Medical Coverage Policy | Serum Biomarker Human Epididymis Protein 4

EFFECTIVE DATE: 01|01|2024
POLICY LAST REVIEWED: 02|07|2024

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
Medicare Advantage Plans
Measurement of Human epididymis protein 4 is not covered for all indications as the evidence is insufficient to determine the effects of the technology on health outcomes.

Commercial Products
Measurement of Human epididymis protein 4 is not medically necessary for all indications as the evidence is insufficient to determine the effects of the technology on health outcomes.

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L**. §27-19-81** described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE
Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable not medically necessary/not covered benefits/coverage.

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 data, in 2023, an estimated 19,710 women will be diagnosed with

ovarian cancer and 13,270 women will die of the disease. The stage at diagnosis is an important predictor of survival; however, most women are not diagnosed until the disease has spread. For the period 2012 to 2018, 57% 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 31%. In contrast, 17% of women diagnosed with localized cancer (stage I) had a 5-year survival rate of 93%. 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 or during primary treatment. Patients undergo regular physical examinations and may have imaging studies. 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 2010 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.

Human epididymis protein 4 (HE4) is a protein that circulates in the serum and has been found to be overexpressed in epithelial ovarian cancer, lung adenocarcinoma, breast cancer, pancreatic cancer, endometrial cancer, and bladder cancer. HE4 is made up of two whey acidic proteins with a four disulfide core domain and has been proposed as a biomarker for monitoring patients with epithelial ovarian cancer.

This evidence review 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

Multiple HE4 test kits have been cleared by the 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-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.

For individuals who have ovarian cancer who receive a measurement of serum biomarker HE4, the evidence includes 7 nonrandomized prospective and retrospective studies comparing the diagnostic accuracy of HE4 with 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 FDA for approval of commercial HE4 tests found that HE4 was not inferior to CA125 for detecting ovarian cancer recurrence. Although a single prospective observational study found that elevated levels of HE4, but not CA 125, at the time of cancer progression was 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 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 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 definitively determine whether HE4 is a useful screening tool. The evidence is insufficient to determine the effects of the technology on health outcomes.

CODING

The following CPT code is not covered for Medicare Advantage Plans and not medically necessary for Commercial products:

86305 Human epididymis protein 4 (HE4)

RELATED POLICIES

Biomarker Testing Mandate
CA-125
Genetic Testing Services
Multimarker Serum Testing Related to Ovarian Cancer

PUBLISHED

Provider Update, April 2024
Provider Update, March 2023, November 2023
Provider Update, April 2022
Provider Update, March 2021
Provider Update, March 2020

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