

Human Epididymis Protein 4 (HE4)

FOR MONITORING RECURRENCE OF PROGRESSIVE DISEASE IN WOMEN WITH EPITHELIAL OVARIAN CANCER

Test Highlights

- Human epididymis protein 4 (HE4) is a secreted protein that is overexpressed and can be elevated in the serum of women with ovarian cancer.
- HE4 increases by 25 percent or greater in 60 percent of women with ovarian cancer relapse or progression.
- HE4 remains constant in 75 percent of women without disease progression.

Disease Overview

- In the United States, ovarian cancer accounts for more deaths than all other gynecologic malignancies combined. Each year, there are an estimated 22,500 new cases and 15,300 deaths from ovarian cancer in the United States.¹
- Although there are numerous histologic types of ovarian cancer, 90–95 percent are epithelial carcinomas.
- Ovarian cancer has often been described as a “silent killer,” but recent studies have shown that there are symptoms that appear in the early stages of the disease. Recognition of these symptoms is critical because early diagnosis improves the probability of cure.
- Currently, less than 20 percent of ovarian cancer cases are diagnosed in stages I or II when the five-year survival rate is greater than 80 percent. Approximately 80 percent of women with ovarian cancer are diagnosed at stage III or IV when the five-year survival rate is 20–30 percent.
- CA 125 is the most commonly used serum marker to monitor therapeutic response and detect disease recurrence in patients treated for epithelial ovarian cancer. The National Comprehensive Cancer Network recommends CA 125 measurement before each treatment cycle and at each follow-up evaluation for women with elevated pretreatment concentrations.² However, CA 125 is not elevated in all patients with epithelial ovarian cancer and may be elevated in benign diseases. Additional markers that complement CA 125 have been investigated and, of these, HE4 has increased sensitivity and specificity over that of CA 125.³

Pathophysiology

- HE4 belongs to the family of whey acidic four-disulfide core (WFDC) proteins with suspected trypsin-inhibitor properties. However, no biological function for HE4 has yet been identified.
- HE4 was first identified in the epithelium of the distal epididymis and originally predicted to be a protease inhibitor involved in sperm maturation.
- HE4 is overexpressed in 93 percent of serous, 100 percent of endometrioid epithelial ovarian cancers, and 50 percent of clear cell (not mucinous) ovarian carcinomas.
- Although it is not tissue-specific, studies have identified HE4 as one of the most useful biomarkers for ovarian cancer.⁴

Indications for Ordering

Monitor for recurrence and disease progression in patients with epithelial ovarian cancer.

Interpretation

- An elevated HE4 concentration is associated with ovarian cancer but is not disease-specific.
- Distribution of HE4 serum concentrations determined in 1,147 women.⁵

	Number of women	0–150 pM	150.1–300 pM	300.1–500 pM	>500 pM
Apparently healthy women					
Premenopausal	76	72	3	0	1
Postmenopausal	103	97	5	0	1
Malignant conditions					
Ovarian cancer	127	27	18	21	61
Endometrial cancer	116	86	15	4	11
Breast cancer	46	40	4	2	0
Lung cancer	50	29	15	6	0
Gastrointestinal cancer	56	47	8	0	1
Benign conditions					
Benign gynecologic disease	347	324	18	1	4
Pregnancy	22	21	1	0	0
Hypertension/congestive heart failure	96	75	16	2	3
Other benign disease	108	82	8	7	11

- A change in HE4 concentration of ≥ 25 percent is considered significant.⁵ An increase of this magnitude suggests recurrence or disease progression, while a decrease of this magnitude suggests therapeutic response.
- In a study of 233 pelvic-mass patients, Moore and colleagues reported that HE4 had a higher sensitivity than CA 125 (72.9 vs. 43.3 percent, respectively) at a specificity of 95 percent in the 67 patients with epithelial ovarian cancer.³ Similar results were reported by Havrilesky et al in a study of early- and late-stage ovarian cancer patients; those who demonstrated HE4 had the highest sensitivity of all other markers evaluated for the detection of both early- and late-stage disease.⁶

Limitations

- Certain histological types of ovarian cancer (e.g., mucinous or germ-cell tumors) rarely express HE4. Therefore, HE4 is not recommended for monitoring of patients with known mucinous or germ-cell ovarian cancer.

- Elevated concentrations of HE4 may be present in individuals with nonmalignant disease. Therefore, concentrations of HE4 cannot be used as absolute evidence for the presence or absence of malignant disease, and the HE4 test should not be used in cancer screening or diagnosis.
- The results of this test should be interpreted only in conjunction with other investigations and procedures in the diagnosis of disease and the management of patients. HE4 testing should not replace any established clinical examination.
- Anti-reagent antibodies (human anti-mouse antibody [HAMA] or heterophilic antibodies) in the patient sample may occasionally interfere with the assay, even though specific blocking agents are included in the buffers.

Methodology

HE4 is measured using a commercially available enzyme-linked immunosorbent assay.

Related Tests

[Cancer Antigen 125 \(0080462\)](#)

References

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2. NCCN Clinical Practice Guidelines in Oncology™. Ovarian Cancer. V1.2008. http://www.nccn.org/professionals/physician_gls/PDF/ovarian.pdf (accessed on May 23, 2010).
3. Moore RG, et al. A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. *Gynecol Oncol* 2009;112(1):40–6.
4. Li J, et al. HE4 as a biomarker for ovarian and endometrial cancer management. *Expert Rev Mol Diagn* 2009;9(6):555–66.
5. HE4 EIA [package insert]. 2008. Malvern, PA: Fujirebio™ Diagnostics, Inc.
6. Havrilesky LJ, et al. Evaluation of biomarker panels for early stage ovarian cancer detection and monitoring for disease recurrence. *Gynecol Oncol* 2008;110(3):374–82.

Test Information

2003020 Human Epididymis Protein 4 (HE4)

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.