Medical Coverage Policy | Maternal Serum Testing for Prediction of Adverse Obstetric Outcomes

EFFECTIVE DATE: 10|01|2026
POLICY LAST REVIEWED: 06|03|2026

OVERVIEW

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 testing is proposed as an adjunct to standard screening to identify pregnant people at risk of preeclampsia and spontaneous preterm birth.

The following test(s) are addressed in this policy:

- PlGF Preeclampsia Screen (PerkinElmer Genetics, Inc) CPT code 0243U
- PreTRM® (Sera Prognostics, Inc®) CPT code 0247U
- PreClaraTM Ratio (sFlt 1/PlGF) (Thermo Fisher Scientific) CPT code 0524U (Test Name Revision Effective 1/1/2026)

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable.

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

The use of maternal serum tests, including maternal serum cell-free RNA tests, with or without additional algorithmic analysis for prediction of preeclampsia is considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

The use of maternal serum tests with or without additional algorithmic analysis for prediction of spontaneous preterm birth is considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Commercial Products
Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. §27-19-81 described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the Evidence of Coverage or Subscriber Agreement for applicable not medically necessary/not covered laboratory benefits/coverage.

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. 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. Annually, more than 70,000 women and 500,000 newborns die from preeclampsia worldwide. In the US, this condition is often detected late, only through clinical diagnosis after organ damage has occurred, necessitating premature delivery. Currently, the risk assessment for preeclampsia is based on maternal medical history and clinical risk factors early in pregnancy. In response to the alarming maternal mortality rates in the US, the Foundation for the National Institutes of Health (FNIH) initiated a public-private partnership in 2024. This initiative aims to develop tools for identifying pregnant women at high risk of early-onset preeclampsia. This project is part of the FNIH Biomarkers Consortium and involves collaboration with the National Institutes of Health (NIH) and eight other partners from life sciences companies, academia, and nonprofit and patient advocacy organizations.

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. 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).

Despite decades of research, accurate identification of women at risk of preeclampsia, particularly prior to the 20th week of gestation, remains challenging. 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. 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. Multivariable preeclampsia risk assessment tools have been developed that incorporate maternal serum biomarkers; several of these tools

have been commercially produced but few have been externally validated. 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 10.41% (about 360,000 births were preterm among 3,600,000 births) in 2024 in the United States and has consistently been approximately 10% for over a decade. Preterm birth rates vary according to race and ethnicity independent of social determinants of health, ranging from 9.16% for Asian women to 14.86% 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. 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. 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.

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. 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.

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.

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. 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.

The Elecsys sFlt-1/PlGF assay was cleared for marketing by the FDA as a prognostic test in February 2025. The test was determined by the FDA to be substantially equivalent to the KRYPTOR system. Therefore, similar to the KRYPTOR system, the Elecsys assay is indicated "as an aid in the risk assessment of pregnant women, with a singleton pregnancy (23+0 to 34+6/7 weeks' gestation) hospitalized for hypertensive disorders of pregnancy (preeclampsia, chronic hypertension with or without superimposed preeclampsia, or gestational hypertension), to develop preeclampsia with severe features within 2 weeks from testing. The sFlt-1/PlGF ratio should be used in conjunction with clinical assessment and routine laboratory testing." Furthermore, the approval states that "The Elecsys sFlt-1 assay should be used only with the Elecsys PlGF assay and the Elecsys PlGF should be used only with the Elecsys sFlt-1 assay to calculate the ratio (sFlt-1:PlGF)."

Other commercially produced, maternal serum biomarker tests for preeclampsia include the Triage PlGF™ (Quidel) and DELFIA Xpress PlGF 1-2-3™ (Revity, formerly PerkinElmer), which are not currently available in the United States.

In May 2025, Mirvie announced the launch of Encompass™, a serum cell-free RNA screening test for preeclampsia that is done via an at-home visit. The performance characteristics of the Encompass test have been established in pregnant individuals age 35 years or older and without a pre-existing major risk factor for preeclampsia, with a singleton pregnancy between 17 weeks 4 days and 22 weeks 0 days gestation. Individuals are not eligible if they have any of the following pre-existing conditions: diabetes, prior pregnancy with preeclampsia, chronic hypertension, renal disease, systemic lupus erythematosus, or antiphospholipid antibody syndrome.

The PreTRM™ test (Sera Prognostics) uses maternal serum biomarkers (insulin-like growth factor bindingprotein-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.

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 (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 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 that measurement of soluble fms-like tyrosine kinase-1 (sFlt-1), PlGF, and the sFlt-1/PlGF ratio can identify women at risk of developing preeclampsia. Two sFlt-1/PlGF ratio tests, KRYPTOR and Elecsys have 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. Clinical validity of the Elecsys test was determined using archived samples from the PRAECIS cohort. PRAECIS included a racially diverse population reflective of US diversity. While PRAECIS proposed a cutoff for the sFlt-1:PlGF ratio of ≥40 for KRYPTOR and <38 for Elecsys, other publications have proposed various cutoffs. The clinical decision that would be informed by the test is unclear. While several RCTs have been conducted using various biomarker tests, including the Elecsys test, it is unclear what clinical decision(s) the tests are meant to inform and at what cutoffs. 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 2 RCTs 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 women who may be at risk of preterm birth, based on evidence from 2 industry-sponsored cohort studies. However, a RCT 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. In the PRIME RCT of clinically low-risk singleton pregnancies, screening with the PreTRM test and targeted preventive management was associated with significantly reduced neonatal morbidity and shorter neonatal hospital length of stay compared with standard obstetric care, without a significant effect on gestational age at delivery. Similar results were seen in a nonrandomized prospective trial of clinically low-risk singleton pregnancies that used historical controls. It is unclear if outcomes in the PRIME RCT were driven by the intervention bundle, nurse communications, or confounding due to patient and provider unblinding in the screen-guided arm. Outcomes for the 42.3% of screen-guided, high-risk patients who refused the intervention bundle were not reported. 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 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.

For individuals who are pregnant without known risk factors for preeclampsia who receive maternal cell-free RNA testing, the evidence includes observational clinical validity studies. Relevant outcomes are test validity, maternal and perinatal morbidity and mortality, symptoms, functional outcomes, quality of life, hospitalizations, and resource utilization. Observational studies evaluating the predictive ability of serum cell-free RNA screening in pregnant women without known risk factors for preeclampsia are limited to clinical validity studies conducted in individuals in the second trimester. Consequently, its utility for screening asymptomatic women in the first trimester to guide selection for aspirin prophylaxis, as recommended by current guidelines, remains unknown. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

CODING

Medicare Advantage Plans and Commercial Products

The following CPT code(s) are considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:

PlGF Preeclampsia Screen

0243U Obstetrics (preeclampsia), biochemical assay of placental-growth factor, time-resolved fluorescence immunoassay, maternal serum, predictive algorithm reported as a risk score for preeclampsia

PreTRM®

0247U Obstetrics (preterm birth), insulin-like growth factor-binding protein 4 (IGFBP4), sex hormone-binding globulin (SHBG), quantitative measurement by LC-MS/MS, utilizing maternal blood, combined with clinical data, reported as predictive-risk stratification for spontaneous preterm birth (Text Revised Effective 10/1/2026)

PreClaraTM Ratio (sFlt 1/PlGF)

0524U Obstetrics (preeclampsia), sFlt- 1/PlGF ratio, immunoassay, utilizing serum or plasma, reported as a value (Test Name Revision Effective 1/1/2026)

RELATED POLICIES

Biomarker Testing Mandate

PUBLISHED

Provider Update, August 2026
Provider Update, May 2025

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