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Development of an External Quality Assessment (EQA) Programme for Pre-Eclampsia Markers

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Introduction

Pre-eclampsia is a poorly understood complication of pregnancy, affecting 2-8% of pregnant women worldwide, with a UK rate of approximately 3%.

The classical clinical features of pre-eclampsia are new onset hypertension and proteinuria developing in pregnancy and resolving after delivery. However the International Society for the Study of Hypertension in Pregnancy (ISSHP) have recently redefined pre-eclampsia as *'the presence of de novo hypertension after 20 weeks' gestation accompanied by proteinuria and/or evidence of maternal acute kidney injury (AKI), liver dysfunction, neurological features, haemolysis or thrombocytopenia, or foetal growth restriction'.*[1]

Due to the relatively common and non-specific symptoms, approximately 70% of those suspected of having the condition do not have it – biomarkers to assist in the diagnosis have been evaluated for many years.

Soluble fms-like tyrosine kinase-1 (sFlt-1 or sVEGFR-1) and placental growth factor (PlGF) and the sFlt-1/PlGF ratio have emerged as promising biomarkers to help diagnose and rule out pre-eclampsia.

The National Institute for Health and Care Excellence (NICE) in the UK published guidelines on the use of these tests in pre-eclampsia as follows:

'The Triage PlGF test and the Elecsys immunoassay sFlt-1/PlGF ratio, *are recommended to help rule-out* pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation'[2].

'The Triage PlGF test and the Elecsys immunoassay sFlt-1/PlGF ratio *show promise in helping to diagnose* (rule-in) pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation'[2].

Tests from other manufacturers were not recommended due to lack of clinical studies but updated guidelines are expected to be published July 2022.

In 2020 Weqas developed an EQA programme to assess and monitor the performance of sFLt-1, PlGF and sFlt-1/PlGF ratio. A post-analytical interpretive element is also included with Roche users able to report samples as 'unlikely', elevated risk' or 'high risk', and Triage users able to report samples as 'normal', 'abnormal' or 'highly abnormal'.

Method

Initially spent patient samples were collected and provided by Oxford University Hospitals. These samples were sent out for the first 5 distributions with further samples prepared from EDTA plasma spiked with recombinant sFlt-1 and PlGF. Three samples were distributed every month to approximately 40 participants over a 20 month period.

Results

Material Validation

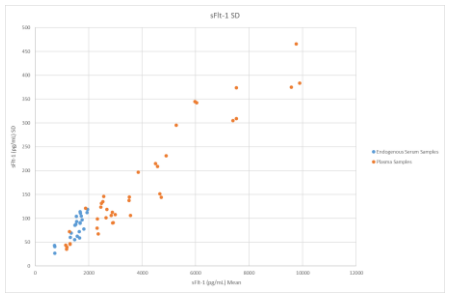
Homogeneity was assessed in house using methods described in ISO 13528 : 2015 'Statistical methods for use in proficiency testing by interlaboratory comparison'. All samples proved homogeneous with sFlt-1 CVs < 1% for samples ranging from 1000 pg/mL to 6000 pg/mL. PlGF CVs were <1 – 1.5 % for samples ranging from 50 – 300 pg/mL.

Stability

Stability was assessed in house with PlGF showing significant deterioration when stored at room temperature. For this reason the samples are shipped on ice packs to maintain stability. sFlt-1 and PlGF appear stable for at least 6 months at -20°C. (Stability data not shown).

EQA Programme Results – Precision Profiles – Quantitative Analytes

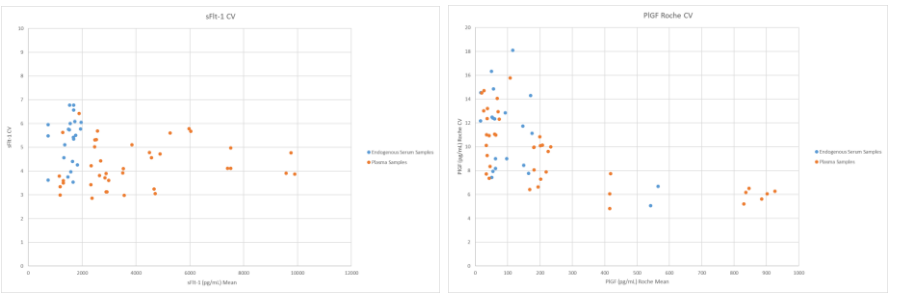
The precision profiles for sFlt-1 and PlGF (Roche), calculated from the overall SD of all participants' results at each concentration are shown in figures 1a & 1b.



Figures 1a & 1b – Precision profiles for sFlt-1 and PlGF (Roche Elecsys)

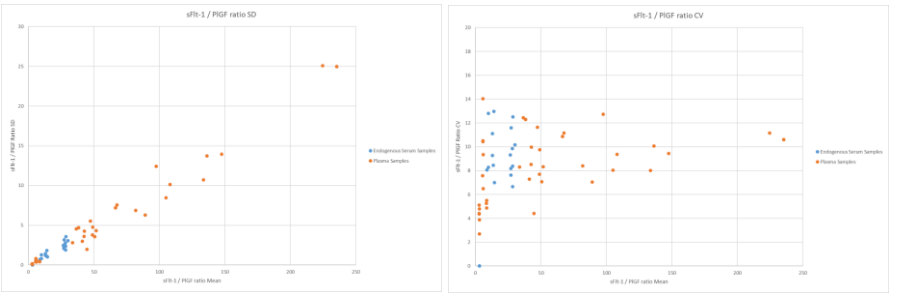
EQA Programme Results – Precision Profiles – Quantitative Analytes

The CVs for sFlt-1 and PlGF (Roche) for participants' results at each concentration are shown in figures 2a & 2b. CVs of 3-7% were observed for the Roche sFlt-1 assay and 5-18% for the Roche PlGF assay.



Figures 2a & 2b – CV Precision profiles for sFlt-1 and PlGF (Roche Elecsys)

The precision profile for sFlt-1/PlGF ratio, calculated from the overall SD of all participants' results at each concentration, and the CVs at each concentration are shown in figure 3a & 3b. CVs of 4-14% were observed for the Roche sFlt-1/PlGF ratio. The Triage PlGF assay reported CVs of 10-25% (data not shown).



Figures 3a & 3b – Precision profiles and CVs for sFlt-1 / PlGF ratio

EQA Programme Results – Interpretive / Qualitative Analytes - Pre-eclampsia Risk

For all endogenous serum samples the sFlt-1/PlGF Ratio was <38 so the Weqas assigned interpretation was 'Unlikely'. For the samples spiked with recombinant sFlt-1 and PlGF results were as follows:

Of 23 samples distributed with a Weqas Interpretation of 'Unlikely', 95% reported 'Unlikely', 4.3% reported 'Elevated Risk', and 0.7% reported 'Very High Risk'.
Of 13 samples with a Weqas interpretation of 'Elevated Risk', 10.4% reported 'Unlikely', 86.9% reported 'Elevated Risk', and 2.7% reported 'Very High Risk'.
Of 12 samples with a Weqas interpretation of 'Very High Risk', 1.3% reported 'Unlikely', 17.2% reported 'Elevated Risk', and 81.5% reported 'Very High Risk'.

For the Triage PlGF, When PlGF <12 (highly abnormal), 100% reported < 12, when PlGF > 100 (test Negative – normal) 94% reported >100.

Figure 4a shows the qualitative results for the Roche interpretation of Pre-eclampsia risk compared to the Roche sFlt-1/PlGF ratio overall mean. Figure 4b shows the qualitative results for the Triage PlGF interpretation compared to the Triage PlGF overall mean.

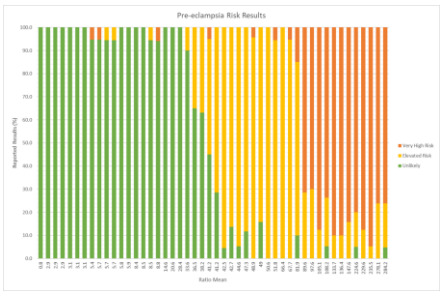


Figure 4a – Roche Pre-eclampsia risk results against the sFlt-1/PlGF ratio overall mean

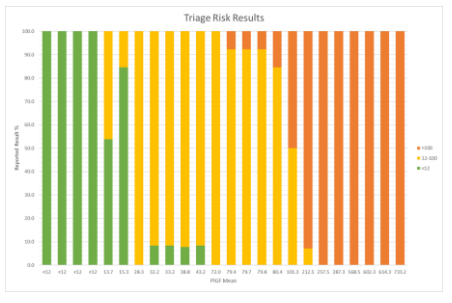


Figure 4b – Triage qualitative results against the Triage PlGF overall mean

Discussion

For both the Roche and Triage methods the majority of interpretative results agreed with the Weqas interpretation. However there was an increased divergence of reported results in samples with concentrations close to interpretive cut-offs. For the Roche the low number of false negatives (6%) supports its use as a rule out test for Pre-eclampsia. For the Triage PlGF, all users correctly identified the highly abnormal samples.

An EQA programme has been successfully established for Pre-eclampsia markers sFlt-1 and PlGF, which allows users to assess and monitor the performance of their quantitative assays and the interpretation of these assays.

1. Brown et al. Hypertension. 2018;72:24-43
2. NICE 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 guidance [DG23] Published: 11 May 2016