BlueCross BlueShield
of Alabama

Name of Blue Advantage Policy*:*

Serum Biomarker Human Epididymis Protein 4 (HE4)

Policy #: 445	Latest Review Date: December 2019
Category: Laboratory	Policy Grade: B

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**.

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

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 in U.S. women. According to Surveillance Epidemiology and End Results (SEER) data, in 2013, an estimated 22,440 women will be diagnosed with ovarian cancer and 14,080 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. According to Surveillance Epidemiology and End Results (SEER) data, for the period 1999-2006, 62% of women with ovarian cancer were diagnosed when the disease had distant metastases (Stage IV) and this was associated with a 28.9% five-year survival rate. In contrast, 14.8% of women diagnosed with localized cancer (Stage 1) had a 92.5% five-year survival rate. 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 the follow-up 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 carbohydrate 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 in ovarian cancer that was in complete remission did not find a significant difference in overall survival when treatment for remission was initiated when 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 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 in 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. ROMA has been cleared by the FDA for predicting risk that an adnexal mass is malignant; this test is considered separately in policy #426, *Multi-marker Serum-Testing Related to Ovarian Cancer.*

KEY POINTS:
This policy was updated with a search of the literature through October 14, 2019.

Summary of Evidence
For individuals who have ovarian cancer who receive measurement of serum biomarker human epididymis protein 4, the evidence includes a prospective study and several retrospective studies comparing the diagnostic accuracy of HE4 and CA-125 for predicting disease progression and/or recurrence. Relevant outcomes are overall survival, disease-specific survival, test accuracy and 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. However, 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 not a clear chain of indirect evidence that changes in management based on HE4 would lead to improved health outcome and no direct evidence from prospective controlled studies on the impact of HE4 testing on health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have adnexal masses who receive measurement of serum biomarker human epididymis protein 4, the evidence includes diagnostic accuracy studies and meta-analyses.

Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and other test performance measures. Meta-analyses have generally found that HE4 and CA-125 have 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 not a clear chain of indirect evidence that changes in management based on HE4 would lead to improved health outcome and no direct evidence from prospective controlled studies on the impact of HE4 testing on health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 overall survival, disease-specific survival, test accuracy and validity, and other test performance measures. The retrospective studies found that levels of HE4 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.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network
The National Comprehensive Cancer Network (NCCN) ovarian cancer guidelines (v.2.2019) states that, for monitoring/follow-up of patients with Stage I-IV ovarian cancer with a complete response to initial treatment, "CA-125 or other tumor marker" should be used at "every visit if initially elevated". The guideline does not specify any marker other than CA-125 for monitoring patients after treatment.

The NCCN guidelines state the following on evaluating undiagnosed pelvic masses: "The FDA has approved the use of HE4 and CA-125 for estimating the risk for ovarian cancer in women with a pelvic mass. Currently the NCCN Panel does not recommend the use of these biomarkers for determining the status of an undiagnosed pelvic mass."

The NCCN guidelines state the following on screening for ovarian cancer: "The literature does not support routine screening for ovarian cancer in the general population, and routine screening is not currently recommended by any professional society. Some physicians follow women with high-risk factors (e.g., those with BRCA mutations, those with a family history) using CA-125 monitoring and endovaginal ultrasound; however, prospective validation of these tests remains elusive."

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (NICE) issued guidance in 2011 on the recognition and initial management of ovarian cancer. The guideline includes the following recommendations:

- Measure serum CA125 in primary care in women with symptoms that suggest ovarian cancer.
- If serum CA125 is 35 IU/ml or greater, arrange an ultrasound scan of the abdomen and pelvis.
- If the ultrasound suggests ovarian cancer, refer the woman urgently for further investigation.
- For any woman who has normal serum CA125 (less than 35 IU/ml), or CA125 of 35 IU/ml or greater but a normal ultrasound:
    - assess her carefully for other clinical causes of her symptoms and investigate if appropriate
    - If no other clinical cause is apparent, advise to return to her GP if her symptoms become more frequent and/or persistent.

Malignancy indices

- Calculate a risk of malignancy index I (RMI I) score (after performing an ultrasound). (The RMI 1 combines CA-125, menopausal status and the ultrasound score).

The NICE guidance did not mention HE4.

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 HE4 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.

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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POLICY HISTORY:
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Medical Policy Group, October 2010
Medical Policy Group, September 2011
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Medical Policy Group, January 2016
Medical Policy Group, December 2016
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Medical Policy Group, February 2018
Medical Policy Group, April 2020: Reinstated policy effective March 24, 2020.