

# Placental Growth Factor (PlGF)-Based Biomarker Testing to Help Diagnose Pre-eclampsia in People With Suspected Pre-eclampsia: A Health Technology Assessment

## Key Messages

### What Is This Health Technology Assessment About?

Pre-eclampsia is a potentially serious condition that affects up to 1 in 20 pregnant people, most often after 20 weeks of pregnancy. Diagnosing pre-eclampsia can be difficult because symptoms and signs differ from person to person. Assessment begins during routine pregnancy appointments, when blood pressure is measured and risk factors for pre-eclampsia are checked. Blood tests have been developed to measure placental growth factor (PlGF), a protein that indicates the function of the placenta. The tests are used along with standard clinical assessment.

This health technology assessment looked at how effective and cost-effective PlGF-based biomarker testing is to help diagnose pre-eclampsia. It also looked at the budget impact of publicly funding PlGF-based biomarker testing and at the experiences, preferences, and values of people with confirmed or suspected pre-eclampsia.

### What Did This Health Technology Assessment Find?

Compared with standard clinical assessment alone, PlGF-based biomarker testing likely improves prediction of pre-eclampsia in people who are between 20 weeks and 36 weeks plus 6 days' gestation. It also may reduce time to diagnosis, severe adverse maternal outcomes, and length of stay in the neonatal intensive care unit, although the evidence is uncertain. PlGF-based biomarker testing may result in little to no difference in other clinical outcomes such as maternal admission to hospital and perinatal adverse outcomes.

We could not determine the cost-effectiveness of PlGF-based biomarker testing given uncertain evidence around important clinical outcomes. We estimate that publicly funding PlGF-based biomarker testing for people with suspected pre-eclampsia in Ontario over the next 5 years would cost an additional \$1.83 million.

The people we spoke with valued PlGF-based biomarker testing to help diagnose pre-eclampsia. They felt that patient education and equitable access should be requirements for implementation, particularly in rural and underserved areas.

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The statements, conclusions, and views expressed in this report do not necessarily represent the views of those we consulted.

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## A Note About Terminology

As a government agency, Ontario Health can play an active role in ensuring that people of all identities and expressions recognize themselves in what they read and hear from us. We recognize that gender identities are individual and that many people who give birth are not women, despite being assigned female sex at birth. Thus, in this health technology assessment, we use gender-inclusive pronouns and terms as much as possible. However, when citing published literature that uses the terms “woman,” “women,” “mother,” “pregnancy,” or “maternal,” we also use these terms for consistency with these cited studies.

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# Abstract

## Background

Pre-eclampsia is a potentially serious condition affecting up to 5% of pregnancies, most frequently after 20 weeks' gestation. Placental growth factor (PlGF)-based tests measure either the blood level of PlGF or the ratio of soluble fms-like tyrosine kinase-1 (sFlt-1) to PlGF. They are intended to complement standard clinical assessment to help diagnose pre-eclampsia in people with suspected pre-eclampsia. We conducted a health technology assessment of PlGF-based biomarker testing as an adjunct to standard clinical assessment to help diagnose pre-eclampsia in pregnant people with suspected pre-eclampsia, which included an evaluation of diagnostic accuracy, clinical utility, cost-effectiveness, the budget impact of publicly funding PlGF-based biomarker testing, and an assessment of preferences and values.

## Methods

We performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each included study using AMSTAR 2, Cochrane Risk of Bias tool, the Quality of Diagnostic Accuracy Studies 2 (QUADAS-2) tool, and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic literature search of the economic evidence. We did not conduct a primary economic evaluation as the impact of the test on maternal and neonatal outcomes is uncertain. We also analyzed the budget impact of publicly funding PlGF-based biomarker testing in pregnant people with suspected pre-eclampsia in Ontario. To contextualize the potential value of PlGF-based biomarker testing, we spoke with people whose pregnancies had been impacted by pre-eclampsia as well as their family members.

## Results

We included one systematic review and one diagnostic accuracy study in the clinical evidence review. The Elecsys sFlt-1/PlGF ratio test using a test cut-off of less than 38 for ruling out pre-eclampsia within 1 week yielded a negative predictive value (NPV) of 99.2% and the DELFIA Xpress PlGF 1-2-3 test using a cut-off of 150 pg/mL or greater for ruling out pre-eclampsia within 1 week yielded a NPV of 94.8% (diagnostic GRADE: Moderate for both tests). All clinical utility outcomes were associated with uncertainties (GRADE: Low).

We included 13 studies in the economic evidence review, most of which concluded that the use of PlGF-based biomarker testing resulted in cost savings. Seven studies were partially applicable to the Ontario health care setting but have some important limitations; the remaining 6 studies were not applicable. We estimated that publicly funding PlGF-based biomarker testing for people with suspected pre-eclampsia in Ontario would lead to an additional annual cost of \$0.27 million in year 1 to \$0.46 million in year 5, for a total additional cost of \$1.83 million over 5 years.

Direct engagement included 24 people who had been impacted by pre-eclampsia during their pregnancies as well as one family member. Participants described the emotional and physical impacts of having suspected pre-eclampsia and subsequent treatments. Those that we spoke with valued shared decision-making and identified potential gaps in patient education, specifically as it relates to symptom management for suspected pre-eclampsia. Overall, the participants viewed PlGF-based biomarker testing positively for its perceived medical benefits and minimal invasiveness. They felt that access to PlGF-based biomarker testing may also improve health outcomes through improved patient

education, care coordination, and patient-centred care (e.g., prompting more frequent prenatal monitoring, when needed). In addition, PlGF-based biomarker testing was perceived to be equally beneficial for family members who may act as the health care proxy in an emergency. Lastly, participants emphasized that there should be equitable access to PlGF-based biomarker testing and support from a care provider should be offered when trying to interpret the results, particularly if the results are accessible through an online patient portal.

## Conclusions

Compared with standard clinical assessment alone in people with suspected pre-eclampsia (gestational age between 20 and 36 weeks + 6 days), PlGF-based biomarker testing as an adjunct to standard clinical assessment likely improves prediction of pre-eclampsia. It may also reduce time to pre-eclampsia diagnosis, severe adverse maternal outcomes, and length of stay in the neonatal intensive care unit, although the evidence is uncertain. PlGF-based biomarker testing may result in little to no difference in other clinical outcomes such as maternal admission to hospital and perinatal adverse outcomes.

The economic literature review showed that PlGF-based biomarker testing was cost-effective for use in people with suspected pre-eclampsia, but with some uncertainties. A primary economic evaluation was not done for this health technology assessment because the impact of the test on maternal and neonatal outcomes is uncertain. Publicly funding PlGF-based biomarker testing for people with suspected pre-eclampsia would lead to an additional cost of \$1.83 million over 5 years.

Publicly funding PlGF-based biomarker testing was viewed favourably by people directly impacted by pre-eclampsia as well as their family members. Those with whom we spoke valued testing to help diagnose suspected pre-eclampsia and valued the potential medical benefits. Participants emphasized that patient education, and equitable access to PlGF-based biomarker testing should be requirements for implementation in Ontario.

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# Objective

This health technology assessment (HTA) evaluates the diagnostic accuracy, clinical utility, and cost-effectiveness of placental growth factor (PLGF)-based biomarker testing as an adjunct to standard clinical assessment to help diagnose pre-eclampsia in people with suspected pre-eclampsia. It also evaluates the budget impact of publicly funding PLGF-based biomarker testing and the experiences, preferences, and values of people with suspected pre-eclampsia.

# Background

## Health Condition

Pre-eclampsia is a potentially serious condition affecting up to 5% of pregnancies, most frequently after 20 weeks' gestation.<sup>1</sup> It is characterized by high blood pressure and signs of end-organ damage to kidneys (proteinuria), liver (liver cell breakdown), brain (swelling, seizures), and blood vessels (blood breakdown, use of platelets leading to risk of bleeding, etc.). Pre-eclampsia may be asymptomatic and, in such cases, may be detected only through routine antenatal testing.<sup>1</sup>

The Society of Obstetricians and Gynaecologists of Canada defines pre-eclampsia as gestational hypertension (blood pressure  $\geq 140/90$  mmHg that develops for the first time at  $\geq 20$  weeks' gestation), with new-onset proteinuria and one or more adverse conditions (defined as a maternal end-organ complication or evidence of uteroplacental dysfunction [Table 1]).<sup>2</sup>

**Table 1: Adverse Conditions That Define Pre-eclampsia Together With Hypertension**

| Adverse conditions             | Follow closely regarding need for delivery  | Deliver regardless of gestational age  |
|--------------------------------|---|--|
| Maternal end-organ dysfunction | Central nervous system<br>Severe headache/visual symptoms   | Eclampsia<br>Posterior reversible leukoencephalopathy syndrome<br>Cortical blindness or retinal detachment<br>Glasgow coma scale < 13<br>Stroke, transient ischemic attack, or reversible ischemic neurological deficit (< 48 h)   |
|                                | Cardiorespiratory<br>Chest pain/dyspnea<br>Oxygen saturation < 97%  | Uncontrolled severe hypertension (over a period of 12 h despite use of three antihypertensive agents)<br>Oxygen saturation < 90%, need for $\geq 50\%$ oxygen for > 1 h, intubation (other than for Caesarean section), pulmonary edema<br>Positive inotropic support<br>Myocardial ischemia or infarction |
|                                | Hematological<br>Low platelet count   | Platelet count < $50 \times 10^9/L$<br>Transfusion of any blood product  |
|                                | Renal<br>Elevated serum creatinine  | Acute kidney injury (creatinine > $150 \mu M$ with no prior renal disease)<br>New indication for dialysis  |
|                                | Hepatic<br>Right upper quadrant or epigastric pain<br>Elevated serum AST and ALT  | Hepatic dysfunction (international normalized ratio > 2 in absence of disseminated intravascular coagulation or warfarin)<br>Hepatic haematoma or rupture  |
| Uteroplacental dysfunction     | Atypical or abnormal nonstress test/ cardiotocography<br>Fetal growth restriction<br>Oligohydramnios<br>Absent or reversed end-diastolic flow by umbilical artery Doppler velocimetry<br>Angiogenic imbalance | Abruption with evidence of maternal or fetal compromise<br>Absent or reversed ductus venosus a-wave by Doppler velocimetry<br>Intrauterine fetal death   |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Source: Adapted from Magee et al.<sup>2</sup>

Pre-eclampsia is a heterogeneous and unpredictable condition, and the established method of clinical diagnosis is through the assessment of a standard set of key symptoms and clinical signs. Suspected

pre-eclampsia may have a negative impact on pregnant people if it involves hospitalization, loss of workdays, and/or anxiety. Previously, people with pre-eclampsia, particularly those with severe pre-eclampsia, have reported poorer quality of life than people with normotensive (normal blood pressure) pregnancies.<sup>3,4</sup> Having a condition that can deteriorate rapidly, being kept in hospital for monitoring, uncertainty about what will happen, and undergoing emergency Caesarean section may also cause pregnant people to experience fear, anxiety, loss of control over their situation, and anxiety about future pregnancies.<sup>5</sup>

If undetected and untreated, pre-eclampsia may result in serious complications for the pregnant person and fetus.<sup>1</sup> The most significant consequences for the pregnant person occur when there is progression to more severe conditions such as HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome and eclampsia (a potentially life-threatening convulsive condition), or complications such as liver hematomas, permanent kidney damage, cardiac failure, or stroke.<sup>6</sup> Negative consequences of pre-eclampsia for the fetus include fetal growth restriction and preterm birth, which can lead to complications and necessitate a stay in a neonatal intensive care unit (NICU).<sup>1</sup>

The only cure for pre-eclampsia is to deliver the placenta (and, therefore, the baby).<sup>1</sup> A pregnant individual diagnosed with pre-eclampsia is monitored to try to advance gestational age safely for as long as possible until a clear maternal and/or fetal indication for delivery occurs.

## Clinical Need and Target Population

According to data from the Public Health Agency of Canada, the rate of pre-eclampsia in Canada was 11.5 per 1,000 deliveries in 2010/11.<sup>7</sup> Among singleton births from Canada-born pregnant people, the rate of pre-eclampsia with delivery occurring between 24 and 36 weeks was estimated at 4 per 1,000 deliveries in the period covering April 1, 2003, through December 31, 2012. According to the data from Ontario's Better Outcomes Registry and Network (BORN), the prevalence of pre-eclampsia in Ontario is about 1.3%.<sup>8</sup>

## Current Options for Diagnosis

Diagnosing pre-eclampsia is challenging because symptoms and signs are highly variable: individuals can be asymptomatic despite severe disease and the disease can progress over several weeks before diagnosis is confirmed.<sup>9</sup> Assessment, therefore, begins during routine antenatal appointments when blood pressure is measured and risk factors for pre-eclampsia are assessed.<sup>10</sup>

People with risk factors (e.g., hypertensive disease during a previous pregnancy, chronic kidney disease, autoimmune disease, type 1 or type 2 diabetes mellitus, chronic hypertension, age over 40 years, first pregnancy, pregnancy interval over 10 years, family history of pre-eclampsia, previous history of pre-eclampsia, body mass index [BMI] of  $\geq 30$  kg/m<sup>2</sup>, pre-existing hypertension, multiple pregnancy) may undergo more frequent blood pressure monitoring, and surveillance is increased for those with significant hypertension and/or proteinuria during pregnancy.<sup>10</sup> People are also advised to seek health care advice if they experience symptoms of pre-eclampsia, including severe headache, vision problems, or pain just below the ribs.<sup>11</sup> If risk factors are adequately identified in the first or early second trimester, pregnant individuals may benefit from low-dose acetylsalicylic acid (ASA) to reduce their risk of developing pre-eclampsia later in pregnancy.<sup>2</sup>

The presence or absence of hypertension alone does not accurately identify or exclude pre-eclampsia.<sup>1</sup> An earlier diagnosis for those with suspected pre-eclampsia is important in order to

monitor and deliver the babies of those who will get pre-eclampsia or to treat with antihypertensives those who do not have pre-eclampsia but do have elevated blood pressure at the end of their pregnancy.

## Health Technology Under Review

Tests that enable an earlier and more accurate prediction of the risk of pre-eclampsia may allow those at low risk to continue to receive care in the community and avoid hospitalization.<sup>1</sup>

Tests have been developed that measure the levels of two proteins in the blood, each of which can be abnormal in people with pre-eclampsia.<sup>1</sup> The first, placental growth factor (PLGF), promotes the development of new blood vessels within the placenta. In pregnant individuals with pre-eclampsia, it is found in abnormally low levels due to diseased and damaged placentas.<sup>1</sup> A cohort study by McLaughlin et al<sup>12</sup> showed low PLGF levels in pregnant women were associated with markedly higher rates of imminent preterm birth, with 43% of the cohort delivering preterm 2 weeks following PLGF testing relative to 1% of women with normal PLGF levels. The second protein, soluble fms-like tyrosine kinase-1 (sFlt-1), occurs in very high levels in individuals with severe pre-eclampsia. The excessive production of sflt-1 is made by the diseased placenta.

Available tests measure either the blood levels of PLGF or the ratio of sFlt-1 to PLGF as biomarkers of underlying placental function and are to be used in conjunction with clinical judgement to assess the level of risk in people with suspected pre-eclampsia.

## Regulatory Information

Seven PLGF-based biomarker tests on the market, four of which are licensed by Health Canada.<sup>13</sup>

### ***DELFLIA Xpress PLGF 1-2-3 (Wallac Oy, Turku, Finland)***

The DELFLIA Xpress PLGF 1-2-3 test (licence no. 65353) The test is intended to help predict the risk of pre-eclampsia in the short term and/or diagnose suspected pre-eclampsia in conjunction with other clinical information.<sup>14</sup> Table 2 lists the manufacturer's recommended cut-offs for the DELFLIA Xpress PLGF 1-2-3 assay.

Table 2: Recommended Cut-Offs for the DELFIA Xpress PlGF 1-2-3 Assay

| Intended use                | Stage of pregnancy  | Decision rule           | Placental growth factor cut-off |
|-----------------------------|---|-------------------------|---------------------------------|
| To help diagnose PE         | <ul style="list-style-type: none"> <li>Wk 20 to wk 33 + 6 d</li> <li>Wk 34 or more</li> </ul>                         | Rule in cut-off         | < 50 pg/mL                      |
| To help diagnose PE         | <ul style="list-style-type: none"> <li>Wk 20 to wk 33 + 6 d</li> <li>Wk 34 or more</li> </ul>                         | Rule out cut-off        | ≥ 150 pg/mL                     |
| Short-term prediction of PE | <ul style="list-style-type: none"> <li>Wk 20 to wk 41</li> <li>Wk 20 to wk 33 + 6 d</li> <li>Wk 34 or more</li> </ul> | Rule out PE within 1 wk | ≥ 150 pg/mL                     |
| Short-term prediction of PE | <ul style="list-style-type: none"> <li>Wk 20 to wk 41</li> <li>Wk 20 to wk 33 + 6 d</li> <li>Wk 34 or more</li> </ul> | Rule out PE within 4 wk | ≥ 150 pg/mL                     |

Abbreviations: PE, pre-eclampsia; PlGF, placental growth factor.

Source: Adapted from Frampton et al.<sup>14</sup>

### **DELFLIA/AUTODEFLIA PlGF 1-2-3 (Wallac Oy, Turku, Finland)**

The DELFLIA/AUTODEFLIA PlGF 1-2-3 (licence no 101611) is used for prenatal and neonatal screening.<sup>15</sup> No studies specific to the use of DELFLIA/AUTODEFLIA PlGF 1-2-3 or its cut-offs, to help diagnose pre-eclampsia in people with suspected pre-eclampsia have been published to date.

### **DELFLIA Xpress sFlt-1/PlGF 1-2-3**

While this ratio test is not currently licensed by Health Canada, it has been assessed for the risk prediction of pre-eclampsia in people with suspected pre-eclampsia.<sup>16</sup>

### **Elecsys sFlt-1/Elecsys PlGF (Roche Diagnostics GmbH, Mannheim, Germany)**

The Elecsys immunoassay sFlt-1/PlGF ratio is formed by combining the results of two electrochemiluminescence immunoassays (the Elecsys PlGF and Elecsys sFlt-1 assays; licence numbers 82584 and 82580, respectively). The sFlt-1/PlGF ratio is intended to help diagnose pre-eclampsia in pregnant women with suspected pre-eclampsia, together with other clinical information.<sup>14</sup> The sFlt-1/PlGF ratio is also intended to help predict pre-eclampsia in the short term (to rule out and rule in) in pregnant women with suspected pre-eclampsia, together with other clinical information.<sup>14</sup> Table 3 lists the manufacturer's recommended cut-offs for the Elecsys immunoassay sFlt-1/PlGF ratio assay.<sup>14</sup>

**Table 3: Recommended Cut-Offs for the Elecsys Immunoassay sFlt-1/PlGF Ratio Assay**

| Intended use                | Stage of pregnancy   | Decision rule          | sFlt-1/PlGF ratio |
|-----------------------------|----------------------|------------------------|-------------------|
| To help diagnose PE         | Wk 20 to wk 33 + 6 d | Rule out cut-off       | 33                |
| To help diagnose PE         | Wk 20 to wk 33 + 6 d | Rule in cut-off        | 85                |
| To help diagnose PE         | Wk 34 to birth       | Rule out cut-off       | 33                |
| To help diagnose PE         | Wk 34 to birth       | Rule in cut-off        | 110               |
| Short-term prediction of PE | Wk 24 to wk 36 + 6 d | Rule out PE for 1 wk   | 38 or less        |
| Short-term prediction of PE | Wk 24 to wk 36 + 6 d | Rule in PE within 4 wk | Over 38           |

Abbreviations: PE, pre-eclampsia; PlGF, placental growth factor.

Source: Adapted from Frampton et al.<sup>14</sup>

**BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor (Thermo Fisher Scientific GmbH, Hennigsdorf, Germany)**

The BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor pre-eclampsia (PE) ratio (licence no. 100012) is formed by combining the results of the BRAHMS sFlt-1 Kryptor and BRAHMS PlGF plus Kryptor assays. The assays are compatible with the BRAHMS Kryptor compact plus analyser and the Kryptor Gold immunoanalyser.<sup>14</sup> The BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio is intended to be used to confirm or exclude a diagnosis of pre-eclampsia after 20 weeks of pregnancy.<sup>14</sup>

In July 2022, the National Institute for Health and Care Excellence in the United Kingdom cited Thermo Fisher as stating that a ratio of more than 85 suggests pre-eclampsia and a high-risk pregnancy, and updated instructions for use (cut-offs) will be released later in 2022.<sup>17</sup>

**Triage PlGF (Quidel, United States)**

While the Triage PlGF test manufactured by Quidel is not currently licensed by Health Canada, it has been assessed for the risk prediction of pre-eclampsia in people with suspected pre-eclampsia.<sup>14</sup> The Triage PlGF test can be used at the point of care and in the laboratory.<sup>14</sup> The test is used with other clinical information to help diagnose pre-eclampsia and can aid in the prognosis of birth in women who are between 20 weeks and 35 weeks pregnant with signs and symptoms of pre-eclampsia. Table 4 lists the manufacturer's recommended cut-offs for the Triage PlGF assay.<sup>14</sup>

**Table 4: Recommended Cut-Offs for the Triage PlGF Test**

| Result                             | Classification                | Interpretation   |
|------------------------------------|-------------------------------|--|
| PlGF < 12 pg/mL                    | Test positive—highly abnormal | Highly abnormal and suggestive of patients with severe placental dysfunction and at increased risk of preterm birth          |
| PlGF between 12 pg/mL and 99 pg/mL | Test positive—abnormal        | Abnormal and suggestive of patients with placental dysfunction and at increased risk of preterm birth                        |
| PlGF ≥ 100 pg/mL                   | Test negative—normal          | Normal and suggestive of patients without placental dysfunction and unlikely to progress to birth within 14 days of the test |

Abbreviations: PlGF, placental growth factor.

Source: Adapted from Frampton et al.<sup>14</sup>



## Ontario, Canadian, and International Context

### Ontario

Testing for PLGF-based biomarkers for risk prediction in people with suspected pre-eclampsia is not publicly funded in Ontario, nor in any other Canadian jurisdictions (Roche Canada, personal communication, January 25, 2022).

Two hospitals in Toronto provide testing for PLGF-based biomarkers for risk prediction in people with suspected pre-eclampsia (Roche Diagnostics, personal communication, January 25, 2022; expert consultants, personal communication, February 18 and 25, 2022).

### Canada

As of 2022, the Society of Obstetricians and Gynaecologists of Canada recommends PLGF-based biomarker testing (e.g., sFlt-1 to PLGF ratio or PLGF alone, if available); if the biomarkers exceed recommended thresholds (criteria specific to the local assay in use), the diagnosis of pre-eclampsia would be strengthened (GRADE level of evidence: Moderate).<sup>2</sup>

### International

The 2021 International Society for the Study of Hypertension in Pregnancy (ISSHP) recommends adding evaluation of angiogenic imbalance, when available, as a marker of uteroplacental dysfunction to be used in conjunction with other clinical tests for the assessment of women with suspected pre-eclampsia (< 37 weeks' gestation; GRADE level of evidence: Moderate; GRADE strength of recommendation: Strong).<sup>18</sup>

In July 2022, the National Institute for Health and Care Excellence in the United Kingdom made the following recommendations<sup>17</sup>:

- The following PLGF-based tests, used with standard clinical assessment, are recommended to help decide on care (to help rule in or rule out pre-eclampsia) for people with suspected preterm (between 20 weeks and 36 weeks + 6 days of pregnancy) pre-eclampsia:
  - DELFIA Xpress PLGF 1-2-3
  - DELFIA Xpress sFlt-1/PLGF 1-2-3 ratio
  - Elecsys immunoassay sFlt1/PLGF ratio
  - Triage PLGF test
- Not all manufacturers indicate their tests for use across the full range of 20 weeks to 36 weeks and 6 days of pregnancy. The tests should be used according to their indications for use
- PLGF-based testing may particularly benefit groups at higher risk of severe adverse pregnancy outcomes, such as people from African, Caribbean, and Asian family backgrounds
- Further research on how well the tests work when people are pregnant with more than one baby is recommended
- Do not use PLGF-based tests to make decisions about whether to offer a planned early birth to people with preterm pre-eclampsia
- Use a PLGF-based test once per episode of suspected preterm pre-eclampsia. Further research is recommended on repeat testing
- BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio is not recommended for routine use in the National Health Service (NHS). Further research is needed to show the accuracy of this test when using specified thresholds

## Equity Context

Racial and ethnic differences in the risk of pre-eclampsia exist, with data from the US suggesting that Black women have the greatest risk and are more likely to experience complications, including long-term cardiometabolic risk—that is, cardiovascular issues (e.g., high blood pressure, heart attack, or stroke) occurring together with metabolic disorders (e.g., obesity, insulin resistance, or diabetes).<sup>19,20</sup>

An Ontario study stated that compared with Canada-born mothers who had an estimated risk of pre-eclampsia resulting in preterm birth of 4.0 per 1,000, the risk of pre-eclampsia and preterm birth was higher for immigrant women from Nigeria (relative risk [RR], 1.79; 95% confidence interval [CI], 1.12–2.84), the Philippines (RR, 1.54; 95% CI, 1.30–1.86), Colombia (RR, 1.68; 95% CI, 1.04–2.73), Jamaica (RR, 2.06; 95% CI, 1.66–2.57), and Ghana (RR, 2.12; 95% CI, 1.40–3.21).<sup>21</sup>

The prevalence of pre-eclampsia in Canadian Indigenous populations is not available in the literature. One study of First Nations people living in Southern Ontario reported that hypertension was present before or during pregnancy in 5.6% (n = 453) of women.<sup>22</sup>

## Expert Consultation

We engaged with experts in the specialty areas of obstetrics, clinical biochemistry, midwifery, and family medicine to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence.

## PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42022329872), available at [crd.york.ac.uk/PROSPERO](http://crd.york.ac.uk/PROSPERO).

# Clinical Evidence

## Research Question

What are the diagnostic accuracy and clinical utility of placental growth factor (PLGF)-based biomarker testing as an adjunct to standard clinical assessment to help diagnose pre-eclampsia in people with suspected pre-eclampsia?

## Methods

During the initial scoping for this report, we identified a systematic review by Frampton et al.<sup>1</sup> In that systematic review, Frampton et al. undertook a literature search for reports limited to English-language documents published between 2000 and 2015.<sup>1</sup> It came to our attention that Frampton et al. was in the process of updating the systematic review from 2016 in collaboration with the National Institute for Health and Care Excellence (NICE) to update the NICE guidance from 2016. On July 27, 2022, NICE published updated guidance on their website. Results from the updated systematic review were posted on the NICE website as committee papers.<sup>17</sup>

Our aim was to leverage the findings of the systematic review by Frampton et al.,<sup>14</sup> supplementing that work with one new study<sup>23</sup> identified during the development of our report.

Two types of study designs were included in the 2016 systematic review by Frampton et al.<sup>14</sup> (and were used as evidence that informed the 2016 NICE guidance):

- "Add-on" study design in which results were used alongside standard clinical assessment to diagnose pre-eclampsia and inform subsequent care decisions. In these studies, test results were revealed to the treating physician
- "Stand-alone" study design in which results were used to diagnose pre-eclampsia but were not used alongside standard clinical assessment to inform care decisions. In these studies, test results were concealed from the treating physician

To ensure continuity between the 2016 and 2022 systematic reviews, Frampton et al.<sup>14</sup> continued with the inclusion of both add-on and stand-alone studies, with a primary focus on the evidence for add-on tests to reflect how these tests are used in clinical practice. Frampton et al.<sup>14</sup> regarded stand-alone test studies as providing supportive evidence of the diagnostic accuracy of the tests.

Similar to the updated systematic review by Frampton et al.<sup>14</sup>, we include "stand-alone studies" in the review to provide supportive evidence to "add-on" studies.

## Clinical Literature Search

We performed a clinical literature search on April 14, 2022, to retrieve studies published from January 1, 2015, to the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Health Technology Assessment Database, and the National Health Service Economic Evaluation Database (NHSEED). We used the EBSCOhost interface to search the Cumulative Index to Nursing and Allied Health Literature (CINAHL).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The content was based on a search previously developed by Frampton et al.<sup>1</sup> in 2016. The date limit used is meant to update the findings from the Frampton et al.<sup>14</sup>

study. The final search strategy was peer-reviewed, using the Peer Review of Electronic Search Strategies (PRESS) checklist.<sup>24</sup>

We created database auto-alerts in MEDLINE, Embase, and CINAHL and monitored them until July 31, 2022. We also performed a targeted grey literature search of the International HTA Database, HTA organizations and regulatory agencies websites, and clinical trial and systematic review registries, following a standard list of sites developed internally. See Appendix 1 for our literature search strategies, including all search terms.

## **Eligibility Criteria**

### STUDIES

#### *Inclusion Criteria*

- English-language, full-text publications
- Studies published from January 2015 to present
- Health technology assessments, systematic reviews, diagnostic or prognostic accuracy studies, randomized controlled trials, comparative observational studies

#### *Exclusion Criteria*

- Editorials, commentaries, case reports, conferences abstracts, letters
- Animal and in vitro studies

### PARTICIPANTS

- Pregnant people between 20 weeks and 36 weeks plus 6 days' gestation suspected of having pre-eclampsia based on standard clinical assessment
- Singleton pregnancies

### INTERVENTIONS

- PlGF-based tests; for example:
  - Quidel Triage PlGF test (not licensed by Health Canada)
  - AutoDELFIa PlGF1-2-3, DELFIa Xpress PlGF1-2-3 test or DELFIa Xpress PlGF1-2-3 test/DELFIa Xpress sFlt-1 test (not licensed by Health Canada) in conjunction with standard clinical assessment
  - Elecsys immunoassay sFlt-1/PlGF ratio in conjunction with standard clinical assessment
  - BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio in conjunction with standard clinical assessment
- Tests are assessed each time they are used for an episode of suspected pre-eclampsia as well as when they are repeated in people with suspected pre-eclampsia who have previously had a PlGF-based test for suspected pre-eclampsia that was negative

### COMPARATORS

- Standard key clinical signs and symptoms based on clinical assessment alone (e.g., hypertension, proteinuria, and fetal growth restriction)
- Another PlGF-based biomarker test
- Reference standard for diagnostic accuracy of pre-eclampsia based on clinical assessment alone

- Reference standard for prognostic accuracy of maternal/neonatal outcomes (e.g., preterm delivery, maternal morbidity) as per how they are defined in the studies

## OUTCOME MEASURES

- Diagnostic/prognostic accuracy
- Hospital admission; length of stay
- Maternal, fetal, and neonatal morbidity/mortality
- Health-related quality of life

Subgroup analyses where data are available:

- Ethnicity (e.g., Black, Indigenous patients)
- Patients between 20 weeks and 34 weeks plus 6 days of pregnancy
- Patients between 35 weeks and 36 weeks plus 6 days of pregnancy
- Presence of comorbidities (e.g., chronic hypertension, diabetes, renal disease, autoimmune disease)

## **Literature Screening**

Two reviewers followed the Cochrane rapid review methods<sup>25</sup> to screen titles and abstracts using Covidence systematic review management software,<sup>26</sup> and obtained the full text of studies that appeared eligible for the review according to the inclusion criteria. One reviewer examined the full-text articles and selected studies that met the inclusion criteria. A second reviewer screened all excluded full-text articles. Any disagreements between reviewers during screening were resolved by consensus. Citation flow and reasons for exclusion for full text articles will be reported according to the PRISMA statement.<sup>27</sup>

## **Data Extraction**

One reviewer extracted relevant data on study design and characteristics, risk-of-bias items, results, and PICO (population, intervention, comparator, outcome). Data extraction accuracy was validated by a second reviewer. We extracted relevant data on study characteristics and risk-of-bias items using a data form to collect information on the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, study duration and years, participant allocation, allocation sequence concealment, blinding, reporting of missing data, reporting of outcomes, whether the study compared two or more groups)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, number of participants missing for each outcome, outcome definition and source of information, unit of measurement, upper and lower limits [for scales], time points at which the outcomes were assessed)

## **Equity Considerations**

We used PROGRESS-Plus, a health equity framework recommended by the Campbell and Cochrane Equity Methods Group, to explore potential inequities for this health technology assessment. Factors that could lead to disadvantage or inequities in the framework include place of residence; race, ethnicity, culture, or language; gender or sex; disability; occupation; religion; education; socioeconomic status; social capital; and other key characteristics that stratify health opportunities and outcomes.<sup>28</sup>

Using the search strategy designed to capture studies relevant to the clinical research questions, we sought but did not identify any evidence on equity issues relevant to how PROGRESS-Plus factors might affect inequity in PlGF-based biomarker testing to help diagnose pre-eclampsia in people with suspected pre-eclampsia across different populations. Thus, equity issues could exist but were not identified in the studies included as part of our analysis.

### **Statistical Analysis**

Frampton et al<sup>14</sup> stated that their assessment of the evidence that met their updated systematic review's inclusion criteria was that meta-analysis would not be feasible due to the limited availability of sufficiently similar outcomes data across the studies. Similar to the original systematic review by Frampton et al<sup>1</sup> in 2016, the authors provided a structured narrative synthesis of the included studies. We similarly provide a narrative synthesis within our HTA.

### **Critical Appraisal of the Evidence**

We assessed risk of bias using AMSTAR 2 for systematic reviews<sup>29</sup> and the Quality of Diagnostic Accuracy Studies 2 (QUADAS-2) tool for diagnostic studies<sup>30</sup> (Appendix 2).

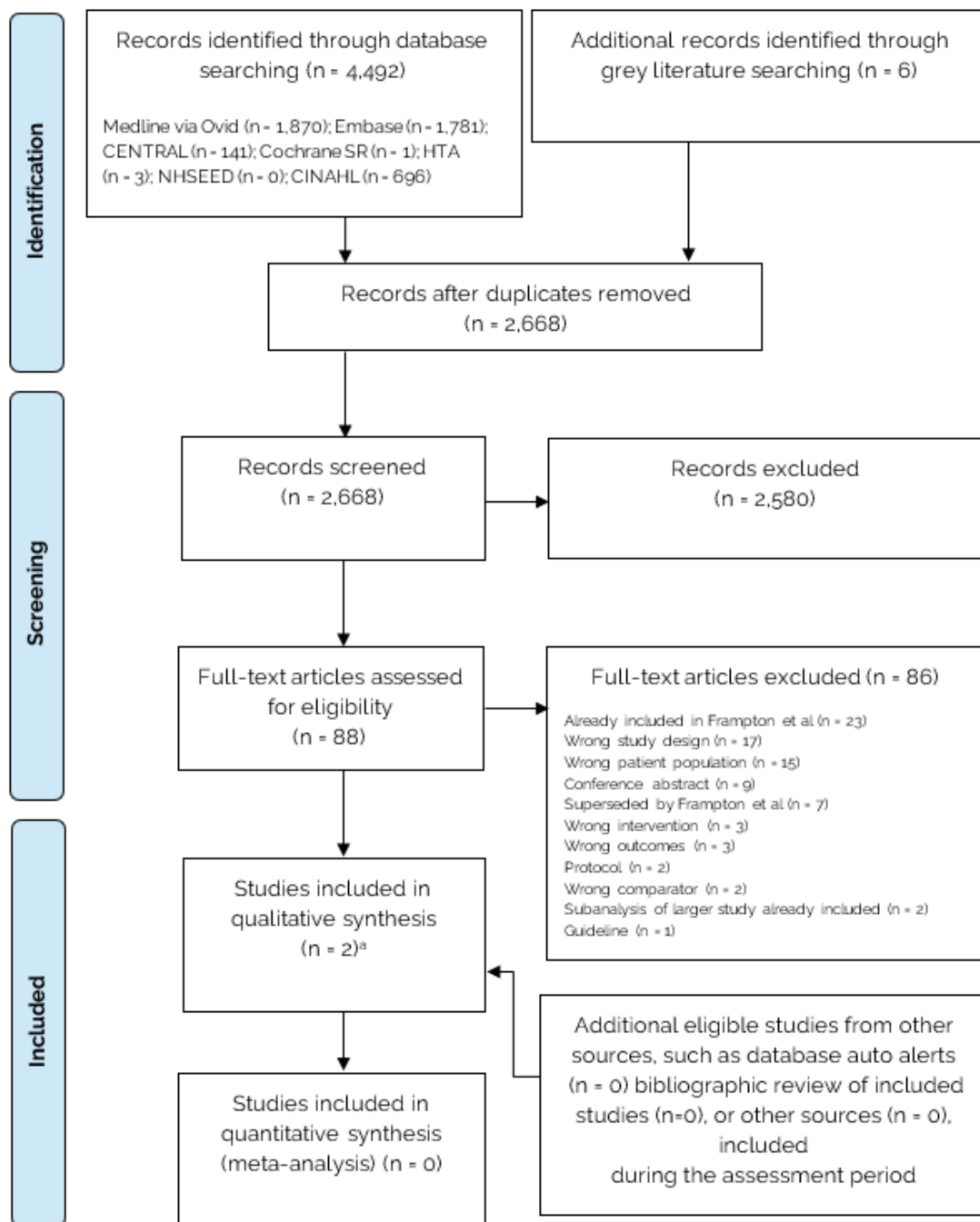
We evaluated the quality of the body of evidence for each clinical outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Handbook*.<sup>31</sup> The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence. Since Frampton et al<sup>14</sup> did not use GRADE within their systematic review, we evaluated the body of evidence based on details that were reported and discussed by the authors.

## **Results**

### **Clinical Literature Search**

The database search of the clinical literature yielded 4,492 citations published from January 1, 2015, to April 14, 2022. We identified six additional studies from other sources, for a total of 2,668 after removing duplicates.

In total, we identified two studies (one systematic review and one diagnostic accuracy study<sup>23</sup>) that met our inclusion criteria. See Appendix 3 for a list of selected studies excluded after full-text review. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.



**Figure 1: PRISMA Flow Diagram—Clinical Search Strategy**

PRISMA flow diagram showing the clinical search strategy. The database search of the clinical literature yielded 4,492 citations published between January 1, 2015, and April 14, 2022. We identified 6 additional eligible studies from other sources. After removing duplicates, we screened the abstracts of 2,668 studies and excluded 2,580. We assessed the full text of 88 articles and excluded a further 86. In the end, we included 2 articles in the qualitative synthesis.

Abbreviations: CINAHL, Cumulative Index to Nursing and Allied Health Literature; NHSEED, National Health Service Economic Evaluation Database; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; SR, systematic review.

<sup>a</sup>Frampton et al<sup>14</sup> and Hughes et al.<sup>23</sup>

Source: Adapted from Page et al.<sup>32</sup>

### Characteristics of Included Studies

Characteristics of the systematic review<sup>14</sup> and diagnostic accuracy study<sup>23</sup> included in our systematic review are shown in Table 5.

Table 5: Characteristics of Included Studies

| Author, year                       | Study design and methods  | Participants  | Intervention   | Outcomes   |
|------------------------------------|---|---|--|--|
| Frampton et al, <sup>14</sup> 2022 | Systematic review of 18 studies: <ul style="list-style-type: none"> <li>• Add-on studies (PIGF-based test is used with standard clinical assessment for diagnosis and care decisions): n = 6 studies<sup>a,b</sup></li> <li>• Stand-alone studies (PIGF-based test is not used with standard clinical assessment for diagnosis and care decisions): n = 10 studies</li> </ul> | Pregnancies at 20–36 weeks' gestation with suspected PE | Triage (not licensed by Health Canada) <ul style="list-style-type: none"> <li>• Elecsys</li> <li>• BRAHMS</li> <li>• DELFIA</li> </ul> | Test performance outcomes: diagnostic accuracy; prognostic accuracy; concordance between tests; time to test result; impact of test result on clinical decision-making; test failure rate; time to diagnosis; proportion of people diagnosed with PE; time to onset of PE/or eclampsia; proportion of people returned to community for less intensive follow-up; number of people admitted to hospital; length of in-patient hospital stay; time to delivery; gestational age at diagnosis PE; use of antihypertensive drugs; health-related quality of life<br>Maternal mortality and morbidity outcomes (e.g., liver failure; renal failure; stroke; eclampsia; emergency Caesarean)<br>Neonatal mortality and morbidity outcomes (e.g., breathing difficulties; neonatal unit length of stay, neonatal resuscitation) |
| Hughes et al, 2022 <sup>23</sup>   | Prospective cohort study (stand-alone)  | Pregnancies at 20–36 weeks' gestation with suspected PE | Elecsys  | Primary objective: to evaluate a sFlt-1/PIGF ratio > 38 at ≤ 35+0 weeks' gestation to predict birth ≤ 14 d<br>Post-hoc secondary objectives: to assess in pregnancies < 37 weeks' gestation, the predictive value of a sFlt-1/PIGF ratio cut-off of 38 to rule out PE ≤ 1 wk and to rule in PE ≤ 4 wk of the baseline visit  |

Abbreviations: PE, pre-eclampsia, PIGF, placental growth factor.

<sup>a</sup> One study (Binder et al<sup>33</sup>) from the systematic review by Frampton et al<sup>14</sup> was excluded from our analysis as the population comprised people with twin pregnancies (i.e., not singleton pregnancies).

<sup>b</sup> The conference abstract by Andersen et al<sup>34</sup> included in the systematic review by Frampton et al<sup>14</sup> was excluded from our analysis because the data were included in a subsequent journal article publication in 2021.<sup>35</sup>

Frampton et al<sup>14</sup> did not explicitly report which studies were carried over from the systematic review of diagnostic studies published in 2016.

Three additional, more recent studies (Andersen et al,<sup>35</sup> Bremner et al,<sup>16</sup> and Hayes-Ryan et al<sup>36</sup>) were later added to the systematic review by Frampton et al<sup>14</sup> before NICE finalized their guidance



recommendations. Full results for the three recent studies were not reported in the clinical evidence review by Frampton et al but were briefly summarized in the economic section of the committee papers.<sup>14</sup>

Table 6 shows the seven add-on studies (for which tests results were revealed to the treating physician) that were included in the systematic review by Frampton et al.<sup>14</sup>

**Table 6: Characteristics of Add-On (Test Results Revealed to Physician) Studies**

| Study, author, year  | Location (centres)  | Design                          | Intervention and comparator   | Total population analyzed  | Outcome types  |
|--|---|---------------------------------|---|--|--|
| <b>TRIAGE PlGF test (not licensed by Health Canada)</b>      |   |                                 |   |  |  |
| PARROT Ireland, Hayes-Ryan et al, 2021 <sup>36</sup>         | Ireland (7 maternity units)                                 | Stepped-wedge cluster RCT       | Intervention: test results revealed to treating physician plus usual care<br>Comparator: test results not revealed to treating physician; usual care only | N = 2,309 patients<br>Intervention: n = 1,057 patients<br>Comparator: n = 1,234 patients | Comparative clinical outcomes: composite measures of maternal and neonatal morbidity |
| PARROT, Duhig et al, 2019 <sup>37</sup>                      | United Kingdom (11 maternity units)                         | Stepped-wedge cluster RCT       | Intervention: test results revealed to treating physician plus usual care<br>Comparator: test results not revealed to treating physician; usual care only | N = 1,023 patients<br>Intervention: n = 576 patients<br>Comparator: n = 447 patients     | Test accuracy; comparative clinical outcomes   |
| MAPPLE, Sharp et al, 2018 <sup>38</sup>                      | United Kingdom, Germany, Austria, and Australia (4 centres) | Prospective observational study | Intervention: MAPPLE study cohort for revealed results<br>Comparator: PELICAN study <sup>39</sup> (stand-alone cohort for concealed results)              | N = 396 patients (Liverpool: 241; Osnabrück: 115; Salzburg: 26; Adelaide: 14)            | Comparative clinical outcomes  |
| Ormesher et al, 2015 <sup>40</sup>                           | United Kingdom (1 hospital)                                 | Prospective observational study | NA; single cohort study   | N = 260 patients   | Test accuracy  |
| <b>Elecsys sFlt-1/PlGF ratio (licensed by Health Canada)</b> |   |                                 |   |  |  |
| INSPIRE, Cerdeira et al, 2019 <sup>41</sup>                  | United Kingdom (1 hospital)                                 | RCT                             | Intervention: revealed test result<br>Comparator: concealed test result   | N = 370 patients<br>Intervention: n = 186<br>Comparator: n = 184                         | Test accuracy; comparative clinical outcomes   |

| Study, author, year   | Location (centres)                         | Design                            | Intervention and comparator   | Total population analyzed | Outcome types                 |
|---|--|-----------------------------------|---|---------------------------|-------------------------------|
| PreOS, Klein et al, 2016 <sup>42</sup>                              | Germany (4 centres) and Austria (1 centre) | Prospective, observational study  | Before- and after-design: before sFlt-1/PlGF test result known, physicians documented clinical decisions. Then result was made available, and decisions revised or confirmed. | N = 209 patients          | Comparative clinical outcomes |
| <b>BRAHMS Kryptor sFlt-1/PlGF ratio (licensed by Health Canada)</b> |  |                                   |   |                           |                               |
| Andersen et al, 2019 <sup>34</sup>                                  | Denmark (1 centre)                         | Retrospective observational study | NA; single cohort study   | N = 501                   | Test accuracy                 |

Abbreviations: NA, not applicable; PlGF, placental growth factor; RCT, randomized controlled trial; sFlt-1, soluble fml-like tyrosine kinase-1.

PARROT<sup>37</sup> and PARROT Ireland<sup>36</sup> for the Triage test (not licensed by Health Canada) and INSPIRE<sup>41</sup> for the Elecsys test (licensed by Health Canada) were randomized controlled trials (RCTs). The RCTs are supported by the single cohort, prospective, observational studies MAPPLE<sup>38</sup> for Triage and PreOS<sup>42</sup> for Elecsys. The evidence for the BRAHMS Kryptor test (licensed by Health Canada) is limited to a single cohort, retrospective, observational study by Andersen et al 2022.<sup>34</sup>

There are no available data for the DELFIA Xpress test (licensed by Health Canada) used as an add-on to standard clinical assessment,

Table 7 shows the 13 stand-alone studies (tests results not revealed to treating physician) that were included in the systematic review by Frampton et al as well as the additional study by Hughes et al<sup>23</sup> (assessing the Elecsys sFlt-1/PlGF ratio test) that we identified in our updated literature search.

**Table 7: Characteristics of Stand-Alone (Test Results Not Revealed to Physician) Studies**

| Study, author, year  | Location (centres)   | Design                            | Intervention and comparator | Total population analyzed   | Outcome types  |
|--|--|-----------------------------------|-----------------------------|---|--|
| <b>TRIAGE PlGF test (not licensed by Health Canada)</b>      |  |                                   |                             |   |  |
| PELICAN, Chappel et al, <sup>43</sup> 2013                   | United Kingdom and Ireland (7 centres)   | Prospective observational study   | NA; single-arm study        | N = 649 patients  | Test accuracy  |
| PEACHES, Bramham et al, 2016 <sup>44</sup>                   | United Kingdom and Ireland (7 centres)   | Retrospective observational study | NA; single-arm study        | N = 579 patients  | Test accuracy, test concordance (validation cohort of the PELICAN study) |
| PETRA, Barton et al, 2020 <sup>45</sup>                      | United States and Canada (24 centres)  | Prospective observational cohort  | NA; single arm-study        | N = 757 patients  | Test accuracy  |
| <b>Elecsys sFlt-1/PlGF ratio (licensed by Health Canada)</b> |  |                                   |                             |   |  |
| PROGNOSIS, Zeisler et al, 2016 <sup>46</sup>                 | Argentina, Australia, Austria, Belgium, Canada, Chile, Germany, Netherlands, New Zealand, Norway, Peru, Spain, Sweden, United Kingdom (30 centres) | Prospective observational study   | NA; single-arm study        | Development cohort: 500 patients<br>Validation cohort: 550 patients | Test accuracy  |
| PROGNOSIS, Bian et al, 2019 <sup>47</sup>                    | China, Hong Kong, Japan, Singapore, South Korea, Thailand (25 centres)   | Prospective observational study   | NA; single-arm study        | N = 764 patients<br>N = 690 patients for analysis of fetal outcomes | Test accuracy  |
| ROPE, Rana et al, 2018 <sup>48</sup>                         | United States (1 centre)   | Prospective observational study   | NA; single-arm study        | N = 402 patients  | Test accuracy  |
| Baltajian et al, 2016 <sup>49</sup>                          | United States (1 centre)   | Prospective observational study   | NA; single-arm study        | N = 103 patients  | Test accuracy  |
| Saleh et al, 2016 <sup>50</sup>                              | Netherlands (1 centre)   | Prospective observational study   | NA; single-arm study        | N = 107 patients  | Test accuracy  |
| Wang et al, 2021 <sup>51</sup>                               | China (1 centre)   | Prospective observational study   | NA; single-arm study        | N = 200 patients  | Test accuracy  |
| Hughes et al, 2022 <sup>23</sup>                             | New Zealand (1 centre)   | Prospective observational study   | NA; single-arm study        | N = 222 patients  | Test accuracy  |

| Study, author, year   | Location (centres)                      | Design   | Intervention and comparator                           | Total population analyzed   | Outcome types                   |
|---|---|--|---|---|---------------------------------|
| <b>BRAHMS Kryptor sFlt-1/PlGF ratio (licensed by Health Canada)</b>                           |   |  |   |   |                                 |
| Salahuddin et al, 2016 <sup>52</sup>  | United States (1 centre)                | Observational case control study   | Samples from ROPE study cohort and normative controls | N = 412 patients (ROPE cohort)<br>N = 434 patients (normative controls) | Test accuracy; test concordance |
| <b>DELFLIA Xpress PlGF 1-2-3 (licensed by Health Canada)</b>                                  |   |  |   |   |                                 |
| COMPARE, McCarthy et al, 2019 <sup>53</sup>   | United Kingdom and Ireland (20 centres) | Retrospective analysis of three prospective cohort studies (PEACHES, PELICAN-1, and PELICAN-2) | 3 arms from 3 different studies                       | N = 396 patients  | Test accuracy; test concordance |
| <b>DELFLIA Xpress sFlt-1/PlGF ratio (DELFLIA Xpress sFlt-1 not licensed by Health Canada)</b> |   |  |   |   |                                 |
| Bremner et al, 2022 <sup>16</sup>   | United Kingdom (2 centres)              | Prospective observational study  | NA; single-arm study                                  | N = 369 patients  | Test accuracy                   |

Abbreviations: PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

Source: Adapted from Frampton et al.<sup>14</sup>

The stand-alone test studies mainly report test accuracy results. Stand-alone studies provide data for tests where evidence from add-on studies was limited, specifically the BRAHMS Kryptor test<sup>52</sup> and DELFLIA Xpress PlGF 1-2-3 test.<sup>53</sup>

This health technology assessment will focus on results for PlGF-based biomarker tests that are currently licensed by Health Canada (Elecsys sFlt-1/PlGF Ratio Test, BRAHMS Kryptor sFlt-1/PlGF Ratio Test, DELFLIA Xpress PlGF). Results for tests that were included in Frampton et al<sup>14</sup> but not currently licensed by Health Canada (i.e., Triage PlGF test and DELFLIA ratio test) are considered supporting evidence.

### **Risk of Bias in the Included Studies**

We used A Measurement Tool to Assess Systematic Reviews (AMSTAR 2)<sup>29</sup> to appraise the systematic review by Frampton et al<sup>14</sup> (Appendix 2, Table A1). The overall AMSTAR score was rated as 10/11.

Frampton et al<sup>14</sup> used the QUADAS-2 quality assessment tool<sup>30</sup> to assess the risk of bias and applicability of test accuracy data in the included studies (Appendix 2, Table A2). The risk of bias in RCTs was evaluated by Frampton et al using the Cochrane Risk of Bias tool<sup>54</sup> (Appendix 2, Table A3). For these test accuracy studies and RCTs, we reported the risk of bias as assessed by Frampton et al.

Frampton et al<sup>14</sup> did not report risk of bias for observational studies included in their systematic review. However, Frampton et al stated, "The finalised critical appraisal forms for each study will be considered for inclusion as supplementary information to this report in the NIHR Journals Library."<sup>14</sup>

We assessed the risk of bias in the study by Hughes et al<sup>23</sup> using the QUADAS-2 tool<sup>30</sup> (Appendix 2, Table A2).

For the following outcomes, we present the results as they were reported in the systematic review by Frampton et al<sup>14</sup> with the exception of the study by Hughes et al<sup>23</sup> that we identified in our updated literature search.

### **Accuracy Outcomes**

#### **ACCURACY FOR PREDICTION OF PRE-ECLAMPSIA**

##### *Elecsys sFlt-1/PlGF Ratio Test*

One add-on study and six stand-alone studies reported accuracy for the Elecsys sFlt-1/PlGF ratio test.

In the add-on INSPIRE study,<sup>41</sup> accuracy data were reported for the use of the test cut-off ratio of less than 38 for ruling out pre-eclampsia within 1 week, with a negative predictive value (NPV) of 99.2 (Table 8). No further accuracy data were reported using this test cut-off value.<sup>14</sup>

Positive predictive values (PPVs) may be used to assess the accuracy of the test for ruling in pre-eclampsia. Positive predictive values of 71.4 and 72.0 were reported in both arms of the INSPIRE study, respectively, when a higher cut-off of 85 was applied to predict pre-eclampsia within 4 weeks (Table 8).<sup>41</sup>

**Table 8: Prediction of Pre-eclampsia by Time Point (Elecsys sFlt-1/PlGF Ratio Test)**

| Time point  | Cut-off | Total (N) | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI)     | NPV (95% CI)      |
|---|---------|-----------|----------------------|----------------------|------------------|-------------------|
| <b>INSPIRE,<sup>41</sup> Elecsys ratio (result-revealed arm, using test result only), GA 24 to 37 weeks</b>               |         |           |                      |                      |                  |                   |
| Within 1 wk (rule out)  | < 38    | 186       | 95.8 (78.9–99.9)     | 79.6 (72.6–85.5)     | 41.1 (28.1–55.0) | 99.2 (95.8–100.0) |
| <b>INSPIRE,<sup>55</sup> Elecsys ratio plus standard clinical interpretation (result-revealed arm), GA 24 to 37 weeks</b> |         |           |                      |                      |                  |                   |
| Within 4 wk (rule in)   | ≥ 85    | 186       | 57.1 (39.4–73.7)     | 94.7 (89.8–97.7)     | 71.4 (51.3–86.8) | NR                |
| <b>INSPIRE,<sup>41</sup> Elecsys ratio (result concealed arm), GA 24 to 37 weeks</b>                                      |         |           |                      |                      |                  |                   |
| Within 4 wk (rule in)   | ≥ 85    | 184       | 64.3 (44.1–81.4)     | 95.5 (91.0–98.2)     | 72.0 (50.6–87.9) | NR                |

Abbreviations: CI, confidence interval; GA, gestational age; NPV, negative predictive value; NR, not reported; PlGF, placental growth factor; PPV, positive predictive value.

Source: Adapted from Frampton et al.<sup>14</sup>

Frampton et al<sup>14</sup> stated high NPVs (> 90) were reported at a cut-off of 38 for prediction of pre-eclampsia at various time points in stand-alone studies: PROGNOSIS<sup>46</sup> (within 1, 2, 3, and 4 weeks), PROGNOSIS Asia<sup>56</sup> (within 1 and 4 weeks), Wang et al<sup>51</sup> (within 4 weeks), and ROPE<sup>48</sup> (pre-eclampsia with severe features within 2 weeks).

PPVs ranged from 36.7 to 40.7 at the lower cut-off (< 38), across the study populations in the stand-alone PROGNOSIS study.<sup>46</sup> At a higher cut-off (> 85), PPVs ranged from 59.4 to 76.9 in the ROPE study<sup>48</sup>

and were highest in the subgroup of women admitted to hospital and at less than 34 weeks' gestation. Saleh et al<sup>50</sup> reported a high PPV (> 90) at a test cut-off of greater than 85 for the prediction of pre-eclampsia at study inclusion. Hughes et al<sup>23</sup> reported the ability of the ratio test to rule out pre-eclampsia within 1 week (NPV 96) and to rule in pre-eclampsia within 4 weeks (PPV 63) when using a cut-off of 38 and the same diagnostic criteria as the PROGNOSIS study.

We rated the certainty of the evidence for the Elecsys test as Moderate, downgrading for indirectness (Appendix 2, Table A4, A5).

#### ***BRAHMS Kryptor sFlt-1/PlGF Ratio Test***

One add-on study reported accuracy for prediction of pre-eclampsia using the BRAHMS Kryptor sFlt-1/PlGF ratio test. No stand-alone studies were identified.

Frampton et al<sup>14</sup> did not explicitly report accuracy data for the updated add-on study by Andersen et al.<sup>35</sup> Andersen et al assessed the use of the test to predict pre-eclampsia within 1 or 4 weeks. Negative predictive values were high (> 0.9) at 1 week or 4 weeks when a cut-off of 33 was used. The NPVs generally were lower when a cut-off of 85 was used (Table 9). The PPVs were lower (< 60 at 1 week and < 76 at 4 weeks) when a cut-off of 33 or 85 was used, respectively (Table 9). Confidence intervals were not reported by Andersen et al<sup>35</sup> for these data.

**Table 9: Prediction of Pre-eclampsia by Time Point (BRAHMS Kryptor sFlt-1/PlGF Ratio Test)**

| Timepoint   | Cut-off | Total (n) | Sensitivity | Specificity | PPV | NPV |
|---|---------|-----------|-------------|-------------|-----|-----|
| <b>Andersen et al.<sup>35</sup> BRAHMS Kryptor sFlt-1/PlGF ratio used alongside clinical care, GA 20 to 37 wk<sup>a</sup></b> |         |           |             |             |     |     |
| Within 1 wk   | 33      | 84        | 0.92        | 0.77        | 49  | 97  |
|   | 85      | 84        | 0.76        | 0.92        | 70  | 94  |
| Within 4 wk   | 33      | 125       | 0.82        | 0.78        | 57  | 93  |
|   | 85      | 125       | 0.64        | 0.92        | 75  | 88  |

Abbreviations: GA, gestational age; N, number of patients; NPV, negative predictive value; PlGF, placental growth factor; PPV, positive predictive value; sFlt-1, soluble fms-like tyrosine kinase.

<sup>a</sup>Confidence intervals were not reported by Andersen et al<sup>35</sup> for these data.

Source: Adapted from Frampton et al.<sup>14</sup>

We rated the certainty of the evidence for the BRAHMS test as Low, downgrading for risk of bias (Appendix 2, Table A4, A5).

#### ***DELFLIA Xpress PlGF test***

No add-on studies were identified that reported accuracy outcomes for the DELFLIA Xpress PlGF test.<sup>14</sup>

One stand-alone study by Bremner et al<sup>16</sup> reported results for the prediction of pre-eclampsia using the DELFLIA Xpress PlGF 1-2-3 (licensed by Health Canada) and the DELFLIA sFlt-1: PlGF ratio (not licensed by Health Canada) (Table 10). Overall, both tests had high NPVs and PPVs for ruling in or out pre-eclampsia within 28 days, respectively, for patients who had a gestational age of 20 weeks to 33 weeks and 6 days. The NPVs were high (> 90) but the PPVs were lower (< 40) for predicting pre-eclampsia within 7 days for patients also at a gestational age of 20 weeks to 33 weeks and 6 days.

For patients at 34 weeks' gestation or more, NPVs were high for ruling out pre-eclampsia (> 90) while PPVs were lower (< 40) for ruling in pre-eclampsia within 7 days. For predicting pre-eclampsia within 28 days, NPVs and PPVs were generally low (Table 10).

**Table 10: Prediction of Pre-eclampsia by Time Point (DELFIAXpress PlGF 1-2-3 or DELFIA sFlt-1: PlGF ratio)**

| Test   | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI)     | NPV (95% CI)     |
|--|----------------------|----------------------|------------------|------------------|
| <b>PE within 7 d, GA 20 wk to 33 wk + 6 d, n = 136</b>     |                      |                      |                  |                  |
| DELFIAXpress PlGF ≥ 150 pg/mL (rule out)                   | 72.2 (46.5–90.3)     | 78.0 (69.4–85.1)     | 33.3 (19.1–50.2) | 94.8 (88.4–98.3) |
| DELFIAXpress PlGF < 50 pg/mL (rule in)                     | 38.9 (17.3–64.3)     | 90.7 (83.9–95.3)     | 38.9 (17.3–64.3) | 90.7 (83.9–95.3) |
| DELFIAXpress ratio < 50 (rule out)                         | 50.0 (26.0–74.0)     | 89.0 (81.9–94.0)     | 40.9 (20.7–63.6) | 92.1 (85.5–96.3) |
| DELFIAXpress ratio ≥ 70 (rule in)                          | 38.9 (17.3–64.3)     | 89.8 (82.9–94.6)     | 36.8 (16.3–61.6) | 90.6 (83.8–95.2) |
| <b>PE within 7 days, GA ≥ 34 wk, n = 128</b>               |                      |                      |                  |                  |
| DELFIAXpress PlGF ≥ 150 pg/mL (rule out)                   | 84.2 (60.4–96.6)     | 34.9 (26.0–44.6)     | 18.4 (10.9–28.1) | 92.7 (80.1–98.5) |
| DELFIAXpress PlGF < 50 pg/mL (rule in)                     | 26.3 (9.1–51.2)      | 86.2 (78.3–92.1)     | 25.0 (8.7–49.1)  | 87.0 (79.2–92.7) |
| DELFIAXpress ratio < 50 (rule out)                         | 52.6 (28.9–75.6)     | 78.9 (70.0–86.1)     | 30.3 (15.6–48.7) | 90.5 (82.8–95.6) |
| DELFIAXpress ratio ≥ 90 (rule in)                          | 21.1 (6.1–45.6)      | 93.6 (87.2–97.4)     | 36.4 (9.2–10.9)  | 87.2 (79.7–92.6) |
| <b>PE within 28 days, GA 20 wk to 33 wk + 6 d, n = 136</b> |                      |                      |                  |                  |
| DELFIAXpress PlGF ≥ 150 (rule out)                         | 80.6 (64.0–91.8)     | 90.0 (82.4–95.1)     | 74.4 (57.9–87.0) | 92.8 (85.7–97.0) |
| DELFIAXpress PlGF < 50 (rule in)                           | 47.2 (30.4–64.5)     | 99.0 (94.6–100)      | 94.4 (72.7–99.9) | 83.9 (76.0–90.0) |
| DELFIAXpress ratio < 50 (rule out)                         | 55.6 (38.1–72.1)     | 98.0 (93.0–99.8)     | 90.9 (70.8–98.9) | 86.0 (78.2–91.8) |
| DELFIAXpress ratio ≥ 70 (rule in)                          | 50.0 (32.9–67.1)     | 99.0 (94.6–100.0)    | 94.7 (74.0–99.9) | 84.6 (76.8–90.6) |
| <b>PE within 28 days, GA ≥ 34 wk, n = 128</b>              |                      |                      |                  |                  |
| DELFIAXpress PlGF ≥ 150 pg/mL (rule out)                   | 83.3 (65.3–94.4)     | 36.7 (27.2–47.1)     | 28.7 (19.5–39.4) | 87.8 (73.8–95.9) |
| DELFIAXpress PlGF < 50 pg/mL (rule in)                     | 26.7 (12.3–45.9)     | 87.8 (79.6–93.5)     | 40.0 (19.1–63.9) | 79.6 (70.8–86.8) |
| DELFIAXpress ratio < 50 (rule out)                         | 50.0 (31.3–68.7)     | 81.6 (72.5–88.7)     | 45.5 (28.1–63.6) | 84.2 (75.3–90.9) |
| DELFIAXpress ratio ≥ 90 (rule in)                          | 23.3 (9.9–42.3)      | 95.9 (89.9–98.9)     | 63.6 (30.8–89.1) | 80.3 (72.0–87.1) |

Abbreviations: CI, confidence interval; GA: gestational age; NPV: negative predictive value; PE: pre-eclampsia; PlGF: placental growth factor; PPV: positive predictive value; sFlt-1, soluble fms-like tyrosine kinase.

Source: Adapted from Bremner et al.<sup>16</sup>

We rated the certainty of the evidence for the DELFIA test as Moderate, downgrading for indirectness (Appendix 2, Table A4, A5).

*Triage PlGF test*

One add-on study and two stand-alone studies reported accuracy for the Triage PlGF test.

Ormesher et al<sup>40</sup> (an add-on study) reported test accuracy data for the Triage PlGF test in the prediction of pre-eclampsia, with the highest PPVs achieved when using a test cut-off of 12 pg/mL (Table 11). Ormesher et al did not report confidence intervals in their study. The PPVs and NPVs were calculated and reported by Frampton et al.<sup>14</sup>

**Table 11: Prediction of Pre-eclampsia (Triage PlGF Test)**

| Time point  | Cut-off     | Total (n) | Sensitivity | Specificity | PPV  | NPV  |
|-------------|-------------|-----------|-------------|-------------|------|------|
| Within 2 wk | < 12 pg/mL  | 50        | 51.2        | 100         | 1.00 | 31.0 |
|             | < 100 pg/mL | 50        | 95.1        | 33.3        | 86.7 | 60.0 |
| At any time | < 12 pg/mL  | 128       | 50.0        | 100         | 100  | 56.2 |
|             | < 100 pg/mL | 128       | 77.1        | 33.3        | 89.3 | 79.2 |

Abbreviations: NPV, negative predictive value; PlGF, placental growth factor; PPV, positive predictive value.

Source: Adapted from Frampton et al.<sup>14</sup>

Two stand-alone studies (PETRA<sup>45</sup> and PELICAN<sup>43</sup>) reported NPVs ranging from 53.0 to 90.1 in patients at less than 35 weeks' gestation when using this test with a cut-off PlGF level of 100 pg/mL to predict pre-eclampsia at any time point.<sup>14</sup>

We rated the certainty of the evidence for the Triage test as Moderate, downgrading for risk of bias (Appendix 2, Table A4, A5).

## ACCURACY FOR PREDICTION OF DELIVERY

### *Elecsys sFlt-1/PlGF Ratio Test*

No add-on studies were identified that reported this outcome.

Three stand-alone studies reported prognostic accuracy data for prediction of delivery outcomes: ROPE,<sup>49</sup> Baltajian et al,<sup>49</sup> and PROGNOSIS Asia.<sup>47</sup> While the results from the PROGNOSIS Asia<sup>47</sup> study support the use of the test for ruling out pre-eclampsia requiring delivery within 1 week (NPV: 100), Baltajian et al<sup>49</sup> reported a high PPV (91.0) for the prediction of indicated delivery within 2 weeks.<sup>14</sup> Results from the ROPE<sup>48</sup> study varied by test cut-off and gestational age group, with the highest NPV (94.7) reported for predicting indicated delivery within 2 weeks using a test cut-off of 38 in women at less than 34 weeks' gestation.<sup>14</sup> The COMPARE study also reported high NPVs (> 86.6) for the Elecsys ratio test for a variety of different delivery outcomes.<sup>53</sup>

We did not rate the certainty of the evidence for the accuracy of prediction of delivery for the Elecsys ratio test because no add-on studies were available.

### *BRAHMS Kryptor sFlt-1/PlGF Ratio Test*

No data were identified for prediction of delivery outcomes for this test from add-on or stand-alone studies.<sup>14</sup>



We did not rate the certainty of the evidence for the accuracy of prediction of delivery for the BRAHMS Kryptor sFlt-1/PlGF ratio test because no add-on or stand-alone studies were available.

#### *DELFIA Xpress PlGF Test*

No data were identified from add-on studies. One stand-alone study, COMPARE, reported NPVs greater than 91.2 for a range of delivery-related outcomes.<sup>14</sup>

We did not rate the certainty of the evidence for the accuracy of prediction of delivery for the DELFIA Xpress PlGF test because no add-on studies were available.

#### *Triage PlGF Test*

Two add-on studies reported accuracy data for the Triage PlGF test. No standalone studies were identified.

Ormesher et al.<sup>40</sup> (an add-on study) reported test accuracy data for the prediction of preterm delivery by test-birth interval in women at less than 37 weeks' gestation (Table 12).<sup>14</sup> Higher PPVs were achieved when the lower test cut-off of 12 pg/mL was used and were similar between women who delivered within 14 days of the test (96.9) and those who delivered at any time after the test (95.1).<sup>14</sup> Confidence intervals were not reported by Ormesher et al.<sup>40</sup> The PPVs and NPVs were calculated and reported by Frampton et al.<sup>14</sup>

**Table 12: Prediction of Preterm Delivery (< 37 Weeks) by Test-Birth Interval (Triage PlGF Test)**

| Time point  | Cut-off     | Total (N) | Sensitivity | Specificity | PPV  | NPV  |
|---|-------------|-----------|-------------|-------------|------|------|
| <b>Ormesher et al.<sup>40</sup> Triage PlGF, test concealed, &lt; 37 weeks' gestation</b> |             |           |             |             |      |      |
| Within 2 wk   | < 12 pg/mL  | 88        | 44.9        | 94.7        | 96.9 | 32.1 |
|   | < 100 pg/mL | 88        | 84.1        | 26.3        | 80.6 | 31.3 |
| At any time   | < 12 pg/mL  | 255       | 74.2        | 97.7        | 95.1 | 66.5 |
|   | < 100 pg/mL | 255       | 79.7        | 72.7        | 73.1 | 79.3 |

Abbreviations: NPV, negative predictive value; PlGF, placental growth factor; PPV, positive predictive value.

Source: Adapted from Frampton et al.<sup>14</sup>

Data from the concealed arm only of the add-on PARROT<sup>37</sup> study provided high NPV values (> 95) for prediction of pre-eclampsia requiring delivery within 2 weeks of the test (in women at < 35 weeks' gestation) (Table 13) while PPVs were less than 50.<sup>14</sup>

**Table 13: Prediction of Pre-eclampsia Requiring Delivery Within 2 Weeks (Triage PlGF Test)**

| Time point  | Cut-off     | Total (N) | Sensitivity (95% CI) | Specificity (95% CI) | PPV <sup>a</sup> (95% CI) | NPV <sup>a</sup> (95% CI) |
|---|-------------|-----------|----------------------|----------------------|---------------------------|---------------------------|
| PARROT, <sup>37</sup> Triage test, result concealed, GA 20 to 35 wk |             |           |                      |                      |                           |                           |
| Within 2 wk   | < 12 pg/mL  | 265       | 74.4<br>(57.9–87.0)  | 84.1<br>(78.6–88.6)  | 44.6<br>(36.2–53.4)       | 95.0<br>(91.7–97.0)       |
|   | < 100 pg/mL | 265       | 94.9<br>(82.7–99.4)  | 57.2<br>(45.9–59.3)  | 25.7<br>(22.8–28.8)       | 98.3<br>(93.9–99.6)       |

Abbreviations: CI, confidence interval; GA, gestational age; NPV, negative predictive value; PlGF, placental growth factor; PPV, positive predictive value.

<sup>a</sup> Confidence interval calculated by Frampton et al.<sup>14</sup>

Source: Adapted from Frampton et al.<sup>14</sup>

For the prediction of pre-eclampsia requiring preterm delivery (< 37 weeks) in women at 35 to 36+6 weeks' gestation, the PARROT<sup>37</sup> study reported a higher NPV for the 100 pg/mL test cut-off (97.1) than for the 12 pg/mL cut-off (86.8) while PPVs were 18.5 and 24.4 respectively (Table 14).

**Table 14: Prediction of Pre-eclampsia Requiring Preterm Delivery (< 37 Weeks) (Triage PlGF Test)**

| Time point  | Cut-off     | Total (N) | Sensitivity (95% CI)             | Specificity (95% CI)             | PPV (95% CI)                     | NPV                              |
|---|-------------|-----------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| PARROT, <sup>37</sup> Triage test, result concealed, GA 35+0 to 36+6 wk |             |           |                                  |                                  |                                  |                                  |
| Before 37 weeks' gestation  | < 12 pg/mL  | 170       | 37.0<br>(19.4–57.6)              | 78.3<br>(70.7–84.8)              | 24.4 <sup>a</sup><br>(15.3–36.6) | 86.8 <sup>a</sup><br>(83.0–89.9) |
|   | < 100 pg/mL | 170       | 96.2 <sup>a</sup><br>(80.4–99.9) | 23.6 <sup>a</sup><br>(16.9–31.4) | 18.5 <sup>a</sup><br>(16.8–20.4) | 97.1 <sup>a</sup><br>(83.0–99.6) |

Abbreviations: CI, confidence interval; GA, gestational age; N, number of patients; NPV, negative predictive value; pg, picogram; PPV, positive predictive value.

<sup>a</sup> Confidence interval calculated by Frampton et al.<sup>14</sup>

Source: Adapted from Frampton et al.<sup>14</sup>

We did not rate the certainty of the evidence for the accuracy of prediction of delivery using the Triage PlGF test because data were only available for the concealed arm of the add-on PARROT study. Additionally, the Triage PlGF test is not licensed by Health Canada.

#### ACCURACY FOR REPEAT TESTING TO RULE IN/OUT PRE-ECLAMPSIA

No data were identified from add-on studies on the test accuracy of repeat PlGF-based testing.<sup>14</sup>

Zeisler et al.<sup>57</sup> (a stand-alone study) conducted a post-hoc analysis of the PROGNOSIS validation cohort (N = 550), to investigate whether repeat testing after 2 to 3 weeks could identify women at risk for developing pre-eclampsia (sFlt-1/PlGF ratio > 38) after it was initially ruled out (Elecsys sFlt-1/PlGF ratio ≤ 38).<sup>14</sup> No further information was reported by Frampton et al.<sup>14</sup>

The NICE 2022 guidance<sup>17</sup> states "not much more evidence was found for repeat PlGF testing" in the updated systematic review by Frampton et al<sup>14</sup> (compared with their systematic review from 2016).

Because no studies were identified, we did not rate the certainty of the evidence.

### ***Clinical Utility Outcomes***

Clinical outcomes reported in stand-alone test accuracy studies were not discussed by Frampton et al,<sup>14</sup> as these lack a control group and do not assess interpretation of the test alongside standard clinical assessment.

Frampton et al<sup>14</sup> reported clinical utility outcomes in the four add-on studies that compare use of the test alongside standard clinical assessment (test result revealed) with standard clinical assessment only (test result concealed): PARROT and MAPPLE studies (Triage PlGF test, not licensed by Health Canada) and the INSPIRE and PreOS studies (Elecsys sFlt-1/PlGF ratio test).

### **TIME TO PRE-ECLAMPSIA DIAGNOSIS**

#### ***Elecsys sFlt-1/PlGF Ratio Test***

Time to diagnosis was shorter in the revealed arm of the INSPIRE<sup>41</sup> study, although not significantly different between study arms (Table 15).<sup>14</sup>

Time to PE diagnosis was not reported in the MAPPLE or PreOS studies.<sup>38,42</sup>

We rated the certainty of the evidence for Elecsys test as Low, downgrading for risk of bias (Appendix A2, Table A6).

Table 15: Time to Pre-eclampsia Diagnosis

| Study                                 | Outcome  | Group   | Revealed                 | Concealed                | Difference   |  |
|---------------------------------------|--|---|--------------------------|--------------------------|--|--|
| <b>Triage PlGF test</b>               |  |   |                          |                          |  |  |
| PARROT <sup>37,58</sup>               | Time (d) to diagnosis, median (IQR); N               | Total   | 1.9 (0.5–9.2); N = 573   | 4.1 (0.8–14.7); N = 446  | Adjusted time ratio = 0.36 (95% CI, 0.15–0.87; <i>P</i> = .027), |  |
|                                       |  | PlGF < 12 pg/mL                                       | 1.0 (0.3–4.5); n = 130   | 2.0 (0.3–9.0); n = 106   | Adjusted time ratio = 0.17 (95% CI, 0.03–1.06)                   |  |
|                                       |  | PlGF 12–100 pg/mL                                     | 2.0 (0.9–8.70); n = 212  | 4.6 (1.0–14.5); n = 173  | Adjusted time ratio = 0.66 (95% CI, 0.09–4.95)                   |  |
|                                       |  | PlGF > 100 pg/mL                                      | 22.8 (8.4–39.2); n = 229 | 30.3 (5.9–65.1); n = 156 | Adjusted time ratio = 0.13 (95% CI, 0.16–1.07)                   |  |
| PARROT Ireland <sup>59</sup>          | Time (d) to diagnosis, median (IQR); N               | Total   | 8 (1–23); N = 1,017      | 7 (1–25); N = 1,202      | Adjusted risk ratio = 0.92 (95% CI, 0.56–1.49; <i>P</i> = .73)   |  |
| <b>Elecsys sFlt-1/PlGF ratio test</b> |  |   |                          |                          |  |  |
| INSPIRE <sup>41</sup>                 | Time (d) to PE diagnosis within 7 d, median (IQR); N | Total   | 0 (0–2); N = 186         | 0 (0–3); N = 184         | 0 days <sup>a</sup> ; <i>P</i> = .7777 <sup>a</sup>              |  |
|                                       |  | Time (d) to PE diagnosis within 28 d, median (IQR); N | Total                    | 2 (0–9); N = 186         | 4 (0–10.5); N=184  | 2 days <sup>a</sup> ; <i>P</i> = .5641 <sup>a</sup>  |
|                                       |  | Time (d) to PE diagnosis at any time, median (IQR); N | Total                    | 7 (0–29); N = 186        | 9.5 (0–32); N=184  | 2.5 days <sup>a</sup> ; <i>P</i> = .638 <sup>a</sup> |

Abbreviations: CI, confidence interval; IQR, interquartile range; PE, pre-eclampsia; PlGF, placental growth factor.

<sup>a</sup> Absolute difference calculated by Frampton et al.<sup>14</sup>

Source: Adapted from Frampton et al.<sup>14</sup>

### *Triage PlGF Test*

In the PARROT<sup>37,58</sup> study, use of the Triage PlGF test alongside standard clinical assessment (test result revealed) was associated with a 64% reduction in time to diagnosis of pre-eclampsia (95% CI, 13% to 85%; *P* = .027) (Table 15).<sup>14</sup> Time to diagnosis was shorter in the revealed trial arm in all three PlGF-level subgroups.<sup>14</sup>

The post-hoc analysis from the PARROT Ireland<sup>59</sup> study contradicts the results of the PARROT<sup>37</sup> trial (no significant difference between trial arms) (Table 15),<sup>14</sup> which used a similar trial design (11 maternity units and duration of 17 months) and PlGF platform but different primary outcomes (time from

enrolment to diagnosis in the PARROT trial and maternal and neonatal morbidity in the PARROT Ireland trial).

We rated the certainty of the evidence for Triage test as Low, downgrading for risk of bias and inconsistency (Appendix A2, Table A6).

## TIME TO DELIVERY

### *Elecsys sFlt-1/PLGF Ratio Test*

Time to delivery was not reported in the INSPIRE<sup>41</sup> or PreOS<sup>42</sup> studies.<sup>14</sup>

### *Triage PLGF Test*

For the Triage PLGF test, time to delivery was longer overall in the revealed arm of the PARROT study compared with the concealed arm (19.0 vs 17.8 days); however, when stratified by PLGF level, the time to delivery was shorter in women with very low levels of PLGF (< 12 pg/mL) in the revealed group compared with the concealed group regardless of gestational age (Table 16).<sup>37,58</sup> In general, time to delivery was longer in women at less than 35 weeks' gestation. In the MAPPLE study, time to delivery was 6 days shorter in the revealed arm compared with the concealed arm (95% CI 2.0 to 10.0 days shorter) and was also shortest in women with very low PLGF levels (Table 16).<sup>38</sup>

**Table 16: Time to Delivery: Studies Included in Systematic Review by Frampton et al**

| Study                   | Outcome   | Group  | Revealed            | Concealed           | Difference                                    |
|-------------------------|---|--|---------------------|---------------------|---|
| <b>Triage PLGF test</b> |   |  |                     |                     |   |
| PARROT <sup>37,58</sup> | Time to delivery (d), geometric mean (SD); N                        | Total  | 19.0 (3.1); N = 573 | 17.8 (3.1); N = 446 | Adjusted ratio of means: 1.10 (CI 0.99-1.24)  |
|                         | Time to delivery (days), median (IQR) <sup>a</sup>                  | <b>In women &lt; 35 weeks' gestation at testing:</b>                 |                     |                     |   |
|                         |   | PLGF < 12 <sup>b</sup>   | 12 (6-22)           | 17 (7-25)           | Not reported                                  |
|                         |   | PLGF 12-100  | 26 (16-36)          | 27 (18-35)          | Not reported                                  |
|                         |   | PLGF > 100   | 50 (32-75)          | 50 (35-76)          | Not reported                                  |
|                         |   | <b>In women 35 weeks to 36 weeks + 6 days' gestation at testing:</b> |                     |                     |   |
|                         |   | PLGF < 12  | 4 (2-8)             | 8 (5-12)            | Not reported                                  |
|                         |   | PLGF 12-100  | 13 (7-18)           | 11 (4-18)           | Not reported                                  |
|                         |   | PLGF > 100   | 20 (13-28)          | 21 (11-28)          | Not reported                                  |
| MAPPLE <sup>38,b</sup>  | Interval (days) from first test to delivery, median, (quartiles); N | Total  | 24 (4-52); N = 397  | 29 (11-59); N = 287 | Median difference: -6.0 95% CI, -2.0 to -10.0 |
|                         |   | PLGF < 12  | 3 (1-13); n = 116   | 9 (3-16); n = 69    | Not reported                                  |
|                         |   | PLGF 12-100  | 19 (6-43); n = 137  | 23 (11-40); n = 97  | Not reported                                  |
|                         |   | PLGF > 100   | 48 (32-69); n = 143 | 61 (37-90); n = 121 | Not reported                                  |

Abbreviations: IQR, interquartile range; PLGF, placental growth factor; SD, standard deviation.

<sup>a</sup> Number not reported for subgroups.

<sup>b</sup> Unadjusted indirect comparison.

Source: Adapted from Frampton et al.<sup>14</sup>

We rated the certainty of the evidence for Triage test as Low, downgraded for risk of bias and inconsistency (Appendix A2, Table A6).

## PRE-ECLAMPSIA DIAGNOSIS

### *Elecsys sFlt-1/PlGF Ratio Test*

The proportion of women diagnosed with pre-eclampsia within 7 days, 28 days, or at any time was higher in the revealed arm compared with concealed arm in the INSPIRE<sup>41</sup> study (Table 17).<sup>14</sup> Of those with a pre-eclampsia diagnosis, a higher proportion of the test-revealed group (9% higher) was diagnosed with severe pre-eclampsia compared with the test-concealed group (Table 18). Klein et al<sup>42</sup> did not report the frequency of pre-eclampsia diagnoses for women in the PreOS study before and after test results were available to clinicians.<sup>14</sup>

**Table 17: Pre-eclampsia Diagnosis by Time Point**

| Study                                 | Outcome  | Group                    | Revealed       | Concealed      | Difference   |
|---------------------------------------|--|--------------------------|----------------|----------------|--|
| <b>Triage PlGF test</b>               |  |                          |                |                |  |
| PARROT <sup>37,58</sup>               | PE diagnosis by clinician at any time, % (n/N) | Total                    | 36 (205/573)   | 35 (155/446)   | 1.0 <sup>a</sup>   |
|                                       |  | PlGF < 12 <sup>c</sup>   | 73.8 (96/130)  | 66.0 (70/106)  | 7.0 <sup>a</sup>   |
|                                       |  | PlGF 12–100 <sup>c</sup> | 39.6 (84/212)  | 37.0 (64/173)  | 4.5 <sup>a</sup>   |
|                                       |  | PlGF > 100 <sup>c</sup>  | 10.0 (23/229)  | 12.2 (19/156)  | 0.4 <sup>a</sup>   |
| MAPPLE <sup>38,b</sup>                | PE diagnosis at any time, % (n/N)              | Total                    | 52.9 (193/397) | 61.3 (176/287) | 8.4 <sup>a</sup> ; risk ratio (95% CI), 0.86 (0.75–0.99) |
|                                       |  | PlGF < 12 <sup>c</sup>   | 48.6 (51/116)  | 97.1 (67/69)   | 48.5 <sup>a</sup>  |
|                                       |  | PlGF 12–100 <sup>c</sup> | 53.1 (69/137)  | 74.2 (72/97)   | 21.1 <sup>a</sup>  |
|                                       |  | PlGF > 100 <sup>c</sup>  | 56.2 (73/143)  | 30.6 (37/121)  | 25.6 <sup>a</sup>  |
| <b>Elecsys sFlt-1/PlGF ratio test</b> |  |                          |                |                |  |
| INSPIRE <sup>41</sup>                 | PE within 7 days, % (n/N)                      | Total                    | 12.9 (24/186)  | 9.7 (18/184)   | 3.2 <sup>a</sup> ; <i>P</i> = .344                       |
|                                       | PE within 28 days, % (n/N)                     | Total                    | 18.8 (35/186)  | 15.2 (28/184)  | 3.6 <sup>a</sup> ; <i>P</i> = .357                       |
|                                       | PE at any time, % (n/N)                        | Total                    | 25.2 (47/186)  | 20.6 (38/184)  | 4.6 <sup>a</sup> ; <i>P</i> = .291                       |

Abbreviations: CI, confidence interval; PE, pre-eclampsia; PlGF, placental growth factor.

<sup>a</sup> Absolute percent difference calculated by Frampton et al.<sup>14</sup>

<sup>b</sup> Unadjusted indirect comparison.

<sup>c</sup> pg/mL

Source: Adapted from Frampton et al.<sup>14</sup>

Table 18: Severe Pre-eclampsia

| Study                                 | Outcome   | Group  | Revealed      | Concealed     | Difference                                      |
|---------------------------------------|---|--|---------------|---------------|---|
| <b>Triage PlGF test</b>               |   |  |               |               |   |
| PARROT <sup>37,58</sup>               | Severe PE (ACOG definition), n/N (%)            | Total  | 27 (155/573)  | 24 (106/446)  | 3.0 <sup>a</sup> ; aOR 1.22 (95% CI, 0.71–2.12) |
|                                       |   | PlGF < 12 <sup>c</sup>   | 56.2 (73/130) | 46.2 (49/106) | 10.0 <sup>a</sup>                               |
|                                       |   | PlGF 12–100 <sup>c</sup>   | 30.2 (64/212) | 28.3 (49/173) | 1.9 <sup>a</sup>                                |
|                                       |   | PlGF > 100 <sup>c</sup>  | 7.9 (18/229)  | 4.5 (7/156)   | 3.4 <sup>a</sup>                                |
| <b>Elecsys sFlt-1/PlGF ratio test</b> |   |  |               |               |   |
| INSPIRE <sup>41</sup>                 | Severe PE (ACOG criteria), % <sup>b</sup> (n/N) | Total  | 72.3 (34/47)  | 63.3 (24/38)  | 9.0 <sup>a</sup> ; <i>P</i> = .366              |
|                                       |   | Severe PE with 2 or more criteria for severity, % <sup>b</sup> (n/N) | 12.7 (6/47)   | 18.4 (7/38)   | 5.7 <sup>a</sup> ; <i>P</i> = .471              |

Abbreviations: ACOG, American College of Obstetrics and Gynecology; aOR, adjusted odds ratio; CI: confidence interval; PE: pre-eclampsia; PlGF: placenta growth factor.

<sup>a</sup> Absolute Percent difference calculated by Frampton et al.<sup>14</sup>

<sup>b</sup> Proportion of those diagnosed with PE.

<sup>c</sup> pg/mL.

Source: Adapted from Frampton et al.<sup>14</sup>

We rated the certainty of the evidence for the Elecsys test as Low, downgrading for risk of bias and imprecision (Appendix A2, Table A6).

### *Triage PlGF Test*

In the PARROT randomized controlled trial (RCT),<sup>37,58</sup> a higher proportion of women were diagnosed with pre-eclampsia (1% higher) or severe eclampsia (3% higher) in the test-revealed arm compared with the concealed arm, with the highest differences observed in women with very low PlGF levels (Table 17).<sup>14</sup> In contrast, the MAPPLE<sup>38</sup> study observed a lower proportion of women diagnosed with pre-eclampsia in the revealed arm compared with the concealed arm (8.4%), with larger differences between the study arms observed when stratified by PlGF level (Table 17).<sup>14</sup>

Frampton et al.<sup>14</sup> further compared the number of people diagnosed with pre-eclampsia in the PARROT and PARROT Ireland trials (Table 19) and noted subtle differences in the populations enrolled and examined. For example, a higher proportion of women with suspected fetal growth restriction (inconsistently present in pre-eclampsia, sometimes preceding and sometimes following diagnosis of pre-eclampsia) were recruited to the PARROT Ireland trial (approximately 55% in PARROT Ireland compared with 16% PARROT UK) and the incidence of pre-eclampsia among the UK trial participants was higher (approximately 35% in PARROT compared with 14% in PARROT Ireland).<sup>14</sup>

Table 19: Diagnosis of Pre-eclampsia<sup>a</sup>: PARROT Versus PARROT Ireland

| Study                        | Revealed          | Concealed         | Risk estimate |
|------------------------------|-------------------|-------------------|---------------|
| PARROT <sup>58</sup>         | 205/573 (36%)     | 155/446 (35%)     | Not reported  |
| PARROT Ireland <sup>36</sup> | 138/1017 (13.57%) | 177/1202 (14.73%) | Not reported  |

<sup>a</sup> Diagnosis of pre-eclampsia: PARROT used the International Society for the Study of Hypertension in Pregnancy (ISSHP) 2014 guidelines<sup>60</sup> whereas PARROT Ireland used the National Institute for Health and Clinical Excellence 2010 guidelines on hypertension in pregnancy.<sup>61</sup>

Source: Adapted from Frampton et al.<sup>14</sup>

The PARROT Ireland<sup>36</sup> investigators noted that while the trial results did not support the routine incorporation of PlGF-based testing neither did they exclude the potential benefits of these tests.<sup>14</sup>

We rated the certainty of the evidence for the Triage test as Low, downgrading for risk of bias and inconsistency (Appendix A2, Table A6).

## MATERNAL ADVERSE OUTCOMES

### Elecsys sFlt-1/PlGF Ratio Test

Maternal outcomes were reported in the PreOS study<sup>42</sup> in relation to different sFlt-1/PlGF ratios but not for the comparison of interest (revealed versus concealed).<sup>14</sup> The INSPIRE<sup>41</sup> study reported the frequency of selected outcomes only (Table 20), with severe hypertension and hepatic dysfunction reported most frequently.<sup>14</sup> No statistically significant differences were observed between trial arms for these outcomes; however, it should be noted the study was not powered to detect differences for these outcomes.<sup>14</sup>

Table 20: Maternal Adverse Outcomes: Elecsys sFlt-1/PlGF Ratio Test

| Study                                 | Outcome  | Revealed      | Concealed     | Difference <sup>a</sup> |
|---------------------------------------|--|---------------|---------------|-------------------------|
| <b>Elecsys sFlt-1/PlGF ratio test</b> |  |               |               |                         |
| INSPIRE <sup>41</sup>                 | Pulmonary edema, % (n/N)   | 0.5 (1/186)   | 0.5 (1/184)   | 0; <i>P</i> = .99       |
|                                       | Placental abruption, % (n/N)                                     | 1.1 (2/186)   | 2.7 (5/184)   | 1.6; <i>P</i> = .25     |
|                                       | Severe hypertension (in women with a PE diagnosis only), % (n/N) | 46.8 (22/47)  | 52.6 (20/38)  | 5.8; <i>P</i> = .59     |
|                                       | Creatinine > 97, % (n/N)   | 4.8 (9/186)   | 4.4 (8/184)   | 0.4; <i>P</i> = .82     |
|                                       | Platelets < 100, % (n/N)   | 2.2 (4/186)   | 3.8 (7/184)   | 1.6; <i>P</i> = .349    |
|                                       | ALT double the normal, % (n/N)                                   | 17.7 (33/186) | 12.5 (23/184) | 5.2; <i>P</i> = .159    |
|                                       | Eclampsia, % (n/N)   | 0 (0/186)     | 0 (0/184)     | Not applicable          |

Abbreviations: ALT, alanine transaminase; PE, pre-eclampsia; PlGF, placental growth factor.

<sup>a</sup> Absolute percent difference calculated by Frampton et al.<sup>14</sup>

Source: Adapted from Frampton et al.<sup>14</sup>

We rated the certainty of the evidence for Elecsys test as low, downgrading for risk of bias and imprecision (Appendix A2, Table A6).



*Triage PLGF test*

In the PARROT<sup>58</sup> study, maternal outcomes were a composite of severe maternal adverse outcomes as defined by the fullPIERS (Preeclampsia Integrated Estimate of Risk) model.<sup>62</sup> The fullPIERS model was developed to predict adverse maternal outcomes occurring in the 48 hours after hospital admission with pre-eclampsia.<sup>62</sup> The adverse outcomes predicted by the model included major organ dysfunction and death.<sup>62</sup>

The frequency of any fullPIERS<sup>62</sup> adverse maternal outcomes was lower in the trial arm where the Triage PLGF test results were revealed compared with the concealed arm (3.8% vs 5.4%; adjusted odds ratio [OR] 0.32 [95% CI, 0.11–0.96;  $P = .043$ ; Table 21).

**Table 21: Severe Maternal Adverse Outcomes: TRIAGE PLGF Test**

| Study                        | Outcome  | Group                    | Revealed        | Concealed        | Difference  |
|------------------------------|--|--------------------------|-----------------|------------------|---|
| <b>Triage PLGF test</b>      |  |                          |                 |                  |   |
| PARROT <sup>37,58</sup>      | Severe maternal adverse outcomes (defined by the fullPIERS consensus), % (n/N) | Total                    | 3.8 (22/573)    | 5.4 (24/446)     | 1.0 <sup>a</sup> ; aOR (95% CI), 0.32 (0.11–0.96); $P = .043$ |
|                              |  | PLGF < 12 <sup>c</sup>   | 6.2 (8/130)     | 5.7 (6/106)      | aOR 0.87 (0.09–8.02)  |
|                              |  | PLGF 12–100 <sup>c</sup> | 3.8 (8/212)     | 6.9 (12/173)     | aOR: 0.15 (0.03–0.92)   |
|                              |  | PLGF > 100 <sup>c</sup>  | 2.6 (6/229)     | 3.8 (6/156)      | aOR: 0.29 (0.02–4.34)   |
| PARROT Ireland <sup>36</sup> | Maternal morbidity composite % (n/N)   | Total                    | 32.5 (330/1017) | 38.02 (457/1202) | Risk ratio (95% CI), 1.01 (0.76–1.36)                         |
| MAPPLE <sup>38,b</sup>       | Adverse maternal outcomes, % (n/N)   | Total                    | 11.9 (47/396)   | 10.1 (29/287)    | Risk ratio (95% CI), 1.17 (0.76–1.82)                         |
|                              |  | PLGF < 12 <sup>c</sup>   | 21.6 (25/116)   | 17.4 (12/69)     | 4.2 <sup>a</sup>  |
|                              |  | PLGF 12–100 <sup>c</sup> | 11.7 (16/137)   | 8.2 (8/97)       | 3.5 <sup>a</sup>  |
|                              |  | PLGF > 100 <sup>c</sup>  | 4.2 (6/143)     | 7.4 (9/121)      | 3.2 <sup>a</sup>  |

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; fullPIERS, Preeclampsia Integrated Estimate of Risk; PLGF, placental growth factor.

<sup>a</sup> Absolute percent difference as calculated by Frampton et al<sup>14</sup>

<sup>b</sup> Unadjusted indirect comparison.

<sup>c</sup> pg/mL

Source: Adapted from Frampton et al.<sup>14</sup>

While the PARROT<sup>58</sup> trial used a similar trial design and PLGF platform as the PARROT Ireland<sup>36</sup> study, the studies had different primary outcomes (time from enrolment to diagnosis in PARROT and maternal and neonatal morbidity in PARROT Ireland).<sup>14</sup> To facilitate direct comparison between the two PARROT trials, the PARROT Ireland investigators conducted post-hoc analyses using the same composites to define adverse outcomes as the PARROT study (the maternal and neonatal adverse outcomes) and found no evidence of significant benefit to support the incorporation of PLGF testing into routine clinical investigations for women presenting with suspected preterm pre-eclampsia (maternal morbidity,  $P = .58$ ) (Table 22).<sup>14</sup>

Table 22: Maternal Adverse Outcomes<sup>a</sup>: PARROT Versus PARROT Ireland

| Study                        | Revealed     | Concealed    | Risk estimate   |
|------------------------------|--------------|--------------|---|
| PARROT <sup>58</sup>         | 22/573 (4%)  | 24/446 (5%)  | aOR (95% CI; <i>P</i> value) 0.32 (0.11–0.96; <i>P</i> = .04) |
| PARROT Ireland <sup>36</sup> | 106 (10.42%) | 131 (10.90%) | aRR (95% CI; <i>P</i> value) 1.10 (0.79–1.52; <i>P</i> =.58)  |

Abbreviations: aOR, adjusted odds ratio; aRR, adjusted risk ratio; CI, confidence interval.

<sup>a</sup> Maternal deaths, eclampsia, stroke, parenteral infusion of third-line antihypertensive, myocardial infarction, blood oxygen saturation less than 90%, intubation (other than for Caesarean section), pulmonary edema, transfusion of blood products, platelet count less than  $50 \times 10^9$  platelets per L, hepatic dysfunction, severe acute kidney injury, dialysis, placental abruption.

Source: Adapted from Frampton et al.<sup>14</sup>

As noted by the PARROT Ireland<sup>36</sup> study authors, potential explanations for the differing results may be due to the PARROT Ireland study being underpowered to detect significant differences in the composite co-primary endpoints (maternal and neonatal morbidity) and subtle differences in the populations enrolled and examined.<sup>14</sup>

In the MAPPLE<sup>38</sup> study, the composite outcome "maternal adverse outcomes" was reported in 47 (11.9%) of women in the revealed Triage PlGF test results arm and 29 (10.1%) of women in the comparator (risk ratio: 1.17; 95% CI, 0.76–1.82).<sup>14</sup> Frampton et al.<sup>14</sup> assumed that this composite includes the fullPIERS-defined outcomes, as many of the individual fullPIERS outcomes were also reported separately in the MAPPLE study.

No maternal deaths were reported in either trial arm in the PARROT<sup>58</sup> or MAPPLE<sup>38</sup> studies. The PARROT Ireland<sup>36</sup> study reported one maternal death in the intervention arm (death 10 weeks after delivery due to acute complications of a known underlying cardiac condition).<sup>14</sup>

We rated the certainty of the evidence for the Triage test as low, downgrading for risk of bias and inconsistency (Appendix A2, Table A6).

## FETAL MORTALITY

### *Elecsys sFlt-1/PlGF Ratio*

The PreOS<sup>42</sup> and INSPIRE<sup>41</sup> studies did not report data for this outcome for the Elecsys sFlt-1/PlGF ratio test.<sup>14</sup>

### *Triage PlGF Test*

Rates of intrauterine fetal death were similar in the revealed and concealed arms of the Triage PlGF test and the PARROT<sup>37</sup> study, respectively, but slightly higher stillbirth rates were observed in the concealed arm of the MAPPLE<sup>38</sup> study, particularly in the subgroup of women with very low PlGF levels (< 12 pg/mL) (Table 23).<sup>14</sup>

We rated the certainty of the evidence for the Triage test as low, downgrading for risk of bias and imprecision (Appendix A2, Table A6).

**Table 23: Fetal Mortality Outcomes: Studies Included in the Systematic Review by Frampton et al**

| Study                   | Outcome                           | Group                    | Revealed    | Concealed   | Difference <sup>a</sup> |
|-------------------------|-----------------------------------|--------------------------|-------------|-------------|-------------------------|
| <b>Triage PlGF test</b> |                                   |                          |             |             |                         |
| PARROT <sup>37</sup>    | Intrauterine death, % (n/N)       | Total                    | 1.2 (7/573) | 1.3 (6/446) | 0.1                     |
|                         |                                   | PlGF < 12 <sup>b</sup>   | 3.1 (4/130) | 3.8 (4/106) | 0.7                     |
|                         |                                   | PlGF 12–100 <sup>b</sup> | 0.5 (1/212) | 1.2 (2/173) | 0.7                     |
|                         |                                   | PlGF > 100 <sup>b</sup>  | 0 (0/229)   | 1.3 (2/156) | 1.3                     |
| MAPPLE <sup>38</sup>    | Stillbirth, % (n/N <sup>a</sup> ) | Total                    | 0.2 (1/433) | 2.3 (7/299) | 2.1                     |
|                         |                                   | PlGF < 12 <sup>b</sup>   | 0.8 (1/124) | 5.8 (4/69)  | 5.0                     |
|                         |                                   | PlGF 12–100 <sup>b</sup> | 0 (0/158)   | 2.9 (3/105) | 2.9                     |
|                         |                                   | PlGF > 100 <sup>b</sup>  | 0 (0/151)   | 0 (0/125)   | Not applicable          |

Abbreviations: PlGF, placental growth factor.

<sup>a</sup> Absolute percent difference calculated by Frampton et al.<sup>14</sup>

<sup>b</sup> pg/mL.

Source: Adapted from Frampton et al.<sup>14</sup>

## GESTATIONAL AGE AT DELIVERY

### Elecsys sFlt-1/PlGF Ratio Test

No statistically significant difference in gestational age at delivery was observed between revealed and concealed arms in the INSPIRE<sup>41</sup> study (Table 24).<sup>14</sup>

**Table 24: Gestational Age at Delivery: Elecsys sFlt-1/PlGF Ratio Test**

| Study                                 | Outcome   | Group | Revealed                  | Concealed                 | Difference <sup>a</sup> |
|---------------------------------------|---|-------|---------------------------|---------------------------|-------------------------|
| <b>Elecsys sFlt-1/PlGF ratio test</b> |   |       |                           |                           |                         |
| INSPIRE <sup>41</sup>                 | Gestational age (wk at delivery, median [IQR]); N | Total | 38.4 (37.3–39.6); N = 186 | 38.1 (37.1–39.3); N = 184 | 0.3; <i>P</i> = .479    |

Abbreviations: IQR: interquartile range; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

<sup>a</sup> Absolute percent difference as calculated by Frampton et al.<sup>14</sup>

Source: Adapted from Frampton et al.<sup>14</sup>

Klein et al.<sup>42</sup> (PreOS study) performed an analysis of intended clinical decisions made before and after sFlt-1/PlGF ratio test results were revealed to the clinical team for 188 women. In women for whom a decision was changed after the test result was revealed, the gestational age at delivery was generally lower in those for whom the change was in favour of an intervention (e.g., hospitalization, use of steroids to induce fetal lung maturity) compared with those for whom the clinical decision was reversed (e.g., not to hospitalize or induce lung maturity).<sup>14</sup>

We rated the certainty of the evidence for the Elecsys test as Low, downgrading for risk of bias and imprecision (Appendix A2, Table A6).

**Triage PLGF Test**

In the PARROT<sup>37,58</sup> study there was no difference in mean gestational age at delivery between revealed and concealed trial arms overall or within subgroups of women stratified by PLGF level.<sup>14</sup> However, women with very low PLGF levels (< 12 pg/mL) delivered earlier, on average, in both trial arms (mean < 35 weeks' gestation) (Table 25).<sup>14</sup> In the MAPPLE<sup>38</sup> study, women delivered, on average, at a gestational age of 1.4 weeks earlier in the revealed arm than women in the concealed arm (95% CI, 0.9 to 2.0 weeks earlier). Women with very low PLGF levels (< 12 pg/mL) delivered at an earlier gestational age in both trial arms (median < 32 weeks) (Table 25).<sup>14</sup>

**Table 25: Gestational Age at Delivery: Triage PLGF Test**

| Study                   | Outcome  | Group                    | Revealed                  | Concealed                 | Difference <sup>a</sup>                         |
|-------------------------|--|--------------------------|---------------------------|---------------------------|---|
| <b>Triage PLGF test</b> |  |                          |                           |                           |   |
| PARROT <sup>37,58</sup> | GA (wk) at delivery, mean (SD); N <sup>b</sup>           | Total                    | 36.6 (3.0); N = 573       | 36.8 (3.0); N = 446       | Mean difference (95% CI), -0.52 (-0.63 to 0.73) |
|                         |  | PLGF < 12 <sup>c</sup>   | 33.4 (3.13); n = 130      | 34.4 (3.72); n = 106      | Mean difference (95% CI), -0.03 (-1.72 to 1.66) |
|                         |  | PLGF 12–100 <sup>c</sup> | 36.7 (2.48); n = 212      | 37.1 (2.04); n = 173      | Mean difference (95% CI), -0.40 (-1.25 to 0.45) |
|                         |  | PLGF > 100 <sup>c</sup>  | 38.3 (1.75); n = 229      | 38.2 (2.33); n = 156      | Mean difference (95% CI), 0.36 (-0.44 to 1.16)  |
| MAPPLE <sup>38</sup>    | GA (wk) at delivery, median, (quartiles); N <sup>b</sup> | Total                    | 34.9 (32.0–37.1); N = 433 | 36.7 (33.6–38.6); N = 299 | Median difference (95% CI), -1.4 (-0.9 to -2.0) |
|                         |  | PLGF < 12 <sup>c</sup>   | 31.2 (29.0–33.4); n = 124 | 31.9 (29.3–34.1); n = 69  | Not reported                                    |
|                         |  | PLGF 12–100 <sup>c</sup> | 35.0 (33.3–36.8); n = 158 | 35.7 (34.1–37.9); n = 105 | Not reported                                    |
|                         |  | PLGF > 100 <sup>c</sup>  | 37.4 (36.1–38.4); n = 151 | 38.4 (37–39.9); n = 125   | Not reported                                    |

Abbreviations: CI, confidence interval; GA, gestational age; PLGF: placenta growth factor; SD: standard deviation.

<sup>a</sup> Absolute percent difference calculated by Frampton et al.

<sup>b</sup> Number of infants.

<sup>c</sup> pg/mL.

Source: Adapted from Frampton et al.<sup>14</sup>

We rated the certainty of the evidence for the Triage test as Low, downgrading for risk of bias and inconsistency (Appendix A2, Table A6).

## PERINATAL AND NEONATAL MORTALITY

*Elecsys sFlt-1/PLGF Ratio Test*

Neonatal and perinatal mortality were not reported in the INSPIRE<sup>41</sup> or PreOS<sup>42</sup> studies.<sup>14</sup>

*Triage PLGF Test*

The Triage PLGF test was the only assay to report this outcome. Perinatal deaths (defined as deaths from 24 weeks' gestation, including stillbirths, to 7 completed days after birth) were reported at a lower frequency in the revealed arm (0.5%) compared with the concealed arm (3.0%) in the MAPPLE<sup>38</sup> study but at similar frequencies (1.0%) in both arms of the PARROT<sup>37</sup> study (Table 26).<sup>14</sup>

**Table 26: Perinatal Mortality: Triage PLGF Test**

| Study                   | Outcome   | Group              | Revealed    | Concealed   | Difference  |
|-------------------------|---|--------------------|-------------|-------------|---|
| <b>Triage PLGF test</b> |   |                    |             |             |   |
| PARROT <sup>37</sup>    | Perinatal deaths, <sup>b</sup> %<br>(n/N)               | Total <sup>e</sup> | 1.0 (6/573) | 1.0 (4/446) | 0 <sup>f</sup> ; aOR (95% CI), 1.00 (0.61–1.63)             |
| MAPPLE <sup>38,a</sup>  | Perinatal deaths, <sup>c</sup> %<br>(n/N <sup>d</sup> ) | Total <sup>e</sup> | 0.5 (2/433) | 3.0 (9/299) | 2.5 <sup>f</sup> ; risk ratio (95% CI),<br>0.16 (0.03–0.74) |

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; PLGF, placental growth factor.

<sup>a</sup> Unadjusted indirect comparison.

<sup>b</sup> Defined as deaths from 24 weeks gestation, including those defined as stillbirths, to 7 completed days after birth.

<sup>c</sup> Definition not reported. Frampton et al<sup>14</sup> assumed it to be the same as that of the PARROT study.

<sup>d</sup> Number of infants.

<sup>e</sup> Data were not stratified by PLGF level for these outcomes.

<sup>f</sup> Absolute percent difference calculated by Frampton et al.<sup>14</sup>

Source: Adapted from Frampton et al.<sup>14</sup>

Overall, less than 1% of women experienced early or late neonatal death in the MAPPLE<sup>38</sup> and PARROT<sup>37</sup> studies respectively (Table 27).<sup>14</sup> Late neonatal deaths were reported at the highest frequency in women with very low PLGF levels in the concealed arm of the PARROT<sup>37</sup> study (1.0%). Data were not stratified by PLGF level for these outcomes in the MAPPLE<sup>38</sup> study.<sup>14</sup>

Table 27: Neonatal Mortality: Triage PLGF Test

| Study                   | Outcome   | Group                    | Revealed    | Concealed   | Difference       |
|-------------------------|---|--------------------------|-------------|-------------|------------------|
| <b>Triage PLGF test</b> |   |                          |             |             |                  |
| PARROT <sup>37</sup>    | Early neonatal death, % (n/N) <sup>b</sup>                | Total                    | 0 (0/573)   | 0 (0/446)   | Not applicable   |
|                         | Late neonatal deaths (8–27 complete days of life), %; n/N | Total                    | 0.5 (3/573) | 0.2 (1/446) | 0.3 <sup>d</sup> |
|                         |   | PLGF < 12 <sup>c</sup>   | 0.8 (1/130) | 1.0 (1/106) | Not reported     |
|                         |   | PLGF 12–100 <sup>c</sup> | 0.9 (2/212) | 0.0 (0/173) | Not reported     |
|                         |   | PLGF > 100 <sup>c</sup>  | 0.0 (0/229) | 0.0 (0/156) | Not reported     |
| MAPPLE <sup>38,a</sup>  | Early neonatal deaths, %; n/N <sup>b</sup>                | Total                    | 0.2 (1/433) | 0.7 (2/299) | 0.5 <sup>d</sup> |

Abbreviation: PLGF, placental growth factor.

<sup>a</sup> Unadjusted indirect comparison.

<sup>b</sup> Assumed by Frampton et al<sup>14</sup> to be within 7 days of birth.

<sup>c</sup> pg/mL.

<sup>d</sup> Absolute percent difference calculated by Frampton et al.<sup>14</sup>

Source: Adapted from Frampton et al.<sup>14</sup>

Neonatal and perinatal mortality were not reported in the INSPIRE<sup>41</sup> or PreOS<sup>42</sup> studies.<sup>14</sup>

We rated the certainty of the evidence for Triage test as low, downgrading for risk of bias and inconsistency (Appendix A2, Table A6).

## PERINATAL AND NEONATAL ADVERSE COMPOSITE OUTCOMES

### *Elecsys sFlt-1/PLGF Ratio Test*

No studies reported this outcome for the Elecsys sFlt-1/PLGF ratio test.<sup>14</sup>

### *Triage PLGF Test*

Data were available for this outcome for the Triage PLGF test only. The composite "perinatal adverse outcomes" was reported in the PARROT<sup>37,58</sup> study and included the following: any grade of intraventricular hemorrhage, seizure, any grade of retinopathy of prematurity, respiratory distress syndrome, bronchopulmonary dysplasia or necrotizing enterocolitis (stage 2 or 3), perinatal death, and late neonatal death.<sup>14</sup> Frequencies of this composite outcome were not significantly different between revealed and concealed arms but were higher in the group of women with very low PLGF levels (< 12 pg/mL) (Table 28).<sup>14</sup>

In contrast, the composite perinatal adverse outcome (assumed to include the same components as that of PARROT<sup>37,58</sup>) was reported at a higher frequency in the revealed arm of the MAPPLE<sup>38</sup> study (30.4%) compared with the concealed arm (20.1%).<sup>14</sup> The composite, including neonatal outcomes, was only reported at a higher frequency in the revealed arm than in the concealed arm, both in total study population and in each PLGF level subgroup. This composite outcome was more commonly reported with lower PLGF levels and the difference between revealed and concealed arms was also greater with lower PLGF levels.<sup>14</sup>

Table 28: Perinatal and Neonatal Adverse Outcomes: Triage PLGF Test

| Study                   | Outcome  | Group   | Revealed       | Concealed      | Difference  |
|-------------------------|--|---|----------------|----------------|---|
| <b>Triage PLGF test</b> |  |   |                |                |   |
| PARROT <sup>37</sup>    | Perinatal adverse outcomes, <sup>a</sup> % (n/N) | Total   | 15 (86b/573)   | 14 (63/446)    | 1.0 <sup>d</sup> ; aOR (95% CI): 1.45 (0.73–2.90)         |
|                         |  | PLGF < 12 <sup>c</sup>                          | 37.7 (49/130)  | 25.5 (27/106)  | aOR (95% CI): 1.95 (0.64–6.00)                            |
|                         |  | PLGF 12–100 <sup>c</sup>                        | 11.8 (25/212)  | 13.3 (21/173)  | aOR (95% CI): 1.62 (0.45–5.89)                            |
|                         |  | PLGF > 100 <sup>c</sup>                         | 5.2 (12/229)   | 5.8 (9/156)    | aOR (95% CI): 3.84 (0.29–51.31)                           |
| MAPPLE <sup>38</sup>    | Perinatal adverse outcomes <sup>b</sup> % (n/N)  | Total   | 30.4 (131/433) | 20.1 (60/299)  | 10.3 <sup>d</sup> ; risk ratio (95% CI): 1.51 (1.15–1.98) |
|                         |  | Neonatal adverse outcomes, <sup>e</sup> % (n/N) | Total          | 30.4 (131/433) | 17.1 (51/299)   |
|                         |  | PLGF < 12 <sup>c</sup>                          | 60.7 (74/124)  | 39.1 (27/69)   | 21.6 <sup>d</sup>   |
|                         |  | PLGF 12–100 <sup>c</sup>                        | 23.4 (37/158)  | 13.3 (14/105)  | 10.1 <sup>d</sup>   |
|                         |  | PLGF > 100 <sup>c</sup>                         | 13.3 (20/151)  | 7.2 (9/125)    | 6.1 <sup>d</sup>  |

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; PLGF, placental growth factor.

<sup>a</sup> Unadjusted indirect comparison.

<sup>b</sup> Number of infants.

<sup>c</sup> pg/mL.

<sup>d</sup> Absolute percent difference calculated by Frampton et al.<sup>14</sup>

<sup>e</sup> The NICE Expert Advisory Group assumed this excludes perinatal death but notes minor inconsistencies in numbers reported between text and tables within the MAPPLE publication.<sup>14,17</sup>

Source: Adapted from Frampton et al.<sup>14</sup>

The PARROT<sup>37,58</sup> and MAPPLE<sup>38</sup> studies reported the frequencies of the individual components of the composite adverse neonatal outcomes. Frampton et al stated the overall frequencies for these outcomes were comparable in the PARROT study but were generally higher for the revealed arm of the MAPPLE study compared with the concealed arm.<sup>14</sup> However, effect estimates were not reported. While the PARROT study reported the frequency of seizures in the total study population (< 1%), the NICE Expert Advisory Group was not confident of the accuracy of any of the reported data in the PARROT study, as the figures reported for the total number of cases of retinopathy of prematurity were incomplete.<sup>14,17</sup>

Frampton et al compared perinatal adverse outcomes in the PARROT<sup>36</sup> and PARROT Ireland<sup>36</sup> trials using adjusted risk estimates (Table 29).<sup>14</sup> Both studies showed no significant difference in perinatal adverse outcomes between the revealed and concealed groups.<sup>14</sup>

Table 29: Perinatal Adverse Outcomes<sup>a</sup>: PARROT Versus PARROT Ireland

| Study                        | Revealed         | Concealed        | Risk estimate  |
|------------------------------|------------------|------------------|--|
| PARROT <sup>58</sup>         | 86/573 (15%)     | 63/446 (14%)     | Adjusted odds ratio (95% CI; <i>P</i> value):<br>1.45 (0.73–2.90; <i>P</i> = NR)     |
| PARROT Ireland <sup>36</sup> | 87/1,017 (8.55%) | 85/1,202 (7.07%) | Adjusted risk ratio (95% CI; <i>P</i> value):<br>1.66 (0.81 to 3.42; <i>P</i> = .17) |

Abbreviations: CI, confidence interval; NR, not reported.

<sup>a</sup> Any grade of intraventricular hemorrhage, seizure, any grade of retinopathy of prematurity, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis (stage 2 or 3).

Source: Adapted from Frampton et al.<sup>14</sup>

We rated the certainty of the evidence for the Triage test as Low, downgrading for risk of bias and inconsistency (Appendix A2, Table A6).

## ONSET OF LABOUR

### *Elecsys sFlt-1/PLGF Ratio Test*

No studies reported this outcome for the Elecsys sFlt-1/PLGF ratio test.<sup>14</sup>

### *Triage PLGF Test*

Onset of labour was reported in the PARROT<sup>37,58</sup> study only. A higher proportion of women had a prelabour Caesarean section in the revealed arm (40%) compared with the concealed arm (35%) (Table 30).<sup>14</sup>

Table 30: Onset of Labour: Triage PLGF Test

| Study                   | Outcome                     | Group | Revealed     | Concealed    | Difference <sup>a</sup> |
|-------------------------|-----------------------------|-------|--------------|--------------|-------------------------|
| <b>Triage PLGF test</b> |                             |       |              |              |                         |
| PARROT <sup>37,58</sup> | Spontaneous                 | Total | 14 (79/573)  | 17 (78/446)  | 3                       |
|                         | Induced                     | Total | 46 (263/573) | 47 (210/446) | 1                       |
|                         | Prelabour Caesarean section | Total | 40 (230/573) | 35 (158/446) | 5                       |

Abbreviations: PLGF, placental growth factor.

<sup>a</sup> Absolute percent difference calculated by Frampton et al.<sup>14</sup>

Source: Adapted from Frampton et al.<sup>14</sup>

We rated the certainty of the evidence for the Triage test as Low, downgraded for risk of bias and imprecision (Appendix A2, Table A6).



## PRETERM AND EARLY PRETERM DELIVERY

### *Elecsys sFlt-1/PLGF Ratio Test*

No studies reported this outcome for the Elecsys sFlt-1/PLGF ratio test.<sup>14</sup>

### *Triage PLGF Test*

The rates of preterm delivery (< 37 weeks' gestation) were similar between trial arms in the PARROT<sup>37,58</sup> study but the MAPPLE<sup>38</sup> study reported higher proportions of women delivering before 37 or 34 weeks' gestation in the revealed arm compared with the concealed arm (Table 31).<sup>14</sup>

**Table 31: Preterm and Early Preterm Delivery: Triage PLGF Test**

| Study                   | Outcome  | Revealed       | Concealed      | Difference        |
|-------------------------|--|----------------|----------------|-------------------|
| <b>Triage PLGF test</b> |  |                |                |                   |
| PARROT <sup>37,58</sup> | Preterm delivery < 37 wk, % (n/N)                    | 41 (234/573)   | 37 (167/446)   | 4.0 <sup>b</sup>  |
| MAPPLE <sup>38,a</sup>  | Preterm delivery < 37 wk, % (n/N) <sup>c</sup>       | 70.2 (304/433) | 52.8 (158/299) | 17.4 <sup>b</sup> |
|                         | Early preterm delivery < 34 wk, % (n/N) <sup>c</sup> | 38.6 (167/433) | 27.8 (83/299)  | 10.8 <sup>b</sup> |

Abbreviations: aOR, adjusted odds ratio; PLGF, placental growth factor.

<sup>a</sup> Unadjusted indirect comparison.

<sup>b</sup> Absolute difference calculated by Frampton et al.<sup>14</sup>

<sup>c</sup> Paper reports frequencies by PLGF level subgroup only. The frequencies were summed by Frampton et al.<sup>14</sup> for the whole study population.

Source: Adapted from Frampton et al.<sup>14</sup>

We rated the certainty of the evidence for Triage test as Low, downgrading for risk of bias and inconsistency (Appendix A2, Table A6).

## MATERNAL ADMISSIONS TO HOSPITAL OR SPECIALIST CARE UNITS

### *Elecsys sFlt-1/PLGF Ratio Test*

No statistically significant difference in maternal admissions was observed at any time point in the INSPIRE<sup>41</sup> study (Table 32), although the proportion of women admitted within 24 hours or 7 days due to suspected pre-eclampsia were higher in the revealed arm compared with the concealed arm.<sup>14</sup> In the PreOS<sup>42</sup> study, the majority of intended clinical decisions were unchanged after the sFlt-1/PLGF ratio test result was revealed; however, 5.9% of clinical decisions changed in favour of hospitalization compared with 11.0% changing in favour of not hospitalizing the mother.<sup>14</sup>

The INSPIRE<sup>41</sup> study did not report on the proportion of women admitted to different levels of care (e.g., intensive care units or other critical care units).<sup>14</sup>

Table 32: Maternal Admissions: Elecsys sFlt-1/PlGF Ratio Test

| Study                                 | Outcome   | Revealed      | Concealed      | Difference          |                          |
|---------------------------------------|---|---------------|----------------|---------------------|--------------------------|
|                                       |   |               |                | Risk ratio (95% CI) | Risk difference (95% CI) |
| <b>Elecsys sFlt-1/PlGF ratio test</b> |   |               |                |                     |                          |
| INSPIRE <sup>41</sup>                 | Any maternal admission, % (n/N)                     | 38.7 (72/186) | 31.5 (58/184)  | 1.22 (0.93 to 1.62) | 0.07 (-0.02 to 0.17)     |
|                                       | Admission for suspected PE within 24 hours, % (n/N) | 32.3 (60/186) | 26.1 (48/184)  | 1.24 (0.89 to 1.70) | 0.06 (-0.03 to 0.15)     |
|                                       | Admission for suspected PE within 1 week, % (n/N)   | 37.6 (70/186) | 35 (65/184)    | 1.06 (0.1 to 1.39)  | 0.02 (-0.07 to 0.12)     |
|                                       | Admission for suspected PE until delivery, % (n/N)  | 67 (126/186)  | 72.8 (134/184) | 0.93 (0.82 to 1.06) | -0.05 (-0.14 to 0.04)    |

Abbreviations: CI, confidence interval; PE, pre-eclampsia; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

Source: Adapted from Frampton et al.<sup>14</sup>

We rated the certainty of the evidence for the Elecsys sFlt-1/PlGF Ratio Test as Low, downgrading for risk of bias and inconsistency (Appendix A2, Table A6).

#### *Triage PlGF Test*

No data on maternal admissions were reported in the PARROT<sup>37,58</sup> or MAPPLE<sup>38</sup> studies.<sup>14</sup>

## NEONATAL ADMISSION TO HOSPITAL OR SPECIALIST CARE UNITS

### *Elecsys sFlt-1/PlGF Ratio Test*

The INSPIRE<sup>41</sup> study reported no difference in admission rates to the special care baby unit (SCBU) between revealed and concealed arms when the Elecsys sFlt-1/PlGF ratio test was assessed (Table 33).

Table 33: Admission to Neonatal or Specialist Care Unit

| Study                                 | Outcome                                       | Group                    | Revealed       | Concealed      | Difference                            |
|---------------------------------------|---|--------------------------|----------------|----------------|---------------------------------------|
| <b>Triage PlGF test</b>               |   |                          |                |                |                                       |
| PARROT <sup>37,58</sup>               | Neonatal unit admission, % (n/N)              | Total                    | 34.0 (195/573) | 32.7 (146/446) | Paper stated no differences observed  |
|                                       |   | PlGF < 12 <sup>a</sup>   | 71.5 (93/130)  | 58.5 (62/106)  | aOR (95% CI), 2.37 (0.63–7.92)        |
|                                       |   | PlGF 12–100 <sup>a</sup> | 34.4 (73/212)  | 31.2 (54/173)  | aOR (95% CI), 2.37 (0.76–7.37)        |
|                                       |   | PlGF > 100 <sup>a</sup>  | 12.7 (29/229)  | 17.3 (27/156)  | Not reported                          |
| MAPPLE <sup>38,b</sup>                | Neonatal unit admission, % (n/N) <sup>b</sup> | Total                    | 45.5 (190/433) | 39.8 (117/299) | Risk ratio (95% CI), 1.14 (0.95–1.37) |
|                                       |   | PlGF < 12 <sup>a</sup>   | 81.7 (94/124)  | 82.8 (53/69)   | Not reported                          |
|                                       |   | PlGF 12–100 <sup>a</sup> | 46.4 (71/158)  | 43.8 (46/105)  | Not reported                          |
|                                       |   | PlGF > 100 <sup>a</sup>  | 16.7 (25/151)  | 14.4 (18/125)  | Not reported                          |
| <b>Elecsys sFlt-1/PlGF ratio test</b> |   |                          |                |                |                                       |
| INSPIRE <sup>41</sup>                 | SCBU admission, % (n/N)                       | All women                | 18.3 (34/186)  | 15.2 (28/184)  | <i>P</i> = .430                       |

Abbreviations: aOR: adjusted odds ratio; CI, confidence interval; PlGF, placenta growth factor; SCBU, special care baby unit.

<sup>a</sup> pg/mL.

<sup>b</sup> Number of infants.

Source: Adapted from Frampton et al.<sup>14</sup>.

We rated the certainty of the evidence for the Elecsys sFlt-1/PlGF ratio test as Low, downgrading for risk of bias and imprecision (Appendix A2, Table A6).

#### *Triage PlGF Test*

No difference in rates of admission to a neonatal unit were observed between revealed and concealed arms in the PARROT<sup>37,58</sup> and MAPPLE<sup>38</sup> studies (Table 33).<sup>14</sup> Admission rates were higher for babies born to mothers with lower PlGF levels.<sup>14</sup>

We rated the certainty of the evidence for the Triage PlGF Test as Low, downgrading for risk of bias and imprecision (Appendix A2, Table A6).

## LENGTH OF STAY IN HOSPITAL OR UNIT

### *Elecsys sFlt-1/PlGF Ratio Test*

No studies reported this outcome for the Elecsys sFlt-1/PlGF ratio test.<sup>14</sup>

#### *Triage PlGF Test*

There was no difference in the mean number of inpatient nights among women admitted to hospital between the revealed and concealed arms in the PARROT<sup>37,58</sup> study (Table 34).<sup>14</sup>

Table 34: Maternal Length of Stay: Triage PLGF Test

| Study                   | Outcome   | Revealed             | Concealed            | Difference                         |
|-------------------------|---|----------------------|----------------------|------------------------------------|
| <b>Triage PLGF test</b> |   |                      |                      |                                    |
| PARROT <sup>37,58</sup> | Mean number of nights in inpatient care (SE); N | 7.43 (0.36); N = 573 | 7.26 (0.38); N = 446 | -0.06 (-0.22 to 0.09) <sup>a</sup> |

Abbreviations: PLGF, placental growth factor; SE, standard error.

<sup>a</sup> Effect measure not specified in the PARROT study.

Source: Adapted from Frampton et al.<sup>14</sup>

There was no difference in the mean length of stay for babies admitted to the neonatal unit or special care baby unit between the revealed and concealed arms in the PARROT<sup>37</sup> study; however, the length of stay in the neonatal intensive care or high-dependency unit was 10.6 days shorter in the revealed arm than for the concealed arm (Table 35).<sup>14</sup>

Table 35: Nights in Neonatal Unit: Triage PLGF Test

| Study                   | Outcome  | Revealed    | Concealed    | Difference  |
|-------------------------|--|-------------|--------------|---|
| <b>Triage PLGF test</b> |  |             |              |   |
| PARROT <sup>37,58</sup> | Mean number of nights in neonatal unit <sup>a,b</sup> (SE) | 22.1 (25.9) | 24.6 (35.2)  | Not reported  |
|                         | Mean number of nights in SCBU <sup>b</sup> (SE)            | 14.7 (14.4) | 13.09 (12.6) | Paper stated no difference between groups           |
|                         | Mean number of nights in NICU/HDU <sup>b</sup> (SE)        | 15.2 (1.7)  | 24.2 (3.8)   | Mean difference (95% CI)<br>-10.6 (-20.81 to -0.47) |

Abbreviations: CI, confidence interval; HDU, high dependency unit; NICU: neonatal intensive care unit; SCBU: special care baby unit; SE: standard error.

<sup>a</sup> Level of neonatal care not specified.

<sup>b</sup> Of those admitted.

Source: Adapted from Frampton et al.<sup>14</sup>

We rated the certainty of the evidence for the Triage PLGF test as Low, downgraded for risk of bias and imprecision (Appendix A2, Table A6).

## QUALITY OF LIFE

No quality of life outcomes were reported in the published studies.

## SUBGROUP ANALYSES

Frampton et al referred readers to the appendix of the committee papers for results on the a priori subanalyses.<sup>14</sup> However, an explicit summary of results, discussion, or conclusion for each a priori subanalysis was not reported.

## ONTARIO STUDY RELEVANT TO THIS HEALTH TECHNOLOGY ASSESSMENT

The observational study conducted by McLaughlin et al<sup>12</sup> did not meet our inclusion criteria and was not included in our evidence review, as the comparator group was not standard care alone. However,

this study complements the studies included in our HTA because the authors evaluated maternal and perinatal pregnancy outcomes associated with maternal PLGF levels in high-risk pregnancies in Ontario. Pregnant women with suspected risk of placental dysfunction, hypertensive disorders of pregnancy, or fetal growth restriction completed PLGF testing using the Elecsys PLGF test between 20 weeks and 35 weeks plus 6 days' gestation.<sup>12</sup>

Of the 979 pregnant women, 289 had low PLGF levels (29.5%) and 690 had normal PLGF levels (70.5%).<sup>12</sup> The survival probability of ongoing pregnancy free from preterm birth was significantly reduced in women with low PLGF levels, relative to women with normal PLGF levels, within 2 weeks following PLGF testing (standardized survival difference, -0.43 [95% CI, -0.76 to -0.09]) and within 4 weeks following PLGF testing (standardized survival difference, -0.62 [95% CI, -0.87 to -0.38]).<sup>12</sup> Women with low PLGF levels were more likely to develop early-onset pre-eclampsia (adjusted OR, 58.2 [95% CI, 32.1–105.4]) and have a stillbirth (adjusted OR, 15.9 [95% CI, 7.6–33.3]) relative to women with normal PLGF levels.<sup>12</sup>

### **Ongoing Studies**

We are aware of the following ongoing studies that have potential relevance to our research question.

- PARROT 2 (<https://parrot2.medscinet.com/default.aspx?lang=1>), a multi-centre RCT of revealed versus concealed repeat placental growth factor (PLGF)-based testing in women presenting with suspected pre-eclampsia between 22+0 and 35+6 weeks' gestation
- Randomized Open-label Control Trial to Evaluate if the Incorporation of sFlt-1/PLGF Ratio in the Diagnosis and Classification of PE Improves Maternal and Perinatal Outcomes in Women with the Suspicion of the Disease (EuroPE) (<https://clinicaltrials.gov/ct2/show/NCT03231657>)
- sFlt-1/PLGF Ratio: Impact on the Management of Patients with Suspected Pre-eclampsia (<https://ichgcp.net/clinical-trials-registry/NCT05228002>)
- Preeclampsia Ratio (sFlt-1/PLGF) (PRECOG) (<https://clinicaltrials.gov/ct2/show/NCT03289611>)

### **Discussion**

Three of the PLGF-based biomarker tests included in the evidence review are licensed by Health Canada (Elecsys ratio, BRAHMS ratio, DELFIA Xpress PLGF) while two are not currently licensed (Triage PLGF and DELFIA ratio). In this review, our focus is on currently licensed devices; evidence from unlicensed PLGF-based biomarker assays is considered supporting evidence.

While the BRAHMS ratio test is licensed by Health Canada, definitive cut-off thresholds for ruling in and ruling out pre-eclampsia are being developed by the manufacturer and are expected to be available at the end of 2022.<sup>17</sup> When the NICE clinical expert committee reviewed the BRAHMS ratio test, they noted that the instructions for use did refer to two thresholds but did not indicate whether these two thresholds should be used individually or together or whether they should be used to rule in or rule out pre-eclampsia.<sup>17</sup> The committee concluded that, even based on the information from the current instructions for use, it is not clear how to interpret the test result and that the test's accuracy using one or both thresholds had not been validated in a population independent from the one used to set this threshold.<sup>17</sup>

Frampton et al stated that research is still needed on the diagnostic accuracy and analytical validity of the DELFIA Xpress PLGF 1-2-3 test and BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio, as very sparse evidence for both these tests was identified.<sup>14</sup> There was also a paucity of evidence for repeat PLGF-based biomarker testing.<sup>14</sup>

## **Accuracy Outcomes**

### **ELECSYS RATIO TEST**

Most of the evidence for the Elecsys ratio test was based on the INSPIRE study,<sup>41</sup> which was a prospective, interventional, parallel-group RCT of 370 women with suspected pre-eclampsia who were between 24 weeks and 37 weeks of pregnancy. The trial compared the Elecsys ratio test, together with clinical assessment, with clinical assessment alone.

For diagnostic accuracy, the Elecsys ratio test, together with standard clinical assessment, has a high NPV for ruling out PE within a week in people with suspected pre-eclampsia who are between 24 and 37 weeks' gestation.<sup>14</sup> Using GRADE to assess the implications of different testing scenarios focusing on accuracy (Appendix 2 Table A4), we rated the certainty of the evidence related to the accuracy of the Elecsys ratio test to predict pre-eclampsia as Moderate (Appendix 2, Table A5). This was based on the presumed influence of the accuracy data on patient important outcomes (e.g., maternal/perinatal morbidity and mortality). We determined that the directness of the evidence (i.e., true positives, true negatives, false positives, and false negatives) for outcomes that are important to patients had some uncertainty but overall, the test accuracy (and patient important outcomes) would generally support the ratio test's usefulness.

### **DELFLIA XPRESS PLGF**

Evidence for the DELFLIA Xpress PLGF test was based on a prospective stand-alone study (i.e., test results were not used in conjunction with clinical assessment).<sup>16</sup> This study also provided accuracy estimates for the DELFLIA Xpress sFlt-1/PLGF 1-2-3 ratio assay, using specified thresholds. Although the study design did not strictly fit our inclusion criteria, we considered (as did Frampton et al<sup>14</sup>) stand-alone studies as supportive evidence for the assessment of accuracy. Similar to the Elecsys ratio test, we rated the certainty of the evidence related to the accuracy of the DELFLIA Xpress PLGF test to predict pre-eclampsia as Moderate (Appendix 2, Table A5).

### **ACCURACY UNCERTAINTIES**

Frampton et al acknowledged that there are still some uncertainties and evidence gaps.<sup>14</sup> For example, the evidence on test performance for *ruling in* pre-eclampsia is limited in both volume and relevance. The PARROT trial<sup>37</sup> assessed test performance for the Triage PLGF cut-off (rule in: < 12 pg/mL); however, results were only reported for the trial arm in which PLGF test results were concealed from the treating clinician. The INSPIRE trial<sup>41</sup> did not report test accuracy at cut-off values suggestive of pre-eclampsia diagnosis (i.e., rule-in values). However, Frampton et al noted that PPVs of 71.4 and 72.0 were reported in the revealed and concealed arms of INSPIRE respectively, when a higher cut-off of 85 was applied to predict (rule in) pre-eclampsia within 4 weeks.<sup>14</sup>

## **Clinical Utility Outcomes**

Many clinical utility outcomes were reported across the included studies, with heterogeneity in the way they were assessed and reported. The two single-arm, add-on, observational cohort studies<sup>35,40</sup> did not assess the effect of using the PLGF or sFlt-1/PLGF ratio tests on clinical outcomes because they lacked a control arm in which the test result was concealed. As such, any clinical outcomes reported in these studies were not reported in the systematic review by Frampton et al.<sup>14</sup> Similarly, clinical outcomes reported in stand-alone test accuracy studies were not evaluated, as these also lacked a control group and did not assess the use of the test alongside standard clinical assessment.

Clinical outcomes were reported in the four add-on studies that compared the use of PlGF-based biomarker testing alongside standard clinical assessment (test result revealed) with standard clinical assessment only (test result concealed): the PARROT<sup>37</sup> RCT, the observational MAPPLE<sup>38</sup> study (Triage PlGF test), the INSPIRE<sup>41</sup> RCT, and the observational PreOS<sup>42</sup> study (Elecsys sFlt-1/PlGF ratio test). No clinical outcomes data were available for the BRAHMS Kryptor sFlt-1/PlGF ratio test or DELFIA Xpress PlGF tests.<sup>14</sup> The observational MAPPLE study was a comparison of two cohorts of pregnant women, selected under different circumstances, over different years, and for different reasons (Table 6). The observational PreOS study was a before-and-after design: Before sFlt-1/PlGF test results were known, physicians documented clinical decisions; the result was then made available, and the physicians' decisions were revised or confirmed. A major limitation of the PreOS study was the large number of women who were excluded from the analysis due to delayed reporting by the physician of their clinical decision (i.e., they recorded their decisions after results of the biomarker test were revealed to them) and outcomes (confirmed diagnosis of pre-eclampsia or delivery) taking place before the intended procedures were recorded by the physician.<sup>14</sup>

The PARROT<sup>37</sup> trial data suggested that using a PlGF test improved maternal outcomes. In PARROT, the number of women with adverse outcomes was significantly lower in the revealed group (4%) than in the concealed group (5%). Incidence of placental abruption and severe pre-eclampsia was also lower with test use in the INSPIRE study<sup>41</sup> (no statistically significant difference). However, the INSPIRE trial was not powered to detect differences in adverse maternal outcomes. The NICE clinical expert committee concluded there was some evidence that PlGF-based biomarker testing in general could improve management decisions and clinical outcomes for women with suspected preterm pre-eclampsia, although there was considerable uncertainty about this.<sup>17</sup>

Incidence of perinatal and neonatal mortality and complications were similar in the PlGF-based biomarker test and control arms of the PARROT<sup>37</sup> trial, respectively.<sup>14</sup> There was a very low number of these clinical events and the trial was not powered to show differences. Because some of the clinical events happen rarely, it is difficult to do trials to assess how PlGF-based biomarker testing affects them.<sup>14</sup> The NICE clinical expert committee concluded that, because of the rarity of some conditions (e.g., intraventricular hemorrhage, respiratory distress syndrome, and death), the effect of using PlGF-based tests on neonatal outcomes is uncertain.<sup>17</sup> However, the committee agreed there was some evidence that they influence management decisions that could improve care.<sup>17</sup>

## CLINICAL UTILITY UNCERTAINTIES

Most of the published evidence available is on the Triage PlGF test and the Elecsys sFlt-1/PlGF ratio.

The findings of both trials were mixed in terms of the extent to which the interventions evaluated were clinically effective. For example, in the PARROT trial,<sup>37</sup> the Triage PlGF test,<sup>37</sup> used alongside standard clinical management (results revealed), was associated with a reduction in time to diagnosis of pre-eclampsia (64%), lower odds of maternal adverse outcomes (68%), and a non-statistically significant increase in time to delivery.<sup>14</sup> However, there were no differences between revealed and concealed testing arms for outcomes, including rates of preterm delivery (< 37 weeks), gestational age at delivery, and perinatal and neonatal outcomes.

In the INSPIRE trial,<sup>41</sup> there was no statistically significant difference between the trial arms in pre-eclampsia-related hospital admissions within 24 hours of the test—the primary outcome. However, 100% of participants in the reveal arm admitted to hospital were correctly diagnosed with pre-eclampsia versus 83% in the concealed arm. The authors considered that this test can increase the

proportion of high-risk patients admitted without influencing the admission rate itself. A post-hoc analysis showed there was no statistically significant difference between the trial arms in the time to pre-eclampsia diagnosis. In addition, there were no statistically significant differences between trial arms for many of the secondary clinical outcome measures. The authors recommended larger studies of the Elecsys test to evaluate its potential in reducing adverse outcomes.

Frampton et al suggested that there may be a number of potential explanations for the limited clinical impact in the studies of these two tests.<sup>14</sup> One of these might be that the pragmatic "real world" design and implementation of these interventions produce the level of effects that would be typically seen in clinical practice (in contrast to greater levels of efficacy expected in a highly protocol-driven and patient-selective clinical trial).<sup>14</sup>

### ALIGNMENT WITH GUIDELINES

Our HTA aligns with recent Canadian<sup>2</sup> and international<sup>18</sup> guidelines that acknowledge uncertainties with the use of these tests, especially with regard to clinical utility outcomes. Of note, the International Society for the Study of Hypertension in Pregnancy (ISSHP) stated familiar challenges with regard to the use of PLGF-based biomarker tests<sup>18</sup>:

1. The term "suspected pre-eclampsia" has been used for a broad range of women. ISSHP advises that "suspected pre-eclampsia" be used for no more than a 24-hour duration.
2. Many women included in studies with "suspected pre-eclampsia" would have already satisfied the ISSHP's broad definition of pre-eclampsia. It is possible that the ability of angiogenic markers to predict "delivery with pre-eclampsia within 14 days" may have been driven by the fact that many of the women already had pre-eclampsia. Alternatively, angiogenic markers may add further risk stratification among women who already meet diagnostic criteria for pre-eclampsia
3. The understanding about how best to use angiogenic marker testing is complicated, as there are numerous assays and cut-off values (with PLGF varying with gestational age) and PLGF-based biomarker testing is promoted as a test for pre-eclampsia rather than as one for uteroplacental dysfunction.
4. It is not known how PLGF-based biomarker testing adds to prediction of adverse outcomes.

These challenges aside, the ISSHP moved to incorporate angiogenic marker testing into clinical practice as another marker of uteroplacental dysfunction but not as a sole criterion for diagnosing pre-eclampsia.<sup>18</sup> Because making a diagnosis of pre-eclampsia is such an important clinical decision, Magee et al suggested all centres are encouraged to evaluate patient preferences, resources, outcomes, and costs associated with use of these tests in their own clinical populations.<sup>18</sup>

The NICE guidance reiterated that PLGF-based biomarker testing is not a substitute for clinical assessment. Instead PLGF-based testing gives the clinician more evidence to help them make an informed decision.<sup>17</sup> Additionally, the NICE guidance stated that a low PLGF test result can be associated with other conditions affecting the placenta and does not always mean a woman has pre-eclampsia.<sup>17</sup> The NICE clinical expert committee further stated that the PLGF-based test results can be very useful to help with clinical decision-making, particularly for women who had hypertension or proteinuria before becoming pregnant. The committee concluded that PLGF-based test results should be used alongside clinical information for decision-making.<sup>17</sup>



## COMPLEMENTARY EVIDENCE FROM ONTARIO

The Ontario study by McLaughlin et al showed that low PlGF levels in high-risk pregnant women were strongly associated with increased rates of imminent preterm birth as well as related adverse outcomes, including early-onset preeclampsia and stillbirth.<sup>12</sup> The authors suggested that in addition to supporting the integration of PlGF testing into tertiary care centres, their findings support a role for PlGF testing as a contingency screening tool in remote communities.<sup>12</sup> The associated risks of imminent preterm birth, early-onset preeclampsia, and stillbirth may warrant referral of high-risk women with low PlGF levels to higher-level centres.<sup>12</sup> In this context, PlGF testing has the potential to overcome some of the challenges of providing obstetric care to women in remote or rural regions of Ontario.<sup>12</sup>

## Strengths and Limitations

The strengths of our methodological approach included the following:

- We updated the literature search of the updated systematic review by Frampton et al<sup>14</sup> and included an additional study
- The systematic review includes evidence for two aspects of the PlGF biomarker tests: diagnostic accuracy and clinical utility
- We incorporated an analysis of the quantitative preference evidence (see the Preferences and Values Evidence section on page 84)
- Our conclusions align with recent Canadian and international guidelines

However, we were limited by the following:

- Use of unpublished systematic review by Frampton et al. The expected publication date is spring 2023

## Conclusions

Compared with standard clinical assessment alone in patients who have suspected pre-eclampsia (between 20 weeks and 36 weeks + 6 days' gestation), PlGF-based biomarker testing (e.g., Elecsys ratio, DELFIA PlGF) as an adjunct to standard clinical assessment:

- Likely improves accuracy of predicting pre-eclampsia (Elecsys ratio, DELFIA PlGF, Triage PlGF) (GRADE: Moderate)
- May reduce:
  - Time to pre-eclampsia diagnosis (Triage PlGF) (GRADE: Low)
  - Severe adverse maternal outcomes (Triage PlGF) (GRADE: Low)
  - Length of stay in the neonatal intensive care unit (Triage PlGF) (GRADE: Low)
- May result in little to no difference in:
  - Time to delivery (GRADE: Low)
  - Gestational age at delivery (GRADE: Low)
  - Preterm delivery (GRADE: Low)
  - Maternal admission to hospital (GRADE: Low)
  - Perinatal/neonatal adverse outcomes (GRADE: Low)

- Neonatal admission to hospital/specialist care unit (GRADE: Low)
- Maternal length of stay in hospital (GRADE: Low)

# Economic Evidence

## Research Question

What is the cost-effectiveness of placental growth factor (PLGF)-based biomarker testing as an adjunct to standard clinical assessment to help diagnose pre-eclampsia in people with suspected pre-eclampsia?

## Methods

### ***Economic Literature Search***

We performed an economic literature search on April 21, 2022, to retrieve studies published from January 1, 2015, until the search date. The time period was chosen because a prior systematic review conducted by the National Institute for Health and Care Excellence (NICE)<sup>1</sup> undertook a literature search between 2000 and 2015. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE, Embase, and the Cumulative Index to Nursing & Allied Health Literature (CINAHL) and monitored them for the duration of the assessment period. We also performed a targeted grey literature search following a standard list of websites developed internally, which includes the International Health Technology Assessment (HTA) Database and the Tufts Cost-Effectiveness Analysis Registry. See the Clinical Literature Search section, above, for further details on methods and sources used. See Appendix 1 for our literature search strategies, including all search terms.

### ***Eligibility Criteria***

#### STUDIES

##### *Inclusion Criteria*

- English-language full-text publications
- Studies published from January 2015 to present
- Cost-benefit analyses, cost-effectiveness analyses, cost-minimization analyses, or cost-utility analyses

##### *Exclusion Criteria*

- Narrative reviews, editorials, case reports, commentaries, abstracts, letters, and unpublished studies

#### PARTICIPANTS

##### *Inclusion Criteria*

- Pregnant people, between 20 weeks' and 36 weeks + 6 days' gestation with pre-eclampsia confirmed by clinical assessment
- Singleton pregnancy

##### *Exclusion Criteria*

- Pregnant people at less than 20 weeks' gestation; pregnant people not suspected of having pre-eclampsia
- Non-singleton pregnancy

## INTERVENTIONS

- PIGF-based tests; for example:
  - Quidel Triage PIGF test in conjunction with standard clinical assessment
  - AutoDELFIA PIGF 1-2-3 or DELFIA Xpress PIGF 1-2-3 test/DELFIA Xpress sFlt-1 test in conjunction with standard clinical assessment
  - Elecsys immunoassay sFlt-1/PIGF ratio in conjunction with standard clinical assessment
  - BRAHMS sFlt-1 Kryptor/BRAHMS PIGF plus Kryptor pre-eclampsia (PE) ratio in conjunction with standard clinical assessment
- Each test will be assessed at first use for each episode of suspected pre-eclampsia, and when the tests are repeated in people with suspected pre-eclampsia who have had a PIGF-based test for suspected pre-eclampsia that was negative

## COMPARATORS

- Clinical assessment alone, based on standard key clinical signs and symptoms (e.g., hypertension, proteinuria, and fetal growth restriction)
- Another PIGF-based biomarker test

## OUTCOME MEASURES

- Costs
- Health outcomes (e.g., quality-adjusted life-years [QALYs])
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios

### **Literature Screening**

A single reviewer conducted an initial screening of titles and abstracts using EndNote<sup>32</sup> and obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

### **Data Extraction**

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios [ICERs])

### **Study Applicability and Limitations**

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by NICE in the United Kingdom to inform the development of NICE's clinical guidelines.<sup>63</sup> We modified the wording of the questions to remove references from guidelines and to make it specific to Ontario. Next, we separated the checklist into two sections. In the first section, we assessed the applicability of each study to the

research question (directly, partially, or not applicable). In the second section, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be directly applicable.

## Results

### ***Economic Literature Search***

The search of the economic literature yielded 143 citations published between January 1, 2015, until April 21, 2022. We identified four additional eligible studies from the grey literature, for a total of 98 after removing duplicates. We identified two additional eligible studies from other sources included during the assessment period.<sup>64,65</sup> In total, we identified 13 studies that met our inclusion criteria.<sup>1,14,64-74</sup> Figure 2 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.<sup>32</sup>

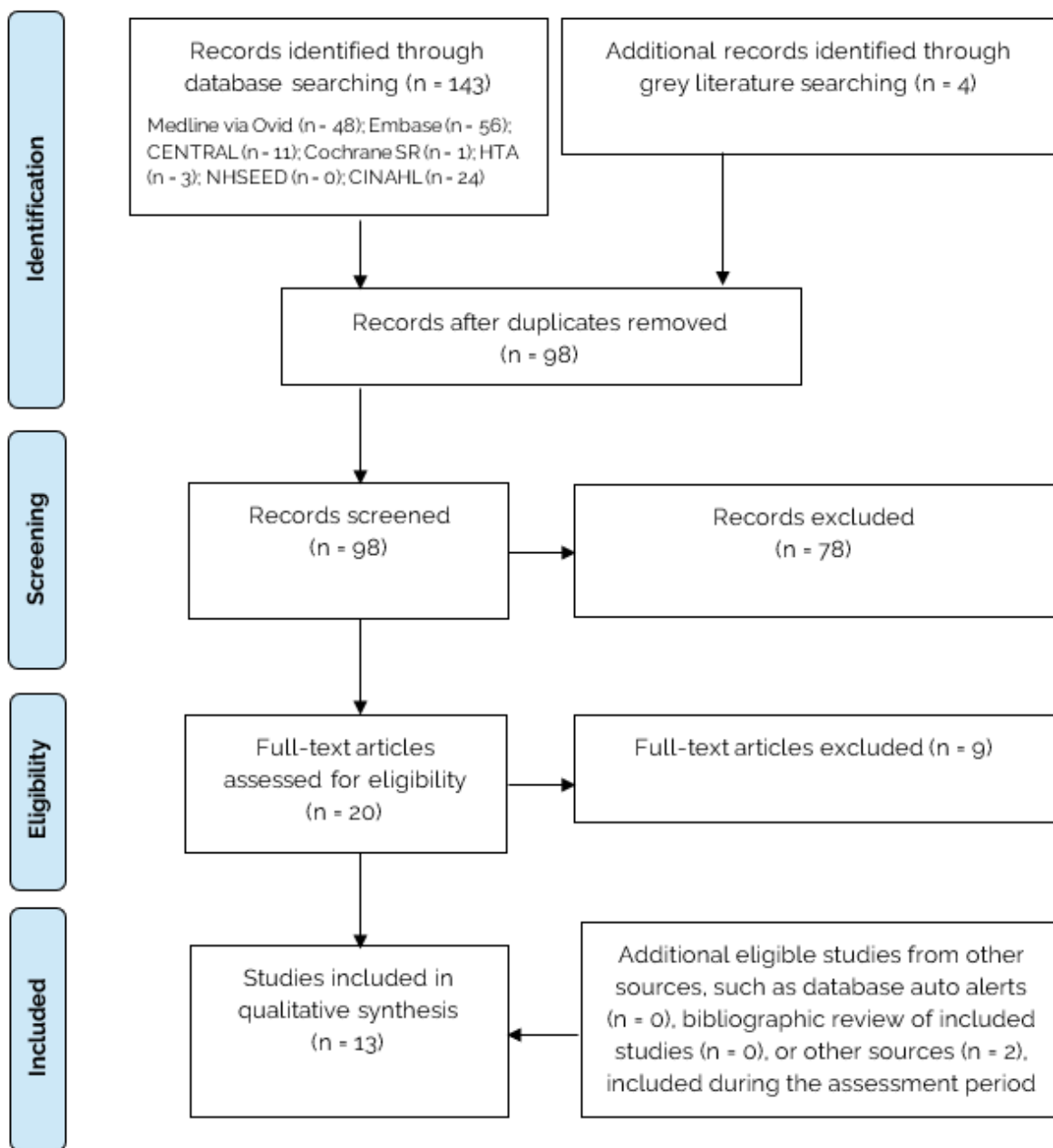


Figure 2: PRISMA Flow Diagram—Economic Search Strategy

PRISMA flow diagram showing the economic search strategy. The database search of the economic literature yielded 143 citations published between January 1, 2015, and April 21, 2022. We identified four additional eligible studies from other sources. After removing duplicates, we screened the abstracts of 98 studies and excluded 78. We assessed the full text of 20 articles and excluded a further nine. We also identified two studies from other sources. In the end, we included 13 articles in the qualitative synthesis.

Abbreviations: CINAHL, Cumulative Index to Nursing and Allied Health Literature; HTA, health technology assessment; NHSEED, National Health Service Economic Evaluation Database; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; SR, systematic review.

Source: Adapted from Page et al.<sup>32</sup>

### **Overview of Included Economic Studies**

A total of 13 economic studies met the inclusion criteria.<sup>1,14,64-74</sup> Ten studies<sup>1,64-72</sup> were previously captured in an economic systematic literature review by Frampton et al., as part of the 2022 NICE diagnostic guidance on PlGF-based testing.<sup>14</sup> We included two studies in the Frampton et al systematic review that were not picked up in our search.<sup>73,74</sup> In addition, we included a cost-utility analysis conducted by the NICE Decision Support Unit (DSU) in 2022 (Kearns et al).<sup>14,75</sup> We present the study design, populations, outcomes, time horizons, and study results in Table 36. We further summarized their findings below.

### **Studies Included in the NICE Economic Systematic Review by Frampton et al**

We included 10 studies<sup>1,64-72</sup> from the economic systematic review by Frampton et al.<sup>14</sup> Five of these 10 studies evaluated the Elecsys sFlt-1/PlGF ratio test,<sup>67-70,72</sup> two evaluated the Triage PlGF test,<sup>66,71</sup> two assessed more than one PlGF-based biomarker test,<sup>1,65</sup> and one did not report which PlGF-based biomarker test(s) were evaluated.<sup>64</sup> Most of the studies utilized a decision-tree structure with a short time horizon. Only one study conducted a cost-utility analysis and included QALYs as an outcome.<sup>1</sup>

The Frampton et al<sup>14</sup> economic systematic review concluded that PlGF-based biomarker testing has the potential to reduce maternal adverse events and decrease the number of individuals who receive inappropriate treatment, such as unnecessary hospitalizations, due to misdiagnosis of pre-eclampsia. Only one<sup>65</sup> out of the ten included studies did not find PlGF-based biomarker testing to be cost-saving. Five studies<sup>1,64-66,71</sup> considered single testing (i.e., no repeat test), four<sup>68-70,72</sup> of which reported the cost-saving results. The remaining study, which did not consider repeat testing in the reference case, reported an incremental cost of £3,710 per additional correctly identified case of pre-eclampsia.<sup>65</sup> Four studies considered repeat testing in the base case, and all of these studies reported cost savings.<sup>68,69,70,72</sup> One study considered a single test in the base case and repeat testing in the scenario analysis<sup>67</sup> (see Table 36).

### **Economic Studies Published After 2021**

We identified two economic studies published after 2021, which were not captured in the Frampton et al economic systematic review.<sup>73,74</sup> Both studies assessed the cost-effectiveness of the sFlt-1/PlGF ratio test as an adjunct to standard clinical assessment compared with standard clinical assessment alone. One was a decision-tree model based on a retrospective observational study and the other one was a decision-tree model based on a prospective observational study.

Chantraine et al<sup>73</sup> conducted a 1-year cost-analysis from the Belgian public payer perspective using clinical parameters from the PROGNOSIS study, a single-arm prospective observational study. The study found that the use of the sFlt-1/PlGF ratio test as an adjunct to the current standard clinical assessment was expected to result in a cost savings of €712 per person compared with standard clinical assessment alone owing to a reduction in unnecessary hospitalizations. Under the PlGF-based biomarker testing strategy, 19.8% of individuals were hospitalized before a confirmed diagnosis of pre-eclampsia, of whom 36.8% subsequently developed pre-eclampsia, resulting in a false positive rate of 12.5%. Under the standard clinical assessment strategy, 36.1% of individuals were hospitalized before a diagnosis of pre-eclampsia, of whom 26.4% subsequently developed pre-eclampsia, resulting in a false positive rate of 26.6%.

Khosla et al<sup>74</sup> conducted a cost-effectiveness study from a US payer perspective using clinical parameters from a prospective observational cohort study. This study assessed the incidence of pre-eclampsia and distribution of sFlt-1/PlGF values of 459 pregnant persons between 23+0 weeks' and

34+6 weeks' gestation. The study found that the use of PlGF-based biomarker testing as an adjunct to standard clinical assessment could reduce the number of individuals admitted to hospital for suspected pre-eclampsia by 34% (from 490 to 323). As a result, there was an average expected cost savings of \$1,050 (USD, 2020) per person.

### **Cost-Utility Analysis Conducted by the NICE Decision Support Unit**

The NICE Decision Support Unit (DSU) developed by Kearns et al<sup>14,75</sup> conducted a cost-utility analysis to compare PlGF-based biomarker testing alone or as an adjunct to standard clinical assessment with standard clinical assessment alone. (Note that the final NICE HTA has not been published, and we summarized the findings of the DSU economic evaluation based on the draft report.) The analysis included five different PlGF-based biomarker testing strategies: the Triage PlGF test alone, the DELFIA Xpress PlGF 1-2-3 test alone, the Elecsys sFlt-1 to PlGF ratio test alone, the BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio test alone, and Elecsys sFlt-1 to PlGF ratio test combined with standard clinical assessment. Elecsys was the only PlGF-based biomarker test that was further evaluated as an adjunct to standard clinical assessment.

The analysis also included two standard clinical assessment arms as comparators. One was based on the NICE diagnostic guidelines (DG23) for pregnant people with pre-eclampsia and one was based on the standard clinical assessment used in the INSPIRE clinical trial. To model the impact of PlGF-based biomarker testing on clinical outcomes, the authors consulted seven clinical experts to estimate the proportion of pregnant people who would be admitted to hospital, given the standard clinical assessment and results of PlGF-based biomarker testing. The analysis also considered three roles of PlGF-based biomarker testing:

- *To rule out pre-eclampsia:* For persons in whom the original decision was to admit (based on the clinical assessment), a proportion are subsequently no longer admitted depending on the PlGF-based biomarker testing results. The decision is unchanged for persons in whom the original decision was not to admit
- *To rule out and rule in pre-eclampsia:* For persons in whom the original decision was to admit (based on the clinical assessment), a proportion are subsequently no longer admitted depending on the PlGF-based biomarker testing results; for persons who were not admitted in the original decision, 100% of those with high-risk PlGF-based biomarker testing results are admitted and 30% of those with an intermediate-risk test result are admitted
- *To rule out pre-eclampsia and cautious rule-in:* For persons in whom the original decision was to admit (based on the clinical assessment), a proportion are no longer subsequently admitted, depending on the PlGF-based biomarker testing results; for persons in whom the original decision was not to admit, 50% of those with a high-risk test result are admitted

In the reference case analysis, all PlGF-based biomarker test strategies were used to rule out pre-eclampsia. The costs considered in this analysis included the cost of the PlGF-based biomarker test, cost of managing gestational hypertension and pre-eclampsia, costs associated with maternal resource use (e.g., delivery, intensive care, ward stays), and short- and long-term neonatal costs (e.g., neonatal unit stays, cost of follow-up, neonatal complications). QALY estimates for PlGF-based biomarker testing and comparators were derived by considering quality of life associated with delivery, maternal adverse events, postnatal care, and neonatal adverse events. Several scenario analyses were conducted, including those that involved the use of PlGF-based biomarker testing to rule out and rule in pre-eclampsia but excluding those that involved neonatal outcomes.



The reference case results found that all PlGF-based biomarker test strategies resulted in an increase in cost and QALYs when compared with either standard clinical assessment. The incremental costs ranged from £2.80 to £47.00 per person, and the incremental QALYs ranged from 0.0007 to 0.0058 per person over a lifetime. The Triage test compared with the DG23 standard clinical assessment resulted in an ICER of £47,393 per QALY. All other PlGF-based biomarker testing strategies resulted in ICERs below £16,500 per QALY and were considered cost-effective at a willingness-to-pay of £20,000 per QALY. The analysis found that there was relatively little variation in total costs and QALYs between different testing strategies. However, the net health effects were largest for the Elecsys sFlt-1/PlGF ratio test as an adjunct to standard clinical assessment and lowest for the two standard clinical assessments.

Most sensitivity analysis results were similar to the reference case results and found that all PlGF-based biomarker testing strategies resulted in ICERs below £12,500 per QALY. However, when neonatal outcomes were excluded, all testing strategies produced ICERs that exceeded £20,000 per QALY. The results were also sensitive to assumptions regarding the role of testing. When the use of PlGF-based biomarker testing was considered to rule out and rule in pre-eclampsia, most of the PlGF-based biomarker testing strategies dominated (i.e., less costly and more effective) both standard clinical assessments, with the exception of the Triage and DELFIA tests compared with the INSPIRE standard clinical assessment. Both of these testing strategies resulted in ICERs of around £15,000 per QALY. When the use of PlGF-based biomarker testing was considered to rule out and rule in pre-eclampsia and neonatal outcomes were excluded, all testing strategies remained dominant when compared with the DG23 standard clinical assessment. When compared with the INSPIRE standard clinical assessment, results varied depending on the clinical management decisions used (e.g., testing to rule out and standard rule-in versus testing to rule out and cautious rule-in). Overall, the use of PlGF-based biomarker testing to rule out and rule in pre-eclampsia resulted in more favorable cost-effectiveness outcomes compared with the use of the test for rule-out purposes only.

Table 36: Results of Economic Literature Review—Summary

| Author, year, country                         | Analytic technique, study design, perspective, time horizon   | Population   | Intervention(s) and comparator(s)  | Results  |  |  |
|---|---|--|--|--|--|--|
|   |   |  |  | Health outcomes  | Costs  | Cost-effectiveness   |
| Chantraine et al, 2021, <sup>73</sup> Belgium | Type of analysis: cost analysis<br>Study design: decision tree<br>Perspective: Belgian public payer<br>Time horizon: 12 months<br>Discount rate: NR<br>Source of clinical evidence: PROGNOSIS <sup>46</sup> | Pregnant people presenting with clinical suspicion of PE or at risk for developing PE, between 24 weeks and 36 weeks + 6 days' gestation | Intervention: sFlt-1/PlGF ratio test + standard clinical assessment<br><br>Comparator: standard clinical assessment<br><br>Repeat test: Yes, option for repeat testing included; unclear if it is in the base case | Proportion of people hospitalized:<br><ul style="list-style-type: none"><li>Intervention: 19.8%</li><li>Comparator: 36.1%</li></ul> Difference:<br><ul style="list-style-type: none"><li>Intervention vs comparator: -16.3% (calculated)</li></ul> Proportion of hospitalized people who developed PE:<br><ul style="list-style-type: none"><li>Intervention: 36.8%</li><li>Comparator: 26.4%</li></ul> Difference<br><ul style="list-style-type: none"><li>Intervention vs comparator: 10.4% (calculated)</li></ul> | Cost: Euro (€) Cost-year: NR<br><br>Mean cost per person:<br><ul style="list-style-type: none"><li>Intervention: €2,767</li><li>Comparator: €3,479</li></ul> Mean difference:<br><ul style="list-style-type: none"><li>Intervention vs comparator: -€712 per patient</li></ul> | Reference case:<br>The sFlt-1/PlGF ratio test + standard clinical assessment resulted in cost savings of €712 per patient<br><br>Sensitivity analysis: PSA was not conducted. Results were sensitive to hospitalization rates under standard clinical assessment |

| Author, year, country                | Analytic technique, study design, perspective, time horizon  | Population                          | Intervention(s) and comparator(s)  | Results   |  |   |
|--------------------------------------|--|-------------------------------------|--|---|--|---|
|                                      |  |                                     |  | Health outcomes   | Costs  | Cost-effectiveness  |
| Khosla et al, 2021, <sup>74</sup> US | Type of analysis: cost analysis<br>Study design: decision tree<br>Perspective: US payer<br>Time horizon: NR<br>Discount rate: NR<br>Source of clinical evidence: PROGNOSIS <sup>46</sup> | People presenting with suspected PE | Intervention: sFIt-1/PIGF ratio test + standard clinical assessment<br><br>Comparator: standard clinical assessment<br><br>Repeat test: Included in a sensitivity analysis | <p><i>Mean per 1,000 persons</i></p> <p>People admitted to hospital:</p> <ul style="list-style-type: none"> <li>Intervention: 323</li> <li>Comparator: 490</li> </ul> <p>Mean difference:</p> <ul style="list-style-type: none"> <li>Intervention vs comparator: -167</li> </ul> <p>People admitted to hospital who developed PE:</p> <ul style="list-style-type: none"> <li>Intervention: 190 (58.8%)</li> <li>Comparator: 200 (40.9%)</li> </ul> <p>Mean difference</p> <ul style="list-style-type: none"> <li>Intervention vs comparator: -10</li> </ul> | <p>Cost: USD (\$)</p> <p>Cost year: 2020</p> <p>Mean cost per person:</p> <ul style="list-style-type: none"> <li>Intervention: \$2,871</li> <li>Comparator: \$3,921</li> </ul> <p>Mean difference:</p> <ul style="list-style-type: none"> <li>Intervention vs comparator: -\$1,050 per person</li> </ul> | <p>Reference case: sFIt/PIGF ratio test + standard clinical assessment resulted in a cost savings of \$1,050 per person</p> <p>Sensitivity analysis: PSA was not conducted. Results were found to be sensitive to hospitalization costs</p> |

| Author, year, country  | Analytic technique, study design, perspective, time horizon   | Population   | Intervention(s) and comparator(s)  | Results  |  |   |
|--|---|--|--|--|--|---|
|  |   |  |  | Health outcomes  | Costs  | Cost-effectiveness  |
| Kearns et al, 2021 <sup>75</sup> (cited in the NICE UK, primary economic evaluation—DSU report <sup>24</sup> ), UK | Type of analysis: cost-utility analysis<br>Study design: decision tree<br>Perspective: public payer<br>Time horizon: NR<br>Discount rate: 3.5%<br>Source of clinical evidence: PARROT UK, <sup>37</sup> INSPIRE, <sup>41</sup> COMPARE, <sup>53</sup> Simon et al <sup>76</sup> | People with suspected PE between 20 weeks and 36 weeks + 6 days' gestation | Interventions: PLGF test (Triage PLGF test, DELFIA Xpress PLGF 1-2-3 test, Elecsys sFlt-1 to PLGF ratio test, and the BRAHMS sFlt-1 Kryptor/ BRAHMS PLGF plus Kryptor PE ratio test) as a stand-alone test to rule out PE; PLGF test (Elecsys) as an adjunct to standard clinical assessment to rule out PE<br><br>Comparators: standard clinical assessment based on DG23; standard clinical assessment based on INSPIRE<br><br>Repeat test: not considered | Mean QALYs:<br><ul style="list-style-type: none"> <li>Triage: 17.6117</li> <li>Elecsys: 17.6139</li> <li>Elecsys (as an adjunct test): 17.6151</li> <li>DELFIA: 17.6137</li> <li>BRAHMS: 17.6151</li> <li>Comparator (DG23): 17.6110</li> <li>Comparator (INSPIRE): 17.6093</li> </ul> Mean difference:<br><ul style="list-style-type: none"> <li>Interventions vs either comparator: Always &lt; 0.006 QALYs</li> </ul> | Cost: GBP (£)<br>Cost year: NR<br>Mean costs:<br><ul style="list-style-type: none"> <li>Triage: £10,248</li> <li>Elecsys: £10,262</li> <li>Elecsys (as an adjunct): £10,256</li> <li>DELFIA: £10,225</li> <li>BRAHMS: £10,230</li> <li>Comparator (DG23): £10,215</li> <li>Comparator (INSPIRE): £10,223</li> </ul> Mean difference:<br><ul style="list-style-type: none"> <li>Triage vs DG23: £33.2</li> <li>Elecsys vs DG23: £47.0</li> <li>Elecsys (as an adjunct) vs DG23: £412</li> <li>DELFIA vs DG23: £10.5</li> <li>BRAHMS vs DG23: £14.6</li> <li>Triage vs INSPIRE: £25.5</li> <li>Elecsys vs INSPIRE: £39.3</li> <li>Elecsys as an adjunct vs INSPIRE: £33.6</li> <li>DELFIA vs INSPIRE: £2.8</li> <li>BRAHMS vs INSPIRE: £6.9</li> </ul> | Reference case:<br>Except for Triage vs DG23, all other interventions versus either comparator resulted in ICERs < £16,500/QALY and were cost-effective at a WTP of £20,000. Triage vs DG23 resulted in an ICER of £47,393/QALY<br><br>Sensitivity analysis:<br>PSA found results were robust. DSA found that results were more favourable for interventions when the test was used to rule out and rule in PE. Results were sensitive to whether neonatal outcomes were considered |

| Author, year, country                     | Analytic technique, study design, perspective, time horizon  | Population  | Intervention(s) and comparator(s)  | Results   |   |   |
|---|--|---|--|---|---|---|
|   |  |   |  | Health outcomes   | Costs   | Cost-effectiveness  |
| Myrhaug et al, 2020, <sup>65</sup> Norway | Type of analysis: cost-effectiveness and budget impact analysis<br>Study design: decision tree<br>Perspective: public payer<br>Time horizon: NR<br>Discount rate: not discounted<br>Source of clinical evidence: INSPIRE <sup>41</sup>             | People with suspected PE between 20 weeks and 36 weeks + 6 days' gestation                            | Intervention: PLGF tests (Elecsys sFlt-1/PLGF ratio test or Triage PLGF test or BRAHMS Kryptor sFlt-1/PLGF ratio test) + standard clinical assessment<br><br>Comparator: standard clinical assessment<br><br>Repeat test: Not considered | Number of people admitted within 24 h of assessment out of cohort (n = 6,000):<br><ul style="list-style-type: none"><li>Intervention: 1,942</li><li>Comparator: 1,566</li></ul> Difference:<br><ul style="list-style-type: none"><li>Intervention vs comparator: 376 hospitalizations</li></ul> Correctly identified cases of PE out of cohort (n = 6,000):<br><ul style="list-style-type: none"><li>Intervention: 777</li><li>Comparator: 489</li></ul> Difference:<br><ul style="list-style-type: none"><li>Intervention vs comparator: 287 cases</li></ul> | Cost: Norwegian Krone (NOK)<br>Cost year: 2020<br>Mean cost per person<br><ul style="list-style-type: none"><li>Intervention: 14,994 NOK</li><li>Comparator: 12,920 NOK</li></ul> Mean difference:<br><ul style="list-style-type: none"><li>Intervention vs comparator: 2,087 NOK</li></ul> | Reference case: PLGF testing + standard clinical care resulted in 43,000 NOK per additional correctly identified case of PE<br><br>Sensitivity analysis: PSA was not conducted; DSA was conducted on varying PLGF-based biomarker test costs, and results (i.e., incremental cost per additional correctly identified PE) were similar to those of the reference case |
| Duhig et al, 2019, <sup>66</sup> UK       | Type of analysis: cost-effectiveness analysis<br>Study design: decision tree with Monte Carlo Simulation<br>Perspective: public payer<br>Time horizon: NR<br>Discount rate: not discounted<br>Source of clinical evidence: PARROT UK <sup>37</sup> | People with suspected PE between 20 weeks and 36 weeks + 6 days' gestation with a singleton pregnancy | Intervention: Triage PLGF test + standard clinical assessment<br>Comparator: standard clinical assessment<br>Repeat test: Not considered   | Mean number of maternal adverse events avoided per 1,000 people:<br><ul style="list-style-type: none"><li>Intervention: NR</li><li>Comparator: NR</li></ul> Mean difference:<br><ul style="list-style-type: none"><li>Intervention vs comparator: -15 maternal adverse events</li></ul>   | Cost: GBP (£)<br>Cost year: 2016/17<br>Mean cost<br><ul style="list-style-type: none"><li>Intervention: NR</li><li>Comparator: NR</li></ul> Mean difference:<br><ul style="list-style-type: none"><li>Intervention vs comparator: -£147 per person tested</li></ul>                         | Reference case: Triage PLGF test + standard clinical assessment resulted in an average of 15 fewer maternal adverse events per 1,000 people and an average weighted cost savings of £147 per person<br><br>Sensitivity analysis: PSA found that there was a 72% probability that the intervention is cost-effective at a £20,000 WTP for an adverse event prevented   |

| Author, year, country                              | Analytic technique, study design, perspective, time horizon  | Population  | Intervention(s) and comparator(s)   | Results   |   |   |
|--|--|---|---|---|---|---|
|  |  |   |   | Health outcomes   | Costs   | Cost-effectiveness  |
| <b>Giardini et al, 2021,<sup>64</sup> Italy</b>    | Type of analysis: cost analysis<br>Study design: cost analysis alongside observational study<br>Perspective: public payer<br>Time horizon: NR<br>Discount rate: not discounted<br>Source of clinical evidence: current study <sup>64</sup> | People with a singleton pregnancy who accessed the ER for blood pressure increase after 20 weeks' gestation | Intervention: PLGF testing + standard clinical assessment<br>Comparator: standard clinical assessment<br>Repeat test: Not considered                                  | N/R   | Cost: Euro (€)<br>Cost year: 2016<br>Mean cost per person:<br>• Intervention: €2,242 (calculated)<br>• Comparator: €2,634<br>Mean difference:<br>• Intervention vs comparator: -€ 401 | Reference case:<br>PLGF testing + standard clinical assessment was estimated to result in cost savings of €401 per patient attributed to avoidable hospitalization<br>Sensitivity analysis: Not conducted   |
| <b>Hodel et al, 2019,<sup>67</sup> Switzerland</b> | Type of analysis: cost and budget impact analysis<br>Study design: decision tree<br>Perspective: public payer<br>Time horizon: 5 years<br>Discount rate: 3.5%<br>Source of clinical evidence: PROGNOSIS <sup>46</sup>                      | People with suspected PE  | Intervention: Elecsys sFlt-1/PLGF ratio test + standard clinical assessment<br>Comparator: standard clinical assessment<br>Repeat test: Included as scenario analyses | Total number of people hospitalized for a simulated cohort of 6,084 women<br>• Intervention: 822 women<br>• Comparator: 1,160 women<br>Difference:<br>• Intervention vs comparator: -338 hospitalizations | Cost: Euro (€)<br>Cost year: NR<br>Mean cost per person:<br>• Intervention: €10,579<br>• Comparator: €10,925<br>Mean difference:<br>• Intervention vs comparator: -€346               | Reference case:<br>Elecsys sFlt-1/PLGF ratio test + standard clinical assessment resulted in cost savings of €346 per patient<br>Sensitivity analysis: PSA was not conducted. Results were most sensitive to variations in hospitalizations and hospitalization costs |

| Author, year, country                      | Analytic technique, study design, perspective, time horizon  | Population  | Intervention(s) and comparator(s)   | Results                                       |   |   |
|--|--|---|---|---|---|---|
|  |  |   |   | Health outcomes                               | Costs   | Cost-effectiveness  |
| Figueira et al, 2018, <sup>68</sup> Brazil | <p>Type of analysis: cost analysis</p> <p>Study design: decision tree</p> <p>Perspective: public and private health care payer</p> <p>Time horizon: NR</p> <p>Discount rate: not discounted</p> <p>Source of clinical evidence: PROGNOSIS<sup>46</sup></p> | <p>People with suspected PE between 24 weeks and 36 weeks + 6 days' gestation</p> | <p>Intervention: Elecsys sFlt-1/PIGF ratio test + standard clinical assessment</p> <p>Comparator: standard clinical assessment</p> <p>Repeat test: Yes, included in the base case</p> | <p>Intervention: NR</p> <p>Comparator: NR</p> | <p>Cost: Brazilian Real (R\$)</p> <p>Cost year: 2016</p> <p><i>Mean cost per 1,000 patients</i></p> <p>Public payer perspective</p> <ul style="list-style-type: none"> <li>Intervention: R\$7,45,682</li> <li>Comparator: R\$7,643,742</li> </ul> <p>Private payer perspective</p> <ul style="list-style-type: none"> <li>Intervention: R\$14,515,905</li> <li>Comparator: R\$15,151,750</li> </ul> <p><i>Mean difference per 1,000 patients</i></p> <p>Public payer perspective:</p> <ul style="list-style-type: none"> <li>Intervention vs comparator: -R\$185,060</li> </ul> <p>Private payer perspective:</p> <ul style="list-style-type: none"> <li>Intervention vs comparator: -R\$635,844</li> </ul> | <p>Reference case: Elecsys sFlt-1/PIGF ratio test + standard clinical assessment resulted in cost savings of R\$185.06 per patient and R\$635.84 per patient from the public and private payer perspectives respectively.</p> <p>Sensitivity analysis: PSA was not conducted. Results were most sensitive to variation of costs by ±10% for hospitalization and sFlt-1/PIGF test.</p> |

| Author, year, country                               | Analytic technique, study design, perspective, time horizon  | Population   | Intervention(s) and comparator(s)  | Results  |  |  |
|---|--|--|--|--|--|--|
|   |  |  |  | Health outcomes  | Costs  | Cost-effectiveness   |
| <b>Schlembach et al, 2018,<sup>69</sup> Germany</b> | Type of analysis: cost-effectiveness analysis<br>Study design: decision tree<br>Perspective: public payer<br>Time horizon: NR<br>Discount rate: not discounted<br>Source of clinical evidence: PROGNOSIS <sup>46</sup> | People with suspected PE between 24 weeks and 36 weeks + 6 days' gestation | Intervention: Elecsys sFlt-1/PIGF ratio test + standard clinical assessment<br><br>Comparator: standard clinical assessment<br><br>Repeat test: Yes, included                  | Number of people hospitalized out of cohort (n = 204):<br><ul style="list-style-type: none"> <li>Intervention: 49</li> <li>Comparator: 91</li> </ul> Difference<br><ul style="list-style-type: none"> <li>Intervention vs comparator: -42 hospitalizations</li> </ul> Hospitalized people who developed PE:<br><ul style="list-style-type: none"> <li>Intervention: 20</li> <li>Comparator: 27</li> </ul> Difference<br><ul style="list-style-type: none"> <li>Intervention vs comparator: -7</li> </ul> | Cost: Euro (€)<br>Cost year: 2017<br>Mean cost per person:<br><ul style="list-style-type: none"> <li>Intervention: €429</li> <li>Comparator: €790</li> </ul> Mean difference:<br><ul style="list-style-type: none"> <li>Intervention vs comparator: -€361</li> </ul>       | Reference case:<br>Elecsys sFlt-1/PIGF ratio test + standard clinical assessment resulted in cost savings of €361 per patient<br><br>Sensitivity analysis: PSA was not conducted. Results were sensitive to hospitalization costs, hospitalization rates, and LOS                                |
| <b>Frusca et al, 2017,<sup>70</sup> Italy</b>       | Type of analysis: Budget impact analysis<br>Study design: decision tree<br>Perspective: public payer<br>Time horizon: 5 years<br>Discount rate: 3%<br>Source of clinical evidence: PROGNOSIS <sup>46</sup>             | People with suspected PE between 24 weeks and 36 weeks + 6 days' gestation | Intervention: Elecsys sFlt-1/PIGF ratio test + standard clinical assessment<br><br>Comparator: standard clinical assessment<br><br>Repeat test: Yes, included in the base case | Intervention: NR<br>Comparator: NR   | Cost: Euro (€)<br>Cost year: 2015<br><br>Mean cost per person<br><ul style="list-style-type: none"> <li>Intervention: €1,714</li> <li>Comparator: €2,384</li> </ul> Mean difference<br><ul style="list-style-type: none"> <li>Intervention vs Comparator: -€671</li> </ul> | Reference case:<br>Elecsys sFlt-1/PIGF ratio test + standard clinical assessment resulted in cost-savings of €671 per person compared with standard clinical assessment alone<br><br>Sensitivity analysis: PSA was not conducted. Results were found to be sensitive to hospital admission costs |



| Author, year, country                        | Analytic technique, study design, perspective, time horizon  | Population   | Intervention(s) and comparator(s)  | Results                            |  |  |
|--|--|--|--|------------------------------------|--|--|
|  |  |  |  | Health outcomes                    | Costs  | Cost-effectiveness   |
| Duckworth et al, 2016, <sup>71</sup> England | Type of analysis: cost analysis<br>Study design: decision tree<br>Perspective: Public payer<br>Time horizon: NR<br>Discount rate: not discounted<br>Source of clinical evidence: PELICAN <sup>43</sup> | People aged ≥ 16 years with suspected PE between 20 and 35 weeks' gestation with a singleton or twin pregnancy | Intervention: Triage PLGF test + standard clinical assessment<br><br>Comparator: standard clinical assessment<br><br>Repeat test: Not considered | Intervention: NR<br>Comparator: NR | Cost: GBP (£)<br>Cost year: 2013/2014<br>Mean cost:<br>• Intervention: NR<br>• Comparator: NR<br>Mean difference:<br>• Intervention vs comparator: -£635 per person tested | Reference case:<br>Triage PLGF test + standard clinical assessment resulted in cost savings of £635 per person tested<br><br>Sensitivity analysis: 95% probability that intervention is cost savings. Results were robust to changes made to model assumptions |

| Author, year, country                 | Analytic technique, study design, perspective, time horizon   | Population   | Intervention(s) and comparator(s)  | Results  |  |   |
|---------------------------------------|---|--|--|--|--|---|
|                                       |   |  |  | Health outcomes  | Costs  | Cost-effectiveness  |
| Frampton et al, 2016, <sup>1</sup> UK | Type of analysis: cost-utility analysis<br>Study design: decision tree<br>Perspective: Public payer and personal social services<br>Time horizon: NR<br>Discount rate: not discounted<br>Source of clinical evidence: SR <sup>1</sup> | People with suspected PE between 20 weeks and 36 weeks + 6 days' gestation | Interventions: PlGF tests (Triage PlGF test, Elecsys sFlt-1/PlGF ratio test) + standard clinical assessment<br>Comparator: standard clinical assessment<br>Repeat test: Not considered | <p><i>People presenting at &lt; 35 weeks' gestation</i></p> <p>Mean QALYs</p> <ul style="list-style-type: none"> <li>• Triage: 0.39445</li> <li>• Elecsys: 0.39434</li> <li>• Comparator: 0.39368</li> </ul> <p>Mean difference:</p> <ul style="list-style-type: none"> <li>• Triage vs. comparator: 0.00077</li> <li>• Elecsys vs. comparator: 0.00066</li> </ul> <p><i>People presenting between 35 and 37 weeks' gestation</i></p> <p>Mean QALYs:</p> <ul style="list-style-type: none"> <li>• Triage: 0.3954</li> <li>• Elecsys: 0.3954</li> <li>• Comparator: 0.3954</li> </ul> <p>Mean difference:</p> <ul style="list-style-type: none"> <li>• Triage vs. comparator: 0</li> <li>• Elecsys vs. comparator: 0</li> </ul> | <p>Cost: GBP (£)</p> <p>Cost year: 2014</p> <p><i>People presenting at &lt; 35 weeks' gestation</i></p> <p>Mean cost</p> <ul style="list-style-type: none"> <li>• Triage: £6,048</li> <li>• Elecsys: £6,456</li> <li>• Comparator: £8,945</li> </ul> <p>Mean difference:</p> <ul style="list-style-type: none"> <li>• Triage vs. comparator: -£2,897</li> <li>• Elecsys vs. comparator: -£2,489</li> </ul> <p><i>People presenting between 35 and 37 weeks' gestation</i></p> <p>Mean cost</p> <ul style="list-style-type: none"> <li>• Triage: £3,393</li> <li>• Elecsys: £3,584</li> <li>• Comparator: £3,758</li> </ul> <p>Mean difference:</p> <ul style="list-style-type: none"> <li>• Triage vs. comparator: -£365</li> <li>• Elecsys vs. comparator: -£174</li> </ul> | <p>Reference case:</p> <p>For people presenting at &lt; 35 weeks' gestation, both interventions were less costly and more effective than the comparator</p> <p>For people presenting between 35 and 37 weeks' gestation, both interventions were less costly than the comparator, but showed no difference in effectiveness</p> <p>Sensitivity analysis: PSA was not conducted. Results were sensitive to LOS in the NICU</p> |

| Author, year, country                | Analytic technique, study design, perspective, time horizon  | Population  | Intervention(s) and comparator(s)  | Results  |  |   |
|--------------------------------------|--|---|--|--|--|---|
|                                      |  |   |  | Health outcomes  | Costs  | Cost-effectiveness  |
| Vatish et al, 2016, <sup>72</sup> UK | Type of analysis: cost-effectiveness analysis<br>Study design: decision tree<br>Perspective: public payer<br>Time horizon: NR<br>Discount rate: not discounted<br>Source of clinical evidence: PROGNOSIS <sup>46</sup> | People with suspected PE between 24+0 and 36+6 weeks' gestation | Intervention: Elecsys sFlt-1/PlGF ratio test + standard clinical assessment<br><br>Comparator: standard clinical assessment<br><br>Repeat test: Yes, included in base case | Number of hospitalized people out of cohort (n = 1,050):<br><ul style="list-style-type: none"><li>Intervention: 16%</li><li>Comparator: 36%</li></ul> Difference:<br><ul style="list-style-type: none"><li>Intervention vs comparator: -213 persons</li></ul> Hospitalized patients who developed PE:<br><ul style="list-style-type: none"><li>Intervention: 38%</li><li>Comparator: 27%</li></ul> Difference:<br><ul style="list-style-type: none"><li>Intervention vs comparator: 11% (calculated)</li></ul> | Cost: GBP (£)<br>Cost year: 2014<br>Mean cost per person:<br><ul style="list-style-type: none"><li>Intervention: £3,794</li><li>Comparator: £4,138</li></ul> Mean difference:<br><ul style="list-style-type: none"><li>Intervention vs comparator: -£344</li></ul> | Reference case:<br>Elecsys sFlt-1/PlGF ratio test + standard clinical assessment resulted in cost savings of £344 per patient compared with standard clinical assessment alone.<br><br>Sensitivity analysis: PSA was not conducted. Results were found to be sensitive to hospitalization rates and LOS |

Abbreviations: DG23, NICE diagnostic guidance 23; DSA, deterministic sensitivity analysis; DSU, Decision Support Unit, ER, emergency room; ICER, incremental cost-effectiveness ratio; LOS, length of stay; N/A, not applicable; NICU, neonatal intensive care unit; NR, not reported; NOK, Norwegian kroner; QALY, quality-adjusted life year; PE, pre-eclampsia; PlGF, placental growth factor; PSA, probabilistic sensitivity analysis; RCT, randomized control trial; sFlt-1, soluble fms-like tyrosine kinase 1; SR, systematic review; USD, United States dollar; WTP, willingness to pay; GBP, British Pound.

### **Applicability of the Included Studies**

Table A7 in Appendix 4 provides the results of the quality appraisal checklist for the economic evaluations applied to the included studies. We found that seven studies<sup>14,65,67,69,70,72,73</sup> were partially applicable to the Ontario setting and the remaining six studies<sup>1,64,66,68,71,74</sup> were not applicable. Studies were considered not applicable if the PlGF-based biomarker test evaluated was one that is currently not available in Ontario (e.g., Triage PlGF)<sup>64,66,71</sup> or if the perspective of the study was conducted from a health care system that is considerably different than that of Canada (e.g., the US and Brazil).<sup>68,74</sup>

### **Discussion**

Most of the studies included in our review found that PlGF-based biomarker testing as an adjunct to standard clinical assessment resulted in cost savings compared with standard clinical assessment alone. These results were largely attributed to fewer unnecessary hospitalizations due to the test improving risk prediction of pre-eclampsia and therefore avoiding overtreatment. The analyses were based on either assumptions that hospitalization would be reduced or observational studies, which may have a high risk of bias. However, existing randomized controlled trials (PARROT UK, PARROT Ireland, and INSPIRE) did not show an impact of PlGF-based biomarker testing on hospitalization rates.<sup>36,37,41</sup> This may suggest that while PlGF-based biomarker testing as an adjunct to standard clinical assessment likely improves prediction of pre-eclampsia compared with standard clinical assessment alone, its use in routine clinical practice may not necessarily lead to reduced unnecessary hospitalizations. This is an important consideration when reviewing the included economic studies, as results were highly sensitive to hospitalization rates and costs across most of these studies. Of the two studies that conducted a cost-utility analysis, both found the incremental QALY gains between the PlGF-based biomarker testing and standard clinical assessment strategies to be very small (less than 0.006 QALYs).<sup>1,14</sup>

Most of the included studies focused on the use of the PlGF-based biomarker testing to rule out pre-eclampsia only. Yet, the NICE DSU cost-utility analysis found that PlGF-based biomarker testing produced more favourable cost-effectiveness results when PlGF-based biomarker testing were used to both rule out and rule in pre-eclampsia.<sup>14</sup>

Lastly, there was heterogeneity in the clinical evidence used to inform the analysis across our included economic studies. For instance, a number of studies derived the benefits of PlGF-based biomarker testing from clinical studies (e.g., PROGNOSIS<sup>46</sup>) that evaluated the test as a stand-alone test rather than as an adjunct to standard clinical assessment, which is how it is expected to be used in clinical practice. Furthermore, only some studies considered retesting in their analysis; however, this was not found to be a key driver of results.

### **Conclusions**

Our economic literature review identified 13 studies that evaluated the cost difference and cost-effectiveness of PlGF-based biomarker testing as an adjunct to standard clinical assessment versus standard clinical assessment alone for the risk prediction of pre-eclampsia in people with suspected pre-eclampsia. Most studies found that PlGF-based biomarker testing resulted in cost savings compared to standard clinical assessment alone. None of the included studies were directly applicable to our research question.

## Primary Economic Evaluation

Although we found several published economic evaluations related to our research question, these studies had limitations and their results may not be generalizable to the Ontario setting. Notably, most of these studies found that PlGF-based biomarker testing as an adjunct to standard clinical assessment yielded favourable results compared with standard clinical assessment alone. This was largely attributed to a reduction in unnecessary hospitalizations due to the test improving diagnostic accuracy in predicting pre-eclampsia. The analyses were based on either assumptions that hospitalization would be reduced or observational studies. However, any effect of PlGF-based biomarker testing on hospitalizations has not been demonstrated in existing randomized controlled trials (PARROT UK, PARROT Ireland, and INSPIRE).<sup>36,37,41</sup> As such, the actual impact of the use of these tests in routine clinical practice is unknown.

Additionally, the economic analysis conducted by Kearns et al<sup>14,75</sup> showed that while PlGF-based biomarker testing led to a small increase in costs and QALYs, results were very sensitive to changes in assumptions. An Ontario-focused primary economic evaluation would likely have similar results, limitations, and uncertainties because it would be based on the same clinical evidence. Owing to these limitations, we did not conduct a primary economic evaluation.

# Budget Impact Analysis

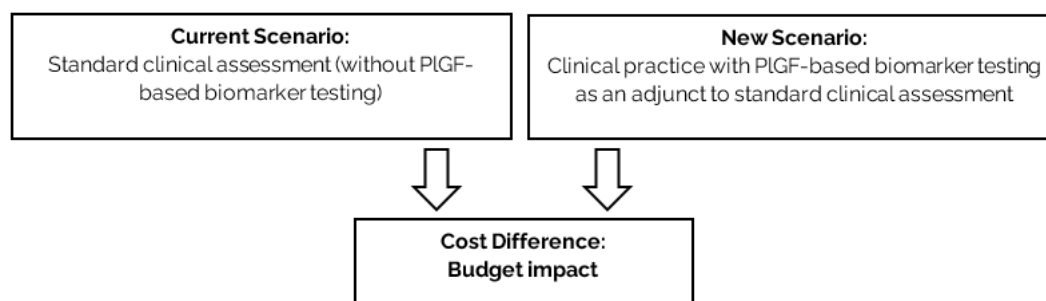
## Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding placental growth factor (PIGF)-based biomarker testing as an adjunct to standard clinical assessment to help diagnose pre-eclampsia in people with suspected pre-eclampsia?

## Methods

### **Analytic Framework**

We estimated the budget impact of publicly funding PIGF-based biomarker testing using the cost difference between two scenarios: (1) current clinical practice without dedicated public funding for PIGF-based biomarker testing (the current scenario), and (2) anticipated clinical practice with dedicated public funding for PIGF-based biomarker testing (the new scenario). Figure 3 presents the budget impact model schematic.



**Figure 3: Schematic Model of Budget Impact**

Flow chart describing the model for the budget impact analysis. The current scenario would explore resource use and total costs without public funding for PIGF-based biomarker testing. The new scenario would explore resource use and total costs with public funding for PIGF-based biomarker testing. The budget impact would represent the difference in costs between the two scenarios.

Abbreviation: PIGF, placental growth factor.

### **Key Assumptions**

- PIGF-based biomarker testing is used as an adjunct to standard clinical assessment of pregnant people with suspected pre-eclampsia
- Currently, there are three PIGF-based biomarker tests available in Ontario (Elecsys, DELFIA Xpress, and BRAHMS). People with suspected pre-eclampsia will be offered one of the three biomarker tests
- No new tests will enter the market in Ontario in the next 5 years in our reference case analysis. In a scenario analysis, we assumed that Triage PIGF (San Diego, CA) will enter the market
- Since there is limited clinical evidence on repeat testing, we assumed each person will only receive one test in our reference case analysis. In a scenario analysis, we assumed that repeat testing would be provided to a proportion of the target population

### Target Population

Recent guidelines from the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the National Institute for Health and Care Excellence (NICE) in the UK have recommended the use of PLGF-based biomarker testing as an adjunct to standard clinical assessment to evaluate the risk of developing pre-eclampsia in people with suspected pre-eclampsia.<sup>2,17</sup> Based on these guidelines, we defined our target population as pregnant people between 20 weeks and 36 weeks + 6 days' gestation with suspected pre-eclampsia. Pregnant people suspected of having pre-eclampsia are typically identified at routine prenatal appointments or emergency department visits, presenting with signs and/or symptoms such as new-onset or worsening of pre-existing hypertension; dipstick proteinuria; epigastric, right upper-quadrant pain; or headaches.<sup>37</sup> However, only a proportion of pregnant people suspected of having pre-eclampsia will go on to develop this condition.

Pre-eclampsia affects up to 5% of all pregnancies globally.<sup>1</sup> Data from the Better Outcomes Registry and Network (BORN) Ontario showed that around 1.3% of pregnant people in Ontario experienced pre-eclampsia between 2017 to 2020 (Table 37). On average, there were around 1,750 cases of pre-eclampsia per year from 2017 to 2020. We therefore assumed that there would be 1,750 pregnancies with pre-eclampsia per year over the next 5 years.

**Table 37: Number of Pre-eclampsia Cases in Ontario, 2017 to 2020**

| Number   | 2017    | 2018    | 2019    | 2020    | Total   |
|--|---------|---------|---------|---------|---------|
| Total number of PE cases                       | 1,672   | 1,820   | 1,770   | 1,734   | 6,996   |
| PE   | 1,091   | 1,203   | 1,111   | 1,077   | 4,482   |
| Pre-existing hypertension with superimposed PE | 359     | 337     | 415     | 398     | 1,509   |
| PE requiring magnesium sulfate                 | 222     | 280     | 244     | 259     | 1,005   |
| Percentage of pregnant people with PE (%)      | 1.2     | 1.3     | 1.3     | 1.3     | 1.3     |
| Total number of pregnancies                    | 138,538 | 138,430 | 139,133 | 135,340 | 551,441 |

Abbreviation: PE, pre-eclampsia.

Years provided: 2017 to 2020; resource type: tabulated data; data provided May 2022.

Source: Better Outcomes Registry and Network (BORN) Ontario.

We expect that most people with pre-eclampsia experience first-onset signs (e.g., high blood pressure, elevated levels of protein in the urine, abnormal lab tests) and/or symptoms (e.g., headaches, visual issues, abdominal pain) before 37 weeks' gestation. It was estimated that around 85% of pregnant people with pre-eclampsia present with new-onset hypertension and proteinuria by 34 weeks' gestation.<sup>77</sup> Irrespective of presenting with first-onset signs or symptoms of pre-eclampsia before 37 weeks' gestation, however, most people with suspected pre-eclampsia are diagnosed after 37 weeks' gestation. We were not able to determine the proportion of individuals with pre-eclampsia who present with signs and/or symptoms between 20 weeks and 36 weeks + 6 days' gestation from the published literature. As such, we approximated that around 70% of people (or  $1,750 \times 70\% = 1,225$ ) with pre-eclampsia would present with signs and/or symptoms between 20 weeks and 36 weeks + 6 days' gestation.

According to the findings from three randomized controlled trials (PARROT UK,<sup>37</sup> PARROT Ireland,<sup>36</sup> and INSPIRE<sup>41</sup>), the proportion of individuals with confirmed pre-eclampsia (individuals diagnosed with pre-eclampsia after entering the trials) out of those with suspected pre-eclampsia (those with signs or symptoms of pre-eclampsia at recruitment) varied considerably (see Table 38 below). In the INSPIRE study, 23% of people who were suspected of having pre-eclampsia were confirmed to have pre-eclampsia and we used this proportion for the reference case analysis. Using this proportion, we estimated that around 5,332 individuals would have suspected pre-eclampsia between 20 weeks and 36 weeks + 6 days' gestation ( $1,225 \div 23\% = 5,332$ ). We used the proportions from the other two trials (PARROT UK: 35%; and PARROT Ireland: 16%) in our scenario analysis. Given that the number of pregnancies and pre-eclampsia cases in Ontario have been relatively stable in recent years, we assumed that the size of our target population would remain constant over the next 5 years. We illustrated the process of estimating our target population in Figure 4.

**Table 38: Suspected Pre-eclampsia and Confirmed Pre-eclampsia Cases in Randomized Clinical Trials**

| Trials                       | Number of confirmed PE cases <sup>a,b</sup> | Number of suspected PE cases <sup>a,c</sup> | Proportion of confirmed PE out of suspected PE cases |
|------------------------------|---|---|--|
| PARROT UK <sup>37</sup>      | 360   | 1,019                                       | 0.35   |
| PARROT Ireland <sup>36</sup> | 345   | 2,219                                       | 0.16   |
| INSPIRE <sup>41</sup>        | 85  | 370   | 0.23   |

Abbreviation: PE, pre-eclampsia.

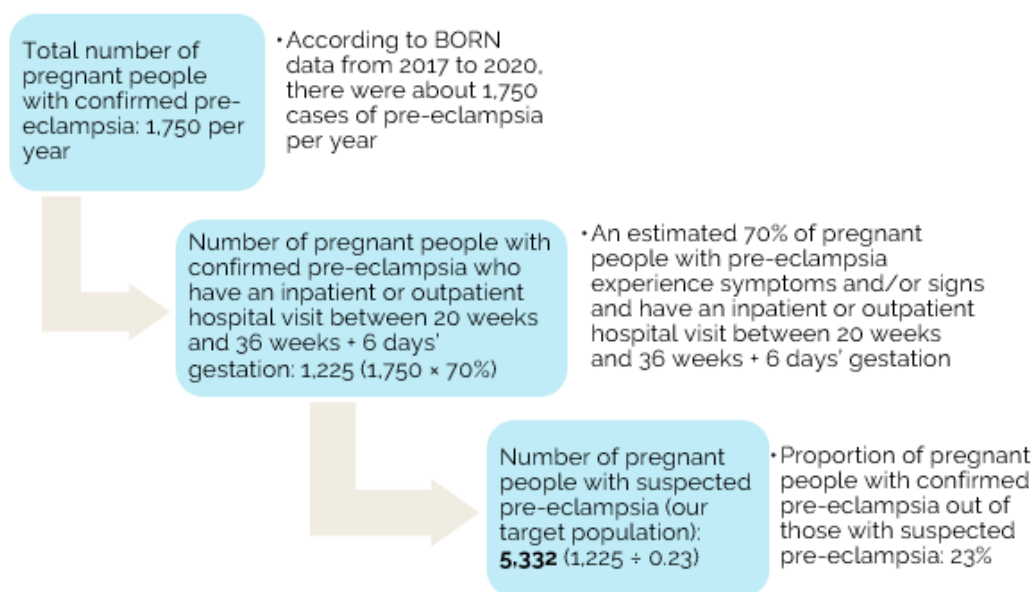
<sup>a</sup> Suspected PE cases refers to pregnant people who present with signs and/or symptoms of PE. Confirmed PE refers to pregnant people who meet the diagnostic criteria of PE.

<sup>b</sup> We combined the number of individuals with PE in both the reveal (intervention) and nonreveal (control) arms in each study. We included individuals with superimposed PE.

<sup>c</sup> We combined the number of individuals with suspected PE in both the reveal (treatment) and nonreveal (control) arms.

Note: Numbers may be inexact due to rounding.





**Figure 4: Process of Estimating Size of Target Population**

Abbreviations: BORN, Better Outcomes Registry & Network.

Note: Numbers may be inexact due to rounding.

### **Current Intervention**

Standard clinical assessment for pregnant people with suspected pre-eclampsia involves the assessment of hypertension in pregnancy; proteinuria; platelet count; and serum creatinine, ALT (alanine aminotransferase) or AST (aspartate aminotransferase), and other routine tests, such as oxygen saturation and platelet count.<sup>2,41</sup> However, because we are considering the use of PLGF-based biomarker testing as an adjunct to standard clinical assessment against standard clinical assessment alone, the costs of standard clinical assessment would cancel out when calculating the budget impact. Therefore, we did not need to consider the cost of standard clinical assessment and, as a result, did not specify which tests would be used.

At present, PLGF-based biomarker testing is not publicly funded to help diagnose pre-eclampsia in Ontario. In the current scenario, we assumed all pregnant people would receive standard clinical assessment only.

### **Uptake of the New Intervention**

The new intervention refers to the addition of PLGF-based biomarker testing as an adjunct to standard clinical assessment to help diagnose pre-eclampsia in people with suspected pre-eclampsia. We estimated the potential uptake of PLGF-based biomarker testing in the new scenario. If publicly funded, we expect that the use of PLGF-based biomarker testing will expand quickly, leading to a high uptake rate. This is because:

- Recent guidelines from SOGC,<sup>2</sup> NICE,<sup>17</sup> and other international agencies<sup>18</sup> have recommended PlGF-based biomarker testing for suspected pre-eclampsia
- PlGF-based biomarker testing is associated with moderate costs (see Resources and Costs below)

Therefore, we estimated that the total uptake of PlGF-based biomarker testing would be 50% in year 1 and gradually increase to 90% in year 5.

Next, we estimated the market shares of different biomarker tests. SOGC recommended the use of PlGF-based biomarker testing but did not specify which ones. Currently, there are three PlGF-based biomarker tests available in Ontario (Elecsys [Elecsys immunoassay sFlt-1/PlGF ratio]; DELFIA PlGF [AutoDELFIA PlGF 1-2-3 or DELFIA Xpress PlGF 1-2-3], and BRAHMS [BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio]). We expected that Elecsys would likely have the largest market share, followed by DELFIA PlGF and BRAHMS based on the following considerations:

- The use of Elecsys as an adjunct to standard clinical assessment was evaluated in a randomized controlled trial (INSPIRE)<sup>41</sup> and numerous test accuracy studies,<sup>14</sup> while there was only a small number of test accuracy studies for DELFIA PlGF and BRAHMS<sup>14</sup>
- The NICE guidelines recommended the Elecsys and the DELFIA Xpress PlGF 1-2-3 test, but not the BRAHMS test due to relatively weaker evidence on test accuracy<sup>17</sup>
- DELFIA PlGF tests can be performed using different platforms, including AutoDELFIA and DELFIA Xpress. The DELFIA Xpress platform has not been used in hospitals in Ontario, but the AutoDELFIA platform has. Both AutoDELFIA and DELFIA Xpress uses the same technology and antibodies. Very similar cut-offs are used in both platforms. AutoDELFIA has the capability to run greater volume of samples on a larger scale, whereas the DELFIA Xpress is a benchtop unit (Claudia Di Schiavi, email communication, September 2022)

The estimated future market shares of PlGF-based biomarker testing are shown in Table 39 and the number of people receiving PlGF-based biomarker testing and standard clinical assessment in the current and future scenarios are shown in Table 40.

**Table 39: Uptake and Market Shares of PlGF-Based Biomarker Testing in the New Scenario**

| Uptake  | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|--------|--------|--------|--------|--------|
| Total uptake of PlGF-based biomarker testing, % | 50     | 60     | 70     | 80     | 90     |
| Elecsys, %                                      | 35     | 40     | 45     | 50     | 55     |
| DELFIA PlGF 1-2-3, %                            | 10     | 14     | 17     | 20     | 23     |
| BRAHMS, %                                       | 5      | 6      | 8      | 10     | 12     |

Note: Numbers may be inexact due to rounding.

**Table 40: Estimated Number of People Receiving PlGF-Based Biomarker Testing and Standard Clinical Assessment**

| Scenario   | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Total  |
|--|--------|--------|--------|--------|--------|--------|
| <b>Current scenario</b>  |        |        |        |        |        |        |
| Standard clinical assessment, N                                | 5,332  | 5,332  | 5,332  | 5,332  | 5,332  | 26,660 |
| <b>New scenario<sup>a</sup></b>                                |        |        |        |        |        |        |
| Standard clinical assessment, N                                | 2,666  | 2,133  | 1,600  | 1,066  | 533    | 7,998  |
| PlGF-based biomarker testing + standard clinical assessment, N | 2,666  | 3,199  | 3,732  | 4,266  | 4,799  | 18,662 |
| Elecsys, n   | 1,866  | 2,133  | 2,399  | 2,667  | 2,933  | 11,998 |
| DELFLA PlGF 1-2-3, n   | 533    | 746    | 906    | 1,066  | 1,226  | 4,477  |
| BRAHMS, n  | 267    | 320    | 427    | 533    | 640    | 2,187  |

Abbreviations: PE, pre-eclampsia; PlGF, placental growth factor.

<sup>a</sup> The annual volume of PlGF-based biomarker testing was calculated by multiplying the uptake rate of each biomarker test by the size of the target population. For example, in the new scenario, the number of pregnant people with suspected PE in year 1 is 5,332 and the uptake rate of the Elecsys test is 35%, so the volume of Elecsys tests theoretically used in year 1 would be 1,866 (5,332 × 35%).

Note: Numbers may be inexact due to rounding.

### **Resources and Costs**

For our budget impact analysis, we only considered the direct costs associated with PlGF-based biomarker testing. We did not include any potential downstream costs associated with PlGF-based biomarker testing for the following reasons:

- Although theoretically, PlGF-based biomarker testing may be used as a rule-out test to prevent unnecessary hospitalizations of low-risk individuals, no difference in hospital admission rates was observed in randomized controlled trials<sup>36,37,41</sup>
- The quality of evidence for PlGF-based biomarker testing on maternal outcomes was low. One trial (PARROT UK<sup>37</sup>) showed beneficial effects of PlGF-based biomarker testing, but these benefits were not demonstrated in the other two trials (PARROT Ireland<sup>36</sup> and INSPIRE<sup>41</sup>). Also, the PARROT UK<sup>37</sup> clinical trial focused on the Triage PlGF test (San Diego, CA), but this test has not been approved by Health Canada
- None of the three randomized controlled trial (PARROT UK, INSPIRE and PARROT Ireland)<sup>36,37,41</sup> found that PlGF-based biomarker testing was associated with improved neonatal outcomes

Therefore, we are uncertain if there would be any downstream cost savings associated with using PlGF-based biomarker testing.

Currently, three PlGF-based biomarker tests (Elecsys, DELFLA PlGF, and BRAHMS) have been used by hospitals in Ontario. We obtained the estimated costs for each test from manufacturers.

- Elecsys immunoassay sFlt-1/PlGF ratio (Roche): Based on the information provided by the manufacturer, the cost is estimated to be around \$125 to \$150 per test. This includes the costs of materials, equipment, and labour (Kara Mosher, email communication, August 2022)

- DELFIA PLGF 1-2-3 (PerkinElmer, AutoDELFLIA, or DELFIA Xpress): The costs may vary depending on the total volume of testing and the platforms used. The cost is estimated to be \$48 per test, which includes the cost of material and equipment (assuming rental of the DELFIA Xpress platform) (Claudia Di Schiavi, email communication, September 2022)
- BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio (Thermo Fisher Scientific): According to the manufacturer, the material and equipment costs are likely to work out to \$50 to \$55 per test (Aida Ansari, email communication, August 2022)

The cost of PLGF-based biomarker testing may vary significantly from hospital to hospital for the following reasons:

- The cost per test depends on the volume of testing
- There are various funding models for the required equipment (e.g., purchasing versus renting). The equipment may also be used to run other tests outside of PLGF-based testing and some hospitals in Ontario have purchased the equipment
- Labour costs associated with running these tests are currently unknown

Based on the cost information received from the manufacturers, we estimated the costs of the three PLGF-based biomarker tests available in Ontario (see Table 41). We aimed to capture the costs of the test kit, lab materials, and equipment in our reference case, assuming there is no need to hire new staff for PLGF-based biomarker testing in the new scenario. In the lower-cost scenario, we excluded equipment costs. In the higher-cost scenario, we included approximate labour costs. Given the uncertainties of the costs associated with PLGF-based biomarker testing, listed above, these cost estimates may not be as accurate as they could be. However, overall, our cost estimates of these tests were consistent with those used in the UK NICE HTA on PLGF-based biomarker testing.<sup>14</sup>

**Table 41: Costs of PLGF-Based Biomarker Testing**

| Test               | Reference case<br>(\$ CAN per test)<br>Cost of testing includes<br>test kit, lab materials, and<br>equipment | Scenario 1-1<br>(\$ CAN per test)<br>Cost of testing includes<br>test kit and lab materials | Scenario 1-2<br>(\$ CAN per test)<br>Cost of testing includes<br>test kit, lab materials,<br>equipment, and staff time |
|--------------------|--|---|--|
| Elecsys            | 125  | 100 <sup>a</sup>  | 150 <sup>b</sup>   |
| DELFLIA PLGF 1-2-3 | 48   | 22 <sup>c</sup>   | 57.6 <sup>b</sup>  |
| BRAHMS             | 52.5   | 42 <sup>a</sup>   | 63 <sup>b</sup>  |

<sup>a</sup> Assumed to be 80% of the test cost in the reference case.

<sup>b</sup> Assumed to be 120% of the test cost in the reference case.

<sup>c</sup> An unpublished study in Ontario suggested that the cost of this test is approximately \$22 per test in Ontario. This cost likely includes only the costs of the testing kits.

### **Internal Validation**

A secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

## Analysis

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results are affected by varying input parameters and model assumptions. We conducted the following sensitivity or scenario analyses:

- *Costs of the tests:* Lower and higher cost estimates of the three biomarker tests (Table 41)
- *Population size:* A smaller and greater target population size, using proportions of confirmed pre-eclampsia (35%) out of suspected pre-eclampsia from PARROT UK<sup>37</sup> ( $1,225 \div 35\% = 3,467$ ) and PARROT Ireland (16%;  $N = 1,225$ ;  $1,225 \div 16\% = 7,879$ ). See Table 38 for further details. A recent Ontario Health HTA showed that a population-wide first-trimester screening program for pre-eclampsia risk that uses a new technique developed by the Fetal Medicine Foundation is more effective than the standard care in reducing the risk of pre-eclampsia.<sup>8</sup> This report led to a recommendation to publicly fund a population-wide first-trimester screening program for pre-eclampsia risk in pregnant people in Ontario. Under such a screening program, we can expect that our population of interest may decrease in size. As such, we included a scenario with a smaller target population size to consider a reduced number of pre-eclampsia cases following the successful implementation of a population-wide first-trimester screening program for pre-eclampsia risk in Ontario
- *New biomarker tests entering the market:* The Triage PlGF test contributed considerably to the medical evidence on PlGF-based biomarker testing, as it was used in the PARROT UK<sup>37</sup> and PARROT Ireland<sup>36</sup> trials. We assumed this test would enter Ontario's market in year 2. The market shares of Triage PlGF were assumed to be 10%, 15%, 20%, and 25% in years 2, 3, 4, and 5, respectively. The market shares of the other three tests will then decrease proportionally over this period compared with the corresponding market shares in the reference case. The NICE economic evaluation reported that the cost of the Triage PlGF test was £43.02 (British pounds [GBP], materials, and equipment).<sup>14</sup> We converted the cost of the Triage PlGF test from GBP to CAD (1 GBP = 1.56 CAD as of July 10, 2022),<sup>78</sup> and the cost was \$67.11 (CAD) per test
- *Repeat testing:* The interval between the first test and subsequent tests is often 2 weeks or longer. It can be a follow-up to the previous episode or due to a new episode of suspected pre-eclampsia. There is limited evidence on how repeat tests perform in clinical practice and whether they provide additional health benefits. The NICE draft report suggested that an estimated 20% to 50% of people could undergo repeat testing.<sup>14</sup> In our scenario, we assumed that 40% of individuals would undergo repeat testing and that the biomarker test used for repeat testing would be the same as the first test
- *A single biomarker test in the market:* We assumed there is only a single biomarker test in the market and estimated the budget impact for each test separately

## Results

### Reference Case

Results of the budget impact analysis are shown in Table 42. The total cost of PlGF-based biomarker testing in the current scenario was assumed to be zero, given that these tests were not publicly funded for suspected pre-eclampsia. Publicly funding PlGF-based biomarker testing would result in additional costs of \$0.27 million in year 1 and \$0.46 million year 5, for a total of \$1.83 million over 5 years.

Table 42: Budget Impact Analysis Results for PLGF-Based Biomarker Testing (Reference Case)

| Scenario                         | Budget impact, \$ million <sup>a,b</sup> |             |             |             |             |             |
|----------------------------------|--|-------------|-------------|-------------|-------------|-------------|
|                                  | Year 1                                   | Year 2      | Year 3      | Year 4      | Year 5      | Total       |
| Current scenario <sup>c</sup>    | 0  | 0           | 0           | 0           | 0           | 0           |
| New scenario                     | 0.27                                     | 0.32        | 0.37        | 0.41        | 0.46        | 1.83        |
| Elecsys                          | 0.23                                     | 0.27        | 0.30        | 0.33        | 0.37        | 1.50        |
| DELFIA PLGF 1-2-3                | 0.03                                     | 0.04        | 0.04        | 0.05        | 0.06        | 0.21        |
| BRAHMS                           | 0.01                                     | 0.02        | 0.02        | 0.03        | 0.03        | 0.11        |
| <b>Budget impact<sup>b</sup></b> | <b>0.27</b>                              | <b>0.32</b> | <b>0.37</b> | <b>0.41</b> | <b>0.46</b> | <b>1.83</b> |

Abbreviation: PLGF, placental growth factor.

<sup>a</sup> In Canadian dollars as of 2022.

<sup>b</sup> Some numbers may appear inexact due to rounding.

<sup>c</sup> Given that standard clinical assessment would be conducted for both current and new scenarios, the costs associated with standard clinical assessment were cancelled out.

### **Sensitivity Analysis**

Table 43 summarizes the results of the sensitivity and scenario analyses. The budget impact result was most sensitive to changes in the size of the target population and the cost of the tests. If the Triage PLGF test enters the Ontario market in the next 5 years, the budget increase would be similar to that of the reference case (under the assumption of no changes in the total volume of biomarker tests). The inclusion of repeat testing would lead to a greater budget increase. Additionally, if Elecsys is the only PLGF-based biomarker test used in Ontario, the budget increase would be greater than that of the reference case.

**Table 43: Budget Impact Analysis Results for PlGF-Based Biomarker Testing (Sensitivity Analysis)**

| Scenario   | Budget impact, \$ million <sup>a,b</sup> |        |        |        |        |       |
|--|--|--------|--------|--------|--------|-------|
|  | Year 1                                   | Year 2 | Year 3 | Year 4 | Year 5 | Total |
| <b>Reference case</b>                                    |  |        |        |        |        |       |
| Budget impact  | 0.27                                     | 0.32   | 0.37   | 0.41   | 0.46   | 1.83  |
| <b>1-1: Lower cost of PlGF-based biomarker testing</b>   |  |        |        |        |        |       |
| Budget impact  | 0.21                                     | 0.24   | 0.28   | 0.31   | 0.35   | 1.39  |
| <b>1-2: Higher cost of PlGF-based biomarker testing</b>  |  |        |        |        |        |       |
| Budget impact  | 0.33                                     | 0.38   | 0.44   | 0.50   | 0.55   | 2.20  |
| <b>2-1: Smaller target population</b>                    |  |        |        |        |        |       |
| Budget impact  | 0.18                                     | 0.21   | 0.24   | 0.27   | 0.30   | 1.19  |
| <b>2-2: Larger target population</b>                     |  |        |        |        |        |       |
| Budget impact  | 0.40                                     | 0.47   | 0.54   | 0.61   | 0.68   | 2.70  |
| <b>3: Triage PlGF Test entering the market in year 2</b> |  |        |        |        |        |       |
| Budget impact  | 0.27                                     | 0.30   | 0.34   | 0.38   | 0.42   | 1.72  |
| <b>4: 40% of people undergoing repeat tests</b>          |  |        |        |        |        |       |
| Budget impact  | 0.38                                     | 0.45   | 0.51   | 0.58   | 0.64   | 2.56  |
| <b>5-1: Only using Elecsys in Ontario</b>                |  |        |        |        |        |       |
| Budget impact  | 0.33                                     | 0.40   | 0.47   | 0.53   | 0.60   | 2.33  |
| <b>5-2: Only using DELFIA PlGF 1-2-3 in Ontario</b>      |  |        |        |        |        |       |
| Budget impact  | 0.13                                     | 0.15   | 0.18   | 0.20   | 0.23   | 0.90  |
| <b>5-3: Only using BRAHMS in Ontario</b>                 |  |        |        |        |        |       |
| Budget impact  | 0.14                                     | 0.17   | 0.20   | 0.22   | 0.25   | 0.98  |

Abbreviation: PlGF, placental growth factor.

<sup>a</sup> In Canadian dollars as of 2022.

<sup>b</sup> Some numbers may appear inexact due to rounding.

## Discussion

In this budget impact analysis, we estimated the costs associated with PlGF-based biomarker testing alone. We did not estimate any potential downstream cost savings associated with testing due to uncertainty in the clinical evidence. It is often complex to quantify the incremental value of adding a new test to an existing clinical pathway. Previous studies showed that PlGF-based biomarker tests have a high negative predictive value, so theoretically, PlGF-based biomarker testing can be used to rule out low-risk people and prevent unnecessary hospitalizations. On the other hand, if PlGF-based biomarker testing is used to rule in pregnant people with suspected pre-eclampsia (i.e., admitting people to hospital whose biomarker test results show high risk, regardless of high- or low-risk results of the standard clinical assessment), it may increase hospitalization rates. However, it is likely that PlGF-based biomarker testing will be used to both rule out and rule in pre-eclampsia in clinical practice. As such, it is difficult to predict how the tests will actually impact hospital admissions of pregnant people suspected of pre-eclampsia in Ontario. Currently the evidence of repeat testing is

limited; however, the PARROT 2 trial will demonstrate the proper frequencies and the added values of repeat testing.<sup>79</sup>

Many published economic studies have assumed that PlGF-based biomarker testing would reduce hospitalizations and, therefore, that the use of these tests may result in cost savings (see the Economic Evidence section for details). However, randomized controlled trials did not show any difference in hospital admissions.<sup>36,37,41</sup> Although no difference in the rates of hospital admissions were observed, clinical studies suggested that PlGF-based biomarker testing may help improve clinical precision and allow more accurate admission of high-risk patients and discharge of low-risk patients without changing the overall admission rate.<sup>14</sup> The use of the test may allow health care providers to identify people at high risk for other adverse outcomes and provide better clinical management. As a result, this may lead to improvement in maternal and/or neonatal outcomes, as has been suggested by the PARROT trial in UK.<sup>37</sup> If we consider the cost savings that may be attributed to potentially better health outcomes associated with PlGF-based biomarker testing, the budget impact would be even smaller.

## Strengths and Limitations

Our study had the following strengths:

- Our key parameters and main assumptions were verified by clinical experts in Ontario
- We considered the PlGF-based biomarker tests currently available in Ontario, as well as tests that may plausibly enter the Ontario market in the future

The following limitations should be noted when interpreting the findings of this analysis:

- We did not consider any potential cost savings associated with PlGF-based biomarker testing due to uncertainty in the clinical evidence

## Conclusions

We estimated that publicly funding PlGF-based biomarker testing in Ontario would result in additional costs of \$0.27 million in year 1 to \$0.46 million in year 5, for a total additional cost of \$1.83 million over the next 5 years.



# Preferences and Values Evidence

## Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those who have lived experience of suspected pre-eclampsia as well as the preferences and perceptions of both patients and providers of placental growth factor (PlGF)-based biomarker testing.

## Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).<sup>80-82</sup> Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to consider to understand the impact of the technology in people's lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we examined the preferences and values of people with suspected pre-eclampsia who underwent PlGF-based biomarker testing in two ways:

- A review by Ontario Health of the quantitative evidence on patient and provider preferences and values
- Direct engagement (interviews) by Ontario Health with people who have lived experience with pre-eclampsia

## Quantitative Evidence

### Research Questions

- What are the preferences and values of patients with suspected pre-eclampsia and providers of PlGF-based biomarker testing as an adjunct to clinical assessment compared with standard clinical assessment alone to help diagnose pre-eclampsia?
- How satisfied are patients and providers with PlGF-based biomarker testing?
- What is the psychological impact of PlGF-based biomarker testing for patients with suspected pre-eclampsia?

## Methods

### LITERATURE SEARCH

We performed a literature search for quantitative preference evidence on April 22, 2022, for studies published from January 1, 2015, to the search date. We used the Ovid interface of MEDLINE and the EBSCO interface in the Cumulative Index to Nursing and Allied Health Literature (CINAHL). The search

was based on the population and intervention of the clinical search strategy, with a methodological filter applied to limit retrieval to quantitative preference evidence.<sup>83</sup> We created database auto-alerts in MEDLINE and CINAHL and monitored them for until July 31, 2022.. See Appendix 1 for literature search strategies, including all search terms.

## ELIGIBILITY CRITERIA

### *Studies*

#### *Inclusion Criteria*

- English-language, full-text publications
- Studies published between January 2015 and April 2022
- Randomized controlled trials, health technology assessments, systematic reviews, observational studies, surveys, questionnaires, discrete-choice experiments
- Utility measures: direct techniques (standard gamble, time trade-off, rating scales) or conjoint analyses (discrete-choice experiments, contingent valuation and willingness-to-pay, probability trade-off)
- Non-utility quantitative measures: direct-choice techniques, decision aids, surveys, questionnaires

#### *Exclusion Criteria*

- Animal and in vitro studies
- Nonsystematic reviews, narrative reviews, abstracts, editorials, letters, case reports, commentaries, and qualitative studies

### *Participants*

#### *Inclusion Criteria*

- Pregnant people, between 20 weeks and 36 weeks plus 6 days, suspected of having pre-eclampsia based on clinical assessment
- Singleton pregnancy

#### *Exclusion Criteria*

- Pregnant people at less than 20 weeks' gestation; pregnant people not suspected of having pre-eclampsia; non-singleton pregnancies

### *Interventions*

#### *Inclusion Criteria*

- PlGF-based biomarker tests; for example:
  - Quidel Triage PlGF test (not licensed by Health Canada)
  - AutoDELFIA PlGF 1-2-3 or DELFIA Xpress PlGF 1-2-3 test/DELFIA Xpress sFlt-1 test (not licensed by Health Canada) in conjunction with standard clinical assessment
  - Elecsys immunoassay sFlt-1/PlGF ratio in conjunction with standard clinical assessment
  - BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor pre-eclampsia (PE) ratio in conjunction with standard clinical assessment
- Tests are assessed each time they are used for an episode of suspected pre-eclampsia as well as when they are repeated in people with suspected pre-eclampsia who have previously had a PlGF-based test for suspected pre-eclampsia that was negative

#### *Exclusion Criteria*

- Biomarker tests that are not PlGF-based

*Outcome Measures*

- Patient/provider preference and patient values (including preference for test attributes/characteristics)
- Patient/provider satisfaction
- Patient psychological impact

**LITERATURE SCREENING**

A single reviewer conducted an initial screening of titles and abstracts using Covidence<sup>26</sup> and obtained the full text of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion.

**DATA EXTRACTION**

We extracted relevant data on study characteristics using a data form to collect information about the following:

- Source (e.g., citation information, contact details, study type)
- Methods (e.g., study design, study duration, participant recruitment)
- Outcomes (e.g., outcomes measured, outcome definitions and sources of information, units of measure, upper and lower limits [for scales], time points at which the outcomes were assessed)

**STATISTICAL ANALYSIS**

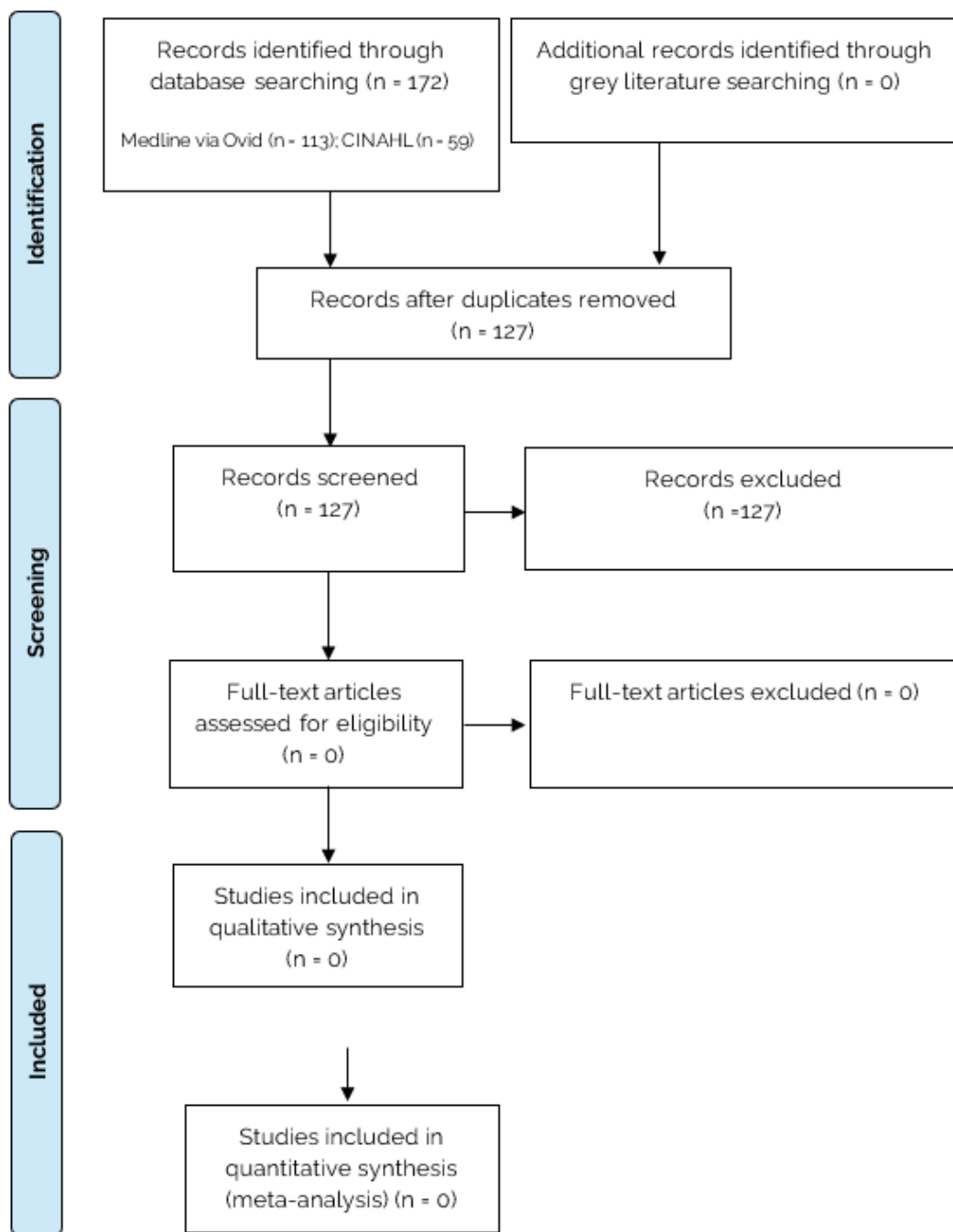
Results are summarized narratively. No additional statistical analyses were conducted beyond those reported in the primary studies.

**CRITICAL APPRAISAL OF EVIDENCE**

We did not undertake a formal critical appraisal of the included studies.

**Results****LITERATURE SEARCH**

The database search of quantitative preference evidence yielded 172 citations published from January 1, 2015, until the search date (April 22, 2022). There were 127 records after removing duplicates. No studies met our inclusion criteria. Figure 5 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the literature search for quantitative evidence of preferences and values.



**Figure 5: PRISMA Flow Diagram—Quantitative Evidence of Preferences and Values Search Strategy**

PRISMA flow diagram showing the quantitative evidence of preferences and values search strategy. The database search of quantitative preference evidence yielded 172 citations published between January 1, 2015, and April 22, 2022. After removing duplicates, we screened the abstracts of 127 studies; none of the studies met our inclusion criteria.

Abbreviations: CINAHL, Cumulative Index to Nursing and Allied Health Literature; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.<sup>32</sup>

**Discussion**

No studies met our inclusion criteria.

**Conclusions**

No studies met our inclusion criteria.

**Direct Patient Engagement****Methods****PARTNERSHIP PLAN**

The partnership plan for this health technology assessment (HTA) focused on consultation to examine the experiences of people who have been directly impacted by pre-eclampsia and their family members as caregivers. We engaged with participants via telephone interviews.

We conducted qualitative interviews, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people with pre-eclampsia, as well as the experiences of family members as caregivers.<sup>84</sup> The sensitive nature of exploring people's experiences of a health condition and their quality of life further supported our choice of methodology.

**PARTICIPANT OUTREACH**

We used an approach called purposive sampling,<sup>85-88</sup> which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of community organizations, clinical experts, and community-based health programs in Ontario that support pregnant people impacted by pre-eclampsia in an effort to increase the public's awareness of our engagement activity and to connect with people who would like to share their lived experiences.

**Inclusion Criteria**

We sought to speak with adults with lived experience of pre-eclampsia and different treatments. Participants did not have to have direct experience with PlGF-based biomarker testing given that access to prenatal care varies across Ontario.

**Exclusion Criteria**

We did not set exclusion criteria for participants who otherwise met the inclusion criteria.

**Participants**

For this project, we spoke with 25 people, including 24 individuals with lived experience with pre-eclampsia. Most of the participants had completed a singleton pregnancy and were not seeking prenatal care at the time of the interview. We also spoke with one family member who shared their experience as a caregiver.

Participants lived primarily in Southern Ontario and reported on their first pregnancy experience. Only one of the participants had direct experience with the health technology under review.

**APPROACH**

At the beginning of the interview, we explained the role of our organization, the purpose of this HTA the risks of participating in this engagement, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information

(Appendix 5) if requested. We then obtained participants' verbal consent before starting the interview. With the participants' consent, we audio-recorded and transcribed the interviews.

Interviews lasted approximately 20 to 60 minutes. The interview was semi-structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment international (HTAi) Interest Group on Patient and Citizen Involvement in Health Technology Assessment.<sup>89</sup> Questions focused on the impact of being diagnosed with pre-eclampsia, participants' experiences accessing care, and perceptions of the benefits or limitations of broad access to PlGF-based biomarker testing to help diagnose those with suspected pre-eclampsia. Please see Appendix 6 for the interview guide.

## DATA EXTRACTION AND ANALYSIS

We used a modified version of a grounded-theory methodology to analyze interview transcripts. This approach allowed us to organize and compare experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.<sup>90,91</sup> We used the qualitative data analysis software program NVivo<sup>92</sup> to identify and interpret patterns in the data. The patterns we identified allowed us to describe the impact pre-eclampsia and its associated treatments had on those interviewed.

## Results

### CARE JOURNEY

#### *Awareness of Pre-eclampsia*

Pre-existing knowledge of pre-eclampsia varied among those interviewed. However, the majority of participants reported having no prior knowledge of the condition or the associated symptoms and trusted their primary care provider to raise concerns.

*I really did not know what was normal or what was not. It was my first pregnancy, and I didn't have any experience with this. So, I had 100 percent blind faith in my care team.*

Several factors appeared to influence whether participants knew about pre-eclampsia or engaged in early health-seeking behaviours (e.g., access to primary care, being a medical professional, or having a known family history of pre-eclampsia or cardiovascular disease). Notably, those who had a general awareness of pre-eclampsia still found it challenging to recognize the signs and symptoms of pre-eclampsia throughout their pregnancy.

*My sister had pre-eclampsia and my husband is also a placental researcher, so he knows a lot about it. Although I knew what pre-eclampsia was, I didn't know what HELLP [hemodialysis, elevated liver enzymes, low platelets] syndrome was. It was really only after I gave birth when I realized I had pre-eclampsia; which is weird because I knew about it.*

Similarly, participants who had developed foundational knowledge of the condition through independent research or through lived experience caring for a family member or a friend with the condition experienced feelings of anxiety, denial, and uncertainty during their own pregnancies.

*I had a friend who actually delivered at 34 weeks due to pre-eclampsia. So, I had heard her experience and that spooked me out because I knew what she had to go through.*

*I'm part of a Reddit group for people who were pregnant at the same time as me and a few women in that group had pre-eclampsia; so, I knew the symptoms, but I was in denial. I was like, "nope, it's all fine—it's because I'm pregnant, that's all."*

In retrospect, most participants said they would have liked to have access to more information about pre-eclampsia and felt it may have given them an opportunity to better prepare for the possibility of an adverse health outcome. This shared value among those interviewed suggests that pregnant people likely face common barriers when trying to appraise symptoms of pre-eclampsia, particularly during their first pregnancy.

*I was due to see my doctor within a few days and probably would have mentioned it, but I don't know, it wasn't that striking. But I also wasn't aware of the symptoms of HELLP syndrome; so, I think the awareness would have helped me with that.*

*They framed it as "you were just very sick." If I was to advocate for stuff going forward, I think they should tell people what it is because I did not know—they said "sick" but when I think "sick," I think I have a cold.*

### **Symptom Monitoring**

When asked to recount any early signs or symptoms of pre-eclampsia, participants commonly reported experiencing significant swelling as well as elevated blood pressure. At the time, these symptoms were perceived to be an expected part of their pregnancy. When it became more challenging to manage the symptoms, particularly when it impacted their ability to work or maintain their daily routine, participants often raised their concerns with their clinicians or someone from their personal support network. In the absence of other signs or symptoms, participants reported that they were not immediately diagnosed with pre-eclampsia and instead advised to monitor the progression of their symptoms. The participants described how they navigated this uncertainty and shared that they were not always sure what kind of symptom progression would warrant medical intervention.

*I was like "mom, I feel like my feet are really swollen!" And I had the doctor measure my legs probably about two or three times. I was really concerned at this point because I couldn't wear anything but flip flops. At one point I couldn't bend my ankles because I was so full of fluid.*

*The only thing I would say after is like I had major swelling in my feet, but everyone told me that's normal after pregnancy.*

*I never understood it and I remember there being a bit of a conflict; like "we want to monitor you a little bit longer" but there was nothing to regulate. I don't believe at that time I was even told to check my blood pressure - I was simply told that if I'm not feeling better to come back.*

There were also reports of impaired vision, difficulty breathing, severe nausea, and upper-quadrant or back pain. Similarly, in the absence of other signs or symptoms, these were dismissed as being an expected part of pregnancy or due to an unrelated cause (for example, overexertion at work).

*I do remember having like kind of floaties when I close my eyes. It was not enough to make me call the doctor though.*

*I started getting spots in my eye—like I was working from home on modified duty due to my pregnancy and I would have to go to sleep.*

*I got quite lightheaded and dizzy several times, but like, I probably didn't eat enough that day or didn't drink enough water and things like that.*

Conversely, some participants did not experience any symptoms of pre-eclampsia throughout their pregnancy. The first signs or symptoms were only detected during a routine post-natal appointment and the diagnosis confirmed with additional testing (for example, a urinalysis). Participants recalled feeling surprised by the diagnosis, particularly in the later stages of their pregnancy. They also reported being closely monitored and, in certain cases, prescribed medication to help regulate elevated blood pressure or other associated symptoms after completing their pregnancy.

*I think what was so surprising to me about the whole thing is that I had a perfectly normal pregnancy up until that appointment. There was nothing! My blood pressure wasn't ever an issue ....*

Pre-eclampsia is often characterized as an unpredictable condition, and this is reflected in each participant's journey to diagnosis. When sharing their experiences, participants gave insight into how this uncertainty impacted their daily lives. Participants often felt that external factors, such as work, significantly impacted their decision-making and overall patient experience. For example, those who had a supportive employer felt it was easier to engage in health-seeking behaviours, whereas participants who did not have access to such support found it more challenging to make similar decisions. In all cases, participants agreed that symptom appraisal is complex for pregnant people with suspected pre-eclampsia and having equitable access to care is important.

*My blood pressure was really high, and I had a stressful job during my pregnancy. Actually, when I went in for that check-up at about 30 weeks, she [doctor] said, "your blood pressure so high—you have to go off work! This is unsafe." My job, though very stressful, is pretty flexible. I got to work from home and kind of make my own hours.*

*No, to be honest, I had a really bad employer that was fighting for me to stay on for as long as possible. I was about 38 weeks and didn't have much support at my office. I was kind of made to feel like I was doing them a disservice.*

*I have an amazing manager who from the day that I went into the hospital, I had to drop work unexpectedly [...]. She was really supportive, and she got all my work off my plate without me having to do anything. And that was of course really helpful because I was worried about that. I care a lot about my job*

*Right now, I have to go to a separate lab to get blood work done and you have to pay to get your results if you want to see them. There's the whole "do I want to pay \$12.00 to see my own results?" It's a whole kind of thing.*

Participants also highlighted how systemic factors such as emerging COVID-19 guidance, the patient–doctor dynamic, and limited hospital resources may have also impacted their ability to access care and self-advocate.



*I kept trying to get in touch with my doctor but because of COVID, it was very hard.*

*I felt really let down. I don't know why they didn't immediately just take me to labour and delivery when my blood pressure was that high. Like if they had just induced me, maybe I wouldn't have gone through everything else that I went through too.*

*So, sure enough we showed up there at 6:00 a.m. like they said, and they were like, "[W]e are swamped. We have all these inductions happening and we really can't take you in at this time. Somebody will call you when we have a bed for you."*

## IMPACT OF PRE-ECLAMPSIA

### *Physical Impacts*

Participants reported physical health outcomes that ranged in severity. Most were diagnosed with early onset or term pre-eclampsia and delivered via Caesarian section (C-section). Leading up to delivery, participants also frequently experienced an acute decline in their health, which prompted additional diagnostic testing. Those we interviewed said it was challenging to process any clinical information or give informed consent while trying to manage the physical impacts of pre-eclampsia. In some cases, participants reported having a spouse or family member act as a health care proxy and advocating on their behalf. It was also common for participants to learn the full extent of the physical impacts only after being discharged from the hospital and given access to their medical record.

*When I had a really confusing day with all these tests and I just felt overwhelmed, my husband dropped everything at work and spent the next day at the hospital with me so he could help advocate and talk to doctors with me.*

*I breastfed my first for over a year so, my husband knew that was important to me. I had no say in the matter at that time just because I was so sick and not healthy enough to make those decisions.*

*And then like, later in the night the pain medication helped a bit but then it got really bad again and I asked them if I could have more of that medication and they told me that if I had more it could possibly harm the baby. I was shocked—I didn't know I was taking a medication that could have affected the baby. I don't even know if they told me what I was taking. I was in quite a lot of pain, so it was hard to be an advocate for your health.*

Participants expressed that their priority while in recovery was the physical well-being of their baby. When reflecting on the physical impacts of pre-eclampsia, participants reported various adverse perinatal outcomes such as low birth weight, kidney disease, dehydration, heart murmurs, and clubfoot. While recovery often required extended stays in the neonatal intensive care unit (NICU), few participants reported needing specialized care a year after completing their pregnancy.

*It wasn't as stressful as I would have assumed it would be, but [this was] because my main focus was on my daughter.*

*Baby was delivered and she was three pounds, so she immediately went to the NICU. So he was born with clubfoot, which we knew at about 20 weeks, and when he was in the NICU they put some steroids in to try to help with the lung development. My baby passed all the stress*

*tests—he was happy, he was moving, his heart rate was solid. There was nothing going on with him.*

*Baby was in the NICU—she got taken right away because she was one pound 13 ounces. So, I was just down the hall from her, and it was nice to be able to at least be at the same hospital.*

In contrast, it was common for participants to receive treatment for adverse maternal health outcomes (such as, elevated blood pressure) several weeks after being discharged from the hospital. Several participants had to manage their condition under the supervision of a cardiologist and were prescribed blood pressure medication. Other participants reported that they joined a community-based health program to help reduce the physical impacts of pre-eclampsia. Some participants also opted to make lifestyle changes to further minimize their risk.

*The only thing that seemed to have stayed, and I'm actually still dealing with it now, is my high blood pressure.*

*My doctor connected me to the community vascular health program. And so, I work with like a health coach there and I'm able to work on goals to decrease my blood pressure and like stabilize it and just be like kind of in my best overall health.*

*I remember I had to be on the blood pressure medication for a couple of months at least before my blood pressure went back to normal.*

Reports of severe maternal health outcomes were often associated with cases of HELLP syndrome. While there were fewer accounts, the physical impacts of this syndrome were significant and life-threatening in most cases. Recovery for participants who were impacted by this condition often involved tertiary-level care and extended stays in the intensive care unit (ICU). One participant shared that they developed kidney disease after being diagnosed with pre-eclampsia and will now need specialized care for the rest of their life.

*The last thing I remember is that the next morning I went to the bathroom, I peed blood and then I had a grand mal seizure. And then the rest is kind of— ... I don't remember a lot.*

*I had some complications. During the birth, I hemorrhaged, so I lost a third of the volume of my blood and I came very close to dying. After transfusions and a longer hospital stay, there were then there were enzymes in my blood, so my liver was active and my blood pressure was also hard to manage.*

*I was just in a room with my husband, and I was in excruciating pain, and they just did the test to see if there was anything. Now, that thought terrifies me and it makes me kind of emotional to think about; if I had gone home, there's a really high potential that I could have seized and died. I had full blown HELLP syndrome, and nobody knew.*

*I've been on the phone all morning because I've been diagnosed with kidney disease. My kidneys are leaking a lot of protein, and I have to change my diet and take different medications; I had pre-eclampsia [that was] so bad that it damaged my kidneys for the rest of my life.*

The most serious potential consequence of pre-eclampsia is the loss of life. We spoke to individuals who had experienced spontaneous loss of their pregnancy due to severe complications from pre-eclampsia. The impact of this loss on the individuals and their families cannot be measured and those who shared their experience emphasized the importance of access to information and preventive care.

### *Emotional Impacts*

The emotional impacts of pre-eclampsia can be significant for patients and their families. Several participants identified the emotional aspect of their diagnosis as being a critical part of their care journey.

*You know, after major surgery you're not supposed to do anything but after you have a C-section, you're supposed to go to the hospital and take care of a child now. There's just that massive level of expectation out of you.*

*I can see how it's really hard if you don't have support to deal with the emotions after the emergency of it. You feel like you've been planning for the birth of your baby, and it's all taken from you so suddenly—you and your baby are sick and everything completely changes. You feel lost. I can understand why there's a lot of depression after a tragic birth like that.*

In fact, many participants reported feeling like they were not in a position to emotionally process their experience until much later in their care journey. Participants attributed this to several factors, including the physical impacts of the condition, lack of trust in the health care system, feeling unsure about how to navigate the perceptions of others after a traumatic birth, and feelings of guilt.

*I had post-traumatic stress disorder from the entire experience, and so I'm not at a point where I'm comfortable thinking about it [family planning], emotionally. Honestly, I feel like I fell through the cracks of the health care system and that I need to look out for myself and try to be there as long as I can for my child.*

*Now that I know all this, it kind of makes me very frustrated. You know, none of this was properly taken care of.*

*My husband wasn't allowed to stay with me, so I was now having to care for this baby without any support. And I was still very weak and very sick and trying to come out of this and I felt very, very isolated and unsure of what to do. How do I care for this baby? I'm still hooked up to all this, all these wires, and can barely get out of bed without support ... I just couldn't wait to get out of there after going to that room*

*Emotionally, it was a lot more difficult because I sort of had to come to terms with everything and there was stuff I didn't necessarily know until after the fact. Like, I did have a thought of, "Oh, I might not survive. What if I die?"*

While participants reported using different strategies to process the emotional impacts of the condition, access to mental health services and communities with a shared lived experience were particularly effective.

*So, I started going to somebody who specializes in like perinatal therapy last year and it's been really great. That has made a really big difference ... [in] my overall anxiety management.*

*That's something that I've had to work on, but I've become very aware of that I am by no means like a "better mom" because of what happened. I don't feel any more worthy because I lost so much blood and thought I was going to die. So, it's nice to see other people have the same thoughts— that's been very helpful for me.*

*So, I'm actually one of the best things I found was an app that has chat rooms where you can actually read on other women's experiences and journeys, and you can ask questions to other women. So, I actually found a lot of support in that.*

*I searched "HELLP Syndrome" and the Preeclampsia Foundation came up, and they had a kind of community forum where you could connect with others and that's where I found a lot of my research and similar stories. I was going through and reading what other people were talking about on this forum and then I had this really deep need to connect with others that truly understand what I went through.*

Participants also valued efforts made by the health care teams to provide patient-centred care and connecting them with different hospital resources throughout their care journey.

*I met with one of the social workers that they provide to parents who have babies in the NICU. So, she was amazing—she actually provided some taxi vouchers for me to be able to get to see baby while I was trying to recover, which was a huge, huge help since my husband and I had just taken a temporary leave of work.*

*The nurse practitioner at the hospital ... put me in contact with a therapist so I could do a session and that I found really, really helpful just to sort of process everything and talk it out. The other support that I got was the social worker. I asked to meet with her because my employer had pointed out to me that I might be eligible for a caregiver leave instead of maternity leave. So, I had to contact the social worker to get the doctor to fill out some form, so I thought I was just like asking for her administrative help but she was really amazing and her response was different than I expected—like she really asked me about my experience. And she told me that I could request a debrief meeting with the OB to talk about what happened.*

*And then the hospital does little ceremonies and different things—there was a candlelight ceremony where basically any like lost infants can be remembered. So, we joined that, which of course, because of COVID it was over Zoom at that time, but it was nice though that because we wouldn't have known about it unless the hospital told us about it.*

When reflecting on their experience, participants also expressed their appreciation for the support they received from caregivers, family members, and friends.

*I definitely spent a lot of time on my phone with family. I think that was my biggest support was my mom actually, even though she couldn't be with me in hospital, she actually took time off work and stayed at my aunt's so she could be close to the hospital in case anything happened. She wanted to be closer within, you know, a good timeframe if I needed her.*

*My husband was immensely supportive, and I think helped me get through it, but if he hadn't understood, or if he had been less supportive like—... It was weird emotions that weren't normal*

*and so if you don't understand that sometimes that can be frustrating for the partner, but he got me through it.*

*My husband was a huge support—I don't know what I would do without him. My husband was ... given [a list of] all these things that he was supposed to look out for, physically, for me. So, he would, like, go through this whole list of things they gave him every day.*

## PLGF-BASED BIOMARKER TESTING

All participants were presented with a general overview of the PLGF-based biomarker testing technology for pre-eclampsia risk prediction. Then they were asked to share their perspectives on prenatal care and what impact, based on their lived experience, broad access to PLGF-based biomarker testing to help diagnose pre-eclampsia would have had on themselves, their caregivers, or others with suspected pre-eclampsia.

### *Perceived Benefits*

Overall, participants had a strong preference for broad access to PLGF-based biomarker testing in Ontario. Key factors that informed this preference included the technology's perceived clinical effectiveness and minimal invasiveness. Those we spoke to did not express concerns over false positives, as they felt these risks could be mitigated through additional testing without causing harm. Overall, participants felt that the health technology aligned with their values, particularly as it relates to preventive and patient-centred care.

*Most definitely. I mean, just to give the doctors even just a little bit more information so that somebody doesn't end up in the NICU, right? They can have a more normal birth or get to have a longer pregnancy, [which] would probably help—that's something that always weighs on my mind. While she didn't stay in [there for] very long, are there going to be problems later on? So yeah, I think that that would be a great asset to all doctors. Even if you did get a false positive, so [what]? You have to do another one? I don't think that would be as terrible, especially if the blood clinic was close to the hospital or the clinic where your doctor is.*

*No. I don't see anything really wrong with it. I mean there could be a false positive, but I mean in my opinion, say you do get a false positive at that moment, that just means you are going to be monitored more closely. [...] I know when you're diagnosed, you get more ultrasounds and [...] more appointments. And if things don't go south and you just simply have that positive and your blood work turns out fine, your urine turns out fine, baby is fine—I mean, the longer you hold them in there, the better, right?*

*In terms of publicly funding, I think the healthier population and the more we protect mothers, the better. I know that even as bad as my case was, there are women out there that die. There's so much worse ... that can happen—I'm one of the lucky ones.*

Some participants commented that the technology may help to increase the public's general awareness of pre-eclampsia and its associated signs or symptoms. Participants also saw potential value in creating a shared language and a way to connect with others impacted by pre-eclampsia.

*One thing that comes to mind for me is that my family is older, and they had never heard the words "pre-eclampsia" or "HELLP syndrome." So, they even though some of them have gone through an experience like what I had or on a lesser scale, they only knew the term "toxemia."*

*I feel like maybe just a little bit like more support for [the postpartum period] would be nice. And I think maybe that's why I'm so excited about the [advocacy] event that's happening because it's a big voice that's going to bring awareness to it. And it's going to be people who really understand what it means, and we're all going to be there supporting each other in one space—I feel like that's really needed, especially the women who don't have their children or maybe a husband or a sister who lost their person to preeclampsia or HELLP syndrome.*

Lastly, participants expressed that they valued having access to their personal health information. Several participants described using their medical records to process the emotional impacts of pre-eclampsia. Given this, the potential to have access to test results earlier on during pregnancy was viewed favourably by all participants. They also felt that having access to this information may encourage patient self-advocacy and other health-seeking behaviours, particularly when making the transition from primary to emergency care.

*I think for me it's just access to information; even still, and a lot of my focus now, is for my girls to know how they would navigate this.*

*If it's an accurate test and [...] those people at high risk can get information sooner and they can know what to expect and feel like they have control of their health care plan. If you could think "I may not make it to term and I may have to have it C-section at some point," just knowing that things may go down a different road may help [individuals] process those emotions too.*

*Unfortunately, it is something that I've read a lot in my support group, [but] I find a lot of women are going into emergency care or labour and delivery and saying, "I have this wrong with me" and they're basically being told to go home—it's unfortunate. And I feel like maybe with a test like that, if it's in their file then maybe when they go to labour and delivery saying, "this and this," then they can look and be like, "okay, well you are at high risk of pre-eclampsia."*

#### **Additional Considerations**

When considering broad access to PlGF-based biomarker testing to help diagnose pre-eclampsia, several participants had conflicting preferences when it came to access to information and shared decision-making. Some participants felt that accessing the results of their PlGF-based biomarker test without a scheduled follow-up with their doctor may increase their anxiety and negatively impact their experience as a patient. While some advocated for the timely release of the results, the majority of those we spoke to valued having access to the information with their doctor present to explain the results and how it potentially relates to other diagnostic tests.

*That's actually a hard question because I like the portal—I get to access it quickly and I may not know exactly what it means [but] I'm one of those people who will see what the blood work says and Google it to learn what specific blood test is for and what numbers mean. On the other hand, when I have these results, if I can't find the answers that I want, I'm stuck waiting for a doctor to explain them to me and then I feel like the anxiety kicks in even more. I feel like it is nice to be able to have a physician there to explain to you what the results mean.*

*Personally, I would want the information—I know having a long background in health care, that the information can be a little bit dangerous in some hands too. For myself, I would feel comfortable accessing the information and I think because I tend to do more research than maybe the average person just on my own.*

*I think I would prefer my doctor to have it first because I feel like I would end up like Googling things and freaking myself out.*

*As much as I'm an impatient person and like information right away, I do think it's probably better to get the information from a physician because it can be scary to get some sort of result and not really know what it means.*

There was also a shared value among the participants for accessible care. Several participants reflected on potential barriers to accessing the technology and they emphasized the PLGF-based biomarker test should be accessible through different health institutions (e.g., walk-in-clinics, family doctors' offices, and hospitals) across Ontario so that barriers are not introduced for those living in underserved populations.

*However, I would like to see this test be more standard in prenatal care. And I would hope standardizing things like this does reduce barriers.*

*So, I cannot imagine how much worse it could be if I didn't hold those privileges and identities—because I'm well aware that maternal health outcomes are worse for racialized women, for example.*

*I just think that it would be a benefit—I have met women who just go to walk-in clinics—like they don't have a family doctor so they have to go into a walk-in clinic, [which will] follow the pregnancy up until whatever point. I just would think it would be stressful going somewhere and then not being able to get that medical information.*

Lastly, some participants considered the potential ancillary costs associated with the test, such as travel costs, time off work, and fees to access blood test results. Many felt that consideration should be given to each patient's unique circumstance and that alternatives be made available to mitigate these costs as much as possible.

*When I answer the question, I'm thinking about my privilege. I live near a major hospital., I can access private blood work if I want—you know what I mean? That wasn't a barrier for me, but I can imagine it would be for some.*

*If they could, if the blood test could be tied in with one of those regular visits, I feel like that would be ideal. And then not having to pay for the results would be ideal because if I remember right, pre-eclampsia disproportionately affects people [with a] lower socioeconomic status. So yeah, making people pay for the results would not be favourable for that population and I would be in favour of Ontario funding that [PLGF-based biomarker testing] so that people can get access to that information. So, it's more equitable across all socioeconomic statuses, right?*

## Discussion

Participants provided diverse perspectives on PLGF-based biomarker testing to help diagnose pre-eclampsia in those with suspected pre-eclampsia. Direct engagement was conducted through telephone interviews and allowed for a thorough examination of the impact of pre-eclampsia on the health, emotional well-being, and decision-making processes of individuals as well as their family members as caregivers.

All interviewed participants had been impacted by pre-eclampsia during their pregnancy or identified as a family member who supported a pregnant person through their experience with pre-eclampsia. Each participant shared their experience monitoring symptoms and accessing prenatal care after or leading up to a pre-eclampsia diagnosis. Detailed accounts of the emotional, physical, and work-life impacts of pre-eclampsia on themselves, their pregnancies, their families' experience as caregivers were shared. The impacts of pre-eclampsia were then further discussed in the context of the participant's preferences and values.

Potential limitations of our engagement included the burden of participation in the context of the health condition and the accessibility of the PlGF-based biomarker tests, with only one participant having direct experience with the technology. Despite this, all of the participants were able to comment on the potential impact of broad access to PlGF-based biomarker testing from multiple perspectives (e.g., individual, caregiver, and societal) using their lived experience as a reference. In this way, direct engagement through interviews generated a robust thematic analysis of diverse perspectives and values among pregnant people seeking prenatal care for suspected pre-eclampsia.

## Conclusions

If undetected or left untreated, pre-eclampsia may result in serious health complications for a pregnant person and their baby. Access to PlGF-based biomarker testing to help diagnose pre-eclampsia in pregnant people with suspected pre-eclampsia was viewed favourably by those interviewed. The health technology was perceived to be minimally invasive and aligned with the participants' values and preferences. Moreover, PlGF-based biomarker testing was perceived to be equally beneficial for family members and caregivers who may act as the health care proxy in an emergency. Participants having lived experienced with pre-eclampsia valued the potential medical benefits of PlGF-based biomarker testing and emphasized that patient education and equitable access are important considerations for implementation of the test in Ontario.



# Conclusions of the Health Technology Assessment

Compared with standard clinical assessment alone in patients with suspected pre-eclampsia (between 20 weeks and 36 weeks + 6 days' gestation), PLGF-based biomarker testing (e.g., Elecsys ratio, DELFIA PLGF) as an adjunct to standard clinical assessment:

- Likely improves prediction of pre-eclampsia (Elecsys ratio, DELFIA PLGF, Triage PLGF)
- May reduce:
  - Time to pre-eclampsia diagnosis (Triage PLGF)
  - Severe adverse maternal outcomes (Triage PLGF)
  - Length of stay in the neonatal intensive care unit (Triage PLGF)
- May result in little to no difference in:
  - Time to delivery
  - Gestational age at delivery
  - Preterm delivery
  - Maternal admission to hospital
  - Perinatal/neonatal adverse outcomes
  - Neonatal admission to hospital/specialist care unit
  - Maternal length of stay in hospital

Our economic literature review identified 13 relevant studies, which showed that PLGF-based biomarker testing was cost-effective for use in people with suspected pre-eclampsia, but with some uncertainties. None of the included studies was directly applicable to the Ontario setting.

We estimated that publicly funding PLGF-based biomarker testing in Ontario would result in additional costs of \$0.27 million in year 1 to \$0.46 million in year 5, for a total additional cost of \$1.83 million over the next 5 years.

Publicly funding PLGF-based biomarker testing to help diagnose pre-eclampsia was viewed favourably by those interviewed. Our direct engagement demonstrated that there are several factors that influence symptom management in people with suspected pre-eclampsia and that health-risk appraisal can be challenging. The majority of the participants perceived PLGF biomarker testing to be minimally invasive and aligned with their values and preferences around patient-centred care. Overall, those with lived experience with pre-eclampsia and their family members valued the potential medical benefits of PLGF-based biomarker testing and emphasized that patient education and equitable access are important considerations for implementation of the test in Ontario.

# Abbreviations

**ASA:** acetylsalicylic acid  
**BMI:** body mass index  
**BORN:** Better Outcomes Registry & Network  
**CI:** confidence interval  
**CINAHL:** Cumulative Index to Nursing and Allied Health Literature  
**GA:** gestational age  
**GRADE:** Grading of Recommendations Assessment, Development, and Evaluation  
**HELLP:** hemolysis, elevated liver enzymes, low platelet count  
**HTA:** health technology assessment  
**ICER:** incremental cost-effectiveness ratio  
**ISSHP:** International Society for the Study of Hypertension in Pregnancy  
**NHS:** National Health Service  
**NHSEED:** NHS Economic Evaluation Database  
**NICE:** National Institute for Health and Care Excellence  
**NICU:** neonatal intensive care unit  
**NPV:** negative predictive value  
**OR:** odds ratio  
**PE:** pre-eclampsia  
**PLGF:** placenta growth factor  
**PPV:** positive predictive value  
**PRESS:** peer review of electronic search strategies  
**QALY:** quality-adjusted life-year  
**QUADAS-2:** Quality of Diagnostic Accuracy Studies 2  
**RCT:** randomized controlled trial  
**RR:** relative risk  
**SD:** standard deviation  
**sFlt-1:** soluble fms-like tyrosine kinase-1  
**SOGC:** Society of Obstetrician and Gynecologists of Canada  
**VEGFR1:** vascular endothelial growth factor receptor 1

# Glossary

**Adverse event:** An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.

**Base case:** In economic evaluations, the base case is the "best guess" scenario, including any assumptions, considered most likely to be accurate. In health technology assessments conducted by Ontario Health, the reference case is used as the base case.

**Budget impact analysis:** A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).

**Cost-benefit analysis:** A cost-benefit analysis is a type of economic evaluation that expresses the effects of a health care intervention in terms of a monetary value so that these effects can be compared with costs. Results can be reported either as a ratio of costs to benefits or as a simple sum that represents the net benefit (or net loss) of one intervention over another. The monetary valuation of the different intervention effects is based on either prices that are revealed by markets or an individual or societal willingness-to-pay value.

**Cost-consequence analysis:** A cost-consequence analysis is a type of economic evaluation that estimates the costs and consequences (i.e., the health outcomes) of two or more health care interventions. In this type of analysis, the costs are presented separately from the consequences.

**Cost-effective:** A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.

**Cost-effectiveness analysis:** Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost-utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.

**Cost-utility analysis:** A cost-utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost-utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.

**Decision tree:** A decision tree is a type of economic model used to assess the costs and benefits of two or more alternative health care interventions. Each intervention may be associated with different

outcomes, which are represented by distinct branches in the tree. Each outcome may have a different probability of occurring and may lead to different costs and benefits.

**Deterministic sensitivity analysis:** Deterministic sensitivity analysis is an approach used to explore uncertainty in the results of an economic evaluation by varying parameter values to observe the potential impact on the cost-effectiveness of the health care intervention of interest. One-way sensitivity analysis accounts for uncertainty in parameter values one at a time, whereas multiway sensitivity analysis accounts for uncertainty in a combination of parameter values simultaneously.

**Dominant:** A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).

**Health-related quality of life:** Health-related quality of life is a measure of the impact of a health care intervention on a person's health. It includes the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction. that represents a person's loss of productivity due to disability, illness, or premature death.

**Incremental cost:** The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.

**Incremental cost-effectiveness ratio (ICER):** The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.

**Multiway sensitivity analysis:** A multiway sensitivity analysis is used to explore uncertainty in the results of an economic evaluation. It is done by varying a combination of model input (i.e., parameter) values simultaneously between plausible extremes to observe the potential impact on the cost-effectiveness of the health care intervention of interest.

**One-way sensitivity analysis:** A one-way sensitivity analysis is used to explore uncertainty in the results of an economic evaluation. It is done by varying one model input (i.e., a parameter) at a time between its minimum and maximum values to observe the potential impact on the cost-effectiveness of the health care intervention of interest.

**Quality-adjusted life-year (QALY):** The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost-utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.

**Reference case:** The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.

**Risk difference:** Risk difference is the difference in the risk of an outcome occurring between one health care intervention and an alternative intervention.

**Scenario analysis:** A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.

**Sensitivity analysis:** Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.

**Standard gamble:** In economic evaluations, standard gamble is a direct method of measuring people's preferences for various health states. In a standard gamble, respondents are asked about their preference for either (a) remaining in a certain health state for the rest of their life, or (b) a gamble scenario in which there is a chance of having optimal health for the rest of one's life but also a chance of dying immediately. Respondents are surveyed repeatedly, with the risk of immediate death varying each time (e.g., 75% chance of optimal health, 25% chance of immediate death) until they are indifferent about their choice. The standard gamble is considered the gold standard for eliciting preferences as it incorporates individual risk attitudes, unlike other methods of eliciting preferences.

**Time horizon:** In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

**Time trade-off:** In economic evaluations, time trade-off is a direct method of measuring people's preferences for various health states. In a time-trade off, respondents are asked about their preference for either (a) living with a chronic health condition for a certain amount of time, followed by death, or (b) living in optimal health but for less time than in scenario (a). That is, respondents decide how much time in good health they would be willing to "trade off" for more time spent in poorer health. Respondents are surveyed repeatedly, with the amount of time spent in optimal health varying each time until they are indifferent about their choice.

**Uptake rate:** In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.

**Utility:** A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.

**Willingness-to-pay value:** A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost-utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

# Appendices

## Appendix 1: Literature Search Strategies

### *Clinical Evidence Search*

**Search date:** April 14, 2022

**Databases searched:** Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CRD Health Technology Assessment Database, NHS Economic Evaluation Database, and CINAHL

**Database segments:** Database: EBM Reviews—Cochrane Central Register of Controlled Trials <March 2022>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to April 13, 2022>, EBM Reviews—Health Technology Assessment <4th Quarter 2016>, EBM Reviews—NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2022 Week 14>, Ovid MEDLINE(R) ALL <1946 to April 13, 2022>

### Search strategy:

- 
- 1 Pre-eclampsia/ (64496)
  - 2 (preeclamp\* or pre eclamp\* or ((suspect\* or predic\* or diagnos\*) adj3 PE)).ti,ab,kf. (107567)
  - 3 ((pregnan\* or gestat\* or matern\*) adj3 tox?emi\*).ti,ab,kf. (6132)
  - 4 ((edema adj2 proteinuria adj2 hypertension) or EPH complex or EPH gestosis).ti,ab,kf. (1252)
  - 5 or/1-4 (128286)
  - 6 Placenta Growth Factor/ (8483)
  - 7 (Placenta\* growth factor\* or PlGF or PGF).ti,ab,kf. (24703)
  - 8 Vascular Endothelial Growth Factor Receptor-1/bl [Blood] (1127)
  - 9 (VEGFR1 or sVEGFR1 or VEGFR 1 or sVEGFR 1).ti,ab,kf. (9044)
  - 10 Maternal Serum Screening Tests/ (898)
  - 11 Serologic Tests/ (102922)
  - 12 Pregnancy Proteins/an, bl [Analysis, Blood] (2416)
  - 13 Membrane Proteins/bl [Blood] (3305)
  - 14 Biological Markers/bl [Blood] (139521)
  - 15 soluble fms-like tyrosine kinase\*.ti,ab,kf. (3420)
  - 16 ((fms-like tyrosine kinase\* or FLT 1 or sFLT 1 or FLT1 or sFLT1) and (triage or test\* or assay\* or immunoassay\* or diagnos\* or detect\* or screen\* or measur\* or analys\* or analyz\* or determin\* or sensitivity or specificity or accuracy or accurate or assessment\* or predict\* or positive or negative or electrochemiluminescen\* or ratio or ratios)).ti,ab,kf. (12376)
  - 17 (alere\* or BRAHMS\* or DELFIA\* or elecsys\* or kryptor\* or perkinelmer\* or quidel\* or roche\* or thermo fisher\* or thermofisher\* or xpress\*).ti,ab,kf. (68243)
  - 18 or/6-17 (355822)
  - 19 5 and 18 (8595)
  - 20 exp Animals/ not Humans/ (16600291)
  - 21 19 not 20 (6282)
  - 22 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (6052416)
  - 23 21 not 22 (6053)
  - 24 limit 23 to english language [Limit not valid in CDSR; records were retained] (5798)
  - 25 limit 24 to yr="2015 -Current" (3480)

26 25 use medall,coch,cctr,clhta,cleed (2015)  
 27 preeclampsia/ (96265)  
 28 (preeclamp\* or pre eclamp\* or ((suspect\* or predic\* or diagnos\*) adj3 PE)).tw,kw,kf. (108146)  
 29 ((pregnan\* or gestat\* or matern\*) adj3 tox?emi\*).tw,kw,kf. (6172)  
 30 ((edema adj2 proteinuria adj2 hypertension) or EPH complex or EPH gestosis).tw,kw,kf. (1266)  
 31 or/27-30 (134746)  
 32 placental growth factor/ (6343)  
 33 (Placenta\* growth factor\* or PlGF or PGF).tw,kw,kf,dv. (24742)  
 34 vasculotropin receptor 1/ (10975)  
 35 (VEGFR1 or sVEGFR1 or VEGFR 1 or sVEGFR 1).tw,kw,kf,dv. (9051)  
 36 maternal serum screening test/ (893)  
 37 serology/ (82121)  
 38 placenta protein/ (2270)  
 39 membrane protein/ (288223)  
 40 biological marker/ (705128)  
 41 or/39-40 (988630)  
 42 exp blood/ (3454984)  
 43 41 and 42 (153569)  
 44 soluble fms-like tyrosine kinase\*.tw,kw,kf,dv. (3425)  
 45 ((fms-like tyrosine kinase\* or FLT 1 or sFLT 1 or FLT1 or sFLT1) and (trriage or test\* or assay\* or immunoassay\* or diagnos\* or detect\* or screen\* or measur\* or analys\* or analyz\* or determin\* or sensitivity or specificity or accuracy or accurate or assessment\* or predict\* or positive or negative or electrochemiluminescen\* or ratio or ratios)).tw,kw,kf,dv. (12392)  
 46 (alere\* or BRAHMS\* or DELFIA\* or elecsys\* or kryptor\* or perkinelmer\* or quidel\* or roche\* or thermo fisher\* or thermofisher\* or xpress\*).tw,kw,kf,dv. (104544)  
 47 or/32-38.43-46 (385711)  
 48 31 and 47 (8468)  
 49 (exp animal/ or nonhuman/) not exp human/ (11391608)  
 50 48 not 49 (7790)  
 51 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (12487700)  
 52 50 not 51 (5864)  
 53 limit 52 to english language [Limit not valid in CDSR; records were retained] (5575)  
 54 limit 53 to yr="2015 -Current" (3207)  
 55 54 use emez (1781)  
 56 26 or 55 (3796)  
 57 53 use medall (2166)  
 58 56 use emez (1781)  
 59 53 use cctr (185)  
 60 53 use coch (30)  
 61 53 use cleed (2)  
 62 53 use clhta (3)  
 63 remove duplicates from 56 (2572)



## CINAHL

| #  | Query   | Results   |
|--|---|-----------|
| S1   | (MH "Pre-Eclampsia+")   | 10,059    |
| S2   | (preeclamp* or pre eclamp* or ((suspect* or predic* or diagnos*) N3 PE))  | 16,908    |
| S3   | ((pregnan* or gestat* or matern*) N3 (toxemi* or toxaemi*))   | 85        |
| S4   | (edema N2 proteinuria N2 hypertension) or EPH complex or EPH gestosis)  | 41        |
| S5   | S1 OR S2 OR S3 OR S4  | 17,272    |
| S6   | (MH "Placenta Growth Factor")   | 28        |
| S7   | (Placenta* growth factor* or PLGF or PGF)   | 1,441     |
| S8   | (MM "Vascular Endothelial Growth Factors")  | 1,264     |
| S9   | (VEGFR1 or sVEGFR1 or VEGFR 1 or sVEGFR 1)  | 218       |
| S10  | (MM "Serologic Tests")  | 695       |
| S11  | (MH "Pregnancy Proteins/BL")  | 358       |
| S12  | (MH "Membrane Proteins")  | 17,056    |
| S13  | (MH "Blood+")   | 74,542    |
| S14  | S12 AND S13   | 913       |
| S15  | (MH "Biological Markers/BL")  | 18,640    |
| S16  | soluble fms-like tyrosine kinase*   | 646       |
| S17  | ((fms-like tyrosine kinase* or FLT 1 or sFLT 1 or FLT1 or sFLT1) and (trriage or test* or assay* or immunoassay* or diagnos* or detect* or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen* or ratio or ratios)) | 825       |
| S18  | (alere* or BRAHMS* or DELFIA* or elecsys* or kryptor* or perkinelmer* or quidel* or roche* or thermo fisher* or thermofisher* or xpress*)   | 9,876     |
| S19  | S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S14 OR S15 OR S16 OR S17 OR S18   | 33,152    |
| S20  | S5 AND S19  | 1,351     |
| S21  | PT (Case Study or Commentary or Editorial or Letter or Proceedings)   | 1,323,608 |
| S22  | S20 not S21   | 1,267     |
| S23  | S20 not S21   |           |
| Limiters - English Language                                    |   | 1,266     |
| S24  | S20 not S21   |           |
| Limiters - Published Date: 20150101-20221231; English Language |   | 696       |

**Economic Evaluation and Cost Effectiveness Search**

Search date: April 21, 2022

**Databases searched:** Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, National Health Service (NHS) Economic Evaluation Database, and CINAHL

**Database segments:** EBM Reviews - Cochrane Central Register of Controlled Trials <March 2022>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to April 20, 2022>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2022 Week 15>, Ovid MEDLINE(R) ALL <1946 to April 19, 2022>

## Search strategy:

- 
- 1 Pre-Eclampsia/ (64529)
  - 2 (preeclamp\* or pre eclamp\* or ((suspect\* or predic\* or diagnos\*) adj3 PE)).ti,ab,kf. (107674)
  - 3 ((pregnan\* or gestat\* or matern\*) adj3 tox?emi\*).ti,ab,kf. (6132)
  - 4 ((edema adj2 proteinuria adj2 hypertension) or EPH complex or EPH gestosis).ti,ab,kf. (1252)
  - 5 or/1-4 (128392)
  - 6 Placenta Growth Factor/ (8494)
  - 7 (Placenta\* growth factor\* or PlGF or PGF).ti,ab,kf. (24714)
  - 8 Vascular Endothelial Growth Factor Receptor-1/bl [Blood] (1128)
  - 9 (VEGFR1 or sVEGFR1 or VEGFR 1 or sVEGFR 1).ti,ab,kf. (9049)
  - 10 Maternal Serum Screening Tests/ (899)
  - 11 Serologic Tests/ (103020)
  - 12 Pregnancy Proteins/an, bl [Analysis, Blood] (2416)
  - 13 Membrane Proteins/bl [Blood] (3306)
  - 14 Biological Markers/bl [Blood] (139562)
  - 15 soluble fms-like tyrosine kinase\*.ti,ab,kf. (3424)
  - 16 ((fms-like tyrosine kinase\* or FLT 1 or sFLT 1 or FLT1 or sFLT1) and (triage or test\* or assay\* or immunoassay\* or diagnos\* or detect\* or screen\* or measur\* or analys\* or analyz\* or determin\* or sensitivity or specificity or accuracy or accurate or assessment\* or predict\* or positive or negative or electrochemiluminescen\* or ratio or ratios)).ti,ab,kf. (12383)
  - 17 (alere\* or BRAHMS\* or DELFIA\* or elecsys\* or kryptor\* or perkinelmer\* or quidel\* or roche\* or thermo fisher\* or thermofisher\* or xpress\*).ti,ab,kf. (68276)
  - 18 or/6-17 (356018)
  - 19 5 and 18 (8601)
  - 20 19 use coch,clhta,cleed (5)
  - 21 economics/ (263731)
  - 22 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (979428)
  - 23 economics.fs. (467315)
  - 24 (econom\* or price or prices or pricing or priced or discount\* or expenditure\* or budget\* or pharmaco-economic\* or pharmaco-economic\*).ti,ab,kf. (1145780)
  - 25 exp "costs and cost analysis"/ (654383)
  - 26 (cost or costs or costing or costly).ti. (311418)
  - 27 cost effective\*.ti,ab,kf. (411305)
  - 28 (cost\* adj2 (util\* or efficacy\* or benefit\* or minimi\* or analy\* or saving\* or estimate\* or allocation or control or sharing or instrument\* or technolog\*)).ab,kf. (269205)
  - 29 models, economic/ (15295)
  - 30 markov chains/ or monte carlo method/ (99581)
  - 31 (decision adj1 (tree\* or analy\* or model\*)).ti,ab,kf. (58224)
  - 32 (markov or markow or monte carlo).ti,ab,kf. (163695)
  - 33 quality-adjusted life years/ (50587)
  - 34 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (99655)
  - 35 ((adjusted adj1 (quality or life)) or (willing\* adj2 pay) or sensitivity analys\*s).ti,ab,kf. (167976)
  - 36 or/21-35 (3105867)
  - 37 19 and 36 (218)
  - 38 37 use medall,cctr (90)

- 39 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)),pt. or Congress.pt. (6056428)
- 40 38 not 39 (90)
- 41 20 or 40 (95)
- 42 limit 41 to english language [Limit not valid in CDSR; records were retained] (91)
- 43 limit 42 to yr="2015 -Current" (63)
- 44 preeclampsia/ (96376)
- 45 (preeclamp\* or pre eclamp\* or ((suspect\* or predic\* or diagnos\*) adj3 PE)).tw,kw,kf. (108253)
- 46 ((pregnan\* or gestat\* or matern\*) adj3 tox?emi\*).tw,kw,kf. (6172)
- 47 ((edema adj2 proteinuria adj2 hypertension) or EPH complex or EPH gestosis).tw,kw,kf. (1266)
- 48 or/44-47 (134875)
- 49 placental growth factor/ (6348)
- 50 (Placenta\* growth factor\* or PlGF or PGF).tw,kw,kf,dv. (24753)
- 51 vasculotropin receptor 1/ (10988)
- 52 (VEGFR1 or sVEGFR1 or VEGFR 1 or sVEGFR 1).tw,kw,kf,dv. (9056)
- 53 maternal serum screening test/ (894)
- 54 serology/ (82207)
- 55 placenta protein/ (2270)
- 56 membrane protein/ (288517)
- 57 biological marker/ (706354)
- 58 or/56-57 (990147)
- 59 exp blood/ (3457499)
- 60 58 and 59 (153663)
- 61 soluble fms-like tyrosine kinase\*.tw,kw,kf,dv. (3429)
- 62 ((fms-like tyrosine kinase\* or FLT 1 or sFLT 1 or FLT1 or sFLT1) and (triage or test\* or assay\* or immunoassay\* or diagnos\* or detect\* or screen\* or measur\* or analys\* or analyz\* or determin\* or sensitivity or specificity or accuracy or accurate or assessment\* or predict\* or positive or negative or electrochemiluminescen\* or ratio or ratios)).tw,kw,kf,dv. (12399)
- 63 (alere\* or BRAHMS\* or DELFIA\* or elecsys\* or kryptor\* or perkinelmer\* or quidel\* or roche\* or thermo fisher\* or thermofisher\* or xpress\*).tw,kw,kf,dv. (104673)
- 64 or/49-55,60-63 (386046)
- 65 48 and 64 (8475)
- 66 Economics/ (263731)
- 67 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (141920)
- 68 Economic Aspect/ or exp Economic Evaluation/ (521553)
- 69 (econom\* or price or prices or pricing or priced or discount\* or expenditure\* or budget\* or pharmaco-economic\* or pharmaco-economic\*).tw,kw,kf. (1166669)
- 70 exp "Cost"/ (654383)
- 71 (cost or costs or costing or costly).ti. (311418)
- 72 cost effective\*.tw,kw,kf. (421203)
- 73 (cost\* adj2 (util\* or efficac\* or benefit\* or minimi\* or analy\* or saving\* or estimate\* or allocation or control or sharing or instrument\* or technolog\*)).ab,kw,kf. (279943)
- 74 Monte Carlo Method/ (77574)
- 75 (decision adj1 (tree\* or analy\* or model\*)).tw,kw,kf. (61648)
- 76 (markov or markow or monte carlo).tw,kw,kf. (167177)
- 77 Quality-Adjusted Life Years/ (50587)
- 78 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (103143)
- 79 ((adjusted adj1 (quality or life)) or (willing\* adj2 pay) or sensitivity analys\*s).tw,kw,kf. (188988)

80 or/66-79 (2659612)  
 81 65 and 80 (240)  
 82 81 use emez (145)  
 83 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (12493496)  
 84 82 not 83 (88)  
 85 limit 84 to english language [Limit not valid in CDSR; records were retained] (85)  
 86 limit 85 to yr="2015 -Current" (56)  
 87 43 or 86 (119)  
 88 87 use medall (48)  
 89 87 use emez (56)  
 90 87 use coch (1)  
 91 87 use cctr (11)  
 92 87 use cleed (0)  
 93 87 use clhta (3)  
 94 remove duplicates from 87 (87)

## CINAHL

| #   | Query   | Results |
|-----|---|---------|
| S1  | (MH "Pre-Eclampsia+")   | 10,078  |
| S2  | (preeclamp* or pre eclamp* or ((suspect* or predic* or diagnos*) N3 PE))  | 16,917  |
| S3  | ((pregnan* or gestat* or matern*) N3 (toxemi* or toxaemi*))   | 85      |
| S4  | (edema N2 proteinuria N2 hypertension) or EPH complex or EPH gestosis)  | 41      |
| S5  | S1 OR S2 OR S3 OR S4  | 17,281  |
| S6  | (MH "Placenta Growth Factor")   | 28      |
| S7  | (Placenta* growth factor* or PLGF or PGF)   | 1,443   |
| S8  | (MM "Vascular Endothelial Growth Factors")  | 1,264   |
| S9  | (VEGFR1 or sVEGFR1 or VEGFR 1 or sVEGFR 1)  | 219     |
| S10 | (MM "Serologic Tests")  | 695     |
| S11 | (MH "Pregnancy Proteins/BL")  | 358     |
| S12 | (MH "Membrane Proteins")  | 17,072  |
| S13 | (MH "Blood+")   | 74,592  |
| S14 | S12 AND S13   | 914     |
| S15 | (MH "Biological Markers/BL")  | 18,630  |
| S16 | soluble fms-like tyrosine kinase*   | 646     |
| S17 | ((fms-like tyrosine kinase* or FLT 1 or sFLT 1 or FLT1 or sFLT1) and (trriage or test* or assay* or immunoassay* or diagnos* or detect* or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen* or ratio or ratios)) | 826     |
| S18 | (alere* or BRAHMS* or DELFIA* or elecsys* or kryptor* or perkinelmer* or quidel* or roche* or thermo fisher* or thermofisher* or xpress*)   | 9,884   |
| S19 | S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S14 OR S15 OR S16 OR S17 OR S18   | 33,154  |
| S20 | S5 AND S19  | 1,352   |
| S21 | (MH "Economics")  | 14,741  |
| S22 | (MH "Economic Aspects of Illness")  | 10,803  |
| S23 | (MH "Economic Value of Life")   | 671     |
| S24 | MH "Economics, Dental"  | 154     |
| S25 | MH "Economics, Pharmaceutical"  | 2,372   |

S26 MW "ec" 194,806  
 S27 (econom\* or price or prices or pricing or priced or discount\* or expenditure\* or budget\* or pharmaco-economic\* or pharmaco-economic\*) 337,847  
 S28 (MH "Costs and Cost Analysis+") 130,779  
 S29 TI cost\* 59,833  
 S30 (cost effective\*) 48,293  
 S31 AB (cost\* N2 (util\* or efficacy\* or benefit\* or minimi\* or analy\* or saving\* or estimate\* or allocation or control or sharing or instrument\* or technolog\*)) 38,291  
 S32 (decision N1 (tree\* or analy\* or model\*)) 10,523  
 S33 (markov or markow or monte carlo) 7,287  
 S34 (MH "Quality-Adjusted Life Years") 5,690  
 S35 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs) 14,106  
 S36 ((adjusted N1 (quality or life)) or (willing\* N2 pay) or sensitivity analysis or sensitivity analyses) 23,177  
 S37 S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 461,002  
 S38 S20 AND S37 41  
 S39 PT (Case Study or Commentary or Editorial or Letter or Proceedings) 1,325,092  
 S40 S38 NOT S39 40  
 S41 S38 NOT S39  
 Limiters - English Language 40  
 S42 S38 NOT S39  
 Limiters - Published Date: 20150101-20221231; English Language 24

### ***Quantitative Evidence of Preferences and Values Search***

**Search date:** April 22, 2022

**Databases searched:** Ovid MEDLINE, Cumulative Index to Nursing & Allied Health Literature (CINAHL)

**Search filter used:** Quantitative preference evidence filter, modified from Selva et al<sup>83</sup>

**Database segment:** Ovid MEDLINE(R) ALL <1946 to April 21, 2022>

**Search strategy:**

- 
- 1 Pre-Eclampsia/ (33931)
  - 2 (preeclamp\* or pre eclamp\* or ((suspect\* or predic\* or diagnos\*) adj3 PE)).ti,ab,kf. (40794)
  - 3 ((pregnan\* or gestat\* or matern\*) adj3 tox?emi\*).ti,ab,kf. (4898)
  - 4 ((edema adj2 proteinuria adj2 hypertension) or EPH complex or EPH gestosis).ti,ab,kf. (598)
  - 5 or/1-4 (52839)
  - 6 Placenta Growth Factor/ (2097)
  - 7 (Placenta\* growth factor\* or PlGF or PGF).ti,ab,kf. (8580)
  - 8 Vascular Endothelial Growth Factor Receptor-1/bl [Blood] (1126)
  - 9 (VEGFR1 or sVEGFR1 or VEGFR 1 or sVEGFR 1).ti,ab,kf. (3294)
  - 10 Maternal Serum Screening Tests/ (571)
  - 11 Serologic Tests/ (21542)
  - 12 Pregnancy Proteins/an, bl [Analysis, Blood] (2146)
  - 13 Membrane Proteins/bl [Blood] (3306)
  - 14 Biological Markers/bl [Blood] (139557)
  - 15 soluble fms-like tyrosine kinase\*.ti,ab,kf. (1382)

- 16 ((fms-like tyrosine kinase\* or FLT 1 or sFLT 1 or FLT1 or sFLT1) and (triage or test\* or assay\* or immunoassay\* or diagnos\* or detect\* or screen\* or measur\* or analys\* or analyz\* or determin\* or sensitivity or specificity or accuracy or accurate or assessment\* or predict\* or positive or negative or electrochemiluminescen\* or ratio or ratios)).ti,ab,kf. (4669)
- 17 (alere\* or BRAHMS\* or DELFIA\* or elecsys\* or kryptor\* or perkinelmer\* or quidel\* or roche\* or thermo fisher\* or thermofisher\* or xpress\*).ti,ab,kf. (18570)
- 18 or/6-17 (197008)
- 19 5 and 18 (3998)
- 20 Attitude to Health/ (85342)
- 21 Health Knowledge, Attitudes, Practice/ (123241)
- 22 Patient Participation/ (28468)
- 23 Patient Preference/ (10247)
- 24 Attitude of Health Personnel/ (129367)
- 25 \*Professional-Patient Relations/ (12388)
- 26 \*Physician-Patient Relations/ (37020)
- 27 Choice Behavior/ (34424)
- 28 (choice or choices or value\* or valuation\* or knowledg\*).ti. (297004)
- 29 (preference\* or expectation\* or attitude\* or acceptab\* or point of view).ti,ab,kf. (676660)
- 30 ((patient\*1 or user\*1 or men or women or personal or provider\* or practitioner\* or professional\*1 or (health\* adj2 worker\*) or clinician\* or physician\* or doctor\* or OBGYN\*1 or gyn?ecologist\* or obstetrici\* or midwife\* or midwives) adj2 (participation or perspective\* or perception\* or misperception\* or perceiv\* or view\* or understand\* or misunderstand\* or value\*1 or knowledg\*)).ti,ab,kf. (168655)
- 31 health perception\*.ti,ab,kf. (3111)
- 32 \*Decision Making/ (45693)
- 33 (patient\*1 or user\*1 or men or women or personal or provider\* or practitioner\* or professional\*1 or (health\* adj2 worker\*) or clinician\* or physician\* or doctor\* or OBGYN\*1 or gyn?ecologist\* or obstetrici\* or midwife\* or midwives).ti. (2776680)
- 34 32 and 33 (8444)
- 35 (decision\* and mak\*).ti. (34123)
- 36 (decision mak\* or decisions mak\*).ti,ab,kf. (184833)
- 37 35 or 36 (186423)
- 38 (patient\*1 or user\*1 or men or women or personal or provider\* or practitioner\* or professional\*1 or (health\* adj2 worker\*) or clinician\* or physician\* or doctor\* or OBGYN\*1 or gyn?ecologist\* or obstetrici\* or midwife\* or midwives).ti,ab,kf. (9199996)
- 39 37 and 38 (117147)
- 40 (discrete choice\* or decision board\* or decision analy\* or decision-support or decision tool\* or decision aid\* or latent class\* or decision\* conflict\* or decision\* regret\*).ti,ab,kf. (44917)
- 41 Decision Support Techniques/ (22178)
- 42 (health and utilit\*).ti. (1758)
- 43 (gamble\* or prospect theory or health utilit\* or utility value\* or utility score\* or utility estimate\* or health state or feeling thermometer\* or best-worst scaling or time trade-off or TTO or probability trade-off).ti,ab,kf. (15571)
- 44 (preference based or preference score\* or preference elicitation or multiattribute or multi attribute).ti,ab,kf. (3405)
- 45 or/20-31,34,39-44 (1464500)
- 46 19 and 45 (197)
- 47 limit 46 to yr="2015 -Current" (118)
- 48 limit 47 to english language (113)

## CINAHL

| #   | Query  | Results |
|-----|--|---------|
| S1  | (MH "Pre-Eclampsia+")  | 10,082  |
| S2  | (preeclamp* or pre eclamp* or ((suspect* or predic* or diagnos*) N3 PE))   | 16,922  |
| S3  | ((pregnan* or gestat* or matern*) N3 (toxemi* or toxaemi*))  | 85      |
| S4  | (edema N2 proteinuria N2 hypertension) or EPH complex or EPH gestosis)   | 41      |
| S5  | S1 OR S2 OR S3 OR S4   | 17,286  |
| S6  | (MH "Placenta Growth Factor")  | 28      |
| S7  | (Placenta* growth factor* or PlGF or PGF)  | 1,443   |
| S8  | (MM "Vascular Endothelial Growth Factors")   | 1,264   |
| S9  | (VEGFR1 or sVEGFR1 or VEGFR 1 or sVEGFR 1)   | 219     |
| S10 | (MM "Serologic Tests")   | 695     |
| S11 | (MH "Pregnancy Proteins/BL")   | 358     |
| S12 | (MH "Membrane Proteins")   | 17,082  |
| S13 | (MH "Blood+")  | 74,620  |
| S14 | S12 AND S13  | 914     |
| S15 | (MH "Biological Markers/BL")   | 18,631  |
| S16 | soluble fms-like tyrosine kinase*  | 646     |
| S17 | ((fms-like tyrosine kinase* or FLT 1 or sFLT 1 or FLT1 or sFLT1) and (triage or test* or assay* or immunoassay* or diagnos* or detect* or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen* or ratio or ratios))   | 826     |
| S18 | (alere* or BRAHMS* or DELFIA* or elecsys* or kryptor* or perkinelmer* or quidel* or roche* or thermo fisher* or thermofisher* or xpress*)  | 9,886   |
| S19 | S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S14 OR S15 OR S16 OR S17 OR S18  | 33,157  |
| S20 | S5 AND S19   | 1,352   |
| S21 | (MH "Attitude to Health")  | 47,829  |
| S22 | (MH "Health Knowledge")  | 34,076  |
| S23 | (MH "Consumer Participation")  | 22,683  |
| S24 | (MH "Patient Preference")  | 1,684   |
| S25 | (MH "Attitude of Health Personnel")  | 50,153  |
| S26 | (MM "Professional-Patient Relations")  | 14,245  |
| S27 | (MM "Physician-Patient Relations")   | 17,154  |
| S28 | (MM "Nurse-Patient Relations")   | 14,746  |
| S29 | TI (choice or choices or value* or valuation* or knowledg*)  | 108,837 |
| S30 | (preference* or expectation* or attitude* or acceptab* or point of view)   | 518,381 |
| S31 | (patient or patients or user or users or men or women or personal or provider* or professional or professionals or (health* N2 worker*) or clinician* or physician* or doctor* or practitioner* or OBGYN* or gynecologist* or gynaecologist* or obstetric* or midwife* or midwives) N2 (participation or perspective* or perception* or misperception* or perceiv* or view* or understand* or misunderstand* or value or values or knowledg*)) | 895,568 |
| S32 | health perception*   | 4,978   |
| S33 | (MH "Decision Making, Shared")   | 2,627   |
| S34 | (MH "Decision Making, Patient")  | 15,607  |
| S35 | (MH "Decision Making, Family")   | 4,169   |
| S36 | (MM "Decision Making")   | 24,878  |

S37 TI (patient or patients or user or users or men or women or personal or provider\* or practitioner\* or professional or professionals or (health\* N2 worker\*) or clinician\* or physician\* or doctor\* or OBGYN\* or gynecologist\* or gynaecologist\* or obstetrici\* or midwife\* or midwives) 1,172,902

S38 S36 AND S37 4,944

S39 TI (decision\* and mak\*) 20,106

S40 (decision mak\* or decisions mak\*) 171,061

S41 S39 OR S40 171,286

S42 (patient or patients or user or users or men or women or personal or provider\* or professional or professionals or (health\* N2 worker\*) or clinician\* or physician\* or doctor\* or practitioner\* or OBGYN\* or gynecologist\* or gynaecologist\* or obstetrici\* or midwife\* or midwives) 3,455,214

S43 S41 AND S42 118,293

S44 (discrete choice\* or decision board\* or decision analy\* or decision support or decision tool\* or decision aid\* or latent class\* or decision\* conflict\* or decision\* regret\*) 33,495

S45 (MH "Decision Support Techniques") 7,521

S46 TI (health and utilit\*) 1,059

S47 (gamble\* or prospect theory or health utilit\* or utility value\* or utility score\* or utility estimate\* or health state or feeling thermometer\* or best worst scaling or time trade off or TTO or probability trade off) 20,001

S48 (preference based or preference score\* or preference elicitation or multiattribute or multi attribute) 1,715

S49 S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S38 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 1,389,253

S50 S20 AND S49 90

S51 S20 AND S49

Limiters - Published Date: 20150101-20221231 59

S52 S20 AND S49

Limiters - Published Date: 20150101-20221231; English Language 59

### **Grey Literature Search**

Performed on: April 25 to 28, 2022

**Websites searched:** Alberta Health Evidence Reviews, Alberta Health Services, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), Ontario Health Technology Assessment Committee (OHTAC), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Université de Québec-Université Laval, Contextualized Health Research Synthesis Program of Newfoundland (CHRSP), Health Canada Medical Device Database, Health Technology Assessment Database (INAHTA), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Australian Government Medical Services Advisory Committee, Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Swedish Agency for Health Technology



Assessment and Assessment of Social Services, Ministry of Health Malaysia Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, SickKids Paediatric Economic Database Evaluation (PEDE) Database, PROSPERO, EUnetHTA, clinicaltrials.gov

**Keywords used:** preeclampsia, pre eclampsia, prééclampsie, placental growth factor, placenta growth factor, PlGF, sFLT, FLT, fms-like tyrosine kinase, fms, biomarker, biomarqueur

Clinical results (included in PRISMA): 7

Economic results (included in PRISMA): 5

Ongoing HTAs (PROSPERO/EUnetHTA/NICE/MSAC): 20

Ongoing clinical trials: 31

## Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: AMSTAR 2 Scores of Included Systematic Review

| Author, year                       | AMSTAR score <sup>a</sup> | (1) Provided study design | (2) Duplicate study selection | (3) Broad literature search | (4) Considered status of publication | (5) Listed excluded studies | (6) Provided characteristics of studies | (7) Assessed scientific quality | (8) Considered quality in report | (9) Methods to combine appropriate | (10) Assessed publication bias | (11) Stated conflict of interest |
|------------------------------------|---------------------------|---------------------------|-------------------------------|-----------------------------|--------------------------------------|-----------------------------|---|---------------------------------|----------------------------------|------------------------------------|--------------------------------|----------------------------------|
| Frampton et al, 2021 <sup>14</sup> | 10                        | ✓                         | ✓                             | ✓                           | ✓                                    | ✓                           | ✓                                       | ✓                               | ✓                                | ✓                                  | X                              | ✓                                |

Note: ✓ means the systematic review addressed this item; X means the systematic review did not address this item.

Abbreviation: AMSTAR, A Measurement Tool to Assess Systematic Reviews.

<sup>a</sup>The maximum possible score is 11. For further details on AMSTAR scoring, see Shea et al.<sup>29</sup>

Table A2: Risk of Bias<sup>a,b,c</sup> Among Diagnostic Accuracy Studies (QUADAS-2 Tool)

| Author, year                           | Risk of bias      |                   |                    |                 | Applicability concerns |                   |                    |
|--|-------------------|-------------------|--------------------|-----------------|------------------------|-------------------|--------------------|
|  | Patient selection | Index test        | Reference standard | Flow and timing | Patient selection      | Index test        | Reference standard |
| <b>Add-on studies<sup>c</sup></b>      |                   |                   |                    |                 |                        |                   |                    |
| <i>Triage PlGF test</i>                |                   |                   |                    |                 |                        |                   |                    |
| PARROT <sup>37</sup>                   | Unclear           | Low               | Low                | Low             | Low                    | High <sup>d</sup> | Low                |
| Ormesher et al, <sup>40</sup> 2018     | Unclear           | Low               | Low                | Low             | Low                    | Low               | Low                |
| <i>Elecsys sFlt-1/PlGF ratio</i>       |                   |                   |                    |                 |                        |                   |                    |
| INSPIRE <sup>41</sup>                  | Low               | Low               | Low                | Low             | Low                    | Low               | Low                |
| <i>BRAHMS Krypor sFlt-1/PlGF ratio</i> |                   |                   |                    |                 |                        |                   |                    |
| Andersen et al, <sup>35</sup> 2021     | Low               | High <sup>e</sup> | Low                | Low             | Low                    | Low               | Low                |
| <b>Stand-alone studies</b>             |                   |                   |                    |                 |                        |                   |                    |
| Bremner et al, <sup>16</sup> 2022      | Low               | Low               | Low                | Low             | Low                    | Low               | Low                |
| Hughes et al, <sup>23</sup> 2022       | Low               | Low               | Low                | Low             | Low                    | Low               | Low                |

Abbreviation: QUADAS, Quality Assessment of Diagnostic Accuracy Studies; PlGF, placental growth factor.

<sup>a</sup>Possible risk-of-bias levels: low, high, unclear.

<sup>b</sup>Ratings of studies included in the systematic review by Frampton et al are as reported by the authors, except for the study by Hughes et al, which we evaluated. Frampton et al did not report risk of bias for most of the stand-alone studies included in their systematic review. However, Frampton et al stated: "The finalised critical appraisal forms for each study will be considered for inclusion as supplementary information to this report in the NIHR Journals Library."

<sup>c</sup>No accuracy data was reported in the PARROT Ireland, PreOS, and MAPPLE study publications.

<sup>d</sup>Accuracy was assessed in the concealed trial arm only, so the PlGF test was not used alongside standard clinical assessment.

<sup>e</sup>Threshold not pre-specified.

Table A3: Risk of Bias<sup>a,b,c</sup> Among Randomized Controlled Trials for the Comparison of PlGF-Based Biomarker Testing and Standard Clinical Assessment with Standard Clinical Assessment Alone

| Author, year                 | Random sequence generation | Allocation concealment | Blinding (participants; personnel) | Blinding (outcome assessors) | Incomplete outcome data | Selective reporting |
|------------------------------|----------------------------|------------------------|------------------------------------|------------------------------|-------------------------|---------------------|
| <b>Add-on studies</b>        |                            |                        |                                    |                              |                         |                     |
| INSPIRE <sup>41</sup>        | Low                        | Low                    | High <sup>d</sup>                  | Low                          | Low                     | High <sup>e</sup>   |
| PARROT <sup>37</sup>         | Low                        | High <sup>f</sup>      | High <sup>d</sup>                  | Low                          | Low                     | Low                 |
| PARROT Ireland <sup>36</sup> | Low                        | Low                    | High <sup>d</sup>                  | Low                          | Low                     | Low                 |

<sup>a</sup> Risk of bias assessed using the Cochrane Risk of Bias Tool for randomized controlled trials.

<sup>b</sup> Possible risk-of-bias levels: low, high, unclear.

<sup>c</sup> Ratings of studies included in systematic review by Frampton et al are as reported by the authors.

<sup>d</sup> Blinding of participants and investigators was not possible or achievable; little weight was given to the absence of blinding for this domain in the overall assessment of the study.

<sup>e</sup> Results were not presented for all the outcomes the authors intended to measure (as stated in the trial protocol).

<sup>f</sup> Lack of apparent concealment of the random allocation, suggesting a potential for selection bias.

Table A4: Examples and Implications of Different Testing Scenarios Focusing on Accuracy

| Example of new test and reference test or strategy  | Putative benefit of new test   | Diagnostic accuracy  |   | Patients' outcomes and expected impact on management   |  |  |  | Balance between presumed outcomes, test complications   |
|---|--|--|---|--|--|--|--|---|
|   |  | Sensitivity  | Specificity   | True positives   | True negatives   | False positives  | False negatives  |   |
| New test: biomarker blood test plus standard clinical assessment<br><br>Reference test: standard clinical assessment. | Simple blood test with short turn-around time to aid in prediction of PE | <i>Elecsys ratio test</i><br>Rule out within 1 wk, 96%<br>Rule in within 4 wk, 57%                 | <i>Elecsys ratio test</i><br>Rule out within 1 wk, 80%<br>Rule in within 4 wk, 95%                  | <b>Presumed influence on patient-important outcomes: (e.g., maternal/perinatal morbidity and mortality)</b>                        |  |  |  | Test accuracy (and therefore outcomes important to patients) would generally support a new test's usefulness. |
|   |  | <i>DELFLIA PIGF test</i><br>Rule out within 1 wk, 72%<br>Rule in within 1 wk, 39%                  | <i>DELFLIA PIGF test</i><br>Rule out within 1 wk, 78%<br>Rule in within 1 wk, 91%                   | Benefit from earlier diagnosis and management  | Almost certain benefit from reassurance                | Likely anxiety from additional testing and possible hospital admission | Possible detriment from delayed diagnosis              |   |
|   |  | <i>DELFLIA ratio test<sup>a</sup></i><br>Rule out within 1 wk, 50%<br>Rule in within 1 wk, 39%     | <i>DELFLIA ratio test<sup>a</sup></i><br>Rule out within 1 wk, 89%<br>Rule in within 1 wk, 90%      | <b>Directness of evidence (test results) for outcomes important to patients (e.g., maternal/perinatal morbidity and mortality)</b> |  |  |  |   |
|   |  | <i>BRAHMS ratio test</i><br>Rule in within 1 wk, 92%   | <i>BRAHMS ratio test</i><br>Rule in within 1 wk, 77%  | Elecsys ratio <sup>b</sup> :<br>Some uncertainty   | <i>Elecsys ratio<sup>b</sup></i> :<br>Some uncertainty | Elecsys ratio <sup>b</sup> :<br>Some uncertainty                       | Elecsys ratio <sup>b</sup> :<br>No uncertainty         |   |
|   |  | <i>Triage PLGF test<sup>a</sup></i><br>Rule in within 2 wk,<br>< 12 pg/mL: 51%<br>< 100 pg/mL: 95% | <i>Triage PLGF test<sup>a</sup></i><br>Rule in within 2 wk,<br>< 12 pg/mL: 100%<br>< 100 pg/mL: 33% | <i>DELFLIA PIGF<sup>c</sup></i> :<br>Some uncertainty  | <i>DELFLIA PIGF<sup>c</sup></i> :<br>Some uncertainty  | <i>DELFLIA PIGF<sup>c</sup></i> :<br>Some uncertainty                  | <i>DELFLIA PIGF<sup>c</sup></i> :<br>No uncertainty    |   |
|   |  |  |   | BRAHMS ratio <sup>d</sup> :<br>Some uncertainty  | BRAHMS ratio <sup>d</sup> :<br>Some uncertainty        | BRAHMS ratio <sup>d</sup> :<br>Some uncertainty                        | BRAHMS ratio <sup>d</sup> :<br>Some uncertainty        |   |
|   |  |  |   | Triage PLGF (< 12) <sup>e</sup> :<br>No uncertainty  | Triage PLGF (< 12) <sup>e</sup> :<br>No uncertainty    | Triage PLGF (< 12) <sup>e</sup> :<br>No uncertainty                    | Triage PLGF (< 12) <sup>e</sup> :<br>No uncertainty    |   |
|   |  |  |   | Triage PLGF (< 100) <sup>f</sup> :<br>Some uncertainty   | Triage PLGF (< 100) <sup>f</sup> :<br>Some uncertainty | Triage PLGF (< 100) <sup>f</sup> :<br>Some uncertainty                 | Triage PLGF (< 100) <sup>f</sup> :<br>Some uncertainty |   |

Footnotes on the following page.

*Footnotes continued from the previous page.*

Abbreviations: FN, false negative; FP, false positive; PE, pre-eclampsia; PlGF, placental growth factor; TN, true negative; TP, true positive.

<sup>a</sup> Not licensed by Health Canada.

<sup>b</sup> Example using Elecsys ratio: rule-out (Cerdeira et al,<sup>41</sup> prevalence, 12.9%) > 38

TP = 10.3%

TN = 69.3%

FP = 17.8%

FN = 2.6%

<sup>c</sup> Example using DELFIA PlGF: rule out (Bremner et al,<sup>16</sup> prevalence, 8% [11/136 patients])  $\geq$  150 pg/mL

TP = 6.2%

TN = 71.8%

FP = 20.2%

FN = 1.8%

<sup>d</sup> Example using BRAHMS ratio test: rule in within 1 week (Andersen et al,<sup>35</sup> prevalence, 17%) 84/501:

TP = 13.1%

TN = 63.9%

FP = 19%

FN = 3.9%

<sup>e</sup> Example using Triage PlGF test: rule in within 2 weeks (Ormesher et al,<sup>40</sup> prevalence, 82%) < 12 pg/mL:

TP = 82%

TN = 18%

FP = 0%

FN = 0%

<sup>f</sup> Example using Triage PlGF test: rule in within 2 weeks (Ormesher et al,<sup>40</sup> prevalence, 82%) < 100 pg/mL:

TP = 27%

TN = 6.0%

FP = 12%

FN = 54%

Source: Adapted from Schünemann et al.<sup>93</sup>

**Table A5: Diagnostic GRADE Evidence Profile for the Comparison of PlGF-Based Biomarker Testing and Standard Clinical Assessment with Standard Clinical Assessment Alone**

| Test   | Risk of bias                          | Inconsistency          | Indirectness <sup>a</sup> | Imprecision                           | Publication bias | Quality      |
|--|---------------------------------------|------------------------|---------------------------|---------------------------------------|------------------|--------------|
| <b>Prediction of PE</b>  |                                       |                        |                           |                                       |                  |              |
| Elecsys ratio test<br>1 add-on RCT, 6 stand-alone observational studies                            | No serious limitations                | No serious limitations | Some uncertainty (-1)     | No serious limitations                | Undetected       | ⊕⊕⊕ Moderate |
| DELFIAXpress, DELFIA ratio test<br>0 add-on studies, 1 stand-alone observational study             | No serious limitations                | No serious limitations | Some uncertainty (-1)     | No serious limitations                | Undetected       | ⊕⊕⊕ Moderate |
| BRAHMS ratio test<br>1 add-on observational study, 0 stand-alone studies                           | Serious limitations (-1) <sup>b</sup> | No serious limitations | Some uncertainty (-1)     | Serious limitations (-1) <sup>c</sup> | Undetected       | ⊕⊕ Low       |
| Triage <sup>d</sup> PlGF test<br>1 add-on observational study, 2 stand-alone observational studies | Serious limitations (-1) <sup>e</sup> | No serious limitations | No uncertainty            | No serious limitations                | Undetected       | ⊕⊕⊕ Moderate |
| <b>Repeat testing to rule in/rule out PE</b>   |                                       |                        |                           |                                       |                  |              |
| 0 studies  | -                                     | -                      | -                         | -                                     | -                | -            |

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PE, pre-eclampsia; PlGF, placental growth factor; RCT, randomized controlled trial.

<sup>a</sup>Based on uncertainties in Table A4: Examples and Implications of Different Testing Scenarios Focusing on Accuracy.

<sup>b</sup>Threshold not prespecified.

<sup>c</sup>Confidence intervals not reported.

<sup>d</sup>Not licensed by Health Canada.

<sup>e</sup>Unclear patient selection.

Table A6A: GRADE Evidence Profile for the Comparison of PlGF-Based Biomarker Testing and Standard Clinical Assessment with Standard Clinical Assessment Alone, by Maternal Outcome

| Test<br>Number of studies,<br>design          | Risk of bias                                 | Inconsistency                             | Indirectness              | Imprecision                              | Publication bias | Upgrade<br>considerations | Quality |
|---|--|---|---------------------------|--|------------------|---------------------------|---------|
| <b>Time to pre-eclampsia diagnosis</b>        |  |   |                           |  |                  |                           |         |
| Elecsys<br>1 RCT                              | Serious<br>limitations (-2) <sup>a,b</sup>   | No serious<br>limitations                 | No serious<br>limitations | No serious<br>limitations                | Undetected       | -                         | ⊕⊕ Low  |
| Triage<br>2 RCTs                              | Serious<br>limitations (-1) <sup>a,c,f</sup> | Serious<br>limitations (-1) <sup>d</sup>  | No serious<br>limitations | No serious<br>limitations                | Undetected       | -                         | ⊕⊕ Low  |
| <b>Time to delivery</b>                       |  |   |                           |  |                  |                           |         |
| Triage<br>1 RCT,<br>1 observational<br>study  | Serious<br>limitations (-1) <sup>a,c</sup>   | Serious<br>limitations (-1) <sup>e</sup>  | No serious<br>limitations | No serious<br>limitations                | Undetected       | -                         | ⊕⊕ Low  |
| <b>Pre-eclampsia diagnosis</b>                |  |   |                           |  |                  |                           |         |
| Elecsys<br>1 RCT                              | Serious<br>limitations (-1) <sup>ab</sup>    | No serious<br>limitations                 | No serious<br>limitations | Serious<br>limitations (-1) <sup>g</sup> | Undetected       | -                         | ⊕⊕ Low  |
| Triage<br>2 RCTs,<br>1 observational<br>study | Serious<br>limitations (-1) <sup>ac</sup>    | Serious<br>limitations (-1) <sup>de</sup> | No serious<br>limitations | No serious<br>limitations                | Undetected       | -                         | ⊕⊕ Low  |
| <b>Maternal adverse outcomes</b>              |  |   |                           |  |                  |                           |         |
| Elecsys<br>1 RCT                              | Serious<br>limitations (-1) <sup>ab</sup>    | No serious<br>limitations                 | No serious<br>limitations | Serious<br>limitations (-1) <sup>h</sup> | Undetected       | -                         | ⊕⊕ Low  |
| Triage<br>2 RCTs,<br>1 observational<br>study | Serious<br>limitations (-1) <sup>ac</sup>    | Serious<br>limitations (-1) <sup>de</sup> | No serious<br>limitations | No serious<br>limitations                | Undetected       | -                         | ⊕⊕ Low  |
| <b>Onset of labour</b>                        |  |   |                           |  |                  |                           |         |
| Triage<br>1 RCT                               | Serious<br>limitations (-1) <sup>a,c</sup>   | No serious<br>limitations                 | No serious<br>limitations | Serious<br>limitations (-1) <sup>h</sup> | Undetected       | -                         | ⊕⊕ Low  |



| Test Number of studies, design            | Risk of bias                               | Inconsistency                            | Indirectness              | Imprecision               | Publication bias | Upgrade considerations | Quality |
|---|--|--|---------------------------|---------------------------|------------------|------------------------|---------|
| <b>Preterm and early preterm delivery</b> |  |  |                           |                           |                  |                        |         |
| Triage<br>1 RCT, 1<br>observational study | Serious<br>limitations (-1) <sup>a,c</sup> | Serious<br>limitations (-1) <sup>e</sup> | No serious<br>limitations | No serious<br>limitations | Undetected       | -                      | ⊕⊕ Low  |

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PlGF, placental growth factor; RCT, randomized controlled trial.

Note: Triage PlGF is not licensed by Health Canada (and the study results are treated as supportive evidence).

<sup>a</sup>Blinding of participants and investigators was not possible or achievable in INSPIRE, PARROT, or PARROT Ireland; little weight was given to the absence of blinding for this domain in the overall assessment of the study.

<sup>b</sup>Results were not presented for all the outcomes the authors intended to measure (as stated in the INSPIRE trial protocol).

<sup>c</sup>Lack of apparent concealment of the random allocation in PARROT, suggesting a potential for selection bias.

<sup>d</sup>Contradictory results between PARROT and PARROT Ireland.

<sup>e</sup>Contradictory results between the PARROT and MAPPLE studies.

<sup>f</sup>Post-hoc analysis.

<sup>g</sup>Low number of patients, especially for the severe PE subgroup.

<sup>h</sup>Low number of patients.

Table A6B: GRADE Evidence Profile for the Comparison of PlGF-Based Biomarker Testing and Standard Clinical Assessment with Standard Clinical Assessment Alone, by Fetal and Neonatal Outcome

| Test<br>Number of studies,<br>design                     | Risk of bias                               | Inconsistency                            | Indirectness              | Imprecision                                 | Publication bias | Upgrade<br>considerations | Quality |
|--|--|--|---------------------------|---|------------------|---------------------------|---------|
| <b>Fetal mortality</b>                                   |  |  |                           |   |                  |                           |         |
| Triage<br>1 RCT,<br>1 observational study                | Serious<br>limitations (-1) <sup>a,c</sup> | No serious<br>limitations                | No serious<br>limitations | Serious<br>limitations<br>(-1) <sup>h</sup> | Undetected       | -                         | ⊕⊕ Low  |
| <b>Gestational age at delivery</b>                       |  |  |                           |   |                  |                           |         |
| Elecsys<br>1 RCT,<br>1 observational study               | Serious<br>limitations (-1) <sup>a,b</sup> | No serious<br>limitations                | No serious<br>limitations | Serious<br>limitations<br>(-1) <sup>h</sup> | Undetected       | -                         | ⊕⊕ Low  |
| Triage<br>1 RCT,<br>1 observational study                | Serious<br>limitations (-1) <sup>a,c</sup> | Serious<br>limitations (-1) <sup>e</sup> | No serious<br>limitations | No serious<br>limitations                   | Undetected       | -                         | ⊕⊕ Low  |
| <b>Perinatal and neonatal mortality</b>                  |  |  |                           |   |                  |                           |         |
| Triage<br>1 RCT,<br>1 observational study                | Serious<br>limitations (-1) <sup>a,c</sup> | Serious<br>limitations (-1) <sup>e</sup> | No serious<br>limitations | No serious<br>limitations                   | Undetected       | -                         | ⊕⊕ Low  |
| <b>Perinatal and neonatal adverse composite outcomes</b> |  |  |                           |   |                  |                           |         |
| Triage<br>1 RCT,<br>1 observational study                | Serious<br>limitations (-1) <sup>a,c</sup> | Serious<br>limitations (-1) <sup>e</sup> | No serious<br>limitations | No serious<br>limitations                   | Undetected       | -                         | ⊕⊕ Low  |

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PE, pre-eclampsia; PlGF, placental growth factor; RCT, randomized controlled trial.

Note: Triage PlGF is not licensed by Health Canada (and the study results are treated as supportive evidence).

<sup>a</sup>Blinding of participants and investigators was not possible or achievable in INSPIRE, PARROT, or PARROT Ireland; little weight was given to the absence of blinding for this domain in the overall assessment of the study.

<sup>b</sup>Results were not presented for all the outcomes the authors intended to measure (as stated in the INSPIRE trial protocol).

<sup>c</sup>Lack of apparent concealment of the random allocation in PARROT, suggesting a potential for selection bias.

<sup>d</sup>Contradictory results between PARROT and PARROT Ireland.

<sup>e</sup>Contradictory results between the PARROT and MAPPLE studies.

<sup>f</sup>Post hoc analysis.

<sup>g</sup>Low number of patients, especially for the severe PE subgroup.

<sup>h</sup>Low number of patients.

Table A6C: GRADE Evidence Profile for the Comparison of PlGF-Based Biomarker Testing and Standard Clinical Assessment with Standard Clinical Assessment Alone, by Hospitalization and Quality of Life Outcome

| Test  | Number of studies, design    | Risk of bias                            | Inconsistency                         | Indirectness           | Imprecision                           | Publication bias | Upgrade considerations | Quality |
|---|------------------------------|---|---------------------------------------|------------------------|---------------------------------------|------------------|------------------------|---------|
| <b>Maternal admissions to hospital or specialist care units</b> |                              |   |                                       |                        |                                       |                  |                        |         |
| Elecsys   | 1 RCT, 1 observational study | Serious limitations (-1) <sup>a,b</sup> | Serious limitations (-1) <sup>f</sup> | No serious limitations | No serious limitations                | Undetected       | -                      | ⊕⊕ Low  |
| <b>Neonatal admission to hospital or specialist care units</b>  |                              |   |                                       |                        |                                       |                  |                        |         |
| Elecsys   | 1 RCT                        | Serious limitations (-1) <sup>a,b</sup> | No serious limitations                | No serious limitations | Serious limitations (-1) <sup>h</sup> | Undetected       | -                      | ⊕⊕ Low  |
| Triage  | 1 RCT, 1 observational study | Serious limitations (-1) <sup>a,c</sup> | No serious limitations                | No serious limitations | Serious limitations (-1) <sup>f</sup> | Undetected       | -                      | ⊕⊕ Low  |
| <b>Length of stay in hospital or unit</b>                       |                              |   |                                       |                        |                                       |                  |                        |         |
| Triage  | 1 RCT                        | Serious limitations (-1) <sup>a,c</sup> | No serious limitations                | No serious limitations | Serious limitations (-1) <sup>f</sup> | Undetected       | -                      | ⊕⊕ Low  |
| <b>Health-related quality of life</b>                           |                              |   |                                       |                        |                                       |                  |                        |         |
| Elecsys   | 0 studies                    | -                                       | -                                     | -                      | -                                     | -                | -                      | -       |
| Triage  | 0 studies                    | -                                       | -                                     | -                      | -                                     | -                | -                      | -       |

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.

Note: Triage PlGF is not licensed by Health Canada (and the study results are treated as supportive evidence).

<sup>a</sup>Blinding of participants and investigators was not possible or achievable in INSPIRE, PARROT, or PARROT Ireland; little weight was given to the absence of blinding for this domain in the overall assessment of the study.

<sup>b</sup>Results were not presented for all the outcomes the authors intended to measure (as stated in the INSPIRE trial protocol).

<sup>c</sup>Lack of apparent concealment of the random allocation in PARROT, suggesting a potential for selection bias.

<sup>d</sup>Contradictory results between PARROT and PARROT Ireland.

<sup>e</sup>Contradictory results between PARROT and MAPPLE studies.

<sup>f</sup>Post-hoc analysis.

<sup>g</sup>Low number of patients; especially for the severe PE subgroup.

<sup>h</sup>Low number of patients

<sup>i</sup>Inconsistency between the INSPIRE and PreOS studies.

<sup>j</sup>Wide confidence intervals.

### Appendix 3: Selected Excluded Studies—Clinical Evidence

For transparency, we have provided a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

| Citation   | Primary reason for exclusion             |
|--|--|
| Duhig KE, Webster LM, Sharp A, et al. Diagnostic accuracy of repeat placental growth factor measurements in women with suspected preeclampsia: A case series study. <i>Acta Obstet Gynecol. Scand.</i> 2020;99(8):994-1002. <sup>94</sup>  | Not primary diagnostic research          |
| Cheng YKY, Law LW, Leung TY, et al. Soluble fms-like tyrosine kinase-1, placental growth factor and their ratio as a predictor for pre-eclampsia in East Asians. <i>Pregnancy Hyperten.</i> 2018;11:61-65. <sup>95</sup>   | Ineligible population                    |
| Choi R, Park MJ, Oh Y, et al. Preeclampsia screening using the ratio of soluble fms-like tyrosine kinase-1 to placental growth factor during pregnancy in pregnant Korean women. <i>Clin Lab.</i> 2020;66(9):01. <sup>96</sup>   | Ineligible population                    |
| Heimberger S, Mueller A, Ratnaparkhi R, et al. Angiogenic factor abnormalities and risk of peripartum complications and prematurity among urban predominantly obese parturients with chronic hypertension. <i>Pregnancy Hypertens.</i> 2020;20:124-30. <sup>97</sup>   | Ineligible population                    |
| McLaughlin K, Snelgrove JW, Audette MC, Syed A, Hobson SR, Windrim RC, Melamed N, et al. PlGF (placental growth factor) testing in clinical practice: evidence from a Canadian tertiary maternity referral center. <i>Hypertens.</i> 2021 Jun;77(6):2057-65. <sup>12</sup>   | Not a comparator of interest             |
| Sabria E, Lequerica-Fernandez P, Lafuente-Ganuzza P, et al. Addition of N-terminal pro-B natriuretic peptide to soluble fms-like tyrosine kinase-1/placental growth factor ratio > 38 improves prediction of pre-eclampsia requiring delivery within 1 week: a longitudinal cohort study. <i>Ultrasound Obstet Gynecol.</i> 2018;51(6):758-67. <sup>98</sup> | No relevant outcomes                     |
| Saleh L, van den Meiracker AH, Geensen R, et al. Soluble fms-like tyrosine kinase-1 and placental growth factor kinetics during and after pregnancy in women with suspected or confirmed pre-eclampsia. <i>Ultrasound Obstet Gynecol.</i> 2018;51(6):751-57. <sup>99</sup>   | Ineligible comparator/reference standard |
| Wiles K, Bramham K, Seed PT, et al. Placental and endothelial biomarkers for the prediction of superimposed pre-eclampsia in chronic kidney disease. <i>Pregnancy Hypertens.</i> 2021;24:58-64. <sup>100</sup>   | Ineligible population                    |
| Villalain C, Herraiz I, Valle L, et al. Maternal and perinatal outcomes associated with extremely high values for the sflt-1 (soluble fms-like tyrosine kinase 1)/plgf (placental growth factor) ratio. <i>J Am Heart Assoc.</i> 2020;9(7):e015548. <sup>101</sup>   | Ineligible comparator/reference standard |

## Appendix 4: Results of Applicability Checklists for Studies Included in the Economic Literature Review

Table A7: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of PlGF-Based Biomarker Testing

| Author, year, country   | Is the study population similar to the question? | Are the interventions similar to the question? | Is the health care system studied sufficiently similar to Ontario? | Were the perspectives clearly stated? If yes, what were they? | Are all direct effects included? Are all other effects included where they are material? | Are all future costs and outcomes discounted? If yes, at what rate? | Is the value of health effects expressed in terms of quality-adjusted life-years? | Are costs and outcomes from other sectors fully and appropriately measured and valued? | Overall judgment <sup>a</sup> |
|---|--|--|--|---|--|---|---|--|-------------------------------|
| Chantraine et al, 2021, <sup>73</sup> Belgium   | Yes  | Yes  | No   | Yes, Belgian public health care payers' perspective           | No, neonatal costs excluded  | Unclear   | No  | No   | Partially applicable          |
| Khosla et al. 2021, <sup>74</sup> United States   | Yes  | Yes  | No   | Yes, US payer perspective                                     | No, neonatal costs excluded  | Unclear   | No  | No   | Not applicable                |
| Kearns et al, 2021 <sup>75</sup> (NICE UK, Decision Support Unit Model,) 2021, <sup>14</sup> UK | Yes  | Yes  | No   | Yes, NHS and Personal Social Services perspective             | Yes  | Yes, 3.5%   | Yes   | No   | Partially applicable          |
| Myrhaug et al. 2020, <sup>65</sup> Norway   | Yes  | Yes  | No   | Unclear   | No, neonatal costs excluded  | No  | No  | No   | Partially applicable          |
| Duhig et al. 2019, <sup>66</sup> UK   | Yes  | Yes  | No   | Yes, NHS cost perspective                                     | Yes  | No  | No  | Yes  | Not applicable                |
| Giardini et al. 2019, <sup>64</sup> Italy   | Yes  | Yes  | No   | Unclear   | No, neonatal costs excluded  | No  | No  | No   | Not applicable                |
| Hodel et al. 2019, <sup>67</sup> Switzerland  | Yes  | Yes  | No   | Yes, Swiss health care perspective                            | No, neonatal costs excluded  | Yes, 3.5%   | No  | No   | Partially applicable          |
| Figueira et al. 2018, <sup>68</sup> Brazil  | Yes  | Yes  | No   | Yes, Brazilian public and private payer perspective           | Yes  | No  | No  | Yes  | Not applicable                |

| Author, year, country                         | Is the study population similar to the question? | Are the interventions similar to the question? | Is the health care system studied sufficiently similar to Ontario? | Were the perspectives clearly stated? If yes, what were they?   | Are all direct effects included? Are all other effects included where they are material? | Are all future costs and outcomes discounted? If yes, at what rate? | Is the value of health effects expressed in terms of quality-adjusted life-years? | Are costs and outcomes from other sectors fully and appropriately measured and valued? | Overall judgment <sup>a</sup> |
|---|--|--|--|---|--|---|---|--|-------------------------------|
| Schlembach et al. 2018, <sup>69</sup> Germany | Yes  | Yes  | No   | Yes, German health care perspective   | No, neonatal costs excluded  | No  | No  | No   | Partially applicable          |
| Frusca et al. 2017, <sup>70</sup> Italy       | Yes  | Yes  | No   | Yes, Italian health care payer perspective  | Yes  | Yes, 3%   | No  | Yes  | Partially applicable          |
| Duckworth et al. 2016, <sup>71</sup> England  | Yes  | Yes  | No   | Yes, Commissioner perspective; the organization responsible for buying health within the NHS in England | No, neonatal costs excluded  | No  | No  | No   | Not applicable                |
| Frampton et al. 2016, <sup>1</sup> UK         | Yes  | Yes  | No   | Yes, NHS and Personal Social Services perspective   | Yes  | No  | Yes   | Yes  | Not applicable                |
| Vatish et al. 2016, <sup>72</sup> UK          | Yes  | Yes  | No   | Yes, NHS payer's perspective  | Yes  | No  | Yes   | No   | Partially applicable          |

Abbreviations: NHS, National Health Service; PlGF, placental growth factor.

Table A8: Studies Not Applicable to the Ontario Setting

| Studies   | Reasoning  |
|---|--|
| Khosla et al. 2021, <sup>74</sup> United States | Health care system in the US is considerably different from that of Canada   |
| Duhig et al, 2019, <sup>66</sup> UK             | Triage PIGF test has not been approved by Health Canada  |
| Giardini et al, 2021, <sup>64</sup> Italy       | Triage PIGF test has not been approved by Health Canada  |
| Figueira et al. 2018, <sup>68</sup> Brazil      | Health care system in Brazil is considerably different from that of Canada   |
| Duckworth et al. 2016, <sup>71</sup> England    | Triage PIGF test has not been approved by Health Canada.   |
| Frampton et al. 2016, <sup>1</sup> UK           | Frampton and coauthors have updated their analysis. Their new economic analysis results from 2021 <sup>14</sup> were not same as these from 2016. We consider the findings from 2021 <sup>14</sup> partially applicable and those from 2016 not applicable |

## Appendix 5: Letter of Information

Ontario Health is conducting a review of **Placental Growth Factor (PlGF)-based biomarkers** to help diagnose pre-eclampsia in those with suspected pre-eclampsia. The purpose is to understand whether this technology should be publicly funded in Ontario.

An important part of this review involves learning more about the experiences of patients, families, and caregivers to better understand the context and impact of preeclampsia.

### *What Do You Need From Me*

- Willingness to share your story
- 20-40 minutes of your time for a phone
- Permission to audio- (not video-) record the interview

### *What Your Participation Involves*

If you agree to share your experiences, you will be asked to have an interview with Ontario Health staff. The interview will last about 20-40 minutes. It will be held over the telephone and with your permission, the interview will be audio-taped. The interviewer will ask you questions about your or your loved one's condition and your perspectives about care options in Ontario.

Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

### *Confidentiality*

All information you share will be kept confidential and your privacy will be protected except as required by law. The results of this review will be published, however, no identifying information will be released or published. Any records containing information from your interview will be stored securely until project completion. After the project's completion, the records will be destroyed.

### *Risks to participation*

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experiences.

If you are interested, please contact us before July 15, 2022:

Isabelle Labeca

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## Appendix 6: Interview Guide

### Introduction

Thank you – again, if at any point you would like for me to pause or to completely stop the recording, please do not hesitate to let me know. Now before we begin, I would like to see if you have any questions regarding the project or our work at Ontario Health in general.

Description of Ontario Health: Ontario Health is a government agency, which can be viewed as an extension of the Ministry of Health and Long-Term Care. The role of the Health Technology Assessment program is to use scientific methods to analyze evidence and assess new and existing healthcare services and medical devices. Our reviews cover three (3) domains of evidence: clinical, economic impact, and preferences and values. In addition, each health technology assessment includes recommendations for the Ministry on whether these health services and/or medical devices should be publicly funded.

The aim of the Patient and Public Partnering team is to ensure that equal consideration is given to the lived experience and preferences of patients, families, and caregivers through evidence generation.

Description of Technology Under Review: For this health technology assessment, we are reviewing placental growth factor (PlGF)-based biomarker testing. This is a blood test that is typically ordered later in pregnancy (up to 36 weeks) to help healthcare providers diagnose pregnant people who are suspected of having pre-eclampsia (e.g., already showing signs of pre-eclampsia like high blood pressure). The results from the biomarker test can be used to adjust the care plan to the pregnant person's risk for developing pre-eclampsia. It is important to note that, currently, PlGF-based biomarker tests are not publicly funded in Ontario.

Aim of Direct Engagement: the goal of today's interview is to learn from your experience with pre-eclampsia and to get a better understanding of your values, decision-making, and preferences in relation to prenatal care.

### Journey to Findings

I'd like to start by asking you to please describe the events that led up to the diagnosis of preeclampsia.

- Probes/prompts: Routine prenatal care? Family history? Symptoms (e.g., headaches, swelling, visual disturbance)?
- Probes/prompts: Barriers to access? Rural setting?
- Probes/prompts: Self-advocacy? Support team? Who was coordinating care?

### Access to Information about Pre-Eclampsia

What information about pre-eclampsia was available to you prior to becoming pregnant? After?

- Probes/prompts: Thoughts or feelings after receiving the information?
- Probes/prompts: Primary source of information? Was it accessible?
- Probes/prompts: Access to informal sources of information (e.g., social media groups)?
- Probes/prompts: Understanding of the implications of preeclampsia in relation to your care plan?
- Probes/prompts: Was HELLP syndrome mentioned?

## Impact of Pre-eclampsia Diagnosis and Related Treatments

After confirming the diagnosis, what happened next?

- Probes/prompts: Monitoring as an outpatient or inpatient? Self-monitor blood pressure?
- Probes/prompts: Support from the care team?
- Probes/prompts: Access to care? Barriers?
- Probes/prompts: Impact on decisions related to family planning?

## Broad Access to PlGF-based Biomarker Testing (hypothetical inquiry)

Does broad access to biomarkers align with your preferences and values? Why or why not?

- Probes/Prompts: Perceived impacts (i.e., emotional, physical, or work-life)?
- Probes/Prompts: Access? Comfort? Timing? Frequency/Feasibility (patient adherence)?
- Probes/Prompts: Online access to test results?

Would you have any concerns with publicly funding broad access to PlGF-based biomarker testing in Ontario? Why or why not?

- Probes/Prompts: Perceived barriers (i.e., access, equity, or false positives)?

## Conclusion

- Thank you - those are all the questions that I have today but is there anything else you would like to add?
- Finally, do you have any questions for me?

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Ontario Health is an agency of the Government of Ontario. Our mandate is to connect and coordinate our province's health care system in ways that have not been done before to help ensure that Ontarians receive the best possible care. We work to support better health outcomes, patient experiences, provider experiences and value for money spent.

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