NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

PlGF based testing to help diagnose suspected pre-eclampsia (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)

Diagnostics Consultation Document 2 – Comments

Diagnostics Advisory Committee date: 10 February 2016

THEME: General

Comment number	Name and organisation	Section number	Comment	Response
1	Roche Diagnostics	1.1 & 5.6	Roche Diagnostics would like to thank the Committee for their careful and thorough consideration of the evidence presented on the PLGF-based tests (Elecsys immunoassay sFlt-1/PlGF ratio and Triage PlGF) and for their conclusion of provisionally recommending the use of these tests (with standard clinical assessment) for the rule-out of pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days gestation.	Thank you for your comment which the Committee considered.
2	Roche Diagnostics	4.6	The details of the PROGNOSIS study were published on 07 January 2016: Zeisler et al. N Engl J Med 2016;374:13-22. DOI: 10.1056/NEJMoa1414838	Thank you for your comment which the Committee considered. The External Assessment Group had confirmed that these published data from PROGNOSIS are in agreement with those cited in the diagnostics assessment report, which were taken from the unpublished academic manuscript supplied by Roche.

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Diagnostics Consultation Document 2 – Comments

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				The following sections of the diagnostics guidance document have been updated: 4.6, 4.9 and table 8 in section 4.14 with the newly available data.

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Diagnostics Consultation Document 2 – Comments

Diagnostics Advisory Committee date: 10 February 2016

THEME: Rule-out of pre-eclampsia

Comment number	Name and organisation	Section number	Comment	Response
3	Roche Diagnostics	1.1	The PROGNOSIS study demonstrated that in pregnant women with suspected preeclampsia between 24 weeks and 36 weeks and 6 days of gestation pre-eclampsia could be ruled out with a high negative predictive value using the Elecsys immunoassay sFlt-1/PlGF ratio. It is important to mention that rule-out pre-eclampsia was found in women with suggested pre-eclampsia in the short term (one week).	Thank you for your comment which the Committee considered. The Committee acknowledges that the Elecsys immunoassay sFlt-1/PlGF ratio is indicated for use up to 36 weeks and 6 days of gestation, but concluded that PlGF-based tests would be more clinically useful in women presenting before 35 weeks' gestation. This consideration is detailed in section 5.5 of the diagnostics guidance document.

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Diagnostics Consultation Document 2 – Comments

Diagnostics Advisory Committee date: 10 February 2016

THEME: Rule-in of pre-eclampsia

Comment number	Name and organisation	Section number	Comment	Response
4	Roche Diagnostics	1.2	In PROGNOSIS pre-eclampsia could be predicted (ruled-in) in women with suspected pre-eclampsia between 24 weeks and 36 weeks and 6 days of gestation in the short term (four weeks).	Thank you for your comment which the Committee considered. The Committee acknowledges that the Elecsys immunoassay sFlt-1/PlGF ratio is indicated for use up to 36 weeks and 6 days of gestation, but concluded that PlGF-based tests would be more clinically useful in women presenting before 35 weeks' gestation. This consideration is detailed in section 5.5 of the diagnostics guidance document.
5	Roche Diagnostics	5.8 & 6.2	The Committee commented that the PLGF-based tests are helpful in ruling-in pre-eclampsia, but concluded that this could lead to more unnecessary medical intervention and therefore recommended further research. The Elecsys immunoassay sFlt-1/PlGF ratio demonstrated a positive predictive value of 36.7% for ruling-in of pre-eclampsia within four weeks using a cut-off of 38. Ruling-in pre-eclampsia within four weeks will	Thank you for your comment which the Committee considered. The Committee was concerned that clinicians with less specialist expertise in managing preterm pre-eclampsia would place too much emphasis on a positive PlGF-based test, and not enough emphasis on clinical assessment, which would result in the unnecessary early delivery of the baby. This concern is detailed in section 5.10 of the diagnostics guidance

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THEME: Rule-in of pre-eclampsia

Comment number	Name and organisation	Section number	Comment	Response
			not be used to decide to deliver a baby sooner but to assess the risk for developing pre-eclampsia in the short-term by allowing increased surveillance on a group of women for whom there is currently no way of knowing that they require increased surveillance. Identification of a high risk of women for developing pre-eclampsia will allow timely referral to a day unit or to hospital for this surveillance to be initiated. Moreover, [redacted] has commented that that "no single clinical test is used to deliver a woman with preeclampsia. Rather, a consideration of clinical condition, biochemical parameters, gestational age and clinical acumen is used together to decide the optimal time for delivery. The Elecsys immunoassay sFlt1/PLGF ratio merely allows this clinical activity to be focussed on the at risk group more effectively than the current clinical abilities." Since the publication of the PROGNOSIS study in NEJM on the 7th January 2016 (Zeisler et al. N Engl J	document. The Committee heard from clinical experts that low levels of PlGF probably indicate placental disease. However, this guidance considers the use of PlGF-based testing only in helping to diagnose suspected pre-eclampsia. The recommendations in this guidance do not consider the use of PlGF-based testing for conditions other than suspected pre-eclampsia and this guidance is not intended to provide advice on the diagnosis or management of placental disease. If placental disease is suspected, additional clinical surveillance may be required. This information has been added to a text box following the section 1 recommendations. The External Assessment Group has noted that data on fetal adverse outcomes given in the supplementary appendix of the PROGNOSIS study are the same as those already given in the unpublished academic manuscript submitted by

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Diagnostics Consultation Document 2 – Comments

Diagnostics Advisory Committee date: 10 February 2016

THEME: Rule-in of pre-eclampsia

Comment number	Name and organisation	Section number	Comment	Response
			Med 374;13-22. DOI: 10.1056/NEJMoa1414838). / we would like to bring to the Committee's attention the data in the supplementary appendix of the above publication, which provides further information regarding the rule-in in relation to maternal & fetal adverse outcomes (an sFlt-1/PlGF ratio greater than 38 was predictive of the presence of fetal adverse outcomes within 4 weeks). More recently, [redacted] informed us that "preliminary data from the interventional study (INSPIRE) being conducted in Oxford has re-iterated the excellent negative predictive value of the test (99.2% NPV) as well as the ability of the assay to correctly identify patients who are at higher risk of actually developing the disease. The sFlt1/PLGF test has been used to triage patients with suspected pre-eclampsia into low and high surveillance categories and has not been used to determine the need for delivery."	Roche, except for a slight difference in the way that the data are presented. This data was considered by Committee when developing its recommendations. The Committee noted that the INSPIRE trial is ongoing (section 5.18 of the diagnostics guidance document), and preliminary results are currently not available.
6	Alere	5.7	RULE-IN USE	Thank you for your comment which the Committee

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			The endpoint of an "adjudicated diagnosis of pre-eclampsia" used in the PELICAN and PETRA studies allows for the comparison between a new test (i.e., PlGF test) and the best possible diagnostic performance of current, but imperfect, clinical markers when interpreted by an expert panel at the end of pregnancy. However, the current definition of pre-eclampsia (the comparator) fails to identify a substantial number of women who might ultimately have a severe adverse outcome. By example, in the PETRA study, there were 27 fetal/neonatal deaths in the ≤34w+6d group. All of these women met criteria for "rule-in" of pre-eclampsia by PlGF testing (≤100 pg/mL) and 23/27 (85%) had a very low (≤12pg/mL) level of PlGF. Of these 27 pregnancies, only 17 met the CG107 guideline definition of pre-eclampsia. 22% of women	considered. The Committee noted that the current definition of pre-eclampsia as described in the NICE guideline on hypertension in pregnancy is narrower than the expanded definition of pre-eclampsia which is often used in clinical practice in the NHS (section 5.3 in the diagnostics guidance document). The Committee noted that PlGF is also a biomarker for placental disease, and heard from clinical experts on the Committee that the occurrence of placental disease does not mean that pre-eclampsia is present. The Committee noted that the requirements for the surveillance and management of placental disease are not well defined and noted that surveillance and management of this disease were beyond the scope of this guidance. This consideration has been added in section 5.2 of the diagnostics guidance document.

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THEME: Rule-in of pre-eclampsia

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			had a final adjudicated diagnosis of "no disease", despite the severe adverse outcome. Because of the imperfect comparator, Alere's clinical investigators evaluate the rule-in performance of PlGF ≤12 pg/mL by calculating the proportion of women who require preterm medical delivery [99% PPV; denominator is 280 women] in addition to calculating the proportion of women who meet criteria for preterm pre-eclampsia [99% PPV; denominator is reduced to 249 women]. Knowing, at first presentation, that a very high likelihood of preterm medical delivery exists, will help clinicians identify a greater number of pregnancies requiring increased surveillance [280 versus 249 in PETRA] and, in doing so, will identify those pregnancies with increased risk for fetal/neonatal death. While a recommendation for adoption of the "rule-out" use of PlGF tests is a positive development for both	The Committee also noted that the end point of preterm delivery is not equivalent to the end point of pre-eclampsia needing preterm delivery, because preterm delivery can be for various reasons, not just pre-eclampsia (section 5.8 of the diagnostics consultation document). The Committee was concerned that clinicians with less specialist expertise in managing preterm pre-eclampsia could place too much emphasis on a positive PlGF-based test, and not enough emphasis on clinical assessment, which could result in the unnecessary early delivery of the baby. This concern is detailed in section 5.10 of the diagnostics guidance document. The Committee heard from clinical experts that low levels of PlGF probably indicate placental disease. However, this guidance considers the use of PlGF-based testing only in helping to diagnose suspected pre-eclampsia. The recommendations in this

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THEME: Rule-in of pre-eclampsia

Comment number	Name and organisation	Section number	Comment	Response
			reducing resource utilisation and patient anxiety, we consider that not recommending the "rule-in" use of PlGF tests [to identify women requiring increased surveillance, with a 99% PPV for preterm medical delivery] is ill-founded. The "rule-in" group of pregnant women identified with a PlGF level of ≤12 pg/mL includes the majority (85%, PETRA) of pregnancies likely to fail, many of whom are because the severity of the disease is missed by standard clinical assessment/ This leads to a severe adverse outcome due to inappropriate clinical management rather than a bad outcome in very early severe disease, for which we agree the outcome will be poor irrespective of PlGF testing. We request that the Committee reviews the criteria being used to not approve PlGF testing for rule-in. The test, when used at first presentation, delivers a 99% PPV for either the endpoint of preterm delivery or preterm pre-eclampsia AND identifies the group of	guidance do not consider the use of PlGF-based testing for conditions other than suspected pre-eclampsia and this guidance is not intended to provide advice on the diagnosis or management of placental disease. If placental disease is suspected, additional clinical surveillance may be required. This information has been added to a text box following the section 1 recommendations in the guidance

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			pregnancies where fetal/neonatal death might occur. Such a test will appropriately increase the level of surveillance and, when integrated into standard assessment, will not on it's own trigger delivery of the pregnancy.	

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THEME: The PreOS study

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7	Roche Diagnostics	5.8 & 6.2	The PreOS study found a strong association of the Elecsys immunoassay sFlt-1/PlGF ratio and pre-eclampsia as well as maternal and fetal adverse outcomes. This is in line with the results of the PROGNOSIS study. That's why we believe that the study should be transferable to clinical practice in the NHS.	Thank you for your comment which the Committee considered. The Committee noted that the study was done in Germany and Austria, and heard from a clinical expert on the Committee that although the care pathways on admission and surveillance are likely to be slightly different to those in the UK, the results are probably generalisable to clinical practice in the NHS. The Committee decided to change the wording in section 5.9 of the diagnostics guidance document to reflect this consideration.

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THEME: Further research

Comment number	Name and organisation	Section number	Comment	Response
8	Roche Diagnostics	General	We would welcome an opportunity to discuss with the Committee and take advice regarding your proposed recommendations for further research.	Thank you for your comment which the Committee considered.
9	Perkin Elmer	General	We acknowledge requirement for more evidence for our inclusion and we are already working on this.	Thank you for your comment which the Committee considered.