Serum Biomarker Human Epididymis Protein 4 (HE4)

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 124 (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.

Background

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 approximately 22,240 women will be diagnosed with ovarian cancer and 14,030 women will die of the disease. 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 1) 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.

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 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 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.
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This policy 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. The Risk of Ovarian Malignancy Algorithm (ROMA) combines HE4, CA-125 and menopausal status into a numeric score. ROMA has been cleared by FDA for predicting risk that an adnexal mass is malignant; this test is considered separately in policy, Proteomics-based Testing for the Evaluation of Ovarian (Adnexal) 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 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).

Related Policies:
Proteomics-Based Testing for the Evaluation of Ovarian (Adnexal) Masses

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

Policy

Serum biomarker human epididymis protein (HE4) is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy 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 medical policy.

When Serum Biomarker Human Epididymis Protein 4 (HE4) is covered

Not applicable.

When Serum Biomarker Human Epididymis Protein 4 (HE4) is not covered

Serum Biomarker Human Epididymis Protein 4 (HE4) measurement is considered investigational for all indications.

Policy Guidelines

For individuals who have ovarian cancer who receive measurement of serum biomarker HE4, the evidence includes 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 FDA for approval of commercial HE4 tests found that HE4 was not inferior to
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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. No prospective studies were identified that compared survival and other health outcomes in patients managed with and without HE4 testing, alone or in combination with CA-125 or other disease markers. 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 HE4, the evidence includes multiple 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. 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 HE4 is a useful screening tool. The evidence is insufficient to determine the effects of the technology on health outcomes.

The HE4 test is investigational for all indications.

Billing/Coding/Physician Documentation Information

This policy 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 service codes: 86305

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Originally discussed in policy named: Tumor Markers


Medical Director – 10/2010

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

Medical Director – 9/2011

Policy Implementation/Update Information


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

10/16/12 Description section updated. Reference added. (btw)

4/30/13 Specialty Matched Consultant Advisory Panel review 4/17/2013. Description section revised. The Evidence Based Guideline section updated to indicate; “There is no established cut-off for determining when an HE4 test is positive, when used for identifying disease progression or recurrence. Moreover, a survival advantage of early detection of ovarian cancer recurrence using HE4 levels or other biomarkers has not
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been established. No published studies were identified evaluating use of the HE4 test to screen asymptomatic women for ovarian cancer.” (btw)

10/1/13 Revised the dates and statistical figures in the Description section. Removed the following statement from the Evidence Based Guideline section; “The 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, and used different cut-offs for identifying a recurrence.” Removed the When not recommended section and included the information in the Evidence Based Guideline section. Senior Medical Director review 9/14/2013. Reference added. (btw)


2/29/16 Updated Policy Guidelines section. Reference added. No change to policy statement. (lpr)

5/31/16 Specialty Matched Consultant Advisory Panel review 4/27/2016. No change to policy. (lpr)

5/26/17 Updated Policy Guidelines section. Reference added. Specialty Matched Consultant Advisory Panel review 4/26/2017. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.