

# Quality assessment of pre-eclampsia markers – from sample exchange to UK NEQAS provision

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## Background

Pre-eclampsia is a multisystem hypertensive disorder of pregnancy that affects approximately 3% of all pregnancies. Traditionally the diagnosis of pre-eclampsia has relied upon the use of clinical features and non-specific biochemical markers which have inherent errors. More recently angiogenic biomarkers have been proposed as diagnostic tools and for risk stratification for pre-eclampsia.

The use of two diagnostic tests to assess the risk of a women developing pre-eclampsia have been recommended by NICE in Diagnostic Guidance 23<sup>1</sup>. One is the Triage PLGF test (Alere International) which is a point of care fluorescence immunoassay, using plasma samples. The other assays are Elecsys PLGF and sFlt-1 tests (Roche Diagnostics) which are sandwich electrochemiluminescence immunoassays. Results obtained can be used to calculate the sFlt-1/PLGF ratio in serum samples.

## Aims

Here we compare results from a sample exchange programme with those from the Pilot UK NEQAS for Pre-eclampsia Markers and assess pre-eclampsia marker assay performance.

## Methods

In the sample exchange programme 92 single donation samples from women at risk of pre-eclampsia were distributed to 13 laboratories on three occasions. These were compared with UK NEQAS results for more than 60 distributions of three liquid specimens. Specimens were initially the same as those for the UK NEQAS 1<sup>st</sup> Trimester Maternal Serum Screening scheme and were of significantly lower concentration but since January 2019 have been better targeted for the pre-eclampsia clinical application.

Participants in both studies submitted results for sFLT-1, PIGF and/or the sFLT-1/PIGF ratio. Mean concentrations and %CVs for each of the analytes were calculated and compared. In the sample exchange analysis this was performed solely on Roche platforms and laboratories were asked to provide details of which analytical platform they used (either the e411, e602 or e801). This enabled an average bias to be calculated for each Roche analytical platform and compared with similar UK NEQAS data.

Additionally as part of the sample exchange programme participants were asked to provide an interpretation based on clinical information given with the specimens. The interpretations given by the participating laboratories were compared to the mean interpretation. This in turn was determined by using the mean sFlt-1/PIGF ratio and comparing it to well defined published cut offs ( $\leq 38$  – PE ruled out,  $> 38$  to  $\leq 85$  – high risk of PE,  $> 85$  – diagnosis of PE highly likely)<sup>2</sup>.

## Results

For the sample exchange, of the 92 samples sent out 86 results were returned with 6 short samples or no results being the cause of results not being returned. Mean concentration ranges and %CV ranges for PIGF, sFlt-1 and sFlt-1/PIGF ratio for samples distributed in the sample exchange can be seen in table 1 below.

Test	Mean concentration range	%CV range
PIGF	31.4 to 441.1 pg/mL	24.15 to 11.09
sFlt-1	1306.7 to 12545.0 pg/mL	1.17 to 8.26
sFlt-1/PIGF ratio	7.31 to 161.6	9.20 to 14.61

Table 1. Mean concentration and %CV range for PIGF, sFLT-1 and sFLT-1/PIGF ratio for the sample exchange.

Mean concentrations for PIGF in the UK NEQAS Pilot scheme ranged from  $<10$  to 34 pg/mL and %CVs were consistently less than 10%. In the UK NEQAS scheme the %CVs for the sFLT-1/PIGF ratio were frequently greater than 15% for the laboratories that submitted results.

The average percent bias of each sample distributed in the sample exchange (where enough data was available) was calculated at an individual analyser level against the overall sample mean. In figure 1a it can be seen that the e801 is positively biased compared to the e411 analyser. Figures 1b and c shows the reverse of 1a with the ratio giving a larger compounded effect.

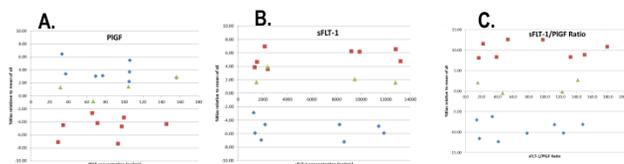


Figure 1 Average percent bias relative to the overall mean versus concentration for A. PIGF B. sFLT-1 and C. sFLT-1/PIGF ratio. The individual Roche platforms can be visualised by colour with the e801 in blue, e602 in green and e411 in red.

These figures are in accord with UK NEQAS scheme data, providing some reassuring evidence that EQA samples issued are appropriate. In May 2021, median BIAS figures (i.e., cumulative deviation from the consensus mean target values) for the 2010/e411 and e601/e801 method groups were respectively +4.8% and +9.1% for PLGF, +7.0% and +2.5% for sFLT-1 and +10.3% and 0% for sFLT-1/PLGF.

In order to determine if there was any difference clinically in the interpretation produced with the results in the sample exchange the participants were asked to provide an interpretation. From table 2 it can be seen that out of 86 results returned 92% of these showed concordance with each other. Only 8% differed (6 samples) and on closer inspection these were on two borderline samples which produced mean ratio results of 86.8 and 36.2.

Table 2. Number and percentage of interpretations correlating with the mean interpretation in participants of the sample exchange.

Total results	86	
Total correlating with mean interpretation	79	92%
Total not correlating with mean interpretation	6	8%

## Conclusions

Analytical agreement is encouragingly good with %CVs for the PIGF and sFLT-1 less than 15% in both the sample exchange and UKNEQAS pilot scheme. Even for the ratio which is using two measured tests the variability is generally acceptable. The slightly higher %CV seen for PIGF (greater than 10%) was for the concentration at the lower end. Additionally, this concentration showed the largest spread of %CVs between analysers. This is perhaps to be expected as the lower limit of quantitation is approached for an assay with a wide measuring range.

A slight difference in the mean bias was seen between the Roche analytical platforms for PIGF, sFlt-1 and ratio. Clinical comparisons revealed that this only had a small impact in a few borderline samples. The routine use of these tests is still in its infancy and it is critically important that there is good awareness of analytical issues so as to ensure their optimal clinical application.

## References

1. PIGF-based testing to help diagnose suspected pre-eclampsia. NICE Diagnostics guidance [DG23], published 2016.
2. Hypertension. 2014;63:346-352.