Final Research Report

Study title:	**Evaluating the Roche Elecsys pre-eclampsia assay for ruling out pre-eclampsia in patients with uncertain diagnosis.**
REC reference:	**17/LO/0850**
IRAS project ID:	**222667**

Introduction

Pre-eclampsia toxaemia (PET) is a condition that affects pregnant women and is characterised by proteinuria and hypertension during pregnancy from 20 weeks gestation or later. It is associated with an increased morbidity and mortality for both mother and neonate, and is thought to affect about 3-5% of pregnancies (Mol *et al.* 2016). The symptoms of onset of PET can be non-specific, women may present with headaches, visual disturbances, epigastric pain or oedema, so the condition can be difficult to diagnose. In addition, hypertension is a condition that affects approximately 10% of pregnancies (Rudra *et al.*2011), so the number of women presenting with symptoms that suggest PET should be part of the differential diagnosis is significant. It is thought that PET and eclampsia account for an average of 7 deaths a year (McCarthy and Kenny, 2012).

Aims of the Study

The aim of this study was to determine whether the Elecsys Pre-Eclampsia assay would be successful in assessing women who present to the day bed unit and triage in Wishaw General Hospital who have non-specific symptoms of PET, to assist in management of patients in a cost effective manner.

Study Outcomes

The study managed to recruit 24 consenting patients who were followed through for the outcome of their pregnancy to correlate clinical outcome with the result collected when they first presented.

Method Verification

The method verification went well for the assays, both of which performed well for linearity and imprecision studies. The limit of blank and limit of detection levels were higher than those stated by the manufacturer, though low enough to remain clinically insignificant. Trueness of PlGF was assessed and the assay performed well, however with no external quality assessment scheme available for sflt-1 at the time this was not investigated in this assay. An investigation into haemolysis, lipaemia and icteric indices indicated that the levels stated by the manufacturer were consistent with performance.

Participant Outcomes

Of the 24 patients, 15 patients did not develop PET (Figure 1). Of these, 10 had sflt-1/PlGF ratios of <38, indicating negative for risk of PET. Real-time testing of these patients would have been interpreted as a low risk group that should be followed up in the community unless newly presenting symptoms should arise. The other 5 patients had ratios >5 and testing would have been interpreted as closer monitoring required.

Of the 24 patients, the other 9 developed PET, and all of these patients had sflt-1/PlGF ratios greater than 38. Real time testing of these patients would have suggested closer monitoring required.

PlGF levels were significantly lower at presentation with symptoms suggestive of PET in the participants who developed pre-eclampsia (n = 9) compared with those who did not develop

pre-eclampsia (n = 15; $p < 0.01$) and sflt-1 levels were significantly higher at presentation with symptoms suggestive of PET in the participants who developed pre-eclampsia compared with those who did not develop pre-eclampsia ($p < 0.001$). The participants who did not develop PET had a significantly lower ratio than participants who developed PET ($p < 0.05$).

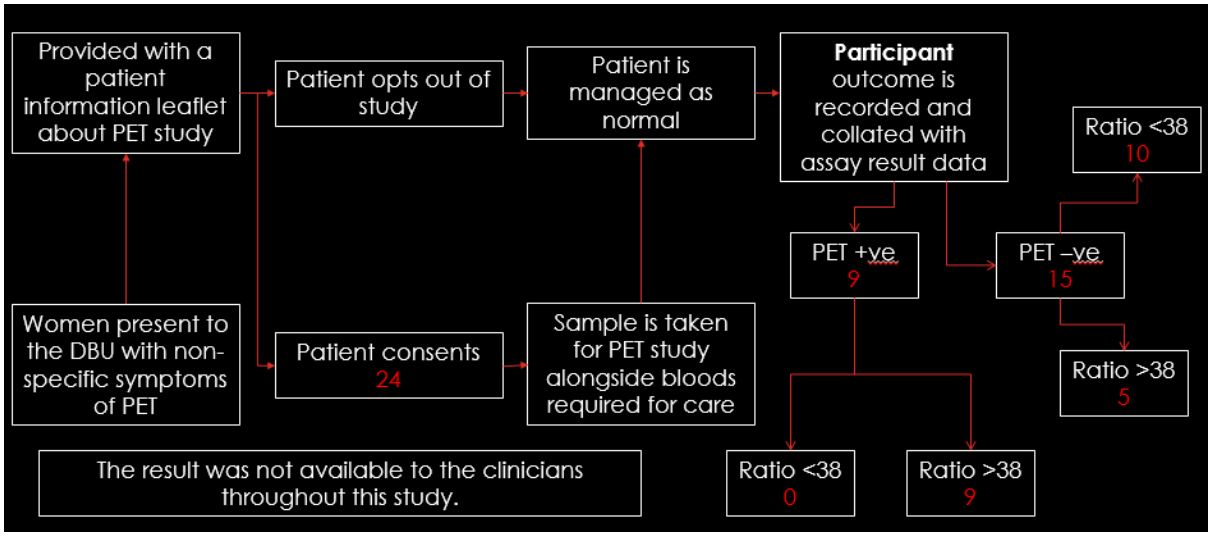

Figure 1: Illustrates the study design from presentation to outcome. The number of participants is denoted in red.

Diagnostic accuracy

The diagnostic accuracy of the sflt-1/PlGF ratio (Figure 2), as indicated by the data collected in this study, gave a sensitivity of 100%, specificity of 73%, negative predictive value of 100% and a positive predictive value of 69% with a proposed cut-off of 38 for diagnostic decision making. The better cut-off as proposed by the data from this study would be 53.4, giving a higher specificity and positive predictive value with the same level of sensitivity and negative predictive value.

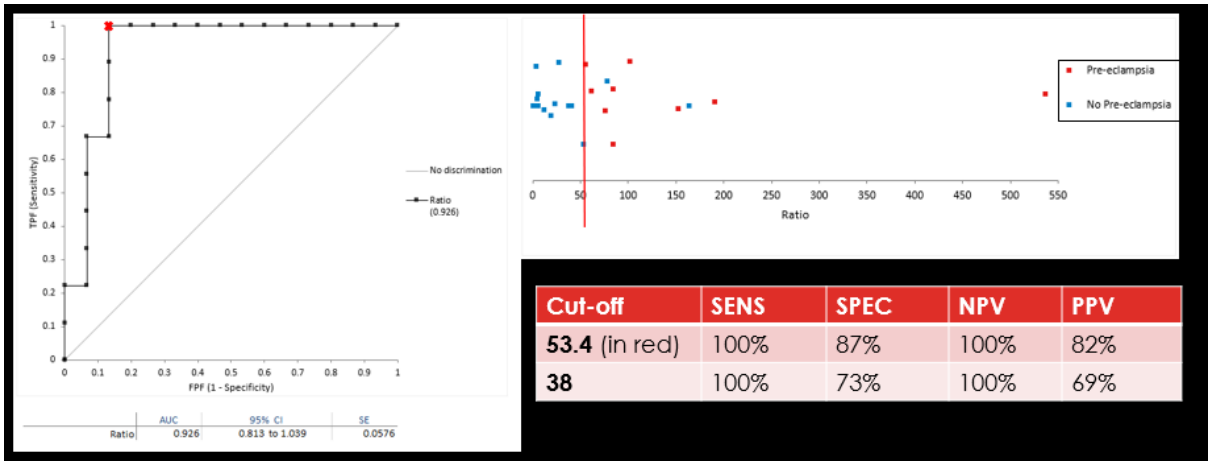

Figure 2: Graphs represent the area under the ROC curve (AUC) of the sflt-1/PlGF ratio (left) and the distribution of participants in this study (top right).Table outlines test accuracy metrics for the best fitting cut-off based on this study data (53.4) and the cut-off proposed by Roche (38).

The diagnostic accuracy of the sflt-1/PlGF ratio proved better than the use of the sflt-1 or PlGF assays on their own (AUC of 87% and 85% respectively compared to 93% for the ratio).

	NHSL study best cut-off	PROGNOSIS	NHSL study Ratio	NHSL study PlGF
Cut-off	<53.4	<38	<38.6	>228.3
Sensitivity	100%	80%	100%	100%
Specificity	87%	78.3%	73%	47%
NPV	100%	99.3%	100%	100%
PPV	82%	-	69%	53%
AUC	0.926 (95% CI 0.813 – 1.039)	0.861 (95% CI 0.798 – 0.924)	-	0.852 (95% CI 0.691 – 1.013)

Figure 3: Table outlines test accuracy metrics for this study compared to those in the PROGNOSIS study, and looks at the diagnostic accuracy of each individual assay (sflt-1 and PLGF) alone for comparison to combined assays.

Repeat Presentations

Only two participants within the study presented on two occasions throughout the duration of the study. One of these participants didn't develop PET, and the ratio remained consistent over the 9 week gap between these presentations. The other participant did develop PET, and the ratio increased significantly between presentations across 6 days. This information assists in illustrating that the ratio can change quickly, and that a negative result at any stage during pregnancy will not be appropriate for ruling out PET altogether.

With time, it appeared PlGF increased marginally and sflt-1 decreased marginally across nine weeks of pregnancy, in the patient who did not develop PET. The opposite was true, where PlGF decreased marginally and sflt-1 increased marginally across 6 days in the patient who did develop PET.

	Result on 1st visit			Result on 2nd visit			Difference in results			Time from 1st to 2nd visit
	PlGF	Sflt-1	Ratio	PlGF	Sflt-1	Ratio	PlGF	Sflt-1	Ratio	-
Pt 1 – PET neg	457.2	2254	**4.9**	504.5	2048	**4.1**	47.3	-206	**-0.8**	9 weeks
Pt 2 – PET pos	87.25	4890	**56**	70	5960	**85**	-17.25	1070	**29**	6 days

Figure 4: Table outlines the results produced for two patients who presented twice throughout the study.

Additional Studies in Lanarkshire

Negative Control Samples

Samples from 17 randomly selected patients were collected and anonymised that met the following criteria:

- Under monitoring during their pregnancy due to thyroid disease and were otherwise well
- At >20 weeks gestational age

These samples were analysed for sflt-1/PlGF ratio as negative control samples for the study. All 17 samples tested with sflt-1/PlGF ratios below the cut-off (38) that would suggest patients are low risk and unlikely to develop PET within the next 7 days. All but two of these samples tested with ratios below 10.

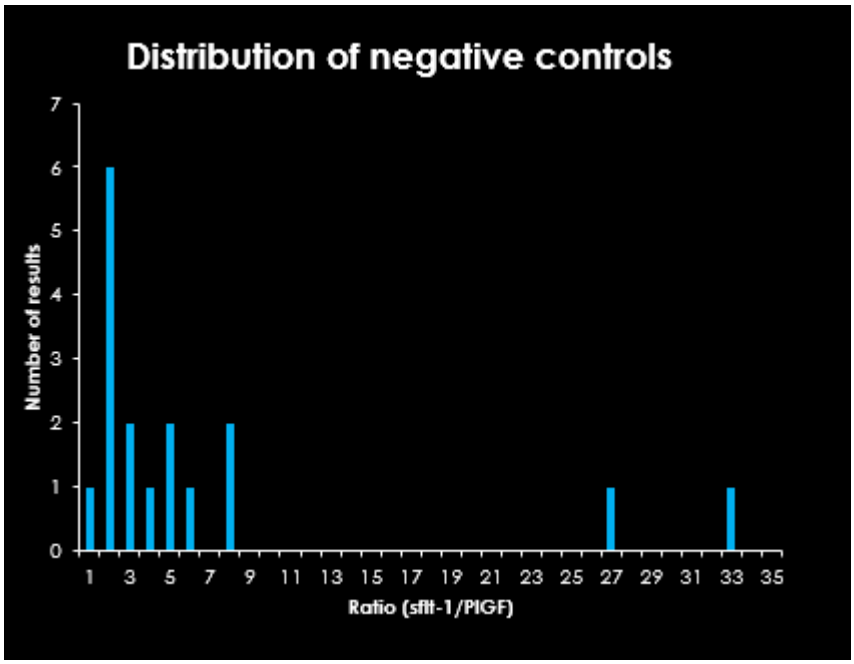

Figure 6: Figure illustrates the distribution of the ratio results among the negative control samples.

Audit

An audit was conducted that looked at the laboratory requests coming from the maternity day bed unit and triage at Wishaw General Hospital between the 1st of October and 31st December 2017. The following information was derived from this audit:

- 42% of all requests coming from the day bed unit or triage within this time frame were for BP profile or ?PET.
- 56.5% of the patients associated with these requests had a length of stay between 2 and 24 hours for their visit.
- 56% of presentations were of women at 35 weeks gestation or later

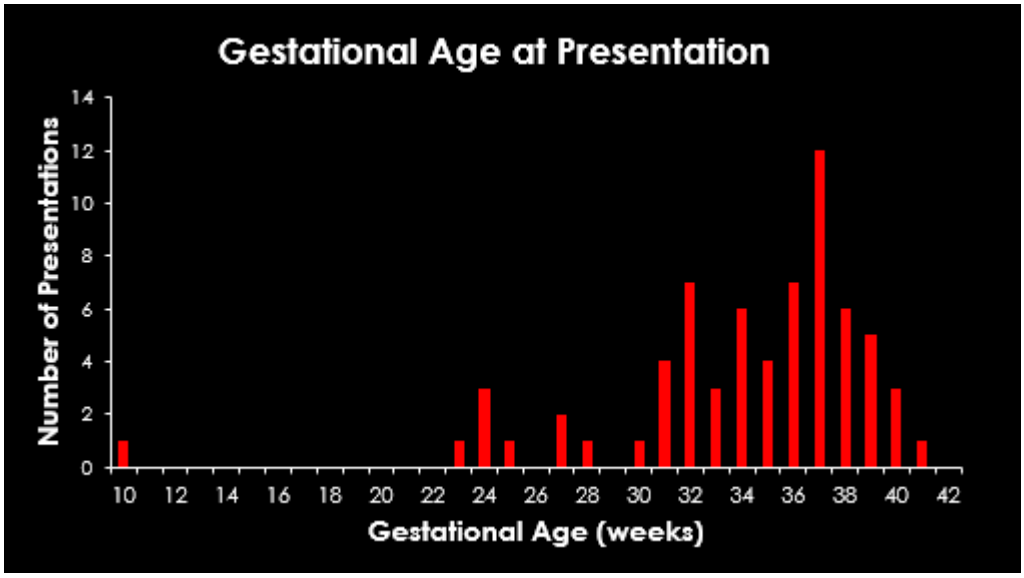

Figure 5: Graph illustrates the distribution of the gestational age of patients presenting with symptoms suggestive of PET to the day bed unit or Triage in Lanarkshire within a 3 month period.

Discussion

The National Institute for Health and Care Excellence (NICE) released a diagnostics Guidance on PlGF-based testing in 2016 that indicated that the use of the assay is cost effective on patients presenting between 20 weeks gestation and 34 weeks and 6 days gestation. The protocols advised for use of the assay that are currently being implemented elsewhere in the UK indicate that testing is not recommended in patients at 35 weeks gestation or later as at this stage closer monitoring is required regardless of any assay outcome, and therefore loses cost-effectiveness.

It also states that at this later stage of pregnancy, the decision making involved around management of PET is less severe and it argues that the assay will assist in difficult decision making more at earlier stages of pregnancy where delivery is required for the welfare of the mother, but continued pregnancy is required for welfare of the foetus.

Some studies have suggested that the assay sensitivity falls at later stage pregnancy as the parameters measured will change in the lead up to labour naturally, but more studies into these markers throughout pregnancy may assist in strengthening these claims.

Conclusion

It is clear that there is need for diagnostic assistance in management of patients developing symptoms suggestive of PET, and that the sflt-1/PlGF ratio is an encouraging tool in this area. The studies and information available on the use of this test are building a good case for its use, and clinicians are certainly eager for such a test and the assistance it may provide. The following can be concluded from this study:

- The diagnostic accuracy stated in the literature is applicable to the population of participants in this study.
- This study supports that the sflt-1/PlGF ratio has higher diagnostic accuracy than PlGF testing alone.

There were several challenges to this study, the main challenge being recruiting participants. As the study aimed to take samples at the time of presentation in order to ensure applicable outcomes, the patients had only a brief opportunity to read the participant information leaflet and decide on giving consent. Midwives are very busy, and understandably it was an additional undertaking to approach patients who met the criteria. In the end the total recruitment of the study came to only 24 participants. A larger population would provide stronger evidence for the study outcomes.

Future Work

Further questions arose in the undertaking of this study that if addressed complete appreciation of the impact of such a test would have on management of these patients:

- Can this assay be cost effective for NHSL (a smaller population than that of other studies)?
- Could it end up being misused? Clinicians will likely be grateful for the assistance this assay can provide, and may be tempted to use the assay where patients do not meet the criteria – this would render its implementation less cost-effective, but more useful in assisting management of patients should it be used properly.
- At present we are conducting an audit of requests from maternity triage for PET bloods to establish:
    - the population presenting in Lanarkshire year round
    - whether the test could be cost effective regardless of variations in this throughout the year

References

Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ (2016) Pre-eclampsia *Lancet* 387; pp999-1011

McCarthy FP, Kenny LC (2012) Hypertension in Pregnancy *Obstetrics, Gynaecology and Reproductive Medicine* 22:6 pp141-147

National Institute for Health and Care Excellence (NICE) May (2016) 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*

Rudra P, Basak S, Patil D, Latoo MY (2011) Recent Advances in Management of Pre-Eclampsia *British Journal of Medical Practitioners* 4 (3)