Medical Coverage Policy | Serum Biomarker Human Epididymis Protein 4

EFFECTIVE DATE: 09|26|2003
POLICY LAST UPDATED: 08|01|2017

OVERVIEW
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 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.

MEDICAL CRITERIA
Not applicable

PRIOR AUTHORIZATION
Not applicable

POLICY STATEMENT
BlueCHiP for Medicare and Commercial Products
Measurement of HE4 is not medically necessary for all indications as the evidence is insufficient to determine the effects of the technology on health outcomes.

COVERAGE
Benefits may vary between groups/contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage or Subscriber Agreement for services not medically necessary.

BACKGROUND
Human epididymis protein 4 is a novel biomarker that has been cleared by the FDA 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.

Ovarian cancer is the fifth most common cause of cancer mortality among U.S. women. According to Surveillance Epidemiology and End Results (SEER) data, in 2013, an estimated 22,240 women would be diagnosed with ovarian cancer and 14,030 women would 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 to 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% to 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 of patients with ovarian cancer after primary treatment. Patients undergo regular physical examinations. In addition, managing patients with serial measurement of the biomarker cancer 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 randomized controlled trial (RCT) with women having ovarian cancer that was in

complete remission did not find a significant difference in overall survival when treatment for remission was initiated after CA 125 concentration exceeded twice the limit of normal compared with delaying treatment initiation until symptom onset.

Another serum biomarker, cleared by the U.S. Food and Drug Administration (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 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 for 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.

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. FDA determined that this device was substantially equivalent to a cancer antigen 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 human epididymis protein 4 (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, developed with Fujirebio Diagnostics), an automated version of the HE4 EIA test, was cleared for marketing by FDA for the same indications. The ARCHITECT™ HE4 test is being distributed in the United States by Quest Diagnostics (Madison, NJ).

For individuals who have ovarian cancer who receive measurement of serum biomarker human epididymis protein 4 (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 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 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 improved health outcome. 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 diagnostic accuracy studies and meta-analyses. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and other test performance measures. Metaanalyses have generally found that HE4 and CA 125 have 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 improved health outcome. 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. Therefore, this service is considered not medically necessary for BlueCHiP for Medicare and Commercial products.

CODING

BlueCHiP for Medicare and Commercial Products
The following CPT code is considered not medically necessary:
86305 Human epididymis protein 4 (HE4)

RELATED POLICIES

CA-125
Multimarker Serum Testing Related to Ovarian Cancer

PUBLISHED

Provider Update, October 2017
Provider Update, January 2017
Provider Update, January 2016
Provider Update, December 2014
Provider Update, July 2013
Provider Update, February 2012
Provider Update, April 2011
Provider Update, October 2009

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