FEP 2.04.66 Serum Biomarker Human Epididymis Protein 4

Effective Date: April 15, 2018

Related Policies:
2.04.62 Proteomics-Based Testing for the Evaluation of Ovarian Masses

Serum Biomarker Human Epididymis Protein 4

Description

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.

FDA REGULATORY STATUS

In June 2008, the HE4 EIA test kit (Fujirebio Diagnostics, Sweden) was cleared for marketing by the 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.

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 through the 510(k) process for the same indications. The ARCHITECT™ HE4 test is being distributed in the United States by Quest Diagnostics (Madison, NJ).
FDA product code: OIU.

POLICY STATEMENT

Measurement of human epididymis protein 4 is **investigational** for all indications.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

RATIONALE

Summary of Evidence

For individuals who have ovarian cancer who receive a measurement of serum biomarker HE4, the evidence includes 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 accuracy and 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 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 accuracy and 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 accuracy and 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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) ovarian cancer guidelines (v.3.2017) state that, for monitoring and follow-up of patients with stage I to IV ovarian cancer with a complete response to initial treatment, “CA-125 [cancer antigen 125] or other tumor marker” should be used at “every visit if initially elevated”.[22] The guidelines do not specify any marker other than CA 125 for monitoring patients after treatment.

NCCN guidelines state the following on evaluating undiagnosed pelvic masses: “The FDA has approved the use of HE4 [human epididymis protein 4] and CA-125 for estimating the risk for ovarian cancer in women with a pelvic mass. Currently the NCCN Panel does not recommend the use of these biomarkers for determining the status of an undiagnosed pelvic mass.”

NCCN guidelines state the following on screening for ovarian cancer:

> “Randomized data do not yet support routine screening for ovarian cancer in the general population, and routine screening is not currently recommended by any professional society. Some physicians

follow women with high-risk factors (eg, those with *BRCA* mutations, those with a family history) using cancer antigen 125 (CA-125) monitoring and endovaginal ultrasound; however, prospective validation of these tests remains elusive."

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (NICE) issued guidance in 2011 on the detection and initial management of ovarian cancer.[23] The guidance included the following recommendations:

- "Measure serum CA125 in primary care in women with symptoms that suggest ovarian cancer.
- If serum CA125 is 35 IU/ml or greater, arrange an ultrasound scan of the abdomen and pelvis.
- If the ultrasound suggests ovarian cancer, refer the woman urgently for further investigation.
- For any woman who has normal serum CA125 (less than 35 IU/ml), or CA125 of 35 IU/ml or greater but a normal ultrasound:
  - assess her carefully for other clinical causes of her symptoms and investigate if appropriate
  - if no other clinical cause is apparent, advise to return to her GP if her symptoms become more frequent and/or persistent.

Malignancy indices

- Calculate a risk of malignancy index I (RMI I) score (after performing an ultrasound…). [The RMI 1 combines CA 125, menopausal status and the ultrasound score]."

The guidance did not mention HE4.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force updated its recommendations for screening for ovarian cancer in December 2012.[24] The Task Force recommended against screening for ovarian cancer in asymptomatic women (D recommendation). HE4 was not specifically discussed.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY

Date	Action	Description
December 2011	New Policy	
June 2012	Update Policy	Policy statement changed to read not medically necessary. Related policies added.
December 2013	Update Policy	Policy updated with literature search. No change to policy statement. References 1, 2, 5-7, and 9 added.
June 2014	Update Policy	Policy updated with literature review. No change to policy statement. References 5, 7-12, 18 added.
June 2015	Update Policy	Policy updated with literature review. Policy statement unchanged. References 7, and 11-12 added.
June 2016	Update Policy	Policy updated with literature review through November 3, 2015. Policy statement unchanged. Reference 6 added.
March 2018	Update Policy	Policy updated with literature review through October 25, 2017; reference 2, 8, 14 and 20 added. Policy statement unchanged.