



MASSACHUSETTS

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Medical Policy

Serum Biomarker Human Epididymis Protein 4

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Policy Number: 290

BCBSA Reference Number: 2.04.66 (For Plan internal use only)

NCD/LCD: N/A

Related Policies

Multimarker Serum Testing Related to Ovarian Cancer #[249](#)

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

Measurement of human epididymis protein 4 is [INVESTIGATIONAL](#) for all indications.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

| | Outpatient |
|--|---------------------------------------|
| Commercial Managed Care (HMO and POS) | This is not a covered service. |
| Commercial PPO and Indemnity | This is not a covered service. |
| Medicare HMO BlueSM | This is not a covered service. |
| Medicare PPO BlueSM | This is not a covered service. |

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT code is considered investigational for **Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:**

CPT Codes

| CPT codes: | Code Description |
|------------|----------------------------------|
| 86305 | Human epididymis protein 4 (HE4) |

Description

Ovarian Cancer

Ovarian cancer is the fifth most common cause of cancer mortality among U.S. women. According to Surveillance Epidemiology and End Results data, in 2021, an estimated 21,410 women will be diagnosed with ovarian cancer and 13,770 women will die of the disease.¹ The 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 28.9%. In contrast, 14.8% of women diagnosed with localized cancer (stage I) had a 5-year survival rate of 92.5%. Epithelial ovarian tumors account for 85% to 90% of ovarian cancers.²

Treatment

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 the 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 measurements 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 in women with 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 to delaying treatment initiation until symptom onset.³

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 2 whey acidic proteins with a 4 disulfide core domain and has been proposed as a biomarker for monitoring patients with epithelial ovarian cancer.

Evaluation of Adnexal Masses

This evidence review also addresses the 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 a surgical referral to a specialist with expertise in ovarian cancer is warranted. The Risk of Ovarian Malignancy Algorithm (ROMA) test combines HE4, CA 125, and menopausal status into a numeric score. The ROMA test has been cleared by U.S. Food and Drug Administration (FDA) for predicting the risk that an adnexal mass is malignant; this test and other combination biomarker tests, are considered separately in policy #249 (multimarker serum testing related to ovarian cancer).

Summary

Human epididymis protein 4 (HE4) is a novel biomarker that has been cleared by the U.S. Food and Drug Administration 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.

Summary of Evidence

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, disease-specific survival, test 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. Although a single prospective observational study found elevated levels of HE4, but not CA 125, at the time of cancer progression to be significantly associated with reduced overall survival, 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 overall survival, 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 a serum biomarker HE4 test, 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 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 determine definitively whether HE4 testing is a useful screening tool. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Policy History

| Date | Action |
|--------|--|
| 2/2022 | Annual policy review. Description, summary, and references updated. Policy statements unchanged. |
| 2/2021 | Annual policy review. Description, summary, and references updated. Policy statements unchanged. |
| 1/2020 | Annual policy review. Description, summary, and references updated. Policy statements unchanged. |

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|----------------|--|
| 2/2019 | Annual policy review. Description, summary, and references updated. Policy statements unchanged. |
| 3/2018 | Annual policy review. New references added. |
| 1/2017 | Annual policy review. New references added. |
| 1/2016 | Annual policy review. New references added. |
| 12/2015 | Added coding language. |
| 5/2015 | Annual policy review. New references added. |
| 5/2014 | Annual policy review. New references added. |
| 12/2013 | Annual policy review. New references added. |
| 3/2013 | Annual policy review. No changes to policy statement. |
| 11/2011-4/2012 | Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements. |
| 9/2011 | Reviewed - Medical Policy Group – Urology, Obstetrics and Gynecology. No changes to policy statements. |
| 7/2011 | Reviewed - Medical Policy Group – Hematology and Oncology. No changes to policy statements. |
| 12/3/2010 | New policy describing ongoing non-coverage of serum biomarker human epididymis protein 4 (HE4), effective 12/3/2010. |

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

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