2.04.152 Maternal Serum Biomarkers for Prediction of Adverse Obstetric Outcomes			
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Section:	4.0 OB/Gyn/Reproduction	**Page:**	Page 1 of 33

Policy Statement

I. The use of maternal serum biomarker tests with or without additional algorithmic analysis for prediction of preeclampsia is considered **investigational.**

II. The use of maternal serum biomarker tests with or without additional algorithmic analysis for prediction of spontaneous preterm birth is considered **investigational.**

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding

The following codes may be used for these tests:

- **0243U:** Obstetrics (preeclampsia), biochemical assay of placental-growth factor, time-resolved fluorescence immunoassay, maternal serum, predictive algorithm reported as a risk score for preeclampsia
- **0247U:** Obstetrics (preterm birth), insulin-like growth factor-binding protein 4 (IBP4), sex hormone-binding globulin (SHBG), quantitative measurement by LC-MS/MS, utilizing maternal serum, combined with clinical data, reported as predictive-risk stratification for spontaneous preterm birth

Description

Improved accuracy of the identification of pregnant people at risk of preeclampsia and spontaneous preterm birth has the potential to reduce maternal and perinatal morbidity and mortality. Assessment of historical risk and clinical factors represents the traditional approach to diagnosis and planning interventions. Maternal serum biomarker testing is proposed as an adjunct to standard screening to identify pregnant people at risk of preeclampsia and spontaneous preterm birth.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests. Therefore, maternal serum biomarker tests would be provided by CLIA licensed laboratories.

The B·R·A·H·M·S sFlt-1/ PlGF KRYPTOR Test System (Thermo Fisher Scientific) was cleared for marketing by the FDA as a prognostic test through the De Novo process (DEN220027) in May 2023.[13,] The Test System includes quantitative determination of placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) in human serum and plasma. The clearance letter states that the Test System is to be used 'along with other laboratory tests and clinical assessments to aid in the risk assessment of pregnant women (singleton pregnancies between gestational age 23+0 to 34+6/7 weeks) hospitalized for hypertensive disorders of pregnancy (preeclampsia, chronic hypertension with or without superimposed preeclampsia, or gestational hypertension) for progression to preeclampsia with severe features (as defined by the American College of Obstetricians and Gynecologists (ACOG) guidelines) within 2 weeks of presentation.'

Commercially produced, maternal serum biomarker tests for preeclampsia include the Triage PlGF™ (Quidel), Elecsys sFlt-1/PlGF™ (Roche Diagnostics), and DELFIA Xpress PlGF 1-2-3™ (PerkinElmer).[14,] These commercially produced tests are not currently available in the United States.

The PreTRM™ test (Sera Prognostics)[15,] uses maternal serum biomarkers (insulin-like growth factor binding protein-4 [IBP4] and sex hormone binding globulin [SHBG]) in combination with biometric measures to assess the risk of spontaneous preterm birth. According to the manufacturer, the PreTRM test is only intended to be used in women aged 18 years or older, who are asymptomatic (that is, with no signs or symptoms of preterm labor, with intact membranes, and with no first trimester progesterone use) with a singleton pregnancy. The PreTRM test is performed via a single blood draw during the 19th week of gestation.

Rationale

Background

Preeclampsia

Hypertensive disorders in pregnancy affected approximately 1 in 7 delivery hospitalizations between 2017 and 2019 in the US with a prevalence of approximately 1 in 5 delivery hospitalizations among Black women and 1 in 3 among women aged 45 to 55 years.[1,] Preeclampsia is defined as new onset maternal hypertension and proteinuria or new onset hypertension and significant end-organ dysfunction (with or without proteinuria) after the 20th week of gestation.[2,]

Maternal complications of preeclampsia include progression to eclampsia, placental abruption, and a life-threatening complication known as the hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. In the fetus, preeclampsia can lead to fetal growth restriction and intrauterine fetal death. Preeclampsia can develop in nulliparous women with no known risk factors.[3,] Maternal factors associated with an increased risk of preeclampsia include advanced maternal age, presence of a chronic illness such as diabetes mellitus, chronic hypertension, chronic kidney disease, or systemic lupus erythematosus, obesity, multiple gestations, and a prior history of preeclampsia. Preeclampsia can also develop in the postpartum period. In women determined to be at increased risk of developing preeclampsia, the use of daily, low-dose aspirin beginning in the 12th week of gestation is associated with a reduction in risk and is recommended by the U.S.

Preventive Services Task Force (USPSTF) and the American College of Obstetricians and Gynecologists (ACOG).[4,5,]

Despite decades of research, accurate identification of women at risk of preeclampsia, particularly prior to the 20th week of gestation, remains challenging.[3,] Standard methods for preeclampsia risk-factor assessment are based on medical and obstetric history and clinical assessment, including routine maternal blood pressure measurement at each prenatal visit.[4,] The use of maternal serum biomarker assays as an adjunct to standard preeclampsia risk assessment has been suggested as a mechanism that could improve accurate identification of at-risk individuals. More accurate identification of risk could create an opportunity for additional assessment, surveillance, and interventions that would ultimately reduce the maternal and fetal or newborn morbidity and mortality associated with preeclampsia. Individual maternal serum biomarkers, such as serum placental growth factor (PlGF), soluble Fms-like tyrosine kinase 1 (s-Flt 1), and pregnancy-associated plasma protein A (PAPP-A) have been investigated as predictors of preeclampsia.[6,] Multivariable preeclampsia risk assessment tools have been developed that incorporate maternal serum biomarkers; several of these tools have been commercially produced (see Regulatory Status) but few have been externally validated.[7,] Clinically useful risk assessment using maternal serum biomarker testing would need to show increased predictive value over standard assessment of preeclampsia risk without serum biomarker testing.

Spontaneous Preterm Birth

Preterm birth is defined as birth occurring between the 20th and 37th week of pregnancy and can be spontaneous following preterm labor and rupture of membranes or iatrogenic due to clinical interventions for maternal or fetal medical indications. The preterm birth rate was estimated by the Centers for Disease Control (CDC) to be 10.1% (about 360,000 births were preterm among 3,600,000 births) in 2020 in the United States and has consistently been approximately 10% for over a decade.[8,] Preterm birth rates vary according to race and ethnicity independent of social determinants of health, ranging from 8.5% for Asian women to 14.4% for non-Hispanic Black women. Prior preterm birth is the strongest predictor of a subsequent preterm birth, although absolute risk varies according to the gestational age of the prior preterm birth and maternal clinical factors.[9,] Characteristics in a current pregnancy that increase the risk of preterm birth include cervical changes (shortened length and/or early dilation), vaginal bleeding or infection, and maternal age under 18 years or over 35 years. Smoking, pre-pregnancy weight, interpregnancy interval, maternal stress, and lack of social support have also been associated with an increased risk of preterm birth. Despite recognition of risk factors, most preterm births occur without clearly identifiable maternal risk factors.[10,] Maternal consequences of preterm delivery include intrapartum and postpartum infection. Psychosocial adverse effects including postpartum depression have been reported. Infants born preterm have an increased risk of death up to 5 years of age relative to full-term infants. Preterm birth is also associated with morbidity extending into adulthood.[11,]

Cervical length is one measure available to clinicians to assess risk of preterm birth. Shortened cervical length prior to 24 weeks gestation is associated with an increased risk of preterm birth. The ACOG recommends ultrasonographic assessment of cervical length in the second trimester to identify women at an increased risk of preterm birth.[11,] In women with a prior history of preterm birth, serial measurement of cervical length using transvaginal ultrasound is recommended, although optimal timing of measurements has not been clinically established. In women without a history of preterm birth or other risk factors, universal ultrasonographic screening of cervical length in women has not been demonstrated to be an effective strategy due to the overall low incidence in this group. In women determined to have a shortened cervix and therefore an increased risk of preterm birth, the use of either vaginal or intramuscular progesterone supplementation has been associated with a reduced risk of preterm birth. There are some limitations in assessment of cervical length in predicting risk of preterm birth. These limitations include uncertainty as to what constitutes “shortened” length, with transvaginal ultrasound measurements ranging from <15 mm to <25 mm

implicated in indicating increased risk and uncertainty regarding ideal timing of ultrasonographic assessment.[11,]

Given the limitations of cervical length assessment in predicting risk of preterm birth, the use of other biomarkers has been suggested as a mechanism that could improve accurate identification of women at risk of preterm birth, including maternal serum biomarkers.[12,]

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Maternal Serum Biomarker Testing for Preeclampsia in Pregnant People Without Known Risk Factors

Clinical Context and Test Purpose

In the US, the US Preventive Services Task Force (USPSTF) and the American College of Obstetricians and Gynecologists (ACOG) recommend screening for hypertensive disorders in asymptomatic pregnant persons with blood pressure measurements throughout pregnancy, including in the first trimester. Based on screening, USPSTF and ACOG recommend the use of low-dose aspirin as preventive medication starting at 12 weeks of gestation in persons who are at high risk for preeclampsia and consideration of low-dose aspirin in persons with more than one moderate risk factor. The USPSTF and ACOG criteria for high and moderate risk for preeclampsia are clinical, demographic and sociodemographic.[4,5,16,] Currently, maternal serum biomarkers are not included in either USPSTF guidelines or ACOG risk factor assessment when determining appropriate candidates for aspirin prophylaxis.

However, the International Federation of Gynecology and Obstetrics (FIGO) recommends that all pregnant people are screened for preeclampsia in the first trimester using both clinical risk factors and maternal serum biomarkers and support use of the Fetal Medicine Foundation (FMF) algorithm to identify high risk persons. The FMF algorithm produces a risk score based on a combination of clinical risk factors, maternal age, mean arterial pressure (MAP), mean uterine artery (UtA) pulsatility index (PI) measurements and maternal placental growth factor (PlGF).[6,]

The use of multianalyte maternal serum biomarker assays is proposed as an adjunct to screening based on patient history and clinical characteristics to identify pregnant people at risk of preeclampsia and to determine potential therapies that could prevent development of preeclampsia.

The following PICO was used to select literature to inform this review:

Populations
The relevant population of interest is pregnant people without known risk factors for the development of preeclampsia who are being screened for preeclampsia in the first trimester for selection for low-dose aspirin therapy. US women have a higher prevalence of predisposing comorbidities compared with women in Europe and therefore performance characteristics of proposed screening tests are needed in US populations.

Interventions
The test being considered is use of maternal serum biomarker testing with or without additional algorithmic analysis to predict risk of preeclampsia.

Single biomarkers that have been investigated for prediction of preeclampsia include placental growth factor (PlGF) and soluble Fms-like tyrosine kinase 1 (sFlt-1). The predictive ability of the sFlt-1/PlGF ratio has also been investigated. A review of reviews conducted by Townsend et al (2018)[17,] on preeclampsia risk prediction identified sFlt-1 and PlGF as the maternal serum biomarkers with the most robust evidence available.

sFlt-1 is not useful for screening for preeclampsia during the first trimester because levels of sFlt-1 increase at 21 to 24 weeks of gestation.[6,]

Commercially produced, maternal serum biomarker assays include the DELFIA XPress PlGF 1-2-3, which measures serum pregnancy-associated plasma protein-A (PAPP-A) and PlGF and the Elecsys sFlt-1/PlGF, which assesses the ratio of PlGF to sFlt-1. These commercially produced tests are not currently available in the United States.

The B·R·A·H·M·S sFlt-1/ PlGF KRYPTOR Test System is the only test cleared for marketing in the US. The KRYPTOR system is cleared for use in hospitalized pregnant people between gestational age 23+0 to 34+6/7 weeks. As such, it would not be within the cleared indication for use in screening asymptomatic women in the first trimester for selection for aspirin therapy.

Comparators
The following practice is currently being used to identify pregnant people at risk of preeclampsia: standard clinical management without the use of maternal serum biomarker tests.

The USPSTF and ACOG criteria for high and moderate risk for preeclampsia for selection for low-dose aspirin therapy starting in the first trimester are clinical, demographic and sociodemographic, Clinical management beyond the first trimester involvescontinued assessment of medical history and clinical risk factors, such as serial blood pressure measurement and screening for proteinuria as part of prenatal care.[4,5,16,]

Outcomes
The general outcomes of interest are accurate identification of people at risk of preeclampsia who may be suitable candidates for interventions to prevent preeclampsia, which in turn could reduce maternal and fetal morbidity. Aspirin for women at high risk is currently the only guideline recommended method of prevention of preeclampsia. Maternal outcomes include progression to eclampsia, placental abruption, and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome and fetal outcomes include fetal growth restriction and intrauterine fetal death.

Study Selection Criteria
For the evaluation of clinical validity of the maternal serum biomarker tests for preeclampsia, studies that meet the following eligibility criteria were considered:

- The study includes a validation cohort independent of the development cohort.
- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);

- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

Given the large number of studies that have been performed, this review will not evaluate all individual studies but will summarize available systematic reviews, particularly those that report performance characteristics in the first trimester.

Agrawal et al (2019)[18,] conducted a systematic review that included 40 observational studies (N=92,687) on the predictive ability of PlGF testing in women without known risk factors (Table 1). Studies that analyzed PlGF in conjunction with other biomarkers were excluded. The timing of PlGF testing was <14 weeks in 15 studies, ≥14 weeks in 25 studies, and ≥19 weeks in 18 studies. Most studies (37/40) used a definition of preeclampsia that required presence of proteinuria. Two studies evaluated the KRYPTOR system. Six studies were conducted in the US; 2 of these included first trimester populations. In all studies, the chosen PlGF cutoff was not predetermined but was calculated based on maximizing accuracy and ranged from 41 to 382 pg/mL in studies in which it was reported. Individual study sensitivity and specificity ranged from 7% to 93% and 51% to 97%, respectively. When all studies were included in a pooled analysis, sensitivity was 61% (95% confidence interval [CI], 53 to 69%), specificity was 85% (95% CI, 82 to 88%) and heterogeneity was high (I^2=99%).

Table 1. Systematic Reviews on the Clinical Validity of Individual Maternal Serum Biomarkers in Women Without Known Risk Factors for Preeclampsia

Study	Biomarker(s)	N	Number of studies	Sensitivity	Specificity
Agrawal et al (2019)[18,]	PlGF	92,687	40	61% (95% CI, 53 to 69%)	85% (95% CI, 82 to 88%)
Subgroup: <14 weeks	PlGF	NR	15	50% (95% CI, 36 to 64%)	89% (95% CI, 85 to 91%)

CI: confidence interval; PlGF: placental growth factor; sFlt-1: soluble Fms-like tyrosine kinase 1.

Nonrandomized Studies

Individual clinical validity studies will be reviewed in this section if they meet criteria described in 'Selection Criteria' above and include performance characteristics for a first trimester population in the US or use a test cleared in the US.

The 2 US clinical validity studies identified in the Agarwal (2019) systematic review described above[19,20,] did not use a validation cohort independent of the development cohort (i.e., did not have predefined PlGF cutoffs for high and low risk) and will not be reviewed further.

Clinical validity studies of the KRYPTOR system[21,22,23,24,] did not include women in the first trimester and will not be reviewed further in this section.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

In current clinical practice, the management decision that could be altered by the measurement of maternal serum biomarkers in pregnant persons without known risk factors is the decision to start low-dose aspirin therapy in the first trimester. To demonstrate utility, using maternal serum biomarkers in addition to guideline-based risk factors to identify women at high risk who would benefit from aspirin therapy would have to be superior to risk assessment based on guideline-based (USPSTF and ACOG) recommended risk factors alone.

Currently, there are no FDA-cleared or approved maternal serum biomarkers indicated to assess preeclampsia risk in the first trimester or to select women for aspirin therapy.

Chain of Evidence

The systematic review supporting the USPSTF recommendation regarding low-dose aspirin therapy in asymptomatic pregnant people included 18 trials. The trials used various tools to identify asymptomatic pregnant people who were at increased risk of preeclampsia. Only one trial (ASPRE) used an externally validated risk prediction model that included PlGF along with other clinical characteristics and biomarkers, to identify pregnant people for inclusion.[5,]

Rolnik et al (2017) reported results of the ASPRE trial.[25,] ASPRE was a double-blind, placebo-controlled trial including 1776 women with singleton pregnancies (11+0 through 13+6 weeks gestation) who were at high risk for preterm preeclampsia. The participants were randomized to receive aspirin (150 mg per day) or placebo from enrollment until 36 weeks of gestation. The trial was conducted at 13 maternity hospitals in the United Kingdom, Spain, Italy, Belgium, Greece, and Israel. The Fetal Medicine Foundation (FMF) algorithm was used to select women for inclusion. The FMF algorithm includes PlGF as one of its components. PlGF was measured using the DELFIA Xpress system. The primary outcome was delivery with preeclampsia before 37 weeks gestation. The median age was 31 years; 66% of participants were White, 26% were Black. The primary outcome occurred in 1.6% (n=13) of participants in the aspirin group versus 4.3% (n=35) of participants in the placebo group (odds ratio=0.38; 95% CI, 0.20 to 0.74; p<.01). There were no significant between-group differences in the incidence of neonatal adverse outcomes or other adverse events.

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility through a chain of evidence. There are no prospective observational studies with predefined cutoffs conducted in a first trimester, US population reporting performance characteristics of any test, including the test cleared for use in the US.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs or observational studies were identified comparing health outcomes in women undergoing serum biomarker testing in addition to guideline-based risk assessment versus guideline-based risk assessment alone..

Section Summary: Maternal Serum Biomarker Testing for Preeclampsia in Women Without Known Risk Factors

The evidence evaluating the predictive ability of maternal serum biomarker measurement in pregnant women without known risk factors includes systematic reviews of clinical validity studies and one RCT of aspirin therapy in asymptomatic women identified as high risk using an algorithm that includes PlGF. The clinical validity studies primarily included populations in Europe and tests that are not cleared for use in the US. PlGF cutoffs for identifying high risk pregnant people were not prespecified and varied significantly. The RCT used a test not cleared for use in the US to identify women for enrollment.

Maternal Serum Biomarker Testing for Preeclampsia in Pregnant People With Known Risk Factors

Clinical Context and Test Purpose

Biomarker testing has been proposed as a tool to triage care in the second and third trimesters in pregnant people with known risk factors. For example, the test could be useful in the decision regarding inpatient versus outpatient care, frequency and method of surveillance, or the timing of delivery.

The following PICO was used to select literature to inform this review:

Populations

The relevant population of interest is pregnant people with known risk factors for the development of preeclampsia or with suspected preeclampsia. In particular, the biomarker test might be useful in pregnant people for whom clinicians are uncertain regarding risk of developing preeclampsia based on clinical factors alone such as those with borderline hypertension, or non-specific symptoms.
US women have a higher prevalence of predisposing comorbidities compared with women in Europe and therefore performance characteristics are needed in US populations.

Interventions

The test being considered is use of maternal serum biomarker assays to predict risk of preeclampsia. The use of maternal serum biomarker assays to predict risk of preeclampsia involves measuring serum biomarkers with or without additional algorithmic analysis that includes clinical factors, and analyzing the results as an adjunct to maternal risk factors. Results of testing could be used to determine potential therapies to prevent development of preeclampsia.

Single biomarkers that have been investigated for prediction of preeclampsia include PlGF and sFlt-1. The predictive ability of the sFlt-1/PlGF ratio has also been investigated. A review of reviews conducted by Townsend et al (2018)[17,] on preeclampsia risk prediction identified sFlt-1 and PlGF as the maternal serum biomarkers with the most robust evidence available.

Commercially produced, maternal serum biomarker assays include the DELFIA XPress PlGF 1-2-3, which measures serum PAPP-A and PlGF, and the Elecsys sFlt-1/PlGF, which assesses the ratio of PlGF to sFlt-1. These commercially produced tests are not currently available in the United States. The B·R·A·H·M·S sFlt-1/ PlGF KRYPTOR Test System is the only test cleared by the FDA in the US. The KRYPTOR system is cleared for use in hospitalized pregnant people between gestational age 23+0 to 34+6/7 weeks. The product sheet available on the manufacturer website suggests a cutoff of 85 for the sFlt-1/PlGF ratio but does not indicate which clinical decision the test is meant to inform and whether the test is meant to be used as a rule-in or rule-out test at that cutoff.[26,] The FDA De Novo letter indicates that the KRYPTOR test labeling must include the following statements:[13,]

- "The test result is intended as an aid in the management of the patient, and not to be used to replace clinical judgement."
- "The test result is not to be used to aid in the diagnosis of preeclampsia or conditions resulting from progression of preeclampsia."
- "The test result is not to be used to aid in decisions of hospital discharge."
- "The test result is not to be used to aid in decisions of pregnancy delivery."
- "The test is not intended to inform the healthcare provider about whether or not changes in immediate treatment, including medication or hospitalization, are needed."

Comparators

The following practice is currently being used to identify pregnant people at risk of preeclampsia: standard clinical management without the use of maternal serum biomarker assays. Standard

clinical management involves assessment of medical history and clinical risk factors, including serial blood pressure measurement and screening for proteinuria as part of prenatal care.

Outcomes

The general outcomes of interest are accurate identification of people at risk of preeclampsia who may be suitable candidates for interventions to prevent preeclampsia, which in turn could reduce maternal and fetal morbidity. Maternal outcomes include progression to eclampsia, placental abruption, and HELLP syndrome and fetal outcomes include fetal growth restriction and intrauterine fetal death.

Study Selection Criteria

For the evaluation of clinical validity of the maternal serum biomarker tests for preeclampsia, studies that meet the following eligibility criteria were considered:

- The study includes a validation cohort independent of the development cohort.
- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

Given the large number of studies that have been performed, this review will not evaluate all individual studies but will summarize available systematic reviews, particularly those that report performance characteristics in the second and third trimester.

The systematic review conducted by Agrawal et al (2018)[27,] assessing the diagnostic accuracy of the sFlt-1/PlGF ratio for prediction of preeclampsia included 7 studies conducted in women at high-risk of developing preeclampsia based on clinical characteristics (that is, with known risk factors), all assessing risk after the 19th week of gestation (Table 2). Two studies were conducted in US populations. Among the included studies, sensitivity ranged from 67% to 100%, and specificity ranged from 68% to 100%. When pooled, sensitivity was 85% (95% CI, 66% to 94%) and specificity was 87% (95% CI, 76% to 93%). Heterogeneity was high for both measures (I^2=75% and 79%, respectively).

Table 2. Systematic Reviews on the Clinical Validity of Individual Maternal Serum Biomarkers in Women With Known Risk Factors for Preeclampsia

Study	Biomarker(s)	N	Number of studies	Sensitivity	Specificity
Agrawal et al (2018)[27,]	sFlt-1/PlGF ratio	1083	7	85% (95% CI, 66 to 94%)	87% (95% CI, 76 to 93%)

CI: confidence interval; NR: not reported; OR: odds ratio; PlGF: placental growth factor; sFlt-1: soluble Fms-like tyrosine kinase 1.

Lim et al (2021) conducted a systematic review analyzing sFlt-1 and PlGF individually and in combination as the sFlt-1/PlGF ratio in predicting adverse obstetric outcomes.[28,] The review only included studies of women (N=9246) with suspected or confirmed preeclampsia. All of the 33 included studies were observational (prospective cohort, retrospective cohort, or case control), and were heterogeneous in a number of important factors, including the definition of preeclampsia used in the study, the method of evaluating biomarkers and cut-off values, the definition of adverse obstetric outcomes, and the methods for reporting results. The timing of biomarker testing ranged from 18 to

40 weeks gestation. Performance characteristics are shown in Table 3; evidence on sFlt-1 was too limited to pool. Although both PlGF and the sFlt-1/PlGF ratio were associated with AUROC values that suggested acceptable statistical discrimination for the outcomes analyzed, the results are limited by significant heterogeneity and/or imprecision for nearly all outcomes.

Table 3. Results from a Systematic Review of the Clinical Validity of Individual Maternal Serum Biomarkers for Prediction of Adverse Obstetric Outcomes

Study	Biomarker(s)	Delivery within <7 days	Delivery within <14 days	Preterm birth	Small for gestational age or fetal growth restriction	Perinatal mortality	Pulmonary edema	Any adverse maternal outcome	Any adverse maternal or perinatal outcome
Lim et al 2021[28,]	PlGF								
Number of studies		5	6	7	8	NR	NR	NR	NR
Sensitivity (95% CI)		57% (42 to 72%)	74% (48 to 89%)	79% (54 to 89%)	67% (46 to 82%)				
Specificity (95% CI)		71% (56 to 82%)	75% (64 to 84%)	71% (56 to 82%)	77% (66 to 86%)				
AUROC (95% CI)		0.68 (0.64 to 0.72)	0.80 (0.76 to 0.83)	0.79 (0.75 to 0.82)	0.79 (0.76 to 0.83)				
Test for heterogeneity (95% CI)		I^2=96% (94 to 99%)	I^2=99% (98 to 99%)	I^2=99% (99 to 100%)	I^2=99% (99 to 100%)				
	sFlt-1/PlGF ratio								
Number of studies			4	5	5	4	4	5	6
Sensitivity (95% CI)			78% (70 to 85%)	74% (59 to 85%)	70% (51 to 84%)	78% (63 to 89%)	72% (30 to 94%)	67% (46 to 82%)	68% (59 to 75%)
Specificity (95% CI)			82% (78 to 86%)	80% (67 to 89%)	59% (42 to 74%)	61% (46 to 74%)	64% (50 to 76%)	77% (66 to 86%)	86% (74 to 93%)
AUROC (95% CI)			0.87 (0.15 to 1.00)	0.84 (0.80 to 0.87)	0.69 (0.65 to 0.73)	0.78 (0.74 to 0.82)	0.70 (0.66 to 0.74)	0.79 (0.75 to 0.82)	0.79 (0.75 to 0.82)
Test for heterogeneity (95% CI)			I^2=33% (0 to 100%)	I^2=98% (97 to 99%)	I^2=98% (97 to 99%)	I^2=86% (71 to 100%)	I^2=80% (97 to 99%)	I^2=94% (56 to 100%)	I^2=90% (80 to 100%)

AUROC: area under the receiver operating characteristic; CI: confidence interval; NR: not reported; PlGF: placental growth factor; sFlt-1: soluble fms-like tyrosine kinase-1.

Nonrandomized Studies

Individual clinical validity studies will be reviewed in this section if they meet criteria described in 'Selection Criteria' above and include performance characteristics for a second or third trimester population in the US or use a test cleared in the US.

The 2 US clinical validity studies identified in the Agarwal (2018) systematic review described above[29,30,] did not use a validation cohort independent of the development cohort (i.e., did not have predefined PlGF cutoffs for high and low risk) and will not be reviewed further.

KRYPTOR System

Four studies have reported performance characteristics of the KRYPTOR system in the second and third trimester.[21,22,23,24,] Three of the studies[21,22,23,] reported performance characteristics for both derived and predefined cutoffs. The summary below focuses on the predefined cutoffs.

Characteristics of the studies are shown in Table 4; results are shown in Table 5. Limitations of the studies are described in Tables 6 and 7.

Thadhani et al (2022) reported results of the largest study of the KRYPTOR system.[24,] PRAECIS (Preeclampsia Risk Assessment: Evaluation of Cut-offs to Improve Stratification; NCT03815110) was a prospective, blinded, multicenter (18 centers) study conducted in the US between 2019 and 2021. The centers included tertiary care and community hospitals in urban and suburban settings. PRAECIS enrolled 1014 pregnant women with singleton pregnancies; 299 in a derivation cohort and 715 in a validation cohort. The participants were between 23+0 and 34+6 weeks gestation with a hypertensive disorder of pregnancy as defined by ACOG. The primary outcome was the development of preeclampsia with severe features within 2 weeks of enrollment which was adjudicated by a committee of maternal fetal medicine experts blinded to the local diagnosis. Preeclampsia with severe features was defined, in short, as (1) severe hypertension; (2) thrombocytopenia; (3) impaired liver function; (4) severe persistent right upper quadrant or epigastric pain; (5) progressive renal insufficiency; (6) pulmonary edema; (7) new-onset cerebral or visual disturbances; and (8) headache unresponsive to medication. See the publication for more specifics on the components of the definition of preeclampsia. Using the development cohort, a sFlt-1:PlGF ratio of ≥40 was chosen as the cutoff that provided the highest sensitivity while maintaining specificity of 70%. The results that follow are for the validation cohort using the cutoffs of 40 for the sFlt-1:PlGF ratio. The validation cohort (n=556) was racially diverse including 6% Asian, 30% Black, 53% White and 16% Hispanic participants. The mean age was 32 years and the mean gestational age at enrollment was 30 weeks. 46% of participants had used aspirin during pregnancy. The incidence of the primary outcome was 33.5%. The overall performance characteristics of the test for predicting preeclampsia with severe features were: 94% sensitivity (95% CI, 89 to 96), 75% specificity (95% CI, 70 to 79), 65% PPV (95% CI, 59 to 71) and 96% NPV (95% CI, 93 to 98). In the subgroup of participants who identified as Black race (n=169), the positive and negative predictive values 66% (95% CI, 51 to 67) and 99% (95% CI, 94 to 100), respectively. Subgroup analyses were not reported by aspirin use during pregnancy. Given that aspirin lowers the risk of preeclampsia, the PPV might differ across subgroups of women who did and did not take aspirin during pregnancy. There were 51 adverse maternal outcomes. Adverse maternal outcomes occurred in 16% of the group with a ratio ≥40 compared to 3% of the group with a ratio <40 (risk ratio, 5.8; 95% CI, 2.8 to 12.2). There were 288 adverse fetal and neonatal outcomes. Adverse fetal and neonatal outcomes occurred in 80% of the group with a ratio ≥40 compared to 26% in the group with a ratio <40 (risk ratio, 3.1; 95% CI, 2.5 to 3.8). There were 9 fetal deaths, 8 of which were in the group with a ratio ≥40.[24,]

Table 4. Characteristics of Studies of Clinical Validity of the KRYPTOR system

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test
Andersen (2015)[21,]	Banked samples from pregnant women (singleton) from Denmark Enrolled between 2010 and 2014 Included samples from 2 cohorts: cohort of women with preeclampsia (n=39); cohort of non-hypertensive pregnancies (n=76) Median GA at blood sampling, 38 to 39 weeks Median age, 39 y	Retrospective; Case-control	Preeclampsia defined as repeated BP above 90 mmHg diastolic and/or 140 mmHg systolic; values of +1 or more for protein in urine Early-onset, prior to 34+0 weeks Late-onset, 34+0 onwards	Predefined cutoffs for sFlt–1/PlGF: Early-onset, 33 ('rule-out') 85 ('rule-in') Late-onset, 33 ('rule-out') 110 ('rule-in')
van Helden (2015)[23,]	Banked samples from pregnant women (singleton), source not specified	Retrospective; Case-control	Preeclampsia defined as new	Predefined cutoffs for

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test
	Years of sample collection not specified Included samples from patients with preeclampsia (n=51) and patients undergoing an 'inconspicuous course of pregnancy' (n=51) Mean GA at blood sampling, 34 weeks Mean age, 31 y		onset of hypertension and proteinuria after 20 weeks of gestation Early onset, clinical signs started before week 34	sFlt–1/PlGF: Early-onset, 33 ('rule-out') 85 ('rule-in') Late-onset, 33 ('rule-out') 110 ('rule-in')
Droge (2017)[22,]	Banked samples from pregnant patients in Germany Enrolled in 2 clinical studies conducted between 2007 to 2010 and 2013 to 2014 that measured sFlt-1 and PlGF in patients with and without preeclampsia and/or fetal growth restriction Performance characteristics provided for case-control analysis including 33 patients with preeclampsia and 132 age-matched healthy controls Mean age, 30 to 31 y 96% White; 2% Black; 2% Asian	Retrospective; Case-control	Preeclampsia defined according to guidelines of International Society for the Study of Hypertension in Pregnancy	Predefined cutoffs for sFlt–1/PlGF: 33, 38, 85
Thadhani (2022)[24,] **PRAECIS (NCT03815110)**	18 centers in the US between 2019 and 2021 Pregnant women (singleton) between 23+0 and 34+6 weeks gestation with a hypertensive disorder of pregnancy as defined by ACOG Mean age, 32 y Mean GA at enrollment, 30 weeks 6% Asian, 30% Black, 53% White, 16% Hispanic 46% aspirin use in pregnancy	Prospective	Preeclampsia with severe features	Cutoff from development cohort applied in validation cohort sFlt–1/PlGF: 40

ACOG: American College of Obstetricians and Gynecologists; BP: blood pressure; CI: confidence interval; GA: gestational age; NR: not reported; PlGF: placental growth factor; sFlt-1: soluble fms-like tyrosine kinase-1.

Table 5. Results of Studies of Clinical Validity of the KRYPTOR system

Study	Initial N	Final N	Excluded Samples	Prevalence or Incidence of Condition	Clinical Validity (95% Confidence Interval)			
					Sensitivity	Specificity	PPV	NPV
Andersen (2015)[21,]	N=115 n=39 cases n=76 controls	N=115	0	34%				

Study	Initial N	Final N	Excluded Samples	Prevalence or Incidence of Condition	Clinical Validity (95% Confidence Interval)			
Early-onset, sFlt–1/PlGF <33 cutoff					89% (52 to 100)	71% (42 to 92)	67% (35 to 90)	91% (59 to 100)
Early-onset, sFlt–1/PlGF >85 cutoff					78% (40 to 97)	100% (77 to 100)	100% (59 to 100)	88% (62 to 98)
Late-onset, sFlt–1/PlGF <33 cutoff					93% (78 to 99)	32% (21 to 45)	40% (29 to 52)	91% (71 to 99)
Late-onset, sFlt–1/PlGF >110 cutoff					53% (34 to 72)	67% (55 to 79)	44% (28 to 62)	75% (62 to 86)
van Helden (2015)[23],	N=102 n=51 cases n=51 controls	N=102	0	50%				
Early-onset, sFlt–1/PlGF <33 cutoff					100% (91 to 100)	84% (71 to 93)	83% (70 to 93)	100% (92 to 100)
Early-onset, sFlt–1/PlGF >85 cutoff					100% (91 to 100)	84% (71 to 93)	83% (70 to 93)	100% (92 to 100)
Late-onset, sFlt–1/PlGF <33 cutoff					100% (72 to 100)	86% (73 to 94)	65% (38 to 86)	100% (92 to 100)
Late-onset, sFlt–1/PlGF >110 cutoff					64% (31 to 89)	100% (93 to 100)	100% (59 to 100)	93% (82 to 98)
Droge (2017)[22],	N=165 n=33 cases n=132 controls	N=165	0	20%				
sFlt–1/PlGF ≥33 cutoff					91% (76 to 97)	73% (65 to 80)	NR	NR
sFlt–1/PlGF ≥38 cutoff					91% (76 to 97)	76% (68 to 82)	NR	NR
sFlt–1/PlGF ≥85 cutoff					88% (73 to 95)	89% (82 to 93)	NR	NR
Thadhani (2022)[24],				34%				
Overall	N=715	159 (met criteria for severe preeclampsia at enrollment)	556	sFlt–1/PlGF ≥40 cutoff	94% (89 to 96)	75% (70 to 79)	65% (59 to 71)	96% (93 to 98)
Participants who identified as Black race			169	sFlt–1/PlGF ≥40 cutoff	NR	NR	66% (51 to 67)	99% (94 to 100)

CI: confidence interval; GA: gestational age; NPV: negative predictive value; NR: not reported; PlGF: placental growth factor; PPV: positive predictive value; sFlt-1: soluble fms-like tyrosine kinase-1.

Table 6. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Andersen (2015)[21],	2: Context unclear given samples were taken at 38 to 39 weeks		3. Not compared to clinical factors	1. No delivery or fetal outcomes reported	1. No follow-up for delivery or post-delivery

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
	4, 5: Study population entirely Dutch, includes women with known preeclampsia and known to be non-hypertension				
van Helden (2015)[23],	3, 5: Study population demographics not provided		3. Not compared to clinical factors	1. No delivery or fetal outcomes reported	1. No follow-up for delivery or post-delivery
Droge (2017)[22],	2: Context unclear given variation in timing of sample collection 5: Lack of racial diversity		3. Not compared to clinical factors	1. No delivery or fetal outcomes reported	1. No follow-up for delivery or post-delivery
Thadhani (2022)[24],	2. Unclear which clinical decision the test might inform		3. Not compared to clinical factors	6: Subgroup analyses not performed for aspirin use during pregnancy	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use; 5: Enrolled study populations do not reflect relevant diversity; 6: Other
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest; 4: Other
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose; 4: Other
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).; 6: Other
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined); 2: Other

Table 7. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Andersen (2015)[21],	1. Retrospective design with no description of how samples were selected					
van Helden (2015)[23],	1. Retrospective design with no description of how samples were selected					
Droge (2017)[22],	1. Retrospective design with no description of how samples were selected					
Thadhani (2022)[24],						

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience); 3: Other
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests; 2: Other
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described; 5: Other
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4: Other
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data; 4: Other
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported; 3: Other

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility through a chain of evidence. There is one prospective observational study (PRAECIS) conducted in a second and third trimester US population reporting performance characteristics of the test cleared for use in the US. PRAECIS included a racially diverse population reflective of US diversity. While PRAECIS proposed a cutoff for the sFlt-1:PlGF ratio of 40 measured using the KRYPTOR system, other publications have proposed various cutoffs. The clinical decision that would be informed by the test is unclear.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Randomized Controlled Trials

5 RCTs have compared health outcomes for patients managed with and without a PlGF or sFlt-1/PlGF ratio test in the second or third trimester.[31,32,33,34,35,] Four of the RCTs were conducted in Europe and one was conducted in South America. All 5 RCTs used tests that are not currently cleared in the US. Three of the RCTs used PlGT or sFlt-1/PlGF ratio results to guide intensity of surveillance.[31,33,35,] One RCT used sFlt-1/PlGF ratio results to guide surveillance and hospital admission decisions[32,] and 1 RCT used PlGT results to guide timing of delivery decisions.[34,] Results of the trials are discussed below and were mixed. A single trial found that time to preeclampsia diagnosis was shorter and maternal severe adverse outcomes were reduced in the group with care guided by PlGF results compared to usual care. Another trial found that the proportion of women with progression to preeclampsia with severe features was significantly lower in the group guided by PlGF results compared to usual care group. In contrast, the remaining 3 trials did not find that management adding PlGF or sFlt-1/PlGF ratio testing improved outcomes.

Duhig et al (2019) reported results of the PARROT multicenter, pragmatic, stepped-wedge, cluster-randomised RCT conducted in 11 maternity units in the UK in 2016 and 2017 (ISRCTN16842031).[31,] The study included 1023 pregnant women (singleton) with suspected pre-eclampsia between 20+0 and 36+6 weeks gestation. During the usual care periods (n=447 women), PlGF measurements were taken but were concealed from clinicians and women. During the intervention periods (n=576 women), the circulating PlGF measurement was revealed and a clinical management algorithm was used. Samples were processed for PlGF measurements using the Triage test (Quidel). The clinical management algorithm incorporated PlGF measurement into the National Institute for Health and

Care Excellence (NICE) guidance for the management of hypertensive pregnancies. Specifically, for PlGF > 100 (normal), the algorithm recommended continuing with usual management; for PlGF between 12 and 100 (low result) the algorithm recommended consideration of increased surveillance; for PlGF<12 (very low result), the algorithm recommended assessing as preeclampsia. The primary outcome was the time from presentation with suspected pre-eclampsia to documented pre-eclampsia. Preeclampsia was as defined by the International Society for the Study of Hypertension in Pregnancy 2014 statement and cases were reviewed by a central adjudication panel who were masked to trial allocation. The mean age of participants was 32 years and the mean gestational age at enrollment was 32 to 33 weeks. Racial and ethnic make up was 66% of participants were White; 13% were Black; 12% were Indian, Pakistani Bangladeshi or Sri Lankan. 41% of participants had been prescribed prophylactic aspirin. The median time to pre-eclampsia diagnosis was 4.1 days with concealed testing compared to 1.9 days with revealed testing (time ratio=0.36, 95% CI, 0.15 to 0.87; p=.03). In the concealed testing group, 24 (5%) versus 22 (4%) of the revealed testing group experienced maternal severe adverse outcomes (adjusted odds ratio=0.32, 95% CI, 0.11 to 0.96; p=.04). There was not a statistically significant difference in perinatal adverse outcomes (15% vs 14%) or gestational age at delivery (36.6 weeks vs 36.8 weeks).

Cerdeira et al (2019) reported results of the INSPIRE (Interventional Study Evaluating the Short-Term Prediction of Preeclampsia/Eclampsia In Pregnant Women With Suspected Preeclampsia) trial (ISRCTN87470468).[32,] INSPIRE was an RCT conducted at a single tertiary center in the UK between 2015 and 2017 including 381 pregnant women (singleton) between 24+0 and 37+0 weeks of gestation with a clinical suspicion of preeclampsia. INSPIRE compared standard clinical management alone (n=186) to standard clinical management along with sFlt-1/PlGF ratio result (n=184). Blood samples were collected and processed for all participants but results were revealed only for women randomized to the sFlt-1/PlGF ratio group. In the sFlt-1/PlGF reveal group, a ratio of ≤38 was considered to confer low risk of developing preeclampsia within 7 days and discharge was advised if appropriate given the clinical picture. A ratio >38 was deemed elevated risk and a low threshold for admission and increased surveillance was advised. Final management decisions were at the clinician's discretion. sFlt-1 and PLGF were measured using the Elecsys test (Roche). The primary outcome was preeclampsia-related inpatient admission within 24 hours of the test, within 7 days, or by delivery. Preeclampsia related inpatient admission was defined as an admission driven by suspicion of preeclampsia, where preeclampsia was recorded as a differential diagnosis and ongoing blood pressure monitoring, assessment of proteinuria, and preeclampsia blood samples had been requested. Outcome assessors were blinded to sFlt-1/PlGF result and trial group assignment. The median age was 31 years and the median gestational age at enrollment was 34 weeks. 90% of participants were White. Aspirin use during pregnancy was not described. Preeclampsia occurred in 23% (85) of participants. The number of primary outcome admissions was not significantly different between groups (n=48, nonreveal versus n=60, reveal; p=.19). Adverse maternal-fetal outcomes were similar for both groups.[32,]

Hayes-Ryan et al (2021) reported results of the PARROT Ireland trial (NCT02881073).[33,] PARROT Ireland was a stepped wedge cluster RCT conducted in 7 hospitals in Ireland between 2017 and 2019. The trial enrolled 2313 pregnant women (singleton) between 20+0 and 36+6 weeks gestation with symptoms suggestive of preeclampsia. Participants were randomized to usual care (per national guidelines; n=1057) or usual care plus PlGF testing (n=1234). In the PlGF group, a management algorithm was provided that was based on both the degree of hypertension present and the PlGF result. The algorithm recommended increased surveillance and frequency of review for participants with an abnormal or highly abnormal PlGF result (<100 pg/mL and <12 pg/mL, respectively). Final decisions regarding management remained with the treating clinician. PlGF testing was performed using the Triage test (Quidel). The co-primary outcomes were composite maternal morbidity and composite neonatal morbidity. The maternal morbidity composite included: placental abruption, intensive care admission, central nervous system compromise, cardiorespiratory compromise, hematological compromise, kidney compromise, and severe hypertension. The neonatal morbidity composite included: perinatal death, neonatal intensive care unit admission, birthweight ≤5th

percentile, Apgar score <7 at 5 minutes, umbilical artery acidosis at birth, admission to neonatal unit, respiratory distress syndrome, intraventricular hemorrhage, retinopathy of prematurity, confirmed infection, and necrotizing enterocolitis. All preeclampsia diagnoses were reviewed by a central adjudication panel including a clinical doctor and a research midwife who were blinded to treatment group and PlGF result. The mean age of participants was 32 years and the mean gestational age at enrollment was 32 weeks. 90% of participants were European, 3% of participants were African Caribbean or African. The use of aspirin among participants varied across hospitals, from 6% to 48%, and also varied across treatment groups , 28% versus 19% in intervention versus control. There was not a statistically significant difference in the maternal morbidity composite: 38% (457/1202) in the usual care group versus 32% (330/1017) in the PlGF group (adjusted risk ratio=1.01; 95% CI, 0.76 to 1.36; p=.92). Nor was there a statistically significant difference in the neonatal morbidity composite: 43% (527/1202) in the usual care group versus 47% (484/1017) in the PlGF group (adjusted risk ratio=1.03; 95% CI, 0.89 to 1.21; p=.67). Post-hoc analysis was performed adjusting the maternal morbidity composite for use of aspirin and was reported to result in similar results.[33,]

Peguero et al (2021) reported results of an RCT conducted at 7 maternity units in Spain between 2016 and 2019 including 178 pregnant women (singleton) with late preterm preeclampsia from 34+0 to 36+6 weeks gestation (NCT02373839).[34,] The participants were assigned to planned delivery based on PlGF results (n=88) or expectant management under usual care following Spanish guidelines (n=90). A blood sample was collected and analyzed for all participants but results were revealed only in the PlGF group. PlGF was measured using the Elecsys test. In the PlGF group, planned delivery was recommended if PlGF was below 60 pg/mL. The coprimary outcomes were maternal progression to preeclampsia with severe features as defined by ACOG and neonatal outcome morbidity at hospital discharge determined by the morbidity assessment index for newborns (MAIN) score. The hypothesis for the neonatal coprimary outcome was a noninferiority hypothesis. The mean age of participants was 33 years and the mean gestational age at enrollment was 35 weeks. 51% of participants were White. 21% of participants received low-dose aspirin prophylaxis. The proportion of women with progression to preeclampsia with severe features was significantly lower in the PlGF group (22%) than in the usual care group (42%; adjusted relative risk=0.5; 95% CI, 0.33 to 0.76; p<.01). The proportion of infants with neonatal morbidity was not statistically significantly different between groups (14% versus 18% in PlGF versus usual care) and did not contain the noninferiority margin (adjusted relative risk=0.77; 95% CI, 0.39 to 1.53; p=.45). [34,]

De Oliveira et al (2023) reported results of the PREPARE (Prematurity Reduction by Preeclampsia Care) trial (NCT03073317).[35,] PREPARE was a stepped-wedge, cluster RCT conducted in 7 tertiary centers in Brazil from 2017 to 2019. The trial enrolled 1250 pregnant patients (singleton) between 20+0 and 36+6 weeks gestation with suspected or confirmed preeclampsia. The control group (n=566) was managed according to local treatment guidance. The intervention group (n=684) consisted of 2 risk stratification components. Risk of adverse maternal outcomes related to preeclampsia was estimated using an algorithm called fullPIERS which combines maternal symptoms, signs and laboratory tests.[36,] In addition, samples were collected for sFlt-1/PlGF ratio measured using the Elecsys test. If sFlt-1/PlGF ≤38 and fullPIERS <10%, patients were considered low risk and clinicians received recommendations to defer delivery, unless clinical conditions deteriorated, with repeat testing. If sFlt-1/PlGF >38 or fullPIERS ≥10%, patients were considered not low risk, and clinicians received recommendations to increase surveillance. The primary outcome was the proportion of patients with preterm preeclampsia who delivered at <37 weeks gestation/total deliveries. The median age of participants was 30 years, and the median gestational age at enrollment was 33 weeks. The ethnicities were reported as: 47% White, 15% Black, 37% Brown-mixed. 17% of participants received low dose aspirin supplementation. 60% of patients in the intervention group were classified as not low risk based on sFlt-1/PlGF or fullPIERS test; most of these were not low risk based on sFlt-1/PlGF alone. The authors acknowledged difficulties with statistical analyses. The denominators vary across outcomes between using the total number of deliveries at the sites and the number of deliveries for preeclampsia. For the primary outcome, 1.1% (375/35,129 total births) in the intervention group versus 1.4% (365/26,847 total births) delivered prior to 37 weeks; however, after adjustment for

confounders, the adjusted risk ratio indicated increased risk of the primary outcome in the intervention group (adjusted risk ratio=1.5; 95% CI, 1.0 to 2.0; p=.03). When the denominator was limited to patients with preeclampsia, there was no difference in the proportion of deliveries before 37 weeks (72% vs 66%; adjusted p=.93). The median time from enrollment to delivery was longer in the control group (6.5 vs 9 weeks; adjusted p<.01).[35,]

Section Summary: Maternal Serum Biomarker Testing for Preeclampsia in Pregnant People With Known Risk Factors

Studies evaluating maternal serum biomarker measurement have found sFlt-1, PlGF, and the sFlt-1/PlGF ratio associated with development of preeclampsia in women with known risk factors. However, evidence on clinical utility of maternal serum biomarker measurement is limited due to lack of consensus on cutoffs and related clinical management decisions and inconsistency in results from RCTs. One sFlt-1/PlGF ratio test (KRYPTOR) has been cleared in the US. The KRYPTOR test was not used in any of the RCTs. It is unclear what clinical decision(s) the KRYPTOR test is meant to inform and at what cutoffs.

Maternal Serum Biomarker Testing for Spontaneous Preterm Birth in Pregnant People Without Known Risk Factors

Clinical Context and Test Purpose

Accurate identification of pregnant people at risk of delivering preterm could impact management decisions and reduce maternal and fetal morbidity and mortality. Maternal serum biomarker testing is proposed as an adjunct to standard methods to accurately identify women at risk of spontaneous preterm birth and to determine potential therapies that could prevent preterm birth.

The following PICO was used to select literature to inform this review:

Populations

The relevant population of interest is pregnant people without known risk factors for spontaneous preterm birth.

Interventions

The test being considered is maternal serum biomarker testing with or without additional algorithmic analysis to predict risk of preterm birth. The use of maternal serum biomarker testing to predict risk of spontaneous preterm birth involves measuring serum biomarkers with or without additional algorithmic analysis that includes clinical factors, and analyzing the results within the context of maternal risk factors. Results of testing could be used to determine potential therapies to prevent spontaneous preterm birth.

Biomarkers that have been investigated for prediction of spontaneous preterm birth in women without known risk factors include insulin-like growth factor binding protein-4 (IBP4) and sex hormone binding globulin (SHBG).

The commercially produced PreTERM test (Sera Prognostic)[15,] combines measures of IBP4 and SHBG in an algorithmic analysis that includes biometric measures to assess the risk of spontaneous preterm birth. The PreTRM test is only intended for use in pregnant women with a singleton pregnancy and no signs or symptoms of preterm labor, with intact membranes, and with no first trimester progesterone. The PreTRM test is performed via a single blood draw during the 19th week of gestation.

Comparators

The following practice is currently being used to identify pregnant people at risk of spontaneous preterm birth: standard clinical management without serum biomarker testing for spontaneous

preterm birth. Standard clinical management involves assessment of medical history, clinical and modifiable risk factors, and measurement of cervical length.

Outcomes

The general outcomes of interest are accurate identification of people at risk of spontaneous preterm birth who may be suitable candidates for interventions to prevent preterm birth, which in turn could reduce maternal and fetal morbidity. These outcomes include intrapartum and postpartum infection, and psychosocial adverse effects in the mother. In infants born preterm, outcomes include avoiding or preventing complications due to immature organ systems and fetal or neonatal mortality.

Study Selection Criteria

For the evaluation of clinical validity of the maternal serum biomarker tests for spontaneous preterm birth, studies that meet the following eligibility criteria were considered:

- The study includes a validation cohort independent of the development cohort.
- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Nonrandomized Studies

Saade et al (2016) reported on the development and validation of IBP4 and SHBG testing for prediction of spontaneous preterm birth in the Proteomic Assessment of Preterm Risk (PAPR) study.[37,] The PAPR study prospectively enrolled 5501 women with a singleton pregnancy and without risk factors for spontaneous preterm birth from the 17th to 28th week of gestation. Analysis of serum samples collected during the development phase of PAPR identified IBP4 and SHBG as potential predictors of spontaneous preterm delivery based on an analysis of 44 biomarkers. In addition, the optimal timing of serum sampling was determined to be from 19 weeks, 0 days to 21 weeks, 6 days. Following delivery, investigators identified 217 cases of spontaneous preterm birth and 4292 controls. Using a cut-off of <37 versus ≥37 gestational weeks, the IBP4/SHBG ratio sensitivity was 75% and specificity 74% (95% CI not reported). This corresponded to an AUROC of 0.75 (95% CI, 0.56 to 0.91). Lowering the gestational age cut-off to 35 weeks, sensitivity improved to 100%, specificity 83%, and AUROC 0.93 (95%, CI 0.81 to 1.00) (Table 8). A limitation of the study was the lack of cervical measurement by transvaginal ultrasound in 2/3 of study participants.

Markenson et al (2020) assessed the clinical validity of the IBP4/SHBG ratio for prediction of spontaneous preterm birth in The Multicenter Assessment of a Spontaneous Preterm Birth Risk Predictor (TREETOP) study.[38,] TREETOP prospectively enrolled 5011 women with a singleton pregnancy who were asymptomatic for preterm birth. TREETOP was planned as a 2-phase study. In the first phase of the study 1251 (of 5011) women were randomly selected for inclusion. Of those 1251 women, 847 who had serum sampling conducted from 19 weeks, 1 day to 20 weeks, 6 days (the optimal timing determined in PAPR) were ultimately included in the results. A cut-off of <32 weeks gestational age was associated with an AUROC of 0.71 (95% CI, 0.55 to 0.87). When stratified according to body mass index (BMI) that was either >37 kg/m2 or ≤22 kg/m2, the AUROC improved to 0.76 (95% CI, 0.59 to 0.93) (Table 8). No data were reported for other potential maternal factors that could impact the predictive ability of the IBP4/SHBG ratio, such as maternal age and cervical length. Sensitivity and specificity were also not reported by Markenson et al. Assessment of these measures is planned for inclusion in the currently unpublished 2nd phase of the TREETOP study.

Both the PAPR and TREETOP studies were funded by Sera Prognostics, the manufacturer of the PreTRM test.[15,]

Table 8. Diagnostic Accuracy of the IBP4/SHBG Ratio for Prediction of Spontaneous Preterm Birth

Study	Cut-Off Point(s)	Sensitivity	Specificity	AUROC
PAPR[37,]	<37 weeks	75% (95% CI, NR)	74% (95% CI, NR)	0.75 (95% CI, 0.56 to 0.91)
	<35 weeks	100% (95% CI, NR)	83% (95% CI, NR)	0.93 (95% CI, 0.81 to 1.00)
TREETOP[38,]	<32 weeks	NR	NR	0.71 (95% CI, 0.55 to 0.87)
	<32 weeks and pre-pregnancy BMI >37 kg/m2 or ≤22 kg/m2	NR	NR	0.76 (95% CI, 0.59 to 0.93)

BMI: body mass index; CI: confidence interval; NR: not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility through a chain of evidence. Evidence from the PAPR and TREETOP studies did not demonstrate clinical validity due to the imbalance of sensitivity and specificity in PAPR and the limited evidence on measures of diagnostic accuracy in TREETOP.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Branch et al (2023) conducted a RCT[39,] that compared the rate of spontaneous preterm birth in low risk women who underwent testing with PreTRM versus those who had no PreTRM testing (Table 9). PreTRM testing incorporates the IBP4/SHBG ratio and maternal clinical characteristics into an algorithmic risk assessment. Women with a singleton pregnancy with cervical length ≥2.5 cm and no clinical risk factors for spontaneous preterm birth were randomized to testing with PreTRM (n=595) or no testing (n=596). Women who were randomized to the PreTRM testing group and had a positive screen (33.3% [198/595]) were offered a preterm birth prevention protocol that included progesterone supplementation (either weekly intramuscular 17-hydroxyprogesterone 250 mg or daily vaginal progesterone 200 mg), serial measurement of cervical length, low-dose aspirin (81 mg/day), and additional clinical monitoring. Women randomized to PreTRM testing who had a negative screen received undefined standard obstetric care, as did women randomized to the no testing group and women in any group who had unusable serum samples.

No difference was found in the rate of spontaneous preterm birth among woman managed with PreTRM (2.7% [16/589]) versus without PreTRM (3.5% [21/593]; p=.41). There was also no clear difference in neonatal gestational age at delivery or in length of neonatal intensive care stay (Table 10). The trial had numerous methodological limitations (Tables 11 and 12). Notably, the trial was terminated after 10 months due to insufficient funding. In addition to the limitations delineated in Tables 11 and 12, the study protocol was amended mid-study, changing prespecified neonatal outcomes.

Table 9. PreTRM RCT Study Characteristics

Study	Countries	Sites	Dates	Population	Interventions	
					PreTRM testing	No PreTRM testing
Branch et al 2021[39,]	US	NR; multiple sites described as clinic-based, community-based and hospital-based	2018-2019 (early termination)	Pregnant women >18 years of age Cervical length >2.5 cm No medical contraindications to continuing pregnancy Intact membranes No signs or symptoms of preterm labor	n=595	n=596

NR: not reported.

Table 10. PreTRM RCT Study Results

Study	Spontaneous Preterm Birth	Gestational Age at Delivery	NICU Length of Stay
Branch et al 2021[39,]			
Intervention	2.7% (16/589)	39.1 weeks (IQR, 38.6 to 39.7)	0.7 (SD, 3.8) days
Control	3.5% (21/593)	39.1 weeks (IQR, 38.7 to 39.7)	1.4 (SD, 9.5) days
p value	.41	.46	.49

IQR: interquartile range; NICU: neonatal intensive care unit; SD: standard deviation.

Table 11. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Branch et al 2021[39,]	4; Black women were underrepresented	5; Uptake of prevention protocol in screen-positive women incompletely reported and varied according to protocol component	1; The "standard obstetric care" comparator is undefined and may have varied according to study site	4; Positive screening result derived from results of an unpublished pilot study	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 12. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Branch et al 2021[39],		4; Blinding is unclear. The study is described as open-label in the registered protocol but blinding is not clearly reported in the publication		4; Woman randomized to screening with unusable serum sample added to no screening group (n=not reported) 7; Trial was terminated early (at 10 months) by the sponsors due to insufficient funding	4; Trial was underpowered; 1,208 women were enrolled of a planned enrollment of approximately 10,000	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Maternal Serum Biomarker Testing for Spontaneous Preterm Birth in Pregnant People Without Known Risk Factors

The IBP4/SHBG ratio demonstrated acceptable discrimination, based on AUROC, in identifying asymptomatic women who may be at risk of preterm birth when stratified according to gestational age of 32, 35, and 37 weeks based on evidence from 2 industry-sponsored observational studies. However, a randomized trial did not find a difference in risk of preterm birth with use of the PreTRM test, which includes the IBP4/SHBG ratio as part of an algorithmic analysis, versus no use. There were also no differences in neonatal outcomes between women who underwent PreTRM testing versus no testing.

Maternal Serum Biomarker Testing for Spontaneous Preterm Birth in Pregnant People With Known Risk Factors

Clinical Context and Test Purpose

Accurate identification of pregnant people at risk of delivering preterm could impact management decisions and reduce maternal and fetal morbidity and mortality. Maternal serum biomarker testing is proposed as an adjunct to standard methods to accurately identify women at risk of spontaneous preterm birth and to determine potential therapies that could prevent preterm birth.

The following PICO was used to select literature to inform this review:

Populations
The relevant population of interest is pregnant people with known risk factors for spontaneous preterm birth.

Interventions
The test being considered is maternal serum biomarker testing with or without additional algorithmic analysis to predict risk of preterm birth. The use of maternal serum biomarker testing to predict risk of spontaneous preterm birth involves measuring serum biomarkers with or without additional algorithmic analysis that includes clinical factors, and analyzing the results within the context of maternal risk factors. Results of testing could be used to determine potential therapies to prevent development of preeclampsia.

The PreTRM test[15,] is not indicated for use in women with known risk factors for spontaneous preterm birth.

Comparators
The following practice is currently being used to identify pregnant people at risk of preeclampsia: standard clinical management without serum biomarker testing for spontaneous preterm birth. Standard clinical management involves assessment of medical history, clinical and modifiable risk factors, and measurement of cervical length.

Outcomes
The general outcomes of interest are accurate identification of people at risk of spontaneous preterm birth who may be suitable candidates for interventions to prevent preterm birth, which in turn could reduce maternal and fetal morbidity. These outcomes include intrapartum and postpartum infection, and psychosocial adverse effects in the mother. In infants born preterm, outcomes include a reduction in complications due to immature organ systems and fetal or neonatal mortality.

Study Selection Criteria
For the evaluation of clinical validity of the maternal serum biomarker tests for spontaneous preterm birth, studies that meet the following eligibility criteria were considered:

- The study includes a validation cohort independent of the development cohort.
- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
Systematic Reviews
A systematic review of 72 observational studies (N=89,786) conducted by Conde-Agudelo et al (2011)[40,] evaluated 30 biomarkers for prediction of spontaneous preterm birth. The review included cohort, cross-sectional, or case-control studies conducted in women with singleton pregnancy and without symptoms indicating impending spontaneous preterm birth. Of the 30 biomarkers assessed in the review, 18 were serum biomarkers that included:

- Activin-A
- A-disintegrin and metalloprotease-12
- Alkaline phosphatase
- C-reactive protein

- Endoglin
- Ferritin
- Granulocyte colony-stimulating factor
- Interferon-Y
- Interleukin-10
- Interleukin-2
- Interleukin-6
- Placental protein 13
- Pregnancy-associated plasma protein A
- Pregnancy-specific beta-1-glycoprotein
- Relaxin
- Soluble intercellular adhesion molecule
- Thrombin-antithrombin III complex
- Tumor necrosis factor alpha

Serum alpha-fetoprotein and estriol were specifically excluded from the review, as they were previously established as having minimal utility in predicting spontaneous preterm birth.[41,] The predictive ability of 7 biomarkers evaluated in multiple studies appears in Table 13; none demonstrated adequate predictive ability suitable for use in clinical practice. The remaining 11 biomarkers were assessed in single studies and were also poor predictors of spontaneous preterm birth based on low sensitivity.

Table 13. Results of a Systematic Review of the Predictive Value of Individual Biomarkers Assessed in Multiple Studies[40,]

Biomarker	Cut-off Point(s)	Number of Studies	N	Sensitivity	Specificity	Test for Heterogeneity (I^2; 95% CI NR)
C-reactive protein	<32 weeks	2	162	27% (95% CI, 19 to 38%)	77% (95% CI, 66 to 84%)	0%
	<34 weeks	3	990	21% (95% CI, 16 to 27%)	65% (95% CI, 62 to 69%)	57%
	<37 weeks	7	3964	37% (95% CI, 33 to 41%)	51% (95% CI, 33 to 41%)	94%
Ferritin	<32 weeks	5	2054	32% (95% CI, 25 to 39%)	86% (95% CI, 84 to 87%)	3%
	<34 weeks	3	924	23% (95% CI, 17 to 29%)	83% (95% CI, 80 to 86%)	95%
	<37 weeks	6	3054	28% (95% CI, 24 to 32%)	82% (95% CI, 80 to 83%)	0%
Granulocyte colony-stimulating factor	<34 weeks	2	2066	27% (95% CI, 24 to 31%)	76% (95% CI, 74 to 78%)	84%
	<37 weeks	2	2642	28% (95% CI, 26 to 31%)	75% (95% CI, 73 to 77%)	0%
Interleukin-6	<34 weeks	2	1718	22% (95% CI, 18 to 26%)	77% (95% CI, 74 to 79%)	0%
Pregnancy-associated plasma protein	<34 weeks	2	55,565	13% (95% CI, 11 to 15%)	94% (95% CI, 93 to 94%)	61%
	<37 weeks	4	61,768	11% (95% CI, 10 to 12%)	93% (95% CI, 93 to 93%)	15%
Relaxin	<34 weeks	3	1249	22% (95% CI, 16 to 29%)	45% (95% CI, 42 to 48%)	71%

Biomarker	Cut-off Point(s)	Number of Studies	N	Sensitivity	Specificity	Test for Heterogeneity (I^2; 95% CI NR)
	<37 weeks	5	1749	38% (95% CI, 31 to 45%)	58% (95% CI, 56 to 61%)	69%
Thrombin-antithrombin III complex	<37 weeks	2	971	43% (95% CI, 38 to 49%)	59% (95% CI, 55 to 63%)	84%

CI: confidence interval; NR: not reported.

No studies evaluating maternal serum biomarkers with algorithmic analysis in women with known risk factors for spontaneous preterm birth were identified.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility through a chain of evidence. Testing of individual biomarkers did not demonstrate clinical validity based on low sensitivities, and no studies assessing biomarker testing with algorithmic analysis were identified.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs comparing women with versus without serum biomarker testing were identified.

Section Summary: Maternal Serum Biomarker Testing for Spontaneous Preterm Birth in Pregnant People with Known Risk Factors

A systematic review analyzing the predictive ability of individual maternal serum biomarkers did not identify any biomarker that adequately identified women at risk of spontaneous preterm birth based on high sensitivity and specificity. No studies assessing maternal serum biomarkers as part of an algorithmic analysis were identified, nor were any RCTs comparing management with versus without serum biomarker testing.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Obstetricians and Gynecologists and The Society for Maternal-Fetal Medicine

The American College of Obstetricians and Gynecologists (ACOG) issued practice bulletins in 2020 on preeclampsia[4,] and 2021 on preterm birth.[11,] Maternal serum biomarker screening is described as

investigational and is not recommended by ACOG as a factor included in risk assessment for either preeclampsia or spontaneous preterm birth.

The 2021 joint ACOG-Society for Maternal-Fetal Medicine (SMFM) guidance on the use of aspirin for prevention of preeclampsia does not include results of maternal serum biomarker testing among the risk factors to be used to identify women at risk of preeclampsia.[42,]The guidance was reaffirmed in October 2022.

International Federation of Gynecology and Obstetrics

The International Federation of Gynecology and Obstetrics (FIGO) Initiative on Preeclampsia (PE) published a guide for first trimester screening and prevention of preeclampsia in 2019.[6,]The writing committee included representation from the National Institutes of Health (US Department of Health and Human Services) and the Society for Maternal-Fetal Medicine (Washington, DC). The guideline states that 'All pregnant women should be screened for preterm PE during early pregnancy by the first-trimester combined test with maternal risk factors and biomarkers as a one-step procedure.' The guidance further states that 'The best combined test is one that includes maternal risk factors, measurements of mean arterial pressure (MAP), serum placental growth factor (PlGF) and uterine artery pulsatility index (UTPI).' The combined test referred to in the guidance is the Fetal Medicine Foundation (FMF) risk calculator.

International Society for the Study of Hypertension in Pregnancy

The International Society for the Study of Hypertension in Pregnancy (ISSHP) issued practice guidelines in 2021 on classification, diagnosis and management of hypertension in pregnancy.[43,] The ISSHP committee included US representation. The guidelines make the following recommendation: 'To the assessment of women suspected of having pre-eclampsia (<37 weeks), we recommend adding evaluation of angiogenic imbalance, when available, as a marker of uteroplacental dysfunction to be used in conjunction with other clinical tests.' The quality of the evidence for the recommendation was rated as 'Moderate' and the strength of recommendation was rated as 'Strong'. Angiogenic imbalance was defined as reduced PlGF (<5th centile for gestational age) or increased sFlt/PlGF ratio.

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (NICE) published guidance in 2022 on PLGF-based testing to help diagnose suspected preterm pre-eclampsia.[44,] The guidance recommends use of four tests 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 and 6 days of pregnancy) pre-eclampsia. The tests are: DELFIA Xpress PLGF 1-2-3, DELFIA Xpress sFlt-1/PLGF 1-2-3 ratio, Elecsys immunoassay sFlt-1/PLGF ratio, Triage PLGF Test. The guidance states that "BRAHMS sFlt-1 KRYPTOR/BRAHMS PLGF plus KRYPTOR PE ratio is not recommended for routine use in the NHS. Further research is needed to show the accuracy of this test when using specified thresholds."

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (USPSTF) issued updated recommendations in 2023 on screening for hypertensive disorders of pregnancy.[16,] The recommendation states: "Several models have been developed with the aim of identifying pregnant individuals who are at risk of developing preeclampsia. Many of these models include variables for medical history, patient characteristics, blood serum biomarkers (e.g., serum placental growth factor), mean arterial pressure (MAP), and ultrasound readings (e.g., Doppler uterine artery pulsatility index). The most extensively researched of these are various iterations of the Fetal Medicine Foundation (FMF) model. Currently, risk assessment and risk prediction tools are being used to inform the use of aspirin for prevention of preeclampsia; however, no randomized controlled trials (RCTs) have incorporated the use of a risk prediction model to evaluate the optimal frequencies or intervals of screening for hypertensive disorders of pregnancy. In the absence of clinical implementation studies, it is not yet clear whether screening informed by risk prediction models would necessarily be superior to risk evaluations based on clinical history

taking. Moreover, it remains to be seen whether risk-based screening protocols, regardless of the risk-assessment approach used, could improve outcomes relative to usual care screening."
The USPSTF issued updated recommendations in 2021 on the use of aspirin for the prevention of preeclampsia.[5,] The USPSTF recommendation notes "predictive models that combine risk factors to identify pregnant persons at risk for preeclampsia, such as serum biomarkers, uterine artery Doppler ultrasonography, and clinical history and measures, have been developed. However, there is limited evidence from external validation and implementation studies to demonstrate sufficient accuracy of predictive models for clinical use."

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 14.

Table 14. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
ISRCTN85912420[b]	Does repeat placental growth factor blood sample testing reduce harm from pre-eclampsia to babies? (PARROT 2)	1280	Mar 2023
NCT03231657	Randomizated Open-label Control Trial to Evaluate if the Incorporation of sFlt1/PlGF Ratio in the Diagnosis and Classification of PE Improves Maternal and Perinatal Outcomes in Women With the Suspicion of the Disease (EuroPE Study)	2536	Nov 2023
NCT03151330	Serum Assessment of Preterm Birth: Outcomes Compared to Historical Controls	2,100	Nov 2023
NCT05131282	A Case-control Study to Investigate SerumMarkers in Predicting Preeclampsia	300	Dec 2023
NCT04766866	Protocol of the PE37 Study: A Multicenter Randomized Trial of Screening With sFlt1/PlGF and Planned Delivery to Prevent Preeclampsia at Term	9132	Dec 2024
NCT05521776	Impact of First-trimester Preeclampsia Screening on Perinatal and Maternal Morbidity : a Multicenter Randomized Trial	14,500	Oct 2025
NCT05228002	sFlt-1/PlGF Ratio: Impact on the Management of Patients With Suspected Pre-eclampsia	160	Jul 2025
NCT04301518[a]	Prematurity Risk Assessment Combined With Clinical Interventions for Improving Neonatal outcoMEs	6,500	Dec 2026
Unpublished			
NCT03455387	Evaluation of the SerumMarkers sFLt1 and PlGF for the Prediction of the Complications of the Placental Vascular Pathologies in the 3rd Quarter of the Pregnancy	233	Dec 2019
NCT03289611	Preeclampsia Ratio (sFlt-1/PlGF) Evaluation for Clinical and Obstetrical Guidance (PRECOG)	84	Aug 2020

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.
[b] Registered in the ISRCTN registry. ISRCTN registry is a clinical trial registry recognized by the World Health Organization (WHO) and the International Journal of Medical Journal Editors (ICMJE).

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0243U	Obstetrics (preeclampsia), biochemical assay of placental-growth factor, time-resolved fluorescence immunoassay, maternal serum, predictive algorithm reported as a risk score for preeclampsia
	0247U	Obstetrics (preterm birth), insulin-like growth factor-binding protein 4 (IBP4), sex hormone-binding globulin (SHBG), quantitative measurement by LC-MS/MS, utilizing maternal serum, combined with clinical data, reported as predictive-risk stratification for spontaneous preterm birth

Type	Code	Description
	0390U	Obstetrics (preeclampsia), kinase insert domain receptor (KDR), Endoglin (ENG), and retinol-binding protein 4 (RBP4), by immunoassay, serum, algorithm reported as a risk score
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
04/01/2022	New policy.
04/01/2023	Annual review. No change to policy statement. Literature review updated.
08/01/2023	Coding update.
04/01/2024	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Maternal Serum Biomarkers for Prediction of Adverse Obstetric Outcomes 2.04.152 **Policy Statement:** I. The use of maternal serum biomarker tests with or without additional algorithmic analysis for prediction of preeclampsia is considered **investigational.** II. The use of maternal serum biomarker tests with or without additional algorithmic analysis for prediction of spontaneous preterm birth is considered **investigational.**	**Maternal Serum Biomarkers for Prediction of Adverse Obstetric Outcomes 2.04.152** **Policy Statement:** I. The use of maternal serum biomarker tests with or without additional algorithmic analysis for prediction of preeclampsia is considered **investigational.** II. The use of maternal serum biomarker tests with or without additional algorithmic analysis for prediction of spontaneous preterm birth is considered **investigational.**