



## In women who have a pelvic mass Have you tried this new ovarian Ca biomarker?

⤵ You should: It's been 25 years since a test for ovarian cancer was introduced to assist us

### CASE

**Apprehension over a chance of cancer**  
She was frightened of the ovarian cyst that her gyn detected during an annual exam, thinking that he might find that she had ovarian cancer. She was only 45 years old, after all, dreaming of many more birthdays, desiring to be there to see her children marry, hoping to play with her grandchildren.

Now, she had to shoulder the anxiety of wondering what might be discovered at surgery. Well, did she have ovarian cancer? Was she going to die far, far too young?

According to the American Cancer Society, approximately 21,550 new cases of ovarian cancer were diagnosed last year and 14,600 women died of the disease. In fact, in the United States, ovarian cancer is the most common cause of death from a gynecologic malignancy.

To our frustration, ovarian cancer typically isn't diagnosed until it has reached an advanced stage.

What we've needed, and what would greatly advance women's health, are new tests to identify ovarian cancer at an early stage. That dream hasn't been realized, but we can be pleased that a new test for the glycoprotein *human epididymis protein 4*, or HE4, will improve our ability to properly treat women in whom ovarian cancer has been diagnosed.

### Snapshot of the new test

HE4 is expressed in normal male and female reproductive tract epithelium and in pulmonary epithelium. Its biologic function hasn't been fully characterized, but it may be an inhibitor of trypsin.

A team of researchers led by Leroy Hood reported in 1999 that HE4 was over-expressed in ovarian cancer tissues.<sup>1</sup> Their discovery translated to development\* of an ELISA blood test for HE4 that has value in detecting and managing ovarian cancer.

HE4 is overexpressed in:

- approximately 90% of women who have serous ovarian cancer
- 99% of women who have endometrioid ovarian cancer
- 50% of women who have clear-cell cancer.
- mucinous and germ-cell ovarian cancers do *not* over-express HE4. The normal range of circulating

HE4 is  $\leq 150$  picomoles/L, or picomolar (pM). In one study, the mean serum HE4 level in healthy control women was 41 pM; in those who had ovarian cancer, 1,125 pM.<sup>2</sup>

### Recurrence and progression of ovarian Ca monitored with HE4

The assay for HE4 has been approved by the US Food and Drug Administration to aid in monitoring the recurrence and the progression of epithelial ovarian cancer. **The test is not FDA-approved for making a diagnosis of ovarian cancer.**

The National Comprehensive Cancer Network recommends that, for women who have ovarian cancer *and* an elevated level of CA 125 at the time of their diagnosis, the level of CA 125 be measured before each cycle of chemotherapy. This approach helps to ensure that disease activity is accurately monitored and progression is detected quickly—enabling the oncologist to switch as necessary to a more effective regimen.

Measuring both CA 125 *and* HE4 before each cycle of chemotherapy likely improves the accuracy of the determination of a patient's true clinical status. An increase of 25% or more across sequential HE4 measurements suggests recurrence or

\*By Fujirebio Diagnostics. The test is available through Quest Diagnostics.

## Preop studies of a pelvic mass

### Pelvic ultrasonography is critical; the platelet count is valuable

Determining the presence of a malignancy is a major goal in the preoperative evaluation of a woman who has a pelvic mass. As I noted, referring a patient in whom you suspect ovarian cancer or pelvic malignancy to a specialty center for care increases her chance of survival.

Pelvic US is critical and the platelet count is useful in the preoperative evaluation of a pelvic mass. Here's how to apply these studies.

**Sonographic findings** in an ovarian cyst that raise the risk of an ovarian malignancy include:

- solid tumor with irregular borders
- ascites
- detection of four or more papillary structures in the cyst or tumor
- ovarian cyst diameter greater than 10 cm
- Doppler demonstration of significant blood flow into the cyst or tumor.<sup>1</sup>

US findings that suggest the ovarian cyst is **benign** include:

- unilocular cyst
- no solid cyst component greater than 7 mm in diameter
- smooth cyst surface
- no significant blood flow into the cyst on Doppler imaging.<sup>1</sup>

**The platelet count** is routinely available to you preoperatively because it is automatically reported as part of a complete blood count.

In a woman who has a pelvic mass, a preop platelet count of  $\geq 400 \times 103/\mu\text{L}$ , signifying **thrombocytosis**, is associated with an increased risk of malignancy.<sup>2,3</sup> A study of 102 patients who had a benign pelvic mass and 139 patients whose tumor was malignant or classified as borderline determined that **thrombocytosis** was present in 16% of women who had a benign pelvic mass and 56% of women who had a malignant or borderline tumor.<sup>2</sup>

Preoperative thrombocytosis has also been reported in children and adolescents who have a germ cell tumor.<sup>3</sup>

**The lesson?** Before you operate on a pelvic mass, check the platelet count!

#### References

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progression of disease. Conversely, a stable HE4 level across sequential measurements is reassuring.

#### Specificity: HE4 versus CA 125

Many women who have benign gynecologic disease have an elevated concentration of circulating

CA 125—in fact, as many as 50% of women who have advanced endometriosis.<sup>3</sup> In contrast to what is seen when CA 125 is measured, the HE4 level is, typically, within the normal range in women who have endometriosis: In one study, the mean level of HE4 was 41 pM in healthy con-

trol women and 46 pM in women who had ovarian endometriosis.<sup>2</sup> Contrast that with the mean CA-125 level in the same groups of subjects: 9 U/mL in healthy controls and 44 U/mL in women who had ovarian endometriosis.

Other studies have also reported a low rate of HE4 elevation in women who have benign gynecologic disease. In one study, only 7% of 347 women who had benign gynecologic disease also had an elevated level of HE4.

#### HE4 helps plan the care of women with a pelvic mass

Of approximately 300,000 women who are hospitalized annually because of an ovarian cyst or a pelvic mass, fewer than 10% are given a diagnosis of invasive ovarian cancer. Many authorities believe that a woman who has ovarian cancer has a greater chance of being cured of her disease if she receives initial, and then subsequent, treatment from a trained gynecologic oncologist at a high-volume center.<sup>4</sup>

A major challenge for us is to accurately identify, before initial surgery, those women whose pelvic mass or ovarian cyst is most likely to be ovarian cancer. Proper identification would permit us, appropriately, to refer them to a specialty center.

Measuring HE4 and CA 125 in **combination** may represent a significant advance in our ability to accurately identify and triage patients who are at high risk of serous and papillary ovarian cancer. In one study of postmenopausal women who had a pelvic mass,<sup>5</sup> tandem measurement of HE4 and CA 125 resulted in:

- preoperative identification of 93% of women who had ovarian cancer or a tumor of low malignant potential

- misidentification (false-positive result) of high risk of ovarian cancer in only 25% of women whose pelvic mass was, in fact, benign.

#### Consider taking this step forward now

If you haven't measured HE4 in your patients who have a pelvic mass or a complex ovarian cyst, consider evaluating the utility of this assay in your practice. There's good reason to do so: HE4 is the first new marker for ovarian cancer that has been made available to us in 25 years. ☺



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#### References

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