



**BlueCross BlueShield  
of Alabama**

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**Name of Blue Advantage Policy:**  
**Serum Biomarker Human Epididymis Protein 4 (HE4)**

Policy #: 445

Latest Review Date: December 2022

Category: Laboratory

**ARCHIVED EFFECTIVE 11/1/2023**

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**BACKGROUND:**

*Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational\*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
  - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
  - *Furnished in a setting appropriate to the patient's medical needs and condition;*
  - *Ordered and furnished by qualified personnel;*
  - *One that meets, but does not exceed, the patient's medical need; and*
  - *At least as beneficial as an existing and available medically appropriate alternative.*

*\*Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill **Original Medicare** for covered services that are related to **clinical trials** that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

## **POLICY:**

### **Effective for dates of service on or after March 24, 2020:**

**Blue Advantage will treat measurement of human epididymis protein 4 (HE4) for any and all indications as a non-covered benefit and as investigational.**

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**Effective for dates of service February 26, 2018 through March 23, 2020, refer to LCD L36954.**

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### **Effective for dates of service prior to February 26, 2018:**

**Blue Advantage will treat measurement of human epididymis protein 4 (HE4) for any and all indications as a non-covered benefit and as investigational.**

*Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

## **DESCRIPTION OF PROCEDURE OR SERVICE:**

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 carbohydrate 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 2022, an estimated 19,880 women will be diagnosed with ovarian cancer and 12,810 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 five-year survival rate of 31%. In contrast, 17% of women diagnosed with localized cancer (stage I) had a five-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 the 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 measurements 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 in women with 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 to 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.

## **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) test combines HE4, CA 125, and menopausal status into a numeric score. The ROMA test has been cleared by U.S. Food and Drug Administration (FDA) for predicting the risk that an adnexal mass is malignant.

## **KEY POINTS:**

This policy was updated with a search of the literature through October 18, 2022.

## **Summary of Evidence**

For individuals who have ovarian cancer who receive a measurement of serum biomarker HE4, the evidence includes seven nonrandomized prospective and retrospective studies comparing the diagnostic accuracy of HE4 with CA 125 for predicting disease progression and/or recurrence. Relevant outcomes are OS, disease-specific survival, test validity, other test performance measures, and change in disease status. Data submitted to the U.S. FDA 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 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 (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 outcome.

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 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 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 outcome.

### **Practice Guidelines and Position Statements**

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### **American College of Obstetricians and Gynecologists**

Guidelines from the American College of Obstetricians and Gynecologists (ACOG) on evaluation and management of adnexal masses (2016, reaffirmed 2021) state that measurement of cancer antigen 125 (CA 125) is the most extensively studied serum marker to be used in combination with imaging to determine the likelihood of malignancy. The authors also suggest that measurement of CA 125 is most useful for identification of nonmucinous epithelial cancer in postmenopausal women. Although the guideline mentions that human epididymis protein 4 (HE4) has recently been identified as a biomarker that may be useful for distinguishing between benign and malignant masses, no further recommendations regarding HE4 are provided.

In 2017 (reaffirmed 2021), a committee opinion document from ACOG and the Society of Gynecologic Oncology stated that tumor markers such as CA 125 and transvaginal ultrasound, alone or in combination, have not improved early detection or survival in women with average risk for ovarian cancer. There is also a potential for harm if surgery is performed in response to a positive test result.

### **National Comprehensive Cancer Network**

The National Comprehensive Cancer Network (NCCN) ovarian cancer guidelines (v.5.2022) state that, for monitoring and follow-up of patients with stage I to IV ovarian cancer with a complete response to initial treatment, “CA-125 [cancer antigen 125] or other tumor marker” should be used at “every visit if initially elevated”. The guidelines do not specify any marker other than CA 125 for monitoring patients after treatment. The guidelines also recommend “CA-125 or other tumor markers as clinically indicated” for patients referred with newly diagnosed ovarian cancer after recent surgical procedure.

Elsewhere, the NCCN guideline provides the following comment about screening using HE4: “Some evidence suggests that HE4 [human epididymis protein 4] may be a useful prognostic marker in patients with ovarian cancer, decreases during response to treatment, and may improve early detection of recurrence relative to CA-125 alone.” The NCCN guidelines currently do not recommend routine HE4 as part of preoperative workup because results vary across studies.

Several biomarker combination tests have received Food and Drug Administration approval for estimating the risk of ovarian cancer in patients with adnexal masses and planned surgery. The Risk of Ovarian Malignancy Algorithm (ROMA) test includes HE4 plus CA-125 plus menopausal status, the OVA1 test includes five markers including CA-125 (but not HE4), and the OVERA test includes 5 markers including both CA-125 and HE4. The NCCN guidelines state the following about using these biomarker tests. Currently, the NCCN Panel does not recommend the use of these biomarker tests for determining the status of an undiagnosed adnexal/pelvic mass.”

The NCCN guidelines state the following on screening for ovarian cancer: “Very few biomarkers have been tested prospectively to determine whether they can detect ovarian cancer or predict development of ovarian cancer in women who have no other signs or symptoms of cancer. Data show that several markers (including CA-125, HE4, mesothelin, B7-H4, decoy receptor 3 [DcR3], and spondin-2) do not increase early enough to be useful in detecting early-stage ovarian cancer.”

### **National Institute for Health and Care Excellence**

In 2011, NICE recommended using CA 125 to test for ovarian cancer in patients presenting to primary care providers with symptoms of ovarian cancer. No other biomarker tests are mentioned in the NICE guidance

### **U.S. Preventive Services Task Force Recommendations**

The U.S. Preventive Services Task Force (USPSTF) updated its recommendations for screening for ovarian cancer in February 2018. USPSTF recommended against screening for ovarian cancer in asymptomatic women (D recommendation). HE4 was not specifically discussed.

**KEY WORDS:**

Human epididymis protein 4, HE4, HE4 EIA test, ARCHITECT HE4

**APPROVED BY GOVERNING BODIES:**

Multiple HE4 test kits have been cleared by the Food and Drug Administration through the 510(k) process and summarized in the table below. 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. Serum Human Epididymis 4 Tests Cleared by the Food and Drug Administration**

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 product code: OIU.

**BENEFIT APPLICATION:**

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

**CURRENT CODING:****CPT Codes:**

86305	Human epididymis protein 4 (HE4)
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## REFERENCES:

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## **POLICY HISTORY:**

Adopted for Blue Advantage, August 2010

Available for comment September 4-October 18, 2010

Medical Policy Group, October 2010

Medical Policy Group, September 2011

Medical Policy Group, April 2013

Medical Policy Group, September 2013

Medical Policy Group, March 2014

Medical Policy Group, March 2015

Medical Policy Group, January 2016

Medical Policy Group, December 2016

Medical Policy Group, December 2017

Medical Policy Group, February 2018

Medical Policy Group, April 2020: Reinstated policy effective March 24, 2020.

Medical Policy Group, December 2020

Medical Policy Group, December 2021

Medical Policy Group, December 2022

Medical Policy Group, November 2023: Archived effective 11/1/2023.

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*This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of*

*common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.*

*This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.*