NICE National Institute for Health and Care Excellence

NICE guidance

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

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces DG23 and DG49.

1 Recommendations

1.1 The following placental growth factor (PLGF)-based tests, used with standard clinical assessment, are recommended to help decide on care (to help rule in or rule out pre-eclampsia) for people with suspected preterm (between 20 weeks and 36 weeks and 6 days of pregnancy) pre-eclampsia:

- DELFIA Xpress PLGF 1-2-3
- DELFIA Xpress sFlt-1/PLGF 1-2-3 ratio
- Elecsys immunoassay sFlt-1/PLGF ratio
- Triage PLGF Test.

  Not all manufacturers indicate their tests for use across the full range of 20 weeks to 36 weeks and 6 days of pregnancy. The tests should be used according to their indications for use (see section 2).

1.2 PLGF-based testing may particularly benefit groups at higher risk of severe adverse pregnancy outcomes, such as people from African, Caribbean and Asian family backgrounds.

1.3 Further research is recommended into how well the tests work when people are pregnant with more than 1 baby (see section 4.3).

1.4 Do not use PLGF-based tests to make decisions about whether to offer a planned early birth to people with preterm pre-eclampsia. The NICE guideline on hypertension in pregnancy has recommendations on timing of birth.

1.5 Use a PLGF-based test once per episode of suspected preterm pre-eclampsia. Further research is recommended on repeat testing (see section 4.2).

1.6 BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio is not recommended

for routine use in the NHS. Further research is needed to show the accuracy of this test when using specified thresholds (see section 4.1).

Why the committee made these recommendations

The DELFIA Xpress PLGF 1-2-3 test was not previously recommended by NICE because there was not enough evidence on its accuracy. High-quality evidence now shows that this test, and the DELFIA Xpress sFlt-1/PLGF 1-2-3 ratio assay, have good accuracy for preterm pre-eclampsia.

NICE previously recommended the Elecsys immunoassay sFlt-1/PLGF ratio and Triage PLGF Test to help rule out pre-eclampsia. But they were not recommended to help diagnose (rule in) pre-eclampsia because of concerns that this could result in people being unnecessarily offered early births. Data now shows that this is not the case.

Modelling shows that all these tests are cost effective compared with standard assessment when used to help diagnose (rule in) or exclude (rule out) preterm pre-eclampsia. So these tests are recommended to help plan safe care and a safe birth for people with pre-eclampsia, and also to identify people unlikely to develop pre-eclampsia, and therefore reduce unnecessary hospitalisation. The tests may work differently in people who are pregnant with more than one baby. Therefore, NICE has recommended further research to find out how well the tests work in this group.

There is not enough evidence on whether or not the test should be repeated. Therefore, NICE has recommended testing just once when a person presents with possible symptoms of preterm pre-eclampsia (an episode) and recommended further research on if repeat testing improves outcomes.

There is new data for BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio, which was originally not recommended. But the data is lower quality than that for the other tests. Data on test sensitivity and specificity is from 2 studies, 1 that was small and 1 that did not specify the test threshold to use in advance. There is not enough good-quality data to assess how well it works and its cost effectiveness. There is also uncertainty about how the company intends the test to be used. So this test is still not recommended.

2 The diagnostic tests

Clinical need and practice

2.1 Pre-eclampsia is a potentially serious complication of pregnancy, thought to be related to problems with the development of the placenta. It requires referral to a specialist and hospital admission to monitor the mother and unborn baby, and is only cured by the birth of the baby. Pre-eclampsia is characterised by high blood pressure (hypertension) and proteinuria, which is when the kidneys leak protein into the urine. Either, on its own indicates 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 urine output).

2.2 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. Gestational hypertension and pre-eclampsia may also affect the unborn baby by slowing growth or leading to premature birth.

2.3 This is a full update of NICE's diagnostics guidance on placental growth factor (PLGF)-based testing to help diagnose suspected pre-eclampsia (DG23), which was published in 2016. The original guidance recommended the Triage PLGF Test and the Elecsys immunoassay sFlt-1/PLGF ratio, used with standard clinical assessment and subsequent clinical follow up, to help rule out pre-eclampsia. Further research was recommended on using these tests to rule in pre-eclampsia. The DELFIA Xpress PLGF 1-2-3 test and BRAHMS sFlt-1 Kryptor/ BRAHMS PLGF plus Kryptor PE ratio were not recommended for routine adoption in the NHS.

The diagnostic and care pathway

Identifying and managing the risk of developing pre-eclampsia

2.4 Recommendations on management of pre-eclampsia in NICE's guideline on antenatal care include measuring blood pressure and doing urinalysis for protein at each antenatal visit to check for pre-eclampsia. The guideline also recommends determining risk factors for pre-eclampsia at the booking appointment (by 10 weeks of pregnancy). NICE's guideline on hypertension in pregnancy describes risk factors for pre-eclampsia. It defines pre-eclampsia as new-onset hypertension (over 140 mmHg systolic or over 90 mmHg diastolic) after 20 weeks of pregnancy plus 1 or more new-onset conditions. If a woman presents with some but not all of these criteria, they are considered to have suspected pre-eclampsia. If they are under 37 weeks of pregnancy, this would be suspected preterm pre-eclampsia.

Managing pregnancy with gestational hypertension with or without pre-eclampsia

2.5 NICE's guideline on hypertension in pregnancy includes recommendations on managing gestational hypertension and pre-eclampsia in pregnancy, including timing the birth in women with pre-eclampsia.

The interventions

Triage PLGF Test (Quidel)

2.6 The Triage PLGF Test can be used at the point of care and in the laboratory. The test is used with other clinical information to help diagnose preterm pre-eclampsia, and as an aid in the prognosis of birth, in women who are between 20 weeks and 35 weeks pregnant with signs and symptoms of pre-eclampsia. The Triage PLGF kit costs £1,000 (excluding VAT) and can do 25 tests. The cost per test used in the economic model (incorporating additional cost components

such as machine costs, reagents, service charges, training and staff costs) was £49.58.

Table 1 Recommended cut-offs for the Triage PLGF Test

Result	Classification	Interpretation
Placental growth factor (PLGF) less than 12 pg/ml	Test positive – highly abnormal	Highly abnormal and suggestive of patients with severe placental dysfunction and at increased risk of preterm birth
PLGF between 12 pg/ml and 99 pg/ml	Test positive – abnormal	Abnormal and suggestive of patients with placental dysfunction and at increased risk of preterm birth
PLGF 100 pg/ml or more	Test negative – normal	Normal and suggestive of patients without placental dysfunction and unlikely to progress to birth within 14 days of the test

Elecsys immunoassay sFlt-1/PLGF ratio (Roche)

2.7 The Elecsys immunoassay sFlt-1/PLGF ratio is formed by combining the results from 2 electrochemiluminescence immunoassays (the Elecsys PLGF and Elecsys sFlt-1 assays), which are compatible with the Roche Cobas e automated clinical chemistry analysers. The sFlt-1/PLGF ratio is intended to help diagnose pre-eclampsia, together with other diagnostic and clinical information. The sFlt-1/PLGF ratio is also intended to help predict pre-eclampsia in the short term (rule out and rule in) in pregnant women with suspected pre-eclampsia, together with other diagnostic and clinical information. The Elecsys sFlt-1 reagent kit and the Elecsys PLGF reagent kit cost £3,310.78 each and can do 100 tests. They are intended to be used together, with each sFlt-1/PLGF ratio test costing £66.21 (excluding VAT). The cost per test used in the economic model (incorporating additional cost components such as machine costs, reagents, service charges, training and staff costs) was £79.23.

Table 2 Recommended cut-offs for the Elecsys immunoassay sFlt-1/PLGF ratio

Intended use	Stage of pregnancy	Decision rule	sFlt-1/PLGF ratio
To help diagnose pre-eclampsia	Week 20 to week 33 plus 6 days	Rule out cut-off	33
To help diagnose pre-eclampsia	Week 20 to week 33 plus 6 days	Rule in cut-off	85
To help diagnose pre-eclampsia	Week 34 to birth	Rule out cut-off	33
To help diagnose pre-eclampsia	Week 34 to birth	Rule in cut-off	110
Short-term prediction of pre-eclampsia	Week 24 to week 36 plus 6 days	Rule out pre-eclampsia for 1 week	38 or less
Short-term prediction of pre-eclampsia	Week 24 to week 36 plus 6 days	Rule in pre-eclampsia within 4 weeks	Over 38

DELFIA Xpress PLGF 1-2-3 test and DELFIA Xpress sFlt-1 kit (PerkinElmer)

2.8 The DELFIA Xpress PLGF 1-2-3 can be used on its own or with the DELFIA Xpress sFlt-1 kit. The tests are intended to help diagnose pre-eclampsia and for short-term prediction of suspected pre-eclampsia together with other biochemical and clinical information.

2.9 The company specifies threshold values for the DELFIA Xpress PLGF 1-2-3 test when used alone (see table 3):

Table 3 DELFIA Xpress PLGF 1-2-3 cut-offs

Intended use	Stage of pregnancy	Decision rule	PLGF cut-off
To help diagnose pre-eclampsia	Week 20 to week 33 plus 6 days Week 34 or more	Rule in cut-off	Less than 50 pg/ml

Intended use	Stage of pregnancy	Decision rule	PLGF cut-off
To help diagnose pre-eclampsia	Week 20 to week 33 plus 6 days Week 34 or more	Rule out cut-off	150 pg/ml or more
Short-term prediction of pre-eclampsia	Week 20 to week 41 Week 20 to week 33 plus 6 days Week 34 or more	Rule out pre-eclampsia within 1 week	150 pg/ml or more
Short-term prediction of pre-eclampsia	Week 20 to week 41 Week 20 to week 33 plus 6 days Week 34 or more	Rule out pre-eclampsia within 4 weeks	150 pg/ml or more

2.10 The company specifies threshold values for DELFIA Xpress 1-2-3 used with the DELFIA Xpress sFlt-1 (see table 4):

Table 4 DELFIA Xpress sFlt-1/PLGF ratio cut-offs

Intended use	Stage of pregnancy	Decision rule	sFlt-1/PLGF ratio
To help diagnose pre-eclampsia	Week 20 to week 33 plus 6 days	Rule in cut-off	70 or over
To help diagnose pre-eclampsia	Week 34 or more	Rule in cut-off	90 or over
Short-term prediction of pre-eclampsia	Week 20 to week 41 Week 20 to week 33 plus 6 days Week 34 or more	Rule out pre-eclampsia within 1 week	50 or less
Short-term prediction of pre-eclampsia	Week 20 to week 41 Week 20 to week 33 plus 6 days Week 34 or more	Rule out pre-eclampsia within 4 weeks	50 or less

2.11 The DELFIA Xpress PLGF 1-2-3 kit costs £722 (excluding VAT) and the DELFIA

Xpress sFlt-1 kits costs £944 (excluding VAT). Each can do 96 tests (that is 96 PLGF tests alone or 96 sFlt-1/PLGF ratio tests). The cost per test used in the economic model (incorporating additional cost components such as machine costs, reagents, service charges, training and staff costs) was £37.41 for DELFIA Xpress PLGF 1-2-3 and £71.41 for the DELFIA Xpress sFlt-1/PLGF ratio.

BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio (ThermoFisher)

2.12 The BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio is formed by combining the results from the BRAHMS sFlt-1 Kryptor and BRAHMS PLGF plus Kryptor assays. The assays are compatible with the BRAHMS Kryptor compact plus analyser and the Kryptor Gold immunoanalyser. The BRAHMS sFlt-1 Kryptor/ BRAHMS PLGF plus Kryptor PE ratio is intended to be used to confirm or exclude a diagnosis of pre-eclampsia after 20 weeks of pregnancy. The BRAHMS sFlt-1 Kryptor and BRAHMS PLGF plus Kryptor kits cost £825 each and can do 75 tests. The cost per test used in the economic model (incorporating additional cost components such as machine costs, reagents, service charges, training and staff costs) was £52.28.

2.13 The company says that a ratio of more than 85 suggests pre-eclampsia and a high-risk pregnancy. At consultation on the draft guidance, it said that updated instructions for use will be released later in 2022 (see section 3.6).

The comparator

The comparator is no further assessment beyond clinical assessments already done, such as blood pressure measurement, urinalysis and fetal monitoring, to help diagnose preterm pre-eclampsia and make decisions about care.

3 Committee discussion

The diagnostics advisory committee considered evidence from several sources on the BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio, DELFIA Xpress PLGF 1-2-3 test, DELFIA Xpress sFlt-1/PLGF ratio, Elecsys immunoassay sFlt-1/PLGF ratio and Triage PLGF Test. Evidence was considered from the diagnostics assessment report and an overview of that report, and the decision support unit's (DSU) report and updated model. Full details of all the evidence are in the project documents for this guidance on the NICE website.

The condition

PLGF-based tests are likely to substantially benefit women with suspected preterm pre-eclampsia

3.1 A patient expert explained that pregnancy can be a particularly worrying time for expectant mothers if they had preterm pre-eclampsia or complications from hypertension in a previous pregnancy. Placental growth factor (PLGF)-based testing can reassure pregnant women with hypertension who are anxious about complications and risks to the baby and themselves, and increase their confidence in treatment plans. A patient expert highlighted an Action on Pre-eclampsia report that stated that women from African, Asian or Caribbean family backgrounds have a higher risk of developing pre-eclampsia and that PLGF tests may particularly benefit higher risk groups. Clinical experts said that the tests can improve risk assessment and enable early planning for a safe birth. They said they may also help avoid stressful last-minute medical interventions. Early planning for at-risk pregnancies also means women at centres without facilities for preterm baby care can be safely transferred to a suitably equipped centre in good time. This improves the outcome for the baby and can avoid stressful situations, such as the mother and baby being cared for in different centres. Another benefit of the tests is better identification of women who will not develop preterm pre-eclampsia, reducing unnecessary hospitalisation. The committee considered that this was particularly relevant during the COVID-19 pandemic to help reduce spread of the virus. Clinical experts also highlighted the benefits of

using the tests for shared decision making, with test results helping discussions.

Clinical effectiveness

PLGF-based test results should be used alongside clinical information for decision making

3.2 The committee considered the PARROT and INSPIRE trials, which assessed PLGF-based tests as part of a clinical algorithm that included using the tests alongside clinical judgement to make decisions about care. The PARROT trial was a multicentre, pragmatic, stepped wedge cluster randomised controlled trial of 1,023 women with suspected preterm pre-eclampsia who were between 20 weeks and 36 weeks and 6 days of pregnancy. It was done in 11 maternity units in the UK and used the Triage PLGF Test. The INSPIRE trial was a prospective, interventional, parallel-group, randomised clinical trial of 370 women with suspected pre-eclampsia who were between 24 weeks and 37 weeks of pregnancy. It was based in a single UK tertiary referral hospital and used the Elecsys immunoassay sFlt1/PLGF ratio. Clinical experts said that the tests are not a substitute for clinical assessment. Instead PLGF-based testing gives the clinician more evidence to help them make an informed decision. Clinical experts also explained that a low PLGF test result does not always mean a woman has pre-eclampsia and can be associated with other conditions affecting the placenta. They did however highlight that PLGF-based test results can be very useful to help with clinical decision making, particularly for women who had hypertension or proteinuria before becoming pregnant. The committee concluded that PLGF-based test results should be used alongside clinical information for decision making.

PLGF-based testing did not lead to unnecessary early births in UK trials

3.3 In the original guidance (DG23) published in 2016, the committee was concerned that too much emphasis might be placed on PLGF test results indicating preterm pre-eclampsia, which could result in the unnecessary early birth of the baby.

Since this guidance was published, the NICE guideline on hypertension in pregnancy has been updated to include recommendations on deciding the timing of birth in women with pre-eclampsia. In the PARROT trial, the proportions of births before 37 weeks in the test and control arms of the trial were similar. In the PARROT, PARROT Ireland (a multicentre, pragmatic, stepped wedge cluster randomised controlled trial done in 7 maternity units throughout Ireland) and INSPIRE trials, weeks of pregnancy before birth were also similar in the test and control arms. Clinical experts said that this reflects current practice because the tests are used to help with decisions about hospitalisation and whether to transfer to a specialist unit, not to guide decisions about birth. They also pointed out that about half the centres that participated in the PARROT trial were not specialist centres, which reduced concern about how the tests would be used if they were adopted more widely. The committee concluded that there was evidence that use of the tests did not lead to unnecessary early births.

Maternal outcomes: evidence from trials suggests potential improvements with PLGF-based testing and better decisions about care

3.4 The PARROT trial data suggested that using a PLGF test improved maternal outcomes. In PARROT, the number of women with adverse outcomes, defined by the fullPIERS consensus, was lower in the revealed group (4%) than the concealed group (5%), and this difference was statistically significant. Incidence of placental abruption and severe pre-eclampsia was also lower with test use in the INSPIRE trial but not statistically significantly so. The clinical experts explained that the INSPIRE trial was not powered to detect differences in the adverse maternal outcomes that it assessed. In the INSPIRE trial, the proportion of women who had confirmed pre-eclampsia within 7 days of testing who were admitted to hospital was greater in the test use arm of the trial (100%) than the control arm (83%). At the second committee meeting, the committee considered the PARROT Ireland randomised controlled trial. It found that integrating PLGF testing into routine clinical investigations for women with suspected preterm pre-eclampsia had no significant effect on maternal morbidity. Clinical experts highlighted differences between the PARROT and PARROT Ireland study cohorts. PARROT Ireland had a higher proportion of women with suspected fetal growth restriction (55%) than PARROT (16%). Also, the incidence of pre-eclampsia in

PARROT was higher (35%) than in PARROT Ireland (14%). They also noted that PARROT Ireland had only recruited just over half the proposed participants (2,313 out of a planned 4,000; or 58%) and may have been underpowered to detect significant differences. The committee concluded that there was some evidence that PLGF-based test use could improve management decisions and clinical outcomes for women with suspected preterm pre-eclampsia, although there was considerable uncertainty about this.

Neonatal outcomes: the effect of PLGF-based testing is uncertain but some evidence suggests it may improve decisions about care

3.5 Incidence of perinatal and neonatal mortality and complications in the test and control arms of the PARROT trial were similar. Clinical experts explained that there was a very low number of these clinical events and that the trial was not powered to show differences. The committee considered that it was uncertain whether the differences were down to test use or chance. Clinical experts explained that intraventricular haemorrhage (IVH) and respiratory distress syndrome (RDS) can be devastating for babies and their families. But because they happen rarely, it is difficult to do trials to assess how tests affect them. A clinical expert said that, in a stratified analysis of the PARROT data, more women with a PLGF test result of less than 12 pg/ml who delivered before 35 weeks of pregnancy were given antenatal corticosteroids 7 days before birth in the revealed group (39%) than the concealed group (16%). They explained that this meant the women who had the PLGF test had better clinical care because antenatal corticosteroids reduce the risk of RDS, IVH and death in preterm babies. A clinical expert also pointed out that the number of nights that babies spent in the intensive care or high-dependency unit was only 15.2 nights in the test arm of PARROT, compared with 24.2 nights in the control arm. The committee concluded that, because of the rarity of IVH, RDS and death, the effect of using PLGF-based tests on neonatal outcomes is uncertain. But it agreed there was some evidence that they influence management decisions that could improve care.

The DELFIA Xpress tests have established rule in and rule out thresholds, but the BRAHMS Kryptor test does not

3.6 In the original guidance, the committee did not recommend the DELFIA Xpress PLGF 1-2-3 test or BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio test for routine adoption in the NHS. It said that further research should be done by the companies to show their clinical effectiveness, including diagnostic accuracy and analytical validity. No new data was found for how these 2 tests affect management decisions or clinical outcomes (such as maternal or neonatal outcomes). However, there was new evidence on test accuracy. Since the original guidance, rule in and rule out thresholds have been established for the DELFIA Xpress PLGF 1-2-3 test based on performance of the test compared with the Triage PLGF and Elecsys immunoassay sFlt-1/PLGF ratio tests (McCarthy et al. 2018 and Giblin et al. 2020). A prospective study using these preset thresholds was also considered at the second committee meeting (Bremner et al. 2022). A quality assessment of this study indicated a low risk of bias and no applicability concerns. This study also provided accuracy estimates for the DELFIA Xpress sFlt-1/PLGF 1-2-3 ratio assay, using specified thresholds. The external assessment group (EAG) identified 2 studies that compared the BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio with the Elecsys test. One indicated highly correlated results (Salahuddin et al. 2016) but the authors of the other study (Cheng et al. 2019) indicated that results from the different manufacturers' immunoassays were significantly different, and that sFlt-1/PLGF rule in and rule out criteria are manufacturer-specific, not interchangeable, and require separate clinical validation. At consultation on the draft guidance, the BRAHMS test manufacturer provided detail from updated instructions for use, which it plans to release in the second half of 2022. This included reference to thresholds for the BRAHMS ratio test of 85, which the company already said should be used to rule in pre-eclampsia (see section 2.13), and 66, based on Andersen et al. (2021; see section 3.13). In the committee meeting, the company said that 66 should be used to rule out pre-eclampsia and 85 to rule it in. However, the committee noted that, although the instructions for use did refer to these 2 thresholds, they did not say whether they should be used as single thresholds or together, or whether they should be used to rule in or rule out pre-eclampsia. Clinical experts said that this could lead to uncertainty in how to interpret test results. The committee concluded that, even based on the information from the updated instructions for use, it is not clear how to interpret the test result. It also noted that the test's

accuracy using the threshold of 66 had not been validated in a population independent from the one used to set this threshold (see section 3.13). The committee further concluded that there was now some evidence on the accuracy of the DELFIA Xpress tests, which could address the request for further data in the original guidance.

Repeat PLGF-based testing evidence is still limited

3.7 The original guidance made a research recommendation on using repeat PLGF-based testing. Not much more evidence was found for repeat PLGF testing for this assessment, but the clinical experts pointed out that ongoing work, for example the PARROT 2 trial, will provide further data in the future. The committee concluded that the research recommendation made in DG23 about repeat testing should be retained in this guidance (see section 4.2).

Cost effectiveness

The DSU model is suitable for decision making

3.8 At the first committee meeting, the committee was concerned about the EAG's model and approach to modelling. The standard assessment costs and quality-adjusted life years (QALYs) in the EAG's model were different for the Elecsys immunoassay sFlt-1/PLGF ratio and the Triage PLGF Test. The EAG explained this was because it used data from the control arm of the INSPIRE trial for the Elecsys test and from the PARROT trial for the Triage PLGF Test. But clinical experts said that there were important differences between the 2 trial populations, for example pre-eclampsia incidence. The committee noted that using different populations to assess standard assessment for different tests made interpreting results more difficult, and could lead to a biased assessment. The level of pre-eclampsia in the test use and non-test use arms of the individual models was also different, particularly for the Elecsys model. This was because the EAG used unadjusted data from the trials, and the pre-eclampsia incidence was higher in the test use arm. A clinical expert said that this was caused by chance allocation to trial arms. There was also uncertainty about whether the populations modelled

accurately represented women with suspected preterm pre-eclampsia who would have the PLGF-based tests in the NHS. The committee would have preferred the same model for standard assessment to be used for all tests, and for the model to be based on a population that accurately represents women with suspected preterm pre-eclampsia in the NHS. The committee concluded that more work on the model was needed to address these concerns before any recommendations could be made. As a result of these concerns, NICE commissioned the DSU to carry out further modelling work. For the second committee meeting, the DSU provided an updated model and analyses. The committee said that the DSU's model addressed its previous concerns and concluded that it was suitable for decision making.

It is appropriate to consider cost-effectiveness estimates of the tests when used to help rule out and rule in preterm pre-eclampsia

3.9 The DSU provided cost-effectiveness estimates when the PLGF-based tests were used to rule out preterm pre-eclampsia only, and when the tests were used to rule in and rule out preterm pre-eclampsia. The committee recalled that data from recent studies provided reassurance that using positive results from the tests to inform care did not lead to earlier births (see section 3.3). Clinical experts said that training and education on these tests focuses on using them to identify women who have a higher risk of developing preterm pre-eclampsia, rather than as a trigger for offering an early birth. The committee concluded that, provided the tests are used alongside clinical judgement (see section 3.2) and are not used to decide on timing of birth (see section 3.14), it is appropriate to use the tests to help diagnose preterm pre-eclampsia. Therefore, it was appropriate to consider cost-effectiveness results from the DSU's model in which the tests were used to help rule in and rule out preterm pre-eclampsia.

The Elecsys and Triage tests used to rule out and rule in preterm pre-eclampsia are cost effective

3.10 When used for rule in and rule out in the DSU's base-case analysis, testing using

the Elecsys immunoassay sFlt-1/PLGF ratio or Triage PLGF Test typically dominated standard assessment (that is, they led to lower costs and provided more QALYs). Tests were less cost effective when neonatal outcomes were removed from the model, but incremental cost-effectiveness ratios (ICERs) only increased to above £20,000 per QALY gained when decisions about care based on test results were based on the PreOS trial (a multicentre, prospective, open-label, non-interventional study in 150 women with suspected pre-eclampsia) and standard assessment was modelled based on the INSPIRE trial. The committee concluded that the Elecsys and Triage tests were cost effective, compared with standard assessment, when used to rule out and rule in preterm pre-eclampsia.

The DELFIA Xpress PLGF 1-2-3 used to rule out and rule in preterm pre-eclampsia is cost effective

3.11 Costs-effectiveness estimates for the DELFIA Xpress PLGF 1-2-3 used to rule in and rule out preterm pre-eclampsia, compared with standard assessment, from the DSU's model were similar to those for the Elecsys immunoassay sFlt-1/PLGF ratio and Triage PLGF Test (see section 3.10). The committee recalled that the thresholds for this test were set based on giving the same accuracy as the Triage and Elecsys tests (see section 3.6). The DSU used data from the COMPARE study for the DELFIA Xpress PLGF 1-2-3 in its model. COMPARE was a secondary analysis of samples from 3 prospective cohort studies, including 396 women with suspected pre-eclampsia or babies suspected to be small for gestational age, before 35 weeks and between 35 and 36 weeks of pregnancy. The DSU noted that this study had no prespecified threshold, which was a concern. Comments received on the DSU report included reference to a recently published prospective study (Bremner et al. 2022) that provided further diagnostic accuracy evidence for the DELFIA Xpress PLGF 1-2-3 test using prespecified cut-offs. The committee was satisfied that there was enough data to show how well the test worked. It concluded that the DELFIA Xpress PLGF 1-2-3 was cost effective, compared with standard assessment, when used to rule out and rule in preterm pre-eclampsia.

The DELFIA Xpress sFlt-1/PLGF 1-2-3 ratio is cost effective when used to rule out and rule in preterm pre-eclampsia

3.12 The Bremner et al. (2022) study (see section 3.11) also provided accuracy estimates for the DELFIA Xpress sFlt-1/PLGF ratio. Because this study had accuracy estimates from the DELFIA Xpress PLGF 1-2-3 alone from the same population, the DSU was able to include this test in its model. The results for this test, compared with standard assessment, were similar to the DELFIA Xpress PLGF 1-2-3 alone. When the DELFIA Xpress sFlt-1/PLGF ratio and DELFIA Xpress PLGF 1-2-3 alone were compared with each other, rather than with standard assessment, the DELFIA Xpress sFlt-1/PLGF ratio was in general dominated (that is, it had higher costs and produced fewer QALYs). But the committee noted that differences in costs and QALYs were small, and that there was uncertainty about their relative cost effectiveness. The committee also noted that the cost of doing the DELFIA Xpress sFlt-1/PLGF ratio was higher than the DELFIA Xpress PLGF 1-2-3 alone, and questioned whether commissioners would want to use the more expensive test without evidence of benefit. Clinical experts said that there may be some additional benefit to including a measurement of sFlt-1 because it may improve test performance. The committee concluded that the DELFIA Xpress sFlt-1/PLGF 1-2-3 ratio was cost effective, compared with standard assessment, when used to rule out and rule in preterm pre-eclampsia. It said that commissioners could make a decision to add the DELFIA Xpress sFlt-1 assay to the DELFIA Xpress PLGF 1-2-3 assay, based on locally available costs.

There is not enough data to recommend the BRAHMS Kryptor ratio test and it's not clear how the test is intended to be used

3.13 For the BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio test, the DSU's initial modelling used accuracy estimates from the Simon et al. (2020) study. The committee noted that this study used a threshold of 38 for rule out that was not specified by the manufacturer (see section 3.6). This was also a case-control study that was not done in the UK and included participants from a high-risk population that were already known to have pre-eclampsia or fetal growth restriction, rather than a population with suspected preterm pre-eclampsia. The committee noted that for this reason, the EAG had excluded this study from its original report. The committee said that it had concerns about the

size and case-control design of the Simon et al. study. At consultation, a consultee noted that Andersen et al. (2021) gave further diagnostic accuracy evidence for the BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio test (see section 3.6). This retrospective study included 501 pregnant women with suspected pre-eclampsia. It calculated diagnostic accuracy for previously suggested threshold values of 33 and 85 and determined a further ratio of 66, which the authors described as optimal. They concluded that this single threshold could be used as a simpler alternative to dual thresholds. The committee noted that this was not a prespecified threshold. The DSU did a quality assessment of Anderson et al. using QUADAS-2, and concluded that this could have biased the study results. The committee highlighted the importance of using separate populations to establish test thresholds and assess accuracy at a given threshold to obtain reliable estimates of performance. It noted that data was available for the DELFIA Xpress tests from studies with prespecified thresholds (see section 3.11 and section 3.12). The committee acknowledged the extra detail from the updated instructions for use for the BRAHMS ratio test but, as previously noted, this did not clear up the uncertainty about how the test should be interpreted (see section 3.6). The committee acknowledged the new evidence from Andersen et al. but concluded that there was still too much uncertainty about the diagnostic performance of the BRAHMS ratio test to recommend routine adoption. A study using a prespecified threshold, or thresholds, done in a population not used to derive these thresholds (external validation) was needed to demonstrate performance (see section 4.1).

PLGF-based tests should not be used to make decisions about timing of birth in women with preterm pre-eclampsia

3.14 The committee recalled that data from trials had reassured it that using the tests to help rule in preterm pre-eclampsia had not led to unnecessary early births. Clinical experts emphasised that if the tests were used more widely, it was important that they were not used to make decisions about timing of birth. The committee concluded that it was important to highlight this in the recommendations.

Research considerations

Research is needed on test cut-offs for women pregnant with more than 1 baby

3.15 The INSPIRE and PARROT studies only included women pregnant with 1 baby. Clinical experts said that PLGF or sFlt-1 levels may differ in pregnancies with more than 1 baby because of increased placental mass. Therefore, specialists using the tests in this group would interpret the results with caution and potentially not use the specified cut-offs. They said that research is needed to find out if different cut-offs are needed.

There is no international standard reference material for PLGF testing

3.16 The committee noted that there is currently no international standard or reference method procedure for PLGF or sFlt-1 testing. This is important for the external quality assurance of laboratories offering this testing, and the committee encouraged the development of such standards.

4 Recommendations for further research

4.1 A high-quality test accuracy study is needed for the BRAHMS sFlt-1 Kryptor/ BRAHMS PLGF plus Kryptor PE ratio test, using thresholds defined by the company, done in a population independent from that used to establish the test's thresholds, and with the test used as intended in the NHS.

4.2 Further research is recommended on repeat PLGF (placental growth factor)-based testing, with standard clinical assessment, in women presenting with suspected preterm pre-eclampsia, who have had a previous PLGF-based test result (see section 3.7). This should include:

- exploring the different scenarios in which repeat testing may be indicated
- the appropriate intervals between PLGF-based tests
- the diagnostic accuracy of repeat PLGF-based testing in women with suspected preterm pre-eclampsia.

4.3 Further research is recommended into how well the tests work when women are pregnant with more than 1 baby to find out if different cut-offs are needed (see section 3.15).

5 Implementation

NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

In addition, NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for developing specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 4 into our guidance research recommendations database and highlight these recommendations to public research bodies.

6 Diagnostics advisory committee members and NICE project team

Committee members

This topic was considered by the diagnostics advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the test to be assessed. If it is considered there is a conflict of interest, the member is excluded from participating further in that assessment.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Additional specialist committee members took part in the discussions for this topic:

Specialist committee members

Sarah Findlay
Lay specialist committee member

Joanna Girling
Consultant in obstetric medicine, obstetrics and gynaecology, West Middlesex University Hospital, and Chelsea and Westminster Hospital NHS Foundation Trust

Shonagh Haslam
Consultant clinical biochemist, Lancashire Teaching Hospitals NHS Foundation Trust

Jenny Myers
Consultant obstetrician and professor of obstetrics and maternal medicine, St Mary's Hospital

Andrew Sharp
Senior clinical lecturer in obstetrics, Liverpool Women's NHS Foundation Trust and the

University of Liverpool

Elaine Sheehan
Specialist midwife for hypertension and maternal medicine, St George's University Hospitals NHS Foundation Trust

Nigel Simpson
Senior lecturer and consultant in obstetrics and gynaecology, the University of Leeds and Leeds Teaching Hospitals Trust

Manu Vatish
Professor of obstetrics, University of Oxford

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.

Simon Webster
Topic lead

Thomas Walker
Technical adviser

Donna Barnes
Project manager

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