

Evidence Based Guideline

Serum Biomarker Human Epididymis Protein 4 (HE4)

File Name:	serum_biomarker_human_epididymis_protein_4_(HE4)
Origination:	1/2010
Last CAP Review:	4/2012
Next CAP Review:	4/2013
Last Review:	4/2012

Description of Procedure or Service

Human epididymis protein 4 (HE4) is a potential new biomarker for detecting ovarian cancer early and for monitoring disease progression and recurrence. It 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, a biomarker with limited specificity.

Background

Ovarian cancer is the fifth most common cause of cancer mortality in U.S. women; in 2010, it is estimated that ovarian cancer will account for approximately 14,000 deaths, 5% of the cancer deaths in women. 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 5-year survival rate of 27.6%. In contrast, the 15% of women diagnosed with localized cancer (Stage 1) had a 5-year survival rate of 93.5%. Epithelial ovarian tumors account for 85–90% of ovarian cancers.

Several factors contribute to the frequent late-stage diagnosis of ovarian cancer. First, symptoms are nonspecific, e.g., abdominal pain; persistent indigestion and bloating; urinary urgency; fatigue and weight loss, and many women do not immediately seek medical consultation. When women seek care, doctors frequently do not recognize the implications of the symptoms and diagnosis can be delayed. Furthermore, there is no reliable test to differentiate between benign and malignant pelvic masses. Generally, women are evaluated with a pelvic examination and ultrasound, and when they are found to have a pelvic mass, they are referred for surgery. The standard treatment for epithelial ovarian cancer is surgical staging and primary cytoreductive surgery followed by chemotherapy in most cases. Health outcomes tend to be better for women with ovarian cancer who are treated by gynecologic oncologists. The proteomics-based OVA1™ (Fremont, CA.) is cleared by the FDA for assessing the likelihood of malignancy in women with adnexal masses. Following treatment for ovarian cancer, women continue to be monitored for disease recurrence.

In addition to the tests and procedure discussed above, there is interest in identifying biomarkers that can be used to manage patients with symptoms suggestive of ovarian cancer or with a diagnosis of ovarian cancer. Currently, the most widely used biomarker is CA-125, a high-molecular-weight protein antigen. Testing for CA-125 in women with a pelvic mass suggestive of ovarian cancer is common practice. However, although elevated serum CA-125 levels are highly correlated with epithelial ovarian cancer (elevated in about 80% of cases), levels can also be elevated by benign gynecological and medical conditions, such as endometriosis; congestive heart failure; and cirrhosis, limiting the specificity for distinguishing between benign and malignant masses. Moreover, CA-125 levels tend to be higher in premenopausal women, increasing the likelihood of false-positives when used in this population. After treatment for ovarian cancer, serial measurement

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of CA-125 has been used to detect early recurrence of disease. A rising CA-125 level has been found to correlate with disease recurrence, although a survival advantage of detecting recurrence early with CA-125 compared to symptomatic detection has not yet been demonstrated.

Another serum biomarker, recently cleared by the FDA for monitoring patients with epithelial ovarian cancer, is human epididymis protein 4 (HE4). HE4 is made up of two whey acidic proteins with a four 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 it a candidate to replace or complement CA-125. Tests for HE4 are FDA-approved for monitoring women known to have epithelial ovarian cancer. Although HE4 tests are not FDA-approved for evaluating women with ovarian masses to aid in the identification of malignant tumors, these tests have been investigated for this indication and are available outside of the U.S. for evaluating women with pelvic masses.

Regulatory Status

In June 2008, the HE4 EIA test kit (Fujirebio Diagnostics, Sweden) was cleared for marketing by the 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. 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).

Related Policies:

Analysis of Proteomic Patterns in Serum to Identify Cancer
Proteomics-Based Testing for the Evaluation of Ovarian (Adnexal) Masses

*****Note: This Evidence Based Guideline is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

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Measurement of serum biomarker human epididymis protein 4 (HE4) to monitor disease progression and recurrence in women diagnosed with epithelial ovarian cancer is not recommended based on the scientific evidence.

There are limited data on the diagnostic performance of the HE4 test used to monitor disease progression and recurrence in women diagnosed with epithelial ovarian cancer. The only available data on the diagnostic test performance are in FDA documents. The reported studies were small, retrospective and may have included duplicate data on the same women, using different cut-offs for identifying a recurrence. There is no established cut-off for determining when an HE4 test is positive for any of its proposed uses. No further validation studies have been published. In addition, no data are available from prospective studies on the clinical utility of any application of the HE4 test or its use to screen asymptomatic women.

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Medical Evidence regarding Serum Biomarker Human Epididymis Protein 4 (HE4) indicates it is not recommended in the following situations

Measurement of serum biomarker human epididymis protein 4 (HE4) is not recommended for any application including, but not limited to:

- Diagnosing malignant disease in women with signs or symptoms suggestive of ovarian cancer.
- Monitoring disease progression or recurrence in women with epithelial ovarian cancer.
- Screening asymptomatic women for ovarian cancer.

Benefits Application

This evidence based guideline relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this guideline.

Billing/Coding/Physician Documentation Information

This guideline may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 86305

Scientific Background and Reference Sources

Originally discussed in policy named: Tumor Markers

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.66, 8/2010

Medical Director – 10/2010

Tumor Marker Policy Separated – New Evidence Based Guideline – Serum Biomarker Human Epididymis Protein 4 (HE4)

Specialty Matched Consultant Advisory Panel – 4/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.66, 8/11/2011

Medical Director – 9/2011

Specialty Matched Consultant Advisory Panel – 4/2012

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Policy Implementation/Update Information

5/24/11 Tumor Marker policy separated. Serum Biomarker Human Epididymis Protein 4 (HE4) converted from corporate medical policy to evidence based guideline. "Description" section rewritten. "Measurement of serum biomarker human epididymis protein 4 (HE4) to monitor disease progression and recurrence in women diagnosed with epithelial ovarian cancer is not recommended based on the scientific evidence." Specialty Matched Consultant Advisory Panel review 4/27/2011. References added. (btw)

10/11/11 "Description" section updated. Medical Director review 9/21/2011. Reference added. (btw)

5/15/12 Specialty Matched Consultant Advisory Panel review 4/18/2012. No change to guideline intent. (btw)

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