Healthcare Improvement Scotland | SHTG Advice on health technologies

SHTG Recommendation
March 2023

An adaptation for NHSScotland of guidance published by the National Institute for Health and Care Excellence (NICE)

Placental growth factor (PlGF)-based testing to help diagnose suspected preterm pre-eclampsia

Recommendations for NHSScotland

1. The following placental growth factor (PlGF)-based tests, used with standard clinical assessment, are recommended as an option to help clinicians rule in or rule out 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 are suitable for use across the 20 weeks to 36 weeks and 6 days of pregnancy range. The tests should be used according to their indications for use.

2. Using PlGF-based testing may particularly benefit groups of people who have a higher risk of developing pre-eclampsia and having severe adverse pregnancy outcomes, such as people from African, Caribbean and Asian family backgrounds, or people from more deprived areas.

3. A positive PlGF-based test used alongside standard clinical assessment can help clinicians make a diagnosis of pre-eclampsia. The PlGF-based test does not indicate the severity of the condition. PlGF-based test results should not be used to make decisions about timing of birth in people with preterm pre-eclampsia. The NICE guideline on hypertension in pregnancy has recommendations on timing of birth.

4. A PlGF-based test should be used once per episode of suspected preterm pre-eclampsia. Further research is recommended on repeat testing. This should include:

   - exploring the different scenarios in which repeat testing may be indicated
   - the appropriate intervals between PlGF-based tests, and

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- the diagnostic accuracy of repeat PlGF-based testing.

5. 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.

6. Further research is recommended into how the test will be used in people who are pregnant with more than one baby, and whether different test result thresholds are needed.

This Scottish Health Technology Group (SHTG) recommendation is based on guidance produced by the National Institute for Health and Care Excellence (NICE) in 2022. This guidance was considered and modified following an SHTG adaptation process. NHSScotland is required to consider SHTG Recommendations.

What were we asked to look at?

Diagnostics Guidance published by NICE in 2022 recommends four PlGF-based tests, intended for use alongside standard clinical assessment, to help rule in or rule out preterm pre-eclampsia. SHTG was asked by the Scottish Government Maternal and Infant Health Policy team to adapt the NICE guidance for NHSScotland, to inform a Scotland-specific approach to the use of PlGF-based testing.

Why is this important?

Pre-eclampsia is a potentially serious complication in pregnancy, affecting up to 6% of pregnancies in the UK. Severe pre-eclampsia develops in around 1–2% of UK pregnancies. Approximately 10% of pregnant people will require further assessment and/or monitoring for suspected pre-eclampsia. In 2021, there were 52,584 pregnancies booked for maternity care in NHSScotland.[1] Based on this, an estimated 5,260 pregnant people per year will present with suspected pre-eclampsia in NHSScotland.

There is currently limited access to PlGF-based testing across Scotland, and variation in how local laboratories are set-up to deliver these tests. Three of the four tests recommended by NICE require a specific laboratory analytics platform, and the fourth is a point-of-care test. Many Scottish biochemistry laboratories use platforms that are not compatible with the PlGF-based tests recommended by NICE.

What was our approach?

We conducted an SHTG adaptation based on a review of guidance produced by NICE in July 2022. The European Network for Health Technology Assessment (EUnetHTA) adaptation toolkit was used to assess the relevance, reliability and transferability of the NICE guidance.

As part of the adaptation process, the views, perspectives and experience of 15 topic experts were obtained via three rounds of questioning. An initial draft adaptation by SHTG was distributed to topic experts. The experts were asked to consider whether the NICE recommendations were appropriate for Scotland and if so, whether they should be adopted with no changes, or adapted to make them more relevant to the NHSScotland context.

The draft SHTG adaptation document was reviewed based on the responses received. The revised draft and the anonymised responses to the first round of questioning, were returned to the experts for a second round of questioning, and 12 of the 15 experts responded. Further changes were made to the draft based on the responses received, and circulated for a final round. No further questioning was required in the final round. The experts were asked to review the responses of their peers to the second round of questions, and the changes made to the document, and to get in touch if they had any further comments.

The comments received by the topic experts are included in the SHTG adaptation. The comments were available for consideration by SHTG Council to inform the final recommendations.

What next?

SHTG's Recommendations on PlGF-based testing will be shared with NHS boards, obstetrics and gynaecology clinical teams, clinical biochemistry and laboratory teams, the Scottish Perinatal Network and the Scottish Clinical Biochemistry Network.

The Scottish Perinatal Network is well-positioned to work with NHS boards and the clinical community across Scotland in disseminating this work at a national level, and working with the Scottish Clinical Biochemistry Network. Scottish Government will provide support to the Scottish Perinatal Network on this, ensuring the SHTG Recommendations are highlighted to Clinical Directors and Heads of Midwifery, who also provide channels of communication and dissemination at the NHS board level.

Key points

NICE guidance on PlGF-based testing to help diagnose suspected preterm pre-eclampsia (published in July 2022) has been adapted for NHSScotland. The NICE guidance was appraised, and no barriers to use relating to relevance, reliability and transferability of the evidence were identified.

1. Based on a review of the evidence, in terms of clinical effectiveness, NICE concluded that the use of PlGF-based tests to rule in and rule out preterm pre-eclampsia have the potential to reduce time to diagnosis, reduce maternal adverse outcomes, and improve decisions about care.
2. The economic evaluation by NICE reported that PlGF-based tests are cost effective, providing more quality-adjusted life years (QALYs) at lower costs when compared with standard assessment. This is achieved through a reduction in the resource impact of false negative diagnoses, and by the avoidance of unnecessary hospital admissions in people who can be safely managed out of hospital. PlGF-based tests remained cost effective in all the modelled scenarios. The extent of cost savings and improvement to outcomes varied depending on the evidence used to model the effectiveness of standard assessment and how test results affect clinical decision making.
3. NICE recommends four PlGF-based tests. The decision on tests to use in NHSScotland should be made locally within each health board. This will depend on factors such as the existing analysers, geography and cost. NICE do not recommend any test over another.
4. The diagnosis of pre-eclampsia may be made based on the onset of new significant sustained hypertension and proteinuria alone. PlGF-based testing is likely to be most useful in pregnant people when the diagnosis of preterm pre-eclampsia is less clear.

SHTG Council considerations

In making recommendations for Scotland, the Council took into account the NICE guidance and the evidence review underpinning it, and the views of the Scottish topic experts.

1. The Council members discussed the potential benefits of PlGF-based testing in improving the care of pregnant people with suspected preterm pre-eclampsia and the appropriate targeting of treatment for patients. They noted that PlGF-based tests may particularly benefit groups of people who have a higher risk of developing pre-eclampsia and having severe adverse pregnancy outcomes, for example pregnant people from African, Asian or Caribbean backgrounds. People from more deprived areas may also have a greater risk of developing pre-eclampsia.
2. The Council highlighted the potential savings that could be realised through the use of PlGF-based testing, via the avoidance of unnecessary hospital admissions when preterm pre-

eclampsia can safely be ruled out, and the appropriate targeting of treatments for people with confirmed preterm pre-eclampsia.

3. PlGF-based testing is not used routinely anywhere in NHSScotland. The Council acknowledged that introducing PlGF-based tests would have implications for laboratory services, including staff workload and training.
4. The Council discussed whether some boards may be able to run the tests on behalf of other boards, and that this could help ensure equity of access to testing. The Council noted that out of area testing will affect the turnaround time from sample to a result, especially in remote and rural areas. Clinical experts advised that a test result within 4 hours is optimal, but that the test results will still be useful with a longer turnaround time.
5. The Council were mindful of the ongoing research around PlGF-based testing, particularly PARROT-2, which will provide information on the impact of testing on parent and fetal/neonatal outcomes, and data on the use of repeat testing within an episode of preterm pre-eclampsia.
6. The Council agreed that PlGF-based tests should be equally accessible to people living in remote and rural areas across Scotland. The availability of PlGF-based testing as part of a laboratory platform or a point-of-care test may help to ensure that tests are available to suit local geographies.

Introduction

SHTG recommendations on the use of PlGF-based tests are based on a review of Diagnostics Guidance produced by NICE in July 2022.[2] This document summarises the information that was used to inform SHTG's recommendations.

Fifteen topic experts from Scotland participated in a survey exercise that informed the development of the recommendations for NHSScotland.

Health technology description

PlGF is a placentally-derived biomarker that is detectable in the circulation of pregnant people. The levels of PlGF become abnormally low in pre-eclampsia. PlGF-based tests are intended for use alongside current standard of care. The value proposition of PlGF-based tests is to improve the risk assessments of people with suspected pre-eclampsia; enabling early planning for a safe birth in people with pre-eclampsia or avoiding unnecessary hospitalisations for people who do not have pre-eclampsia.

Soluble fms-like tyrosine kinase-1 (sFlt-1) is another placentally-derived biomarker which is altered in pre-eclampsia. With pre-eclampsia, sFlt-1 levels are elevated. Some of the tests considered by NICE involve calculating a sFlt-1 to PlGF ratio.

A low PlGF test does not always mean that a person has pre-eclampsia, as it can be associated with other conditions affecting the placenta. The clinical experts consulted by NICE said that PlGF-based testing gives the clinician more evidence to make informed decisions and is especially useful in certain groups of people, for example those who had hypertension or proteinuria before becoming pregnant.

The NICE guidance recommends four tests, described below. A fifth test, the BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio, ThermoFisher Scientific, was not recommended because of a lack of good quality data on how well it works, its cost effectiveness and uncertainty around how the manufacturer intends the test to be used.

Triage® PlGF test (Quidel)

The Quidel Triage® PlGF test is run on the Triage® MeterPro analyser. It is positioned as either a point-of-care or laboratory-based test. The test takes less than 30 minutes to run (from blood draw to result). The manufacturer website states that:

> 'The Quidel Triage® PlGF Test is used in conjunction with other clinical information as an aid in the diagnosis of preterm pre-eclampsia and as an aid in the prognosis of delivery, in women presenting with signs and symptoms of pre-eclampsia after 20 weeks and prior to 35 weeks of gestation.'[3]

According to the manufacturer's website, the thresholds for a highly abnormal, abnormal and normal result are as detailed in *Table 1.*[3]

Table 1: Thresholds for the Triage® PlGF test[3]

Result	Classification	Interpretation
PlGF < 12 pg/mL	Highly Abnormal	Highly abnormal and suggestive of patients with severe placental dysfunction and at increased risk for preterm delivery with pre-eclampsia.
PlGF ≥ 12 pg/mL and < 100 pg/mL	Abnormal	Abnormal and suggestive of patients with placental dysfunction and at increased risk for preterm delivery with pre-eclampsia.
PlGF ≥ 100 pg/mL	Normal	Normal and suggestive of patients without placental dysfunction and unlikely to progress to delivery with pre-eclampsia within 14 days of the test.

Elecsys® immunoassay sFlt-1/PlGF ratio (Roche)

The Elecsys® immunoassay sFlt-1/PlGF ratio measures the level of PlGF relative to sFlt-1 in serum samples from pregnant people with suspected pre-eclampsia. The ratio is derived by combining the results from two electrochemiluminescence immunoassays. These are compatible with the Roche Cobas® series analysers.

The recommended thresholds given in the NICE guidance and manufacturer's instructions for use are set out in *Table 2.* 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 people with suspected pre-eclampsia, together with other diagnostic and clinical information.

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)

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. Both tests are run using the 6000 DELFIA® Xpress random access immunoanalyser.

Using the DELFIA® Xpress PlGF 1-2-3 test alone, the process time is approximately 30 minutes. Using the DELFIA® Xpress PlGF 1-2-3 test and the DELFIA® Xpress sFlt-1 test together takes a few minutes longer. The immunoanalyser is able to process samples simultaneously, leading to a throughput of approximately 40 results per hour.

The cut-offs as per the manufacturer's instructions for DELFIA® Xpress PlGF 1-2-3 are detailed in *Table 3*, and the threshold values for DELFIA Xpress 1-2-3 used with the DELFIA Xpress sFlt-1 are in *Table 4.* The instructions for use state that the cut-offs should be used as guidance, and that each laboratory must validate their own cut-offs for the management of pre-eclampsia in people with suspected pre-eclampsia.

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 41	Rule in cut-off*	Less than 50 pg/ml
		Rule out cut-off*	150 pg/ml or more
Short-term prediction of pre-eclampsia	Week 20 to 41	Rule out pre-eclampsia within 1 week/4 weeks*	150 pg/ml or more

**The instructions for use include different sensitivities/specificities/negative predictive values for 1 week and 4 weeks, and/or for the different stages of pregnancy.*

Table 4: DELFIA® Xpress sFlt-1/PlGF 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
To help diagnose pre-eclampsia	Week 20 to 41	Rule out cut-off*	50 or less
Short-term prediction of pre-eclampsia	Week 20 to week 41	Rule out pre-eclampsia within 1 week/4 weeks*	50 or less

**The instructions for use include different sensitivities/specificities/negative predictive values for 1 week and 4 weeks, and/or for the different stages of pregnancy.*

Epidemiology and predicted patient volume

NICE's hypertension in pregnancy guideline defines pre-eclampsia as new-onset hypertension (over 140 mmHg systolic or over 90 mmHg diastolic) after 20 weeks of pregnancy plus one or more new-onset conditions. If a pregnant person meets some but not all of these criteria, they have suspected pre-eclampsia. If they are under 37 weeks of pregnancy, this would be suspected preterm pre-eclampsia.

Pre-eclampsia is a potentially serious complication of pregnancy thought to be related to problems with the development of the placenta. It affects up to 6% of pregnancies in the UK, and severe pre-eclampsia develops in around 1–2% of UK pregnancies. Pre-eclampsia is one of the hypertensive disorders contributing to 8–10% of all preterm births.[4]

Early signs of pre-eclampsia include hypertension and protein in the urine (proteinuria).[4] Other symptoms include headache, visual disturbances, right upper quadrant abdominal pain, oedema (swelling of the hands, face or feet) and low urine output. If pre-eclampsia is not detected and monitored, it can lead to potentially life-threatening complications including eclampsia, HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome, disseminated intravascular coagulation, stroke or organ dysfunction. Pre-eclampsia may also affect the unborn baby by slowing growth or causing a premature birth. The only cure for pre-eclampsia is the birth of the baby.

People with suspected pre-eclampsia need to be assessed and managed carefully to reduce parent and fetal morbidity and improve outcomes. There can be a significant degree of uncertainty surrounding the likelihood of rapid deterioration and serious complications, as people with pre-eclampsia have varying clinical courses of disease. The principal symptoms of hypertension and

proteinuria are not specific to pre-eclampsia. The positive predictive value of hypertension and proteinuria to predict pre-eclampsia related adverse events is only approximately 20%.[5] This means that many people who are monitored and/or admitted for suspected pre-eclampsia do not go on to develop complications.

In 2021, there were 52,584 pregnancies registered for care in NHSScotland.[1] Taking this as an approximation of total pregnancies and assuming that 10% of pregnant people are monitored for suspected pre-eclampsia, 6% of pregnant people are diagnosed with pre-eclampsia, and up to 2% are diagnosed with severe pre-eclampsia, approximately 5,260 people would be expected to need further assessment and monitoring for suspected pre-eclampsia per year in NHSScotland. Up to 3,155 of these people would receive a diagnosis of pre-eclampsia (severe in 1,052 people).

Adaptation toolkit used to review the evidence

A robust and exhaustive Diagnostic Assessment Report (DAR) and NICE Decision Support Unit (DSU) report were prepared to inform the NICE guidance, which included a synthesis of the clinical-effectiveness and cost-effectiveness evidence, and an economic model.[6]

The European Network for Health Technology Assessment (EUnetHTA) adaptation toolkit was used to assess the relevance, reliability and transferability of the evidence. The toolkit focuses on five domains of a health technology assessment report:

- the use of the technology
- safety
- effectiveness
- economic evaluation, and
- organisational elements.

No significant issues relating to relevance, reliability and transferability of the evidence underpinning the NICE guidance were identified using the toolkit.

Summary of clinical- and cost-effectiveness evidence

The clinical-effectiveness evidence largely comes from two UK-based randomised controlled trials (RCTs), the PARROT trial (Triage®) and the INSPIRE trial (Elecsys®). The results are summarised in *Table 5*. Alongside the RCTs, prospective observational studies and expert opinion were used to inform the economic model. The trials evaluated the addition of PlGF-based tests to standard clinical assessment of pregnant people with suspected pre-eclampsia. They report on the prognostic accuracy of the tests and a range of parent, fetal and neonatal clinical-effectiveness outcomes. The findings are mixed in terms of the extent to which the tests were clinically effective. Overall the evidence suggests that the use of PlGF-based tests to rule out and rule in pre-eclampsia has the potential to improve outcomes (for example, reduced time to diagnosis and fewer maternal adverse

outcomes). The economic evaluation found that the improved outcomes were achieved at a lower costs when compared with standard assessment. Cost savings were driven by less intensive treatment for those who have (i) a false negative diagnosis with standard assessment who would be correctly identified as having pre-eclampsia using a PlGF-based test, or (ii) avoided admissions for those who would have received a false positive diagnosis with standard assessment alone.

The QALY benefits associated with PlGF-based tests were small, and there was uncertainty about the impact of PlGF-based tests on improving neonatal outcomes, the accuracy of standard assessment, and how PlGF-based tests influence decision making. These uncertainties could each have a negative impact on the incremental estimates of cost and QALYs. While tests were least cost effective when neonatal outcomes were removed from the model, incremental cost-effectiveness ratios (ICERs) remained cost effective under most assumptions. The evidence reviewed by NICE is summarised in the guidance document.[2]

Table 5: Main results from PARROT and INSPIRE trials

Trial outcome	Revealed PlGF test result	Concealed PlGF test result	Difference
PARROT trial (n=1,019)			
Primary outcome Time to diagnosis, median days (IQR)	1.9 (0.5 to 9.2)	4.1 (0.8 to 14.7)	Time ratio = 0.36 (95% CI 0.15 to 0.87, p=0.027), corresponding to a 64% reduction in time to diagnosis (13 to 85%)
Number of people with adverse outcomes, defined by fullPIERS consensus n/N (%)	22/573 (4)	24/446 (5)	Adjusted OR 0.32 (95% CI 0.11 to 0.96, p=0.043)
Other outcomes. *No difference in: time to delivery; preterm delivery (<37 weeks); number of nights in inpatient care (maternal outcome); perinatal adverse outcomes; and perinatal deaths.*			
INSPIRE trial (n=370)			
Primary outcome Admission for suspected pre-eclampsia within 24 hours of the test n/N (%)	60/186 (32.3)	48/184 (26.1)	Risk ratio (95% CI) 1.24 (0.89 to 1.70) Risk difference (95% CI) 0.06 (-0.03 to 0.15)
Proportion patients admitted	100%	83%	p=0.038

who developed pre-eclampsia within 7 days	24/24 people who developed pre-eclampsia were admitted	15/18 people who developed pre-eclampsia were admitted	
Other outcomes. *No difference in: maternal outcomes (pulmonary oedema, abruption and eclampsia) or perinatal and neonatal outcomes (gestational age at delivery).*			

Organisational issues / context

Implementation considerations raised in NICE guidance

The topic experts consulted for the NICE guidance noted the following practical considerations with regard to implementing PlGF-based testing:

- More time for quality assurance per test would be necessary when tests are performed at point of care.
- The use of different PlGF-based test platforms in the same maternity unit may cause confusion with interpretation of test results.
- Preference for use of a particular test might depend on existing laboratory facilities.
- The point-of-care tests may not necessarily be used at the point of care, and samples may be sent to another laboratory for processing.

NICE state that all PlGF-based tests require quality assurance of their long-term performance for UKAS (United Kingdom Accreditation Service) accreditation. An external quality assurance scheme administered by NEQAS (External Quality Assessment Services) involves sending standard serum samples to hospitals for reference calibration and checking. The Roche Elecsys® and PerkinElmer DELFIA® tests are included in this scheme, but the Quidel Triage® test is not. Users of the Quidel test would need an alternative approach for demonstrating that the results are robust and valid.

A Resource Impact Template has also been produced by NICE to accompany their guidance.

Implementation considerations raised by Scottish experts

As part of this adaptation, the Scottish topic experts were asked what barriers they foresee to implementation of the NICE guidance in NHSScotland. Fifteen topic experts from NHSScotland were consulted via three rounds of questioning. There was representation from seven NHS boards, and respondents included consultant obstetricians, a consultant neonatologist and experts from laboratory services.

Eleven experts raised concerns about how this change to the service would be funded. Two experts commented that any potential resources released in the clinical setting by implementing PlGF-based testing are not automatically made available to the laboratories, who already have limited budgets. One expert described how after a pilot period of using the test in NHS Fife, implementation was not possible because of lack of funding, despite the required analysers being installed and in routine operation. Costs will be greatest for laboratories that need to acquire equipment and ensure adequate staffing and training.

Four of the 15 experts raised concerns about the use of point-of-care tests and near patient testing. These require proper laboratory oversight to ensure safe implementation. Quality assurance measures are required to ensure safe use of the equipment and give validity to clinical decision points. While some health boards have point-of-care test teams, they may not have the resource available to take on the support of additional services. The assays should be performed by an accredited provider.

Scottish experts also noted the importance of consistent service delivery, for example, out-of-hours testing, transportation infrastructure and turnaround times. These issues are especially pertinent in remote and rural communities. One expert noted that smaller units serving rural communities could be more likely to have delays with reporting results, and it is in these areas where robust decision making around admission and discharge are particularly important.

One expert highlighted that the successful implementation of PlGF-based testing depends on 'buy-in' from the obstetric clinical community, and integration into a defined clinical pathway.

Laboratory infrastructure in Scotland

PlGF-based testing is not provided routinely anywhere in NHSScotland. Introducing PlGF-based testing would have a considerable impact on laboratory services across NHSScotland.

Of the four PlGF-based tests recommended by NICE, three are tied to the availability of a specific laboratory analytics platform (the Elecsys® test from Roche, and the two DELFIA® tests from PerkinElmer). The majority of Scottish biochemistry laboratories have invested in other platforms for which there is currently no linked PlGF-based test. The other PlGF-based test (Quidel Triage®) is a point-of-care test, which could either be delivered within biochemistry laboratories or in clinical settings. Before point-of-care tests can be incorporated into existing care pathways, consideration also needs to be given to clinical and/or laboratory capacity to carry out the tests, as well as the quality assurance of the testing process.

The DELFIA® Xpress PlGF 1-2-3 and the DELFIA® Xpress sFlt-1 kit are run using the 6000 DELFIA® Xpress random access immunoanalyser, which is not currently used by any site in NHSScotland. NHS Greater Glasgow & Clyde and NHS Lothian have an AutoDELFIA® immunoassay system for prenatal and neonatal screening, which can run the DELFIA® Xpress PlGF 1-2-3 test but not the SFlt-1 test. The

manufacturers advise that the AutoDELFIA® immunoassay system is a batch analyser, which is less suitable when a faster turnaround time is required.

The Elecsys® sFlt-1/PlGF ratio test has been used in the context of research in NHS Fife, NHS Lanarkshire, NHS Lothian and in NHS Dumfries and Galloway, which all have access to a Roche diagnostic machine. The manufacturers advise that there are also Roche diagnostic machines in use in NHS Ayrshire & Arran, NHS Greater Glasgow and Clyde, NHS Western Isles and the Golden Jubilee National Hospital. They are not currently used for PlGF-based testing.

The Quidel Triage® PlGF test is run on the Triage® MeterPro analyser. The Triage® PlGF test is not currently used in NHSScotland. There are approximately 30 Triage® MeterPro analysers in use in NHSScotland to run other diagnostic tests (for example, troponin, D-dimer and drug screening). Most (approximately 20) are used in a primary care setting.

Diagnostic pathways for PlGF-based testing

Current standard pathway

The current standard clinical assessments to help diagnose preterm pre-eclampsia and make decisions about care include blood pressure measurement, urinalysis and fetal monitoring.

Pregnant people are monitored for high blood pressure and protein in their urine during routine antenatal care. If proteinuria is identified on a dipstick test, a spot urinary protein:creatine ratio or 24 hour urine collection is recommended to quantify the level of proteinuria. Twenty-four hour urine collection may require an overnight stay in hospital. When pre-eclampsia is identified, referral to a specialist and hospital admission is recommended for parent and fetal monitoring. If the pregnant person is not admitted, ongoing regular monitoring is required.[6]

The standard pathway used in NHSScotland matches the standard clinical assessment described in the NICE guidance.

A diagnostic pathway with PlGF-based testing

The way an NHSScotland board might integrate PlGF-based testing into their current diagnostic pathway will depend on the test available to them. The pathway proposed by NHS Fife is included in Appendix 1. NHS Fife have access to a Roche diagnostic machine to run the Elecsys® immunoassay sFlt-1/PlGF ratio.

Equalities considerations

The NICE guidance states that PlGF-based tests may particularly benefit higher risk groups. The NICE guidance refers to a report by Action on Pre-eclampsia, which notes that pregnant people from African, Asian or Caribbean backgrounds are more likely to die in pregnancy, and have a higher risk of developing pre-eclampsia compared with white pregnant people.[7] People from more deprived

areas also appear to have a greater risk of developing pre-eclampsia and could also benefit from the availability of PlGF-based testing.[8]

NHSScotland will have to consider how to make the tests equally accessible to people living in remote and rural areas. If samples need to be sent to laboratories that are far away, this may increase the time before the results are available to the treating clinicians. This would have implications for the usefulness of the test.

Summary of Scottish topic experts' survey responses

Full details on the questions asked, and the responses received, can be obtained from SHTG on request.

First round of questioning

Fifteen topic experts responded to the first round of questioning (experts are listed in the acknowledgements section). The key findings from this are summarised below.

- Eleven out of 15 experts agreed or strongly agreed with the guidance produced by NICE. Respondents said the guidance was 'robust' and 'high quality' and that the test was clinically useful when used alongside standard clinical assessment. Two experts said that the tests were helpful to clarify diagnosis, avoid unnecessary admissions, provide reassurance and appropriately target treatment. One noted that testing may be especially useful in people from whom a diagnosis of pre-eclampsia is uncertain, another saying it had value particularly in pregnant people with pre-existing hypertension and/or proteinuria.
- Four experts neither agreed nor disagreed with the guidance by NICE. Reasons given were that:
    - the real world benefit to patient care has not been robustly demonstrated
    - it depends on proper implementation within a defined clinical pathway
    - it is was out with their area of expertise, and
    - the fourth part of NICE's recommendation (around the timing of birth) was not clear.
- No one disagreed or strongly disagreed with the NICE guidance.
- Ten out of 15 experts agreed or strongly agreed that the NICE guidance is an accurate interpretation of the evidence base. One of the ten experts who agreed had concerns around NICE's economic model underestimating some costs, in particular the cost per Elecsys® sFlt-1/PlGF ratio test and the cost associated with the quality control requirements.
- One expert disagreed that the NICE guidance was an accurate interpretation of the evidence base, because of concerns around statement 4 (on the timing of birth), and this was raised in the second round of questioning. Four experts neither agreed nor disagreed. One felt that they couldn't comment without doing their own appraisal of the evidence, one felt it was out

with their area of expertise, one raised concerns about the PARROT-Ireland trial (the results of which are at odds with the PARROT and INSPIRE trial), and one said that buy-in from the obstetric services and triggering of a defined clinical pathway was crucial to the success of the implementation of this test.

- Twelve out of 15 experts said that guidance for NHSScotland should support the case for the use of PlGF-based tests, used with standard clinical assessment, to help decide on care for people with suspected preterm pre-eclampsia.
- The most common theme in the expert responses related to finance and are described in the 'Implementation considerations raised by Scottish experts' section. Two experts questioned the appropriateness of spending money on implementing PlGF-based testing in the current economic climate. One expert highlighted that business cases need to consider not only the costs of equipment/reagents, but also of staff time, external quality assessment (EQA), UKAS accreditation, transportation costs and the interface for the transfer of results. Consideration will also need to be given to the turnaround time for tests and out-of-hours service provision, both of which will impact on staffing resources.

Second round of questioning

Twelve experts responded to the second round of questioning. They were asked to read and reflect on the anonymised responses in round 1, and reconsider their position. The key findings from this round of questioning are summarised below.

- Eleven out of 12 experts said that the guidance for NHSScotland should support the case for the use PlGF-based tests, used with standard clinical assessment, to help decide on care for people with suspected preterm pre-eclampsia. No one changed their mind from round 1. Feedback included that the evidence supported the use of PlGF-based testing, that it was a good addition to the diagnostic toolkit, and that it had the potential to reduce the burden associated with preterm delivery. Two experts raised the current inequity of access that exists in the United Kingddom, with testing being more readily available in England than in Scotland. Three experts noted that the technology and the associated evidence base is evolving, and that PlGF-based testing has the potential to be used in other pregnancy risk assessments in the future. One expert re-iterated their concerns about how this addition to the service will be funded.
- One of the 12 experts said that the guidance for NHSScotland should not support the case for the use of PlGF-based testing. They felt that while PlGF-based testing helps to label pre-eclampsia, it does not generally change patient care.
- In round 1, one expert suggested that the fourth point of the recommendation could be reworded to make it a little clearer. Experts in round 2 were asked for suggestions for rewording. The following was proposed in the draft presented in round 3:

  > A positive PlGF-based test can help confirm a diagnosis of pre-eclampsia, however it does not indicate the severity of the condition. PlGF-based test results should not be considered

in the decision to deliver a baby once the diagnosis of pre-eclampsia has been made. The NICE guideline on hypertension in pregnancy has recommendations on timing of birth.

- In round 1, one expert suggested that the first point of the recommendation was reworded to emphasise that the decision to use PlGF-based testing should lie with the clinician looking after the patient. The following rewording was proposed (changes in red):

  > The following placental growth factor (PlGF)-based tests, used with standard clinical assessment, are recommended as an option to help clinicians 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.

  In round 2, nine out of 12 experts agreed with the changes, but three had concerns about watering down the recommendation given that the test is already technically available. The changes were made for the third round, but the issue was raised with SHTG Council.

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- Dr Neil Smart, Scottish Health Technologies Group Council Chair, Healthcare Improvement Scotland, and Consultant Anaesthetist, NHS Greater Glasgow & Clyde

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References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly-used terms in Health Technology Assessment (HTA) is available from htaglossary.net.

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Appendix 1: NHS Fife proposed pathway to diagnose pre-eclampsia

VHK MATERNITY ASSESSMENT

PlGF Ratio Test to Rule Out Pre-Eclampsia

NHS Fife

Suspected Pre-Eclampsia between 20+0 and 36+6 weeks
(singleton pregnancy only)
Routine maternal and fetal assessment including assessment of maternal symptoms and signs, BP, urinalysis by dipstix and ACR, bloods, CTG if >26wks

Isolated new hypertension *OR*
Isolated new gestational proteinuria
(ACR ≥ 30mg/mmol
or dipstix ≥ 2+ if ACR not readily available) *OR*
Worsening chronic hypertension *OR*
Worsening proteinuria in pre-existing renal disease/diabetes

New significant sustained hypertension
(BP>140/90mmHg on profile)
AND
Significant Proteinuria
(ACR≥ 30mg/mmol)

Treat as Pre-Eclampsia
Do not request PlGF ratio. Senior medical review for management plan. See pre-eclampsia guideline

Request PlGF ratio test in addition to PET bloods
(select PET and PlGF bundle on Trak)
(call lab to let them know you are sending PlGF ratio test)

sFlt/PlGF Ratio ≤ 38

Rules out pre-eclampsia for next 7 days

Can discharge home: community or outpatient f/u
Consider retest after 14 days if in clinical condition

sFlt/PlGF Ratio 39-84

Intermediate result:
20% risk of pre-eclampsia in next 7 days

Increased surveillance
Admit if needing to start antihypertensive for BP.
2 x week Outpatient Daycare for BP profile.
Consider retest after 7 days dependant on clinical condition

sFlt/PlGF Ratio ≥ 85

Diagnosis of pre-eclampsia confirmed

Senior medical review
Discuss plan with consultant
Likely inpatient management (minimum alternate day Daycare)
Do not repeat PlGF test
A positive angiogenic marker test is not an *isolated* indication for delivery <37 weeks