



Australian Government
Department of Health

Application 1706

Angiogenic and anti-angiogenic markers for identification and management of preeclampsia

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au

Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):

Corporation name:

ABN:

Business trading name:

Primary contact name: REDACTED

Primary contact numbers

Business: **REDACTED**

Mobile: **REDACTED**

Email: **REDACTED**

Alternative contact name: REDACTED

Alternative contact numbers

Business: **REDACTED**

Mobile: **REDACTED**

Email: **REDACTED**

2. (a) Are you a lobbyist acting on behalf of an Applicant?

Yes

No

(b) If yes, are you listed on the Register of Lobbyists?

Not applicable

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Angiogenic and anti-angiogenic markers for identification and management of preeclampsia.

4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Preeclampsia is a pregnancy specific condition resulting in maternal hypertension and multisystem dysfunction. Preeclampsia affects 4-5% of pregnancies and continues to be a leading cause of maternal and perinatal mortality and morbidity.

Preeclampsia is traditionally diagnosed as pregnancy induced maternal hypertension in conjunction with pregnancy induced proteinuria. However, it is now recognised as a multi-system disorder which can affect maternal hepatic, haematological, neurological, cardio-respiratory, and other systems, as well as the fetoplacental unit leading to fetal growth restriction (FGR). Preeclampsia involving particularly the hepatic and haematological systems is called the HELLP (Haemolysis, Elevated Liver enzymes, Low Platelets) syndrome. The clinical features of preeclampsia do not necessarily indicate disease severity or likely rate of disease progression but result in heightened levels of surveillance and investigation to avoid potential adverse pregnancy outcomes. These clinical features are not specific to women who have preeclampsia, so levels of surveillance and intervention in pregnancy are increased for a significant number of women who do not have this disease.

Women with preeclampsia have abnormal levels of angiogenic and anti-angiogenic factors with low levels of placental growth factor (PlGF) and high levels of placental soluble fms-like tyrosine kinase-1 (sFlt-1). The sFlt-1 / PlGF ratio increases several weeks before the onset of clinical symptoms and signs of preeclampsia and is more marked in cases of early onset and severe disease and can be used to improve recognition and management of this disease and reduce costs of health care.

5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

Women identified as having clinical and/or biochemical symptoms and signs of preeclampsia will be offered an sFlt-1 / PlGF test as a means of confirming the likelihood of this diagnosis and the immediate severity of disease.

The results of the sFlt-1 / PlGF test can be used to:

Identify a cohort of women who do not, in fact, have preeclampsia and who can be managed along the normal antenatal pathway.

Identify a cohort of women at intermediate risk of preeclampsia who would benefit from an increased level of outpatient assessment. This may include repeat sFlt-1 / PlGF testing later in the pregnancy.

Identify a cohort of women at high risk of imminent adverse outcome who can be managed through timely admission and preparation for delivery to mitigate these risks to maternal and fetal outcome.

6. (a) Is this a request for MBS funding?

- Yes
 No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

- Amendment to existing MBS item(s)
 New MBS item(s)

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

Not applicable

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

Not applicable

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

- i. A new item which also seeks to allow access to the MBS for a specific health practitioner group
- ii. A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
- iii. A new item for a specific single consultation item
- iv. A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

- Yes
- No

(g) If yes, please advise:

Not applicable

7. What is the type of service:

- Therapeutic medical service
- Investigative medical service
- Single consultation medical service
- Global consultation medical service
- Allied health service
- Co-dependent technology
- Hybrid health technology

8. For investigative services, advise the specific purpose of performing the service (which could be one or more of the following):

- i. To be used as a screening tool in asymptomatic populations
- ii. Assists in establishing a diagnosis in symptomatic patients
- iii. Provides information about prognosis
- iv. Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
- v. Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

9. Does your service rely on another medical product to achieve or to enhance its intended effect?

- Pharmaceutical / Biological
- Prosthesis or device
- No

10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

Not applicable

(b) If yes, please list the relevant PBS item code(s):

Not applicable

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

Not applicable

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Not applicable

11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

Not applicable

(b) If yes, please provide the following information (where relevant):

Not applicable

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

Not applicable

(d) Are there any other sponsor(s) and/or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

12. Please identify any single and / or multi-use consumables delivered as part of the service?

Nil

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

13. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: in-vitro diagnostic test

Manufacturer's name: This application does not seek reimbursement for patented technologies

Sponsor's name: This application does not seek reimbursement for patented technologies

- (b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

Class III

AIMD

N/A

14. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

Yes (If yes, please provide supporting documentation as an attachment to this application form)

No

- (b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

Yes (if yes, please provide details below)

No

sFlt-1

ARTG listing, registration or inclusion number: 181222

TGA approved indication(s), if applicable: n/a

TGA approved purpose(s), if applicable: IVDs that are intended to be used for the qualitative and/or quantitative determination of proteins specific to clinical chemistry in a clinical specimen

PIGF

ARTG listing, registration or inclusion number: 181221

TGA approved indication(s), if applicable: n/a

TGA approved purpose(s), if applicable: IVDs that are intended to be used for the qualitative and/or quantitative determination of clinical chemistry hormones in a clinical specimen

15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

Not applicable

16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

Not applicable

PART 4 – SUMMARY OF EVIDENCE

17. Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	Review	Preeclampsia. Mol et al. Lancet 2016; 387: 999-1011.	Comprehensive review of this obstetric syndrome.	doi: 10.1016/S0140-6736(15)00070-7.	March 2016
2.	Guideline	SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014 Lowe SA et al. Aust NZ J Obstet Gynaecol 2015; 55: e1-29.	Describes the current national guidelines for diagnosis and management of preeclampsia.	doi: 10.1111/ajo.12399.	October 2015
3.	Nested case control study.	Circulating angiogenic factors and the risk of preeclampsia. Levine RJ et al. N Engl J Med 2004; 350: 672-683.	Describes changes in sFlt-1 and PlGF in preeclamptic pregnancies and controls. Identifies the increase in sFlt-1 and decrease in PlGF seen in preeclamptic pregnancies.	doi: 10.1056/NEJMoa031884	February 2004
4.	Nested case control study	Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. Levine RJ et al. N Engl J Med 2006; 194: 1034-1041	Describes use of the sFlt-1: PlGF ratio as a predictive tool for preeclampsia	doi: 10.1056/NEJMoa055352	September 2006

5.	<p>Prospective multicentre observational study.</p> <p>Recruited women clinically suspected of having preeclampsia.</p> <p>Included Royal Hospital for Women, Melbourne</p>	<p>Predictive value of the sFlt-1:PIGF ratio in women with suspected preeclampsia.</p> <p>Zeisler H et al. N Engl J Med 2016; 374: 13-22</p>	<p>Developed prediction cut-offs and validated these in a second cohort.</p> <p>sFlt:PIGF <38 predictive of absence of preeclampsia.</p> <p>Described screening efficacy in relation to 1 and 4 week outcomes.</p>	doi: 10.1056/NEJMoa1414838	January 2016
6	Cost-effectiveness study (Germany)	<p>Schlembach et al. Economic assessment of the use of the sFlt-1/PIGF ratio test to predict preeclampsia in Germany, BMC Health Services Research (2018) 18:603</p>	<p>Cost-effectiveness of sFlt-1/PIGF when used to rule out occurrence of PE.</p> <p>Cost savings of €361 per patient when compared to no test scenario</p>	https://doi.org/10.1186/s12913-018-3406-1	2018
7	Cost-effectiveness study (UK)	<p>Vatish et al, sFlt-1/PIGF ratio test for preeclampsia: an economic assessment for the UK, Ultrasound Obstet Gynecol. 2016 Dec;48(6):765-771</p>	<p>Cost-effectiveness of sFlt-1/PIGF when used to rule out occurrence of PE.</p> <p>Cost savings of £344 per patient when compared to no test scenario</p>	doi: 10.1002/uog.15997	November 2016
8	Cost-effectiveness study (Italy)	<p>Frusca et al, Budget impact analysis of sFlt-1/PIGF ratio as prediction test in Italian women with suspected preeclampsia J Matern Fetal Neonatal Med . 2017 Sep;30(18):2166-2173</p>	<p>Cost-effectiveness of sFlt-1/PIGF when used to rule out occurrence of PE.</p> <p>Cost savings of €2384 per patient when compared to no test scenario</p>	doi:10.1080/14767058.2016.1242122	September 2017

9	Cost-effectiveness study (Brazil)	Figueira et al, Economic evaluation of sFlt-1/PIGF ratio test in preeclampsia prediction and diagnosis in two Brazilian hospitals Pregnancy Hypertens. 2018 Jul;13:30-36	Cost-effectiveness of sFlt-1/PIGF when used to rule out occurrence of PE. Cost savings of BRL185 (public) -636 (private) per patient when compared to no test scenario.	doi: 10.1016/j.preghy.2018.04.014.	July 2018
10	Cost-effectiveness study (Japan)	Ohkuchi et al, Economic evaluation of the sFlt-1/PIGF ratio for the short-term prediction of preeclampsia in a Japanese cohort of the PROGNOSIS Asia study Hypertension Research volume 44, pages 822–829 (2021)	Cost-effectiveness of sFlt-1/PIGF when used to rule out occurrence of PE. Cost savings of 16,373 JPY per patient when compared to no test scenario.		

18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). Please do not attach full text articles, this is just intended to be a summary.

	Type of study design*	Title of research	Short description of research	Website link to research	Date
1.	Patient data base at Royal Women`s Hospital Melbourne		1700 completed entries of pregnancies tested with sFlt-1/PIGF ratio at the RWH. Data includes; outcomes of test, gestational age at birth, Date of Delivery Labour Type Mode of Delivery, Antenatal Time in Hospital, Any Maternal, Co-morbidities, Labour or Baby comments.		

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

19. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):

- Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)
- The Royal College of Pathologists of Australasia (RCPA)
- Royal Australian and New Zealand College of Radiologists (RANZCR)
- Society of Obstetric Medicine of Australia and New Zealand (SOMANZ)
- Australasian Society for Ultrasound in Medicine (ASUM)
- The Royal Australian College of General Practitioners (RACGP)

20. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):

None identified

21. List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):

- Australian Action on Preeclampsia Inc. (AAPEC)

22. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:

- Roche Diagnostics
- Thermo Fisher
- PerkinElmer

23. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):

Name of expert 1: REDACTED

Name of expert 2: REDACTED

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

The PICO presented in this section describes sFlt-1/PlGF ratio testing being implemented in the Australian health care system in its current state. An appendix is provided in this Application Form to describe sFlt-1/PlGF ratio testing should the *Structured prenatal risk assessment for preterm preeclampsia* algorithm as proposed in the simultaneous MSAC application, also be implemented.

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:

Definition:

Preeclampsia is a pregnancy specific condition that affects multiple organ systems. It is most typically defined as a condition with pregnancy induced increased blood pressure (above 140mmHg systolic and/or 90mmHg diastolic) combined with dysfunction in at least one of renal, hepatic, haematological, neurological or respiratory systems and/or with evidence of placental insufficiency and fetal growth restriction.

A more extended description of the systemic anomalies associated with preeclampsia is reported in the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) guideline (2014).

Preeclampsia has been categorised as early (delivery <34 weeks) or preterm (delivery <37 weeks) or late (delivery >37 weeks' gestation) in onset.

Natural history:

Although the aetiology of preeclampsia is not fully understood, both the placenta and the maternal vascular endothelium are centrally involved in the pathophysiology of the disease. The majority of cases that are severe and lead to early (<34 weeks' gestation) delivery are associated with placental insufficiency. Poor placental implantation causes placental hypoxia, altering release of angiogenic factors that impact both placental development and the maternal endothelium. Vascular endothelial dysfunction results in the end stage features (vasoconstriction, hypertension and organ dysfunction) seen in a woman who is symptomatic for the disease.

The development of clinical symptoms and signs of preeclampsia is associated with further angiogenic dysregulation and exacerbation of disease. The health and wellbeing of the patient will continue to decline until the pregnancy is delivered – which includes delivery of the placenta.

The identification of pre-clinical and clinical stages of disease provide an opportunity for identification of women at high risk and for intervention before a woman becomes symptomatic.

Burden of disease:

Preeclampsia causes significant maternal and perinatal mortality and morbidity. Mothers that develop preeclampsia may have an eclamptic fit and/ or other neurological sequelae (such as a cerebrovascular accident), renal and hepatic impairment can be long lasting, haematological dysfunction can lead to postpartum haemorrhage, and significant uncontrolled hypertension is also associated with placental abruption.

Worldwide, the disease is one of the commonest causes of maternal mortality and approximately 60,000 mothers die from the morbidities of preeclampsia each year. Whilst maternal deaths are rare in Australia, this is part due to clinical supervision and the decision to deliver women affected by severe preeclampsia to break the pathological cycle of disease (by removing the placenta). Preterm delivery has a very significant impact on the fetus and is associated with 500,000 deaths worldwide p.a. Approximately 15%

of admissions in Australian neonatal intensive care units are the result of severe early onset preeclampsia. Approximately 1,200 infants are born prematurely (<34 weeks) in Australia because of maternal preeclampsia each year.

Women who develop preeclampsia during pregnancy have an increased risk of hypertension in later life and of other cardiovascular diseases and stroke. The risk is most significant in those women who have early onset / severe preeclampsia. Severe early onset preeclampsia carries a similar ongoing risk for cardiovascular disease as smoking.

Preterm birth is also associated with increased risks of neurodevelopmental disability, increased special educational needs and ongoing cardiovascular and metabolic disease.

25. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

The sFlt-1 / PIGF ratio is proposed to be used for prediction, identification and management of preeclampsia in pregnancies from 24 weeks gestation.

Prediction and Identification

Women who have signs and or symptoms of preeclampsia (and in whom preeclampsia is not already diagnosed)

Suspicion of preeclampsia can be due to any of the below;

- New onset of increased blood pressure
- Exacerbation of pre-existing hypertension
- New onset proteinuria
- Exacerbation of pre-existing proteinuria
- Preeclampsia related clinical features (epigastric pain, excessive oedema, headache, visual disturbances, sudden weight gain)
- Abnormal uterine artery Doppler sonography
- Fetal growth restriction

For management, planning and decision making among women diagnosed with preeclampsia

The rate of change of the sFlt-1/PIGF ratio in consecutive tests indicates the severity of preeclampsia and the rate of progression of the disease, including earlier onset disease and placental dysfunction.

Women who developed preeclampsia had a greater ratio change over two weeks compared with those who did not develop preeclampsia [Zeisler 2019], indicating it is appropriate to re-test in 1–2 weeks to determine the trend.

26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

Currently managed through routine antenatal care until clinical symptoms and signs suspicious of preeclampsia develop.

PART 6b – INFORMATION ABOUT THE INTERVENTION

27. Describe the key components and clinical steps involved in delivering the proposed medical service:

Management of women who present with clinical features of preeclampsia, but have a test result <38

For women with signs and symptoms of preeclampsia, an sFlt-1/PIGF ratio test result <38 would rule out preeclampsia in the next 2–4 weeks.

These women can be managed as outpatients depending on their individual circumstances and the symptoms with which they have presented. Individualised management will be dependent on other clinical and ultrasound risk factors: if no new symptoms occur, most clinics would review in 2–4 weeks.

Retesting sFlt-1/PIGF ratio should cease upon cessation of clinical features of preeclampsia.

Management of women with a ratio test result of 38–85

Women who return a ratio test of 38–85 will require greater surveillance, mostly as outpatients, with a retest after 1–2 weeks to assess any change in the markers. Dependent on the retest and the clinical context, further ratio testing may be necessary. These women are considered at higher risk and should be informed of symptoms requiring more immediate medical attention. Regular BP monitoring is also recommended.

In a real-world study, Dröge et al found that the remaining pregnancy duration for women with a sFlt-1/PIGF-ratio of 38–85 was 23 days (IQR, 9–46) if they were <34 weeks of gestation and 6 days (IQR, 2–12) if they were >34 weeks [Droge et al, 2021]. Additionally, Zeisler et al showed the importance of the rate of change (delta) between two measurements. Women who developed preeclampsia had a delta sFlt-1/PIGF between tests two weeks apart of 31.22 whereas these who did not develop the disease had a delta of 1.45 [Zeisler 2019]. It is therefore advisable to re-test in 1–2 weeks and determine the trend.

Criteria for hospital admission (ratio test result of 38–85)

Women should be hospitalised when there are clear signs and symptoms indicating preeclampsia and/or suspected fetal compromise.

Clear clinical signs indicate a need to admit regardless of the sFlt-1/PIGF ratio. If symptoms indicate diagnosis, women are often admitted for monitoring over longer periods of time. Clinical features that form part of the diagnosis include high blood-pressure, protein in urine, severe upper abdominal pain or abnormal uterine artery Doppler sonography as well as high ratio scores, as described by the Oxford protocol and INSPIRE study [Cerdeira 2019].

Ratio testing can inform decision making in routine clinical practice. In the PreOs study, the ratio result changed the hospitalisation decision in 16.9% of mothers; in 11.0% of the women, the initial decision to hospitalise was changed to no hospitalisation, while in 5.9% the revised decision was hospitalisation [Klein 2016].

Management of women with a test result >85

Women in this group probably have, or will develop, preeclampsia and require intensive monitoring, typically as inpatients.

Using a ratio cut-off value of ≥ 85 has been assessed as a secondary endpoint of the INSPIRE trial; the study found that a ratio of 85 had a positive predictive value of 71.7% to rule in preeclampsia within 4 weeks [Cerdeira 2021]. Furthermore, in the ROPE study, among women suspected of having preeclampsia, an sFlt-1/PIGF ratio >85 had a positive predictive value of 74% among patients presenting at <34 weeks for the presence of severe preeclampsia within 2 weeks [Rana 2018].

Patients in this group will typically be admitted to hospital eventually, due to either worsening preeclampsia, or the need for closer monitoring.

In the absence of severe symptoms or suspected fetal compromise, women can be managed as outpatients, discharged home and with close follow-up monitoring unless or until disease progresses.

Criteria for hospital admission (ratio test result of >85)

Women should be hospitalised when there are clear signs and symptoms indicating preeclampsia.

Patients with diagnosed preeclampsia are usually hospitalised. The majority of patients in this group will be admitted to hospital eventually, either because they have preeclampsia, or because they need to be closely monitored (92% were hospitalised in the ROPE study among patients who had an sFlt1/PlGF ratio over 85) [Rana 2012]. The ratio is particularly useful between 24–34 weeks of gestation, facilitating the very complex, individually-based and integrated clinical decision-making process regarding optimal timing of a likely preterm delivery.

Women with a ratio >200 are at an increased risk for fetal adverse events and require intensive monitoring [Rana 2012, Gaccioli 2018, Garcia-Manau 2021]. If FGR is confirmed, the ratio tends to be higher but remains stable for longer and other parameters, such as cardiotocography and Doppler ultrasound, may be better indications for admission. As high ratios are found in severe FGR, it does not necessarily lead to earlier development or more severe preeclampsia.

28. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

No trademarked components are involved.

29. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

Not applicable.

30. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

No anticipated limitations on provision

31. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:

No additional healthcare resources

32. If applicable, advise which health professionals will primarily deliver the proposed service:

Shared Care General Practitioners
Obstetricians
Midwives

33. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

Not applicable

34. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

Not applicable

35. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:

PlGF/SfLT biomarkers assays can be run in any NATA accredited laboratory

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select ALL relevant settings):

- Inpatient private hospital (admitted patient)
- Inpatient public hospital (admitted patient)
- Private outpatient clinic
- Public outpatient clinic
- Emergency Department

- Private consulting rooms – GP
- Private consulting rooms – specialist
- Private consulting rooms – other health practitioner (nurse or allied health)
- Private day surgery clinic (admitted patient)
- Private day surgery clinic (non-admitted patient)
- Public day surgery clinic (admitted patient)
- Public day surgery clinic (non-admitted patient)
- Residential aged care facility
- Patient's home
- Laboratory
- Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

The test needs to be available in both inpatient and outpatient settings.

The test needs to be available to both public and private patients.

The biochemical component of the test needs to be performed in a laboratory.

37. Is the proposed medical service intended to be entirely rendered in Australia?

- Yes
- No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

38. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

The sFlt-1/PIGF test is proposed to be used predictively in place of standard diagnostic tests administered at 24-36 weeks gestation.

The comparator is therefore the following standard diagnostic tests;

- Blood pressure
- Urine protein:creatinine ratio test
- Proteinuria reagent strip test
- Full blood count
- Renal function test
- Serum electrolytes
- Hepatic transaminases

39. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

- Yes (please list all relevant MBS item numbers below)
- No

40. Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):

In the absence of sFlt-1/PIGF testing women identified as being at risk of developing preeclampsia would be managed through increased monitoring including repeat diagnostic testing, clinical assessments, pregnancy day care monitoring, and pre-emptive hospitalisations.

While the biochemical comparators in paragraph 38 above help diagnose preeclampsia, none of them have the predictive capacity of the sFlt-1/PIGF test.

41. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

- In addition to (i.e. it is an add-on service)
- Instead of (i.e. it is a replacement or alternative)

(b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:

Not applicable

42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):

The additional information provided by the sFlt-1/PIGF test results in management decisions for women with suspected preeclampsia that are better correlated with preeclampsia outcomes than are current diagnostic procedures alone.

The sFlt-1/PIGF ratio test reduces unnecessary hospitalisation of women at low risk of developing preeclampsia in the short term while also identifying high-risk individuals requiring appropriate management. Reducing unnecessary hospitalisations and outpatient visitations has been demonstrated to result in significant cost savings in healthcare systems.

The PROGNOSIS study demonstrated that without sFlt-1/PIGF testing, 36% of women were hospitalised before a diagnosis of preeclampsia. If the additional information from the sFlt-1/PIGF test had been available, the proportion of women hospitalised could have been reduced to around 16% (Vatish 2016).

Published cost-effectiveness modelling based on the PROGNOSIS study estimated cost savings of between \$206 and \$1063 AUD per patient eligible for sFlt-1/PIGF testing.

Cost savings estimated in literature (PROGNOSIS)	Savings per patient	AUD <small>(www.xe.com July 2021)</small>
Schlembach et al. 2018 (Germany)	€ 361	\$ 570
Frusca et al. 2017 (Italy)	€ 673	\$ 1063
Vatish et al. 2016 (UK)	£ 344	\$ 633
Ohkuchi et al. 2021 (Japan)	¥ 16,373	\$ 206
	Average	\$ 618

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

43. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

The PROGNOSIS study demonstrated that without the sFlt-1/PIGF test, 36% of women were hospitalised before a diagnosis of preeclampsia, of whom 27% went on to develop preeclampsia. If the additional information from the test had been available, the proportion of women hospitalised could have been reduced to around 16%, of whom 38% would have subsequently developed preeclampsia.

Preeclampsia causes significant maternal and perinatal mortality and morbidity. Mothers that develop preeclampsia may have an eclamptic fit and/ or other neurological sequelae (such as a cerebrovascular accident), renal and hepatic impairment can be long lasting, haematological dysfunction can lead to postpartum haemorrhage, and significant uncontrolled hypertension is also associated with placental abruption.

Women who develop preeclampsia during pregnancy have an increased risk of hypertension in later life and of other cardiovascular diseases and stroke. The risk is most significant in those women who have early onset / severe preeclampsia. Severe early onset preeclampsia carries a similar ongoing risk for cardiovascular disease as smoking.

Preterm birth is also associated with increased risks of neurodevelopmental disability, increased special educational needs and ongoing cardiovascular and metabolic disease.

44. Please advise if the overall clinical claim is for:

- Superiority
 Non-inferiority

45. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Safety Outcomes:

Better clinical management guided by sFlt-1/PlGF testing has been shown to facilitate early recognition of developing preeclampsia, thereby reducing the incidence of maternal adverse events such as;

- eclamptic fits and / or other neurological sequelae (such as a cerebrovascular accident)
- renal and hepatic impairment
- haematological dysfunction and postpartum haemorrhage
- placental abruption

Preeclampsia is also associated with preterm birth which increases risks of neurodevelopmental disability, increased special educational needs and ongoing cardiovascular and metabolic disease in the child. Early anticipation of preterm birth allows timely administration of evidence based interventions that optimise the outcome of premature infants, such as; corticosteroid and magnesium treatments to improve respiratory and neurological function and outcomes respectively.

Clinical Effectiveness Outcomes:

sFlt-1/PlGF testing enables improved clinical management of pregnancies identified as high-risk, or symptomatic of preeclampsia, moreover, it identifies pregnancies not at high-risk of preeclampsia, which leads to a significant reduction in over treatment, to normal pregnant women, e.g., minimises unnecessary hospitalisations.

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

46. Estimate the prevalence and/or incidence of the proposed population:

Latest release from the Australian Bureau of Statistics stated that there were 305,832 registered births in 2019, a decrease of 3.0% from 2018.

<https://www.abs.gov.au/statistics/people/population/births-australia/latest-release>

This figure is used in place of accurate figures of pregnancies per year.

47. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

Current analysis of the patient data base at RWH indicates that 10% of an antenatal population would receive an average of 2 sFlt-1/PIGF tests per pregnancy.

48. How many years would the proposed medical service(s) be required for the patient?

The patient would only be eligible for the test whilst pregnant.

49. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

Current analysis of the patient data base at RWH indicates that 10% of an antenatal population would be eligible for sFlt-1/PIGF testing.

50. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:

Estimated uptake and utilisation is provided below. No leakage beyond targeted populations is anticipated.

Three year estimates for utilisation	Year 1	Year 2	Year 3
Births per year (ABS)	305,832	305,832	305,832
Percentage of pregnancies estimated to become eligible for sFlt-1/PIGF testing due to clinical signs and symptoms of preeclampsia.	10%	10%	10%
Total eligible patient population	30,583	30,583	30,583
Average number of sFlt-1/PIGF tests performed per eligible patient	2	2	2
sFlt-1/PIGF utilisation per year	61,166	61,166	61,166
Cumulative utilisation	61,166	122,333	183,499

PART 8 – COST INFORMATION

51. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

Applicant is in the process of consultation with relevant service providers

52. Specify how long the proposed medical service typically takes to perform:

Turnaround expected to be within a day

53. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

Category 6 PATHOLOGY SERVICES
Quantitative determination of placental growth factor (PIGF) and of placental soluble fms-like tyrosine kinase-1 (sFlt-1) to predict, identify or manage preeclampsia in pregnancies from 24 gestational weeks.
Fee: \$**.**

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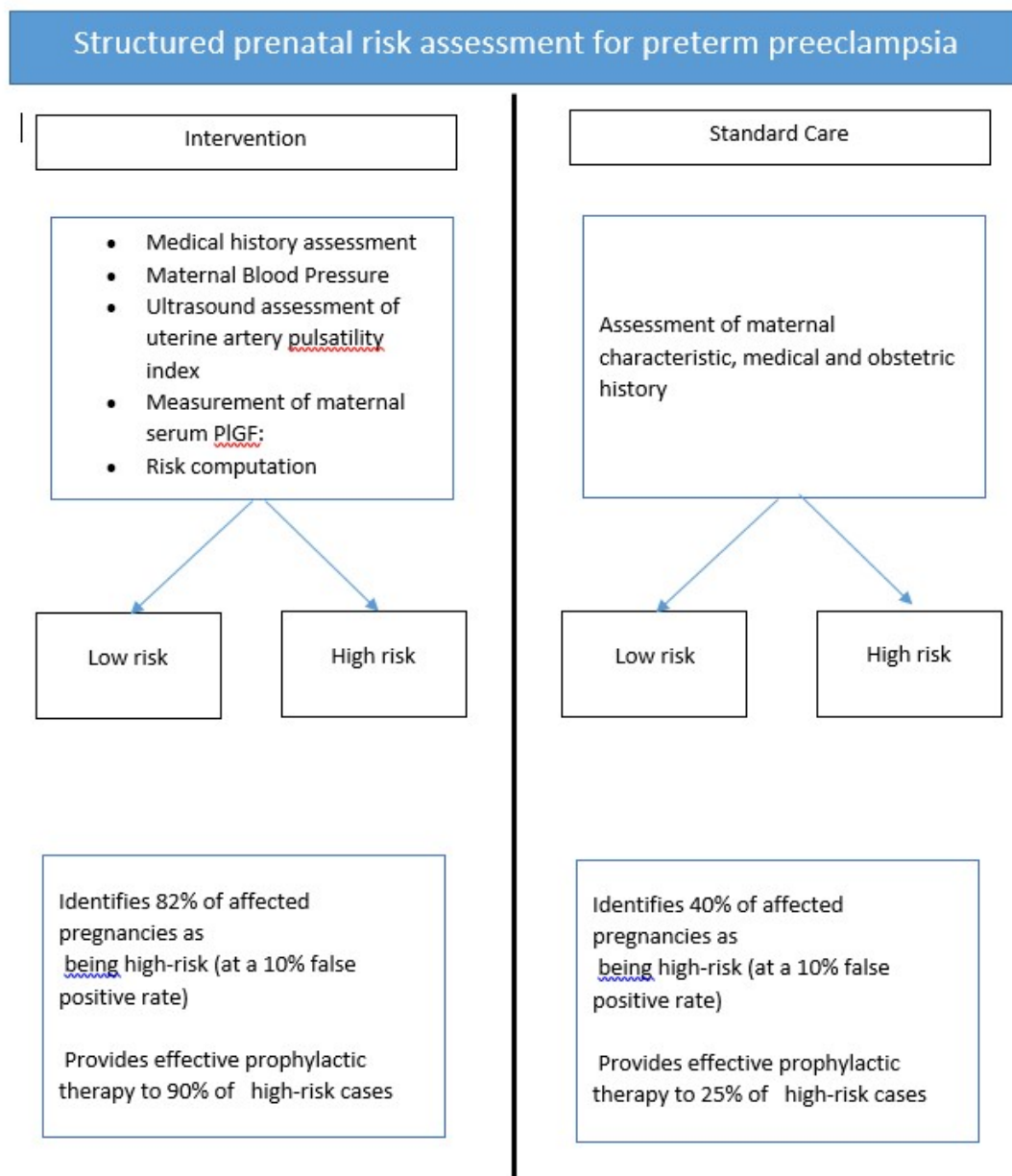
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Appendix

Effects of the implementation of the early pregnancy *Structured prenatal risk assessment for preterm preeclampsia* algorithm.

Low dose aspirin (LDA) administered in early pregnancy

In the event that the *Structured prenatal risk assessment for preterm preeclampsia* is successfully implemented into Australian healthcare system, low-dose aspirin (LDA) will be prescribed to a greater number of pregnant women as summarised briefly below.



However, research has demonstrated that LDA administered in early pregnancy does **not** result in a statistically significant difference in sFlt-1 / PIGF values during the latter half of pregnancy (Mayer-Pickel 2019). The increased uptake of LDA is therefore not expected to have any artifactual effect on the measurement of the sFlt-1 / PIGF ratio, nor on the detection of clinical signs and/or symptoms

(if and when they appear), or the clinical utility of sFlt-1 / PlGF in predicting and managing preeclampsia.

Patient populations

The additional information provided to clinicians by the implementation of the algorithm proposed in *Structured prenatal risk assessment for preterm preeclampsia* allows clinicians to proactively monitor patients identified as high-risk of developing preeclampsia in later pregnancy.

Women identified as high-risk through first trimester risk assessment should receive closer antenatal surveillance in anticipation of identifying developing signs and symptoms of preeclampsia (eg, using sFlt-1 / PlGF testing), thereby allowing for more timely diagnosis of preeclampsia and the institution of appropriate therapies to minimise maternal and perinatal morbidity.

The implementation on the *Structured prenatal risk assessment for preterm preeclampsia* is therefore expected to complement the clinical and resource utilisation benefits of sFlt-1 / PlGF testing as demonstrated in the literature.

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