BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.66 Serum Biomarker Human Epididymis Protein 4

Annual Effective Policy Date: April 1, 2024

Original Policy Date: December 2023

Related Policies:

2.04.62 - Multimarker Serum Testing Related to Ovarian Cancer

Serum Biomarker Human Epididymis Protein 4

Description

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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 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.

OBJECTIVE

The objectives of this evidence review are to evaluate whether testing of serum human epididymis protein 4 improves the net health outcome for individuals with ovarian cancer, with adnexal masses, or who are asymptomatic and not at high-risk of ovarian cancer.

POLICY STATEMENT

Measurement of human epididymis protein 4 is **not medically necessary** for all indications.

POLICY GUIDELINES

None

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA 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 the U.S. 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: chemiluminescent microparticle immunoassay; HE4: human epididymis protein 4; EIA: enzymatic immunoassay.
FDA product code: OIU.

RATIONALE

Summary of Evidence

For individuals who have ovarian cancer who receive a measurement of serum biomarker human epididymis protein 4 (HE4), the evidence includes 7 nonrandomized prospective and retrospective studies comparing the diagnostic accuracy of HE4 with cancer antigen 125 (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 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 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 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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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.[33,] 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.[34,] 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”.[35,] 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 guidelines 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 5 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.[36,] No other biomarker tests are mentioned in the NICE guidance.

U.S. Preventive Services Task Force Recommendations

The **U.S. Preventive Services Task Force** updated its recommendations for screening for ovarian cancer in February 2018.[37,] The Task Force recommended against screening for ovarian cancer in asymptomatic women (D recommendation). HE4 was not specifically discussed.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2023	New policy	Policy updated with literature review through October 18, 2022; references added. Policy statement unchanged. FEP Benefit changes. FEP new policy