected pre-eclampsia between 24 weeks and 36 weeks plus 6 days of gestation, using a cut-off value of 38, was 99% (PROGNOSIS study). The Committee heard from clinical experts that PlGF-based tests indicate that the placenta is functioning correctly, which gives them confidence to return a woman with a negative PlGF-based test result to community care. It heard further that all women who return to community care, including the small number of women with false negative PlGF-based test results, would still be monitored, so if symptoms of pre-eclampsia reappeared they would be picked up by community midwives and the women would be referred back to the day unit for further assessment. The Committee therefore concluded that the use of PlGF-based tests for the rule-out of pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 36 weeks plus 6 days of gestation was safe and would help to avoid unnecessary hospital admissions.

5.7 The Committee considered the use of PlGF-based tests for the rule-in of pre-eclampsia. The Committee noted that the positive

predictive value for the Triage PlGF test for the rule-in of pre-eclampsia needing delivery within 14 days in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation, using a cut-off value of 12 picograms/ml, was 70% (PELICAN study 2013). It also noted that the positive predictive value for the Elecsys immunoassay sFlt-1/PlGF ratio for the rule-in of pre-eclampsia within 4 weeks in women presenting with suspected pre-eclampsia between 24 weeks and 36 weeks plus 6 days of gestation, using a cut-off value of 38, was 39% (PROGNOSIS study). It heard from clinical experts on the Committee that although the PlGF-based tests are helpful for ruling-in pre-eclampsia, they do not help with the decision on when to deliver the baby. The decision on when to deliver is based on clinical symptoms that indicate risk to the mother or baby, rather than the presence of pre-eclampsia alone. The Committee was concerned that in women with suspected pre-eclampsia and a positive PlGF-based test, a decision may be made to deliver the baby sooner on the basis of the PlGF-based test result alone, rather than on clinical symptoms indicating risk to the mother or baby. The Committee concluded that the use of PlGF-based tests for the rule-in of pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 36 weeks plus 6 days of gestation could lead to more unnecessary medical intervention resulting in a greater number of premature babies being delivered.

5.8 The Committee considered how the results of PlGF-based tests would be used in clinical practice. It was concerned that although PlGF-based tests could be used to safely rule-out pre-eclampsia in women presenting with suspected pre-eclampsia (see section 5.6), the interpretation of positive test results to rule-in pre-eclampsia is more difficult. The Committee was concerned that if a PlGF result was available and the result was positive for rule-in of pre-

eclampsia, too much emphasis might be placed on this result, and not enough emphasis on clinical assessment, which would result in the unnecessary early delivery of the baby (see section 5.7). The Committee concluded that PlGF-based testing could not be limited only to the rule-out of pre-eclampsia in NHS clinical practice. The Committee also concluded that until further research is done on the use of PlGF-based tests for the rule-in of pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation, the tests should not be recommended for routine use.

5.9 The Committee considered the results of the economic analysis and noted that the model included short-term outcomes. It also noted that there was very little difference in quality-adjusted life years (QALYs) for PlGF-based test strategies compared with standard clinical assessment in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation. Further, there was no difference in QALYs for PlGF-based strategies compared with standard clinical assessment in women presenting with suspected pre-eclampsia between 35 weeks and 36 weeks plus 6 days of gestation. The Committee concluded that PlGF-based test strategies could be considered to have comparable short-term clinical benefit to standard clinical assessment, but did have benefits in terms of cost savings (see section 5.11).

5.10 The Committee considered long-term outcomes after premature birth. It heard from a clinical expert on the Committee that babies born very prematurely are at higher risk of long-term adverse outcomes such as cerebral palsy. It heard further that these adverse outcomes are very rare, but would have a significant impact on the quality of life of both the child and the parents. Clinicians would take this into consideration when making decisions

on when to deliver a fetus in a woman with pre-eclampsia at less than 34 weeks' gestation. The Committee noted that long-term adverse outcomes for the baby were not included in the economic model and concluded that the QALYs in the economic model were therefore likely to have been underestimated. However, the Committee concluded further that any underestimation was likely to be small because of the rarity of these adverse events.

5.11 The Committee considered the cost savings in the economic analysis. It heard from the External Assessment Group that the high negative predictive value of the PlGF-based tests for the rule-out of pre-eclampsia in women with suspected pre-eclampsia was driving the cost savings. This happens because using the PlGF-based tests to assess pre-eclampsia results in fewer false positive results compared with standard clinical assessment, so fewer women are admitted to hospital unnecessarily. Immediate delivery of the fetus is also reduced, which results in fewer premature babies needing time in a neonatal intensive care unit. The Committee noted that most of the cost savings came from using the PlGF-based tests to rule-out pre-eclampsia; through monitoring women in a community care setting rather than admitting them to hospital unnecessarily, and through reducing the number of early deliveries and therefore premature babies. The Committee concluded that these cost savings are plausible if the PlGF-based test results are implemented correctly in clinical practice.

5.12 The Committee considered the difference in cost savings between the different gestational age groups. It noted that for women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation, cost savings of PlGF-based test strategies compared with standard clinical assessment ranged between £2488 and £2896. However, for women presenting with

suspected pre-eclampsia between 35 weeks and 36 weeks plus 6 days of gestation, cost savings of PlGF-based test strategies compared with standard clinical assessment ranged between £174 and £365. The Committee further noted its conclusion on the clinical utility of PlGF-based tests at different gestation ages (see section 5.4). The Committee concluded that the tests show most promise in those women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation, because on the basis of limited evidence, both clinical utility and cost savings appear likely to be greater in this group compared with women presenting with suspected pre-eclampsia between 35 weeks and 36 weeks plus 6 days of gestation.

5.13 The Committee considered whether repeat testing would be done in clinical practice. It noted that the economic evaluation did not include repeat testing, and that no diagnostic accuracy data were available on repeat testing. However, the economic evaluation did include sensitivity analyses doubling and tripling the cost of the test. Results showed that PlGF-based testing remained cost saving compared with standard clinical assessment. The Committee concluded that the costs of PlGF-based tests are not prohibitive to repeat testing, but the effect on clinical outcomes is unknown. The Committee heard from a clinical expert that repeat testing is often not indicated because a woman who presented with suspected pre-eclampsia, but had a negative PlGF-based test result, may have no symptoms of pre-eclampsia a week later based on standard assessment, and therefore would not need a PlGF-based test. In other cases, repeat testing is indicated and would normally be done 2 weeks later unless a woman presents again with suspected pre-eclampsia before 2 weeks after the previous test. The Committee concluded that research on when repeat testing should be done, and the diagnostic accuracy of repeat testing would be useful.

5.14 The Committee considered whether PlGF-based testing could replace the need for quantitative proteinuria testing in the assessment of pre-eclampsia. It noted that the assessment did not identify any evidence on this question and an exploratory cost analysis suggested that cost savings may only increase slightly if PlGF-based testing replaced quantitative proteinuria compared with using both tests together. The Committee heard from clinical experts that PlGF-based testing could potentially replace quantitative proteinuria testing in the future.

5.15 The Committee considered the advantages and disadvantages of near-patient testing compared with laboratory-based testing. It noted that laboratory-based testing was used in the base-case economic evaluation, and a scenario cost-analysis was done on near-patient testing. The Committee heard from a clinical expert that the advantages of near-patient testing include an instant result to inform patient care, which may result in a reduction in waiting times for patients and a reduction in unnecessary admittance to hospital while waiting for a result. It also heard that the disadvantages of near-patient care include: midwife time to do the test may take them away from patient care; the risk of lack of compliance with the standard operating procedure; the risk of inadequate training in doing the test and interpreting the results. The Committee noted further that an exploratory cost-analysis on near-patient testing suggested there may be a slight increase in costs savings compared with laboratory-based testing. The Committee concluded that if adopted in the future, each hospital should make their own decision on whether to implement laboratory-based testing or near-patient testing.

Research considerations

5.16 The Committee considered the ongoing and planned research on PlGF-based tests. It heard from an expert on the Committee that

PlGF-based testing is being used with data collection at Liverpool Women's NHS Foundation Trust and that these data may be available soon. It heard further that a small study is due to start in January 2016: Placental growth factor to assess and diagnose hypertensive pregnant women (PARROT). This is a study of PlGF-based testing for the assessment of suspected pre-eclampsia, which will be done across 6 centres in England. The aim of the study is to evaluate the implementation of PlGF-based tests by investigating whether PlGF measurement in women presenting with suspected pre-eclampsia between 20 weeks and 37 weeks' gestation decreases the time to a diagnosis of pre-eclampsia. The study will also collect data on clinical outcomes, but is not powered to show a significant difference in outcomes. The Committee concluded that women with suspected pre-eclampsia who are eligible to enrol in this study should be encouraged to do so. The Committee concluded further that it is difficult to carry out research into adverse outcomes arising from early delivery because the outcomes are rare and therefore a study would need to be very large.

6 Proposed recommendations for further research

6.1 Further research is recommended on the use of the Triage PlGF test and Elecsys immunoassay sFlt-1/PlGF ratio, with standard clinical assessment, to rule-in pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation (see section 5.7). This should specifically investigate how a positive PlGF-based test result used to rule-in pre-eclampsia would affect management decisions on time to delivery and the outcomes associated with this.

6.2 Further research is recommended on the use of repeat PlGF-based testing (Triage PlGF test and Elecsys immunoassay sFlt-1/PlGF ratio), with standard clinical assessment, in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation, who have had a negative PlGF-based test result that was used to rule-out pre-eclampsia (see section 5.13). This should include:

- exploration of the different scenarios in which repeat testing may be indicated
- the appropriate intervals between PlGF-based tests
- the diagnostic accuracy of PlGF-based testing in women with suspected pre-eclampsia who have previously had 1 or more negative PlGF-based test results.

7 Implementation

NICE will support this guidance through a range of activities to promote the recommendation for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for the development of specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 6 into its guidance research recommendations database (available on the NICE website) and highlight these recommendations to public research bodies.

8 Related NICE guidance

Published

- Safe midwifery staffing for maternity settings (2015) NICE guideline NG4
- Diabetes in pregnancy (2015) NICE guideline NG3
- Antenatal and postnatal mental health (2014) NICE guideline CG192
- Intrapartum care for healthy women and babies (2014) NICE guideline CG190

- Caesarean section (2011) NICE guideline CG132
- Pregnancy and complex social factors (2010) NICE guideline CG110
- Hypertension in pregnancy (2010) NICE guideline CG107
- Weight management before, during and after pregnancy (2010) NICE public health guidance PH27
- Inducing labour (2008) NICE guideline CG70
- Stroke and transient ischaemic attack in over 16s (2008) NICE guideline CG68
- Antenatal care for uncomplicated pregnancies (2008) NICE guideline CG62
- Postnatal care up to 8 weeks after birth (2006) NICE guideline CG37

Under development

NICE is developing the following guidance (details available from the NICE website):

- Preterm labour and birth. NICE guideline (publication expected November 2015)
- Intrapartum care for high risk women. NICE guideline (publication expected January 2017)

9 Review

NICE updates the literature search at least every 3 years to ensure that relevant new evidence is identified. NICE will contact product sponsors and other stakeholders about issues that may affect the value of the diagnostic technology. NICE may review and update the guidance at any time if significant new evidence becomes available.

Adrian Newland
Chair, Diagnostics Advisory Committee
October 2015

10 Diagnostics Advisory Committee members and NICE project team

Diagnostics Advisory Committee

The Diagnostics Advisory Committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the Committee members who participated in this assessment appears below.

Standing Committee members

Professor Adrian Newland
Chair, Diagnostics Advisory Committee

Dr Mark Kroese
Vice Chair, Diagnostics Advisory Committee and Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

Professor Ron Akehurst
Professor in Health Economics, School of Health and Related Research (ScHARR), University of Sheffield

Dr Phil Chambers
Research Fellow, Leeds Institute of Cancer and Pathology, University of Leeds

Dr Sue Crawford
GP Principal, Chillington Health Centre

Professor Erika Denton
National Clinical Director for Diagnostics, NHS England, Honorary Professor of Radiology, University of East Anglia and Norfolk and Norwich University Hospital

Dr Steve Edwards
Head of Health Technology Assessment, BMJ Evidence Centre

Mr David Evans

Lay member

Dr Simon Fleming

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

Mr John Hitchman

Lay member

Professor Chris Hyde

Professor of Public Health and Clinical Epidemiology, Peninsula Technology Assessment Group (PenTAG)

Mr Matthew Lowry

Director of Finance and Infrastructure, Doncaster and Bassetlaw Hospitals NHS Foundation Trust

Dr Michael Messenger

Deputy Director and Scientific Manager National Institute for Health Research Diagnostic Evidence Co-operative, Leeds

Dr Peter Naylor

GP, Chair Wirral Health Commissioning Consortia

Dr Dermot Neely

Consultant in Clinical Biochemistry and Metabolic Medicine, Newcastle upon Tyne NHS Trust

Ms Gail Norbury

Consultant Clinical Scientist, Guy's Hospital

Dr Deirdre Ryan

Consultant Cellular Pathologist, Royal London Hospital

Dr Steve Thomas

Consultant Vascular and Cardiac Radiologist, Sheffield Teaching Hospitals Foundation Trust

Mr Paul Weinberger

Chief Executive Officer, DiaSolve Ltd, London

Professor Anthony Wierzbicki

Consultant in Metabolic Medicine and Chemical Pathology, St Thomas' Hospital

Specialist Committee members

Mrs Ann Marie Barnard

Lay member

Dr Jenny Myers

Senior Lecturer and Consultant Obstetrician, Maternal and Fetal Health Research Centre, Central Manchester Foundation Trust

Mr Nigel Simpson

Senior Lecturer in Obstetrics and Gynaecology, and Honorary Consultant, Division of Women and Children's Health, University of Leeds

Ms Suzanne Thomas

Midwifery lead for the Manchester Placenta Clinic and St Mary's Rainbow Clinic, Maternal and Fetal Health Research Centre, Central Manchester Foundation Trust

Professor Jimmy Walker

Professor of Obstetrics and Gynaecology, St James University Hospital Trust

Mr David Wells

Pathology General Manager, Viapath, St Thomas' Hospital

NICE project team

Each diagnostics assessment is assigned to a team consisting of a Technical Analyst (who acts as the topic lead), a Technical Adviser and a Project Manager.

Rebecca Albrow

Topic Lead (until July 2015)

Frances Nixon

Topic Lead (from August 2015)

Sarah Byron

Technical Adviser

Robert Fernley

Project Manager

11 Sources of evidence considered by the Committee

The diagnostics assessment report was prepared by Southampton Health Technology Assessments Centre.

- Frampton G, Jones J, Payne L, et al. 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. September 2015.

Registered stakeholders

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

Manufacturers/sponsors:

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

Professional/specialist 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

Others:

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