

Elecsys® HE4 and CA 125 II and their use in the risk assessment of epithelial ovarian cancer by ROMA (Risk of Ovarian Malignancy Algorithm)

Indication:

Ovarian cancer is the fourth most common cause of cancer-related death in women worldwide. The highest incidence is found in economically advanced regions including North America, Europe, Australia and New Zealand. Ovarian cancer, the most lethal form of gynecological cancer, is potentially curable if diagnosed early¹ and treated by surgeons familiar with the management of ovarian cancer.^{2,3} However, the symptoms of ovarian cancer are related to the presence of adnexal masses and are often vague and unspecific. Thus, 70-75% of ovarian cancers are detected at a late stage. According to the International Agency for Research on Cancer, the five-year survival rate of ovarian cancer patients is 46%. However, when the disease is diagnosed earlier, the survival rate increases to 94%.

HE4 belongs to the family of whey acidic four-disulfide core (WFDC) proteins with suspected trypsin inhibitor properties. HE4 was first determined in the epithelium of the distal epididymis.⁴ This biomarker has very low expression in epithelia of respiratory and reproductive tissues including ovary, but high expression in ovarian cancer tissue.⁵ Additionally high secreted levels can be found in the serum of ovarian cancer patients.⁶ HE4, a novel tumor marker, is expected to help in the risk assessment of epithelial ovarian cancer.

The combined use of HE4 and CA 125 increases sensitivity and improves the management of ovarian cancer therapy.

- HE4 and CA 125 II are complementary markers and their combined use increases diagnostic accuracy for all age groups. By measuring both markers together the strengths of both markers can be combined to ensure optimized sensitivity and specificity for primary diagnosis – especially for patients with pelvic mass and detection of recurrence during follow-up.^{7,8}
- The dual marker combination CA 125 and HE4 is a more accurate predictor of malignancy than either alone. Huhtinen et al. reported a 78.6% sensitivity at 95% specificity in ovarian carcinoma vs. endometriotic cysts.

ROMA increases the diagnostic value of the dual marker combination HE4 and CA 125

- Measured values of HE4 and CA 125 II can be combined in an algorithm called ROMA. This algorithm includes additionally the menopausal status. Several published studies show that ROMA helps in the triage of pre- and postmenopausal women suspected for ovarian cancer. Moore et al. found that the algorithm correctly classified 94% of women with epithelial ovarian cancer. This high accuracy helps to stratify the women into low- and high-risk groups and thus may contribute to better diagnosis, treatment and outcome.^{8,9}



Risk estimation in patients with pelvic mass with Risk of Ovarian Malignancy Algorithm (ROMA)⁹

ROMA is used to aid in the assessment of risk of epithelial ovarian cancer in patients presenting with pelvic mass. The algorithm takes into account the Elecsys HE4 and Elecsys CA 125 II values as well as the menopausal status of the patient and calculates a predictive probability of finding epithelial ovarian cancer on surgery.

Calculation of predictive index

A predictive index (PI) is calculated for premenopausal and postmenopausal patients separately using equations (1) and (2) below. To calculate the PI, the assay values obtained from the Elecsys HE4 and Elecsys CA 125 II are inserted into the equations below depending on the menopausal status of the women.

(1) Premenopausal

$$PI = -12.0 + 2.38 * \ln[HE4] + 0.0626 * \ln[CA\ 125]$$

(2) Postmenopausal

$$PI = -8.09 + 1.04 * \ln[HE4] + 0.732 * \ln[CA\ 125]$$

where, LN = Natural Logarithm. (Do not use LOG = Log₁₀).

Calculation of ROMA value

To calculate the ROMA value, insert the calculated value for PI into following equation:

$$ROMA\ value\ (\%) = \exp(PI) / [1 + \exp(PI)] * 100$$

where, $\exp(PI) = e^{PI}$

NOTE: These equations were used for the calculation of ROMA values with the Elecsys HE4 assay from 28.75 to 3847 pmol/L and with the Elecsys CA 125 II assay from 6.42 to 5000 U/mL.

Results of the multicenter evaluation study performed by Roche¹⁰

The effectiveness of ROMA using Elecsys HE4 in combination with the Elecsys CA 125 II for risk estimation of epithelial ovarian cancer of patients presenting with pelvic mass was determined in an international multi-center clinical trial using repository samples. In the prospective study a total of 384 patients were included and the predictive probability for ovarian cancer as well as the ability for separation into a low and a high risk group for finding epithelial ovarian cancer based on ROMA values were determined.

Stratification into low risk and high risk groups

The following cut-points were used in order to provide a specificity level of 75% for the Elecsys HE4 and Elecsys CA 125 II assay combination:

Premenopausal women

ROMA value \geq 11.4% = High risk of finding epithelial ovarian cancer

ROMA value < 11.4% = Low risk of finding epithelial ovarian cancer

Postmenopausal women

ROMA value \geq 29.9% = High risk of finding epithelial ovarian cancer

ROMA value < 29.9% = Low risk of finding epithelial ovarian cancer

The risk stratification of all 384 patients presenting with pelvic mass using the ROMA values for the Elecsys HE4 and Elecsys CA 125 II assay combination is shown in the following table:

Patient groups presenting with pelvic mass	Premenopausal patients			Postmenopausal patients		
	N	ROMA < 11.4%	ROMA ≥ 11.4%	N	ROMA < 29.9%	ROMA ≥ 29.9%
Stage I-II EOC ^a	16	6 (37.5 %)	10 (62.5 %)	16	6 (37.5 %)	10 (62.5 %)
Stage I-III ^b EOC	21	7 (33.3 %)	14 (66.7 %)	34	9 (26.5 %)	25 (73.5 %)
Stage I-IV EOC	25	7 (28.0 %)	18 (72.0 %)	53	10 (18.9 %)	43 (81.1 %)
Stage III-IV EOC	9	1 (11.1 %)	8 (88.9 %)	37	4 (10.8 %)	33 (89.2 %)
Unstaged EOC	12	2 (16.7 %)	10 (83.3 %)	44	2 (4.5 %)	42 (95.5 %)
benign	157	118 (75.2 %)	39 (24.8 %)	93	71 (76.3 %)	22 (23.7 %)

^a EOC = Epithelial ovarian cancer

^b Stage I-III^b and Stage I-III^c (Omentum negative, lymph node positive) EOC.

Accurate stratification of women with stage I -IV epithelial ovarian cancer:

- 83.3% were correctly classified into the high risk group
- 75.6% were correctly classified into the low risk group
- Positive predictive value: 64.9%
- Negative predictive value: 90%

Elecsys® HE4 assay characteristics:

	Elecsys HE4	Elecsys CA 125 II
Testing time	18 min.	18 min.
Test principle	One-step sandwich assay	One-step sandwich assay
Calibration	2 point calibration	2 point calibration
Traceability	HE4 EIA from Fujirebio Diagnostics, Inc.	Enzymun-Test CA 125 II method, which in turn has been standardized against the CA 125 II RIA from Fujirebio Diagnostics, Inc.
Sample material	<ul style="list-style-type: none"> • Serum collected using standard sampling tubes or tubes containing separating gel • Li-heparin plasma, K₂-EDTA and K₃-EDTA plasma 	
Sample volume	10 µL	20 µL
Detection limit	15.0 pmol/L (defined by LoD)	0.60 U/mL (defined by LDL)
Measuring range	15-1,500 pmol/L	0.6-5,000 U/mL
Repeatability	cobas e 411 analyzer, Elecsys® 2010 analyzer: 1.3 - 1.8 % cobas e 601 / e 602 modules, E170: 1.5 - 1.9 %	cobas e 411 analyzer, Elecsys® 2010 analyzer: 1.4 - 3.3 % cobas e 601 / e 602 modules, E170: 0.9 - 1.6 %
Intermediate imprecision	cobas e 411 analyzer, Elecsys® 2010 analyzer: 2.7 - 4.3 % cobas e 601 / e 602 modules, E170: 2.8 - 3.4 %	cobas e 411 analyzer, Elecsys® 2010 analyzer: 2.5 - 4.2 % cobas e 601 / e 602 modules, E170: 1.5 - 2.5 %

Order information:

Material	Product configuration	Material number
Elecsys HE4	100 tests	05950929 190
Elecsys HE4 CalSet	4 x 1 mL	05950945 190
PreciControl HE4	2 x 1 mL each	05950953 190
Elecsys CA 125 II	100 tests	11776223 322
Elecsys CA 125 II CalSet	4 x 1 mL	11776240 322
PreciControl Tumormarker	2 x 3 mL each of PreciControl Tumormarker 1 and 2	11776452 122
Diluent Universal	2 x 16 mL sample diluent or 2 x 36 mL sample diluent	11732277 122 or 03183971 122

References:

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- 5 Drapkin, R., von Horsten H.H., Lin Y., Mok S.C., Crum C.P., Welch W.R., Hecht J.L. (2005). Human epididymis protein 4 (HE4) is a secreted glycoprotein that is overexpressed by serous and endometrioid ovarian carcinomas. *Cancer Res*; 65, 2162-2169.
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- 8 Moore, R.G., et al. (2009). A novel multiple marker bioassay utilizing HE4 and CA 125 for the prediction of ovarian cancer in patients with a pelvic mass. *Gynecologic Oncology*; 112, 40-46.
- 9 Malkasian, G.D., et al. (1988). Preoperative evaluation of serum CA 125 levels in premenopausal and postmenopausal patients with pelvic masses: discrimination of benign from malignant disease. *Am. J. Obstet. Gynecol.*; 159, 341-346.
- 10 Roche multicenter evaluation study. Data on file at Roche.

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