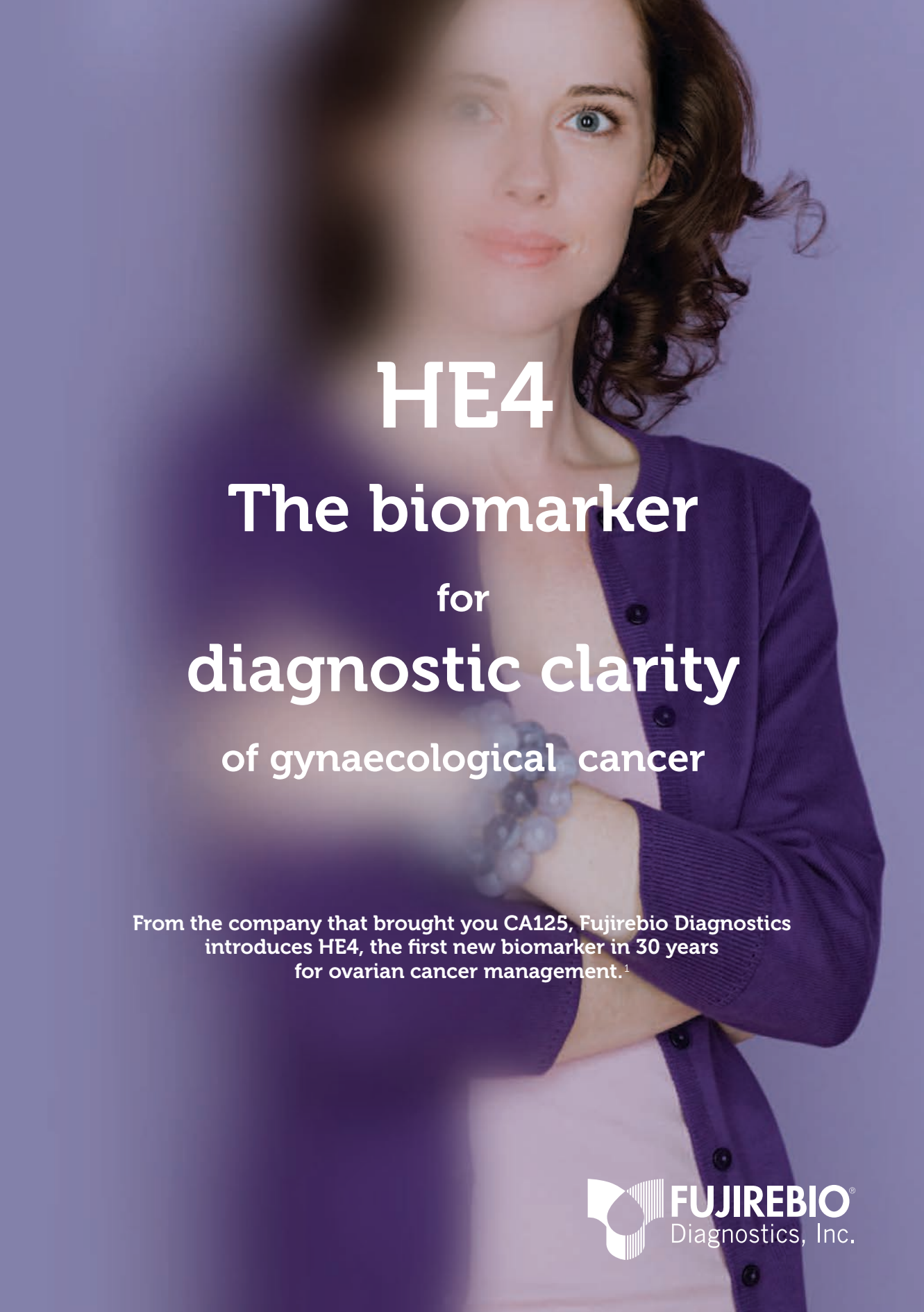

HE4
The biomarker
for
diagnostic clarity
of gynaecological cancer
From the company that brought you CA125, Fujirebio Diagnostics introduces HE4, the first new biomarker in 30 years for ovarian cancer management.[1]
FUJIREBIO®
Diagnostics, Inc.

HE4

Biomarker with increased specificity for ovarian cancer

What is HE4?

Human epididymis protein 4 (HE4), a serum biomarker, is expressed in normal epithelial tissue.

HE4 is detected in high levels in the serum of ovarian cancer patients.

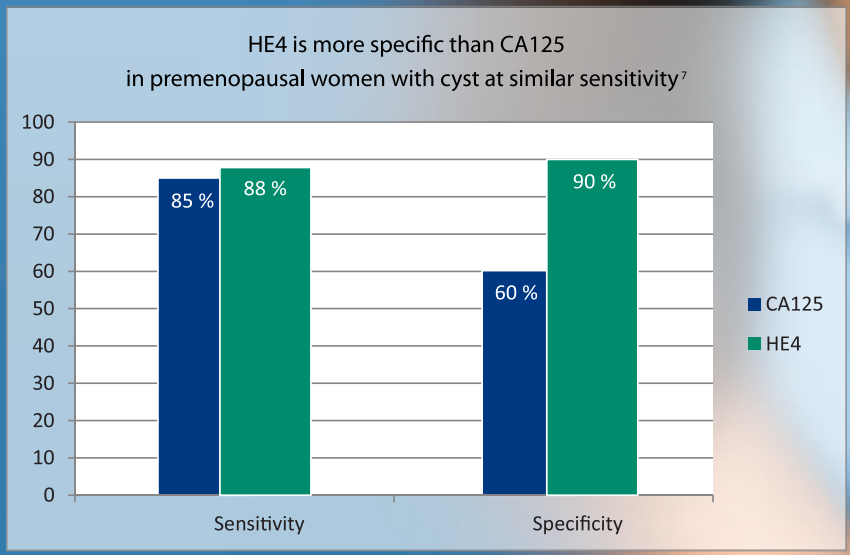
HE4 has shown to be a stable biomarker in which levels do not change in normal physiological conditions. HE4 is not elevated:

- During pregancy [2]
- In any phases of the menstruational cycle or with hormonal treatments [3]
- With hormonal stimulation during IVF treatment [4]

Importance of specific biomarker for management of gynecologic disease

Cysts are a common occurrence, especially in premenopausal women, and the majority of cysts are benign

- Up to 10% of women will have some form of surgery for ovarian mass [5]
- Preoperative differentiation between the benign and the malignant ovarian mass in the premenopausal woman is problematic [6].



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HE4

In benign gynecological conditions, HE4 is less frequently elevated than CA125 [7-10]

In a study of 1042 women with pelvic mass [10]

- HE4 was elevated in only 3% of premenopausal women with endometriosis, while CA125 was elevated in 72%

Benign Disease	Premenopausal HE4	Premenopausal CA125	Postmenopausal HE4	Postmenopausal CA125
Ovarian Cyst	6%	15%	13%	13%
Germ Cell Tumors	2%	19%	0%	25%
Sex Cord Stromal	20%	60%	25%	50%
Cystadenomas	20%	15%	19%	22%
Serious Epithelial	2%	14%	10%	19%
Mucinous Epithelial	7%	17%	18%	18%
Benign, non-specified	5%	35%	14%	18%
Endometriosis/Endometrioma	**3%**	**72%**	**6%**	**18%**
Abscess/PID/Hydrosalpinx	13%	40%	13%	33%
Fibroid	9%	41%	7%	7%
Benign, Other (normal-ovaries)	7%	29%	4%	17%
All Benign Tumors	**6%**	**37%**	**12%**	**20%**

HE4 can aid in conservative management of women with pelvic mass

- According to RCOG guidelines many ovarian masses in the premenopausal women can be managed conservatively to minimize patient morbidity [6]
- HE4 has low false positive rate thus may avoid unnecessary surgeries [11]

HE4 and ROMA™

Combine HE4 and CA125 to better assess risk of pelvic mass malignancy

The combination of CA125 + HE4 has been shown to be a more accurate predictor of disease than either marker alone [12-14].

CA125 and HE4 results are used to calculate ROMA™ (The Risk of Ovarian Malignancy Algorithm) score [15]. ROMA score is used to stratify women as high or low risk for finding ovarian malignancy at surgery.

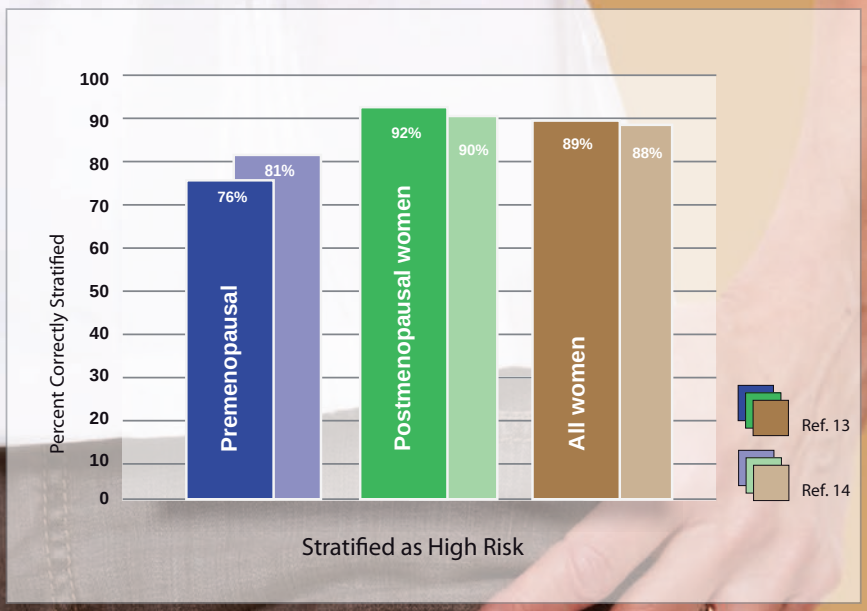
Assessment of ovarian mass is now more clear

In two published clinical studies [13-14]:

- ROMA correctly stratified 89% and 88% of women with epithelial ovarian cancer and low malignant potential tumors into a high risk group [13-14]
- ROMA correctly stratified 75% of women with benign disease into a low-risk group [13-14]

CA125 + HE4 = ROMA™

Improved Stratification of Adnexal Mass [13-14]



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HE4 and ROMA™

ROMA™ is supported by published studies

Ten studies validate the clinical performance of the ROMA algorithm

ROMA Validation Studies					
Country	**Author**	**Year**	**Study Size**	**Sensitivity**	**Specificity**
Asia	Chan	2013	414	89%	87%
Asia	Chen	2014	192	90%	72%
	Karlsen	2012	1218	77%	94%
	Moore	2011	482	94%	75%
	Van Gorp	2011	389	85%	80%
	Jacob	2011	160	85%	86%
	Lenhard	2011	535	77%	95%
	Molina	2011	527	90%	88%
	Montagnana	2011	153	74%	82%
	Ruggeri	2011	259	96%	75%
	Kim	2011	383	87%	94%
	Moore	2008	572	94%	75%

Go to www.he4test.com to see examples of how to

calculate ROMA™ on line

from your CA125 and HE4 results

Use HE4 for monitoring response to therapy and detecting recurrence of ovarian cancer

- HE4 levels were compared to changes in clinical status of disease in serial blood samples from 80 ovarian cancer patients (average ~4 serial samples per patient)[16]
- A positive change in HE4 was defined as an increase in test value that was 25% greater than the previous value of the test

Clinical Status of Disease			
Increase in HE4 concentration	Progression	No Progression	Total
>25%	76 (60%)	57	133
≤25%	50	171 (75%)	221
Total	126	228	354

Total concordance with disease status was observed in 70% (247/354) of patients

- 60% (76/126) of samples with a positive HE4 change correlated with progression
- 75% (171/228) of samples with no change in HE4 correlated with no progression

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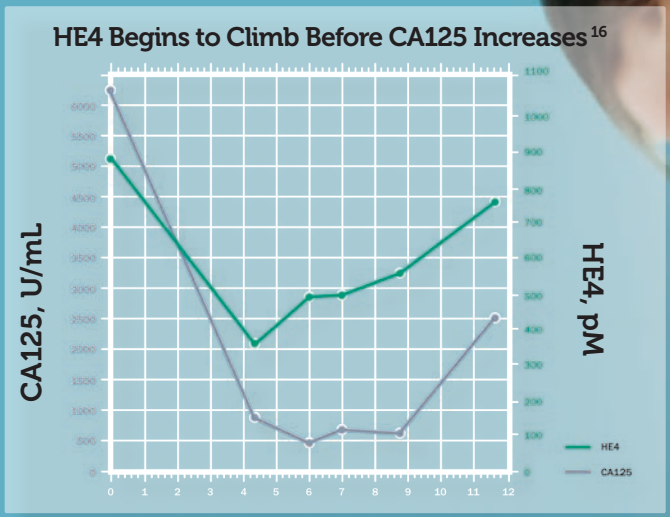
HE4

An aid in the treatment of ovarian cancer

HE4 shows advantages for predicting ovarian cancer recurrences

- Monitor response to therapy in invasive epithelial ovarian cancer[16]
- Correlates with disease progression[16]
- Greater lead time than for CA125 (1-15 months before CA125)[17-19]
- HE4 can be the only elevated biomarker before clinical recurrence[19]
- In some cases HE4 can be more sensitive than imaging[19]



HE4 has been shown to be an independent factor for both the prognosis and prediction of outcome.

- High levels of HE4 before surgery predicts shorter overall survial[20-22] and also HE4 is a predictor of optimal cytoreduction[22-23]
- If measured before start of chemotherapy, HE4 is a strong and independent indicator of worse prognosis[24]

REFERENCES

1. Diamandis E, et al. Cancer Biomarkers: Can we turn recent failures into success? J Natl Cacner inst. 2010; 102-1-6.
2. Moore RG, Miller MC, Eklund EE, et al. Serum levels of the ovarian cancer biomarker HE4 are decreased in pregnancy and increase with age. Am J Obstet Gynecol. 2012;206(4):349.e1-7.
3. Hallamaa M, Suvitie P, Huhtinen K, et al. Serum HE4 concentration is not dependent on menstrual cycle or hormonal treatment among endometriosis patients and healthy premenopausal women. Gynecol Oncol. 2012;125(3):667-72.
4. Hallamaa M, Huhtinen K, Suvitie P, Perheentupa A. Serum concentrations of HE4 change little during in vitro fertilization. Acta Obstet Gynecol Scand. 2014 Apr 15. doi: 10.1111/aogs.12393. [Epub ahead of print]
5. Hilger WS, Magrina JF, Magtibay PM. Laparoscopic management of the adnexal mass. Clin Obstet Gynecol. 2006;49:535-548).
6. Green-top Guideline No. 62, RCOG/BSGE Joint Guideline | November 2011
7. Holcomb K, Vucetic Z, Miller MC, Knapp RC. Human epididymis protein 4 offers superior specificity in the differentiation of benign and malignant adnexal masses in premenopausal women. Am J Obstet Gynecol. 2011;205(4):358.e1-6.
8. Huhtinen K, Suvitie P, Hiissa J, et al. Serum HE4 concentration differentiates malignant ovarian tumours from ovarian endometriotic cysts. Br J Cancer. 2009;100:1315-1319.
9. Park Y, Lee JH, Hong DJ, et al. Diagnostic performances of HE4 and CA125 for the detection of ovarian cancer from patients with various gynecologic and non-gynecologic diseases. Clin Biochem. 2011;44(10-11):884-8.
10. Moore RG, Miller MC, Steinhoff MM, et al. Serum HE4 levels are less frequently elevated than CA125 in women with benign gynecologic disorders. Am J Obstet Gynecol. 2012;206(4):351.e1-8.
11. Romagnolo C, Maggino T, Gion M, Berto P. Budget impact analysis for a regional health care service provider after introduction of HE4 testing for pelvic mass diagnosis. Poster, IGCS 2012.
12. Moore RG, McMeekin DS, Brown AK, 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;112:40-46.
13. Moore RG, Brown AK, Miller MC, et al. The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. Gynecol Oncol. 2008;108:402-408.
14. Moore RG1, Miller MC, Disilvestro P, et al. Evaluation of the diagnostic accuracy of the risk of ovarian malignancy algorithm in women with a pelvic mass. Obstet Gynecol. 2011;118(2 Pt 1):280-8.
15. HE4 EIA Ref. No. 404-10 [package insert]. Göteborg, Sweden: Fujirebio Diagnostics, 2008.
16. Data on file, Fujirebio Diagnostics, Inc.
17. Havrilesky et al. Evaluation of biomarker panels for early stage ovarian cancer detection and monitoring for disease recurrence. Gynecol Oncol. 2008 ;110:374-82
18. Anastasi et al. HE4: a new potential early biomarker for the recurrence of ovarian cancer. Tumor Biol 2010; 31:113-119
19. Schummer et al. Evaluation of ovarian cancer remission markers HE4, MMP7 and Mesothelin by comparison to the established marker CA125. Gynecol Oncol. 2012;125:65-9
20. Paek J, Lee SH, Yim GW, et al. Prognostic significance of human epididymis protein 4 in epithelial ovarian cancer. Eur J Obstet Gynecol Reprod Biol. 2011;158(2):338-42
21. Kalapotharakos G, Asciutto C, Henic E, et al. High preoperative blood levels of HE4 predicts poor prognosis in patients with ovarian cancer. J Ovarian Res. 2012 Aug 21;5(1):20.
22. Braicu EI1, Chekerov R, Richter R, Pop C, Nassir M, Loefgren H, Stamatian F, Muallem MZ, Hall C, Fotopoulou C, Sehouli J, Pietzner K. HE4 expression in plasma correlates with surgical outcome and overall survival in patients with first ovarian cancer relapse. Ann Surg Oncol. 2014 Mar;21(3):955-62.
23. Angioli R, Plotti F, Capriglione S, et al. Can the preoperative HE4 level predict optimal cytoreduction in patients with advanced ovarian carcinoma? Gynecol Oncol. 2013 Mar;128(3):579-83.
24. Steffensen KD, Waldstrøm M, Brandslund I, Jakobsen A. Prognostic impact of prechemotherapy serum levels of HER2, CA125, and HE4 in ovarian cancer patients. Int J Gynecol Cancer. 2011 Aug;21(6):1040-7.

FUJIREBIO®
Diagnostics, Inc.

Contact Information

Fujirebio Diagnostics, Inc.
201 Great Valley Parkway
Malvern, PA 19355
USA
Tel: +1 610 240 3800
Fax: +1 610 240 3949
customerservice@fdi.com

Fujirebio Diagnostics AB
Elof Lindälvs gata 13
414 58 Göteborg
Sweden
Tel: +46 31 85 70 30
Fax: +46 31 85 70 40
info@fdab.com