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.
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 pregnancy
- In any phases of the menstrual cycle or with hormonal treatments
- With hormonal stimulation during IVF treatment

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
- Preoperative differentiation between the benign and the malignant ovarian mass in the premenopausal woman is problematic.

HE4 is more specific than CA125 in premenopausal women with cyst at similar sensitivity
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%

<table>
<thead>
<tr>
<th>Benign Disease</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HE4</td>
<td>CA125</td>
</tr>
<tr>
<td>Ovarian Cyst</td>
<td>6%</td>
<td>15%</td>
</tr>
<tr>
<td>Germ Cell Tumors</td>
<td>2%</td>
<td>19%</td>
</tr>
<tr>
<td>Sex Cord Stromal</td>
<td>20%</td>
<td>60%</td>
</tr>
<tr>
<td>Cystadenomas</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>Serious Epithelial</td>
<td>2%</td>
<td>14%</td>
</tr>
<tr>
<td>Mucinous Epithelial</td>
<td>7%</td>
<td>17%</td>
</tr>
<tr>
<td>Benign, non-specified</td>
<td>5%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Endometriosis/Endometrioma</strong></td>
<td><strong>3%</strong></td>
<td><strong>72%</strong></td>
</tr>
<tr>
<td>Abscess/PID/Hydronephrosis</td>
<td>13%</td>
<td>40%</td>
</tr>
<tr>
<td>Fibroid</td>
<td>9%</td>
<td>41%</td>
</tr>
<tr>
<td>Benign, Other (normal-ovaries)</td>
<td>7%</td>
<td>29%</td>
</tr>
<tr>
<td><strong>All Benign Tumors</strong></td>
<td><strong>6%</strong></td>
<td><strong>37%</strong></td>
</tr>
</tbody>
</table>

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.\(^{13-14}\)

\[\text{CA125 + HE4} = \text{ROMA™} \]
Improved Stratification of Adnexal Mass\(^ {13-14}\)
HE4 and ROMA™

ROMA™ is supported by published studies

Ten studies validate the clinical performance of the ROMA algorithm

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

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

<table>
<thead>
<tr>
<th>Clinical Status of Disease</th>
<th>Increase in HE4 concentration</th>
<th>Progression</th>
<th>No Progression</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;25%</td>
<td>76 (60%)</td>
<td>57</td>
<td>133</td>
</tr>
<tr>
<td></td>
<td>≤25%</td>
<td>50</td>
<td>171 (75%)</td>
<td>221</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>126</td>
<td>228</td>
<td>354</td>
</tr>
</tbody>
</table>

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
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
- Correlates with disease progression
- Greater lead time than for CA125 (1-15 months before CA125)
- HE4 can be the only elevated biomarker before clinical recurrence
- In some cases HE4 can be more sensitive than imaging

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 survival and also HE4 is a predictor of optimal cytoreduction.
- If measured before start of chemotherapy, HE4 is a strong and independent indicator of worse prognosis.
REFERENCES