MEDICAL POLICY

POLICY TITLE	SERUM BIOMARKERS FOR HUMAN EPIDIDYMIS PROTEIN 4 (HE4)
POLICY NUMBER	MP 2.269

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**1/1/2025**

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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Human epididymis protein 4 (HE4) is a novel biomarker that has been cleared by the U.S. Food and Drug Administration (FDA) for monitoring patients 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.

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 2023, an estimated 19,710 women will be diagnosed with ovarian cancer and 13,270 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 2012 to 2018, 57% of women with ovarian cancer were diagnosed when the disease had distant metastases (stage IV), and this was associated with a 5-year survival rate of 31%. In contrast, 17% of women diagnosed with localized cancer (stage I) had a 5-year survival rate of 93%. 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 combines HE4, CA 125, and menopausal status into a numeric score. The Risk of Ovarian Malignancy Algorithm 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 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

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

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. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member’s health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member’s health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. 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								

IX. REFERENCES

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X. POLICY HISTORY

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MP 2.269	**07/07/2020 Consensus Review.** Policy statement unchanged. Product variation statement updated. FEP statement updated. References reviewed and updated. Coding checked with no changes.
	02/01/2021 Consensus Review. No change to policy statement. Background, Rationale and References updated.
	01/19/2022 Consensus Review. Added NCCN statement. Updated references.
	04/07/2023 Consensus Review. Updated background, coding table, and references.
	02/27/2024 Consensus Review. Updated background and references. No changes to coding.
	11/19/2024 Administrative Update. Removed NCCN statement.

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