

MEDICAL POLICY – 2.04.152

Maternal Serum Biomarkers for Prediction of Adverse Obstetric Outcomes

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Replaces: N/A

RELATED MEDICAL POLICIES:

None

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Introduction

Maternal serum biomarker tests use blood samples to look for health problems during pregnancy. These tests can use one or more variables to try to predict health problems. Preeclampsia is unexpected high blood pressure in pregnancy. This condition can cause organ damage to the mother. It can also slow the baby's normal growth. In severe situations, it can be life-threatening for the mother and baby. Spontaneous preterm birth is when the baby is born too early, between the 20th and 37th week of pregnancy. The standard way to check for pre-eclampsia and preterm birth is to identify and monitor known risk factors. The use of maternal serum biomarker tests to predict pre-eclampsia and spontaneous preterm birth is unproven (investigational). More studies are needed to see if this type of testing improves health outcomes.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

| Test | Investigational |
|---------------------------------------|--|
| Maternal serum biomarker tests | <p>The use of maternal serum biomarker tests with or without additional algorithmic analysis for prediction of pre-eclampsia is considered investigational.</p> <p>The use of maternal serum biomarker tests with or without additional algorithmic analysis for prediction of spontaneous preterm birth is considered investigational</p> |

Coding

| 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 (i.e., PGIF Preeclampsia Screen by PerkinElmer Genetics, Inc., Brahms sFlt-1/ PIGF KRYPTOR Test System) |
| 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 (i.e., PreTRM test by Sera Prognostics, Inc.) |
| 0482U | Obstetrics (preeclampsia), biochemical assay of soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PIGF), serum, ratio reported for sFlt-1/PIGF, with risk of progression for preeclampsia with severe features within 2 weeks (new code effective 10/1/2024) |

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information



N/A

Evidence Review

Description

Improved accuracy of the identification of pregnant individuals 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 individuals at risk of pre-eclampsia and spontaneous preterm birth.

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 pregnant individuals and 1 in 3 among pregnant individuals 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 pre-eclampsia include progression to eclampsia, placental abruption, and a life-threatening complication known as 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 pregnant individuals 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 pregnant individuals 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 US Preventive Services Task Force (USPSTF) and the American College of Obstetricians and Gynecologists (ACOG).^{4,5}

Despite decades of research, accurate identification of pregnant individuals 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 pregnant individuals to 14.4% for non-Hispanic Black pregnant individuals. 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 pregnant individuals at an increased risk of preterm birth.¹¹ In pregnant individuals 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 pregnant individuals without a history of preterm birth or other risk factors, universal ultrasonographic screening of cervical length in pregnant individuals has not been demonstrated to be an effective strategy due to the overall low incidence in this group. In pregnant individuals 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 pregnant individuals at risk of preterm birth, including maternal serum biomarkers.¹²

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 clinical validity studies and a randomized controlled trial (RCT) that selected eligible participants based on an algorithm that included biomarker testing results. Relevant outcomes are test validity, maternal and perinatal morbidity and mortality, symptoms, functional outcomes, quality of life, hospitalizations, and resource utilization. The clinical validity studies primarily included populations from Europe and tests that are not cleared for use in the US. Placental growth factor (PIGF) cutoffs for identifying high risk



pregnant persons were not prespecified and varied significantly. The RCT used a test not cleared for use in the US to identify people for enrollment. 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 clinical validity studies and RCTs. Relevant outcomes are test validity, maternal and perinatal morbidity and mortality, symptoms, functional outcomes, quality of life, hospitalizations, and resource utilization. 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 pregnant individuals at risk of developing preeclampsia. One sFlt-1/PIGF ratio test system (KRYPTOR) has been cleared in the US. One prospective observational study (PRAECIS) has been conducted in a second and third trimester, US population reporting clinical validity of the KRYPTOR test system. PRAECIS included a racially diverse population reflective of US diversity. While PRAECIS proposed a cutoff for the sFlt-1: PIGF ratio of 40, other publications have proposed various cutoffs. The clinical decision that would be informed by the test is unclear. While five RCTs have been conducted using various biomarker tests, the KRYPTOR test system has not been used in any RCTs. 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 an RCT and cohort studies. Relevant outcomes are test validity, maternal and perinatal morbidity and mortality, symptoms, functional outcomes, quality of life, hospitalizations, and resource utilization. Measurement of the insulin-like growth factor binding protein-4 (IBP4) and sex hormone binding globulin (SHBG) ratio demonstrated acceptable discrimination in identifying asymptomatic pregnant individuals who may be at risk of preterm birth, based on evidence from two 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 pregnant individuals 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, maternal and perinatal morbidity and mortality, symptoms, functional outcomes, quality of life, hospitalizations, and resource utilization. The systematic review did not identify any



individual biomarker that adequately identified pregnant individuals 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.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in [Table 1](#).

Table 1. 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 | Randomized Open-label Control Trial to Evaluate if the Incorporation of sFlt1/PIGF 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 |
| NCT04766866 | Protocol of the PE37 Study: A Multicenter Randomized Trial of Screening With sFlt1/PIGF and Planned Delivery to Prevent Preeclampsia at Term | 9132 | Dec 2024 |
| NCT05131282 | A Case-control Study to Investigate SerumMarkers in Predicting Preeclampsia | 300 | Dec 2023 |
| NCT04301518^a | Prematurity Risk Assessment Combined With Clinical Interventions for Improving Neonatal outcoMEs | 6500 | Dec 2026 |
| NCT03151330 | Serum Assessment of Preterm Birth: Outcomes Compared to Historical Controls | 2100 | Nov 2023 |



| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|-----------------------------|---|--------------------|-----------------|
| NCT05521776 | Impact of First-trimester Preeclampsia Screening on Perinatal and Maternal Morbidity : a Multicenter Randomized Trial | 14500 | Oct 2025 |
| NCT05228002 | sFlt-1/PlGF Ratio: Impact on the Management of Patients With Suspected Pre-eclampsia | 160 | Jul 2025 |
| 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).

Practice Guidelines and Position Statements

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

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or the 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 preeclampsia⁴, 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 pregnant individuals 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 individuals 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 (PIGF) 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 pregnant individuals 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 PIGF (<5th centile for gestational age) or increased sFlt/PIGF 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."

US Preventive Services Task Force Recommendations

The US 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 US Preventive Services Task Force (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.



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 US 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/ PIGF 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 (PIGF) 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 individuals (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 PIGF (Quidel), Elecsys sFlt-1/PIGF (Roche Diagnostics), and DELFIA Xpress PIGF 1-2-3™ (PerkinElmer).¹³ 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 pregnant individuals 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.

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History

| Date | Comments |
|----------|--|
| 07/01/23 | New policy, approved June 13, 2023. Policy created with literature review through December 21, 2022. Maternal serum biomarker testing is investigational. Added new CPT code 0390U (new code effective 7/1/2023). |
| 05/01/24 | Annual Review, approved April 8, 2024. Policy updated with literature review through January 2, 2024; references added. Policy statements unchanged. Changed the wording from "women" to "pregnant individuals" throughout the policy for standardization. Removed HCPCS code 0390U. |
| 10/01/24 | Coding update. Added new CPT code 0482U. |

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2024 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member



benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

