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HE4 and CA125 serum biomarker monitoring in women with epithelial ovarian cancer

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Abstract.
BACKGROUND: CA125 is the gold standard serum biomarker for monitoring patients with epithelial ovarian cancer (EOC). Human epididymal protein 4 (HE4) is a novel serum biomarker for EOC patients.
OBJECTIVE: The objective of this trial was to examine the utility of measuring serum HE4 levels for monitoring EOC patients and to compare HE4 performance parameters to serum CA125.
METHODS: A retrospective trial using residual longitudinal serum samples drawn during treatment and monitoring from EOC patients. Serum CA125 and HE4 levels were analyzed at each time point, and a velocity of change was calculated and correlated with clinical status. The null hypothesis was that HE4 is inferior to CA125, and this was tested using concordance and two-sided Fisher's exact testing. McNemar's test was used to assess the overall agreement of the two assays with the clinical status.
RESULTS: A total of 129 patients with 272 separate clinical periods and 1739 events (serum samples) were evaluated. Using a 25% change in serum biomarker levels to indicate change in disease status, the accuracy and NPV determined for HE4 versus CA125 were 81.8% versus 82.6% ($p = 0.846$) and 87.4% versus 89.7% ($p = 0.082$), respectively. Concordance comparison of HE4 accuracy / CA125 accuracy was 0.990, indicating HE4 was not inferior to CA125 (McNemar's test p-value = 0.522). Performing a velocity of change analysis, the accuracy and NPV determined for HE4 versus CA125 were 78.3% versus 78.6% ($p = 0.995$) and 74.9% versus 76.3% ($p = 0.815$), respectively. Concordance comparison of HE4 velocity accuracy / CA125 velocity accuracy was 0.996, again indicating HE4 was not inferior to CA125 (McNemar's test p-value = 0.884). The combination of HE4 and CA125 velocity changes showed a similar accuracy of 81.3% ($p = 0.797$ compared to HE4 and CA125 alone) and NPV of 81.1% ($p \geq 0.172$ compared to HE4 and CA125 alone), and an increased sensitivity of 70.5% ($p \leq 0.070$ compared to HE4 and CA125 alone).

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CONCLUSION: HE4 is equivalent to CA125 for monitoring of EOC patients. The combination of CA125 and HE4 velocities is superior to either marker alone.

Keywords: Ovarian cancer, biomarkers, CA125, HE4

1. Introduction

Epithelial Ovarian Cancer (EOC) is the leading cause of mortality from gynecologic cancers in the United States [1]. The high mortality is due to a combination of late stage at diagnosis, high recurrence rates and inability to cure recurrent ovarian cancer. Despite this, the mortality rate for ovarian cancer decreased by 33% between 1976 and 2015 [2], and the 5-year survival rate has improved from 34 months to 52 months, with a relative 5-year survival rate improving from 39% to 45%, over the last 3 decades [3]. Historically, primary treatment of epithelial ovarian cancer included a cytoreductive surgery followed by combination platinum and taxane based chemotherapy. More recently, contemporary management of EOC has moved to neoadjuvant chemotherapy with an interval debulking surgery followed by consolidation chemotherapy, and in many cases maintenance therapy with PARP inhibitors or a VEGF inhibitor such as bevacizumab [4–7]. Many women will have an excellent response to primary treatment, but recurrence rates are high, particularly for patients with advanced stage disease [8]. With successful treatment options it has become increasingly important to have accurate methods of assessing response to treatment, especially in patients undergoing neoadjuvant chemotherapy prior to surgery and for detecting recurrent disease in patients on maintenance therapy. Earlier detection of progressive or recurrent disease is important as the discontinuation of maintenance therapy at the first signs of progression can reduce cumulative toxicities and cost.

Monitoring for recurrent ovarian cancer in the post treatment phase includes a thorough history, physical exam, biomarkers and radiographic imaging as clinically indicated. Traditionally, serum CA125 levels have been used for monitoring women with ovarian cancer while undergoing treatment and in the surveillance phase of their disease. More recently, the biomarker human epididymal protein 4 (HE4) has been cleared by the US FDA as a serum biomarker for the management of women with EOC and has received the same clearance indications as CA125. In women with a pelvic mass, HE4 has been shown to be the single most sensitive biomarker for detecting EOC and performs similarly to CA125 in detection of disease recurrence [9, 10]. This data led to the US FDA clearance of HE4 as a serum biomarker for monitoring women diagnosed with EOC during treatment and follow up, as well as for the risk stratification for EOC in women presenting with a pelvic mass prior to surgery using the Risk of Ovarian Malignancy Algorithm (ROMA) [11].

The objective of the current study was to examine the utility of HE4 in comparison to CA125 for monitoring women with EOC for response to treatment or disease progression during treatment and for detecting recurrent disease in women undergoing surveillance after treatment for EOC.

2. Methods

This study was reviewed and approved by the Women and Infants Hospital of Rhode Island (WIHRI) IRB (Project No. 09-0334). Clinical residual serum samples from women diagnosed with EOC that had been on treatment or undergoing surveillance from January of 1997 to October 2010 had been stored at –80°C and were available through the WIHRI Division of Medical Screening and Special Testing. The residual serum samples were retrieved from storage after initial clinical CA125 testing had been completed. The residual samples had been drawn every 3–5 weeks for patients on chemotherapy and every 3 months during follow up monitoring. The patient's clinical status was obtained for each clinical

visit and at the point of time for each blood draw. Clinical charts were reviewed for disease status and assessment for disease regression, progression and stable disease including no evidence of disease. Disease status was determined through the historical clinical assessment of the treating oncologist clinical notes, imaging reports (CT scans or MRI) and historical serum CA125 measurements made at the time of the original clinical assessment. Using the residual serum, CA125 and HE4 levels were re-analyzed at each time point. New serum levels of CA125 and HE4 were determined and recorded for the residual serum samples using the Abbott ARCHITECT i2000 platform (Abbott Park, Illinois, U.S.A.)

2.1. Assumptions for monitoring disease status

Each patient undergoing chemotherapy treatment or monitoring for recurrent disease had to have a minimum of 2 serial data points, with the majority of the clinical periods having 3 serial serum samples available for evaluation. Patients undergoing treatment were evaluated to either have progression or regression of disease. Patients undergoing monitoring were evaluated and categorized as having either progressive disease (disease progression or recurrence) or non-progressive disease (disease regression, stable disease or no evidence of disease). The assumption was that overall concordance between the ability of CA125 and HE4 to change with disease status (i.e., increase with progressive disease or not change/decrease with non-progressive disease) would be 90%. With a sample size of 385 (serum samples), a two-sided 95% confidence interval for a single proportion using the large sample normal approximation would extend $\pm$ 3% from the observed proportion for an expected proportion of 90%. Thus, 128 patients with a minimum of 3 serial draws from each treatment period would provide for the ability to determine whether the concordance between the overall agreement for the ability of CA125 to monitor disease status and the ability of HE4 to monitor disease status was indeed 90% (within $\pm$ 3%) with 95% confidence.

The null hypothesis that HE4 is inferior to CA125 for monitoring of EOC was tested using concordance and a two-sided Fisher's exact test. McNemar's test was also used to assess the overall agreement of the two assays with the clinical status.

3. Results

All patients included in this trial were diagnosed with an epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer (categorized together as EOC) between January of 1997 and October 2010. The median age of the patient cohort was 60 years (Range: 23 to 86 years, IQR = 16). A total of 129 women with a diagnosis of EOC were identified and included in the analysis, of which 11 women had stage I disease (8.5%), 12 with stage II disease (9.3%), 94 with stage III disease (72.9%), and 12 women with stage IV (9.3%) disease. For the 129 patients, there were a total of 272 clinical periods observed, with 188 of these being treatment period with 1,290 treatment events (serum samples) and 84 monitoring periods with 449 monitoring events (serum samples) for a total of 1739 serum analyses (treatment and monitoring events). Of the 188 treatment periods observed, 72 (38.3%) patients were receiving first line therapy, 50 (26.6%) patients were receiving second line therapy and 66 (35.1%) patients were on third line or greater therapy (Table 1).

Employing an analysis using a 25% change in serum biomarker levels ($\leq$25% increase = non-progressive disease;>25% increase = progressive disease) to indicate a change in disease status (ΔDS), HE4 had an overall accuracy for ΔDS of 81.8% (95% CI: 79.7%–83.7%) with a specificity of 90.5% (95% CI: 88.7%–92.1%), sensitivity of 45.2% (95% CI: 39.2%–51.2%), PPV of 53.2% (95% CI: 46.6%–59.7%) and a NPV of 87.4% (95% CI: 85.4%–89.2%). Analysis of CA125 showed an over-

Table 1
Demographics and clinical events for included patients

Characteristics	Patients (N = 129)
Age in years (median)	60 (Range: 23 to 86, IQR = 16)
*Clinical periods, N (%)	
Treatment	188 (69.1%)
2 Events	8 (4.3%)
≥3 Events	180 (95.7%)
Monitoring	84 (30.9%)
2 Events	5 (6.0%)
≥3 Events	79 (94.0%)
Events (serum samples), N (%)	
Treatment	1290 (74%)
Monitoring	449 (26%)
Stage, N (%)	
I	11 (8.5%)
II	12 (9.3%)
III	94 (72.9%)
IV	12 (9.3%)
Treatment, N = 188 (%)	
First line	72 (38.3%)
Second line	50 (26.6%)
Third line	66 (35.1%)

*A clinical period represents a period of time where serum samples are drawn and clinical status is determined (an event) during either a line of treatment (Treatment period) or during a period of observation where no treatment is being administered (Monitoring period).

all accuracy for ΔDS of 82.6% (95% CI: 80.5%–84.5%) with a specificity of 88.7% (95% CI: 86.7%–90.4%), sensitivity of 56.6% (95% CI: 50.5%–62.5%), PPV of 54.0% (95% CI: 48.1%–59.9%) and a NPV of 89.7% (95% CI: 87.8%–91.4%) (Table 2). A concordance assessment for overall agreement of ΔDS using a 25% change in HE4 or CA125 resulted in a ratio (HE4 accuracy / CA125 accuracy) of 0.990 (Fisher's exact p-value = 0.846). An evaluation of the agreement of the two assays with the clinical status using McNemar's test resulted in a p-value of 0.522. This indicates HE4 is not inferior to CA125 for monitoring EOC when an increase of >25% is used to define progressive disease. Analysis of a >25% increase in CA125 and or HE4 combined showed an overall accuracy for ΔDS of 79.0% (95% CI: 76.8%–81.1%) with a specificity of 81.3% (95% CI: 79.0%–83.5%), sensitivity of 69.3% (95% CI: 63.5%–74.7%), PPV of 46.6% (95% CI: 41.6%–51.5%) and a NPV of 91.9% (95% CI: 90.0%–93.5%).

Performing a velocity of change analysis of serial samples with a serum measurement change of >5 U per month for CA125 levels and >10 pM per month for HE4 to indicate ΔDS, HE4 had an overall accuracy of 78.3% (95% CI: 72.9–83.1%), specificity of 95.0% (95% CI: 90.4–97.8%), sensitivity of 54.5% (95% CI: 44.8–63.9%), PPV of 88.4% (95% CI: 78.4–94.9%) and a NPV of 74.9% (95% CI: 68.3–80.7%). Comparatively, CA125 had an overall accuracy of 78.6% (95% CI: 73.2%–83.3%) with a specificity of 92.5% (95% CI: 87.3%–96.1%), sensitivity of 58.6% (95% CI: 48.8%–67.8%), PPV of 84.4% (95% CI: 74.4%–91.7%) and a NPV of 76.3% (95% CI: 69.7%–82.1%) (Table 3). Concordance

Table 2
Performance parameters for CA125 and HE4 when using a 25% change in serum biomarker levels to indicate a change in disease status (ΔDS)

	CA125	HE4	Concordance Ratio*	Fisher's Exact *p*-value**	HE4+CA125	Fisher's vs. CA125	*p*-value vs. HE4
Sensitivity	56.6% (95%CI: 50.5–62.5%)	45.2% (95%CI: 39.2–51.2%)	0.798	0.008	69.3% (95%CI: 63.5–74.7%)	0.003	0.000
Specificity	88.7% (95%CI: 86.7–90.4%)	90.5% (95%CI: 88.7–92.1%)	1.020	0.155	81.3% (95%CI: 79.0–83.5%)	0.000	0.000
PPV	54.0% (95%CI: 48.1–59.9%)	53.2% (95%CI: 46.6–59.7%)	0.985	0.861	46.6% (95%CI: 41.6–51.5%)	0.055	0.121
NPV	89.7% (95%CI: 87.8–91.4%)	87.4% (95%CI: 85.4–89.2%)	0.974	0.082	91.9% (95%CI: 90.0–93.5%)	0.089	0.001
Accuracy	82.6% (95%CI: 80.5–84.5%)	81.8% (95%CI: 79.7–83.7%)	0.990	0.846	79.0% (95%CI: 76.8–81.1%)	0.558	0.435
LR+	5.01 (95%CI:4.14–6.07)	4.76 (95%CI:3.82–5.93)	—	—	3.71 (95%CI:3.21–4.28)	—	—
LR–	2.04 (95%CI:1.78–2.34)	1.65 (95%CI:1.48–1.84)	—	—	2.65 (95%CI:2.21–3.17)	—	—

*HE4 performance / CA125 performance. **CA125 vs. HE4. LR+ = Likelihood Ratio of a positive test. LR– = Likelihood Ratio of a negative test.

Table 3
Performance parameters for CA125 alone, HE4 alone and HE4+CA125 when using velocity of change of >5 U per month for CA125 serum levels and >10 pM per month for HE4 serum levels to indicate a change in disease status (ΔDS)

	CA125	HE4	Concordance Ratio*	Fisher's Exact *p*-value**	HE4+CA125	Fisher's vs. CA125	*p*-value vs. HE4
Sensitivity	58.6% (95%CI: 48.8–67.8%)	54.5% (95%CI: 44.8–63.9%)	0.930	0.590	70.5% (95%CI: 61.2–78.8%)	0.070	0.019
Specificity	92.5% (95%CI: 87.3–96.1%)	95.0% (95%CI: 90.4–97.8%)	1.027	0.489	88.8% (95%CI: 82.8–93.2%)	0.338	0.064
PPV	84.4% (95%CI: 74.4–91.7%)	88.4% (95%CI: 78.4–94.9%)	1.047	0.631	81.4% (95%CI: 72.3–88.6%)	0.688	0.281
NPV	76.3% (95%CI: 69.7–82.1%)	74.9% (95%CI: 68.3–80.7%)	0.982	0.815	81.1% (95%CI: 74.5–86.6%)	0.309	0.172
Accuracy	78.6% (95%CI: 73.2–83.3%)	78.3% (95%CI: 72.9–83.1%)	0.996	1.000	81.3% (95%CI: 76.1–85.7%)	0.797	0.797
LR+	7.81 (95%CI:4.43–13.76)	10.90 (95%CI:5.43–21.87)	—	—	6.29 (95%CI:4.00–9.89)	—	—
LR–	2.23 (95%CI:1.78–2.79)	2.09 (95%CI:1.70–2.57)	—	—	3.01 (95%CI:2.25–4.03)	—	—

*HE4 performance / CA125 performance. **CA125 vs. HE4. LR+ = Likelihood Ratio of a positive test. LR– = Likelihood Ratio of a negative test.

comparison of agreement for HE4 and CA125 velocities for ΔDS resulted in a ratio (HE4 velocity accuracy / CA125 velocity accuracy) of 0.996 (Fisher's exact *p*-value = 0.995). An evaluation of the agreement of the two assay velocities with the clinical status using McNemar's test resulted in a *p*-value of 0.884. Once again, this indicated that there was no significant difference between HE4 and CA125 velocity for monitoring disease status in women with EOC.

The analysis of using a combination of HE4 and CA125 velocities at the same thresholds reported above had an overall accuracy of 81.3% (95% CI: 76.1–85.7%), specificity of 88.8% (95% CI: 82.8–93.2%), sensitivity of 70.5% (95% CI: 61.2–78.8%), PPV of 81.4% (95% CI: 72.3–88.6%) and a NPV of 81.1% (95% CI: 74.5–86.6%). The combination of HE4 and CA125 improved the performance characteristics when examining accuracy, sensitivity and NPV over that of both CA125 alone

and HE4 alone, although only the increase in sensitivity approached statistical significance (Fisher's exact p-values = 0.070 compared to CA125 and 0.019 compared to HE4).

There were 22 patients with a known elevated serum HE4 level in the preoperative period with 205 treatment events. Examination of the performance of HE4 (using the same 25% threshold for change) in these patients determined an accuracy of 87.8% (95% CI: 82.5–92.0%) specificity of 92.9% (95% CI: 88.1–96.1%), sensitivity of 47.8% (95% CI: 26.8–69.4%), PPV of 45.8% (95% CI: 25.6–67.2%) and a NPV 93.4% (95% CI: 88.7–96.5%).

When examining individual biomarkers HE4 was a marker for disease in 21 of the cases when CA125 was not, and CA125 was a marker for disease in 28 of the cases when HE4 was not. Additionally, 48 patients undergoing 58 treatment and monitoring events were identified that had evidence of disease progression by CA125, HE4, and CT imaging. CA125 was the first biomarker to trend upward for 9 events (15.5%), HE4 was the first biomarker to trend upward for 10 events (17.2%), and both increased simultaneously for 39 events (67.2%). Mean lead time for CA125 elevation prior to progression on imaging was 60 days (95% CI: 43–78, median = 44, range = 0–386). For HE4, mean lead time was 66 days (95% CI: 48–83, median = 46, range = 0–386). There was no significant difference in the average lead times between the two biomarkers ($p > 0.05$).

4. Discussion

The serum biomarker CA125 was first discovered in 1982 as a biomarker for women diagnosed with EOC [12, 13]. Since its discovery, numerous studies have assessed the utility of serum CA125 levels for monitoring women with EOC and have established CA125 as the gold standard for monitoring EOC.

Human epididymal protein 4 (HE4) is a novel biomarker that has been shown to be overexpressed in EOC and can be detected in the sera of these patients [14]. HE4 has been shown to have greater sensitivity and is more often elevated in early-stage disease than CA125 [10, 15]. As well, the combination of HE4 and CA125 has been shown to have greater sensitivity and specificity than either biomarker alone for detecting EOC [10]. Using the residual serum samples from the cohort of patients to gain US FDA clearance for CA125, serum HE4 levels were determined in the residual samples and analyzed as a biomarker for monitoring women with EOC. The results of this data were the basis for the US FDA clearance of HE4 as a biomarker for monitoring patients with EOC and HE4 was granted the same indication as CA125.

The findings in the current study confirms HE4 is equivalent to CA125 for monitoring patients with EOC for recurrence, progression and response to treatment. Havrileskey et al. examined the utility of HE4 with two other biomarkers, MMP7 and glycodelin, for monitoring 27 patients for recurrent ovarian cancer and reported that at least one of the biomarkers was elevated when a recurrence was present providing a 100% sensitivity [15]. In another study, Granato et al. analyzed CA125, HE4 and CA72.4 levels during monitoring 20 patients for recurrent disease and found that 70% of patients had elevated CA125 at the time of recurrence, 85% had increases in both HE4 and CA72.4, and 65% had increases in CA125 and HE4 [16]. Another study examined 34 patients with suspected recurrent ovarian cancer based on imaging and determined that a combination of CA125 and HE4 had a sensitivity of 76% and specificity of 100% for detecting recurrent disease [17]. Additional studies suggest advantages of HE4 over CA125 for detecting recurrences. Schummer et al demonstrated that 5 of 20 patients with recurrent disease were detected by HE4 alone, and in two additional cases recurrence was detected earlier by HE4 than CA125 [18]. Like the findings in the current study, HE4 levels have been shown to detect disease recurrence earlier than CA125. In one study, HE4 increased about 3 months earlier than CA125 in nine patients with recurrent ovarian cancer [19].

The use of accuracy as a performance parameter allowed for the assessment of detecting changes in disease status (ΔDS) including progression, recurrence and regression, as well as identifying patients with stable disease including those with no evidence of disease (NED). A high accuracy indicates the biomarker changes with disease status changes (ΔDS) but is also stable when there is no change in disease status (NED or stable disease). The current study assessed the accuracy of HE4 and CA125 in terms of how often the biomarkers agree with the patient's clinical status, in other words, detecting changes in disease status defined as ΔDS (progressive disease vs. non-progressive disease). Using a change in biomarker level of 25% to indicate a ΔDS, the biomarkers agreed with clinical status in over 80% of the patients. HE4 not only indicated changes in disease status but it also remained stable and correlated with continued remission or stable disease in patients.

A sub-analysis of patients who had CT imaging and biomarker data points prior to the CT imaging was performed. Both biomarkers showed an average lead time of approximately 60 days prior to the demonstration of disease on CT imaging. This analysis provides further support of the equivalent ability of HE4 and CA125 to detect progression or recurrence.

Previous studies examining biomarker monitoring have utilized specific numerical cutoffs, such as 2 times the normal upper limits, or percentage of change for CA125 and HE4 to determine disease status. The current study not only examined percentage change but also employed a novel method analyzing the velocity of change (rate of change over time) of HE4, CA125 and the dual marker combination of HE4 + CA125. Calculating biomarker velocity allows for direct comparison of biomarker performance as opposed to predetermined cut points. The velocity of change for CA125 and HE4 showed a concordance ratio (HE4/CA125) of 0.996, indicating similar accuracy for the two biomarkers. As the velocities agreed with the clinical status of the patient in nearly 80% of cases, this method of analysis can be used to monitor disease status. Some patients may have tumors that express only one of the biomarkers, and thus the combination of both HE4 and CA125 will increase the performance parameters over that of either biomarker alone. In the current study, the combination of HE4 and CA125 improved accuracy and had a significant increase in sensitivity over either marker alone, suggesting a combination of HE4 and CA125 is superior to either alone.

The current study showed there is equivalency between serum CA125 and HE4 for monitoring patients with EOC. Clinically, the initial measurement of both biomarkers would be appropriate to determine the best marker for an individual patient. As demonstrated in this study there are patients where one biomarker is elevated, and the other biomarker is not. In this instance, choosing the biomarker with the higher serum level above its norm would be appropriate. If both biomarkers are only slightly elevated from the normal values, then monitoring both biomarkers may be suitable. The cost of HE4 and CA125 are equivalent so there is no economic advantage of using one biomarker over the other.

The ability to translate early detection of recurrence into meaningful clinical outcomes and improved quality of life continues to be a challenge. With the changing paradigm for the treatment of women with EOC and the increasing use of neoadjuvant chemotherapy and maintenance chemotherapy with PARP inhibitors (PARPi) and VEGF inhibitors, the early detection of recurrent disease or disease that is not responding to treatment is of clinical benefit. Recently the SOLO-2 study group looked at serial CA125 serum levels to detect recurrent disease in women on PARPi maintenance and found CA125 was not an accurate biomarker for recurrent disease in up to 50% of patients [20]. The study examined 195 patients without evidence of progressive disease based on serial CA125 serum levels, and 94 patients were found to have progression based on CT imaging and RECIST criteria providing a negative predictive value of 52%. The findings of the SOLO-2 study indicate that CA125 levels may be suppressed by PARPi and therefore limiting the usefulness of CA125 as a biomarker for patients on PARPi maintenance. Studies examining the effect of PARPi on the expression and serum levels of HE4 need to be performed, as HE4 may be a more robust serum biomarker for patients being treated with PARP inhibitors.

One of the strengths of this study is the large number of patients included relative to other studies on EOC monitoring. This is the largest study to date examining HE4 monitoring in patients with EOC. Data for patients both with and without progressive disease was included, thus allowing for comparison between the two groups. Additionally, both patients receiving treatment and who had completed treatment were included to assess the efficacy of both biomarkers for monitoring during and after treatment. It should be noted that there was an inherent bias in favor of CA125 in this trial, as assessment of ΔDS in the original clinical assessments of patients and reported in the clinical charts included the use of serum CA125 levels as one of the parameters to evaluate patient's disease status clinically. Despite this bias, HE4 still achieved statistical equivalency to CA125 for monitoring EOC. A limitation of this study is the retrospective nature and the variability in clinical assessment for disease status from provider to provider.

In conclusion, we compared HE4 and CA125 for monitoring disease progression or recurrence for women with EOC. Specifically, we evaluated the velocity of change to indicate ΔDS for HE4 and CA125. The accuracy for either biomarker alone was close to 80%, however, combining the two biomarkers increased accuracy and significantly increased sensitivity over either biomarker alone. The use of algorithms calculating the velocities of change for HE4 and CA125 warrants further validation as a method for monitoring patients with EOC.

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Conflict of interest

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