

## Diagnostic utility of angiogenic biomarkers in pregnant women with suspected preeclampsia: A health economics review



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### ABSTRACT

Preeclampsia is a major cause of morbidity and mortality, can be difficult to diagnose, and is associated with significant healthcare costs. The prediction, diagnosis and prognosis of preeclampsia have depended on repeated assessment of women with known risk factors, including intensive monitoring and hospitalization. Many of these women may never go on to develop preeclampsia. Recent developments in the pathogenesis of preeclampsia have shown that maternal serum biomarkers can be used to predict preeclampsia. When the ratio of the anti-angiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) and the pro-angiogenic placental growth factor from the placenta is altered, preeclampsia becomes more likely, providing a diagnostic measurement for risk. The use of angiogenic biomarkers in addition to standard clinical tests can more accurately predict which women are at risk of developing preeclampsia and which are at low or moderate risk, which is likely to streamline the management of pregnant women and target resources in a more efficient way. The studies reviewed here all demonstrate cost savings from use of angiogenic biomarker tests as an addition to standard care.

### 1. Introduction

Preeclampsia is a hypertensive disorder of pregnancy affecting around 3–5% of pregnancies, and is a major cause of maternal and infant morbidity and mortality [1,2]. It can lead to adverse outcomes, and possibly death for the infant or mother [3], and is characterized by the development of hypertension and proteinuria after 20 weeks of pregnancy [4].

Women who develop preeclampsia require intensified management, including hospitalization, and expedited delivery [5]. Screening women in the first half of pregnancy can identify those at risk of preeclampsia and target them for management [6]. Screening includes assessment of clinical risk factors, and nearly all women attend routine clinic visits during their pregnancies and are monitored for preeclampsia by measurement of blood pressure and urinalysis; therefore, women who are at low or moderate risk of developing preeclampsia use up valuable antenatal resources unnecessarily [6].

Until recently, there were no reliable tests to detect preeclampsia before clinical symptoms developed, and diagnosis depended on repeated assessment of women with known risk factors. This led to some women with high-risk factors being hospitalized and intensively monitored but who never developed preeclampsia (false positives), and some women with low or moderate risk factors who were deemed at low risk but who then went on to develop preeclampsia (false negatives) [7].

Management of preeclampsia is associated with significant healthcare costs [8,9]. Direct costs include tests, drugs, hospitalization and delivery, while parental sick leave from work also has an indirect impact on cost.

However, maternal serum biomarkers can be used to predict preeclampsia [5]. Preeclampsia becomes more likely when the anti-angiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) in the maternal circulation increases, and the pro-angiogenic placental growth factor (PlGF) is decreased [10,11]. The sFlt-1/PlGF ratio provides support for triage of pregnant women with suspected preeclampsia.

The supplementary use of angiogenic biomarkers in addition to standard care can more accurately predict which women are at low or moderate risk of developing preeclampsia as well as those at greater risk [12]. This has the potential to reduce both direct and indirect costs; by identifying those women who are false positives, costs are saved from not needing hospitalization or intensive management (both antenatal management, and potential early delivery).

The aim of this article is to summarize the potential uses of angiogenic biomarker testing for the prediction, diagnosis and prognosis of preeclampsia and adverse pregnancy outcomes and to review published studies on the health economics of angiogenic biomarker testing.

### 2. Article selection

A PubMed search was performed using the search string (((pre-

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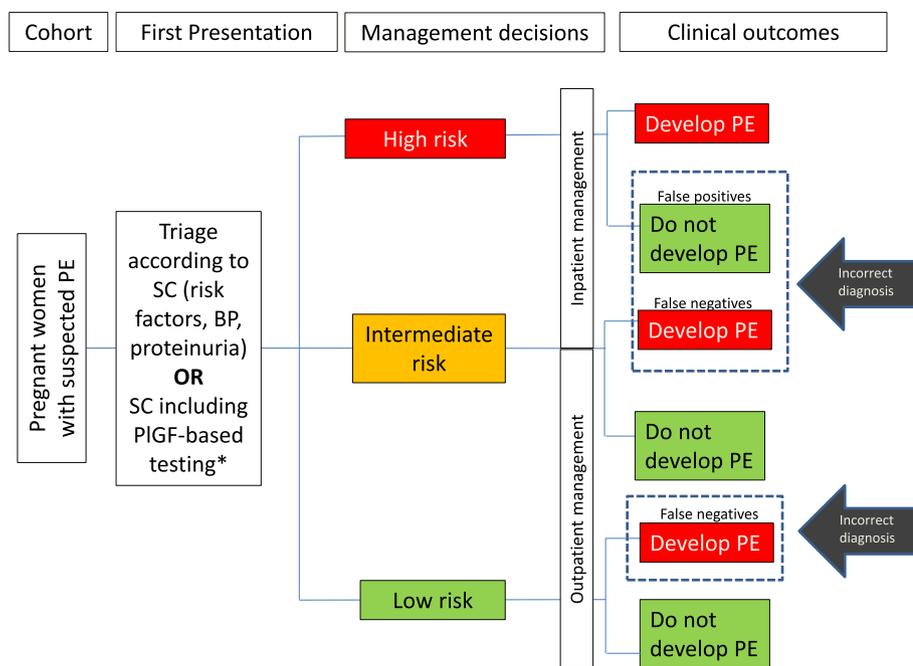
E-mail address: [drschlembach@gmx.net](mailto:drschlembach@gmx.net) (D. Schlembach).

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**Fig. 1.** A generalized decision model for women (adapted from reference [7]) \* Risk stratification and management levels are interpreted differently in different countries and could result in outpatient management or hospitalization. Cut-off levels: PlGF: Test positive, highly abnormal < 12 pg/mL; Test positive, abnormal: 12–100 pg/mL; Normal: > 100 pg/mL. sFlt-1/PlGF ratio, for gestation of 24 weeks to 36 weeks + 6 days: Rule in preeclampsia, > 38, rule out, < 38. BP, blood pressure; PE, preeclampsia; PlGF, placental growth factor; SC, standard care; sFlt-1, soluble fms-like tyrosine kinase-1.

eclampsia[Title] OR preeclampsia[Title] AND budget[Title/Abstract] OR economic[MeSH Terms] AND PlGF[Title/Abstract]. This retrieved nine articles, of which two were excluded (one was a review of existing analyses and one was an interim report). The authors were also aware of one other study and the National Institute for Health and Care Excellence (NICE) guidance, both of which were included in this paper.

**2.1. Angiogenic biomarker testing for the prediction, diagnosis and prognosis of preeclampsia**

Angiogenic biomarker testing can be used at the first patient encounter to predict and diagnose preeclampsia. The Elecsys® sFlt-1/PlGF immunoassay [Roche Diagnostics GmbH, Mannheim, Germany] is the first automated test for preeclampsia [13,14] and allows stratification by sFlt-1/PlGF ratio. A cut-off value for the short-term prediction of preeclampsia in women between 24 weeks 0 days and 36 weeks 6 days of pregnancy was validated [12]. These angiogenic biomarkers can improve current clinical management strategies by concomitantly identifying those at high risk of preeclampsia while also reducing intensity of care in those at much lower risk of disease [15,16].

**2.2. Overview of methods used to assess the health economic impact of angiogenic biomarker-based testing**

Both cost-effectiveness and budget impact models have been considered in this review. A budget impact analysis estimates the financial consequences of adopting a new intervention, and is usually performed in addition to a cost-effectiveness analysis which evaluates whether an intervention provides value (defined as cost in relation to health outcome) compared with an existing intervention.

Decision analytic models have been employed in several analyses to assess the impact of introducing angiogenic biomarker testing compared with standard current clinical practice. When constructing model structures, studies have considered the impact of direct costs associated with diagnosis and management of women who have suspected preeclampsia through to delivery, such as the cost of the angiogenic biomarker test, other routine testing in the clinic, hospitalization, outpatient appointments, medications and preventing and/or treating complications.

The treatment pathway for women with suspected preeclampsia can be either hospitalization for those at high risk, or management in the outpatient setting for those at lower risk. This has implications for resource use. A generalized pathway for patient management is shown in Fig. 1.

Economic modeling uses patient-level data from various sources, including clinical studies such as the PROGNOSIS trial [12]. Some models included options for re-tests if the initial test was negative (sFlt-1/PlGF ratio ≤ 38), and other variables were assessed in sensitivity and scenario analyses.

Routine clinical practice, or standard care varies among countries. In general, standard care includes assessment of clinical biochemistry (including elevated transaminases and low platelets for the mother). The fetus may be assessed by clinical examination, cardiotocography or ultrasound.

In all the analyses, women were categorized into groups according to their test results:

- True positive
- False positive
- True negative
- False negative

The budget impact of adding the angiogenic biomarker ratio test was analyzed for these different scenarios.

**2.3. Summary of included studies**

Nine publications are included in this review [7,17–24]: three looked at the cost-effectiveness of angiogenic biomarker testing and six were a Budget Impact Analysis, performed to estimate the financial consequences of adopting angiogenic biomarker testing as a new intervention. The publications analyzed the effect of including the test in the management of pregnant women in various countries including the UK (four analyses), Germany (two analyses), USA, Italy and Brazil.

In the studies, women were classified for the risk of developing preeclampsia according to their PlGF levels (for example very low [ $< 12$  pg/mL], low [12–100 pg/mL] or normal [ $> 100$  pg/mL] [21], or on their sFlt-1/PlGF ratio results (for example,  $\leq 38$  low,  $> 38 < 85$  intermediate,  $\geq 85$  high [24]). Assigning the women to risk categories

**Table 1**  
Characteristics of the studies reviewed.

Reference	Country	Type of study and setting	Cohort size and gestational weeks	Intended use assessed	Comparator	Patient outcomes	Angiogenic biomarker assessed and cut-offs used
Duckworth et al [21]	UK	Budget Impact Analysis; impact on healthcare budgets	132; < 35 weeks	Clinical decision making and place and frequency of monitoring	Current treatment algorithm and NICE Hypertension in Pregnancy Guideline [29]	- Number of women tested for preeclampsia - Number of women in each PIGF category - Number with eventual diagnosis in each category - Number of women with mild/moderate/severe hypertension in each category	PIGF: < 12 pg/mL ≥ 12 < 100 pg/mL ≥ 100 pg/mL
Figueira et al [17]	Brazil	Budget Impact Analysis; impact in a public and private healthcare practice	1000	Accuracy of diagnosis in predicting preeclampsia	Clinical decisions based on current diagnostic practice	- Number of women hospitalized compared with number of women managed as outpatients	sFlt-1/PlGF ratio: < 38 38–85 > 85
Frusca et al [7]	Italy	Budget Impact Analysis; impact on healthcare budgets	49,455; 24 + 0 to 36 + 6 weeks	Accuracy of diagnosis and targeted management	Baseline examination to rule out preeclampsia (then managed in outpatient setting)	- Low, medium, or high risk of developing preeclampsia	sFlt-1/PlGF ratio: ≤ 38 > 38–85 > 85
Schnettler et al [22]	USA	Cost-effectiveness analysis with a budget impact model; impact on healthcare budgets	149; < 34 weeks	Stratification of risk and appropriate management	Standard care: monitoring of blood pressure, proteinuria, elevated transaminases, platelet count Care as recommended by NICE guidelines [29]	- Number of women in each test category	sFlt-1/PlGF ratio: < 85 ≥ 85
Vatish et al [23]	UK	Budget Impact Analysis; impact on healthcare budgets	1050; 24 + 0 to 36 + 6 weeks	Incremental value of information using the new test	Care as recommended by NICE guidelines [29]	- Cost per patient per episode of care	sFlt-1/PlGF ratio: < 38 38–85 > 85
Schlembach et al [24]	Germany	Cost-effectiveness analysis; impact on healthcare budgets	204; 24 + 0 to 36 + 6 weeks	Incremental value of information using the new test	Management according to the German Society of Gynecology and Obstetrics guideline [26]	- Total cost per patient	sFlt-1/PlGF ratio: ≤ 38; > 38 – < 85 (for gestational weeks 20 + 0–33 + 6) or > 38 – < 110 (gestational week 34 onwards) ≥ 85 (gestational weeks 20 + 0–33 + 6) or ≥ 110 (gestational week 34 onwards)
NICE [20]	UK	Cost-effectiveness analysis; impact on healthcare budgets	24 + 0 to 36 + 6 weeks	Various (12 publications of 4 studies)	Standard clinical assessment using blood pressure, proteinuria, clinical symptoms, fetal growth restriction [30]	- Baseline QALYs from vaginal delivery to 6 months post partum (decrement for cesarean or induced delivery)	Triage: PIGF test: < 12 pg/mL ≥ 12 < 100 pg/mL ≥ 100 pg/mL Elecsys immunoassay: sFlt-1/PlGF ratio: 20 to 33 + 6 weeks, cut-off to rule out = 33, cut-off to rule in: 85 34 weeks to delivery, cut-off to rule out = 33. Cut-off to rule in: 110. Short-term prediction rule out, < 38 DELPHIA Xpress: PIGF 184 pg/mL cut-off in third trimester BRAHMS: sFlt-1/PlGF ratio: Limits to be determined by individual labs

(continued on next page)

Table 1 (continued)

Reference	Country	Type of study and setting	Cohort size and gestational weeks	Intended use assessed	Comparator	Patient outcomes	Angiogenic biomarker assessed and cut-offs used
Hadker et al [18]	UK	Budget Impact Analysis; impact on healthcare budgets	1000	Economic evaluation of the new test	Standard practice: monitoring of blood pressure, proteinuria, serum uric acid, uterine artery Doppler ultrasound	- Patients categorized as no preeclampsia, mild preeclampsia, severe preeclampsia, eclampsia or death	sFlt-1/PlGF ratio: < 85 ≥ 85
Hadker et al [19]	Germany	Budget Impact Analysis; impact on healthcare budgets	1000	Economic evaluation of the new test	Standard practice: monitoring of blood pressure, proteinuria, elevated transaminases, platelet count, serum uric acid, uterine artery Doppler ultrasound	- Patients categorized as no preeclampsia, mild preeclampsia, severe preeclampsia, eclampsia or death	sFlt-1/PlGF ratio: < 85 ≥ 85

NICE, National Institute for Health and Care Excellence; PlGF, placental growth factor; QALYs, quality-adjusted life years; sFlt-1, soluble fms-like tyrosine kinase-1

for preeclampsia and hospitalization allowed estimations of the disposition of women according to risk ratio. For example, using the ratio data, the risk of preeclampsia was ruled out at values of 38 and below ( $\leq 38$ ), as derived from the PROGNOSIS study [12], and it was assumed that these women would not require hospitalization for preeclampsia.

The characteristics of each of the studies are shown in Table 1, with a breakdown of the costs considered in each model in Table 2.

Duckworth et al [21] modeled the resource implications of PlGF alone for angiogenic biomarker testing in women with suspected preeclampsia prior to 35 weeks' gestation compared with standard care. The study took data on resource use from 132 women with suspected preeclampsia in two UK maternity units and used it to assess the budget impact of managing women with suspected preeclampsia for 2 weeks from the date of angiogenic biomarker testing. They found that PlGF testing saved £635 per patient compared with current practice.

A Brazilian analysis by Figueira et al [17] reviewed the effect of introducing the sFlt-1/PlGF ratio test in Brazil, in both a private and a public hospital setting, and measuring its effect in women at 24 weeks to 36 weeks + 6 days gestation. Cost savings were made in both settings (R\$185.06 and R\$635.84 per patient in the public and private setting respectively), mainly through improved diagnostic accuracy and reductions in unnecessary hospitalizations.

Frusca et al [7] estimated the economic impact of introducing the sFlt-1/PlGF ratio test in addition to standard care in the Italian National Health Service. Again using patient-level data derived from the PROGNOSIS study (women at 24 weeks to 36 weeks + 6 days gestation) [12], the authors found that introducing the new test saved €671 per patient, through improved diagnostic accuracy and reduction in hospitalizations.

Pregnant women (< 34 weeks' gestation) in an obstetric unit in the US who presented for evaluation of preeclampsia were studied by Schnettler et al [22]. A cost analysis with a budget impact model was developed to compare the standard approach with measurement of the sFlt-1/PlGF ratio test. The study found that the angiogenic biomarker test improved specificity compared with the standard approach, resulting in savings of \$540 to \$1215 per patient in direct hospital costs and resources, particularly for those women who could be categorized as 'true negatives'.

Set in the UK, Vatish et al [23] assessed the impact of introducing the sFlt-1/PlGF ratio test into clinical practice versus current diagnostic procedures alone from a payer's perspective. Costs were estimated for women from 24 to 36 + 6 weeks' gestation and the authors concluded that testing would be expected to give cost savings of £344 per patient, mainly due to improved diagnostic accuracy and a consequent reduction in unnecessary hospitalization.

Schlembach et al [24] adapted the model used in the UK by Vatish et al [23] for the German payer, to compare cost of diagnosis and management of women with clinical decisions based on standard diagnostic procedures alone, or using the sFlt-1/PlGF ratio test in addition to standard diagnostic procedures. Using patient-level data derived from the PROGNOSIS study (women at 24 weeks to 36 weeks + 6 days gestation) [12], they found that using the test reduced the proportion of women hospitalized and led to a reduction of €361 in the cost per patient.

In its evidence-based recommendations on angiogenic biomarker-based testing, NICE analyzed four angiogenic biomarker tests (the Triage® PlGF test [Alere, Inc., San Diego, CA, USA], the DELFIA® Xpress PlGF 1–2–3 test [PerkinElmer, Wallac Oy, Turku, Finland], the Elecsys® sFlt-1/PlGF ratio test [Roche Diagnostics GmbH, Mannheim, Germany] and the BRAHMS® sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio [Thermo Fisher Scientific GmbH, Hennigsdorf, Germany]) [20]. Diagnostic accuracy and cost-effectiveness were assessed for each of the tests when used with standard care, compared with standard care alone, using an economic model with four components (risk stratification, management, maternal outcomes, fetal and neonatal outcomes). The DELFIA and BRAHMS tests could not be

**Table 2**  
Costs included in each model.

Study	Country	Scenario analyses undertaken	Cost variables in the analysis	Year costs based on
Duckworth et al [21]	UK	<ul style="list-style-type: none"> <li>• Different estimates of the point prevalence of preeclampsia</li> <li>• Best and worst case resource use</li> <li>• Test price at £30 and £70</li> </ul>	Healthcare resource use was based on the current treatment algorithm and the NICE Hypertension in Pregnancy Guideline [29], and assumed that women present at 31 weeks' gestation and have 2 weeks of costs. Routine diagnostic tests and medication were excluded.	2013/2014 financial year
Figueira et al [17]	Brazil	<ul style="list-style-type: none"> <li>• Option for a re-test 2 weeks after the first</li> <li>• Hospitalization rate</li> </ul>	Included: <ul style="list-style-type: none"> <li>- Out-of-pocket costs of the ratio test</li> <li>- Cost of hospitalization, outpatient appointments, antihypertensive medication, regular testing, and the cost of preventing and treating complications</li> <li>- Cost of corticosteroids for all women with a ratio of &gt; 38</li> <li>- Option for a re-test 2 weeks after original negative test excluded</li> <li>- Blood pressure monitoring and other basic procedures</li> </ul>	NS
Frusca et al [7]	Italy	<ul style="list-style-type: none"> <li>• Input variables increased and decreased by 20%</li> </ul>	Included: <ul style="list-style-type: none"> <li>- All direct healthcare costs</li> <li>- Emergency admission costs</li> <li>- NICU costs</li> </ul>	National tariffs in October 2012
Schnettler et al [22]	USA	<ul style="list-style-type: none"> <li>• Cut-off values</li> <li>• Costs varied from 50 to 200%</li> <li>• Ideal and worse case scenarios</li> </ul>	Costs were restricted to the initial patient encounter. Included: <ul style="list-style-type: none"> <li>- Triage evaluations, maternal and fetal radiologic studies, tests of fetal wellbeing, laboratory tests, admissions, consultations, deliveries, and miscellaneous resources (such as intravenous tubing)</li> <li>- The cost of the test was fixed at \$101.14</li> </ul>	2012
Vatish et al [23]	UK	<ul style="list-style-type: none"> <li>• Inpatient length of stay</li> <li>• Proportion of women admitted to hospital</li> <li>• No re-test</li> </ul>	Included: <ul style="list-style-type: none"> <li>- Cost of the ratio test (£65)</li> <li>- Treatment costs associated with hospitalization, outpatient appointments, antihypertensive medication, regular testing, and the cost of preventing and treating complications</li> <li>- Option for a re-test 2 weeks after original negative test</li> <li>- Emergency admission costs</li> <li>- NICU costs</li> </ul>	NS
Schlembach et al [24]	Germany	<ul style="list-style-type: none"> <li>• Option for a re-test 2 weeks after the first</li> <li>• Inpatient length of stay</li> <li>• Hospitalization costs</li> <li>• Proportion of women admitted to hospital</li> </ul>	Included: <ul style="list-style-type: none"> <li>- Ratio test</li> <li>- Treatment costs</li> <li>- Hospitalizations</li> <li>- Outpatient appointments</li> <li>- Anti-hypertensive medication and testing</li> <li>- Costs of preventing and treating complications</li> <li>- Quarterly fee paid to all outpatient doctors for each pregnant woman</li> </ul>	2017
NICE [20]	UK	<ul style="list-style-type: none"> <li>• Scenario analysis to rule out (and not rule in)</li> </ul>	Assumes patient management follows UK guidelines. Included: <ul style="list-style-type: none"> <li>- Test costs taken from company literature</li> <li>- Other costs taken from NHS reference costs, the British National Formulary and the published literature</li> </ul>	NS
Hadker et al [18]	UK	<ul style="list-style-type: none"> <li>• Incidence of preeclampsia</li> <li>• Sensitivity and specificity of current tests</li> <li>• Proportion of patients stratified as high risk</li> <li>• Cost of the test</li> </ul>	Included: <ul style="list-style-type: none"> <li>- Preeclampsia management costs: physician office visits, physical exams, blood pressure checks, blood and urine tests, cardiotocography</li> <li>- Hospitalization and monitoring</li> <li>- Intensive care and delivery or termination</li> <li>- The cost of the test was set at £31.13</li> </ul>	2009
Hadker et al [19]	Germany	<ul style="list-style-type: none"> <li>• Incidence of preeclampsia</li> <li>• Sensitivity and specificity of current tests</li> <li>• Proportion of patients stratified as high risk</li> <li>• Cost of the test</li> </ul>	Costs derived from German public databases. Included: <ul style="list-style-type: none"> <li>- Preeclampsia management costs: physician office visits, physical exams, blood pressure checks, blood and urine tests, cardiotocography, as well as:</li> <li>- Hospitalization and monitoring</li> <li>- Intensive care and delivery or termination</li> <li>- The cost of the test was set at €34.40</li> </ul>	2009

NICE, National Institute of Health and Care Excellence; NS, not stated; NICU, neonatal intensive care unit.

assessed due to the lack of study data. However, there was a reduction in costs per patient when using either the Triage PIGF test (£365 per patient) or the Elecsys sFlt-1/PIGF ratio (£174 per patient) in women of 35–37 weeks' gestation. The cost savings were much greater when these tests were used in women at < 35 weeks' gestation (£2896 and £2488 per patient, respectively).

In a decision analytical model in which a cohort of 1000 pregnant women receiving UK obstetric care was simulated, Hadker et al [18] assessed the economic impact associated with the improved sensitivity and specificity of using the sFlt-1/PIGF ratio test. The model estimated that the test would be cost saving (£945 per patient) if used at or after 20 weeks' gestation, due to improved classification and subsequent more appropriate management of pregnant women.

Hadker et al [19] used a similar decision analytic model to quantify the economic impact of adding the sFlt-1/PIGF ratio test to current practice at Week 20 of gestation for diagnosing preeclampsia in Germany. This analysis found that the number of both false negative and false positive tests were reduced, increasing diagnostic accuracy and saving €637 per patient.

#### 2.4. The effect of testing on resource utilization and the potential cost-savings from angiogenic biomarker testing

In a systematic review of the literature carried out for a National Health Service (NHS) Health Technology Assessment (PROSPERO) [25], the Triage and Elecsys tests were compared. As part of the

**Table 3**  
Costs savings per patient in each analysis.

Study	Country	Comparator	Cost saving per patient	Range of cost savings per patient from scenario analyses using ratio test
Duckworth et al [21]	UK	Current treatment algorithm and NICE Hypertension in Pregnancy Guideline [29]	£635 (95% CI, -1454, -4)	Savings from £14.63 to £54.91
Figueira et al [17]	Brazil	Clinical decisions based on current diagnostic practice	R\$185.06 (public hospital) R\$635.84 (private hospital)	No re-test after 2 weeks: R\$661.00 (public hospital) R\$1287.26 (private hospital) Increase of the hospitalization rate of women with ratio < 38 from 1.7 to 3.4%: R\$104.71 (public hospital) R\$507.04 (private hospital) Increase of the hospitalization rate in the no-test scenario from 36 to 46%: R\$669.19 (public hospital) R\$1397.02 (private hospital) Input variables increased or decreased by 20%: 5-year per capita savings from €497–773
Frusca et al [7]	Italy	Routine care included: Clinic visit, with measurement of blood count, blood pressure, urine test, creatinine test for kidney function, bilirubin, transaminases, antithrombin, fetal cardiocytography, electrolytes test	€671	Costs varied from 50% to 200%. Cost savings per patient ranged from \$557 to \$2530 Worst case: \$1215 sFlt-1/PIGF ratio cut-off 5 to 200, saved \$841.44 to \$1313.57 per patient Variation cost differences (per patient): - Length of stay 1.6 days: £265 - Admissions increased by 10% only in patients with ratio < 38: cost increased by £56 - Admissions increased by 10%: cost increased by £290 - No re-test: costs reduced by £382 Variations in several parameters of up to 20%: - Introducing a re-test: saving of €257 - Increasing hospitalization costs by 20%: saving of €449 Using test to rule out (and not rule in) preeclampsia: - Increase of £1939 for the Triage test - Increase of £294 for Elecsys
Schnettler et al [22]	USA	Standard care: monitoring of blood pressure, proteinuria, elevated transaminases, platelet count	\$540 (Ideal scenario: \$1215)	Incidence rate reduced by 20%: no change Sensitivity increased by 10%: no change Specificity improved by 10%: decreased to £208 Reduce proportion of high-risk patients to 10%: no change Increase cost of test by 20%: decreased to £928 Increase sensitivity by 10%: no change Increase specificity by 10%: no change Increase % high-risk patients by 5–15%: no change Increase cost of test by 10%: cost savings reduced to €618
Vatish et al [23]	UK	Care as recommended by NICE guidelines [29]	£344	
Schlembach et al [24]	Germany	Management according to the German Society of Gynecology and Obstetrics guideline [26]	€361	
NICE [20]	UK	Standard clinical assessment using blood pressure, proteinuria, clinical symptoms, fetal growth restriction	£365 (Triage PIGF test) £2896 (Triage PIGF < 35 gestational weeks) £2488 (Elecsys, < 35 gestational weeks) £174 (Elecsys, gestational weeks 35–37) £945	
Hadker et al [18]	UK	Standard care	£945	
Hadker et al [19]	Germany	Standard practice	€637	

CI, confidence interval; NICE, National Institute of Health and Care Excellence; PIGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

comparison, an economic analysis was performed. The authors found that there were cost savings associated with both the Triage PIGF test and the Elecsys sFlt-1/PIGF test; in women presenting before 35 weeks' gestation, the savings were £2896 and £2488, respectively. The cost savings were much smaller for women presenting between weeks 35 and 37 (£365 and £174, respectively). Their analysis suggested that these tests could save money if added to routine clinical assessment for preeclampsia.

To build on these data, the studies outlined above have calculated the differences in costs and the savings to be made when using the angiogenic biomarker test in different countries and health systems. The outcomes in terms of cost savings for each of these studies are summarized in Table 3. Cost savings were demonstrated in all the analyses when the angiogenic biomarker test is used compared with standard care alone.

### 3. Discussion

All of the studies reviewed here demonstrated cost savings per patient when the angiogenic biomarkers test was included in the care of pregnant women at risk of developing preeclampsia.

While the studies consistently show similar outcomes, there are many differences between the methodology used. Each study factored in costs, but not all included the same parameters or made the same assumptions (Table 2). For example, most of the studies did not include costs associated with emergency admissions or costs for neonatal intensive care.

As well as costs, there are other, less tangible, outcomes associated with using the angiogenic biomarkers tests, such as quality of life. In the NICE analysis, the committee heard that some women fear a recurrence of preeclampsia after having it in an earlier pregnancy [20]. The test could help with monitoring these patients and reduce anxiety during pregnancy. Long-term implications for child and maternal health, social burdens associated with hospital admission, and the financial impact due to loss of income and additional childcare costs may all impact on overall outcomes, and better management of pregnant women may have an effect on these parameters.

The studies also included sensitivity analyses to examine whether changes in key variables affected the overall results. Variables examined include different point estimates for the incidence of preeclampsia, different costs for the test, best and worst case scenarios for healthcare resource use (including costs such as variations in outpatient care and hospitalization parameters), and using different cut-off points for the test ratio. In each case, the sensitivity analysis showed that the results remain robust to variations in the cost of hospitalization, the cost of the angiogenic biomarkers test, and the cost of routine tests.

In the NICE report, a scenario analysis of the data was performed using the angiogenic biomarker tests to rule out (and not rule in) preeclampsia in patients before 35 weeks' gestation. Under these circumstances, the total cost per patient increased compared with the base case, although the tests remained cost-effective compared with Standard Care (SC).

The angiogenic biomarkers tests used in these economic models have the potential to streamline the stratification of women at risk, thereby improving their management and clinical outcomes. By identifying those women who are less at risk of preeclampsia and managing them in the outpatient scenario, there is a potential saving of costs associated with unnecessary hospitalization. More efficient use of resources will also lead to cost savings, and shorter stays in hospital will reduce indirect costs incurred by pregnant women.

Several bodies have now recommended the use of angiogenic biomarker testing to rule out preeclampsia in women presenting with suspected preeclampsia, including NICE [20] and the German Society of Gynecology and Obstetrics (DGGG) [26]. The most recent European Society of Cardiology (ESC) guidelines for management of cardiovascular disease in pregnancy [27] also suggest using the sFlt-1/PIGF ratio

to rule out preeclampsia in women with suspected disease. The Czech Gynecological and Obstetrical Society guidelines [28] now recommend angiogenic biomarker testing; PIGF is recommended for first trimester screening and sFlt-1/PIGF ratio is recommended for diagnosis in those who have suspected preeclampsia. However, women in which the sFlt-1/PIGF ratio is used to aid in diagnosis are most likely to be those who present with clinical signs and symptoms.

In the future, studies on the use of repeat angiogenic biomarker testing may provide more information about the best use of these tests and further optimize the care of at-risk pregnant women.

### 4. Conclusions

In conclusion, the studies reviewed here all demonstrate that the use of angiogenic biomarker testing as an addition to standard care can help to identify women at risk of developing preeclampsia, leading to improved management and cost savings.

#### Detail of ethics approval

As a health economics study, no ethical approval was required.

#### Declaration of interests

D.S has received grants for Funding of the PreOS – Study by ROCHE, and personal fees from Honoraria for lectures (by ROCHE) outside of the submitted work. M.V. has received personal fees and grants from Roche Diagnostics outside of the submitted work. C.W. and M.H are employees of Roche Diagnostics International Ltd. MH holds stock in F. Hoffmann-La Roche, and is the inventor of a patent of the dynamic of sFlt-1 or endoglin/PIGF ratio as an indicator for imminent preeclampsia and/or HELLP syndrome (PCT/EP2012/072157).

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