
Medical Policy



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(See policy history boxes for previous effective dates)

Title: Maternal Serum Biomarkers for Prediction of Adverse Obstetric Outcomes

Description/Background

Improved accuracy of the identification of women 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 women at risk of preeclampsia and spontaneous preterm birth.

Preeclampsia

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.(1) 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.(2) 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).(3,4) Currently, maternal serum biomarkers are not included in either USPSTF guidelines or ACOG risk factor assessment when determining appropriate candidates for aspirin prophylaxis.

Despite decades of research, accurate identification of women at risk of preeclampsia, particularly prior to the 20th week of gestation, remains challenging.(2) 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.3, 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.5, 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.(6) 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, resulting in reduced maternal and perinatal morbidity and mortality.

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.(7) 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.(8) 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.(9) 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.(10)

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.(10) 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.(10)

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.(11)

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.

Commercially produced, maternal serum biomarker tests for preeclampsia include the Triage PIGF™ (Quidel), Elecsys sFlt-1/PIGF™ (Roche Diagnostics), and DELFIA Xpress PIGF 1-2-3™ (PerkinElmer).(12) These commercially produced tests are not currently available in the United States.

The PreTRM™ test (Sera Prognostics) (13) 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.

The B·R·A·H·M·S PIGF plus KRYPTOR (ThermoFisher Scientific) is an automated immunofluorescent assay using Time-Resolved Amplified Cryptate Emission (TRACETM) technology for the quantitative determination of the concentration of Placental Growth Factor (PIGF) in human serum and plasma (K2 EDTA) on the B·R·A·H·M·S KRYPTOR analyzer.

The B·R·A·H·M·S PIGF plus KRYPTOR is to be used in conjunction with the B·R·A·H·M·S sFlt-1 KRYPTOR 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.

Medical Policy Statement

The use of maternal serum biomarker tests with or without additional algorithmic analysis for prediction of preeclampsia is considered investigational. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

The use of maternal serum biomarker tests with or without additional algorithmic analysis for prediction of spontaneous preterm birth is considered investigational. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

0243U 0247U 0390U

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

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.

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

Clinical Context and Test Purpose

Accurate identification of women at risk of preeclampsia without obvious risk factors has the potential to reduce maternal and perinatal morbidity and mortality. The use of multianalyte maternal serum biomarker assays is proposed as an adjunct to screening based on patient history and clinical characteristics to identify women at risk of preeclampsia and to determine potential therapies that could prevent development of preeclampsia.

The question addressed in this evidence review is: Does use of maternal serum biomarker testing with or without additional algorithmic analysis as an adjunct to standard clinical management improve identification of women at risk of developing preeclampsia and improve maternal or fetal health outcomes relative to standard clinical management alone?

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

Populations

The relevant population of interest is pregnant women without known risk factors for the development of preeclampsia.

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 (PIGF) and soluble Fms-like tyrosine kinase 1 (sFlt-1). The predictive ability of the sFlt-1/PIGF ratio has also been investigated. A review of reviews conducted by Townsend et al (2018)¹⁴, on preeclampsia risk prediction identified sFlt-1 and PIGF as the maternal serum biomarkers with the most robust evidence available.

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

Comparators

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

- 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

Agrawal et al (2019) (15) conducted a systematic review that included 40 observational studies (N=92,687) on the predictive ability of PIGF testing in women without known risk factors (Table 1). Studies that analyzed PIGF in conjunction with other biomarkers were excluded. The timing of PIGF 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. 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 (I²=99%).

A second systematic review conducted by Agrawal et al (2018) (16) assessed the diagnostic accuracy of the sFlt-1/PIGF ratio for prediction of preeclampsia (Table 1). The review included 15 studies, all assessing risk after the 19th week of gestation. Among the 15 included studies (N=20,121), 8 were conducted in women (N =19,038) at low-risk of developing preeclampsia based on clinical characteristics. Sensitivity and specificity ranged widely in the individual studies, which reported sensitivities of 23% to 97% and specificities from 64% to 100%. When pooled, sensitivity was 77% (95% CI, 61% to 88%) and specificity was 94% (95% CI, 88% to 97%) with very high heterogeneity (I²=94% and 100%, respectively).

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) ¹⁵	PIGF	92,687	40	61% (95% CI, 53 to 69%)	85% (95% CI, 82 to 88%)
Agrawal et al (2018) ¹⁶	sFlt-1/PIGF ratio	19,038	8	77% (95% CI, 61% to 88%)	94% (95% CI, 88% to 97%)

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

Nonrandomized Studies

Relevant nonrandomized studies published subsequent to the systematic reviews are described below.

Parry et al (2022) (17) conducted a nested case-control study based on data from a prospective cohort study assessing the relationship between a range of maternal serum biomarkers, including sFlt-1, PIGF, and the sFlt-1/PIGF ratio, and risk of preeclampsia. The study compared 568 cases of preeclampsia with 911 healthy (term delivery with no adverse pregnancy outcomes) controls. Maternal serum samples were collected at 6 to 13 weeks (first visit) and 16 to 21 weeks (second visit). The study found that women who developed preeclampsia were more likely to have sFlt-1 and PIGF levels below normal at both the first visit and the second visit, and a higher sFlt-1/PIGF ratio at both visits relative to controls. However, AUC analyses did not indicate that these measures had acceptable discrimination at either time point. For sFlt-1, the AUC was 0.56 (95% CI, 0.53 to 0.59) at the first visit and 0.54 (95% CI, 0.50 to 0.57) at the second visit. AUCs for PIGF and the sFlt-1/PIGF ratio were 0.56 (95% CI, 0.52 to 0.59) and 0.51 (95% CI, 0.48 to 0.54) at the first visit, and 0.62 (95% CI, 0.59 to 0.65) and 0.57 (95% CI, 0.54 to 0.60) at the second visit. Results were similar for other maternal serum biomarkers (e.g., PAPP-A), and study authors concluded that use of these biomarkers to predict adverse pregnancy outcomes were not supported by the study results.

Mazer Zumaeta et al (2020) (18) conducted a cohort study evaluating the diagnostic accuracy of adding measurement of PIGF and PAPP-A using the DELFIA Xpress assay system to standard clinical management. The study included 60,875 pregnant women undergoing routine, first trimester aneuploidy screening. PIGF and PAPP-A measurement took place at 11 to 13 weeks gestation. The addition of PIGF to maternal clinical characteristics was associated with improvement in the detection rate of preeclampsia at <34 and at <37 weeks ($p < .0001$ for both time points). Inclusion of PAPP-A was not associated with improved detection of preeclampsia at <34 weeks ($p = .08$) but did improve detection rate at <37 weeks ($p < .04$).

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.

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 were identified comparing health outcomes in women undergoing serum biomarker testing, nor were observational studies that reported on health outcomes in women managed with or without biomarker 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. Evidence from systematic reviews did not demonstrate adequate clinical validity based on the balance of sensitivity and specificity associated with the measurement of maternal serum biomarkers.

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 and 2 nonrandomized studies published subsequent to the systematic reviews. Serum biomarker testing was associated with high specificities but lower sensitivities. Direct evidence on clinical utility is limited due to lack of RCTs and heterogeneity among observational studies.

Maternal Serum Biomarker Testing for Preeclampsia in Women With Known Risk Factors

Clinical Context and Test Purpose

The question addressed in this evidence review is: Does use of maternal serum biomarker testing with or without additional algorithmic analysis as an adjunct to standard clinical management improve identification of women at risk of developing preeclampsia and improve maternal or fetal health outcomes relative to standard clinical management alone?

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

Populations

The relevant population of interest is pregnant women with known risk factors for the development of preeclampsia or with suspected preeclampsia.

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 PIGF and sFlt-1. The predictive ability of the sFlt-1/PIGF ratio has also been investigated. A review of reviews conducted by Townsend et al (2018)¹⁴, on preeclampsia risk prediction identified sFlt-1 and PIGF as the maternal serum biomarkers with the most robust evidence available.

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

Comparators

The following practice is currently being used to identify pregnant women 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 women 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:

- 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

Two systematic reviews conducted by Veisani et al (2019) (19) and Agrawal et al (2018) (16) assessed the diagnostic accuracy of sFlt-1, PIGF, and the sFlt-1/PIGF ratio for prediction of preeclampsia in women with known risk factors (Table 2). The Veisani review included 15 studies measuring sFLT-1 or PIGF at gestational weeks 1 to 12 in 1 study and in the 2nd or 3rd trimester in the remaining 14 studies. The review found serum sFlt-1 values above the study cut-off point were associated with an increased risk of preeclampsia based on 3 studies that reported odd ratios ranging from 2.20 to 7.50. The pooled odds ratio for sFlt-1 was 5.20 (95% CI, 1.24 to 9.16) with high heterogeneity (I²=82%). For PIGF, a serum level below the cut-off point was predictive of preeclampsia development based on 4 studies with individual odds ratios ranging from 2.30 to 4.28; pooled odds ratio was 2.53 (95% CI, 1.33 to 3.75) with no heterogeneity (I²=0%).

The systematic review conducted by Agrawal et al (2018) (16) (described above) assessing the diagnostic accuracy of the sFlt-1/PIGF 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). 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 (I²=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	OR
Veisani et al (2019) ¹⁹	sFlt-1	NR	3	NR	NR	5.20 (95% CI, 1.24 to 9.16)
Veisani et al (2019) ¹⁹	PIGF	NR	4	NR	NR	2.53 (95% CI, 1.33 to 3.75)
Agrawal et al (2018) ¹⁶	sFlt-1/PIGF ratio	1083	7	85% (95% CI, 66 to 94%)	87% (95% CI, 76 to 93%)	NR

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

Nonrandomized Studies

McCarthy et al (2019) conducted a retrospective analysis of data from industry-sponsored, prospective cohort studies comparing the diagnostic accuracy of 3 commercially produced maternal serum biomarker tests (Triage PIGF, DELFIA XPress PIGF 1-2-3 and Elecsys sFlt-1/PIGF).⁽¹²⁾ In this analysis, diagnostic accuracy was based on delivery within 14 days of testing due to preeclampsia in women (N=396) less than 35 weeks gestation. Sensitivities were 81% (95% CI, 61% to 93%), 88% (95% CI, 68% to 97%), and 75% (95% CI, 53% to

90%) for the Triage PIGF, DELFIA, and Elecsys tests, respectively. Corresponding specificities were 80% (95% CI, 74% to 84%), 77% (95% CI, 70% to 83%), and 90% (95% CI, 85% to 94%). The area under the receiver operating characteristic (AUROC) was 0.85 (95% CI, 0.75 to 0.95) for the Triage PIGF test, 0.86 (95% CI, 0.76 to 0.95) for the DELFIA test and 0.88 (95% CI, 0.78 to 0.97) for the Elecsys test.

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.

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 were identified.

Lim et al (2021) conducted a systematic review analyzing the clinical utility of sFlt-1 and PIGF individually and in combination as the sFlt-1/PIGF ratio in predicting adverse obstetric outcomes.⁽²⁰⁾ 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 and cut-off values for biomarkers, the definition of adverse obstetric outcomes, and the methods for reporting results. The timing of biomarker testing ranged from 18 to 40 weeks gestation. Evidence on the utility of PIGF and the sFlt-1/PIGF ratio is summarized in Table 3; evidence on sFlt-1 was too limited to pool. Although both PIGF and the sFlt-1/PIGF ratio were associated with AUROC values that suggested acceptable statistical discrimination for the outcomes analyzed, the clinical utility of the results is limited by significant heterogeneity and/or imprecision for nearly all outcomes.

Table 3. Results from a Systematic Review of the Clinical Utility of Individual Maternal Serum Biomarkers for Prediction of Preeclampsia

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 ²⁰	PIGF								
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/PIGF 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; PIGF: placental growth factor; sFlt-1: soluble fms-like tyrosine kinase-1.

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. Evidence from systematic reviews did not demonstrate adequate clinical validity due the limited number of included studies, the imbalance of sensitivity and specificity, and high heterogeneity.

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

Studies evaluating maternal serum biomarker measurement have found sFlt-1, PIGF, and the sFlt-1/PIGF 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 RCTs and heterogeneity among observational studies.

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

Clinical Context and Test Purpose

Accurate identification of pregnant women 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 question addressed in this evidence review is: Does maternal serum biomarker testing with or without additional algorithmic analysis adjunctive to standard clinical management improve identification of women at risk of spontaneous preterm birth and improve maternal or fetal health outcomes relative to standard clinical management alone?

Populations

The relevant population of interest is pregnant women 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)¹³, combines measures of IBP4 and SHBG in an algorithmic analysis that includes biometric measures to assess the risk of spontaneous preterm birth. The PreTERM 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 PreTERM 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 women 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 women 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:

- 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.(21) 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 4,292 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 4). 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.(22) TREETOP prospectively enrolled 5,011 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 4). 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.(13)

Table 4. Diagnostic Accuracy of the IBP4/SHBG Ratio for Prediction of Spontaneous Preterm Birth

Study	Cut-Off Point(s)	Sensitivity	Specificity	AUROC
PAPR ²¹ ,	<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 ²² ,	<32 weeks	NR	NR	0.71 (95% CI, 0.55 to 0.87)
	<32 weeks and pre-pregnancy BMI >37 kg/m ² or ≤22 kg/m ²	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.

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 (2021) conducted a RCT (23) 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 5). 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 6). The trial had numerous methodological limitations (Tables 7 and 8). Notably, the trial was terminated after 10 months due to insufficient funding. In addition to the limitations delineated in Tables 7 and 8, the study protocol was amended mid-study, changing prespecified neonatal outcomes.

Table 5. PreTRM RCT Study Characteristics

Study	Countries	Sites	Dates	Population	Interventions	
					PreTRM testing	No PreTRM testing
Branch et al 2021 ²³	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 6. PreTRM RCT Study Results

Study	Spontaneous Preterm Birth	Gestational Age at Delivery	NICU Length of Stay
Branch et al 2021 ²³			
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 7. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-up ^e
Branch et al 2021 ²³ ,	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 8. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Branch et al 2021 ²³ ,		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.

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. 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.

The only direct evidence on clinical utility comes from a methodologically flawed trial that did not find a significant benefit of PreTRM testing versus no testing.

Section Summary: Maternal Serum Biomarker Testing for Spontaneous Preterm Birth in Women 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 Women With Known Risk Factors

Clinical Context and Test Purpose

Accurate identification of pregnant women 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 question addressed in this evidence review is: Does maternal serum biomarker testing adjunctive to standard clinical management improve identification of women at risk of spontaneous preterm birth and improve maternal or fetal health outcomes relative to standard clinical management alone?

Populations

The relevant population of interest is pregnant women 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 test¹³, 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 women 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 women 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:

- 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) (24) 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- γ
- 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.²⁵ The predictive ability of 7 biomarkers evaluated in multiple studies appears in Table 9; 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 9. Results of a Systematic Review of the Predictive Value of Individual Biomarkers Assessed in Multiple Studies²⁴.

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%
	<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.

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.

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. Testing of individual biomarkers did not demonstrate clinical validity based on low sensitivities, and no studies assessing biomarker testing with algorithmic analysis were identified.

Section Summary: Maternal Serum Biomarker Testing for Spontaneous Preterm Birth in Women 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.

Summary of Evidence

For individuals who are pregnant without known risk factors for preeclampsia who receive maternal serum biomarker testing with or without additional algorithmic analysis, the evidence includes systematic reviews of observational studies and 2 nonrandomized studies published subsequent to the systematic reviews. Relevant outcomes are test validity, and maternal and perinatal morbidity and mortality. Evidence from 2 systematic reviews found serum biomarker testing measuring placental growth factor (PIGF) and the soluble Fms-like tyrosine kinase 1 (sFlt-1)/PIGF ratio was associated with high specificity but low sensitivity. Evidence on clinical utility is limited due to lack of randomized controlled trials (RCTs) and heterogeneity among observational studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are pregnant with known risk factors for preeclampsia who receive maternal serum biomarker testing with or without additional algorithmic analysis, the evidence includes systematic reviews of observational studies and cohort studies. Relevant outcomes are test validity, and maternal and perinatal morbidity and mortality. Studies evaluating the predictive ability of maternal serum biomarker testing have found measurement of sFlt-1, PIGF, and the sFlt-1/PIGF ratio can identify women at risk of developing preeclampsia. No RCTs were identified and heterogeneity was high among the observational studies. Commercially produced assays lack clinical utility as they are not currently available in the United States. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are pregnant without known risk factors for spontaneous preterm birth who receive maternal serum biomarker testing with or without additional algorithmic analysis, the evidence includes a RCT and cohort studies. Relevant outcomes are test validity, and maternal and perinatal morbidity and mortality. Measurement of the insulin-like growth factor binding protein-4 (IBP4) and sex hormone binding globulin (SHBG) ratio demonstrated acceptable discrimination in identifying asymptomatic women who may be at risk of preterm birth, based on evidence from 2 industry-sponsored cohort studies. However, a randomized trial did not find a difference in risk of preterm birth with use of the commercially produced 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 in infants of women who underwent PreTRM testing versus no testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are pregnant with known risk factors for spontaneous preterm birth who receive maternal serum biomarker testing with or without additional algorithmic analysis, the evidence includes a systematic review of observational studies. Relevant outcomes are test validity, and maternal and perinatal morbidity and mortality. The systematic review did not identify any individual 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 (3) and 2021 on preterm birth.⁽¹⁰⁾ 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.²⁶ The guidance was reaffirmed in October 2022.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (USPSTF) issued updated recommendations in 2021 on the use of aspirin for the prevention of preeclampsia.(4) The USPSTF does not include maternal serum biomarker testing among factors used in preeclampsia risk assessment. In addition, the 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."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 10.

Table 10. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT05131282	A Case-control Study to Investigate Serum Markers in Predicting Preeclampsia	300	Dec 2023
NCT04301518 ^a	Prematurity Risk Assessment Combined With Clinical Interventions for Improving Neonatal outcoMEs	6,500	Dec 2026
NCT03151330	Serum Assessment of Preterm Birth: Outcomes Compared to Historical Controls	2,100	Nov 2023
<i>Unpublished</i>			
NCT03455387	Evaluation of the Serum Markers sFLt1 and PIGF for the Prediction of the Complications of the Placental Vascular Pathologies in the 3rd Quarter of the Pregnancy	233	Dec 2019

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

Government Regulations National:

There is no national coverage determination on this topic.

Local:

There is no local coverage determination on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through November 13, 2023, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/24	12/19/23		Joint policy established Added Novel Biomarkers to Detect Risk of Preeclampsia (ThermoFisher Scientific - B·R·A·H·M·S PIGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR) to this policy. Vendor: N/A (ky)

Next Review Date: 4th Qtr, 2024

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: MATERNAL SERUM BIOMARKERS FOR PREDICTION OF ADVERSE OBSTETRIC OUTCOMES

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.