

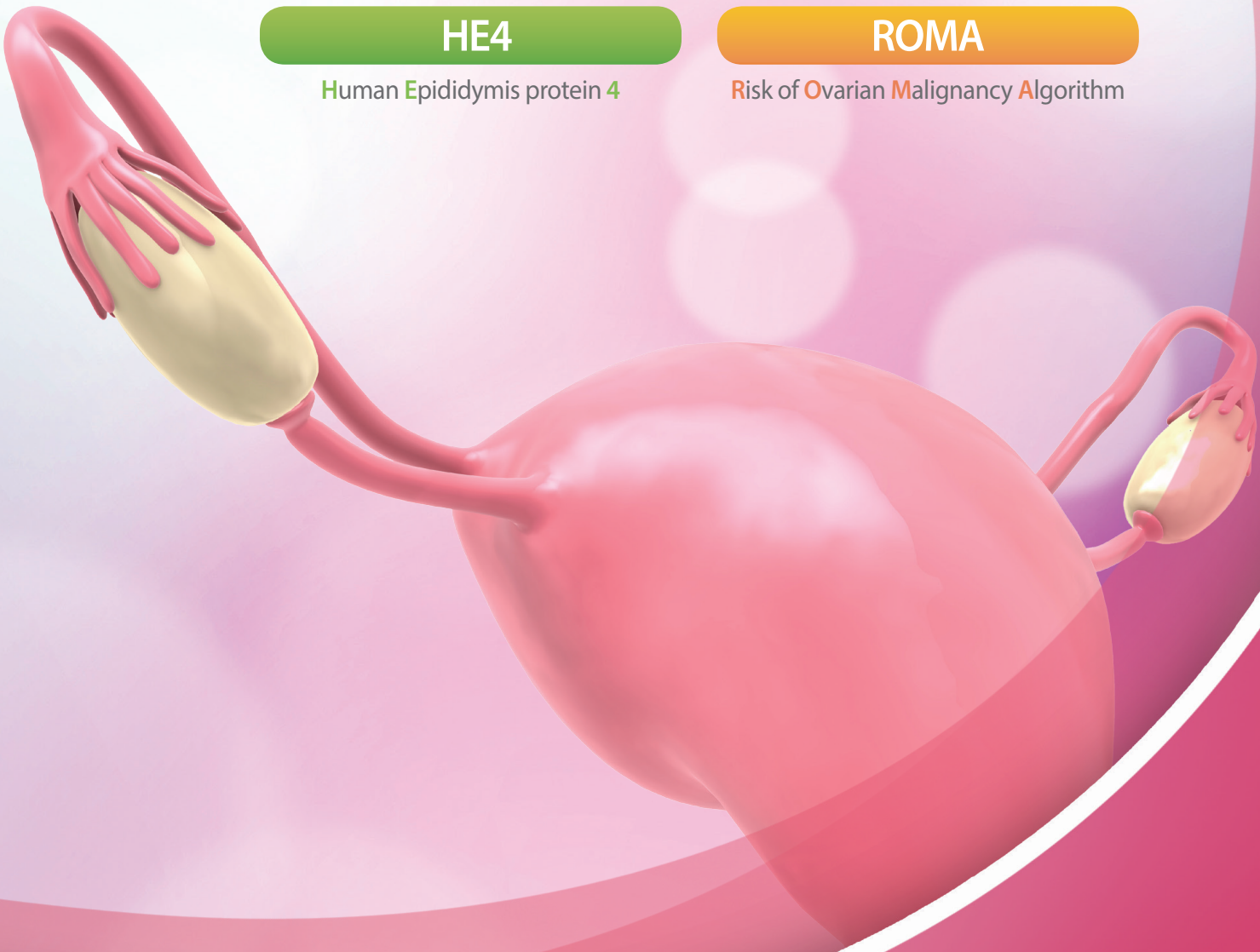
A new tumor marker for ovarian cancer management

HE4

Human Epididymis protein 4

ROMA

Risk of Ovarian Malignancy Algorithm



Ovarian cancer is the second most common gynecological cancer, following cervical cancer, and it is the leading cause of gynecological cancer-related deaths in Western societies. Early-stage ovarian cancer has a favorable prognosis, with a 5-year survival rate of over 90% even without adjuvant chemotherapy. However, for women diagnosed with stage 3 or 4 ovarian cancer, the 5-year survival rate drops to 30%. Ovarian cancer often lacks specific or noticeable early symptoms, leading to late-stage diagnosis, which significantly impacts prognosis. **Therefore, early detection of ovarian cancer is crucial for improving patient outcomes.**

Currently, carbohydrate antigen 125 (CA125) is widely used as a biomarker for monitoring ovarian cancer recurrence and treatment response. However, serum CA125 levels may not increase in 20% of ovarian cancer patients, and its elevation can also occur in other types of benign tumors.

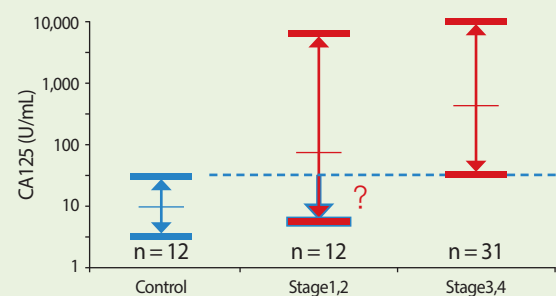
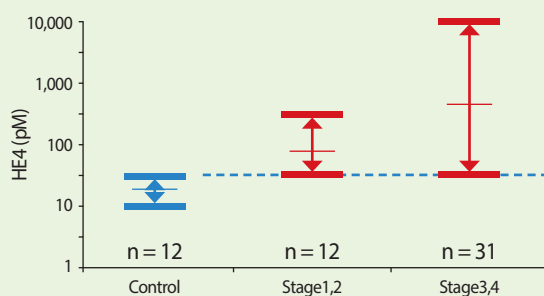
Human Epididymis Protein 4 (HE4), also known as WAP-type four disulfide core 2(WFDC2), is a recently discovered early diagnostic marker for ovarian cancer. It has shown **similar sensitivity to CA125 but higher specificity for ovarian cancer**. Originally discovered in the epithelium of the epididymis, HE4 has been found to be elevated in serum samples of ovarian cancer patients in several studies. It is expected to have potential applications in the early detection of epithelial ovarian cancer, risk stratification of women with pelvic mass, and early detection of recurrence.

Usefulness of HE4 (Human epididymis protein 4) testing

Early ovarian cancer diagnosis

<HE4: Excellent identification of early ovarian cancer lesions>

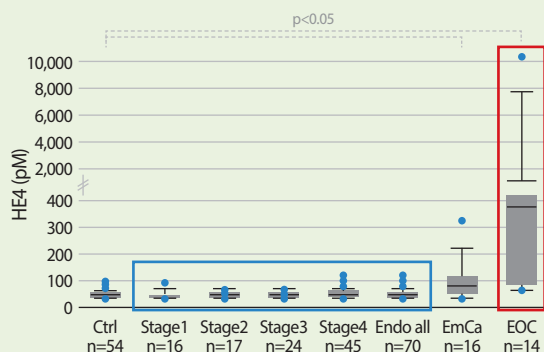
<CA125: Excellent identification of later stages of ovarian cancer>



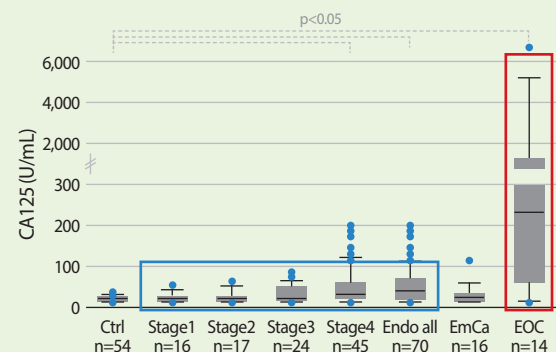
Min-Median-Max-ranges of controls and OvCa-patients, Data adopted from Montagnana et al. *J. Clin. Lab. Anal.*, 2009. The asterisk points to a subpopulation of OvCa-Stage I, II-patients measured with CA125-values below the Max-value of controls.

► HE4 has a higher diagnostic sensitivity than CA125 for early ovarian cancer lesions (HE4 82.7% vs CA125 45.9%)

Differential diagnosis from endometriosis



HE4 : Not elevated in endometriosis • elevated in ovarian cancer



CA125 : significantly elevated in endometriosis in some endometriosis cases • elevated in ovarian cancer

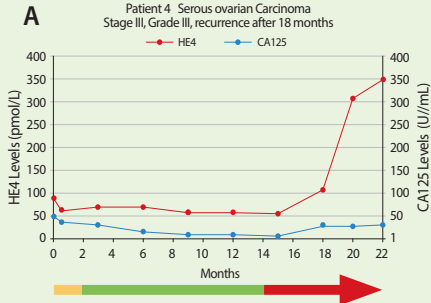
Huhtinen et al.: *Br. J. Cancer*, 2009, 100(8)

► Both HE4 and CA125 may be helpful for differentiating between ovarian cancer and benign endometriosis, but HE4 has superior differentiation capacity

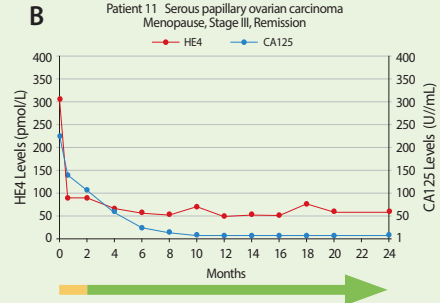
Patient monitoring and assessment

Comparison of changes in serum HE4 and CA125 levels after surgery until recurrence or remission

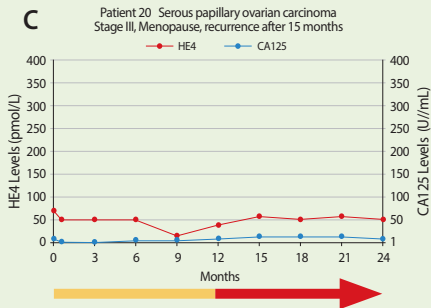
Only HE4 is elevated 2 months before confirming recurrence maintained.



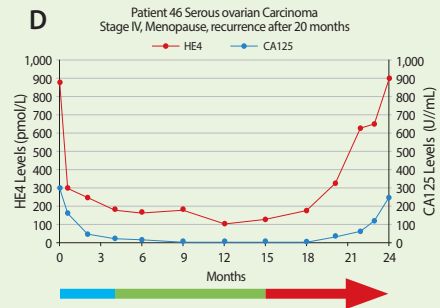
Only HE4 is elevated 2 months before confirming recurrence maintained.



Concentration was not elevated, although the patient relapsed 15 months after first-line therapy after surgery



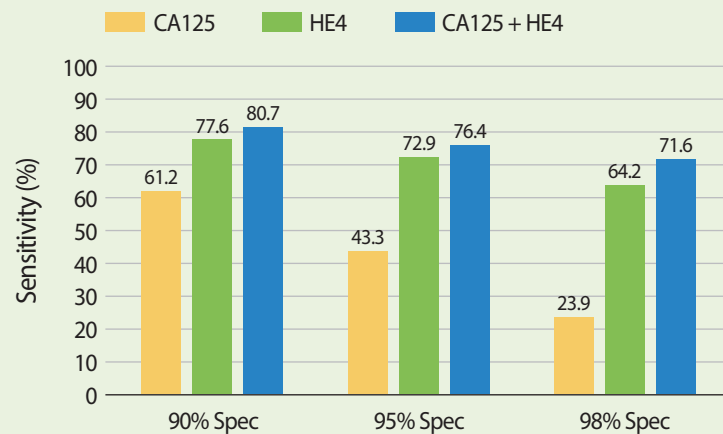
HE4 was elevated 3 months earlier than CA125 in a case of recurrence



Asian Pac J Cancer Prev, 15 (1), 101-105

► HE4 is more strongly associated with postoperative outcomes than CA125

Sensitivity of HE4 + CA125 test



Moore RG et al. Gynecologic Oncology 2008, 111, 402-408

► The combined test has higher sensitivity than both single tests

ROMA (Risk of ovarian malignancy algorithm)

An algorithm designed to assess the likelihood of detecting malignant tumors during surgery based on the blood test results of HE4 and CA125 in pre- and postmenopausal women presenting with a pelvic mass.

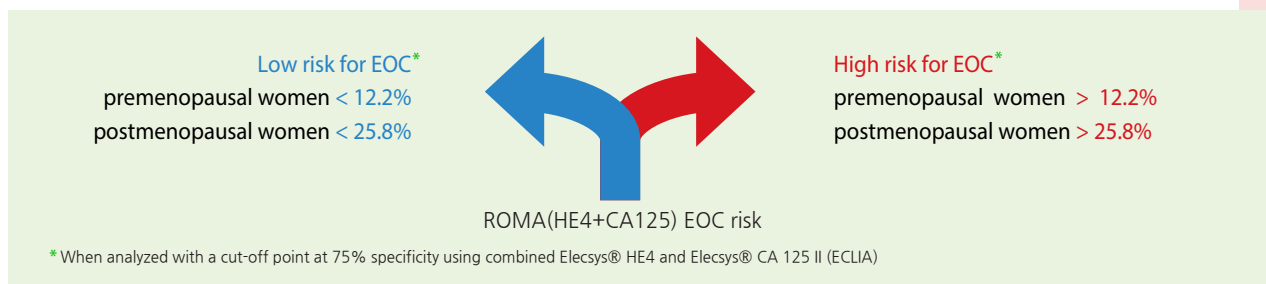
(FDA approval in 2011, We et al 2012)

Prediction of malignant epithelial ovarian cancer (EOC) using ROMA

Group	Pathological diagnosis		Cut off value	Sensitivity	Specificity	Agreement	Area under the curve (AUC, 95%CI)
	Malignant	Benign					
Premenopausal							
High risk	48	16	12.2	88.9%	70.4%	79.6%	0.884(0.813-0.954)
Low risk	6	38					
Postmenopausal							
High risk	63	3	25.8	91.3%	80.0%	89.3%	0.938(0.887-0.988)
Low risk	6	12					

ROMA calculates the predictive probability of detecting EOC and improves the diagnostic value of combined HE4 and CA125 tests. The agreement rate between pathological test results and ROMA analysis in patients with EOC showed a pathological diagnostic accuracy of 79.6% in premenopausal women and 89.3% in postmenopausal women.

► ROMA enhances the diagnostic value of combined testing by calculating the predictive probability of EOC detection



Test information

	HE4	ROMA
Code No.	21626	21638
Method	ECLIA	Calculation
Reference values	< 40yr : ≤ 60.50 40-49yr : ≤ 76.20 50-59yr : ≤ 74.30 60-69yr : ≤ 82.90 ≥ 70yr : ≤ 104.00	Premenopausal: High risk ROMA value ≥ 11.4% Low risk ROMA value < 11.4% Postmenopausal: High risk ROMA value ≥ 29.9% Low risk ROMA value < 29.9%
Unit	pmol/L	%
Schedule	Mon-Sat /1day	Mon-Sat /1day

References

- Havrilesky LJ, Whitehead CM, Rubatt JM, Cheek RL, Groelke J, He Q et al. Evaluation of biomarker panels for early stage ovarian cancer detection and monitoring for disease recurrence. *Gynecol Oncol.* 2008 Sep;110(3):374-82.
- Chen WT, Gao X, Han XD, Zheng H, Guo L, Lu RQ. HE4 as a serum biomarker for ROMA prediction and prognosis of epithelial ovarian cancer. *Asian Pac J Cancer Prev.* 2014;15(1):101-5.
- Ortiz-Muñoz B, Aznar-Oroval E, García García A, Covisa Peris A, Perez Ballesteros P, Sanchez Yepes M et al. HE4, Ca125 and ROMA algorithm for differential diagnosis between benign gynaecological diseases and ovarian cancer. *Tumour Biol.* 2014 Jul;35(7):7249-58.
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