Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1706 – Angiogenic and anti-angiogenic markers for identification and management of preeclampsia

Applicant: **Professor REDACTED/Roche Diagnostics Australia Pty Ltd**

Date of MSAC consideration: **23-24 November 2023**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of angiogenic and anti-angiogenic markers for the identification and management of preeclampsia was received from Professor Redacted / Roche Diagnostics Australia Pty Ltd by the Department of Health and Aged Care.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support the public funding of soluble FMS-like tyrosine kinase-1:placental growth factor (sFlt-1:PlGF) ratio testing to determine the risk or severity of preeclampsia (PE). MSAC considered the evidence supported the negative predictive value of ratio testing to rule out a diagnosis of PE in individuals with signs and/or symptoms of PE, however that the incremental change in management and clinical utility resulting from adding a rule-out diagnosis from ratio testing would likely be minimal in practice because the management of a patient with signs and/or symptoms of PE would be unlikely to be relaxed by a rule-out result from ratio testing. MSAC considered the evidence that ratio testing reduced hospitalisations was biased and insufficiently robust, which made the effectiveness, cost-effectiveness and total financial cost highly uncertain. There was also no evidence presented for the effectiveness of ratio testing in patients with no signs nor symptoms of PE but who were otherwise at risk of PE, so the proposed inclusion of these patients introduced considerable uncertainty regarding test uptake, cost and value. There was insufficient evidence for non-inferior safety. In addition, insufficient evidence was presented to support the claim of value of knowing.

Consumer summary

This was an application from a professor and Roche Diagnostics Australia requesting Medicare Benefits Schedule (MBS) listing of testing angiogenic and anti-angiogenic markers for identification and management of preeclampsia.

Preeclampsia is a complication that can happen during pregnancy. It usually includes high blood pressure in the pregnant person, as well as other signs and symptoms. If it is not managed, preeclampsia can cause serious illness and death in the pregnant person and/or

---

the baby. The only cure for preeclampsia is for the baby to be born and the placenta delivered, so it is often necessary for the baby to be born early (preterm).

This application was for a test that measures biochemical markers in the pregnant person's blood, called soluble FMS-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF). The relative amounts of each of these markers can be used to group pregnant people into low risk, moderate risk or high risk of preeclampsia. The sFlt-1 to PlGF ratio was proposed to be tested after 24 weeks into the person's pregnancy, in people who have signs and symptoms suggestive of preeclampsia, are at high risk of preeclampsia or have already been diagnosed with preeclampsia. The test would be used alongside a range of other standard tests that are done to make the diagnosis of preeclampsia.

MSAC found that the clinical data in the application were overall low quality and uncertain, although the evidence did show that ratio testing can rule out preeclampsia. The applicant claimed that ratio testing will reduce the number of people having to go to hospital because of preeclampsia, but the evidence for this was very variable (some studies showed less people going to hospital after the test, but other studies showed more). Importantly, people who have signs and symptoms of preeclampsia are already closely monitored by healthcare providers, so MSAC considered a rule-out result from ratio testing would be unlikely to relax how closely they are monitored, and so it was unlikely ratio testing would change how these patients are managed in practice. There were no data about the safety of the test or what happens to a person if the test gives the wrong result.

The value for money and financial cost of ratio testing also relied on the assumption that people would be hospitalised less often with ratio testing, but because MSAC had found the evidence of reduced hospitalisation to be unconvincing, there was not enough evidence that this testing would be good value for money or come at an acceptable financial cost.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC did not support MBS listing of angiogenic and anti-angiogenic markers for identification and management of preeclampsia. This was because it was not clear that ratio testing would change management leading to better health outcomes or be good value for money.

3.   Summary of consideration and rationale for MSAC's advice

MSAC noted that this application was for Medicare Benefits Schedule (MBS) listing of angiogenic and anti-angiogenic markers for identification and management of preeclampsia (PE). MSAC considered that PE is a serious condition and is a significant cause of maternal and perinatal mortality and morbidity, and that appropriate treatment may reduce preterm births, PE complications, and improve health outcomes.

MSAC noted the proposed test examines the ratio of soluble FMS-like tyrosine kinase 1 (sFlt-1):placental growth factor (PlGF) at 24+ weeks gestational age. The sFlt-1:PlGF ratio increases several weeks before the onset of otherwise clinically diagnostic signs and symptoms of PE. Based on the sFlt-1:PlGF ratio, the risk of PE was categorised as low risk (ratio <38) (proposed to rule out PE in the near future and the pregnant individual can be managed as normal), or moderate risk (ratio 38–85) (proposed to require increased monitoring, including repeat testing every 1–2 weeks), or high risk (ratio >85) (proposed to mean imminent delivery is likely). MSAC queried whether the cut-points were based on a receiver-operating curve that had not been provided, whether they were pre-specified or post hoc, and overall considered the evidentiary basis for the chosen cut-points had not been made sufficiently clear.

MSAC noted consultation feedback was supportive of this application.

MSAC noted the two populations proposed for ratio testing. Population 1 was patients with signs or symptoms of suggestive of PE (such as high blood pressure) and individuals at increased risk of PE due to other factors (but currently asymptomatic) in whom ratio testing was proposed to allow an earlier diagnosis of PE, and population 2 was patients who have already been diagnosed with PE in whom ratio testing was proposed to help categorise the severity of PE. MSAC noted study results were not disaggregated for populations 1 and 2, and therefore ESC had proposed a consolidated item descriptor. MSAC considered the definition of the asymptomatic "increased risk" population was ambiguous, and the clinical studies supporting the application did not include people asymptomatic for PE (which would also include those who may be receiving aspirin prophylaxis commenced before 16 weeks gestation). MSAC noted UK National Institute for Health and Care Excellence (NICE) guidelines recommend ratio testing only for patients >24 weeks gestation and with either symptoms of PE or chronic hypertension, and considered there may be potential merit in including patients with chronic hypertension, but that there was no evidence of merit in ratio testing for other patients asymptomatic for PE. MSAC considered that if it had supported the PE risk assessment proposed in concurrent application 1705, this would have further enlarged the cohort of asymptomatic 'increased risk' patients, rather than decreased it as the applicant proposed in its pre-MSAC response, given the approximate 10% incidence of breakthrough PE among those taking prophylactic aspirin. Overall, MSAC agreed with ESC that the inclusion of patients without signs or symptoms of PE was not justified and introduced considerable uncertainty regarding test uptake, cost and value.

MSAC noted that PE is not a single condition and there are several diagnostic criteria. MSAC noted the comparator for population 1 was no ratio-based diagnostic testing, with or without current standard tests for diagnosing PE (urine protein:creatinine ratio test, proteinuria reagent strip test, full blood count, and others). For population 2, the comparator was no prognostic ratio testing plus standard medical management for PE - that is, ratio testing was proposed to be used in addition to the range of other existing tests to diagnose and monitor PE.

MSAC noted no direct from test to health outcomes evidence was identified, and a linked evidence approach was used. MSAC agreed with ESC that overall the clinical data were sparse and of low quality, observational and at moderate to high risk of bias.

MSAC considered that overall there was considerable uncertainty in the clinical evidence that was presented, because some studies included pregnant patients from 20+ weeks' gestation, most studies included only symptomatic patients, the generalisability to the Australian population was uncertain, and the studies were at moderate risk of bias. However MSAC noted the evidence showed the negative predictive value (NPV) of a ratio of <38 to rule out PE was 98.6% to 100%, and considered the evidence relating to test accuracy did show the claim of superior test accuracy to rule out a diagnosis of PE was reasonable. However, MSAC considered the confidence intervals on the NPV may have been small because it was bounded by 1. MSAC considered that the NPV decreases as risk (and therefore prevalence) increases, so the NPV for the test will be reduced in pregnant individuals at highest risk of PE. On rule-in value, MSAC considered the evidence from a single US study included patients from 20+ weeks' gestation and had unclear generalisability to the Australian population. MSAC considered the positive predictive value (PPV) for a rule-in diagnosis was better for ratio results >85 (PPV 55-70%) than >38 (PPV 37-58%), but that overall the evidence for rule-in value of ratio testing was poor.

On change of management, MSAC considered that in patients with PE symptoms in whom preterm delivery is being considered, if it could be demonstrated that ratio testing could rule out PE and avoid antenatal steroid administration to quicken fetal lung development, which has diabetogenic risks to the mother and neurocognitive and infection risks to the fetus, then there

could potentially be a management change resulting from ratio testing that may improve health outcomes. However, MSAC considered that the published evidence for reduction in hospitalisation arising from a ratio rest rule-out result was insufficiently robust and highly uncertain, given the variability in results (studies reported -53.3%, -15.0%, and +23.7%). MSAC also considered that patients presenting with signs and symptoms of PE are always intensively investigated and monitored as they can deteriorate rapidly. MSAC therefore considered that although ratio testing may provide additional clinical information, the incremental change in management and clinical utility resulting from adding a rule-out diagnosis from ratio testing would likely be minimal in practice because the management of a patient with signs and/or symptoms of PE would be unlikely to be relaxed by a rule-out result from ratio testing. MSAC noted that in the pre-MSAC response, the applicant suggested that the precision of the hospital admission decision-making is more important than the rate of hospitalisation, however, MSAC considered that the change in hospitalisation rate was material as it affects cost-effectiveness and costs. MSAC noted that evidence was presented showing an association between higher ratio results and time to delivery, but considered it was unclear to what extent any association was attributable to PE. MSAC therefore advised there was insufficient evidence that ratio testing would change management and improve health outcomes.

MSAC noted that no evidence was presented on safety, including no information about misclassification on the basis of the test or the risks from false positives. MSAC noted Klein et al 2016[1] reported expert committee review of hospitalisation decision-making on the basis of ratio testing had resulted in inappropriate decisions in 11% of decisions to hospitalise and 5.9% of decisions not to hospitalise, and considered this demonstrated potential harms. MSAC noted the applicant in the pre-MSAC response commented that a lack of safety data was not an issue as patients will continue to be monitored if they have symptoms. MSAC considered that the claim of non-inferior safety was not supported.

MSAC noted the applicant also claimed ratio testing would provide 'value of knowing', but considered no evidence was provided to substantiate this claim. MSAC noted the applicant's comments about the value patients place on ratio testing in the pre-MSAC response, but agreed with ESC that providing a patient with a test result of unclear validity would be more likely to increase anxiety than reduce it, and so advised the claim of value of knowing was not supported.

MSAC noted the ADAR's economic evaluation was a cost-consequence analysis (CCA), and the base case analysis showed a cost saving of $873 per patient. MSAC noted ESC used this to construct a cost-effectiveness analysis (CEA) that yielded an incremental cost-effectiveness ratio (ICER) of $3,331 per hospital admission avoided. MSAC noted the applicant stated a CUA was infeasible, however considered that the economic evaluation should have included a cost-utility analysis (CUA) or CEA, as given the clinical superiority in terms of test accuracy was supported it was important to include intermediate outcomes, ideally also QALYs, and a possible change in risk groups. MSAC considered the economic model would also have been improved by incorporating testing by clinical risk stratification. MSAC noted the main driver of the model was a reduction in hospitalisation following a rule out diagnosis, and other factors that had a high impact on model outcomes favoured the intervention. MSAC considered that the cost-effectiveness was highly uncertain, as the model was based on the reduction in hospitalisations from a rule-out result from ratio testing, which as above was highly uncertain based on the literature evidence and unlikely to be realised in practice as management of patients with signs and symptoms was unlikely to be relaxed by a rule-out ratio testing result. MSAC considered repeat testing and the number of tests per patient was uncertain, but that this was not a main

[1] Klein E, Schlembach D, et al. (2016). "Influence of the Sflt-1/Plgf Ratio on Clinical Decision-Making in Women with Suspected Preeclampsia." PloS one 11, no. 5 (2016): e0156013.

driver of the economic model. MSAC considered that the model would have been improved by including modelling of multiple births.

MSAC noted an epidemiological approach was used to estimate utilisation, and the ADAR estimated a net financial saving of approximately $29 million per year, comprised of the additional cost of ratio testing that was more than offset by the anticipated reduction in hospitalisation. MSAC considered the financial and budgetary impacts to be highly uncertain, mainly because the cost-offsets may have been overestimated as they were based on uncertain evidence. MSAC considered the financial analysis was also uncertain because costs were not disaggregated for each population, and the estimates did not include testing and management of asymptomatic patients.

Although it did not support public funding, MSAC considered ratio testing may have potential merit in some situations – although these would need to be more tightly defined and supported by evidence. MSAC considered the circumstances under which ratio testing might be useful to help clinical decision making, given the evidence supported the rule-out value of the test. MSAC considered that if a patient in a rural or remote area was classified as low risk, this may provide reassurance that they will not imminently develop PE. Although the evidence supporting the rule-in value of ratio testing was poor, MSAC considered that in rural and remote areas, if a patient was classified as high risk based on ratio testing it may facilitate appropriate transfer to a tertiary facility, which may potentially lead to improved health outcomes for mother and infant. MSAC considered ratio testing may potentially meaningfully change management and improve health outcomes in rural and remote areas, but that no evidence had been presented for this. MSAC noted that in its pre-MSAC response the applicant stated clinical guidelines recommend ratio testing as an adjunct to clinical management of patients with signs and symptoms of PE, however considered that inclusion in guidelines did not necessarily justify public funding.

MSAC considered that in well-established clinical practice patients already diagnosed with PE (population 2) already warrant close monitoring, and so if the applicant was considering resubmission the proposed population should not include already diagnosed patients. MSAC also noted no upper limit of gestation was proposed, and considered the applicant should consider an upper limit of 37 weeks' gestation.

Overall, MSAC did not support public funding of sFlt-1:PlGF ratio testing for the identification and management of PE. MSAC considered that any future resubmission would need to:

- Revise the proposed population.
  - o MSAC recommended excluding patients asymptomatic for PE (except those with chronic hypertension), those with an existing diagnosis of PE, and those >37 weeks gestation – although the applicant would need to justify its revised proposed population.
  - o MSAC considered ratio testing may potentially be useful in rural or remote areas, although evidence would need to be presented to support this.
- Justify the proposed cut-points in ratio test results.
- Provide robust evidence demonstrating the incremental effect of ratio testing on change in management in each proposed population.
- Provide evidence demonstrating the incremental effect on maternal and infant health outcomes.
- Provide updated economic and financial analyses in line with MSAC's advice and taking the above into account.

MSAC noted the applicant had indicated that the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) had advised it is planning to update its guidelines relating to PE (last updated in 2014). MSAC requested the Department write to RANZCOG

seeking more information about its plans to update its guidelines, including its timeline for the update and whether they would include any guidance in relation to ratio testing.

4. Background

MSAC has not previously considered angiogenic and anti-angiogenic markers for the identification and management of preeclampsia.

MSAC Application 1705 – *Structured prenatal risk assessment for preterm preeclampsia* was lodged by Roche Diagnostics Australia Pty Ltd and a professor in parallel with this application, and will be considered by ESC and MSAC at the same time. The interventions and patient populations covered in Applications 1705 and 1706 did not overlap; however, MSAC's advice on Application 1705 may influence its consideration of this application. This is because pregnant people identified as being at high risk of developing preterm preeclampsia at 11+0 to 13+6 weeks gestation using the intervention proposed in Application 1705 may subsequently be considered for soluble FMS-like tyrosine kinase-1:placental growth factor (sFlt-1:PlGF) testing from 24+0 weeks gestation.

In July 2022, the UK National Institute for Health and Care Excellence (NICE) recommended PLGF-based tests in conjunction with standard clinical assessment, to help rule in or rule out suspected preeclampsia and help decide on care.[2]

5. Prerequisites to implementation of any funding advice

The sFlt-1:PlGF ratio test involves the use of in vitro diagnostic (IVD) assays to quantify the levels of serum sFlt-1 and PlGF. A summary of the regulatory status of sFlt-1 and PlGF assays marketed by Roche Diagnostics in Australia is provided in Table 1. During the PASC meeting, the applicant stated that the Roche assay is the assay most likely to be used in Australia.

Table 1 Regulatory details of IVDs marketed by Roche Diagnostics used in sFlt-1:PlGF ratio testing

Serum biomarker	Assay name	Intended use	ARTG registration
sFlt-1	Elecsys sFlt-1	Immunoassay for the in vitro quantitative determination of sFlt-1 in human serum The Elecsys sFlt-1 assay is used in combination with the Elecsys PlGF assay to determine the sFlt-1:PlGF ratio. The sFlt-1:PlGF ratio is intended for use as an aid in the diagnosis of preeclampsia, in conjunction with other diagnostic and clinical information. In addition, the sFlt-1:PlGF ratio is intended for use as an aid in short-term prediction of preeclampsia (rule out and rule in) in pregnant people suspected to have preeclampsia, in conjunction with other diagnostic and clinical information.	ARTG ID 181222 Intended purpose: IVDs intended to be used for the qualitative and/or quantitative determination of proteins specific to clinical chemistry in a clinical specimen

---

[2] "Plgf-Based Testing to Help Diagnose Suspected Preterm Preeclampsia (Pdf)." 2022, accessed 2 August, 2023, https://www.nice.org.uk/guidance/dg49/resources/plgfbased-testing-to-help-diagnose-suspected-preterm-preeclampsia-pdf-1053819586501.

PlGF	Elecsys PlGF	Immunoassay for the in vitro quantitative determination of PlGF in human serum The Elecsys PlGF assay is used in combination with the Elecsys sFlt-1 assay to determine the sFlt-1:PlGF ratio. The sFlt-1:PlGF ratio is intended for use as an aid in the diagnosis of preeclampsia, in conjunction with other diagnostic and clinical information. In addition, the sFlt-1:PlGF ratio is intended for use as an aid in short-term prediction of preeclampsia (rule out and rule in) in pregnant people suspected to have preeclampsia, in conjunction with other diagnostic and clinical information. This assay is intended for the use as one component, in combination with other parameters, to evaluate the risk of early onset preeclampsia during the first trimester of pregnancy.	ARTG ID 181221 Intended purpose: IVDs intended to be used for the qualitative and/or quantitative determination of clinical chemistry hormones in a clinical specimen

Abbreviations: ARTG = Australian Register of Therapeutic Goods, **IVD** = in vitro diagnostic/s, **sFlt-1** = soluble FMS-like tyrosine kinase-1, **sFlt-1:PlGF** = soluble FMS-like tyrosine kinase-1:placental growth factor, **PlGF** = placental growth factor
Source: Adapted from ADAR Table 1

6. Proposal for public funding

The applicant proposed the creation of 2 new MBS items to publicly fund sFlt-1:PlGF ratio testing in pregnant people with signs and symptoms of preeclampsia or at high risk of preeclampsia (Population 1) and those diagnosed with preeclampsia (Population 2).

Table 2 and Note: Amendments made during the commentary in italicised text (additions) and strikethrough (deletions)

Source: ADAR Table 7 Proposed item descriptor population 1

Table 3 provide the proposed MBS item descriptors for Population 1 (AAAA) and Population 2 (BBBB), respectively. As requested by the PICO Advisory Sub-committee (PASC), the proposed MBS items have been modified in the ADAR from those in the ratified PICO to incorporate policy advice that the testing does not need to be specified to be laboratory based, and to add practice notes with reference to:

- clinical judgement being based on the sFlt-1:PlGF ratio rather than the individual values of sFlt-1 and PlGF; and
- information on the interpretation of sFlt-1:PlGF ratio test results.

Table 2   Proposed item descriptor for Population 1

Category 6 – PATHOLOGY SERVICES
MBS item AAAA ~~Laboratory-based q~~*Q*uantitative determination of the ratio of placental soluble FMS-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) from the beginning of the 24th week of pregnancy to evaluate the likelihood of preeclampsia in pregnancies where there are signs and symptoms suggestive of preeclampsia, or where there is an increased risk of preeclampsia.
Fee: $60.00 Benefit: 75% = $45.00 85% = $51.00
Note: The risk of preeclampsia should be judged based on the sFlt-1:PlGF ratio, rather than individual values of sFlt-1 and PlGF. ~~Women with~~ *An* sFlt-1:PlGF ratio <38 ~~are at~~ *indicates* low risk of preeclampsia in the following 2–4 weeks, review in 2–4 weeks and retest if clinical situation changes; ~~women with~~ *an* sFlt-1:PlGF ratio 38–85 ~~are at~~ *indicates* risk of preeclampsia, enhanced monitoring and retest after 1–2 weeks recommended; ~~women with~~ *an* sFlt-1:PlGF ratio >85 ~~most likely have, or will develop,~~ *indicates the development or a diagnosis of* preeclampsia ~~and~~ requir*ing*~~e~~ intensive monitoring.

Table 3   Proposed item descriptor for Population 2

Category 6 – PATHOLOGY SERVICES
MBS item BBBB   Quantitative determination of the ratio of placental soluble FMS-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) from the beginning of the 24th week of pregnancy for the management (by categorising the severity) of diagnosed preeclampsia in preterm pregnancies.
Fee: $60.00 Benefit: 75% = $45.00 85% = $51.00
Note: The ~~risk~~ *severity* of preeclampsia should be judged based on the sFlt-1:PlGF ratio, rather than individual values of sFlt-1 and PlGF.   ~~Women with~~ *An* sFlt-1:PlGF ratio 38–85 ~~are at~~ *indicates* ~~risk of~~ *less severe* preeclampsia, enhanced monitoring and retes*ting* after 1-2 weeks recommended; ~~women with~~ *an* sFlt-1:PlGF ratio >85 ~~most likely have, or will develop,~~ *indicates more severe* preeclampsia ~~and~~ requir*ing*~~e~~ intensive monitoring.

7.   Population

The populations addressed in the ADAR were consistent with the populations specified in the ratified PICO confirmation.

There are 2 proposed populations for sFlt-1:PlGF ratio testing. Both populations consist of pregnant people from 24+0 weeks gestation. In Population 1, no diagnosis of preeclampsia has yet been made, but there are either signs and symptoms suggestive of preeclampsia present, or an increased risk of the development of preeclampsia due to maternal, gestational, or other factors, in the absence of signs of symptoms of preeclampsia. This population is the diagnostic testing population; the test (AAAA) would be used to help establish the presence or absence of preeclampsia. Population 2 consists of pregnant people with a confirmed diagnosis of preeclampsia utilising current standard tests, for whom the sFlt-1:PlGF ratio test (BBBB) would help categorise the severity of preeclampsia.

Patients eligible for AAAA include those with "an increased risk of preeclampsia". However, "increased risk" was not defined, so it was unclear what patient group this is intended to refer to – and the number of patients defined as being at "increased risk" may be large. The ADAR did not address this patient group. Being overweight or obese increases the risk of preeclampsia, and this is around 50% of the pregnant patient population. If the structured risk assessment at 11+0 to 13+6 weeks gestation proposed in application 1705 was supported by MSAC, patients defined as increased risk by that tool (even if treated with aspirin) may also be regarded as at increased risk for the testing proposed in this application. Clinician concern or other subjective factors may also be regarded as defining a patient as being at "increased risk" – the applicant should define this population and estimate its size. The current unclear definition could result in leakage, the extreme of which would be the test becoming a universal part of antenatal care.

The ADAR did not present an upper limit for gestation in either population; however, it did state that the sFlt-1:PlGF ratio test is particularly useful between 24+0 to 34+6 weeks of gestation to inform decision-making regarding the optimal timing of a likely preterm delivery.

8. Comparator

The ADAR presented comparators for Population 1 and Population 2 nominated in the PICO confirmation, as outlined in Table 4. These comparators were applied to the assessment of the sFlt-1:PlGF ratio test presented in the ADAR.

For Population 1, Australian guidelines specify that a diagnosis of preeclampsia can be made when hypertension (above 140 mm Hg systolic and/or 90 mm Hg diastolic) arises after 20 weeks gestation and is accompanied by one or more signs of organ involvement.

Table 4 Nominated comparators for sFlt-1:PlGF ratio testing

Population	Role of sFlt-1:PlGF ratio test	Comparator	Clinical context
Population 1: Pregnant people from 24+0 weeks gestation with signs and symptoms suggestive of preeclampsia or asymptomatic people at increased risk of preeclampsia	Diagnostic test	No triage[a] [diagnostic] testing ± current standard tests that are repeated for diagnosing preeclampsia at 24+0 to 36+6 weeks gestation, including: • Urine protein:creatinine ratio test • Proteinuria reagent strip test • Full blood count • Renal function test • Serum electrolytes • Hepatic transaminases	sFlt-1:PlGF ratio test used in addition to comparator (add-on)
Population 2: Pregnant people from 24+0 weeks gestation with a confirmed diagnosis of preeclampsia	Prognostic/staging test	No prognostic testing plus standard medical management of preeclampsia (which may include repeat current standard tests for monitoring preeclampsia severity)	sFlt-1:PlGF ratio test used in addition to comparator (add-on)

Abbreviations: sFlt-1:PlGF = soluble FMS-like tyrosine kinase-1:placental growth factor
Notes: a = The PICO confirmation describes the role of the sFlt-1:PlGF ratio test in Population 1 as a triage test. The function of the sFlt-1:PlGF ratio test is more accurately described as a diagnostic test.
Source: Adapted from ADAR Table 4

The commentary considered the nominated comparators were as per the ratified PICO 1706. PASC requested the applicant clarify the percentage additional versus replacement tests, and in the ADAR the applicant clarified that the test is to be used in addition to the comparator tests (add-on).

9. Summary of public consultation input

Prior to the October 2023 ESC meeting consultation feedback deadline, consultation input was received from four organisations and eight individuals, of whom two were consumers and six were medical professionals.

Post ESC deadline feedback was received by five organisations and four individuals, all of whom were medical professionals.

The organisations that submitted input were:

• Australian Action on Preeclampsia (AAPEC) x2
• Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)

- Australian Pathology (AP)
- Society of Obstetric Medicine Australia and New Zealand (SOMANZ)x2
- Australasian Diabetes in Pregnancy Society (ADPS)
- Australian Diabetes Society
- Royal Hospital for Women, Randwick NSW

The consultation feedback received was supportive of public funding for angiogenic and anti-angiogenic markers for identification and management of preeclampsia.

The main benefits of public funding received in the consultation feedback included:
- Separates patients with preeclampsia from those with hypertension, allowing tailored treatment/management and intense surveillance for patients identified with preeclampsia.
- Useful in helping with decision making on whether to admit the patient to hospital for observation or transfer her to a higher-level facility for further care and/or birth.
- Allows for a reduction in further blood tests, ultrasound, fetal monitoring and obstetric intervention.
- More reliable and prompt prediction, diagnosis or non-diagnosis, which may lead to better decision making and outcomes, better idea of progression of preeclampsia and fewer hospital admissions.
- Can be reassuring for the patient who has had preeclampsia in a previous pregnancy and is worried about it happening again.
- The high negative predicative value of the test is reassuring to both clinicians and patients.
- This intervention will increase access for at-risk mothers to know if they have a reduced risk of preeclampsia
- It will be beneficial to those patients at high risk of preeclampsia who will be managed prophylactically, but it will be most beneficial to ruling out preeclampsia in low-risk individuals.

No potential disadvantages were noted in the consultation feedback for public funding of this proposal.

Other points raised in the consultation feedback included:
- The introduction of ratio testing has been the most clinically significant breakthrough in the preeclampsia field since the introduction of low-dose aspirin in the 1980s.
- Introducing this new test will need to go hand-in-hand with targeted education on the underlying pathophysiology and appropriate use of the test for relevant health professionals.

10. Characteristics of the evidence base

A literature search was conducted on 6 April 2023 to identify relevant studies and systematic reviews. The relevant studies were included in the ADAR. The characteristics of the clinical evidence base are presented in Table 5. The commentary considered the systematic literature review (SLR) was presented with a clear search strategy that aligned with the ratified PICO 1706. The searches were methodologically sound and used broad search terms to capture relevant clinical evidence. However, database searches were not presented individually; as such, the commentary considered controlled vocabulary or thesaurus terms had not been specifically tailored and optimised for individual databases, meaning relevant references may have been overlooked in the searches.

A total of 9 studies were included from the SLR. None of the studies provided direct from test to health outcomes evidence. Instead, they were focused on diagnostic accuracy and changes in management/downstream outcomes. Due to the nature of the included studies (the majority were prospective observational trials), all were assessed by both the ADAR and commentary as having a moderate to high risk of bias. Only one of the 9 studies included Australian study centres, the rest being conducted elsewhere. A meta-analysis combining results across identified studies was not presented in the ADAR and no justification was given, however the commentary considered that the heterogeneity of study design, population, and outcomes would preclude the undertaking of an informative meta-analysis. As shown in Table 6, the risk of bias across evidence on test accuracy, prognostic accuracy, change in patient management, and health outcomes was assessed to be moderate.

Table 5 Characteristics of the evidence base

Criterion	Type of evidence supplied	Extent of evidence supplied[a]	Overall risk of bias in evidence base
Test accuracy	One validation study Three studies (2 prospective cohorts, 1 randomised control trial) reported on the diagnostic/predictive performance of the sFlt-1:PlGF ratio test in ruling out a diagnosis preeclampsia within 1 week. Three studies (2 prospective cohorts, 1 respective cohort) reported on the diagnostic/predictive performance of the sFlt-1:PlGF ratio test in predicting a diagnosis of preeclampsia within 2 weeks. One prospective study presented the additive value of the sFlt-1:PlGF ratio.	k = 8 n = 3,340	Moderate risk of bias (the commentary)
Prognostic (longitudinal) accuracy of the sFlt-1:PlGF ratio test	Four studies (3 prospective cohorts, 1 retrospective cohort) investigated the association between sFlt-1:PlGF ratio and the time to delivery.	k = 4 n = 1,704	Moderate risk of bias (the commentary)
Change in patient management	Three studies (1 randomised control trial, 1 prospective cohort, 1 retrospective cohort) assessed change in management (including hospital admission) following sFlt-1:PlGF ratio compared to current standard tests.	k = 3 n = 763	Moderate risk of bias (the commentary)
Health outcomes	The evidence presented was the same as that used for change in patient management.	k = 3 n = 763	Moderate risk of bias (the commentary)

Notes: [a] Total of 9 studies included; some studies applied evidence across multiple criteria
Abbreviations: **k** = number of studies, **n** = number of patients, **sFlt-1:PlGF** = soluble FMS-like tyrosine kinase-1:placental growth factor
Source: Constructed during the commentary.

11. Comparative safety

The ADAR stated:

> No studies were identified that specifically investigated the safety of the sFlt-1:PlGF ratio test; however, the authors of the PreOS study outline that 'there were no incidents or indirect harm associated with the use of the sFlt-1:PlGF ratio test in routine clinical practice in this population with suspected preeclampsia' p. 14 of Klein et al 2016.

The commentary considered that it was uncertain whether sFlt-1:PlGF ratio testing was safer, similarly safe, or less safe than standard clinical management, because no evidence was presented for safety.

The ADAR presented data from Klein et al 2016 in which 100% of the change in management decisions regarding induction of delivery and fetal lung maturation were considered appropriate by an independent adjudication committee of 3 experts; however, the initial decision to hospitalise was changed to no hospitalisation in 11% of cases, and the decision not to hospitalise was changed to hospitalise in 5.9% of cases. There was insufficient information presented in the ADAR regarding safety issues in relation to misclassification of the risk of preeclampsia, adverse events associated with incorrect risk stratification, and the follow-up diagnostic and treatment workups. This was particularly notable as the post-hoc analysis of the ROPE study that underpinned the economic analysis showed an increased risk of hospital discharge associated with sFlt-1:PlGF ratio testing in comparison with standard clinical management. No data were supplied in the ADAR that described outcomes for patients that were discharged in the knowledge of their sFlt-1:PlGF ratio test results; therefore, the risks of discharging a patient due to misclassification of the risk of preeclampsia, and the potential downstream health outcomes of this, remain unclear.

As the sFlt-1:PlGF ratio test is a laboratory assessment performed on maternal serum, no safety signals aside from those associated with the routine collection of serum samples would be anticipated; however, the risk of misclassification was not addressed.

12. Comparative effectiveness

The main comparative effectiveness results are summarised below (Table 6).

Table 6 Summary of comparative effectiveness data

Section	Settings	Summary
Test accuracy	Argentina, Australia, Austria, Belgium, Canada, Chile, China, Germany, Hong Kong, Japan, Netherlands, New Zealand, Norway, Peru, Singapore, South Korea, Spain, Sweden, Thailand, UK, USA	• The ADAR presented data that justified the ratio cut-offs and the PROGNOSIS study which was used to validate this is generalisable to clinical practice. • Across the identified studies, the negative predictive value of sFlt-1:PlGF ratio testing with a cut-off of 38 ranged from 98.6% (97.2%, 99.4%) to 100.0% (97.1%, 100.0%) for ruling out preeclampsia within 1 week.
Limitations and missing data	Frequency of testing	• Frequency of testing was not addressed in the ADAR. • Only one trial was presented in the ADAR for multiple pregnancies, and no evidence was presented for serial testing in multiple pregnancies.
Change in management	Variability in the evidence presented	• Results presented in the ADAR were highly variable, and no explanation was provided for the large differences. • One study showed an increase in hospital admissions (~~+21.1%~~ *+23.7%*), and 2 studies showed decreases in admissions (~~-72%~~ *-53.3%* and ~~-16.2%~~ *-15.0%*).
Health outcomes	Long-term health outcomes	• The ADAR stated that results of the test were not expected to influence the incidence or severity of preeclampsia and knowledge of test results was not expected to influence health outcomes. • However, NICE DSU model included long-term health outcomes, including mortality, for gestational parent and infant.
Clinical claim	Additional safety concerns	• While there was considerable uncertainty in the clinical evidence presented, the applicant's claim that the addition of testing resulted in no change in adverse outcomes compared with current standard of care was considered reasonable by the commentary.

Abbreviations: ADAR = applicant developed assessment report, **DSU** = Decision Support Unit, **sFlt-1:PlGF** = soluble FMS-like tyrosine kinase-1:placental growth factor

Test accuracy

The evidence for test accuracy was split into 5 sections:

- Validation of the sFlt-1:PlGF ratio of 38 to rule in/rule out preeclampsia
- Diagnostic/predictive accuracy of the sFlt-1:PlGF ratio test
- Prognostic (longitudinal) accuracy of the sFlt-1:PlGF ratio test to estimate the time to delivery
- The additive value of sFlt-1:PlGF to current clinical tests
- Maternal and fetal health outcomes.

Of the 8 studies presented as evidence (Table 5), only one included sites in Australia (together with 13 other countries: PROGNOSIS), and the remaining evidence came from the USA, the UK, and sites across Asia. No explanation was provided in the ADAR as to how the evidence base was applicable to Australian clinical practice. The commentary considered it was also notable that 2 of the 3 studies were for pregnant people of 20+ weeks gestation, not 24 weeks as per the PICO, which reduced applicability to the target population.

A comprehensive clinical evidence base was presented supporting the accuracy of the sFlt-1:PlGF ratio test. The test had a very high accuracy for ruling out preeclampsia within 1 week (98.6% to 100% accuracy), and the addition of sFlt-1:PlGF >38 information was shown to improve diagnostic/predictive accuracy in a large cohort of women (n=1,035) when compared to clinical criteria (guidelines from the International Society for the Study of Hypertension in Pregnancy[3]); however, it should be noted that this study was conducted in the USA, with participants enrolled between 2009–2012, and from 20+ weeks gestation. As such, the generalisability of the study's conclusions to current clinical practice in Australia was uncertain.

The ADAR stated that the low number of maternal adverse outcomes reported in the studies providing evidence for the accuracy of the test precluded the undertaking of a robust assessment of the relationship between sFlt-1:PlGF ratio and maternal adverse outcomes. The median baseline sFlt-1:PlGF ratio was higher (148.9) in pregnant people who experienced fetal adverse outcomes within 1 week compared with those who did not (7.4). It was demonstrated that the sFlt-1:PlGF >38 ratio test predicted the lack of fetal adverse outcomes within 1 week with very high accuracy (negative predictive value [NPV] 98.9% to 99.5%).

Limitations and missing data

The clinical evaluation presented in the ADAR did not cover the frequency of repeat tests. The commentary considered it was unclear how the frequency of repeat testing could influence the change in management of preeclampsia screening in Australia, and consequently, the usefulness of frequent testing was uncertain.

The ADAR claimed that repeat testing was useful, as the rate of ratio change between tests can provide data on the rate of progression of preeclampsia. However no data were submitted that provided an explanation as to how the rate of ratio change was related to severity of disease; therefore, the commentary considered it remained unclear whether a change in ratio indicated immediate risk. Furthermore, while evidence was presented to show that higher sFlt-1:PlGF ratios

---

[3] Magee, LA, Brown, MA, et al. (2022). "The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice." Pregnancy Hypertension 27: 148-169.

were associated with increased risk between pregnant people, no evidence was presented showing that increasing sFlt-1:PlGF ratio within an individual was associated with a worsening prognosis. The commentary considered this introduced significant uncertainty around the utility and cost-effectiveness of repeat testing.

Furthermore, the ADAR was unclear on what defined 'other factors' in population 1: 'at increased risk of preeclampsia, due to maternal, gestational or other factors, in the absence of signs and symptoms suggestive of preeclampsia (diagnostic testing population)'. The commentary considered this created ambiguity as to what factors will cause a pregnant person to fall into the category of population 1, and would leave it open to interpretation.

Only one trial in the evidence base provided data on the use of sFlt-1:PlGF ratio testing in multiple pregnancies. This was an area of substantial uncertainty considering that neither population addressed in the ADAR excluded multiple pregnancies. There was also no evidence presented on serial testing in multiple pregnancies.

Change in management

The ADAR presented data on how results from the sFlt-1:PlGF ratio test can lead to a change in management by identifying those with suspected preeclampsia who will develop preeclampsia in the near future (population 1). Three studies were presented in support of this claim (Cerdeira et al 2019[4], Klein et al 2016, Suresh et al 2020[5]). In all 3 studies, a change in management resulting from the knowledge of the sFlt-1:PlGF ratio test was observed. In the randomised trial by Cerdeira et al 2019, an increase of 21.2% in admissions was reported. The retrospective analysis of the ROPE study found a decrease in admissions by 72.6%, and the PreOS study reported a decrease in admissions by 16.2%. These studies were reported to be moderate quality in the quality assessment presented in the ADAR.

The ADAR stated that the results of a decrease in admissions found in the PreOS and ROPE studies were more favourable as there was potential to reduce consumption of hospital resources, particularly with pregnant people who are at low risk of preeclampsia (sFlt-1:PlGF ≤38). This was supported by the fact that the ratio test can provide evidence that these people were highly unlikely to develop preeclampsia within 1 week (based on the NPV of 98.5% to 100% associated with a sFlt-1:PlGF ≤38); therefore, these people are unlikely to experience adverse maternal and fetal events and unlikely to require imminent delivery. This evidence lent more credence to the decision to effectively manage these people as outpatients, thereby saving on hospital resources.

The results presented in the ADAR were, however, highly variable (Table 7). One study showed an increase in hospital admissions (+21.2%), and 2 studies showed decreases in admissions (-72.6%, -16.2%). It was reported in the ADAR that increases in admissions in the INSPIRE trial compared to the decreases reported in PreOS and ROPE studies may be explained by differences in study designs. It was also reported that the INSPIRE trial recruited during 2015–2017, and that there has since been substantial advancements in the literature surrounding the effectiveness of sFlt-1:PlGF in establishing preeclampsia development (or ruling it out); therefore, it was suggested that the INSPIRE trial may have featured more conservative attitudes to hospital

---

[4] Cerdeira AS, O'Sullivan J, et al. (2019). "Randomized Interventional Study on Prediction of Preeclampsia/Eclampsia in Women with Suspected Preeclampsia: INSPIRE." Hypertension 74(4): 983-990.

[5] Suresh S, Mueller A, et al. (2020). "Evaluation of Angiogenic Factors in the Decision to Admit Women with Suspected Preeclampsia." Pregnancy Hypertension 21: 124-31. https://doi.org/https://doi.org/10.1016/j.preghy.2020.05.013.

admission, due to clinicians having less confidence in the technology. The commentary considered it was nevertheless still important to consider the results of this trial.

Table 7 Impact of sFLT-1:PIGF ratio testing on hospitalisation based on INSPIRE, PreOS, and ROPE analysis

Trial	Outcome	Comparator (current standard tests)	sFLt-1:PIGF result + current standard tests	Percent ~~difference~~ *change* (%)	Risk ratio (95% CI)
INSPIRE Trial (Cerdeira 2019)	Admission to hospital within 24 hours of the test, n/N (%)	48/184=26.1%	60/186=32.3%	↑~~21.2%~~ *↑23.7%* in the intervention arm	1.24 (0.89, 1.70)
PreOS Trial (Klein 2016)	Hospitalisation	40/118=33.9%	34/118=28.8%	↓~~16.2%~~ *↓15.0%* in the intervention arm	0.85 (0.58, 1.24)[a]
ROPE Trial (Suresh 2020)	Admitted to hospital	225/459=49.0%	105/459=22.9%	↓~~72.6%~~ *↓53.3%* in the intervention arm	0.47 (0.39, 0.56)[a]

Notes: [a] Risk ratio calculated by the assessment group, CIs estimated using normal approximation.
Abbreviations: CI = confidence interval, **sFlt-1:PIGF** = soluble FMS-like tyrosine kinase-1:placental growth factor.
Source: Adapted from ADAR Table 22. ESC's additions are shown in blue italics and deletions in strikethrough.

No explanation was provided in the ADAR for the large differences in reductions to hospital admissions seen in the ROPE and PreOS studies (72.6% and 16.2%, respectively); however, the commentary considered that advancements in the literature surrounding the effectiveness of sFlt-1:PIGF testing occurring after the PreOS study (2016) up to the ROPE study (2019) may have increased clinician confidence in the test and could provide a possible explanation as to the discrepancy between results.

The ADAR provided no evidence for change in management of sFlt-1:PIGF testing to determine the severity of already diagnosed preeclampsia (population 2), although did state that "there are not treatments for the prevention or reduction in severity of preeclampsia in women beyond 20+0 weeks gestation."

Health outcomes

The sFlt-1:PIGF ratio test was not intended to reduce the incidence of or severity of preterm preeclampsia. The results of the sFlt-1:PIGF ratio test were only intended for use as an aid in short-term prediction of preeclampsia in pregnant people with signs and symptoms. Furthermore, it was reported in the ADAR that the results of the test were not expected to influence the incidence or severity of preeclampsia as there are no treatments for the prevention or reduction in severity of preeclampsia. Thus, according to the ADAR, knowledge of test results would not be expected to influence health outcomes. However, utilities and differences in maternal and fetal health outcomes were included in the NICE Decision Support Unit's model and varied by diagnosis of preeclampsia and if the diagnosis was correct. A small incremental QALY gain was reported in the evaluation. In addition to this, long-term consequences conditional on maternal and fetal outcomes including mortality were included in the estimation of incremental benefits. The commentary therefore considered that the ADAR did not adequately capture the impact on the gestational parent and neonatal outcomes following testing.

Downstream health outcomes were reported in the ADAR by hospitalisation status and clinical assessment. The 3 studies presented were the same as those presented for evidence of a change in clinical management. This means that the same issues arose regarding the heterogeneity of study designs and results (see 'Limitations and missing data').

Clinical claim

The applicant claimed that sFlt-1:PlGF ratio testing was superior in effectiveness compared with current standard tests. This claim was made on the improved diagnostic performance of the sFlt-1:PlGF ratio test in establishing the presence or absence of preeclampsia over a timeframe of 1–4 weeks. The sFlt-1:PlGF ratio was non-inferior compared with current standard test in terms of safety, as stated in the ADAR. Both assessments included laboratory testing of maternal serum samples, with no safety signal aside from those associated with the routine collection of serum samples anticipated, resulting in no change in safety outcomes compared with current standard of care.

Testing would be used as an add-on to standard tests for the diagnosis of preeclampsia, as outlined in Australian preeclampsia testing guidelines/practices, so this would not be a standalone test. The commentary considered that while there was considerable uncertainty in the clinical evidence presented, overall the applicant's conclusion on the clinical claim was reasonable.

13. Economic evaluation

Cost-comparison analysis

A summary of the economic evaluation is presented in

Table 8. The ADAR presented a cost-comparison analysis in the form of a decision tree and presented intervention costs per patient (cost savings), costs for a cohort of 100 patients, and reductions in hospital admissions for monitoring for 100 patients. The ADAR did not present health outcomes in the form of life years, quality-adjusted life years (QALYs), or an incremental cost-utility ratio, in contrast with the ratified PICO. As described in the ratified PICO, a cost-minimisation analysis may only be presented in the event of non-inferior efficacy and safety. Given the ADAR concluded that efficacy was superior and safety was non-inferior, a cost-utility analysis was therefore required according to the MSAC Guidelines, and so the commentary considered the ADAR's chosen economic analysis was inappropriate.

The ADAR's argument for deviating from the PICO was the short-term impact of the introduction of sFlt-1:PlGF testing, and the absence of quality-of-life data collected in the relevant trials. The commentary did not consider this justification to be sufficient, as proxy data are routinely used in economic models as part of a linked evidence of health outcomes analysis when trial data are not available. Furthermore, there is at least one published example of a cost-utility analysis of sFlt-1:PlGF testing, including utility decrements for critical care units from 2 possible scenarios with and without neonatal outcomes. This demonstrates the feasibility of conducting cost-utility analyses per MSAC's guidelines, as specified in the ratified PICO and as conducted by NICE.

Table 8   Summary of the economic evaluation

Component	Description
Perspective	Health care system perspective
Population	Pregnant people from 24 weeks gestation with suspected preeclampsia, at high risk of preeclampsia or confirmed preeclampsia
Prior testing	Not required
Comparator	Standard management. This would include assessments for new onset or severe hypertension and proteinuria to establish signs and symptoms or diagnosis of preeclampsia

Component	Description
Type(s) of analysis	Cost analysis/cost consequence analysis
Outcomes	Cost per patient, hospital admissions for monitoring
Time horizon	Up to 15 weeks (from eligibility for sFlt-1:PIGF ratio testing from 24+0 weeks gestation to term delivery at 39 weeks) in the model The time horizon used in the model aligns with the time horizon of the key studies
Computational method	Cohort expected value
Generation of the base case	Trial based. Results of an analysis of the ROPE study (Suresh et al. 2020) are used to generate the base case
Health states	Not applicable (decision tree used)
Cycle length	Not applicable
Transition probabilities	Transition probabilities allocating patients to 'Outpatient' and 'Admit to hospital for monitoring' branches of the decision tree were obtained from the analysis of the ROPE study by (Suresh et al. 2020) and applied without transformation Transition probabilities allocating patients to sFlt-1:PIGF ratio cut-off branches of the decision tree were obtained from the analysis of the ROPE study by (Suresh et al. 2020) and applied without transformation Transition probabilities allocating patients to the 'Preterm delivery <34 weeks', Preterm delivery 34 to 37 weeks' and 'Term delivery >37 weeks' were obtained from the analysis of the ROPE study by (Suresh et al. 2020) and applied without transformation
Discount rate	Not applied. All costs and consequences accrued in less than 1 year
Software	TreeAge Pro (Healthcare Version)

Abbreviations: sFlt-1:PIGF = soluble FMS-like tyrosine kinase-1:placental growth factor.
Source: Adapted from ADAR Table 24

Model structure

The commentary considered that the decision nodes included in the model structure (Figure 1) did not accurately reflect the treatment pathway for preeclampsia. Repeat testing may be required, subject to a number of conditions in both Population 1 and 2, which was not reflected in the decision tree. Patients were categorised into high risk (requiring inpatient admission and monitoring) or low/intermediate risk (requiring outpatient monitoring only) after their initial test, with no possibility of changing categories throughout the course of their pregnancy. This was also inconsistent with the average of 1.7 tests per pregnancy, which was based on unreferenced and undescribed audit data in the ADAR. The commentary considered the model structure should enable low-, intermediate-, and high-risk patients to have inpatient and outpatient monitoring, as the proportion of admitted or non-admitted people would vary dependent on the outcomes of the sFlt-1:PIGF ratio test. Furthermore, the failure to include both maternal and fetal adverse outcomes, and the associated costs and health outcomes, was a significant oversight given the heterogeneity in the presented evidence around incorrect hospital discharge following sFlt-1:PIGF ratio testing. As a result, it was unlikely that the comparative change in management arising from testing was adequately captured, as the intended use of the intervention is to reduce the number of inappropriate admissions given the test's sensitivity.
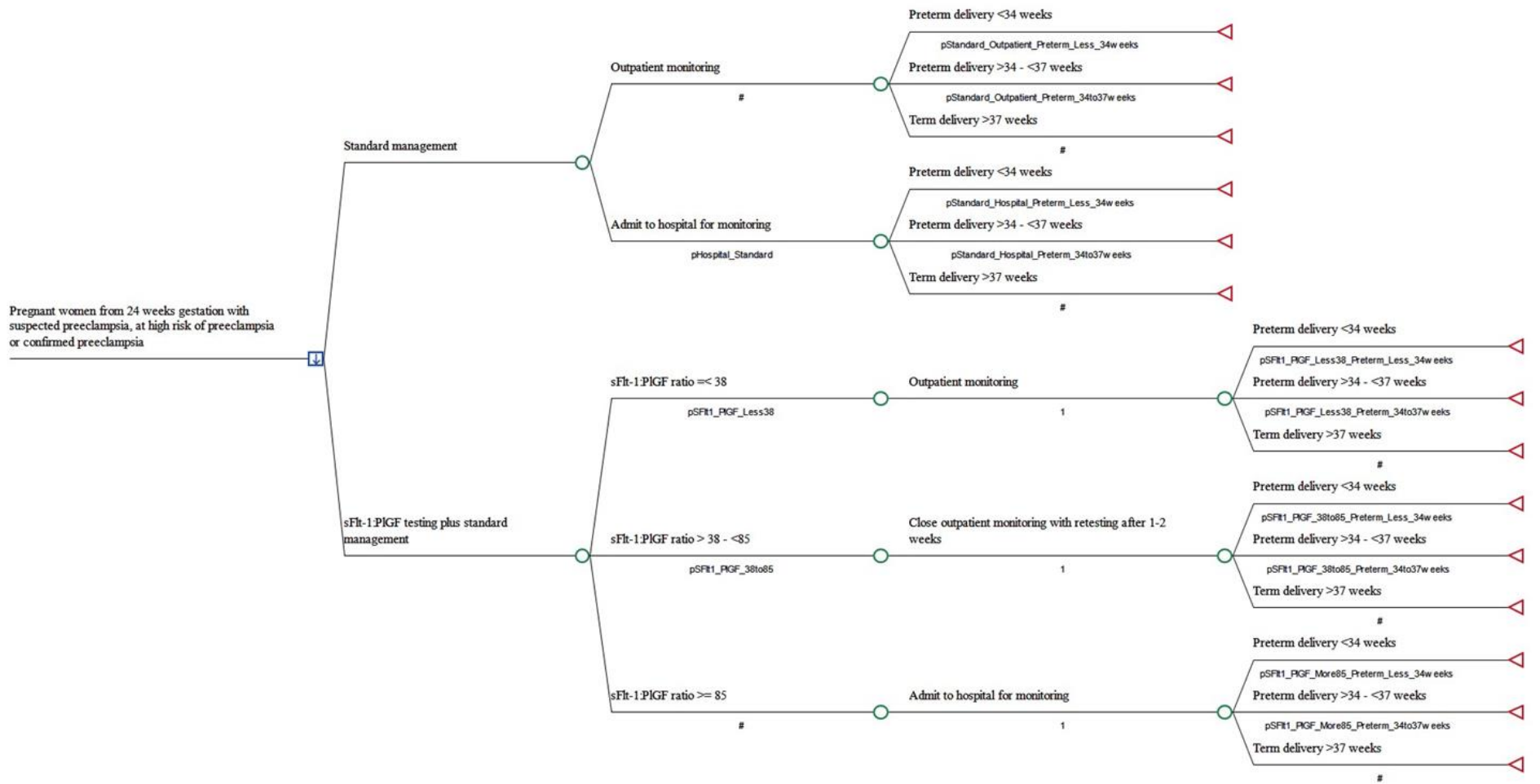
Figure 1 Model structure

Source: ADAR Figure 16

All transition probabilities were derived from Suresh et al 2020, and the ADAR stated that low risk of bias was expected given the use of a single source for clinical inputs; however, this study was evaluated to be moderate risk of bias. The commentary considered that, although the selected study was favourable to the model results, the ROPE study had the largest study cohort of the presented evidence for a change in management; therefore, it remained a suitable choice, despite the risk of bias that came with a retrospective (historical) study design.

As for the ADAR's other inputs and structural choices, the commentary considered the analysis was broadly acceptable with a number of limitations, which can be attributed to the erroneous choice of model structure in line with the PICO criteria:

- The comparator may not be reflective of current clinical management in Australia.
- The time horizon of 15 weeks and absence of discounting of costs and benefits was appropriate given the selected model structure (decision tree); however, the commentary considered this to be an additional limitation given the model did not capture long-term costs and effects.
- The transition probabilities from Suresh et al were not sufficiently granular for modelling patient outcomes, although they were adequately derived and applied in the model.

Model inputs

A second SLR was presented in the ADAR to assess relevant economic evaluations. The search was conducted on 14 April 2023. Search terms and methodology were presented. As with the clinical SLR, database searches were not presented individually; as such, the commentary considered that controlled vocabulary or thesaurus terms had not been specifically tailored and optimised for individual databases, meaning relevant references may have been overlooked in the searches. A total of 6 publications were included, all of which presented cost comparison economic evaluations. The ADAR stated that no published economic evaluations undertook cost-utility analysis or reported incremental cost per QALYs. The SLR did not identify Health Technology Assessment (HTA) submissions, meaning the cost-utility analysis by the NICE Decision Support Unit conducted as part of the assessment for sFlt-1:PlGF ratio test in England was, notably, excluded. This analysis not only demonstrated the feasibility of a cost-utility analysis, but also concluded that sFlt-1:PlGF ratio testing would result in a small increase in QALYs gained versus current clinical management in England. Assuming a QALY gain equivalent to that reported in the NICE Decision Support Unit model (0.0029 to 0.0046), the resulting ICER for an incremental cost of -$873 was sFlt-1:PlGF ratio testing was a dominant strategy (i.e. more effective and less costly); however, as long-term costs and health outcomes were not accounted for, the true ICER of this economic evaluation may be in the north-east quadrant of the cost-effectiveness plane (more effective and more costly), consistent with the analysis undertaken by the NICE Decision Support Unit.

There was also significant uncertainty around the inputs used in the model, as there were large variations in the data on reductions in hospitalisations as a result of sFlt-1:PlGF ratio testing (72.6% reduction reported by Suresh et al 2020, 16.2% reduction reported by Klein et al 2016, and a 21.2% increase in hospitalisations observed in INSPIRE). Although the commentary considered the selected source (Suresh et al 2020) was appropriate and comparatively robust, the results of the analysis should be interpreted with caution, as the primary benefit of sFlt-1:PlGF ratio testing was based on a reduction in hospitalisations. Finally, the frequency of testing used in the model (i.e. 1.7 tests per pregnancy) was based on an audit from the Royal Women's Hospital in Melbourne, a source that has not been assessed for quality or reliability. Given the sensitivity of the model with respect to test frequency, caution should be exercised in the interpretation of these results.

Model healthcare resource use and costs

The ADAR modelled the cost of testing (including standard management), outpatient appointments, and hospital costs. It omitted antihypertensive medication and therapeutic interventions prior to delivery and treating complications, despite these being requested in the PICO. The commentary considered the rationale provided for the exclusion of therapeutic intervention costs was reasonable, as the Australian Refined Diagnosis Related Group (AR-DRG) code used represents a total cost of care; however, antihypertensive medication is administered to some people with moderate/severe preeclampsia after 37 weeks. This could have been included; however, the commentary considered that the addition of this cost would not have a major effect on the results.

The model structure and short time horizon, which were discussed above, meant that preeclampsia-related adverse neonatal and maternal outcomes were excluded from the economic evaluation. However the commentary considered these had the potential to be significantly impacted by the introduction of sFlt-1:PlGF ratio testing and should therefore have been included. In the NICE Decision Support Unit model, the scenario excluding neonatal outcomes led to increases in the ICER – with the exclusion of long-term outcomes having the greatest impact on results. As a result, the commentary reiterated its stance that a cost-utility analysis should have been performed, consistent with the ratified PICO.

Model results

The ADAR presented incremental costs and hospital admissions associated with the introduction of sFlt-1:PlGF ratio testing. The model resulted in a cost saving of $873 per pregnancy and 0.26 fewer admissions to hospital per patient (Table 9). As previously mentioned, the commentary considered a number of outcomes were missing from the analysis, such as long-term health outcomes for gestational parents and their infants, and that the ADAR's model structure potentially underestimated costs for the intervention. In addition to this, there was unexplored uncertainty around the frequency of repeat testing, which would significantly impact the cost savings associated with introducing sFlt-1:PlGF ratio testing. As a result, the commentary considered the net cost savings may have been overestimated by the ADAR.

Table 9   Results of the economic evaluation

Component	sFlt1-PlGF ratio testing plus standard management	Standard management	Increment
Costs (N=100)	$2,797,549	$2,884,813	-$87,264
Cost per patient	**$27,975**	**$28,848**	**-$873**
Hospital admissions for monitoring per patient	0.23	0.49	-0.26
ICER: cost per hospital admission avoided			*$3,331*

Abbreviations: **ICER** = incremental cost-effectiveness ratio; **sFlt-1:PlGF** = soluble FMS-like tyrosine kinase-1:placental growth factor
Source: Adapted from ADAR Table 35 and Post ESC. ESC's additions are shown in blue italics: the ICER was calculated as cost saving per patient divided by hospital admissions avoided.

Table 10 Key drivers of the model

Description	Method/Value	Impact Base case: cost-saving of $873
Reduction in inpatient management	*Base case 53.3% reduction (Suresh 2020), however other studies reported considerably different values (15.0% reduction in Klein 2016; 23.7% increase in Cerdeira 2019).*	*The reduction in inpatient management was the key driver, yet substantial variation has been reported.*
Model structure	The decision tree underestimated costs for the intervention	*High, favoured sFlt-1:PlGF ratio testing*
Frequency of repeat testing	Source of 1.7 tests per pregnancy was uncertain and undescribed	*High, favoured sFlt-1:PlGF ratio testing*
Long term outcomes	Long term maternal and fetal adverse health outcomes and costs were not included.	*High given the heterogeneity in the presented evidence around incorrect hospital discharge following sFlt-1:PlGF ratio testing, favoured sFlt-1:PlGF ratio testing*

Abbreviations: sFlt-1:PlGF = soluble FMS-like tyrosine kinase-1:placental growth factor
Source: Constructed during commentary. ESC's additions are shown in blue italics.

The applicant's clinical expert performed a methodical review of the ADAR's inputs and detailed the steps to validate the TreeAge model. The ADAR did not mention outside sources for external validation purposes, which could be informative for decision-making.

The ADAR's scenario analyses showed that the introduction of sFlt-1:PlGF ratio testing was estimated to be cost-saving in all scenarios (Table 11), with the exception of a higher proportion of patients being at low risk of preeclampsia. While these sensitivity analyses explored the impact of parameter uncertainty in the model, they did not address uncertainty associated with generalisability of the clinical evidence, or structural uncertainty included in the model with respect to repeated testing and the exclusion of maternal and fetal adverse outcomes. In particular, scenarios showing reduced costs associated with inpatient monitoring also showed significant reductions in the estimated cost savings associated with sFlt-1:PlGF ratio testing.

Table 11 Sensitivity analyses

Analyses	Cost per patient
Base case	**-$873**
Number of tests per patient (base case: 1.7)	
1	-$915 (↓5%)
2	-$855 (↑5%)
Proportion of sFlt-1:PlGF ratio tests <38 (base case: 67.8%)	
61.0%	-$2,787 (↓219%)
74.6%	$1,041 (↑219%)
Proportion of sFlt-1:PlGF ratio tests from 38–85 (base case: 9.4%)	
8.5%	-$1,017 (↓16%)
10.3%	-$728 (↑17%)
Cost of inpatient monitoring (base case: $3,887)	
$1,993	-$376 (↓57%)

Abbreviations: sFlt-1:PlGF = soluble FMS-like tyrosine kinase-1:placental growth factor
Source: Adapted from ADAR Table 38

Despite these observations, the commentary considered that sFlt-1:PlGF ratio testing has the potential to be net cost-saving in Australia; however, it is also likely that the cost-offsets presented in the ADAR were overestimated. The extent of these cost-offsets was variable given the issues raised in previous sections, such as the generalisability of the clinical evidence to the Australian setting, the uncertainty in the estimates used for repeat testing and reductions in hospitalisations, and the inadequacy of the model structure.

14. Financial/budgetary impacts

The financial implications to the MBS resulting from the proposed listing of sFlt-1:PlGF ratio test are summarised in Table 12. The ADAR analysed the utilisation and financial impact of the sFlt-1:PlGF ratio test by applying an epidemiological approach and considering financial implications to the MBS, hospitals and Commonwealth. The interventions and populations covered in Applications 1705 and 1706 did not overlap. Therefore, the financial impacts of the two applications would be separate and cumulative, and the budget impact presented in the ADAR covered the population of 1706, only.

The ADAR concluded that the introduction of the sFlt-1:PlGF ratio test would result in a net cost saving for the Commonwealth of approximately $29 million per year over the next 6 calendar years. These projected net cost savings were a result of the anticipated costs to the MBS resulting from funding the sFlt-1:PlGF ratio test, which were more than offset by the anticipated reduction in hospitalisation costs due to a reduced number of admissions (percentage of individuals indicated for hospital admission reduced from 49.0% to 22.9%).

Table 12 Net financial implications of sFlt-1:PlGF ratio testing to the MBS, hospitals and Commonwealth

Parameter	Year 2024	Year 2025	Year 2026	Year 2027	Year 2028	Year 2029
Estimated use and cost of the proposed health technology						
Number of people eligible for sFlt-1:PlGF ratio testing	31,843	31,821	31,799	31,778	31,756	31,735
sFlt-1:PlGF ratio testing uptake rate	100%	100%	100%	100%	100%	100%
Average number sFlt-1:PlGF tests per eligible patient	1.7	1.7	1.7	1.7	1.7	1.7
Number of services of sFlt-1:PlGF testing (AAAA and BBBB combined) (85% benefit = $51.00)	54,132	54,096	54,059	54,022	53,986	53,949
Cost to the MBS (with appropriate copayments excluded)	$2,760,748	$2,758,879	$2,757,010	$2,755,141	$2,753,272	$2,751,403
Net financial impact to the MBS	**$2,760,748**	**$2,758,879**	**$2,757,010**	**$2,755,141**	**$2,753,272**	**$2,751,403**
Change in use and cost of other health technologies						
Change in hospital admissions for monitoring	-8,311	-8,305	-8,300	-8,294	-8,288	-8,283
Change in hospital costs	-$32,304,740	-$32,282,870	-$32,261,001	-$32,239,132	-$32,217,262	-$32,195,393
Net financial implications of sFlt-1:PlGF ratio testing						

Parameter	Year 2024	Year 2025	Year 2026	Year 2027	Year 2028	Year 2029
Overall net cost to Commonwealth (MBS and hospitals)	-$29,543,992	-$29,523,991	-$29,503,991	-$29,483,990	-$29,463,990	-$29,443,989

Abbreviations: sFlt-1:PlGF = soluble FMS-like tyrosine kinase-1:placental growth factor, **MBS** = Medicare Benefits Schedule
Source: Adapted from ADAR Tables 41, 42, 43 and 44

The eligible populations were calculated based on 0.105 patients per birth at ≥24 weeks gestation with signs and symptoms or diagnosis of preeclampsia (from undescribed audit data included in the ADAR), being the estimated proportion of pregnancies indicated for sFlt-1:PlGF ratio testing. Because the population eligible for testing was calculated based on patients with signs or symptoms, it omitted patients with no signs nor symptoms but at increased risk, who would also be eligible for AAAA under the current wording.

The commentary agreed that the methods for calculating incident and prevalent populations were suitable; however, the total number of patients tested with sFlt-1:PlGF in 2024 was overestimated since sFlt-1:PlGF may only become available in early 2024 at the earliest. In addition, the ADAR assumed a 100% uptake rate, which the commentary considered was also not realistic. No disaggregation of utilisation/costs was presented for pregnant people presenting signs and symptoms of preeclampsia (population 1) compared with those with an existing diagnosis (population 2).

Given that the cost-offsets largely arose from the reduction of hospital admissions of pregnant people, there was unexplored uncertainty around the frequency of repeat testing and their implications on hospital admissions. As a result, net cost savings may have been overestimated in the ADAR. In addition, the population modelled in the budget impact has likely been underestimated – the ADAR did not account for those who could be serially re-tested due to their risk stratification, despite their test classifying them as low risk.

Finally, the budgetary impact was largely driven by data provided by a professor, which were undocumented. The commentary therefore considered the estimated budgetary impact was uncertain.

15. Other relevant information

Equality considerations

While preeclampsia can affect any pregnancy, certain patient groups may face unique equality issues when it comes to testing for this condition. These equality considerations are not exclusive to the sFlt-1:PlGF test but are applicable to preeclampsia testing more generally. Some potential equality issues related to preeclampsia testing include:

Socioeconomic disparities: Low-income individuals may face barriers in accessing adequate prenatal care, including preeclampsia testing. Lack of financial resources, limited healthcare facilities in underserved areas, and inadequate insurance coverage can all contribute to disparities in access to timely and accurate testing.

Racial and ethnic disparities: Certain racial and ethnic groups have been found to have a higher risk of developing preeclampsia; however, there may be disparities in the availability and quality of preeclampsia testing for these populations, potentially leading to delayed or missed diagnoses.

Implicit bias: Implicit biases among healthcare providers can influence the decision-making process regarding preeclampsia testing. Biases based on race, ethnicity, age, socioeconomic

status, or other factors may impact the level of attention, recommendation, or access to necessary tests, potentially leading to disparities in diagnosis and treatment.

Geographical disparities: Rural or remote areas may have limited access to the specialised healthcare facilities or resources required for preeclampsia testing. Limited availability of medical professionals, long travel distances, and lack of infrastructure can contribute to delays or reduced access to appropriate testing, affecting individuals living in these areas.

The public funding of the sFlt-1:PlGF test would neither exacerbate nor reduce these equality considerations.

Value of knowing

For pregnant people assessed as high risk (sFlt-1:PlGF >85), it was claimed in the ADAR that, following a decision to admit to hospital, the ratio test would provide additional 'value of knowing' to both patients and clinicians by reducing the anxiety associated with the ambiguity of a person's situation and providing relief in the knowledge that they are within reach of resources should their condition deteriorate.

As per the MSAC Guidelines, the ADAR was required to provide evidence supporting any claim that the key benefit of a test is from its impact in non-health outcomes (value of knowing). The ADAR did not adequately address the benefits and harms of receiving the test information versus what would happen in the absence of the test. The ADAR did not provide a tabulated (or otherwise) assessment of the proposed benefit or harm with reason and evidence. No quantitative evidence was provided to allow the consideration of the proportion of patients who experience the benefits and harms, or the magnitude of such benefits/harms. No qualitative evidence was provided in the absence of quantitative evidence either. Therefore the commentary was unable to make an evidence-based judgement on whether the value of knowing claim was justified, although considered it may be reasonable.

16.   Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues
- Overall, evidence supporting this application was sparse and of low quality. Evidence was not disaggregated for population 1 (risk of preeclampsia) versus population 2 (severity of preeclampsia).

- The evidence examined the sFlt-1:PlGF ratio itself, rather than the change in ratio over time. Ratio change over time may be associated with preeclampsia risk, but there was no evidence on how this can change management and/or improve health outcomes. Rate of change may be used to justify more frequent retesting, with risk of greater usage than was estimated by the applicant.

- The claim of non-inferior safety was not supported by evidence.

- The evidence for reduction in proportion of patients hospitalised was unconvincing, as it varied greatly between studies (studies reported -53.3%, -15.0%, and +23.7%). Further justification of the variability in inputs would assist MSAC's consideration.

- Patients with multiple pregnancies are a group at high risk of preeclampsia, yet very little data was provided for the use of testing in multiple pregnancies.

- Tighter definitions are needed of the at-risk population. Inclusion of the population with no signs nor symptoms of preeclampsia but "where there is an increased risk of preeclampsia" was not clarified by the applicant and introduced considerable uncertainty regarding test uptake, cost and value.

- There was considerable uncertainty about the likelihood of serial testing and implications for outcomes. The ADAR assumed an average of 1.7 tests per patient, however the basis for this figure was not provided and it may be unrealistic.

Economic issues:

- The choice of a cost-consequences analysis was inappropriate, although a cost-effectiveness analysis could be calculated using the ADAR's model, which gave an ICER of $3,331 per hospital admission avoided (without making other adjustments).

- The evidence for a reduction in proportion of patients hospitalised, which was a key driver of the model, may not be sufficiently robust.

- Retesting could change the downstream patient management (in either direction), which was not addressed, although retesting rate was not a key driver of the model. The applicant should consider incorporating retesting by clinical risk stratification into the economic model.

- Further consideration is needed about economic modelling of multiple births and the moderate risk group. MSAC's consideration would also be supported by incorporating a change in risk groupings.

- ESC considered that as the effect of ratio testing had not been established, intermediate outcomes appeared appropriate for the economic modelling.

Financial issues:

- The cost offset from hospitalisations avoided relied on the reduction in the proportion of patients hospitalised, which may not be sufficiently robust.

- If MSAC application 1705 is supported, then the number of people defined as "high risk" in the first trimester would likely substantially increase as there remains a significant incidence of preeclampsia despite aspirin prophylaxis. A sensitivity analysis of the utilisation and financial cost if 1705 is supported would facilitate MSAC's consideration.

Other issues

- The 'value of knowing' claim was unsupported by evidence. Providing a patient with a test result of unclear validity seems more likely to increase anxiety, than reduce it.

ESC discussion

ESC noted that this application requested Medicare Benefits Schedule (MBS) listing of soluble FMS-like tyrosine kinase-1:placental growth factor ratio (sFlt-1:PlGF) testing, to determine the risk of preeclampsia in pregnant people with signs and symptoms of preeclampsia or at high risk of preeclampsia (Population 1, proposed MBS item AAAA), and to determine the severity of preeclampsia in those already diagnosed (Population 2, proposed MBS item BBBB).

ESC noted that in preeclampsia there is impaired trophoblastic invasion, which can cause placental thromboses and infarcts, and that early preeclampsia (before 34 weeks gestation) tends to be more severe and is associated with intrauterine growth restriction (IUGR) and low birth weight. ESC noted preeclampsia is associated with maternal hypertension, and can result in proteinuria, thrombocytopenia and increased risk of miscarriage or stillbirth. There is also a risk of preterm delivery as the ultimate therapeutic option for preeclampsia management, and consequent risk of gestation-dependent neonatal morbidity and mortality. ESC noted that

preeclampsia is antecedent in 10-15% of direct maternal deaths (approximately 1 per year in Australia), and in one third of pre-term births (and approximately 200 deaths per year in Australia). The management of preeclampsia is informed by the gestation at which it occurs, and may include administration of steroids for fetal lung maturation, intravenous magnesium, and stabilisation of haemodynamic or haematological instability prior to delivery. In the Australian setting for rural and remote patients, timely antenatal transfer to a centre with appropriate neonatal intensive care should be considered in preference to post-natal transfer of a premature infant.

MSAC noted that the applicant had also lodged MSAC Application 1705 – Structured prenatal risk assessment for preterm preeclampsia[6], which is being considered by ESC and MSAC concurrently with this application. ESC considered that the interventions and patient populations covered in applications 1705 and 1706 did not overlap, however pregnant people identified as being at high risk of developing preterm preeclampsia at 11+0 to 13+6 weeks gestation using the intervention proposed in Application 1705 may subsequently be considered as being at high risk of preeclampsia given the reduced incidence, but incomplete abolition of events of preeclampsia following aspirin prophylaxis, which this application proposed would indicate them for sFlt-1:PlGF ratio testing from 24+0 weeks gestation. ESC therefore considered that MSAC's advice on Application 1705 may influence its consideration of this application.

ESC noted that in July 2022, the UK National Institute for Health and Care Excellence (NICE) had recommended PlGF-based tests in conjunction with standard clinical assessment, to help rule in or rule out suspected preeclampsia and help decide on care.

ESC noted that consultation feedback was supportive of sFlt-1:PlGF ratio testing, with comments including that it would allow the separation of patients with preeclampsia from those with hypertension, allow for surveillance, help decision-making on antenatal management and delivery timing, lower need for other blood tests and may be reassuring for those who had preeclampsia in a previous pregnancy. ESC noted a systematic review had concluded there is a higher incidence of postpartum depression in women with preeclampsia than in women without preeclampsia, and considered that the risks of postpartum depression should be considered in patients with preeclampsia. ESC noted that all practitioners who manage patients at risk for preeclampsia would require appropriate training in the use of the proposed test. ESC queried whether ratio testing would be available at all relevant pathology centres, but noted that while there is no obligation for providers to offer an MBS-listed test it is anticipated providers would offer it if it became a regular component of antenatal care. ESC considered that hospitalisation may also have access and equity issues for women in more remote areas (due to costs of travel, need to arrange care for other children, and the potential need for transfer if local hospitals did not have capacity to admit), and that reducing hospitalisation may mitigate these concerns.

ESC noted the item descriptor proposed for determining preeclampsia risk (AAAA) included patients with no signs nor symptoms but at "increased risk". ESC considered that evidence had not been presented to support this patient group, and that their inclusion had not been clarified by the applicant. ESC considered that inclusion of this poorly defined group introduced considerable uncertainty regarding test uptake, cost and value, and proposed that this population be removed from the MBS item descriptor (Table 13).

ESC also noted that the upper gestational limit for the test had not been defined. ESC considered that including this in the item descriptor would be appropriate, and suggested the addition of "in preterm pregnancies" to the item descriptor (Table 13).

---

[6] MSAC Application 1705 – Structured prenatal risk assessment for preterm preeclampsia.

Table 13 ESC's revised and combined item descriptor (CCCC)

Category 6 – PATHOLOGY SERVICES
MBS item CCCC Quantitative determination of the ratio of placental soluble FMS-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) from the beginning of the 24th week of pregnancy to evaluate the likelihood of preeclampsia in pregnancies where there are signs and symptoms suggestive of preeclampsia, or for the management (by categorising the severity) of diagnosed preeclampsia in preterm pregnancies. Applicable >2 to 4 weeks after a previous CCCC with ratio result of <38, and 1 week after a previous CCCC with ratio result of 38-85, and no further times during that pregnancy after a ratio result of >85.
Fee: $60.00 Benefit: 75% = $45.00 85% = $51.00
Note: The risk or severity of preeclampsia should be judged based on the sFlt-1:PlGF ratio, rather than individual values of sFlt-1 and PlGF. An sFlt-1:PlGF ratio <38 indicates low risk of preeclampsia in the following 2–4 weeks, review in 2–4 weeks and retest if clinical situation changes; an sFlt-1:PlGF ratio 38–85 indicates risk of preeclampsia, enhanced monitoring and retest after 1–2 weeks recommended; an sFlt-1:PlGF ratio >85 indicates the development or a diagnosis of preeclampsia requiring intensive monitoring.

Note: CCCC combines testing for the risk (AAAA) and severity (BBBB) of preeclampsia, and so is proposed to replace both.
Source: ESC.

ESC noted the current and proposed clinical management algorithm described in the PICO confirmation.

ESC considered the description of standard care for the comparator was reasonable. For assessing risk of preeclampsia (population 1), the comparator was point-of-care testing for proteinuria, or biochemical testing for urine protein:creatinine ratio, together with standard serum biochemistry. There is no current prognostic testing for assessing severity of preeclampsia (population 2), but clinical monitoring also includes repeat biochemistry as for population 1. In both populations, the intervention would be provided in addition to existing care.

ESC considered that the literature search appeared comprehensive, however considered that overall there was little evidence to support this application, and the available evidence was of low quality. ESC noted most of the studies were observational with moderate or high risk of bias, and there was no direct evidence so a linked approach was used. ESC noted only one study was conducted in Australia. ESC noted the evidence base consisted of three studies on the rule-out value of ratio testing (i.e. rule out preeclampsia diagnosis within 1 week), three studies on rule-in value within 2 weeks, four studies on the association between sFlt-1:PlGF ratio and time to delivery, and one study on the additive value of ratio testing to current clinical testing. No studies were provided on change in the ratio over time.

ESC noted no evidence was presented for safety. In the ADAR, the applicant stated that no studies were identified that specifically investigated the safety of the sFlt-1:PlGF ratio test; although the authors of the PreOS study reported that "there were no incidents or indirect harm associated with the use of the sFlt-1:PlGF ratio test in routine clinical practice in this population with suspected preeclampsia"[7]. However, ESC noted the same study reported that expert review of hospitalisation decisions based on ratio testing showed 11% of decisions to hospitalise and 5.9% of decisions to not hospitalise had been inappropriate, and considered that using ratio testing to inform hospitalisation decision-making could have adverse safety implications. ESC further noted that no evidence was presented regarding implications of misclassification or

---

[7] Klein E, et al. (2016). Influence of the sFlt-1/PlGF Ratio on Clinical Decision-Making in Women with Suspected Preeclampsia, *PloS one*: 11(5): e0156013.

potential downstream effects. Overall, ESC considered that insufficient evidence had been presented to support the claim of non-inferior safety.

ESC noted that study results were not disaggregated for populations 1 and 2. ESC considered that if patients have "clinical signs and symptoms" they may not have had proteinuria tests, and hence may not meet the definition of preeclampsia, and/or the two populations may overlap. ESC considered that as the evidence had been presented without disaggregation for risk vs severity and the items were both for the same test, combining the proposed item descriptors would be reasonable (new combined item CCCC to replace AAAA and BBBB, Table 13).

ESC noted that comprehensive evidence was presented supporting the accuracy of the sFlt-1:PlGF ratio test. ESC accepted the evidence showed a sFlt-1:PlGF ratio of <38 had a high accuracy for ruling out preeclampsia within 1 week (98.6% to 100% negative predictive value (NPV)). However, ESC considered it was unclear whether this rule-out value applied to people "at increased risk" but with no signs/symptoms of preeclampsia. ESC also considered that the proposal to retest 2-4 weeks after a ratio result of <38 upon clinical deterioration had uncertain implications for the rule-out value, as the applicant had not defined "deterioration" in the ADAR and in its pre-ESC response had reiterated that it sought not to define deterioration.

In contrast to the strong rule-out evidence, ESC considered the evidence for rule-in value of ratio testing for a result of >38 or >85 was poor (PPV of 37-58% and 55-70% respectively). ESC noted the higher PPV at higher ratios, however considered that the utility of ratio testing was unclear because patients with a ratio >85 were likely to be admitted to hospital anyway and to deliver soon. ESC noted that the evidence showed the ratio test result was associated with time to delivery, but considered that the evidence did not convincingly demonstrate that the expedited delivery could be attributed to adding ratio testing to standard observations and management.

For change in management, ESC noted substantial variation around hospital inpatient management: the ADAR stated the base case figure was a 72.6% decrease in admissions, yet other studies reported an increase in hospital admissions (21.2% increase), or a smaller decrease (16.2% decrease) – however this was a calculation of the 'difference' (i.e. the size of the difference relative to the crude average of intervention and comparator values) rather than of the 'change' (i.e. the size of the difference relative to the comparator value). ESC considered the changes in hospitalisation from comparator to intervention were the relevant figures for decision-making, and the data presented indicated the changes were a 23.7% increase for the INSPIRE trial, a 15.0% decrease for the PreOS trial, and a 53.3% decrease for the ROPE trial (see updates to Table 7). ESC noted that one USA study in 2015-17 had showed clinicians were much more likely to admit patients if aware of their ratio result, yet another similar earlier study had showed ratio testing was associated with fewer admissions. Notwithstanding their incorrect calculation in the ADAR, ESC considered the applicability of results for changes in hospitalisation rate to current clinical practice in Australia was uncertain. ESC considered that the discrepancy may be a result of improved understanding of risk and the associated thresholds, although if so this was not well-identified by the ADAR.

ESC considered that as the evidence did not examine effects of ratio testing on maternal and fetal health outcomes, the clinical significance of the ratio/deterioration relationship was unclear, and so utility of the test had not been established by the evidence.

ESC considered that changes in management that may take place in Australia following ratio testing may not have been captured in the literature or in NICE's modelling. For example, if ratio testing showed that a patient in a remote area had imminent preeclampsia necessitating transfer to a tertiary centre, then transfer of the pregnant patient could be done sooner, more simply and with potentially better health outcomes than a postnatal transfer of the patient with preterm baby. ESC considered that if a preterm delivery were being considered then ratio testing may be

able to rule out preeclampsia and so allow avoidance of antenatal steroid administration to quicken fetal lung development, which has diabetogenic risks to the pregnant patient and neurocognitive and infection risks to the fetus.

ESC noted the clinical evidence presented in the ADAR did not address the frequency of repeat testing, although ESC considered serial retesting was a real possibility. ESC noted the commentary had considered it was unclear how the frequency of repeat testing could influence the management of preeclampsia in Australia and, consequently, that the usefulness of frequent testing was uncertain. ESC noted that the ADAR provided evidence that examined the sFlt-1:PlGF ratio rather than the change in ratio over time, but that the pre-ESC response provided evidence that retesting can change a patient's risk category (Table 14). ESC considered that this evidence indicated a greater rate of ratio change in patients who go on to develop preeclampsia, but considered that this was not evidence of a change in management nor improvement in health outcomes associated with rate of ratio change over time, which ESC considered remained an area of substantial uncertainty for this application.

Table 14 Change in sFlt-1:PlGF ratio from a baseline ratio of 38-85 in patients who developed or did not develop preeclampsia

	Change in sFlt-1:PlGF ratio (change, IQR)	
Baseline sFlt-1:PlGF 38-85	2 weeks after baseline	3 weeks after baseline
Preeclampsia	35.80 (22-87-65.43)	45.81 (33.75-57.86)
No preeclampsia	19.77 (9.26-68.93)	23.84 (-2.77-74.56)

Abbreviations: **IQR** = interquartile range; **sFlt-1:PlGF** = soluble FMS-like tyrosine kinase-1:placental growth factor
Source: Pre-ESC response Table 1: from Zeisler 2019's exploratory analysis of n=550 women enrolled in the PROGNOSIS study.

ESC considered the practice notes on ratio interpretation were an informative decision aid. ESC considered that the frequency of repeated ratio testing should be justified by the evidence, and noted the applicant indicated in the pre-ESC response that it did not intend the MBS to fund serial testing. ESC considered that adding a frequency restriction to the item descriptor would be appropriate to prevent unlimited retesting (Table 13), and noted policy advice that this would be monitored through post-payment compliance. ESC considered the evidence may support retesting after >2-4 weeks where the ratio is <38, and retesting after 1 week where the ratio was 38-85 – but that no evidence was provided to support an appropriate retesting interval when the ratio was >85.

ESC also noted the ADAR's evidence base included studies of singleton pregnancies only, but that in the pre-ESC response the applicant had provided two studies supporting the rule-out value of a sFlt-1:PlGF ratio <38 in twin pregnancies (Table 15). ESC noted the applicant also commented that ratio testing is less discriminatory for preeclampsia in twin pregnancies so results beyond 30 weeks should be interpreted with caution. ESC considered this information about ratio testing in multiple pregnancies may be informative for MSAC.

Table 15 Rule-out value of sFlt-1:PlGF ratio <38 in twin pregnancies

Study	Study design	Patient population	NPV: rule-out PE within 1 week
Binder et al (2020)	Retrospective analysis of prospective cohort study (data collected January 2013 – October 2019)	Twin pregnancies with suspected PE (N=164)	98.8%
De La Calle	Pooled subgroup analysis of PROGNOSIS, STEPS and case-control study	Twin pregnancies enrolled in included studies (N=296)	91.9%

Abbreviations: **NPV** = negative predictive (rule-out) value; **PE** = preeclampsia
Source: Pre-ESC response Table 3: from Binder 2020 p180, and De La Calle 2021 Table 4.

The ADAR stated that results of the test were not expected to influence the incidence or severity of preeclampsia and knowledge of test results was not expected to influence health outcomes. However, the NICE Decision Support Unit model included maternal and neonatal long-term health outcomes, including mortality.

ESC noted the ADAR's economic evaluation was a cost-comparison analysis (CCA) in the form of a decision tree, essentially examining whether the additional cost of ratio testing was offset by cost-offsets from increased management outside hospital. ESC noted the economic analysis presented intervention costs per patient (cost savings), costs for a cohort of 100 patients, and reductions in hospital admissions for monitoring for 100 patients. ESC noted the model was based on a retrospective study that classified patients into two groups of hospitalisation risk with the comparator, versus three groups with the intervention. ESC considered there was therefore no change in effectiveness other than different categorisation. ESC noted the model resulted in a cost saving of $873 per patient ($87,264 per 100 patients) and 0.26 (26 per 100 patients) fewer admissions to hospital per patient.

ESC's validity testing of the model showed that ratio testing reduced the proportion of patients admitted to hospital from 49% to 23%. ESC noted that the model showed the proportion of patients with pre-term deliveries was unchanged by the intervention (29% at <34 weeks, and 28% at >34-<37 weeks), but that under the intervention more pregnant people who progress to pre-term deliveries would be managed out of hospital (<34 weeks: 12% rather than 3% of all patients; >34-<37 weeks: 23% rather than 12%). ESC also considered the purpose of including the delivery outcomes in the model was unclear, as their inclusion greatly increased costs but did not change outcomes. ESC's validity testing with costs of delivery removed found slight differences in the results (cost saving $880 per patient rather than $873), but it considered that this small discrepancy may be due to rounding.

ESC noted that the ADAR concluded efficacy was superior and safety was non-inferior, therefore a cost-effectiveness analysis (CEA) or cost-utility analysis (CUA) was appropriate according to the MSAC Guidelines. ESC also noted that the commentary had identified a CUA conducted by NICE, which demonstrated a CUA is possible for ratio testing, and reported a small gain of 0.0029 to 0.0046 quality-adjusted life years (QALYs). ESC considered that in principle a CEA/CUA was more appropriate than a CCA, however considered that the CCA model results could easily be used to calculate a cost per hospital admission avoided, which is an intermediate outcome. ESC noted that using the ADAR's CCA results to construct a CEA gave an incremental cost-effectiveness ratio (ICER) of $3,331 per hospital admission avoided (without making other adjustments) (Table 9). ESC recalled MSAC's general preference for a CUA over a CEA, and considered that MSAC will need to consider whether a CEA with ICER expressed in terms of cost per hospitalisation averted was sufficiently informative.

ESC considered that the main driver of the economic model was the reduction of hospital inpatient management (Table 10). ESC noted the base case had used the reduction in hospitalisation from the ROPE study, however ESC considered that whether the evidence supported a reduction was uncertain as some studies had showed ratio testing resulted in a smaller reduction or an increase in hospitalisations. ESC considered that it was uncertain whether the evidence of reduced hospital inpatient management was sufficiently robust and the choice of hospitalisation rate sufficiently justified, and that MSAC consideration would be supported by further justification of the variability in model inputs, such as sensitivity analyses of other hospitalisation rates.

ESC considered the model may have underestimated the hospitalisation costs associated with monitoring to some degree, although estimated the magnitude of this potential under estimation was low.

ESC considered that because maternal and neonatal long-term health outcomes had been omitted from the model, the real health benefit of testing was unclear. ESC noted that the NICE model had included some changes in management and maternal and fetal outcomes, and the commentary stated that if a QALY gain equivalent to that reported in the NICE model was assumed here, then the ICER became dominant. ESC considered that as the effect of ratio testing had not been established, intermediate outcomes were appropriate for the economic modelling. ESC further considered that the simplicity of the model was appropriate given the uncertainty that would arise with use of long-term outcomes.

ESC noted the ADAR had assumed 1.7 tests per patient, however ESC considered the basis for this figure was not clarified and it may be highly unrealistic. ESC noted the cost saving per patient increased to $915 if only 1 test per patient was applied, and considered this was marginal. In conjunction with the ADAR's economic model needing 17 tests per person before the cost-saving became a cost, ESC considered that retesting rate was not a key driver of the economic model, although may have financial implications. However, ESC considered that a key group for which re-testing may be important is those identified as being at moderate risk, and that data presented in the pre-ESC response demonstrated that these patients may potentially move risk groups after re-testing (Table 14). ESC considered that a reclassification of risk level may therefore change downstream management, but in an unknown direction. ESC raised whether the economic model should examine re-testing by risk stratification, and considered such analyses may be informative for MSAC.

ESC noted utilisation was estimated using an epidemiological approach, which contrasted with the market share approach the same applicant had used in concurrent application 1705.

ESC noted that the ADAR found the introduction of the sFlt-1:PlGF ratio test would result in a net cost saving for the Commonwealth of approximately $29 million per year over the next six calendar years. These projected net cost savings were a result of the anticipated costs to the MBS resulting from funding the sFlt-1:PlGF ratio test (approximately $2.7 million per year), being more than offset by the anticipated reduction in hospital admissions (from 49.0% to 22.9% of individuals; cost offset approximately -$32 million per year). However, given the uncertainty in the evidence for the difference in hospital admission rate, ESC considered the net cost saving may have been overestimated.

ESC noted the applicant claimed sFlt-1:PlGF ratio testing would also provide 'value of knowing' benefit for patients. However, ESC considered that providing results from a test of unclear validity would more likely increase than reduce anxiety. ESC noted that evidence had not been provided to support the claim of value of knowing, which the MSAC Guidelines state is required.

17. Applicant comments on MSAC's Public Summary Document

Roche wishes to thank the Medical Services Advisory Committee (MSAC) for reviewing and considering our application. While the outcome was disappointing, we respectfully accept the committee's findings.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website