Medical Coverage Policy | Serum Biomarker Human Epididymis Protein 4

EFFECTIVE DATE: 09|26|2003
POLICY LAST UPDATED: 12|06|2016

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 carbohydrate 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 there is insufficient peer reviewed scientific literature that demonstrates that the service is effective.

COVERAGE
Benefits may vary between groups/contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for limitations of benefits/coverage when services are 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 carbohydrate 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.

The evidence for measurement of serum biomarker HE4 in patients who have ovarian cancer 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 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.

The evidence for measurement of serum biomarker HE4 in patients who have adnexal masses 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 (ie, sensitivity, specificity) and several found that HE4 has significantly higher specificity than CA-125 but not sensitivity. Two metaanalyses 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.

The evidence for measurement of serum biomarker HE4 in asymptomatic individuals who are not at high risk of ovarian cancer 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. Thus, the HE4 test is not medically necessary for all indications as there is insufficient peer reviewed literature that demonstrates that the service is effective.

CODING

BlueCHiP for Medicare and Commercial Products
The following CPT code is considered not medically necessary:
86305

RELATED POLICIES

Proteomics-Based Testing Related to Ovarian Cancer
CA-125

PUBLISHED

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
Policy Update, July 2008

REFERENCES

1. SEER. SEER Stat Fact Sheets: Ovary. http://seer.cancer.gov/statfacts/html/ovary.html. Accessed December 23, 2014.

2. 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

3. U.S. Food and Drug Administration. 510(k) substantial equivalence determination decision summary: assay only (K072939). http://www.accessdata.fda.gov/cdrh_docs/reviews/K072939.pdf. Accessed December 23, 2014.

4. U.S. Food and Drug Administration. 510(k) substantial equivalence determination decision summary: assay only (K093957). http://www.accessdata.fda.gov/cdrh_docs/reviews/K093957.pdf. Accessed December 23, 2014.

5. 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

6. 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

7. 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

8. 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

9. 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

10. 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. Sep 29 2015. PMID 26419591