MASSACHUSETTS

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Medical Policy

Maternal Serum Biomarkers for Prediction of Adverse Obstetric Outcomes

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Policy Number: 163

BCBSA Reference Number: 2.04.152 (For Plan internal use only)
NCD/LCD: N/A

Related Policies

None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

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

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

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	This is **not** a covered service.
Commercial PPO and Indemnity	This is **not** a covered service.
Medicare HMO Blue℠	This is **not** a covered service.
Medicare PPO Blue℠	This is **not** a covered service.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following CPT code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
0243U	Obstetrics (preeclampsia), biochemical assay of placental-growth factor, time-resolved fluorescence immunoassay, maternal serum, predictive algorithm reported as a risk score for preeclampsia
0247U	Obstetrics (preterm birth), insulin-like growth factor-binding protein 4 (IBP4), sex hormone-binding globulin (SHBG), quantitative measurement by LC-MS/MS, utilizing maternal serum, combined with clinical data, reported as predictive-risk stratification for spontaneous preterm birth
0390U	Obstetrics (preeclampsia), kinase insert domain receptor (KDR), Endoglin (ENG), and retinol-binding protein 4 (RBP4), by immunoassay, serum, algorithm reported as a risk score

Description

Preeclampsia

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

Maternal complications of preeclampsia include progression to eclampsia, placental abruption, and a life-threatening complication known as the hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. In the fetus, preeclampsia can lead to fetal growth restriction and intrauterine fetal death. Preeclampsia can develop in nulliparous women with no known risk factors.[3,] Maternal factors associated with an increased risk of preeclampsia include advanced maternal age, presence of a chronic illness such as diabetes mellitus, chronic hypertension, chronic kidney disease, or systemic lupus erythematosus, obesity, multiple gestations, and a prior history of preeclampsia. Preeclampsia can also develop in the postpartum period. In women determined to be at increased risk of developing preeclampsia, the use of daily, low-dose aspirin beginning in the 12th week of gestation is associated with a reduction in risk and is recommended by the U.S. Preventive Services Task Force (USPSTF) and the American College of Obstetricians and Gynecologists (ACOG).[4,5,]

Despite decades of research, accurate identification of women at risk of preeclampsia, particularly prior to the 20th week of gestation, remains challenging.[3,] Standard methods for preeclampsia risk-factor assessment are based on medical and obstetric history and clinical assessment, including routine maternal blood pressure measurement at each prenatal visit.[4,] The use of maternal serum biomarker assays as an adjunct to standard preeclampsia risk assessment has been suggested as a mechanism that could improve accurate identification of at-risk individuals. More accurate identification of risk could create an opportunity for additional assessment, surveillance, and interventions that would ultimately reduce the maternal and fetal or newborn morbidity and mortality associated with preeclampsia. Individual maternal serum biomarkers, such as serum placental growth factor (PlGF), soluble Fms-like tyrosine kinase 1 (s-Flt 1), and pregnancy-associated plasma protein A (PAPP-A) have been investigated as predictors of preeclampsia.[6,] Multivariable preeclampsia risk assessment tools have been developed that

incorporate maternal serum biomarkers; several of these tools have been commercially produced (see Regulatory Status) but few have been externally validated.[7,] Clinically useful risk assessment using maternal serum biomarker testing would need to show increased predictive value over standard assessment of preeclampsia risk without serum biomarker testing.

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

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

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

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

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 (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 measurement of sFlt-1, PlGF, and the sFlt-1/PlGF ratio can identify women at risk of developing preeclampsia. One sFlt-1/PlGF 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:PlGF ratio of 40, other publications have proposed various cutoffs. The clinical decision that would be informed by the test is unclear. While 5 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 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, 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.

Policy History

Date	Action
4/2024	Annual policy review. Description, summary, and references updated. Policy statements remain unchanged.
7/2023	Clarified coding information.
4/2023	Annual policy review. Description, summary, and references updated. Policy statements remain unchanged.
4/2022	New medical policy describing ongoing investigational indications. Transferred from MP 400.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References

1. Ford ND, Cox S, Ko JY, et al. Hypertensive Disorders in Pregnancy and Mortality at Delivery Hospitalization United States, 20172019. MMWR Morb Mortal Wkly Rep 2022;71:585-591.
2. Henderson JT, Vesco KK, Senger CA, et al. Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2021 Sep. (Evidence Synthesis, No. 205.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK574449/
3. Society for Maternal-Fetal Medicine (SMFM). Electronic address: pubs@smfm.org. Executive summary: Workshop on Preeclampsia, January 25-26, 2021, cosponsored by the Society for Maternal-Fetal Medicine and the Preeclampsia Foundation. Am J Obstet Gynecol. Sep 2021; 225(3): B2-B7. PMID 34087228
4. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol. Jun 2020; 135(6): e237-e260. PMID 32443079
5. Davidson KW, Barry MJ, Mangione CM, et al. Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality: US Preventive Services Task Force Recommendation Statement. JAMA. Sep 28 2021; 326(12): 1186-1191. PMID 34581729
6. Poon LC, Shennan A, Hyett JA, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention. Int J Gynaecol Obstet. May 2019; 145 Suppl 1(Suppl 1): 1-33. PMID 31111484
7. Chaemsaithong P, Sahota DS, Poon LC. First trimester preeclampsia screening and prediction. Am J Obstet Gynecol. Feb 2022; 226(2S): S1071-S1097.e2. PMID 32682859
8. Hamilton BE, Martin JA, Osterman MJK. Births: Provisional Data for 2020. National Center for Health Statistics. Accessed January 12, 2024. https://www.cdc.gov/nchs/data/vsrr/vsrr012-508.pdf
9. Mazaki-Tovi S, Romero R, Kusanovic JP, et al. Recurrent preterm birth. Semin Perinatol. Jun 2007; 31(3): 142-58. PMID 17531896
10. Cobo T, Kacerovsky M, Jacobsson B. Risk factors for spontaneous preterm delivery. Int J Gynaecol Obstet. Jul 2020; 150(1): 17-23. PMID 32524595
11. Prediction and Prevention of Spontaneous Preterm Birth: ACOG Practice Bulletin, Number 234. Obstet Gynecol. Aug 01 2021; 138(2): e65-e90. PMID 34293771
12. Lucaroni F, Morciano L, Rizzo G, et al. Biomarkers for predicting spontaneous preterm birth: an umbrella systematic review. J Matern Fetal Neonatal Med. Mar 2018; 31(6): 726-734. PMID 28274163
13. U.S. Food & Drug Administration. DEN220027: BRAHMS sFlt-1/ PlGF KRYPTOR Test System. https://www.accessdata.fda.gov/cdrh_docs/pdf22/DEN220027.pdf. Accessed January 8, 2024.
14. McCarthy FP, Gill C, Seed PT, et al. Comparison of three commercially available placental growth factor-based tests in women with suspected preterm pre-eclampsia: the COMPARE study. Ultrasound Obstet Gynecol. Jan 2019; 53(1): 62-67. PMID 29575304
15. Sera Prognostics. PreTRM Test for Risk Management. Accessed January 12, 2024. https://www.pretrm.com/
16. Henderson JT, Webber EM, Thomas RG, et al. Screening for Hypertensive Disorders of Pregnancy: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. Sep 19 2023; 330(11): 1083-1091. PMID 37721606
17. Townsend R, Khalil A, Premakumar Y, et al. Prediction of pre-eclampsia: review of reviews. Ultrasound Obstet Gynecol. Jul 2019; 54(1): 16-27. PMID 30267475
18. Agrawal S, Shinar S, Cerdeira AS, et al. Predictive Performance of PlGF (Placental Growth Factor) for Screening Preeclampsia in Asymptomatic Women: A Systematic Review and Meta-Analysis. Hypertension. Nov 2019; 74(5): 1124-1135. PMID 31522621
19. Myatt L, Clifton RG, Roberts JM, et al. First-trimester prediction of preeclampsia in nulliparous women at low risk. Obstet Gynecol. Jun 2012; 119(6): 1234-42. PMID 22617589

20. Moore GS, Allshouse AA, Winn VD, et al. Baseline placental growth factor levels for the prediction of benefit from early aspirin prophylaxis for preeclampsia prevention. Pregnancy Hypertens. Oct 2015; 5(4): 280-6. PMID 26597741
21. Andersen LB, Frederiksen-Møller B, Work Havelund K, et al. Diagnosis of preeclampsia with soluble Fms-like tyrosine kinase 1/placental growth factor ratio: an inter-assay comparison. J Am Soc Hypertens. Feb 2015; 9(2): 86-96. PMID 25600419
22. Dröge LA, Höller A, Ehrlich L, et al. Diagnosis of preeclampsia and fetal growth restriction with the sFlt-1/PlGF ratio: Diagnostic accuracy of the automated immunoassay Kryptor®. Pregnancy Hypertens. Apr 2017; 8: 31-36. PMID 28501276
23. van Helden J, Weiskirchen R. Analytical evaluation of the novel soluble fms-like tyrosine kinase 1 and placental growth factor assays for the diagnosis of preeclampsia. Clin Biochem. Nov 2015; 48(16-17): 1113-9. PMID 26129879
24. Thadhani R, Lemoine E, Rana S, et al. Circulating Angiogenic Factor Levels in Hypertensive Disorders of Pregnancy. NEJM Evid 2022; 1 (12).
25. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. N Engl J Med. Aug 17 2017; 377(7): 613-622. PMID 28657417
26. Thermo Scientific. Product Specifications: BRAHMS sFlt-1 KRYPTOR. https://www.brahms.de/images/00_downloads/prenatal-screening/product-sheet-sflt1-kryptor-en.pdf. Accessed January 8, 2024.
27. Agrawal S, Cerdeira AS, Redman C, et al. Meta-Analysis and Systematic Review to Assess the Role of Soluble FMS-Like Tyrosine Kinase-1 and Placenta Growth Factor Ratio in Prediction of Preeclampsia: The SaPPPhirE Study. Hypertension. Feb 2018; 71(2): 306-316. PMID 29229743
28. Lim S, Li W, Kemper J, et al. Biomarkers and the Prediction of Adverse Outcomes in Preeclampsia: A Systematic Review and Meta-analysis. Obstet Gynecol. Jan 01 2021; 137(1): 72-81. PMID 33278298
29. Moore Simas TA, Crawford SL, Bathgate S, et al. Angiogenic biomarkers for prediction of early preeclampsia onset in high-risk women. J Matern Fetal Neonatal Med. Jul 2014; 27(10): 1038-48. PMID 24066977
30. Chaiworapongsa T, Romero R, Savasan ZA, et al. Maternal plasma concentrations of angiogenic/anti-angiogenic factors are of prognostic value in patients presenting to the obstetrical triage area with the suspicion of preeclampsia. J Matern Fetal Neonatal Med. Oct 2011; 24(10): 1187-207. PMID 21827221
31. Duhig KE, Myers J, Seed PT, et al. Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial. Lancet. May 04 2019; 393(10183): 1807-1818. PMID 30948284
32. Cerdeira AS, O'Sullivan J, Ohuma EO, et al. Randomized Interventional Study on Prediction of Preeclampsia/Eclampsia in Women With Suspected Preeclampsia: INSPIRE. Hypertension. Oct 2019; 74(4): 983-990. PMID 31401877
33. Hayes-Ryan D, Khashan AS, Hemming K, et al. Placental growth factor in assessment of women with suspected pre-eclampsia to reduce maternal morbidity: a stepped wedge cluster randomised control trial (PARROT Ireland). BMJ. Aug 13 2021; 374: n1857. PMID 34389547
34. Peguero A, Herraiz I, Perales A, et al. Placental growth factor testing in the management of late preterm preeclampsia without severe features: a multicenter, randomized, controlled trial. Am J Obstet Gynecol. Sep 2021; 225(3): 308.e1-308.e14. PMID 33823150
35. De Oliveira L, Roberts JM, Jeyabalan A, et al. PREPARE: A Stepped-Wedge Cluster-Randomized Trial to Evaluate Whether Risk Stratification Can Reduce Preterm Deliveries Among Patients With Suspected or Confirmed Preterm Preeclampsia. Hypertension. Oct 2023; 80(10): 2017-2028. PMID 37431663
36. von Dadelszen P, Payne B, Li J, et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. Lancet. Jan 15 2011; 377(9761): 219-27. PMID 21185591
37. Saade GR, Boggess KA, Sullivan SA, et al. Development and validation of a spontaneous preterm delivery predictor in asymptomatic women. Am J Obstet Gynecol. May 2016; 214(5): 633.e1-633.e24. PMID 26874297
38. Markenson GR, Saade GR, Laurent LC, et al. Performance of a proteomic preterm delivery predictor in a large independent prospective cohort. Am J Obstet Gynecol MFM. Aug 2020; 2(3): 100140. PMID 33345877

39. Branch DW, VanBuren JM, Porter TF, et al. Prediction and Prevention of Preterm Birth: A Prospective, Randomized Intervention Trial. Am J Perinatol. Jul 2023; 40(10): 1071-1080. PMID 34399434
40. Conde-Agudelo A, Papageorghiou AT, Kennedy SH, et al. Novel biomarkers for the prediction of the spontaneous preterm birth phenotype: a systematic review and meta-analysis. BJOG. Aug 2011; 118(9): 1042-54. PMID 21401853
41. Honest H, Forbes CA, Durée KH, et al. Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling. Health Technol Assess. Sep 2009; 13(43): 1-627. PMID 19796569
42. American College of Obstetrics and Gynecology and The Society for Maternal-Fetal Medicine. Practice Advisory: Low-Dose Aspirin Use for the Prevention of Preeclampsia and Related Morbidity and Mortality. December 2021. Accessed January 12, 2024.
43. Magee LA, Brown MA, Hall DR, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis management recommendations for international practice. Pregnancy Hypertens. Mar 2022; 27: 148-169. PMID 35066406
44. National Institute For Health and Care Excellence (NICE). Diagnostics consultation document PLGF-based testing to help diagnose suspected preterm preeclampsia (update of DG23). https://www.nice.org.uk/guidance/indevelopment/gid-dg10040/documents. Accessed January 2, 2024.