

# Ovarian Cancer Markers

## Indications for Ordering

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Adjunct tests for evaluation of an ovarian mass

## Test Description

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Cancer Antigen 125 (CA 125)

- Quantitative electrochemiluminescent immunoassay

Human Epididymis Protein 4 (HE4)

- Quantitative enzyme immunoassay

Risk of Ovarian Malignancy Algorithm (ROMA)

- Quantitative enzyme immunoassay
- Quantitative electrochemiluminescent immunoassay

## Tests to Consider

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### Primary tests

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

- Evaluate and monitor ovarian cancer (usually epithelial subtype)
  - Monitoring requires elevated pretreatment value of CA 125
  - Combination with HE4 may enhance sensitivity
- Not recommended for monitoring breast cancer or germ cell tumors
- Not a stand-alone test for ovarian cancer screening or diagnosis

#### [Human Epididymis Protein 4 \(HE4\) 2003020](#)

- Use with CA 125 to monitor ovarian cancer, usually epithelial subtype, post therapy if pretreatment level was elevated
- Not recommended for monitoring mucinous or germ cell ovarian cancer
- Not a stand-alone test for ovarian cancer screening or diagnosis

#### [Risk of Ovarian Malignancy Algorithm 2012618](#)

- Assess cancer risk, particularly epithelial cell ovarian cancer, in pre- and postmenopausal women with an adnexal mass
- Combines CA 125 and HE4, together with menopausal status, to classify adnexal mass patients into high- or low-risk epithelial ovarian cancer groups
- Not intended as a screening, stand-alone, or tumor-monitoring test
- Tumor monitoring using HE4 and/or CA 125 test should be ordered separately

## Related tests

Granulosa cell tumors

- [Inhibin B 0070413](#)
- [Total Inhibin, Serum 2014109](#)
- [Estradiol, Adult Premenopausal Female, Serum or Plasma 0070045](#)

Germ cell tumors

- [Alpha Fetoprotein, Serum \(Tumor Marker\) 0080428](#)
- [Neuron Specific Enolase 0098198](#)
- [Beta-hCG, Quantitative \(Tumor Marker\) 0070029](#)

## Disease Overview

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### Incidence

- Ovarian cancer – >22,000 new cases and >14,000 deaths annually
  - Epithelial subtype – 40/100,000 for postmenopausal women

### Diagnosis

- Markers cannot be used to diagnose ovarian cancer
- Markers may be useful in evaluation of a pelvic mass in postmenopausal women

### Prognosis

Pretreatment CA 125 and HE4 levels are highly predictive of overall survival

### Pathophysiology

- CA 125
  - Secreted in tumors of epithelial origin (~80% of tumors)
  - Frequency of elevation of CA 125 correlates with
    - Clinically detected stage of cancer (higher elevation of CA 125 levels in later stages)
    - Tumor burden (correlates with stage)
    - Type of tumor (usually in epithelial tumors)
- HE4
  - Secreted in tumors of epithelial origin (~80% of tumors)
  - Relapse
    - HE4 increases by  $\geq 25\%$  in 60% of women with ovarian cancer relapse or progression
    - HE4 remains constant in 75% of women without progression of ovarian cancer

## Monitoring

- CA 125
  - Uses
    - Evaluate ovarian mass
    - Determine pretreatment level for use in monitoring
    - Assess patient response to chemotherapy
    - Detect early relapse
  - Suggested monitoring is every 2-4 months for the first 2 years
  - Absolute serum value of CA 125 before third cycle of chemotherapy is most important factor for predicting progression at 12 months
  - Persistent postoperative elevation suggests poor prognosis
- HE4
  - May be complementary for monitoring when used in conjunction with CA 125
  - May be useful because some individuals do not have elevated CA 125 level but will manifest with elevated HE4 level

## Test Interpretation

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### Results

- CA 125
  - Normal – <35 U/mL
    - Ovarian cancer less likely but not ruled out
    - In patients with ovarian cancer, a rising level compared to baseline level may reflect disease progression
  - Abnormal – ≥35 U/mL
    - Ovarian cancer possible if clinical suspicion is high
    - The higher the level, the greater probability of malignancy
- HE4
  - Normal – ≤140 pmol/L
    - HE4 remains constant in 75% of women without disease progression
    - An elevation in HE4 concentration of ≥25% is clinically significant even if within the normal range
      - An increase of this magnitude suggests recurrence or disease progression
  - Abnormal – ≥141 pmol/L
    - An increase of ≥25% suggests recurrence or disease progression
      - HE4 increases by ≥25% in 60% of women with ovarian cancer relapse or progression
      - The higher the level, the greater the probability of malignancy
    - A decrease of ≥25% suggests therapeutic response

- ROMA
  - Premenopausal
    - >1.14 – high likelihood of finding epithelial ovarian cancer
    - ≤1.14 – low likelihood of finding epithelial ovarian cancer
  - Postmenopausal
    - >2.99 – high likelihood of finding epithelial ovarian cancer
    - ≤2.99 – low likelihood of finding epithelial ovarian cancer

### Limitations

- CA 125 and HE4 tests are not useful in cancer screening
- Individuals with confirmed ovarian carcinoma may have pretreatment CA 125 values in the same range as healthy individuals
- CA 125 levels may be elevated in patients with nonmalignant disease
- Test values for CA 125 are not interchangeable between different laboratories or test platforms
  - Sequential monitoring should be performed at the same laboratory
- ROMA should not be used without an independent clinical/radiological evaluation and is not intended to be a screening test or to determine whether a patient should proceed to surgery