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Utility of a novel serum tumor biomarker HE4 in patients with endometrioid adenocarcinoma of the uterus

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Abstract

Objective—Tumor markers with increased sensitivity and specificity for endometrial cancer are needed to help monitor response to therapy and to detect recurrent disease. Currently, the tumor maker CA125 is utilized in this role with limited value. The objectives of this study were to examine the levels of several novel tumor markers HE4, SMRP, CA72.4 and CA125 as potential markers in patients diagnosed with endometrioid adenocarcinoma of the uterus.

Methods—Preoperative serum samples from surgically staged patients with endometrioid adenocarcinoma of the uterus were analyzed for levels of HE4, SMRP, CA72-4 and CA125. Control samples were obtained from healthy postmenopausal women. Logistic regression models and receiver operating characteristic (ROC) curves were constructed for each tumor marker and for all combinations, with cross-validation analyses to obtain average sensitivities at set specificities of 90%, 95%, and 98%.

Results—Serum samples from 156 healthy subjects and 171 patients with endometrial cancer (122 stage I, 17 stage II, 26 stage III, and 6 stage IV) were analyzed. At a 95% specificity, the sensitivities for differentiating between healthy subjects and all stages of cancer were 45.5% for HE4 and 24.6% for CA125. For stage I disease, HE4 yielded a 17.1% improvement in sensitivity compared with CA125.

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Conclusion—HE4 is elevated in all stages of endometrial cancer and is more sensitive in early-stage endometrial cancer compared to CA125. Further investigation of HE4 as a marker for early detection of recurrent endometrial cancer and monitoring response to therapy is warranted.

Introduction

Approximately 40,100 new cases of uterine cancer are diagnosed in the United States annually, resulting in 7,470 deaths(1). Unlike many malignancies, endometrial cancer patients often exhibit signs and symptoms such as postmenopausal bleeding that lead to the diagnosis of the malignancy in the early stages of the disease. As a result, 70% of endometrial cancers are detected as stage I malignancies and have an excellent prognosis. The need for tumor markers to detect early stage endometrial cancer is not as critical as is the development of markers to detect premalignant or early stage malignancy in ovarian cancer, a cancer that generally presents with treatable, but fundamentally incurable disease. However, certain high risk groups, including women with Lynch syndrome, are at extremely high risk for endometrial cancer and may benefit from a serum marker for early detection.

In addition, for the group of endometrial cancer patients at high risk for recurrence or for patients with systemic and advanced stage disease, sensitive tumor markers for monitoring are needed. Similar to the value of the CA125 tumor marker employed in ovarian cancer, a marker for endometrial cancers that is useful in the early detection of recurrent disease or for the evaluation of response to treatment is critical. Patients diagnosed with stage I disease who have intermediate or high risk factors based on deep myometrial invasion, lymphvascular space invasion or high grade tumors have recurrence rates of 20% to 30% (2;3). At the present time, the detection of recurrent disease is through monitoring for clinical symptoms and the use of imaging modalities, which normally detect disease in advanced stages. Elevated CA-125 levels have been demonstrated to correlate with advanced disease (4-8), however, the use of CA125 for the detection of early recurrent endometrial cancer is limited. Only 10% to 20% of patients with early stage disease and approximately 25% of patients with asymptomatic recurrent disease will have an elevated CA125 level (9;10).

A number of serum tumor markers have been studied for their potential clinical utility in patients with endometrial cancer including CA15.3, CA19.9, CA72.4, CEA, OVX1, and M-CSF (11-15). More recently, proteomic analysis has also been employed to identify novel makers for endometrial cancer such as chaperonin 10 (16). Despite these technical advances, only a few studies have examined multiple markers, such as CA125 and CA19-9, and their expression in the serum of endometrial cancer patients with promising results (17). The objectives of this study were to examine the expression levels of CA125 and the novel serum tumor markers HE4, soluble mesothelin-related peptide (SMRP), and CA72.4 in patients with endometrioid adenocarcinoma of the uterus and to evaluate the detection sensitivity and specificity of these biomarkers to differentiate between healthy women and women with cancer when used alone and in multiple combinations.

Methods

Blood samples were obtained from patients enrolled in a prospective study conducted at Women and Infants Hospital/Brown University and retrospectively from the serum bank at The University of Texas MD Anderson Cancer Center (UTMDACC). All enrolled patients provided written informed consent prior to the collection of any blood samples. The prospective study protocol at Women and Infants' Hospital was reviewed and approved by the institutional review board (IRB) at Women and Infants' Hospital. The serum used for controls were obtained from a serum bank at MD Anderson Cancer Center from an IRB

approved protocol enrolling healthy postmenopausal subjects undergoing annual screening for ovarian cancer and documented not to have any malignancies. Additional endometrial cancer samples were obtained from UTMDACC IRB approved endometrial cancer serum bank.

For patients diagnosed with endometrial cancer (cases) all blood samples were collected in the preoperative period then centrifuged with the serum withdrawn and frozen at −80°C within 4 hours of collection. All patients subsequently underwent surgery consisting of a hysterectomy and bilateral salpingo-oophorectomy with full surgical staging. Staging was conducted by obtaining pelvic washings and performing bilateral pelvic and para-aortic lymph node dissection. Lymph node counts were not required. Only patients with full surgical staging and a pathologically confirmed endometrioid adenocarcinoma of the uterus were included in the study.

Prospectively obtained serum samples from Women and Infants' Hospital were batch analyzed at the laboratories of Fujirebio Diagnostics Inc. (Malvern, PA). The archived serum samples obtained from UTMDACC were batch analyzed on site using Fujirebio kits. Serum levels of CA125, HE4, CA72.4 and SMRP were determined using assays and kits developed by Fujirebio Diagnostic, Inc. and were performed according to the manufacturer's specifications.

Statistical Analysis

Tumor marker levels in normal healthy controls and endometrial cancer patients were compared using the Wilcoxon rank-sum test (Mann-Whitney two sample statistic). The use of logistic regression analysis with constructs of receiver operator characteristic curves and the estimates of sensitivity at set specificities for analysis of multiple markers has been fully described in a previous paper analyzing multiple marker use in ovarian cancer(18). In summary, logistic regression models were estimated for each marker individually and all combination of markers to differentiate between patients with endometrial cancer and normal healthy controls. Receiver operator characteristic (ROC) curves were constructed for each logistic regression model and the area under the curve (ROC-AUC) was compared between each markers or marker combination using a non-parametric method (19). Cross-validation of the logistic regression models using a leave-one-out approach was performed to obtain the average sensitivities at set specificities of 90%, 95% and 98% for each marker individually and in combination with other markers. A level of $P<0.05$ was accepted as statistically significant for all statistical comparisons. Statistical analyses were performed using Intercooled Stata v10.0 (StataCorp, College Station, TX).

Results

Serum samples were obtained from 171 patients with surgically staged endometrial cancer (92 from Women and Infants' Hospital and 79 from MDACC) and from 156 healthy subjects. The median age for cancer patients was 62 years (range 25 to 95) and for controls was 62 years (range 51 to 78). Of the 171 patients with surgically staged endometrial cancer, 122 (71%) were diagnosed with stage I disease, 17 (10%) with stage II disease, 26 (15%) with stage III disease, and 6 (4%) with stage IV disease.

The median serum levels for each tumor marker analyzed are presented in Table 1. The median CA125 and HE4 serum levels were significantly elevated among all endometrial cancer stages relative to the healthy subjects (P<0.0001). When considering stage I patients alone, the median CA125 and HE4 levels were each significantly elevated compared with controls (P=0.0001 and P<0.0001, respectively). Compared with control levels, there was no

statistically significant difference when comparing the levels of CA72.4 or serum SMRP in all endometrial cancer stages combined or in stage I cancers alone (P≥0.1172).

The areas under the receiver operating characteristic curves (ROC-AUC) determined for CA125, HE4, CA72.4 and SMRP alone and in various combinations for differentiation of controls and all stages of endometrial cancer combined and are presented in Table 2. The areas under the ROC curves for all single markers and marker combinations for stage I and stage II-IV cases are presented in Table 3. The following discussion summarizes the key finding in these two tables.

Analysis of the ROC-AUC for individual tumor markers revealed that HE4 had a significantly higher ROC-AUC when compared with CA125, both in, stage I cancers and all cancer stages combined (P=0.0007 and P=0.0009, respectively; Tables 2 and 3). Comparison of the ROC- AUC of CA125 to HE4 for stages II to IV showed HE4 to have a greater ROC-AUC than CA125 (84% versus 75%, respectively), but this difference was not statistically significant (P=0.1125; Table 3).

The combination of CA125 and HE4 significantly increased the ROC-AUC compared to that of CA125 alone for stage I by 12.9% (P<0.0001), stages II-IV by 11.3% (P=0.0106) and all stages of cancer together by 12.3% (P<0.0001). However, the ROC-AUC for the combination of CA125 and HE4 was not significantly increased when compared with that of HE4 alone for stage I cases (P=0.9693) but was significantly different for stages II-IV with an increase in the ROC-AUC of 3.0% (P=0.0157) (Tables 2 and 3).

The combination of CA125, HE4 and SMRP or CA125, HE4 and CA72.4 had the largest ROC-AUC for any triplet combination of markers; however when compared with that of the combination of CA125 and HE4 or with HE4 alone, there was no statistical difference among patients with stage I disease (P≥0.2124) or for all cancer stages combined (P≥0.3227). Conversely, for stages II to IV disease, the triple marker combination of CA125, HE4 and SMRP was slightly better than HE4 alone with an increase in the ROC-AUC by 6.2% (P=0.0087), however, there was not a significant difference compared with the combination of HE4 and CA125 (P=0.0652). However, none of the triple marker combinations were significantly better than either HE4 alone or the combination of CA125 and HE4 when examining all cancer stages combined (p≥0.3227; Table 2 and 3).

The combination of all four tumor markers yielded the largest ROC-AUC for stage I, stage II-IV and all stages combined (ROC-AUC: 76.9%, 89.3% and 79.7%, respectively). When comparing the ROC-AUC for the four-marker combination with that for HE4 alone for stage I cases, as well as for all stages together, no statistically significant differences were found (P=0.9631 and P=0.4154, respectively). However, there was a significant difference between the ROC-AUC for the four-marker combination compared with that for HE4 alone among patients with stage II- IV cancers (89.3% vs. 83.6%, respectively; P=0.0132). The contribution to the improvement in assay sensitivity of the four-marker combination is attributed to SMRP over that of CA72.4, as there was no significant difference seen between the four marker combination and the three marker combination of CA125, HE4 and SMRP for any of the comparisons (P≥0.1913). Equally, there was no statistical difference between the four marker combination and the two marker combination of HE4 and CA125 (P≥0.1058)

HE4 as a single tumor marker achieved the greatest ROC-AUC for stage I, stage II - IV and all stages combined when compared with the single markers CA125, CA72.4 and SMRP. No combination of tumor markers had a significantly higher ROC-AUC than HE4 alone for stage I disease or for all stages together. However, for patients with stage II-IV disease, the triple combination of CA125, HE4 and SMRP yielded a significantly higher ROC-AUC than

did HE4 alone (89.8% vs. 83.6%, respectively; P=0.0087) but no better than the combination of HE4 and CA125 (89.8% vs. 86.6%, respectively; P=0.0652).

Logistic regression analysis was used to compare the sensitivity of each tumor marker for the differentiation of controls versus endometrial cancers at specificities of approximately 90%, 95%, and 98%. These analyses were done for each marker independently, as well as for each of the multiple marker combinations. The sensitivities at predefined specificities are shown in Table 4 for all cancer stages combined; in Table 5 for stage I disease; and in Table 6 for stage II-IV endometrial cancer cases. Of the four individual markers analyzed, HE4 exhibited the highest sensitivity for detecting endometrial cancer. For all combined stages of endometrial cancer, HE4 had a sensitivity of 45.5% at a specificity of 95% compared with 24.6% for CA125, and the multiple marker combination of CA125 and HE4 yielded a sensitivity of 50.1% at a predefined specificity of 95%, an increase of 25.5% in sensitivity over that of CA125 alone (Table 4). For stage I cases, HE4 showed a 17.1% improvement in sensitivity at a specificity of 95% compared with CA125 alone, and the combination of CA125 and HE4 showed a 20.9% improvement in sensitivity at a set specificity of 95% over that of CA125 alone (Table 5). Analysis of patients with stage II-IV disease showed that the sensitivity for HE4 alone was 64.9% and that the combination of CA125 and HE4 yielded a sensitivity of 69.7% at a specificity of 95%, an increase of 32.0% and 36.8%, respectively, over that of CA125 alone (Table 6).

The comparison of the dual marker combination of HE4 and CA125 compared with HE4 alone showed an increase in the sensitivity at a specificity of 95% from 45.5% to 50.1% when all stages of endometrial cancer were analyzed as a group (Table 4). When stage I disease was evaluated, the combination of HE4 and CA125 increased the sensitivity to 41.7% at a specificity of 95%, an increase of 3.8% over that of HE4 alone (Table 5). Analysis of the combination of HE4 and CA125 in patients with stage II to IV disease resulted in a sensitivity of 69.7% at a 95% specificity, representing an increase in sensitivity of 4.8% over HE4 alone (Table 6).

The triple marker combination of HE4, CA125 and SMRP produced a gain in sensitivity of 23.8% over that of CA125 alone when examining all cancer stages together (Table 4). However, there was no gain in sensitivity over the combination of HE4 and CA125. In all comparisons, the triple marker combination of CA125, HE4 and SMRP was no better than the dual combination of CA125 and HE4.

Discussion

Endometrial cancer patients often present with signs or symptoms that result in the diagnosis of their disease in the early stages and therefore most women have an excellent prognosis. With this in mind the utility of a tumor marker used as a screening tool in the general population is not as critical as a marker for early detection in cancers that are most often diagnosed in the late stages such as ovarian and pancreatic cancer. However, for women that are at increased risk for the development of endometrial cancer such as patients with Lynch syndrome, PTEN gene defects, breast cancer patients on Tamoxifen or women with severe obesity and diabetes there may be value in a tumor marker to aid in screening for endometrial cancer. Alternatively, for women already diagnosed with endometrial cancer who are at high risk for recurrence of their disease or for patients with systemic and advanced stage disease, sensitive tumor markers for monitoring are needed.

Uterine cancer is surgically staged, with 75% of patients presenting with stage I disease (20). However, a number of stage I patients will have intermediate or high risk factors based on deep myometrial invasion, lymphvascular space invasion or high grade tumors with

recurrence rates of 20% to 30% (2;3). Patients who fall into the stage I intermediate to high risk categories may benefit from tumor markers that aid in the detection of preclinical disease. Similar to the value of the CA125 tumor marker employed in ovarian cancer, a marker for endometrial cancers that is useful in the early detection of recurrent disease or for the evaluation of response to treatment is critical. Not only would the early detection of recurrent disease be aided by using tumor markers with an increased sensitivity and specificity, but such marker-based assays could also serve as prognostic indicators and as a component of pre-operative evaluations. Collectively, these facets would enhance the care available to endometrial cancer patients.

There have been a number of studies evaluating individual serum tumor markers in endometrial cancer such as CEA, CA72.4, CA19.9, CA15.3, and M-CSF and were shown to be elevated in only 20% to 30% of patients (11-15). The most commonly used tumor marker as an aid in the clinical management of endometrial cancer is CA125. A number of studies involving patients with uterine cancer have shown that serum CA125 levels correlated with advanced stage disease and with the presence of extrauterine disease, such as lymphatic and peritoneal metastases (8;21). Another study reports that only 10% of patients with stage I and II disease have elevated CA125 levels (22). In addition, Beck et al. demonstrated that 15% of stage I uterine cancer patients, as well as 33% of stage II and 62% of stage III patients have elevated CA125 levels (CA125 >35 U/ml) (15). Our data was consistent with these other studies, which indicate that CA125 exhibited a low sensitivity, 20.8% at a specificity of 95%, for surgical stage I endometrial cancers and a sensitivity of 32.9% at a specificity of 95% for patients with stage II-IV disease.

As a single marker, HE4 performed the best in both early and advanced stage endometrial cancers when compared with any of the other markers. The combination of serum HE4 and CA125 raised the sensitivity of detection compared to that of CA125 alone. The comparison of the dual marker combination of CA125 and H4 to HE4 alone showed a statistical significance when evaluating the ROC-AUC curves for stage II to IV cases but no statistical significance when examining all stages combined or stage I cases alone. No other combination of two, three, or four markers yielded sensitivities which were higher when compared to the combination of CA125 and HE4.

When HE4 was tested for the detection of stage I disease, HE4 out-performed all other individual tumor markers and tumor marker panels including CA125. CA125 is commonly used in surveillance of patient with advanced stage endometrial cancer and for monitoring response to treatment. The finding that HE4 is elevated in patients with stage I disease, and presumably small volume disease, suggests that HE4 is a sensitive marker and may be a more effective marker for detecting early recurrences or as a marker for monitoring response to treatment over that of CA125. Further studies will be necessary to determine the role of HE4 in these clinical scenarios.

When examining all stages separately or combined it was clear that the serum tumor marker HE4 contributed the most to any combination of markers in which it was included. The addition of SMRP did show some benefit, however, the addition of other markers to the combination CA125 and HE4 did not provide any substantial gains in sensitivity. Increasing the number of tumor markers used in a multiple marker assay seemed to have diminishing return, and the addition of more than two markers to a set added little value if any.

This study demonstrates the serum tumor marker HE4, with or without the addition of SMRP and or CA125, markedly increases the sensitivity over that of CA125 alone for detecting all stages of endometrial cancer. HE4 alone exhibited a higher sensitivity than did CA125 alone. In addition, HE4 as a single tumor marker outperformed all tumor marker

combinations presented in this study, with the exception of the combination of CA125 and HE4 in patients with stage II to IV disease. These findings suggest that HE4 alone and the combination of HE4 and CA125, as well as SMRP, are excellent candidates for further evaluation of their use in the detection of pre-clinical recurrent disease, response to therapy, prognostic indicators and pre-operative evaluation of endometrial cancer patients.

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Table 1

Serum levels of tumor markers among endometrial cancer patients and healthy individuals.

Tumor Marker	Controls (N = 156) Median (range)	Stage I Cancer (N = 122) Median (range)	P value*	All Cancer Stages (N = 171) Median (range)	P value*
CA125 (U/ml)	11.2 (3.3 – 73.6)	14.5 (3.0 – 432.9)	0.0001	16.6 (3.0 - 1,426.6)	<0.0001
HE4 (pM)	35.4 (18.0 - 127.8)	60.5 (1.1 – 1022.1)	<0.0001	71.5 (1.1 - 4,062.7)	<0.0001
CA72.4 (U/ml)	1.6 (0.9 - 24.4)	1.8 (0.9 - 280.3)	0.7927	1.9 (0.9 - 280.3)	0.1172
Serum SMRP (nM)	0.6 (0.1 - 2.2)	0.6 (0.0 - 13.3)	0.6053	0.6 (0.0 - 13.3)	0.8664

*Wilcoxon rank sum (Mann-Whitney) test p-values for comparison of controls vs. cancer patients

Table 2

Area under the receiver operating characteristic (ROC-AUC) curves for individual and combined tumor marker assays for all Stages of endometrial cancer.

Marker Combination	ROC-AUC (95% CI) (Controls vs. All Endometrial Cancers Stages)	
	All Stages	P-value for comparison of ROC-AUC to HE4
CA125	67.1% (61.3 - 72.9)	0.0007
HE4	78.7% (73.7 - 83.6)	---
CA72.4	55.0% (48.7 - 61.4)	<0.0001
SMRP	50.5% (44.3 - 56.8)	<0.0001
CA125 + HE4	79.4% (74.5 - 84.3)	0.4777
CA125 + CA72.4	66.5% (60.7 - 72.4)	0.0004
CA125 + SMRP	67.3% (61.6 - 73.1)	0.0010
HE4 + CA72.4	78.9% (73.9 - 83.8)	0.3066
HE4 + SMRP	78.8% (73.8 - 83.7)	0.3619
CA125 + HE4 + CA72.4	79.5% (74.6 - 84.4)	0.5289
CA125 + HE4 + SMRP	79.7% (74.8 - 84.5)	0.3654
CA125 + CA72.4 + SMRP	66.8% (61.0 - 72.6)	0.0005
HE4 + CA72.4 + SMRP	79.0% (74.0 - 83.9)	0.2993
CA125 + HE4 + CA72.4 + SMRP	79.7% (74.8 - 84.6)	0.4154

Table 3

Area under the receiver operating characteristic (ROC-AUC) curves for individual and combined tumor marker assays for Stage I and Stage II-IV endometrial cancers.

Marker Combination	ROC-AUC (95% CI) (Controls vs. Endometrial Cancers)			
	Stage I	p-value for comparison of ROC-AUC to HE4	Stages II-IV	p-value for comparison of ROC-AUC to HE4
CA125	63.8% (57.1 - 70.4)	0.0009	75.3% (67.1 - 83.6)	0.1125
HE4	76.7% (70.8 - 82.5)	---	83.6% (75.3 - 91.9)	---
CA72.4	50.9% (44.4 - 57.8)	<0.0001	65.3% (56.6 - 74.0)	0.0013
SMRP	51.8% (44.9 - 58.7)	<0.0001	52.6% (42.8 - 62.4)	0.0001
CA125 + HE4	76.7% (70.9 - 82.6)	0.9693	86.6% (79.3 - 94.0)	0.0157
CA125 + CA72.4	63.1% (56.4 - 69.7)	0.0004	76.5% (68.6 - 84.5)	0.1386
CA125 + SMRP	63.6% (56.9 - 70.2)	0.0007	78.2% (70.3 - 86.1)	0.3524
HE4 + CA72.4	76.9% (71.1 - 82.7)	0.5167	83.6% (75.3 - 91.9)	0.8103
HE4 + SMRP	76.7% (70.9 - 82.5)	0.7413	87.4% (81.1 - 93.7)	0.0496
CA125 + HE4 + CA72.4	76.9% (71.0 - 82.7)	0.9898	86.3% (78.8 - 93.8)	0.0268
CA125 + HE4 + SMRP	76.8% (70.9 - 82.6)	0.9170	89.8% (84.2 - 95.3)	0.0087
CA125 + CA72.4 + SMRP	62.8% (56.0 - 69.5)	0.0003	78.9% (71.2 - 86.6)	0.3943
HE4 + CA72.4 + SMRP	76.9% (71.1 - 82.7)	0.6121	87.1% (80.6 - 93.5)	0.0794
CA125 + HE4 + CA72.4 + SMRP	76.9% (71.1 - 82.8)	0.9631	89.3% (83.6 - 95.0)	0.0132

Table 4

Sensitivities for individual and combined tumor marker assays for all endometrial cancer stages.

Marker Combination	Controls vs. Endometrial Cancer - All Stages Average Sensitivity as Set Specificity of:		
	90%	95%	98%
CA125	34.6%	24.6%	15.6%
HE4	55.0%	45.5%	36.7%
CA72.4	10.2%	7.3%	4.4%
SMRP	11.3%	7.1%	3.1%
CA125 + HE4	57.3%	50.1%	39.8%
CA125 + CA72.4	34.5%	24.6%	16.7%
CA125 + SMRP	34.1%	25.1%	15.6%
HE4 + CA72.4	55.0%	45.0%	36.6%
HE4 + SMRP	53.8%	44.8%	36.3%
CA125 + HE4 + CA72.4	57.2%	48.9%	40.6%
CA125 + HE4 + SMRP	56.6%	48.4%	38.2%
CA125 + CA72.4 + SMRP	34.8%	24.7%	16.8%
HE4 + CA72.4 + SMRP	54.3%	44.8%	36.3%
CA125 + HE4 + CA72.4 + SMRP	57.3%	47.5%	40.0%

Table 5

Sensitivities for individual and combined tumor marker assays in stage I endometrial cancer.

Marker Combination	Controls vs. Endometrial Cancers – Stage I Average Sensitivity at Set Specificity of:		
	90%	95%	98%
CA125	30.0%	20.8%	12.9%
HE4	48.4%	37.9%	29.3%
CA72.4	7.6%	5.8%	3.8%
SMRP	14.4%	8.7%	4.4%
CA125 + HE4	51.6%	41.7%	34.4%
CA125 + CA72.4	29.9%	20.6%	13.6%
CA125 + SMRP	28.8%	20.5%	13.1%
HE4 + CA72.4	48.4%	37.9%	29.8%
HE4 + SMRP	48.3%	38.0%	29.2%
CA125 + HE4 + CA72.4	51.7%	40.7%	34.5%
CA125 + HE4 + SMRP	51.6%	41.7%	33.7%
CA125 + CA72.4 + SMRP	28.6%	20.1%	14.6%
HE4 + CA72.4 + SMRP	48.4%	37.9%	29.8%
CA125 + HE4 + CA72.4 + SMRP	51.7%	39.1%	34.6%

Table 6

Sensitivities for individual and combined tumor marker assays in stage II – IV endometrial cancer.

Marker Combination	Controls vs. Endometrial Cancers – Stage II-IV Average Sensitivity at Set Specificity of:		
	90%	95%	98%
CA125	46.7%	32.9%	22.4%
HE4	71.4%	64.9%	55.1%
CA72.4	17.6%	12.2%	7.0%
SMRP	16.6%	16.2%	12.5%
CA125 + HE4	73.0%	69.7%	52.7%
CA125 + CA72.4	38.8%	30.6%	24.5%
CA125 + SMRP	47.0%	39.4%	20.4%
HE4 + CA72.4	71.4%	65.3%	55.1%
HE4 + SMRP	73.4%	59.5%	49.0%
CA125 + HE4 + CA72.4	72.5%	69.4%	53.5%
CA125 + HE4 + SMRP	73.3%	63.3%	57.3%
CA125 + CA72.4 + SMRP	49.0%	30.8%	27.3%
HE4 + CA72.4 + SMRP	73.5%	61.0%	49.1%
CA125 + HE4 + CA72.4 + SMRP	73.4%	62.1%	57.3%