

POLICY TITLE	SERUM BIOMARKERS FOR HUMAN EPIDIDYDMIS PROTEIN 4 (HEA)
POLICY NUMBER	MP-2.269

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I. POLICY

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

Cross-reference:

MP-2.270 Proteomics-Based Testing Related to Ovarian Cancer

II. PRODUCT VARIATIONS

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[N] = No product variation, policy applies as stated

[Y] = Standard product coverage varies from application of this policy, see below

- [N] Capital Cares 4 Kids
- [N] PPO
- [N] HMO
- [N] SeniorBlue HMO
- [N] SeniorBlue PPO

- [N] Indemnity
- [N] SpecialCare
- [N] POS
- [Y] FEP PPO*

*Refer to FEP Medical Policy Manual MP-2.04.66 Serum Markers for Human Epididymis Protein 4 (HEA). The FEP Medical Policy manual can be found at: www.fepblue.org

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III. DESCRIPTION/BACKGROUND

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Human epididymis protein 4 (HE4) is a potential new 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 CA-125 for monitoring disease progression and recurrence. HE4 has also been proposed as a test to screen for ovarian cancer in asymptomatic women.

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 22,240 women will be diagnosed with ovarian cancer and 14,030 women will die of the disease. (1) Stage at diagnosis is an important predictor of survival; however, most women are not diagnosed until the disease has spread. 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 5-year survival rate of 27.6%. In contrast, the 15% of women diagnosed with localized cancer (Stage I) had a 5-year survival rate of 93.5%. Epithelial ovarian tumors account for 85–90% of ovarian cancers.

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 patients with ovarian cancer following primary treatment. Patients undergo regular physical examinations. In addition, managing patients with serial measurement of the biomarker 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 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. (2)

Another serum biomarker, cleared by the FDA for monitoring patients with epithelial ovarian cancer, is human epididymis protein 4 (HE4). HE4 is made up of 2 whey acidic proteins with a 4 disulfide core domain. It has been found to be overexpressed by epithelial ovarian cancer tumors and to circulate in the serum of patients with epithelial ovarian cancer. Levels of HE4 may be less likely to be elevated due to benign conditions, as is the case with CA-125, which would make HE4 a candidate to replace or complement CA-125. Tests for HE4 are FDA-approved for monitoring women known to have epithelial ovarian cancer. Another possible application of HE4 testing is screening asymptomatic women for ovarian cancer; screening is not an accepted use of the CA-125 test.

This policy does not address use of the HE4 test for evaluating women with ovarian masses who have not been diagnosed with ovarian cancer. Use of the Risk of Ovarian Malignancy Algorithm (ROMA), which includes HE4, CA-125 and menopausal status, is addressed in policy 2.04.62 Proteomics-based Testing for the Evaluation of Ovarian (Adnexal) Masses.

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Regulatory Status

In June 2008, the HE4 EIA test kit (Fujirebio Diagnostics, Sweden) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. 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-cleared 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.

In March 2010, the ARCHITECT™ HE4 (Abbott Diagnostics, UK, co-developed with Fujirebio Diagnostics), an automated version of the HE4 EIA test, was cleared by the FDA for the same indications. The ARCHITECT HE4 test is being distributed in the United States by Quest Diagnostics (Madison, NJ).

IV. RATIONALE

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Assessment of a diagnostic technology typically focuses on 3 parameters: 1) technical performance; 2) diagnostic performance (sensitivity, specificity, and positive and negative predictive value) in appropriate populations of patients; and 3) demonstration that the diagnostic information can be used to improve patient outcomes (clinical utility).

Technical performance of a device is typically assessed with 2 types of studies: those that compare test measurements with a gold standard and those that compare results taken with the same device on different occasions (test-retest).

Diagnostic performance is evaluated by the ability of a test to accurately diagnose a clinical condition in comparison with the gold standard. The sensitivity of a test is the ability to detect a disease when the condition is present (true-positive), while specificity indicates the ability to detect patients who are suspected of disease but who do not have the condition (true-negative). Evaluation of diagnostic performance, therefore, requires independent assessment by the 2 methods in a population of patients who are suspected of disease but who do not all have the disease.

Evidence related to improvement of clinical outcomes with use of this testing assesses the data linking use of a test to changes in health outcomes (clinical utility). While in some cases, tests can be adequately evaluated using technical and diagnostic performance, when a test identifies a new or different group of patients with a disease; randomized trials are needed to demonstrate impact of the test on the net health outcome.

Literature Review

This policy was created with a search of the MEDLINE database through June 2010. The policy was updated regularly, most recently from June 2012 through June 24, 2013. A summary of the key literature is as follows:

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Technical performance

The U.S. Food and Drug Administration (FDA) substantial equivalence determination decision summary documents for the human epididymis protein 4 (HE4) EIA and ARCHITECT HE4 include data on technical performance. (3, 4) For example, the precision of the ARCHITECT HE4 test was assessed at 3 sites; samples were tested in 2 replicates using 2 lots of reagents in 2 separate runs per day for 20 days. Samples included 3 panels of pooled human serum and 3 controls. Total imprecision of the panels ranged from 3.4% to 5.4%. The upper limit of the 95% confidence interval for total imprecision for all samples was 6.1% or lower; this met the predetermined acceptance criteria for imprecision, which was 10% or less. Moreover, the test met acceptance criteria for linearity and stability of samples, as well as observed interference from common endogenous substances (i.e., bilirubin, hemoglobin, and high and low protein concentrations).

Diagnostic performance

Monitoring disease progression and recurrence in women with epithelial ovarian cancer

Since CA-125 is considered standard of care for managing patients with ovarian cancer, the literature review addressed the questions of whether the diagnostic performance of HE4 was superior to CA-125 and whether combined testing with HE4 and CA-125 was superior to CA-125 alone.

FDA documents included information on the diagnostic performance of HE4 for monitoring the progression and recurrence of ovarian cancer. FDA materials addressed the non-inferiority rather than the superiority of HE4 tests to CA-125. A study reported in the 510(k) substantial equivalence determination decision summary for the HE4 EIA assay evaluated whether this test was non-inferior to the CA-125 test. (3) The study included samples from 80 women with epithelial ovarian cancer who were undergoing serial surveillance of cancer progression. Blood samples were obtained from a large cancer center in the United States; they were not drawn specifically for this study. A total of 354 samples were obtained for the 80 women (women had multiple visits over time). Receiver operating curve (ROC) analysis was used to compare the 2 assays, and clinical evidence of progression was used as the reference standard. When a positive change in HE4 level (i.e., to indicate disease progression) was defined as a value at least 25% higher than the previous value of the test, the sensitivity of the test was 76/126 (60.3%), and the specificity was 171/228 (75%). (Note that the unit of analysis was the number of samples rather than the number of women.) The area under the curve (AUC) in the ROC curves was found to be similar (0.725 for HE4 and 0.709 for CA-125, respectively) with overlap in the confidence intervals; according to the authors, this indicated that the HE4 assay was not inferior to the CA-125 assay for detecting cancer progression.

Another analysis estimated the cut-off values and specificity for the HE4 and CA-125 assays at a fixed sensitivity. The specificity values for CA-125 and HE4 were not statistically different at the respective cut-offs and sensitivities; for example, using a cut-off of 15.4% above the previous value for the HE4 test, the sensitivity of the HE4 was 64.3% and the specificity was 69.3%. The specificity of CA-125 at a matching sensitivity was 70.2%; this

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used a cut-off for the CA-125 level of an increase of at least 32.8%. These data were also said to confirm that the HE4 EIA test is not inferior to the CA-125 test for detecting ovarian cancer progression.

The 510(k) substantial equivalence determination decision summary for the ARCHITECT HE4 assay reported data from a retrospective study using remnant serial samples from 76 women diagnosed with epithelial ovarian cancer being monitored after completion of chemotherapy. (4) The eligibility criteria included availability of at least 3 serial specimens; samples could have been drawn during and/or after treatment. Clinical determination of disease progression was used as the reference standard. A positive test was defined as an HE4 level that was 14% higher than the previous reading. Using this cut-off, the sensitivity of the assay for detecting progressive disease was 53/99 events (53.5%). The specificity of the assay was 260/331 (78.5%). Of note, the sensitivity is lower than that reported above for the HE4 EIA at a similar specificity, when a cut-off of a 25% increase was used (sensitivity: 60.3% and specificity: 75%).

The FDA documents noted that there is no clinically accepted cut-off for use in monitoring cancer progression in epithelial ovarian cancer patients using the HE4 assays. As previously mentioned, a study included in the HE4 EIA assay materials defined a positive test as a level that is 25% higher than a previous measurement, and a study on the ARCHITECT HE4 test defined a positive test as an increase of at least 14% in the level of HE4. The FDA documents further state that clinicians may decide whether to use the cut-offs in the studies or another cut-off that reflects their own preferences in the tradeoff between sensitivity and specificity.

In 2012, a study was published by Plotti and colleagues in Italy evaluating the ability of HE4 to predict ovarian cancer recurrence. (5) The study included 34 women with radiological suspicion of ovarian cancer recurrence and a comparison group of 34 women with benign adnexal conditions. Serum samples were obtained 24 hours before surgery. All women with suspected ovarian cancer had recurrent disease confirmed at surgery. HE4 tests were evaluated at 2 cutoffs, greater than 70 pmol/L and greater than 150 pmol/L. The sensitivity of HE4 at the 70 pmol/L cut-off was 74% (25 of 34 cases were identified) and sensitivity of HE4 at the 150 pmol/L cut-off was 26% (9 of 34). The specificity was 100% at both cut-offs. In contrast, the sensitivity and specificity of CA-125 were 35% (12 of 34) and 59%, respectively. Using a combination of HE4 at a cut-off of 70 pmol/L and CA-125, the sensitivity to detect recurrent ovarian cancer was 76% and the specificity was 100%.

Screening asymptomatic women

No published studies were identified that evaluated the diagnostic performance of the HE4 biomarker for screening asymptomatic women for ovarian cancer compared to a reference standard.

A retrospective study published in 2010 by Anderson and colleagues aimed to determine the potential value of using HE4 and other biomarkers in early identification of ovarian cancer in asymptomatic women. (6) The study included 34 women with ovarian cancer and 70 matched controls, all of whom were participating in an unrelated randomized controlled trial (RCT)

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including smokers at increased risk of lung cancer. Blood samples were available for the women between 0 and 18 years before ovarian cancer diagnosis. In descriptive analyses, individual serum markers, including HE4, CA-125, and mesothelin, showed increasing accuracy over time approaching the diagnosis of ovarian cancer. Mean concentrations of these markers, which were measured by visually-read immunoassays, began to increase approximately 3 years before diagnosis but attained detectable levels only within the final year before diagnosis. The study had a small sample size, limiting the ability to conduct quantitative analysis, and included only heavy smokers and therefore may not be representative of the population of women at risk of ovarian cancer.

In 2011, Urban and colleagues retrospectively reviewed preclinical samples to evaluate the potential utility of HE4 and other markers as a secondary screening test in women found to have epithelial ovarian cancer. (7) There were samples from 112 ovarian cancer patients and 706 matched controls. Individuals participated in the Prostate, Lung, Colorectal and Ovarian (PLCO) trial and had been screened annually for 6 years with CA-125. Serum samples to evaluate potential markers were taken from the year proximate to the one in which women were diagnosed with ovarian cancer. (Serum samples were not available for the 4th screen, so they were taken from the 3rd year for the women diagnosed with ovarian cancer between the 3rd and 4th screens.) The investigators evaluated the associations between CA-125, HE4, and levels of 5 other markers with malignancy, accounting for increasing CA-125 levels and adjusting for demographic characteristics. Increase in CA-125 levels was associated with statistically significant increases in all of the markers. Levels of HE4 were most elevated, compared to controls i.e. the highest average HE4 level was 4.26 standard deviations above the mean HE4 level in control samples. The utility of HE4 as a biomarker to screen for ovarian cancer along with CA-125 needs to be further evaluated in prospective studies and confirmed in RCTs that evaluate the impact of screening on health outcomes.

Clinical utility

No prospective studies were identified that compared health outcomes in patients managed with and without HE4 testing, alone or in combination with CA-125 or other disease markers. In addition, no randomized controlled trials evaluating the clinical utility of screening asymptomatic women with HE4 were identified.

Ongoing Clinical Trials

A Trial Using Novel Markers to Predict Malignancy in Elevated-Risk Women (NCT01121640) (8): This is a randomized controlled trial comparing 2 epithelial ovarian cancer screening protocols. One strategy involves assessment of CA-125 at every screen and HE4 at a confirmatory screen and the other involves CA-125 and HE4 assessment at every screen. The primary study outcome is the positive predictive value of the 2 screening protocols. The expected date of study completion is June 2014.

Summary

There are limited data on the diagnostic test performance of the human epididymis protein 4 (HE4) test used to monitor disease progression and recurrence in women after initial treatment

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for epithelial ovarian cancer. There is no established cut-off for determining when an HE4 test is positive, when used for identifying disease progression or recurrence. Available studies have used different cut-offs for identifying a recurrence. Moreover, a survival advantage of early detection of ovarian cancer recurrence using HE4 levels or other biomarkers has not been established. No published studies were identified evaluating use of the HE4 test to screen asymptomatic women for ovarian cancer. Thus, the HE4 test is considered investigational for all indications.

Practice Guidelines and Position Statements

In December 2012, the U.S. Preventive Services Task Force (USPSTF) published an updated recommendation statement on screening for ovarian cancer. (9) The USPSTF recommended against screening for ovarian cancer in asymptomatic women (D recommendation). HE4 was not specifically discussed.

The 2013 National Comprehensive Cancer Network (NCCN) ovarian cancer guideline 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. (10) The guideline does not specify any marker other than CA-125 for monitoring patients after treatment.

The NCCN guideline states the following on screening for ovarian cancer:

“Randomized data do not yet 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.”

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 contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

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VII. DISCLAIMER

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Capital’s 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. Capital 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:

CPT Codes®								
86305								

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HCPCS Code	Description

***Investigational for all diagnosis**

ICD-9-CM Diagnosis Code*	Description

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

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The following ICD-10 diagnosis codes will be effective October 1, 2015:

ICD-10-CM Diagnosis Code*	Description

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

IX. REFERENCES

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9. U.S. Preventive Services Task Force. Screening for ovarian cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. 2012. Available online at: www.guideline.gov. Last accessed July, 2013.
10. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer Version 2.2013. 2013. Available online at: http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Last accessed July, 2013

Other:

Novitas Solutions. Local Coverage Determination ([LCD](#)) L33142 Biomarkers for Oncology. Effective 1/1/14

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X. POLICY HISTORY

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MP-2.269	CAC 5/20/14 Policy criteria removed from MP-2.212 Tumor Markers and Tumor Related Molecular Testing. References updated and rationale added. No changes to policy statements.
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