

## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>SERUM BIOMARKERS FOR HUMAN EPIDIDYMIS PROTEIN 4 (HE4)</b>
<b>POLICY NUMBER</b>	<b>MP 2.269</b>

<b>CLINICAL BENEFIT</b>	<input type="checkbox"/> MINIMIZE SAFETY RISK OR CONCERN. <input checked="" type="checkbox"/> MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. <input type="checkbox"/> ASSURE APPROPRIATE LEVEL OF CARE. <input type="checkbox"/> ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. <input type="checkbox"/> ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. <input type="checkbox"/> ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
<b>Effective Date:</b>	<b>RETIRED 7/1/2026</b>

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### I. POLICY

Measurement of human epididymis protein 4 (HE4) is **investigational** for all indications. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure for these indications.

**Cross-reference:**  
**MP 2.270 Multimarker Serum Testing Related to Ovarian Cancer**

### II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital BlueCross. Please see additional information below, and subject to benefit variations as discussed in Section VI below.

**FEP PPO** - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: <https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>

### III. DESCRIPTION/BACKGROUND

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#### 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 2024, an estimated 19,680 women will be diagnosed with ovarian cancer and 12,740 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 2014 to 2020, 55% of women with

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ovarian cancer were diagnosed when the disease had distant metastases (stage IV), and this was associated with a 5-year 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.

Research from the Ovarian Cancer in Women of African Ancestry (OCWAA) consortium reports that Black women with ovarian cancer have worse survival than White women. Contributors to this disparity may include education level, nulliparity, smoking status, body mass index, diabetes, and postmenopausal hormone therapy duration.

### 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 2 whey acidic proteins with a 4-disulfide core domain and has been proposed as a biomarker for monitoring patients with epithelial ovarian cancer.

### Evaluation of Adnexal Masses

This evidence review also addresses the 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 a 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. The ROMA has been cleared by FDA for predicting the risk that an adnexal mass is malignant; this test is considered separately in evidence review 2.270 (multimarker serum testing related to ovarian cancer).

### Regulatory Status

Multiple HE4 test kits have been cleared by the FDA through the 510(k) process and summarized in Table 1. 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

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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.

**Table 1. Serum Human Epididymis Protein 4 Tests Cleared by FDA**

<b>Test</b>	<b>Manufacturer</b>	<b>Location</b>	<b>Date Cleared</b>	<b>510(k) No.</b>
<b>HE4 EIA Kit</b>	Fujirebio Diagnostics	Malvern, PA	06/09/2008	K072939
<b>ARCHITECT HE4 assay (CMIA)</b>	Fujirebio Diagnostics	Malvern, PA	03/18/2010	K093957
<b>ELECSYS HE4 (CMIA)</b>	Roche Diagnostics	Indianapolis, IN	09/10/2012	K112624
<b>Lumipulse G HE4 Immunoreaction Cartridges</b>	Fujirebio Diagnostics	Malvern, PA	11/24/2015	K151378

CMIA: chemoluminescent microparticle immunoassay; HE4: human epididymis protein 4; EIA: enzymatic immunoassay; FDA: Food and Drug Administration.

FDA product code: OIU.

**IV. RATIONALE**

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**Summary of Evidence**

For individuals who have ovarian cancer who receive a measurement of serum biomarker HE4, the evidence includes 4 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, disease-specific survival, test validity, other test performance measures, and change in disease status. Data submitted to the U.S. Food and Drug Administration for approval of commercial HE4 tests found that HE4 was not inferior to CA 125 for detecting ovarian cancer recurrence. Although a single prospective observational study found elevated levels of HE4, but not CA 125, at the time of cancer progression to be significantly associated with reduced overall survival, 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 outcomes.

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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 overall survival, 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 (i.e., 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 outcomes.

For individuals who are asymptomatic and not at high risk of ovarian cancer who receive screening with a serum biomarker HE4 test, 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 overall survival, 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 determine definitively whether HE4 testing is a useful screening tool. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

**V. DEFINITIONS**

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N/A

**VI. DISCLAIMER**

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*Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.*

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**VII. CODING INFORMATION**

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**Note:** This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

**Investigational therefore not covered:**

Procedure Codes							
86305							

**VIII. REFERENCES**

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1. *Surveillance Epidemiology and End Results Program (SEER). SEER Stat Fact: Ovarian Cancer. n.d.*
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.*
7. *Food and Drug Administration. 510(k) substantial equivalence determination decision summary: assay only (K093957). n.d.*
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, Grenman 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*

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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, Szpurek 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

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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. Anderson GL, McIntosh M, Wu L, et al. Assessing lead time of selected ovarian cancer biomarkers: a nested case-control study. *J Natl Cancer Inst.* Jan 06 2010; 102(1): 26-38. PMID 20042715
31. 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
32. 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
33. 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
34. 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
35. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 3.2024
36. National Institute for Health and Care Excellence (NICE). Ovarian cancer: recognition and initial management [CG122]. 2011. Updated October 2, 2023.
37. U.S. Preventive Services Task Force. Recommendation Statement: Screening for Ovarian Cancer. 2018
38. Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.66, Serum Biomarker Human Epididymis Protein 4. January 2025

**IX. POLICY HISTORY**

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<b>MP 2.269</b>	<b>07/07/2020 Consensus Review.</b> Policy statement unchanged. Product variation statement updated. FEP statement updated. References reviewed and updated. Coding checked with no changes.
	<b>02/01/2021 Consensus Review.</b> No change to policy statement. Background, Rationale and References updated.
	<b>01/19/2022 Consensus Review.</b> Added NCCN statement. Updated references.
	<b>04/07/2023 Consensus Review.</b> Updated background, coding table, and references.

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	<b>02/27/2024 Consensus Review.</b> Updated background and references. No changes to coding.
	<b>11/19/2024 Administrative Update.</b> Removed NCCN statement.
	<b>03/17/2025 Consensus Review.</b> Updated background and references. No changes to coding.
	<b>02/10/2026 Retirement Review.</b> Evicore delegation.

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