Serum Tests for Preeclampsia Risk Assessment

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Next review date: 10/2027

Policy contains: BRAHMS; Elecsys; hypertension; Placental growth factor; preeclampsia; pregnancy; prognosis; risk; soluble fms-like tyrosine kinase-1

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Coverage policy

The following serum tests measuring a soluble fms-like tyrosine kinase-1 (sFlt-1)/Placental growth factor (sFlt-1/PlGF) ratio are investigational/not clinically proven and, therefore, not medically necessary as an adjunct to current clinical criteria for diagnosing or predicting risk of preeclampsia:

- BRAHMS sFlt-1/PlGF KRYPTOR Test System (Brahms Gmbh, part of Thermo Fisher Scientific, Hennigsdorf, Germany)
- Elecsys sFlt-1 and Elecsys PlGF test (Roche Diagnostics, Indianapolis, Indiana)

Limitations

No other limitations were identified.

Alternative covered services

Guideline-directed clinical risk assessment

Background

Hypertensive disorders of pregnancy are a leading cause of maternal and perinatal mortality worldwide. Preeclampsia is a disorder of pregnancy associated with new-onset hypertension, occurring most often after 20 weeks of gestation and frequently near term. Preeclampsia is more prevalent among U.S. Black and Hispanic patients, attributing to approximately 26% of maternal deaths in this population. Fetuses of women with preeclampsia are at increased risk of spontaneous or indicated preterm delivery (Karrar, 2024).

The underlying etiology of preeclampsia is poorly understood, but uteroplacental ischemia is implicated as the principal mechanism. There are two general subtypes of preeclampsia. Early-onset type is attributed to placental defects resulting in placental ischemia, and late-onset type arises due to maternal factors that contribute to microvascular damage affecting maternal blood supply in the presence of a healthy placenta (Karrar, 2024).

Classic diagnostic criteria for preeclampsia are new-onset gestational hypertension, defined as systolic blood pressure 140 mm Hg or higher or diagnostic blood pressure 90 mm Hg or higher on two occasions taken at least four hours apart, and proteinuria. In the absence of proteinuria, other signs and symptoms suggestive of maternal end-organ damage may be used for a preeclampsia diagnosis, including thrombocytopenia, renal insufficiency, pulmonary edema, impaired liver function, or new-onset headache with or without visual disturbance. Women with gestational hypertension and no proteinuria are diagnosed with preeclampsia **without** severe features. Women are diagnosed with preeclampsia **with** severe features when presenting with severe-range blood pressures, defined as systolic blood pressure 160 mm Hg or higher or diastolic blood pressure of 110 mm Hg or higher, or with gestational hypertension and either proteinuria or signs and symptoms suggestive of maternal end-organ damage (American College of Obstetricians and Gynecologists, 2022).

Several risk factors have been associated with increased probability of preeclampsia. These risk factors include: nulliparity; multifetal gestations; preeclampsia in a previous pregnancy; chronic hypertension; pregestational and gestational diabetes; thrombophilia; systemic lupus erythematosus; pre-pregnancy body mass index greater than 30; antiphospholipid antibody syndrome; maternal age of 35 years or older; kidney disease; assisted reproductive technology; and obstructive sleep apnea (American College of Obstetricians and Gynecologists, 2022).

Management of preeclampsia begins with early diagnosis and intervention, with an emphasis on adequate blood pressure control, seizure prevention, and monitoring to try to advance gestational age safely for as long as possible. Prolonged hospitalization and corticosteroids administration may be needed. Detecting patients at high-risk for preeclampsia in the first trimester allows for early intervention and potential reduction in the incidence of preeclampsia and maternal and infant complications. Clinical parameters for detection are limited in their ability to predict preeclampsia early in pregnancy, as symptoms and signs are highly variable. Most cases of preeclampsia occur in healthy nulliparous women with no obvious risk factors. Furthermore, progression from mild to severe preeclampsia is often rapid and difficult to predict (Karrar, 2024).

Individual biochemical markers, biophysical markers, and prediction models have been proposed for prediction of preeclampsia in the first and second trimesters of pregnancy. First-trimester prediction models suffer from high risk of bias and often lack internal and external validation (Tiruneh, 2024; van Eekhout, 2025). Angiogenic biomarkers (e.g., sFlt-1, PlGF, and soluble endoglin) have generated interest, but as yet, no single test can reliably predict preeclampsia (American College of Obstetricians and Gynecologists, 2022; Snell, 2020).

The U.S. Food and Drug Administration (2026) has cleared two Class II prognostic tests for development or progression of preeclampsia to be used in conjunction with clinical assessment and routine laboratory testing. sFlt-1 is a marker of a diseased placenta and occurs in very high levels in individuals with severe preeclampsia. PlGF promotes the development of new blood vessels within the placenta, and abnormally low levels indicate a

diseased placenta. Both immunoassays provide *in vitro* quantitative determination of the ratio of the two angiogenic blood proteins, reflecting placental health.

Both tests are indicated in pregnant women (singleton pregnancies between gestational age 23+0 to 34+6/7weeks) hospitalized for hypertensive disorders of pregnancy (preeclampsia, chronic hypertension with or without superimposed preeclampsia, or gestational hypertension) for predicting progression to preeclampsia with severe features within two weeks of presentation:

- The BRAHMS sFlt-1/PlGF KRYPTOR Test System combines the results of the BRAHMS sFlt-1 Kryptor and BRAHMS PLGF plus Kryptor assays into a ratio and requires the Thermo Scientific BRAHMS KRYPTOR immunoassay platform. When used as intended, the device is a risk predictor for the future progression to preeclampsia with severe features. It is not intended for the diagnosis of preeclampsia with severe features, for decisions of delivery or hospital discharge, or for monitoring by repeated testing (U.S. Food and Drug Administration, 2023). The manufacturer refers to this ratio as the PreClara™ ratio (Thermo Fisher Scientific, 2024).
- The Elecsys sFlt-1 and Elecsys PlGF test uses two electrochemiluminescence immunoassays compatible with Roche Cobas e immunoassay analyzers. Elecsys has two intended uses: 1) to predict the risk of future progression to preeclamspia with severe features; and 2) to help diagnose preeclampsia in pregnant women with suspected preeclampsia, together with other clinical information (U.S. Food and Drug Administration, 2025).

Regulatory clearance of the BRAHMS and Elecsys immunoassays was based on the results of the Preeclampsia Risk Assessment: Evaluation of Cut-offs to Improve Stratification (PRAECIS) multicenter trial. The study enrolled 520 U.S. women with singleton pregnancies between 23+0 and 34+6/7 weeks gestation hospitalized (or being hospitalized) for a hypertensive disorder of pregnancy. Women who met the criteria for preeclampsia with severe features were excluded. All enrollees were followed for two weeks or until delivery within two weeks.

Using the BRAHMS immunoassay, a sFlt-1/PlGF ratio of 40 or higher predicted the development of preeclampsia with severe features within a two-week window with a sensitivity, specificity, positive predictive value, and negative predictive value of 94%, 75%, 65%, and 96%, respectively. The same threshold was also associated with a higher risk of adverse outcomes associated with pregnancy and time to delivery (U.S. Food and Drug Administration, 2023).

Using the Elecsys immunoassay, a sFlt-1/PlGF ratio higher than 38 predicted the development of preeclampsia with severe features within a two-week window with a sensitivity, specificity, positive predictive value, and negative predictive value of 91%, 77%, 67%, and 95%, respectively (U.S. Food and Drug Administration, 2025).

Findings

The best evidence supporting the BRAHMS- and Elecsys-derived sFlt-1/PlGF ratios as angiogenic biomarkers of preeclampsia risk assessment consists of randomized trials defining the diagnostic performance in 1,014 women who meet the enrollment criteria of the PRAECIS trial. The trial inclusion criteria were (Thadhani, 2022):

- Signed informed consent in a pregnant woman ≥ 18 years of age
- Gestational age 23+0 to 34+6/7 weeks
- Singleton pregnancy
- Hospitalized with (or develop while hospitalized) a hypertensive disorder of pregnancy (preeclampsia, chronic hypertension with or without superimposed preeclampsia or gestational hypertension) as defined by American College of Obstetricians and Gynecologists guidelines

The thresholds used for sFlt-1/PlGF rule in and rule out criteria are manufacturer-specific, not interchangeable, and require separate clinical validation. Validation of the cut-offs of the BRAHMS system from the PRAECIS trial in an independent study population has not been published. The sFlt-1/PlGF ratio may aid in predicting progression to preeclampsia with severe features in the short term, but the benefits to maternal outcomes or clinical utility in terms of reduced unnecessary admissions and more targeted surveillance have not been demonstrated. The benefits of the sFlt-1/PlGF ratio in women with a multiple pregnancy or of repeat testing have not been determined.

Current guidelines acknowledge the uncertainties with the use of these tests. The tests should be used as adjuncts to clinical risk assessment and not be used to make decisions about management strategies, as clinical utility has not been established.

Guidelines

The American College of Obstetricians and Gynecologists (2020) concluded that screening with biomarkers or biophysical methods are not reliable predictors of preeclampsia in low-risk women, as most screen–positive patients will not develop the disease and would not benefit from prophylactic intervention. First-trimester and second-trimester biochemical or biophysical parameters cannot accurately predict early-onset preeclampsia or meaningfully impact interventions that improve maternal or fetal outcome.

The American College of Obstetricians and Gynecologists (2024) issued a Clinical Practice Update for the BRAHMS sFlt-1/PlGF KRYPTOR Test System, which preceded the regulatory clearance of Elecsys. The sFlt-1/PlGF ratio should be used only for patients who met the PRAECIS multicenter trial inclusion criteria (Thadhani, 2022), as an adjunct to current clinical criteria for diagnosing or predicting preeclampsia with severe features. All patients hospitalized for hypertensive disorders of pregnancy should continue to receive the current recommended approach for preeclampsia workup and management, including serial blood pressure assessment, symptom monitoring, and laboratory surveillance. A positive sFlt-1/PlGF of 40 or higher is not diagnostic of preeclampsia with severe features. Conversely, while a sFlt-1/PlGF ratio of less than 40 suggests a low likelihood (less than 5%) of developing preeclampsia with severe features within two weeks, it can miss cases of preeclampsia with severe features. Therefore, continued close maternal and fetal surveillance is warranted if there are persistent signs or symptoms of preeclampsia. There are insufficient data to recommend management strategies after a positive or negative test result.

Evidence review

Systematic reviews highlight the performance of the BRAHMS- and Elecsys-derived sFlt-1/PlGF ratios as adjuncts to standard clinical assessment to improve the diagnosis and prediction of preeclampsia in individuals who meet the enrollment criteria in the PRAECIS trial, but found no improvement in pregnancy outcomes (Ontario Health, 2023; Zhang, 2025).

The performance of Elecsys is uncertain in women with twin or multiple pregnancy (Satorres, 2023; Yang, 2024), in monitoring the development of preeclampsia with repeat testing, and in reducing unnecessary hospital admissions (Ontario Health, 2023; Zhang, 2025). Recent randomized controlled trials employing the Elecsys immunoassay results in prediction models confirm these findings. In the PRERISK study, a model based on the sFlt-1/PlGF ratio, gestational age, and the urinary protein-to-creatinine ratio, and a 5% cutoff did not decrease hospitalization in patients with suspected or confirmed preeclampsia (Kluivers, 2025). In the PRECOG study, use of the sFlt-1/PlGF ratio in women hospitalized for suspected preeclampsia before 35 weeks was not associated with a benefit in terms of duration of hospitalization or in maternal and neonatal outcomes (Sibiude, 2025).

In the PARROT-2 trial, an abnormal initial PlGF-based test identified a more severe phenotype of preeclampsia at increased risk of adverse maternal and perinatal outcomes. In women with abnormal initial results, repeat PlGF-based testing was not associated with improved perinatal outcomes. The investigators did not recommend routine repeat PlGF-based testing of all individuals with suspected preeclampsia, particularly in a high-income setting with a low prevalence of adverse outcomes. Careful use of repeat PlGF-based testing to stratify risk may be considered at least two weeks after a normal initial test result, particularly in women who have symptoms or signs of preeclampsia (Hurrell, 2024a, 2024b).

References

On 4/15/2026, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were: “Pre-Eclampsia” (MeSH), “risk assessment” (MeSH), “pre-eclampsia,” “preeclampsia,” “risk,” and “prognosis.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

American College of Obstetricians and Gynecologists. Biomarker prediction of preeclampsia with severe features. *Obstet Gynecol*. 2024;143(6):e153-e154. Doi: 10.1097/AOG.0000000000005576.

American College of Obstetricians and Gynecologists. Gestational hypertension and preeclampsia: ACOG practice bulletin, number 222. *Obstet Gynecol*. 2020;135(6):e237-e260. Doi: 10.1097/aog.0000000000003891.

Hurrell A, Webster L, Sparkes J, et al. Repeat placental growth factor-based testing in women with suspected preterm pre-eclampsia (PARROT-2): A multicentre, parallel-group, superiority, randomised controlled trial. *Lancet*. 2024;403(10427):619-631. Doi: 10.1016/s0140-6736(23)02357-7.(a)

Hurrell A, Webster L, Sparkes J, et al. Repeat placental growth factor-based testing in women with suspected preterm preeclampsia: A stratified analysis of the PARROT-2 trial. *Hypertension*. 2024;81(7):1561-1573. Doi: 10.1161/hypertensionaha.123.22411.(b)

Karrar SA, Martingano DJ, Hong PL. Preeclampsia. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK570611/. Updated February 25, 2024.

Kluivers ACM, Neuman RI, Saleh L, et al. PRERISK study: A randomized controlled trial evaluating a sFlt-1/PlGF-based calculator for preeclampsia hospitalization. *Hypertension*. 2025;82(5):827-838. Doi: 10.1161/hypertensionaha.124.24386.

Ontario Health. Placental growth factor (PlGF)–based biomarker testing to help diagnose preeclampsia in people with suspected pre-eclampsia: A health technology assessment. *Ont Health Technol Assess Ser* [Internet]. 2023;23(3):1-146. https://hqontario.ca/evidence-toimprove-care/health-technology-assessment/reviews-and-recommendations/placental-growthfactor-plgf-based-biomarker-testing-to-help-diagnose-pre-eclampsia-in-people-with-suspectedpre-eclampsia.

Satorres E, Martínez-Varea A, Diago-Almela V. SFlt-1/PlGF ratio as a predictor of pregnancy outcomes in twin pregnancies: A systematic review. *J Matern Fetal Neonatal Med*. 2023;36(2):2230514. Doi: 10.1080/14767058.2023.2230514.

Sibiude J, Winer N, Morel O, et al. SFlt-1/PlGF ratio use does not reduce hospitalisation duration in suspected preeclampsia: The PRECOG study, a multicentre randomised trial. *Sci Rep*. 2025;15(1):39299. Doi: 10.1038/s41598-025-23007-w.

Snell KIE, Allotey J, Smuk M, et al. External validation of prognostic models predicting pre-eclampsia: Individual participant data meta-analysis. *BMC Med*. 2020;18(1):302. Doi: 10.1186/s12916-020-01766-9.

Thadhani R, Lemoine E, Rana S, et al. Circulating angiogenic factor levels in hypertensive disorders of pregnancy. *NEJM Evid*. 2022;1(12):EVIDoa2200161. Doi: 10.1056/EVIDoa2200161.

Thermo Fisher Scientific, Inc. PreClara ratio (sFlt-1/PlGF) for preeclampsia management. https://www.thermofisher.com/us/en/home/clinical/diagnostic-testing/brahms/prenatal-screening/preeclampsia-screening/clinical-solutions.html. Published 2024.

Tiruneh SA, Vu TTT, Moran LJ, et al. Externally validated prediction models for pre-eclampsia: Systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2024;63(5):592-604. Doi: 10.1002/uog.27490.

U.S. Food and Drug Administration. 510(k) substantial equivalence determination decision summary. Assay only. Elecsys sFlt-1 and Elecsys PlGF (Roche Diagnostics, Indianapolis, Indiana). http://www.accessdata.fda.gov/cdrh_docs/reviews/K241453.pdf. Decision date February 7, 2025.

U.S. Food and Drug Administration. Decision summary. Evaluation of automatic class III designation for BRAHMS sFlt-1/PlGF KRYPTOR Test System (Brahms Gmbh, part of Thermo Fisher Scientific, Hennigsdorf, Germany). Predicate 510(k) Number(s): DEN220027. http://www.accessdata.fda.gov/cdrh_docs/reviews/DEN220027.pdf. Decision date May 18, 2023.

U.S. Food and Drug Administration. Product classification database. Searched using the product code QWH. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm. Last updated April 27, 2026.

van Eekhout JCA, Becking EC, Scheffer PG, et al. First-trimester prediction models based on maternal characteristics for adverse pregnancy outcomes: A systematic review and meta-analysis. *Bjog*. 2025;132(3):243-265. Doi: 10.1111/1471-0528.17983.

Yang M, Bai Y, Li M, Lin X, Duan X, Zhang X. Predictive value of the soluble Fms-like tyrosine kinase 1 to placental growth factor ratio for preeclampsia in twin pregnancies: A systematic review and meta-analysis. *Am J Obstet Gynecol MFM*. 2024;6(3):101290. Doi: 10.1016/j.ajogmf.2024.101290.

Zhang L, Li W, Chi X, et al. Predictive performance of sFlt-1,PlGF and the sFlt-1/PlGF ratio for preeclampsia: A systematic review and meta-analysis. *J Gynecol Obstet Hum Reprod*. 2025;54(4):102925. Doi: 10.1016/j.jogoh.2025.102925.

Policy updates

Initial review date: 6/2026 and clinical policy effective date: 7/2026

Related codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy CCP.1557. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

Code	Code description
0524U	Obstetrics (preeclampsia), sFlt-1/PlGF ratio, immunoassay, utilizing serum or plasma, reported as a value. Includes PreClara™ Ratio (sFlt-1/PlGF), Thermo Fisher Scientific.

Code	Code description
0482U	Obstetrics (preeclampsia), biochemical assay of soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF), serum, ratio reported for sFlt-1/PlGF, with risk of progression for preeclampsia with severe features within two weeks. Includes Preeclampsia sFlt-1/PlGF Ratio (PERA), Mayo Clinic, Laboratory Developed Test.