MASSACHUSETTS

Blue Cross Blue Shield of Massachusetts is an Independent Licensee of the Blue Cross and Blue Shield Association

Medical Policy

Serum Biomarker Human Epididymis Protein 4 - HE4

Table of Contents

Policy Number: 290

BCBSA Reference Number: 2.04.66
NCD/LCD: N/A

Related Policies

- Multimarker Serum Testing Related to Ovarian Cancer, #249
- Tumor Markers for Diagnosis and Management of Cancer #536
- Proteomics-based Testing for the Evaluation of Ovarian (Adnexal) Masses #249

Policy

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

Measurement of HE4 for all indications is **INVESTIGATIONAL**.

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 Blue℠	This is **not** a covered service.
Medicare PPO Blue℠	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 (SEER) data, in 2013, an estimated 22,440 women would be diagnosed with ovarian cancer and 14,080 women would die of the disease.[1] 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, the 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 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.[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 (EOC), 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) combines HE4, CA 125, and menopausal status into a numeric score. ROMA has been cleared by FDA for predicting the risk that an adnexal mass is malignant; this test is 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.

For individuals who have ovarian cancer who receive a measurement of serum biomarker HE4, the evidence includes a prospective study and several 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. 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 an 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 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 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 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 the effects of the technology on health outcomes.

Policy History

Date	Action
2/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
3/2018	New references added from BCBSA National medical policy.

1/2017	New references added from BCBSA National medical policy.
1/2016	New references added from BCBSA National medical policy.
12/2015	Added coding language.
5/2015	New references added from BCBSA National medical policy.
5/2014	New references from BCBSA National medical policy.
12/2013	New references from BCBSA National medical policy.
3/2013	BCBSA National medical 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

References

1. Surveillance Epidemiology and End Results Program (SEER). SEER Stat Fact: Ovarian Cancer. n.d.; http://seer.cancer.gov/statfacts/html/ovary.html. Accessed November 8, 2017.
2. Ledermann JA, Raja FA, Fotopoulou C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. Oct 2013;24 Suppl 6:vi24-32. PMID 24078660
3. Rustin GJ, van der Burg ME, Griffin CL, et al. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. Lancet. Oct 2 2010;376(9747):1155-1163. PMID 20888993
4. Food and Drug Administration. 510(k) substantial equivalence determination decision summary: assay only (K072939). n.d.; http://www.accessdata.fda.gov/cdrh_docs/reviews/K072939.pdf. Accessed November 8, 2017.
5. Food and Drug Administration. 510(k) substantial equivalence determination decision summary: assay only (K093957). n.d.; http://www.accessdata.fda.gov/cdrh_docs/reviews/K093957.pdf. Accessed November 8, 2017.
6. Plotti F, Capriglione S, Terranova C, et al. Does HE4 have a role as biomarker in the recurrence of ovarian cancer? Tumour Biol. Dec 2012;33(6):2117-2123. PMID 22875782
7. Braicu EI, Fotopoulou C, Van Gorp T, et al. Preoperative HE4 expression in plasma predicts surgical outcome in primary ovarian cancer patients: results from the OVCAD study. Gynecol Oncol. Feb 2013;128(2):245-251. PMID 23178313
8. Nassir M, Guan J, Luketina H, et al. The role of HE4 for prediction of recurrence in epithelial ovarian cancer patients-results from the OVCAD study. Tumour Biol. Mar 2016;37(3):3009-3016. PMID 26419591
9. Steffensen KD, Waldstrom M, Brandslund I, et al. Identification of high-risk patients by human epididymis protein 4 levels during follow-up of ovarian cancer. Oncol Lett. Jun 2016;11(6):3967-3974. PMID 27313725
10. Vallius T, Hynninen J, Auranen A, et al. Postoperative human epididymis protein 4 predicts primary therapy outcome in advanced epithelial ovarian cancer. Tumour Biol. Feb 2017;39(2):1010428317691189. PMID 28218038

11. Macedo AC, da Rosa MI, Lumertz S, et al. Accuracy of serum human epididymis protein 4 in ovarian cancer diagnosis: a systematic review and meta-analysis. Int J Gynecol Cancer. Sep 2014;24(7):1222-1231. PMID 25078339
12. Ferraro S, Braga F, Lanzoni M, et al. Serum human epididymis protein 4 vs carbohydrate antigen 125 for ovarian cancer diagnosis: a systematic review. J Clin Pathol. Apr 2013;66(4):273-281. PMID 23426716
13. Yang Z, Wei C, Luo Z, et al. Clinical value of serum human epididymis protein 4 assay in the diagnosis of ovarian cancer: a meta-analysis. Onco Targets Ther. Aug 2013;6:957-966. PMID 23901285
14. Yu S, Yang HJ, Xie SQ, et al. Diagnostic value of HE4 for ovarian cancer: a meta-analysis. Clin Chem Lab Med. Aug 2012;50(8):1439-1446. PMID 22868811
15. Wang J, Gao J, Yao H, et al. Diagnostic accuracy of serum HE4, CA125 and ROMA in patients with ovarian cancer: a meta-analysis. Tumour Biol. Jun 2014;35(6):6127-6138. PMID 24627132
16. Dayyani F, Uhlig S, Colson B, et al. Diagnostic performance of risk of ovarian malignancy algorithm against CA125 and HE4 in connection with ovarian cancer: a meta-analysis. Int J Gynecol Cancer. Nov 2016;26(9):1586-1593. PMID 27540691
17. Zhen S, Bian LH, Chang LL, et al. Comparison of serum human epididymis protein 4 and carbohydrate antigen 125 as markers in ovarian cancer: A meta-analysis. Mol Clin Oncol. Jul 2014;2(4):559-566. PMID 24940495
18. Kaijser J, Van Gorp T, Smet ME, et al. Are serum HE4 or ROMA scores useful to experienced examiners for improving characterization of adnexal masses after transvaginal ultrasonography? Ultrasound Obstet Gynecol. Jan 2014;43(1):89-97. PMID 23828371
19. Moszynski R, Szubert S, Szpurek D, et al. Usefulness of the HE4 biomarker as a second-line test in the assessment of suspicious ovarian tumors. Arch Gynecol Obstet. Dec 2013;288(6):1377-1383. PMID 23722285
20. Nikolova T, Zivadinovic R, Evtimovska N, et al. Diagnostic performance of human epididymis protein 4 compared to a combination of biophysical and biochemical markers to differentiate ovarian endometriosis from epithelial ovarian cancer in premenopausal women. J Obstet Gynaecol Res. Dec 2017;43(12):1870-1879. PMID 29027715
21. Anderson GL, McIntosh M, Wu L, et al. Assessing lead time of selected ovarian cancer biomarkers: a nested case-control study. J Natl Cancer Inst. Jan 6 2010;102(1):26-38. PMID 20042715
22. Urban N, Thorpe JD, Bergan LA, et al. Potential role of HE4 in multimodal screening for epithelial ovarian cancer. J Natl Cancer Inst. Nov 2 2011;103(21):1630-1634. PMID 21917606
23. Terry KL, Schock H, Fortner RT, et al. A prospective evaluation of early detection biomarkers for ovarian cancer in the European EPIC cohort. Clin Cancer Res. Sep 15 2016;22(18):4664-4675. PMID 27060155
24. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer Including Fallopian Tube Cancer and Primary Periotneal Cancer. Version 3.2017. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed October 30, 2018.
25. National Institute for Health and Care Excellence (NICE). Ovarian cancer: recognition and initial management [CG122]. 2011; https://www.nice.org.uk/guidance/cg122. Accessed November 8, 2017.
26. U.S. Preventive Services Task Force. Final Recommendation Statement: Ovarian cancer: Screening. 2012; https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/ovarian-cancer-screening1?ds=1&s=ovarian%20cancer%20screening. Accessed October 30, 2018