

EFFECTIVE DATE: 01 | 01 | 2024

POLICY LAST REVIEWED: 01 | 21 | 2026

OVERVIEW

Human epididymis protein 4 (HE4) is a novel biomarker that has been cleared by the U.S. Food and Drug Administration (FDA) for monitoring individuals with epithelial ovarian cancer. HE4 is proposed as a replacement for or a complement to cancer antigen 125 (CA-125) for monitoring disease progression and recurrence. HE4 has also been proposed as a test to evaluate women with ovarian masses and to screen for ovarian cancer in asymptomatic women.

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

Measurement of Human epididymis protein 4 is not covered for all indications as the evidence is insufficient to determine the effects of the technology on health outcomes.

Commercial Products

Measurement of Human epididymis protein 4 is not medically necessary for all indications as the evidence is insufficient to determine the effects of the technology on health outcomes.

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 and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable not medically necessary/not covered laboratory testing benefits/coverage.

BACKGROUND

Ovarian Cancer

Ovarian cancer is the fifth most common cause of cancer mortality among U.S. women. According to Surveillance Epidemiology and End Results data, in 2025, an estimated 20,890 women will be diagnosed with ovarian cancer and 12,730 women will die of the disease. The stage at diagnosis is an important predictor of survival; however, most women are not diagnosed until the disease has spread. For the period of 2014 to 2020, 55% of women with ovarian cancer were diagnosed when the disease had distant metastases (stage IV), and this was associated with a 5-year relative survival rate of 31.4%. In contrast, 19% of women diagnosed with localized cancer (stage I) had a 5-year survival rate of 91.9%. Epithelial ovarian tumors account for 85% to 90% of ovarian cancers.

Treatment

The standard treatment for epithelial ovarian cancer is surgical staging and primary cytoreductive surgery followed by chemotherapy in most cases. There is a lack of consensus about an optimal approach to follow-up of patients with ovarian cancer after or during primary treatment. Patients undergo regular physical examinations and may have imaging studies. In addition, managing patients with serial measurement of the biomarker cancer antigen 125 (CA 125) to detect early recurrence of disease is common. A rising CA 125 level has been found to correlate with disease recurrence and has been found to detect recurrent ovarian cancer earlier than clinical detection. However, a survival advantage of initiating treatment based on early detection with CA 125 has not been demonstrated to date. For example, a 2010 randomized controlled trial (RCT) with women having ovarian cancer that was in complete remission did not find a significant difference in overall survival when treatment for remission was initiated after CA 125 concentration exceeded twice the limit of normal compared with delaying treatment initiation until symptom onset.

Human epididymis protein 4 (HE4) is a protein that circulates in the serum and has been found to be overexpressed in epithelial ovarian cancer, lung adenocarcinoma, breast cancer, pancreatic cancer, endometrial cancer, and bladder cancer. HE4 is made up of two whey acidic proteins with a four disulfide core domain and has been proposed as a biomarker for monitoring patients with epithelial ovarian cancer.

This evidence review also addresses use of the HE4 as a stand-alone test for evaluating women with ovarian masses who have not been diagnosed with ovarian cancer. Such patients undergo a diagnostic workup to determine whether the risk of malignancy is sufficiently high to warrant surgical removal. In patients for whom surgery is indicated, further evaluation may be warranted to determine if surgical referral to a specialist with expertise in ovarian cancer is warranted. The Risk of Ovarian Malignancy Algorithm (ROMA) combines HE4, CA 125, and menopausal status into a numeric score, which is not addressed in this policy.

Regulatory Status

Multiple HE4 test kits have been cleared by the Food and Drug Administration (FDA) through the 510(k) process. The FDA determined that this device was substantially equivalent to a CA 125 assay kit for use as an aid in monitoring disease progression or recurrence in patients with epithelial ovarian cancer. The FDA-approved indication states that serial testing for HE4 should be done in conjunction with other clinical methods used for monitoring ovarian cancer and that the HE4 test is not intended to assess the risk of disease outcomes.

For individuals who have ovarian cancer who receive a measurement of serum biomarker HE4, the evidence includes 7 nonrandomized prospective and retrospective studies comparing the diagnostic accuracy of HE4 with CA 125 for predicting disease progression and/or recurrence. Relevant outcomes are overall survival (OS), disease-specific survival, test validity, other test performance measures, and change in disease status. Data submitted to the FDA for approval of commercial HE4 tests found that HE4 was not inferior to

CA125 for detecting ovarian cancer recurrence. Although a single prospective observational study found that elevated levels of HE4, but not CA 125, at the time of cancer progression was significantly associated with reduced OS, a direct comparison between biomarkers was not provided. Overall, the superiority of HE4 to CA 125 (alone or in combination), the key question in the evidence review, was not demonstrated in the available literature. In addition, there is no established cutoff in HE4 levels for monitoring disease progression, and cutoffs in studies varied. There is no direct evidence from prospective controlled studies on the impact of HE4 testing on health outcomes, and no clear chain of evidence that changes in management based on HE4 would lead to an improved health outcome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have adnexal masses who receive a measurement of serum biomarker HE4, the evidence includes diagnostic accuracy studies and meta-analyses. Relevant outcomes are OS, disease-specific survival, test validity, and other test performance measures. Meta-analyses have generally found that HE4 and CA 125 have a similar overall diagnostic accuracy (ie, sensitivity, specificity), and several found that HE4 has significantly higher specificity than CA 125, but not sensitivity. Two meta-analyses had mixed findings on whether the combination of HE4 and CA 125 is superior to CA 125 alone for the initial diagnosis of ovarian cancer. The number of studies evaluating the combined test is relatively low, and publication bias in studies of HE4 has been identified. In addition, studies have not found that HE4 improves diagnostic accuracy beyond that of subjective assessment of transvaginal ultrasound. There is no direct evidence from prospective controlled studies on the impact of HE4 testing on health outcomes, and no clear chain of evidence that changes in management based on HE4 would lead to an improved health outcome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic and not at high risk of ovarian cancer who receive screening with serum biomarker HE4, the evidence includes several retrospective comparative studies and no prospective studies comparing health outcomes in asymptomatic women managed with and without HE4 screening. Relevant outcomes are OS, disease-specific survival, test validity, and other test performance measures. The retrospective studies found that HE4 levels increased over time in women ultimately diagnosed with ovarian cancer. Prospective comparative studies are needed to definitively determine whether HE4 is a useful screening tool. The evidence is insufficient to determine the effects of the technology on health outcomes.

CODING

Medicare Advantage Plans and Commercial Products

The following CPT code is not covered for Medicare Advantage Plans and not medically necessary for Commercial products:

86305 Human epididymis protein 4 (HE4)

RELATED POLICIES

Biomarker Testing Mandate

Genetic Testing Services

PUBLISHED

Provider Update, March 2026

Provider Update, April 2025

Provider Update, April 2024

Provider Update, March 2023, November 2023

Provider Update, April 2022

REFERENCES

1. Surveillance Epidemiology and End Results Program (SEER). SEER Stat Fact: Ovarian Cancer. n.d.; <http://seer.cancer.gov/statfacts/html/ovary.html>. Accessed November 3, 2025.
2. Ledermann JA, Raja FA, Fotopoulou C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* Oct 2013; 24 Suppl 6: vi24-32. PMID 24078660

3. Harris HR, Guertin KA, Camacho TF, et al. Racial disparities in epithelial ovarian cancer survival: An examination of contributing factors in the Ovarian Cancer in Women of African Ancestry consortium. *Int J Cancer*. Oct 15 2022; 151(8): 1228-1239. PMID 35633315
4. Rustin GJ, van der Burg ME, Griffin CL, et al. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. *Lancet*. Oct 02 2010; 376(9747): 1155-63. PMID 20888993
5. Han Y, Jiang L, Liu K, et al. Predictive Value of HE4 in Platinum-Based Chemotherapy for Ovarian Cancer : A Systematic Review. *Front Oncol*. 2021; 11: 703949. PMID 34307173
6. Food and Drug Administration, 510(k) substantial equivalence determination decision summary: assay only (K072939). n.d.; http://www.accessdata.fda.gov/cdrh_docs/reviews/K072939.pdf. Accessed November 3, 2025.
7. Food and Drug Administration. 510(k) substantial equivalence determination decision summary: assay only (K093957). n.d.; http://www.accessdata.fda.gov/cdrh_docs/reviews/K093957.pdf. Accessed November 3, 2025.
8. Nassir M, Guan J, Luketina H, et al. The role of HE4 for prediction of recurrence in epithelial ovarian cancer patients-results from the OVCAD study. *Tumour Biol*. Mar 2016; 37(3): 3009-16. PMID 26419591
9. Vallius T, Hynninen J, Auranen A, et al. Postoperative human epididymis protein 4 predicts primary therapy outcome in advanced epithelial ovarian cancer. *Tumour Biol*. Feb 2017; 39(2): 1010428317691189. PMID 28218038
10. Potenza E, Parpinel G, Laudani ME, et al. Prognostic and predictive value of combined HE-4 and CA-125 biomarkers during chemotherapy in patients with epithelial ovarian cancer. *Int J Biol Markers*. Dec 2020; 35(4): 20-27. PMID 33126819
11. Salminen L, Gidwani K, Grønman S, et al. HE4 in the evaluation of tumor load and prognostic stratification of high grade serous ovarian carcinoma. *Acta Oncol*. Dec 2020; 59(12): 1461-1468. PMID 33030975
12. Rong Y, Li L. Early clearance of serum HE4 and CA125 in predicting platinum sensitivity and prognosis in epithelial ovarian cancer. *J Ovarian Res*. Jan 04 2021; 14(1): 2. PMID 33397458
13. Samborski A, Miller MC, Blackman A, et al. HE4 and CA125 serum biomarker monitoring in women with epithelial ovarian cancer. *Tumour Biol*. 2022; 44(1): 205-213. PMID 36189508
14. Olsen M, Lof P, Stiekema A, et al. The diagnostic accuracy of human epididymis protein 4 (HE4) for discriminating between benign and malignant pelvic masses: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. Oct 2021; 100(10): 1788-1799. PMID 34212386
15. Suri A, Perumal V, Ammalli P, et al. Diagnostic measures comparison for ovarian malignancy risk in Epithelial ovarian cancer patients: a meta-analysis. *Sci Rep*. Aug 27 2021; 11(1): 17308. PMID 34453074
16. Huang J, Chen J, Huang Q. Diagnostic value of HE4 in ovarian cancer: A meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. Dec 2018; 231: 35-42. PMID 30317143
17. Dayyani F, Uhlig S, Colson B, et al. Diagnostic Performance of Risk of Ovarian Malignancy Algorithm Against CA125 and HE4 in Connection With Ovarian Cancer: A Meta-analysis. *Int J Gynecol Cancer*. Nov 2016; 26(9):1586-1593. PMID 27540691
18. Macedo AC, da Rosa MI, Lumertz S, et al. Accuracy of serum human epididymis protein 4 in ovarian cancer diagnosis: a systematic review and meta-analysis. *Int J Gynecol Cancer*. Sep 2014; 24(7): 1222-31. PMID 25078339
19. Wang J, Gao J, Yao H, et al. Diagnostic accuracy of serum HE4, CA125 and ROMA in patients with ovarian cancer: a meta-analysis. *Tumour Biol*. Jun 2014; 35(6): 6127-38. PMID 24627132
20. Zhen S, Bian LH, Chang LL, et al. Comparison of serum human epididymis protein 4 and carbohydrate antigen 125 as markers in ovarian cancer: A meta-analysis. *Mol Clin Oncol*. Jul 2014; 2(4): 559-566. PMID 24940495
21. Yang Z, Wei C, Luo Z, et al. Clinical value of serum human epididymis protein 4 assay in the diagnosis of ovarian cancer: a meta-analysis. *Onco Targets Ther*. 2013; 6: 957-66. PMID 23901285
22. Ferraro S, Braga F, Lanzoni M, et al. Serum human epididymis protein 4 vs carbohydrate antigen 125 for ovarian cancer diagnosis: a systematic review. *J Clin Pathol*. Apr 2013; 66(4): 273-81. PMID 23426716
23. Yu S, Yang HJ, Xie SQ, et al. Diagnostic value of HE4 for ovarian cancer: a meta-analysis. *Clin Chem Lab Med*. Feb 03 2012; 50(8): 1439-46. PMID 22868811

24. Kaijser J, Van Gorp T, Smet ME, et al. Are serum HE4 or ROMA scores useful to experienced examiners for improving characterization of adnexal masses after transvaginal ultrasonography?. *Ultrasound Obstet Gynecol.* Jan 2014; 43(1): 89-97. PMID 23828371
25. Moszynski R, Szubert S, Szperek D, et al. Usefulness of the HE4 biomarker as a second-line test in the assessment of suspicious ovarian tumors. *Arch Gynecol Obstet.* Dec 2013; 288(6): 1377-83. PMID 23722285
26. Nikolova T, Zivadinovic R, Evtimovska N, et al. Diagnostic performance of human epididymis protein 4 compared to a combination of biophysical and biochemical markers to differentiate ovarian endometriosis from epithelial ovarian cancer in premenopausal women. *J Obstet Gynaecol Res.* Dec 2017; 43(12): 1870-1879. PMID 29027715
27. Gentry-Maharaj A, Burnell M, Dilley J, et al. Serum HE4 and diagnosis of ovarian cancer in postmenopausal women with adnexal masses. *Am J Obstet Gynecol.* Jan 2020; 222(1): 56.e1-56.e17. PMID 31351062
28. Carreras-Dieguez N, Glickman A, Munmany M, et al. Comparison of HE4, CA125, ROMA and CPH-I for Preoperative Assessment of Adnexal Tumors. *Diagnostics (Basel).* Jan 17 2022; 12(1). PMID 35054393
29. Lof P, van de Vrie R, Korse CM, et al. Can serum human epididymis protein 4 (HE4) support the decision to refer a patient with an ovarian mass to an oncology hospital?. *Gynecol Oncol.* Aug 2022; 166(2): 284-291. PMID 35688656
30. Sharma M, Kumar N, Saha S, et al. Role of HE4 in evaluation of adnexal masses and its comparison with CA125, ROMA and RMI in premenopausal women. *Afr Health Sci.* Dec 2024; 24(4): 120-128. PMID 40190516
31. Anderson GL, McIntosh M, Wu L, et al. Assessing lead time of selected ovarian cancer biomarkers: a nested casecontrol study. *J Natl Cancer Inst.* Jan 06 2010; 102(1): 26-38. PMID 20042715
32. Urban N, Thorpe JD, Bergan LA, et al. Potential role of HE4 in multimodal screening for epithelial ovarian cancer. *J Natl Cancer Inst.* Nov 02 2011; 103(21): 1630-4. PMID 21917606
33. Terry KL, Schock H, Fortner RT, et al. A Prospective Evaluation of Early Detection Biomarkers for Ovarian Cancer in the European EPIC Cohort. *Clin Cancer Res.* Sep 15 2016; 22(18): 4664-75. PMID 27060155
34. Eskander R, Berman M, Keder L. Practice Bulletin No. 174: Evaluation and Management of Adnexal Masses. *Obstet Gynecol.* Nov 2016; 128(5): e210-e226. PMID 27776072
35. Committee Opinion No. 716: The Role of the Obstetrician-Gynecologist in the Early Detection of Epithelial Ovarian Cancer in Women at Average Risk. *Obstet Gynecol.* Sep 2017; 130(3): e146-e149. PMID 28832487
36. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 3.2025. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed November 3, 2025.
37. National Institute for Health and Care Excellence (NICE). Ovarian cancer: recognition and initial management [CG122]. 2011. Updated October 2, 2023; <https://www.nice.org.uk/guidance/cg122>. Accessed November 3, 2025.
38. U.S. Preventive Services Task Force. Recommendation Statement: Screening for Ovarian Cancer. 2018; file:///C:/Users/alt/Downloads/ovarian-cancer-final-rec-statement.pdf. Accessed November 3, 2025.

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