Elecsys® HE4

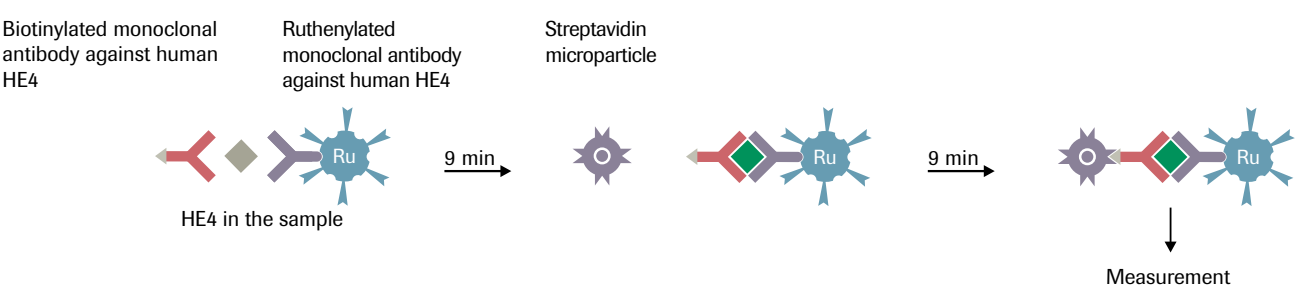
Electro-chemiluminescence immunoassay (ECLIA) for the quantitative determination of human epididymal protein 4 (HE4) in serum and plasma

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 early[1] 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.[4] HE4 was first determined in the epithelium of the distal epididymis. This biomarker has very low expression in epithelia of respiratory and reproductive tissues including ovary, but high expression in ovarian cancer tissue. Additionally, high secreted levels can be found in the serum of ovarian cancer patients. HE4, a novel tumor marker, is expected to help in the risk assessment of epithelial ovarian cancer.

Test principle: one-step sandwich assay



Elecsys technology

ECL (ElectroChemiLuminescence) is Roche's technology for immunoassay detection. Based on this technology and combined with well-designed, specific and sensitive immunoassays, Elecsys delivers reliable results. The development of ECL immunoassays is based on the use of a ruthenium-complex and tripropylamine (TPA). The chemiluminescence reaction for the detection of the reaction complex is initiated by applying a voltage to the sample solution resulting in a precisely controlled reaction. ECL technology can accommodate many immunoassay principles while providing superior performance.

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Life needs answers

Early marker with increased sensitivity for ovarian cancer

- As a single tumor marker, HE4 had the highest sensitivity (at a specificity of 75%) for detecting ovarian cancer, especially in stage I diseases, the early non-symptomatic stage.[5,6]
- Additionally, several publications have reported that HE4 yielded a up to 17% higher sensitivity in early-stage endometrial cancer compared to CA125.[7,8]
- Elevated serum HE4 with normal CA125 would suggest the presence of either ovarian or other type of cancer, for example endometrial cancer.[8]

Good discrimination between benign ovarian masses and cysts and ovary cancer

- Combination of HE4 and CA125 can help in determining whether a pelvic mass is benign or malignant in pre- and post-menopausal women (see ROMA fact sheet).
- The dual marker combination CA125 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.[8]

Improved management of ovarian cancer therapy: HE4 supports CA125 to better monitor ovarian cancer

- HE4 can be used to monitor the disease status in ovarian cancer patients. HE4 levels correlate with clinical response to therapy or recurrence status in women with diagnosis of ovarian carcinoma as determined by CT imaging.[9] HE4 could be an important early indicator for disease recurrence.[10-12]
- In most of ovarian cancer patients both markers are expressed in significant amounts, but there are patients who are positive for only one of the biomarkers HE4 or CA125. The combined use of CA125 and HE4 could facilitate the detection of recurrent disease by reducing the number of biomarker negative patients higher diagnostic accuracy.

Elecsys® HE4 assay characteristics:	
Testing time	18 min.
Test principle	One-step sandwich assay
Calibration	HE4 EIA from Fujirebio Diagnostics, Inc.
Traceability	HE4 EIA from Fujirebio Diagnostics, Inc.
Sample material	• Serum collected using standard sampling tubes or tubes containing separating gel • Li-heparin plasma, K_2-EDTA and K_3-EDTA plasma
Sample volume	10 µL
Detection limit (defined by LoD)	15 pmol/L
Measuring range (lower end defined by LoD)	15 – 1500 pmol/L
Intermediate imprecision	**cobas e** 411 analyzer, Elecsys® 2010 analyzer: 2.7 – 4.3 % **cobas e** 601 / **e** 602 modules, E170: 2.6 – 3.4 %
Repeatability	**cobas e** 411 analyzer, Elecsys® 2010 analyzer: 1.3 – 1.8 % **cobas e** 601 / **e** 602 modules, E170: 1.5 – 1.9 %

Expected values

A study in one clinical center in Germany with the Elecsys HE4 assay on sera from 358 apparently healthy women yielded the following results:

HE4 (pmol/L)			
Age (years)	**N**	**Median**	**95th percentile**
< 40	127	42.0	60.5
40-49	65	44.3	76.2
50-59	60	47.9	74.3
60-69	60	55.0	82.9
≥ 70	46	62.1	104.0

The distribution of HE4 assay values determined in two clinical centers in Spain and Germany with the Elecsys HE4 assay in 896 female specimens is summarized in the table below:

Elecsys HE4 values (pmol/L)		0.0 – 70.0	70.1 – 140.0	140.1 – 500.0	500.1 – 1500.0	> 1500.0
		N (Percentage distribution)				
Apparently healthy						
Premenopausal	90	76 (84.4 %)	13 (14.4 %)	1 (1.1 %)	0 (0.0 %)	0 (0.0 %)
Postmenopausal	106	63 (59.4 %)	40 (37.7 %)	3 (2.8 %)	0 (0.0 %)	0 (0.0 %)
Benign conditions						
Premenopausal	177	160 (90.4 %)	16 (9.0 %)	1 (0.6 %)	0 (0.0 %)	0 (0.0 %)
Postmenopausal	102	62 (60.8 %)	31 (30.4 %)	9 (8.8 %)	0 (0.0 %)	0 (0.0 %)
Pregnancy	50	50 (100 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Non-gynecological disease	35	16 (45.7 %)	6 (17.1 %)	6 (17.1 %)	7 (20.0 %)	0 (0.0 %)
CHF[a]	23	9 (39.1 %)	11 (47.8 %)	3 (13.0 %)	0 (0.0 %)	0 (0.0 %)
Cancer						
OvCa[b], premenopausal	39	12 (30.8 %)	7 (17.9 %)	13 (33.3 %)	5 (12.8 %)	2 (5.1 %)
OvCa, postmenopausal	97	10 (10.3 %)	19 (19.6 %)	34 (35.1 %)	28 (28.9 %)	6 (6.2 %)
Endometrial	49	8 (36.7 %)	20 (40.8 %)	9 (18.4 %)	1 (2.0 %)	1 (2.0 %)
Breast	47	22 (46.8 %)	19 (40.4 %)	5 (10.6 %)	1 (2.1 %)	0 (0.0 %)
Gastrointestinal	46	9 (41.3 %)	20 (43.5 %)	6 (13.0 %)	1 (2.0 %)	0 (0.0 %)
Lung	23	5 (21.7 %)	7 (30.0 %)	10 (43.5 %)	1 (4.3 %)	0 (0.0 %)
Bladder	12	3 (25.0 %)	4 (33.3 %)	4 (33.3 %)	1 (8.3 %)	0 (0.0 %)

[a] *CHF = Congestive heart failure*

[b] *ovarian cancer*

In this study 98% of the apparently healthy women had a HE4 assay value at or below 140 pmol/L. It is recommended that each laboratory establishes its own reference value for the population of interest.

Monitoring of disease status in patients diagnosed with ovarian cancer

The effectiveness of the Elecsys HE4 assay as an aid in monitoring of disease status in ovarian cancer patients was determined by assessing changes in HE4 levels in serial serum samples from 100 patients compared to changes in disease status. This follow-up study contained a total of 375 samples with ≥ 3 samples per patient. A positive change in HE4 was defined as an increase in the value that was at least 20% greater than the previous value of the test. This level of change takes into account the variability of the assay and the biological variability.

58.0% (29 of 50) of the patient samples with a positive change correlated with the disease progression while 84.0% (273 of 325) of the patient serial samples with no significant change in HE4 value correlated with no progression.
The **total concordance was 80.5% (302 of 375)**. The following table presents the data in a 2 x 2 format.

Changes in disease state per sequential pair

Increase in HE4 concentration	Progression	No progression	Total
≥ 20%	29	52	81
< 20%	21	273	294
Total	50	325	375

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
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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4 Kirchhoff, C. Molecular characterization of epididymal proteins. *Rev. Reprod. 1998;3:86-95.*

5 Moore, R.G. et al. The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. *Gynecologic Oncology, 2008; 108, 402-408.*

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8 Huhtinen, K. et al. Serum HE4 concentration differentiates malignant ovarian tumours from ovarian endometriotic cysts. *British J. Cancer, 2009; 100: 1315-1319.*

9 Allard et al. HE4 and CA125 combined for the improved management ovarian cancer. *Oncology 2009; 3: 20-21.*

10 Havrilesky, L. et al. Evaluation of biomarker panels for early stage ovarian cancer detection and monitoring for disease recurrence. *Gynecologic oncology 2008; 110: 374-382.*

11 Allard, W.J., Somers, E., Theil, R., Moore, R.G. Use of a novel biomarker HE4 for monitoring patients with epithelial ovarian cancer. *J Clin Oncol 2009; 26* (May 20 suppl; abstr 5535).

12 Anastasi, E., Marchei, G.G., Viggiani, V., Gennarini, G. et al. HE4: a new potential early biomarker for the recurrence of ovarian cancer. *Tumor Biol., 2010; 31*:113-119.

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