US 20100221752A2

(19) **United States**

(12) **Patent Application Publication**

Gold et al.

(10) **Pub. No.: US 2010/0221752 A2**

(43) **Pub. Date: Sep. 2, 2010**

REPUBLICATION

(54) **OVARIAN CANCER BIOMARKERS AND USES THEREOF**

(75) Inventors: **Larry Gold**, Boulder, CO (US); **Marty Stanton**, Boulder, CO (US); **Edward Brody**, Boulder, CO (US); **Rachel Ostroff**, Westminister, CO (US); **Dominic Zichi**, Boulder, CO (US); **Alex Stewart**, Waltham, MA (US)

Correspondence Address:
SWANSON & BRATSCHUN, L.L.C.
8210 SOUTHPARK TERRACE
LITTLETON, CO 80120 (UNITED STATES)

(73) Assignee: **SomaLogic, Inc.**, Boulder, CO (US)

(21) Appl. No.: **12/574,341**

(22) Filed: **Oct. 6, 2009**

Prior Publication Data

(65) US 2010/0086948 A1 Apr. 8, 2010

Related U.S. Application Data

(60) Provisional application No. 61/103,149, filed on Oct. 6, 2008.

Publication Classification

(51) **Int. Cl.**

G01N 33/567	(2006.01)
G01N 33/53	(2006.01)
G06F 19/00	(2006.01)
G06F 17/18	(2006.01)

(52) **U.S. Cl.** **435/7.21**; 436/86; 436/94; 702/19; 702/181

(57) **ABSTRACT**

The present application includes biomarkers, methods, devices, reagents, systems, and kits for the detection and diagnosis of ovarian cancer. In one aspect, the application provides biomarkers that can be used alone or in various combinations to diagnose ovarian cancer or permit the differential diagnosis of a pelvic mass as benign or malignant. In another aspect, methods are provided for diagnosing ovarian cancer in an individual, where the methods include detecting, in a biological sample from an individual, at least one biomarker value corresponding to at least one biomarker selected from the group of biomarkers provided in Table 1, wherein the individual is classified as having ovarian cancer, or the likelihood of the individual having ovarian cancer is determined, based on the at least one biomarker value.

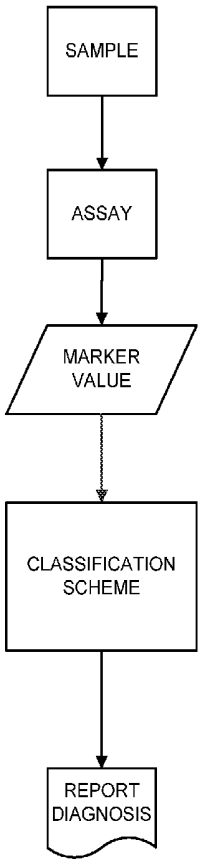


FIG. 1A

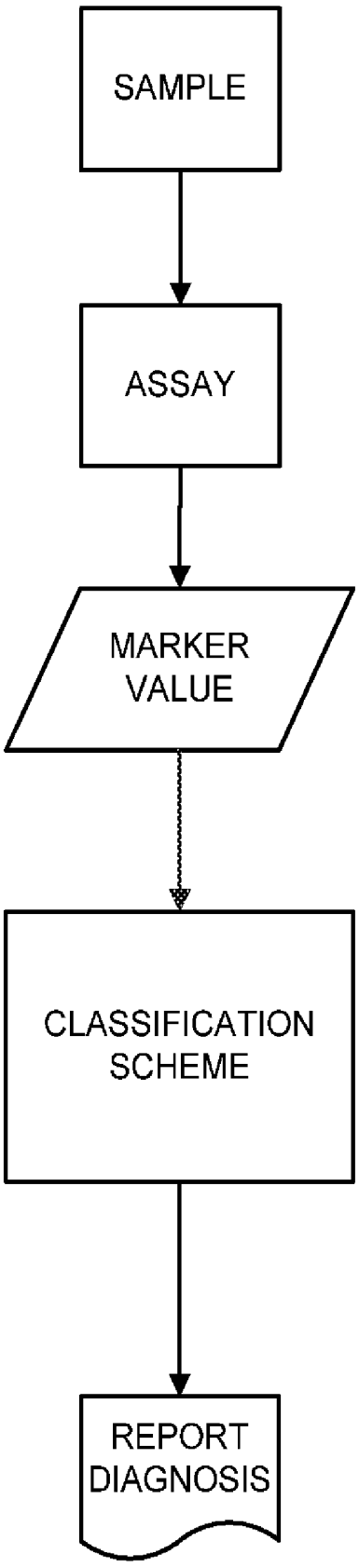

SAMPLE
ASSAY
MARKER VALUE
CLASSIFICATION SCHEME
REPORT DIAGNOSIS

FIG. 1B

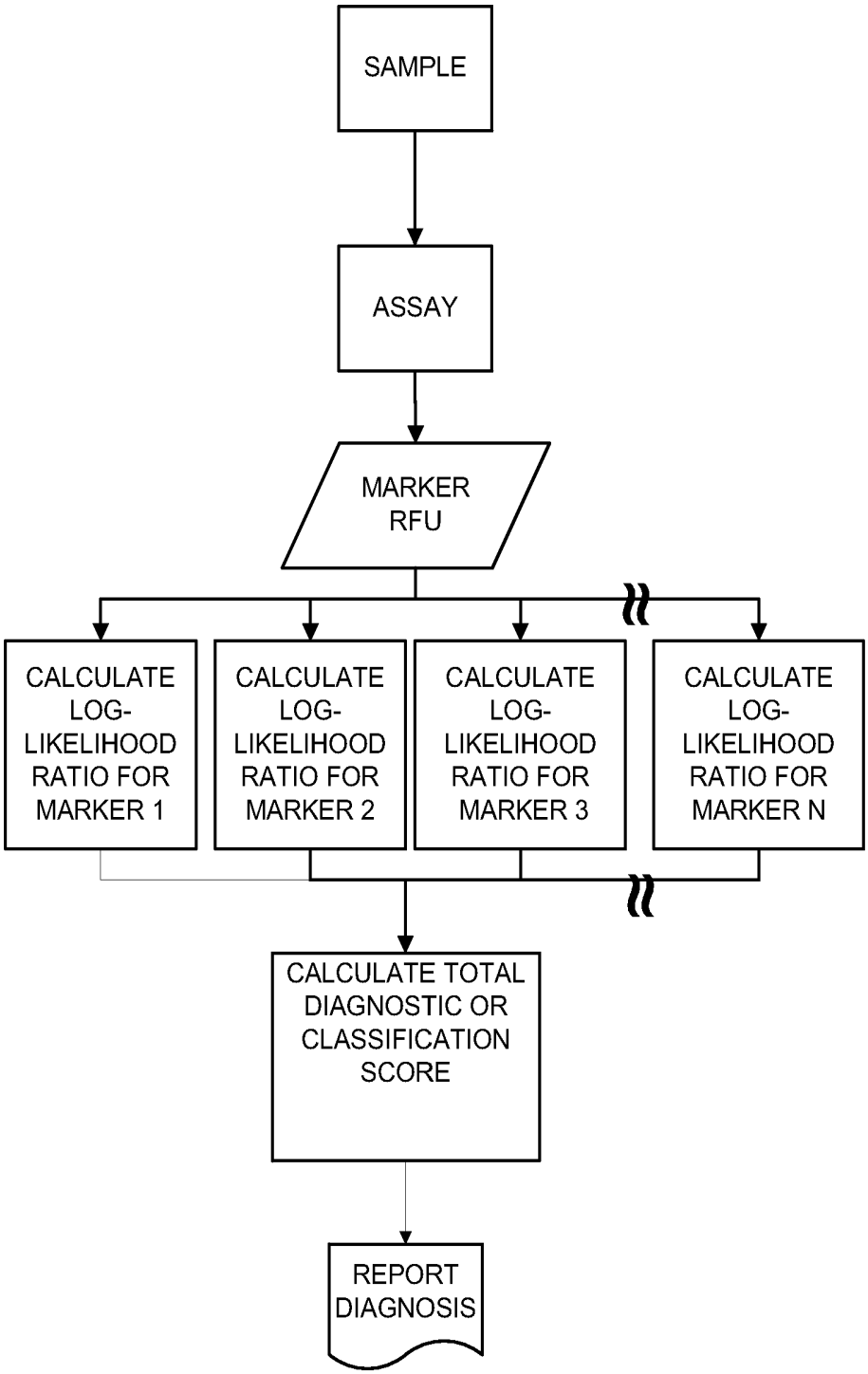

SAMPLE
ASSAY
MARKER RFU
CALCULATE LOG-LIKELIHOOD RATIO FOR MARKER 1
CALCULATE LOG-LIKELIHOOD RATIO FOR MARKER 2
CALCULATE LOG-LIKELIHOOD RATIO FOR MARKER 3
CALCULATE LOG-LIKELIHOOD RATIO FOR MARKER N
CALCULATE TOTAL DIAGNOSTIC OR CLASSIFICATION SCORE
REPORT DIAGNOSIS

FIG. 2

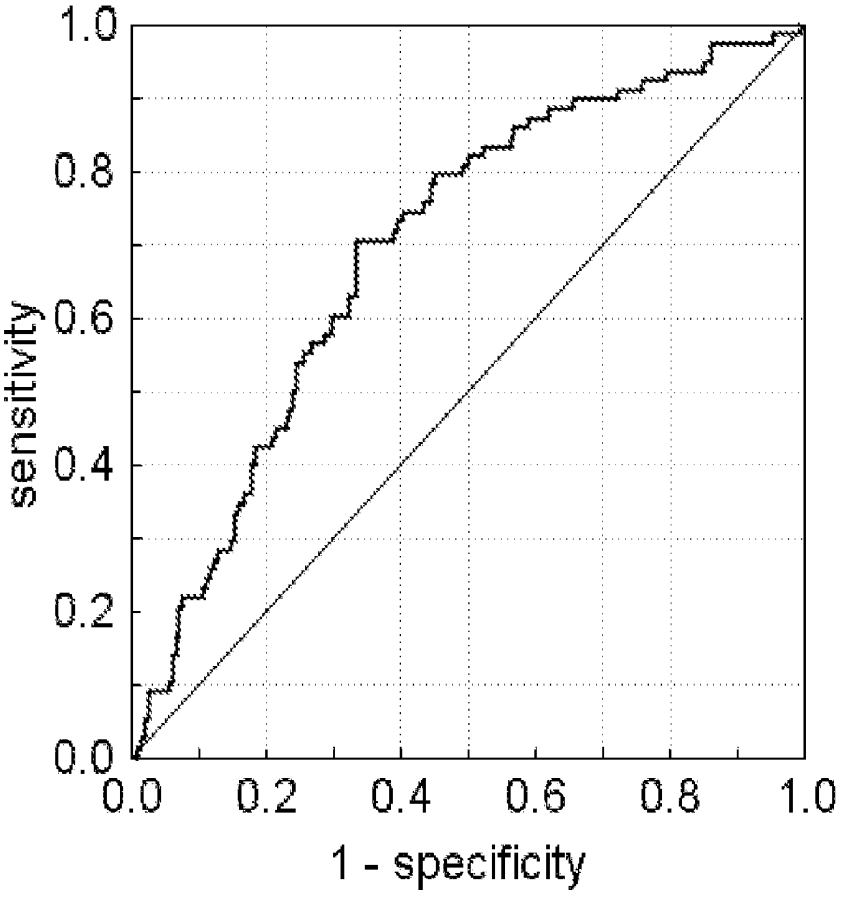


FIG. 3

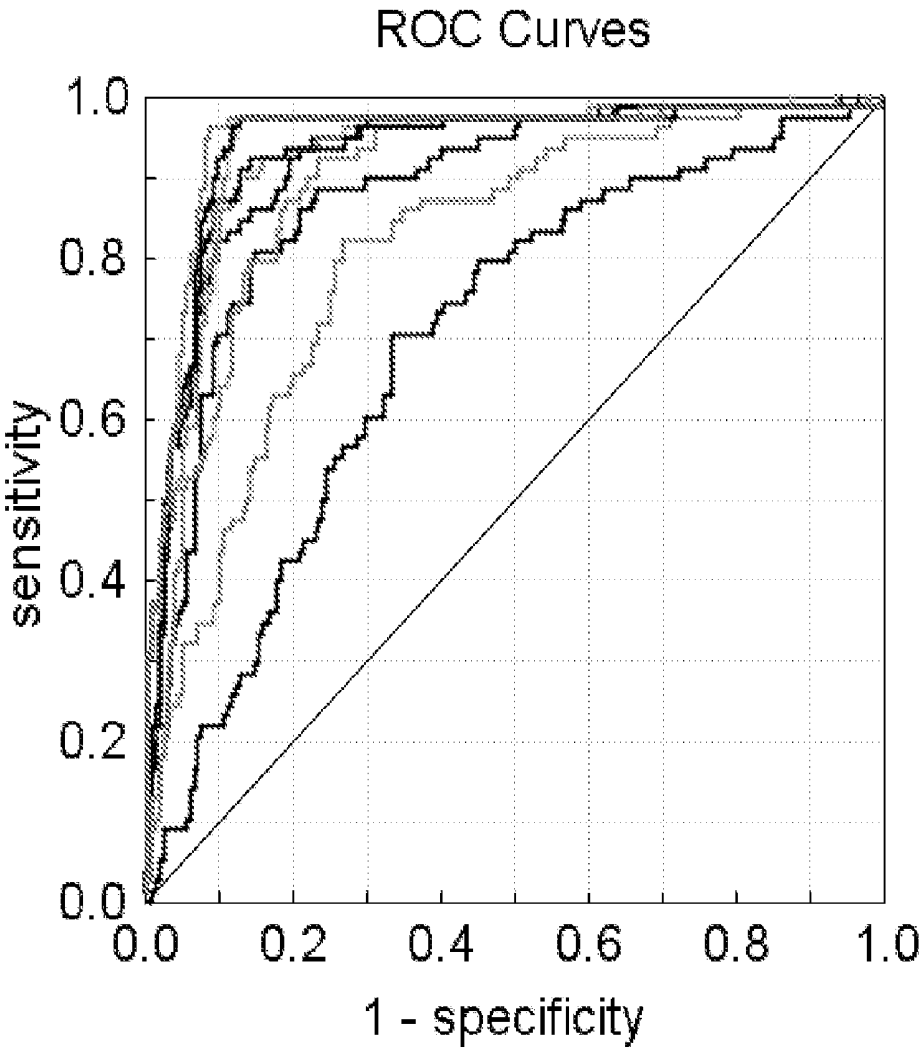


FIG. 4

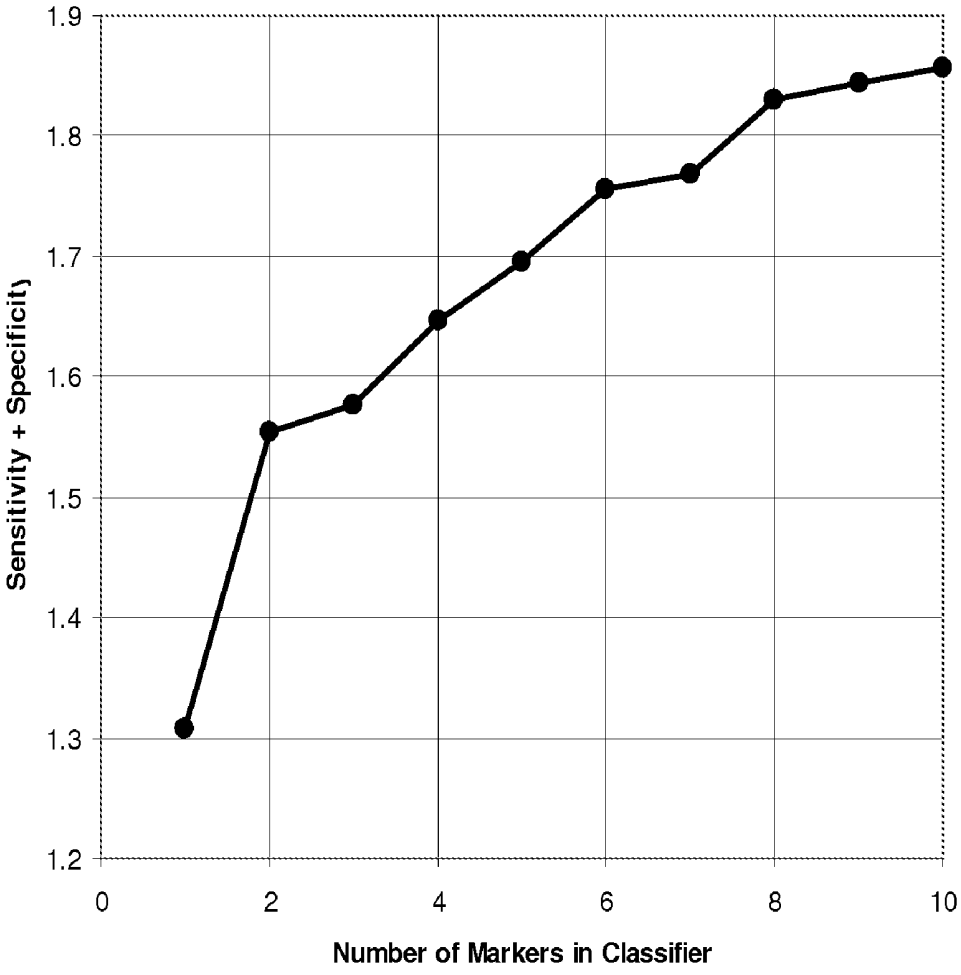

1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
Sensitivity + Specificity
0
2
4
6
8
10
Number of Markers in Classifier

FIG. 5

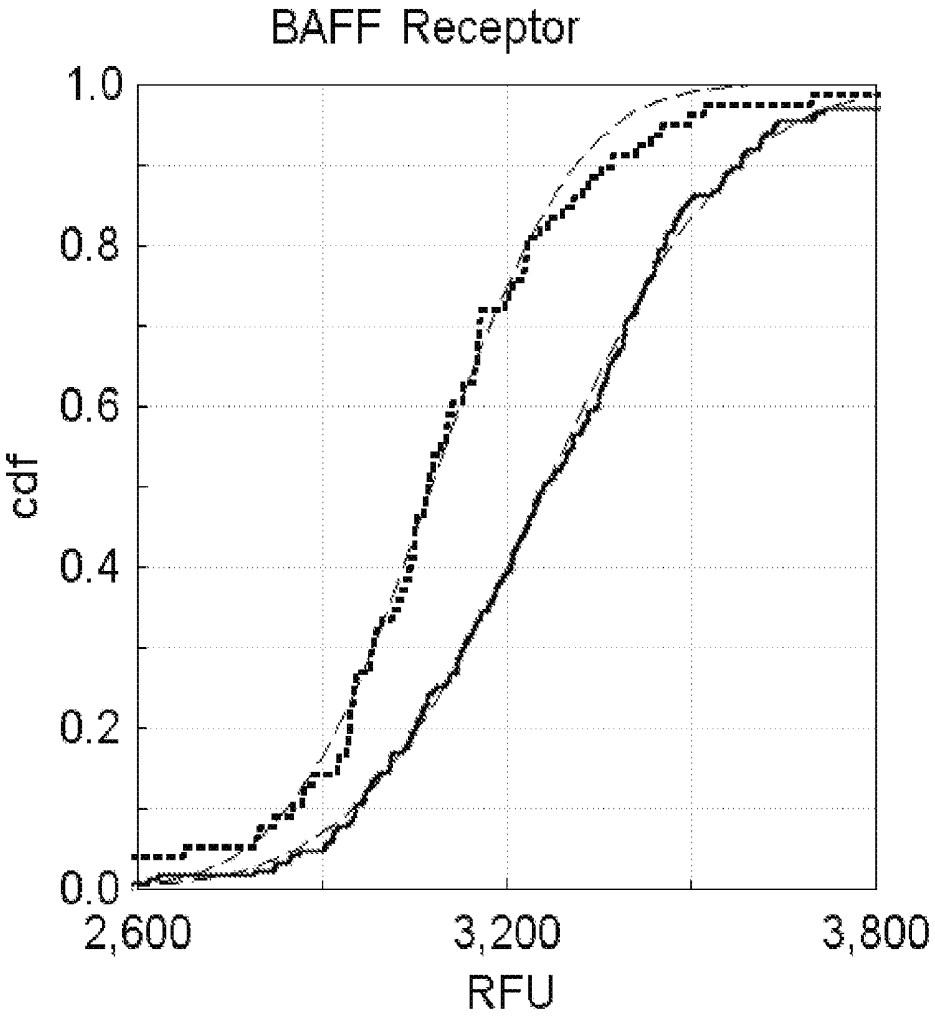


FIG. 6

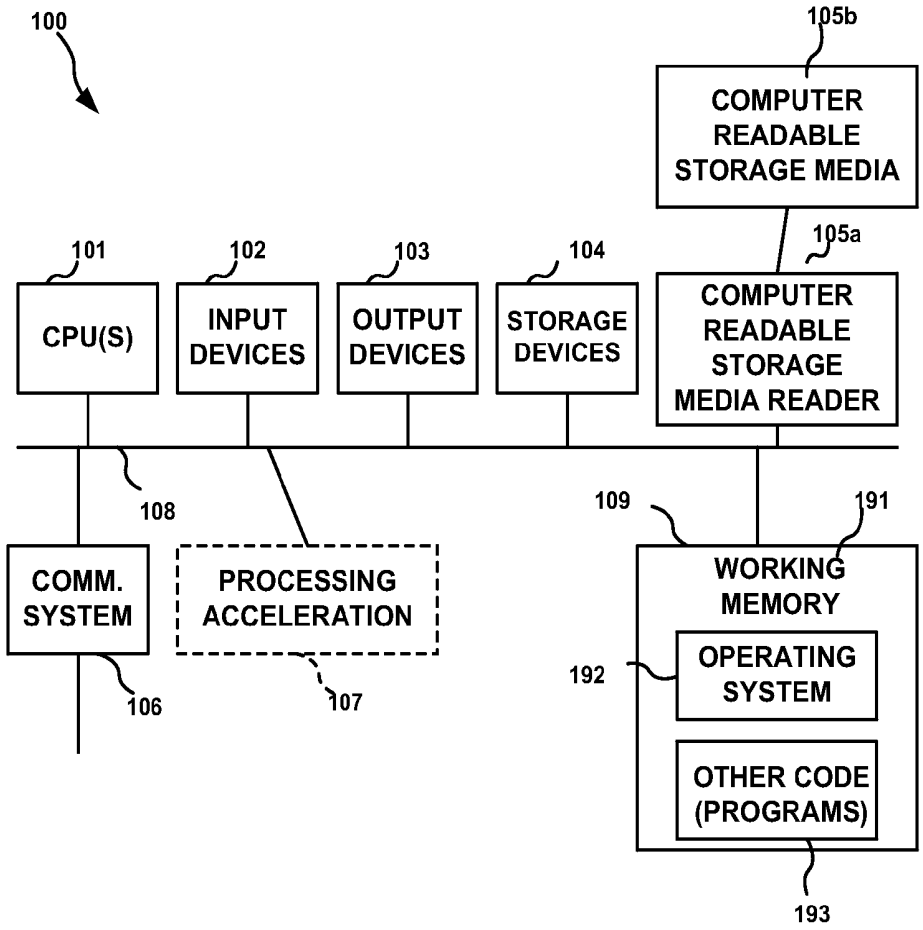

100
105b
COMPUTER READABLE STORAGE MEDIA
105a
101
102
103
104
CPU(S)
INPUT DEVICES
OUTPUT DEVICES
STORAGE DEVICES
COMPUTER READABLE STORAGE MEDIA READER
108
109
191
COMM. SYSTEM
PROCESSING ACCELERATION
WORKING MEMORY
192
OPERATING SYSTEM
OTHER CODE (PROGRAMS)
106
107
193

FIG. 7

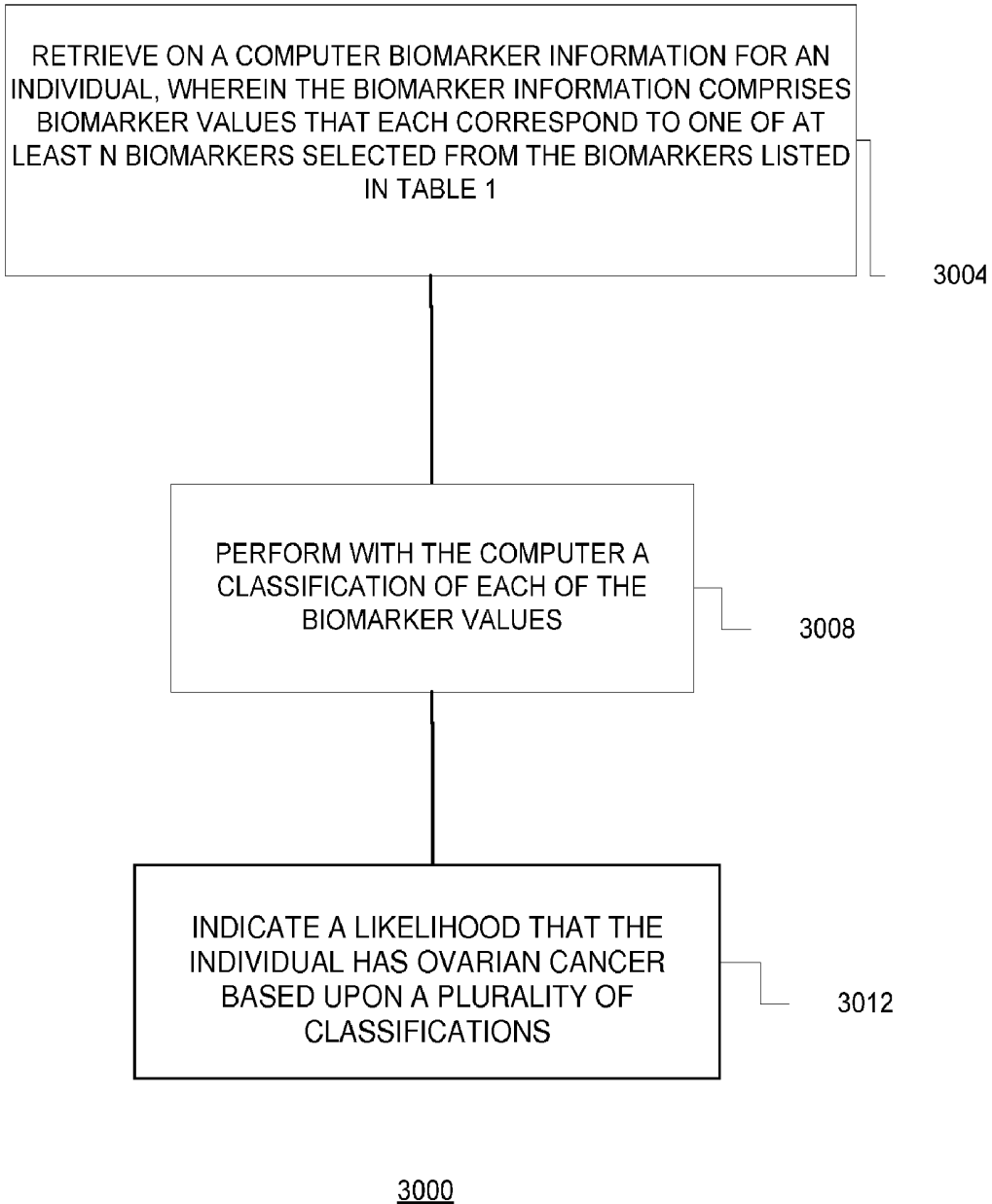

RETRIEVE ON A COMPUTER BIOMARKER INFORMATION FOR AN INDIVIDUAL, WHEREIN THE BIOMARKER INFORMATION COMPRISES BIOMARKER VALUES THAT EACH CORRESPOND TO ONE OF AT LEAST N BIOMARKERS SELECTED FROM THE BIOMARKERS LISTED IN TABLE 1
3004
PERFORM WITH THE COMPUTER A CLASSIFICATION OF EACH OF THE BIOMARKER VALUES
3008
INDICATE A LIKELIHOOD THAT THE INDIVIDUAL HAS OVARIAN CANCER BASED UPON A PLURALITY OF CLASSIFICATIONS
3012
3000

FIG. 8

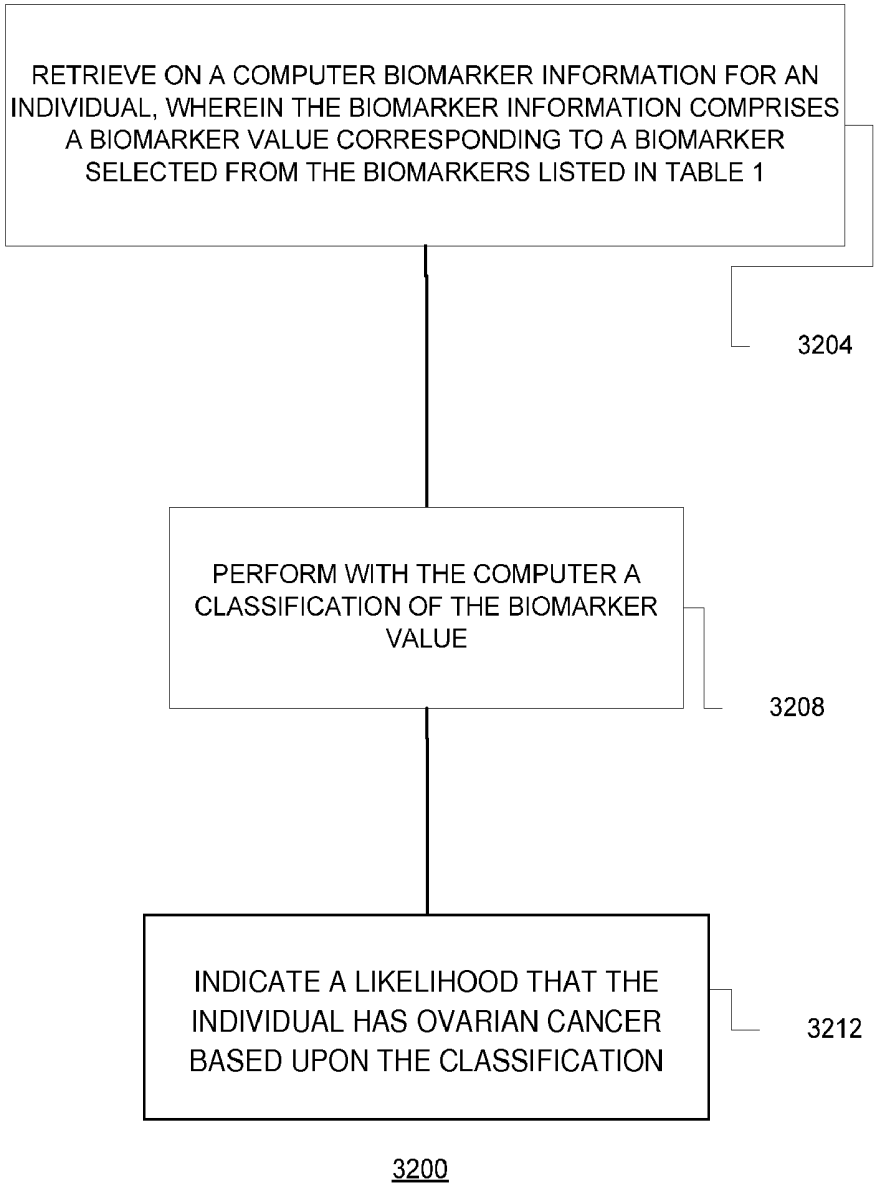
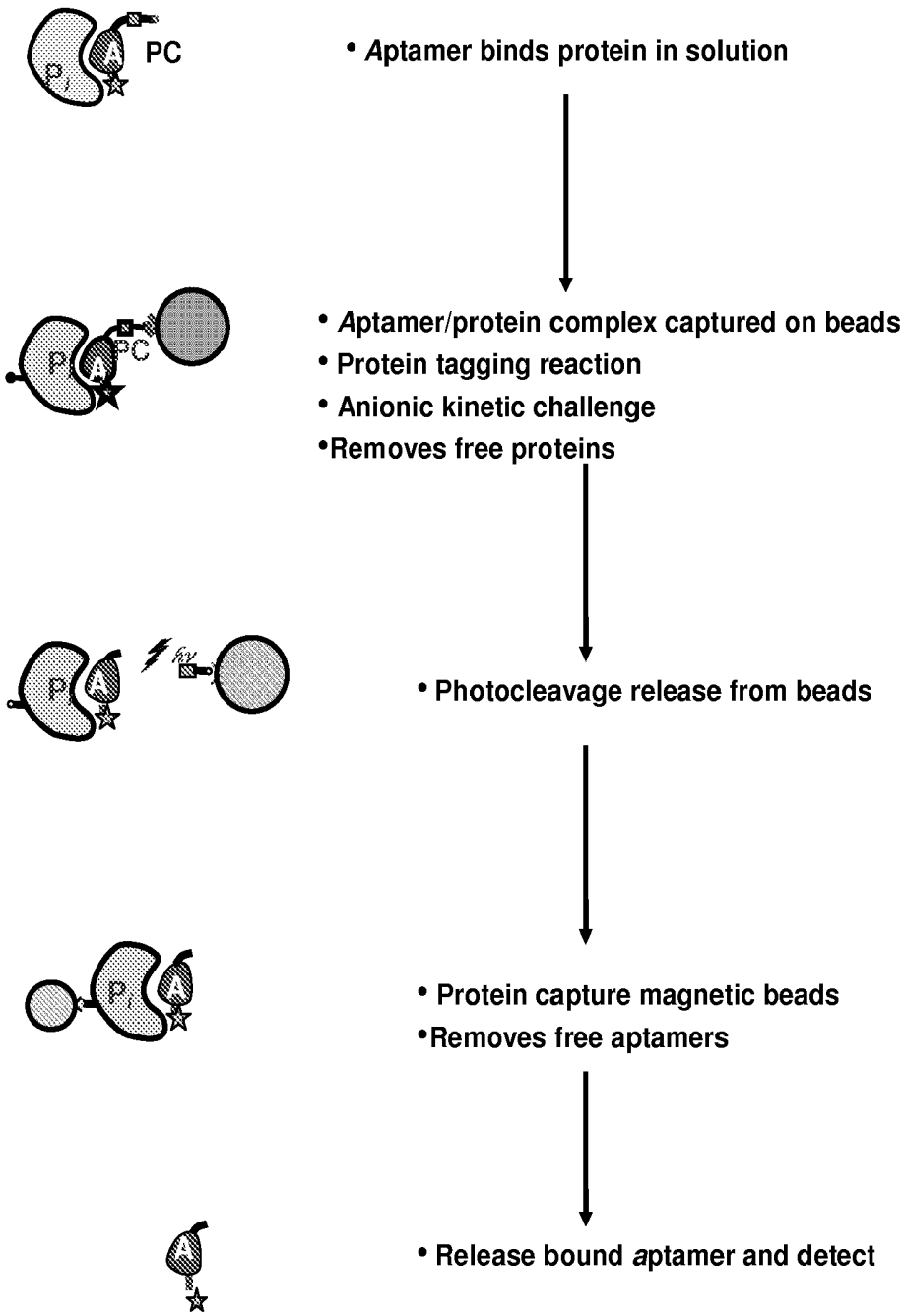

RETRIEVE ON A COMPUTER BIOMARKER INFORMATION FOR AN INDIVIDUAL, WHEREIN THE BIOMARKER INFORMATION COMPRISES A BIOMARKER VALUE CORRESPONDING TO A BIOMARKER SELECTED FROM THE BIOMARKERS LISTED IN TABLE 1
3204
PERFORM WITH THE COMPUTER A CLASSIFICATION OF THE BIOMARKER VALUE
3208
INDICATE A LIKELIHOOD THAT THE INDIVIDUAL HAS OVARIAN CANCER BASED UPON THE CLASSIFICATION
3212
3200

FIG. 9


PC
• Aptamer binds protein in solution
• Aptamer/protein complex captured on beads
• Protein tagging reaction
• Anionic kinetic challenge
•Removes free proteins
• Photocleavage release from beads
• Protein capture magnetic beads
•Removes free aptamers
• Release bound aptamer and detect

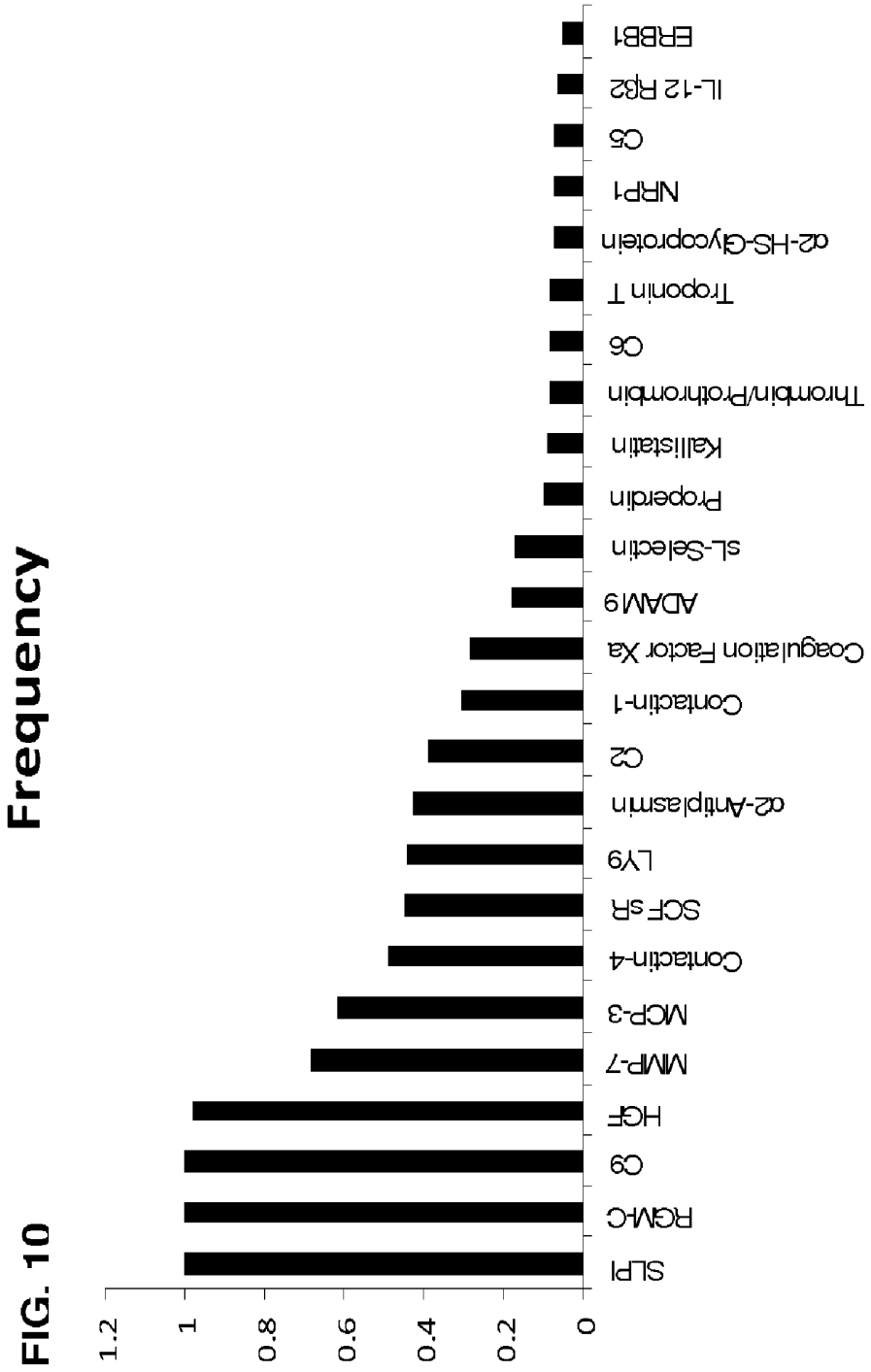

Frequency
1.2
1
0.8
0.6
0.4
0.2
0
SLPI
RGMC
C9
HGF
MMP-7
MCP-3
Contactin-4
SCF sR
LY9
α2-Antiplasmin
C2
Contactin-1
Coagulation Factor Xa
ADAM9
sL-Selectin
Properdin
Kallistatin
Thrombin/Prothrombin
C6
Troponin T
α2-HS-Glycoprotein
NRP1
C5
IL-12 Rβ2
ERBB1

FIG. 10

FIG. 11

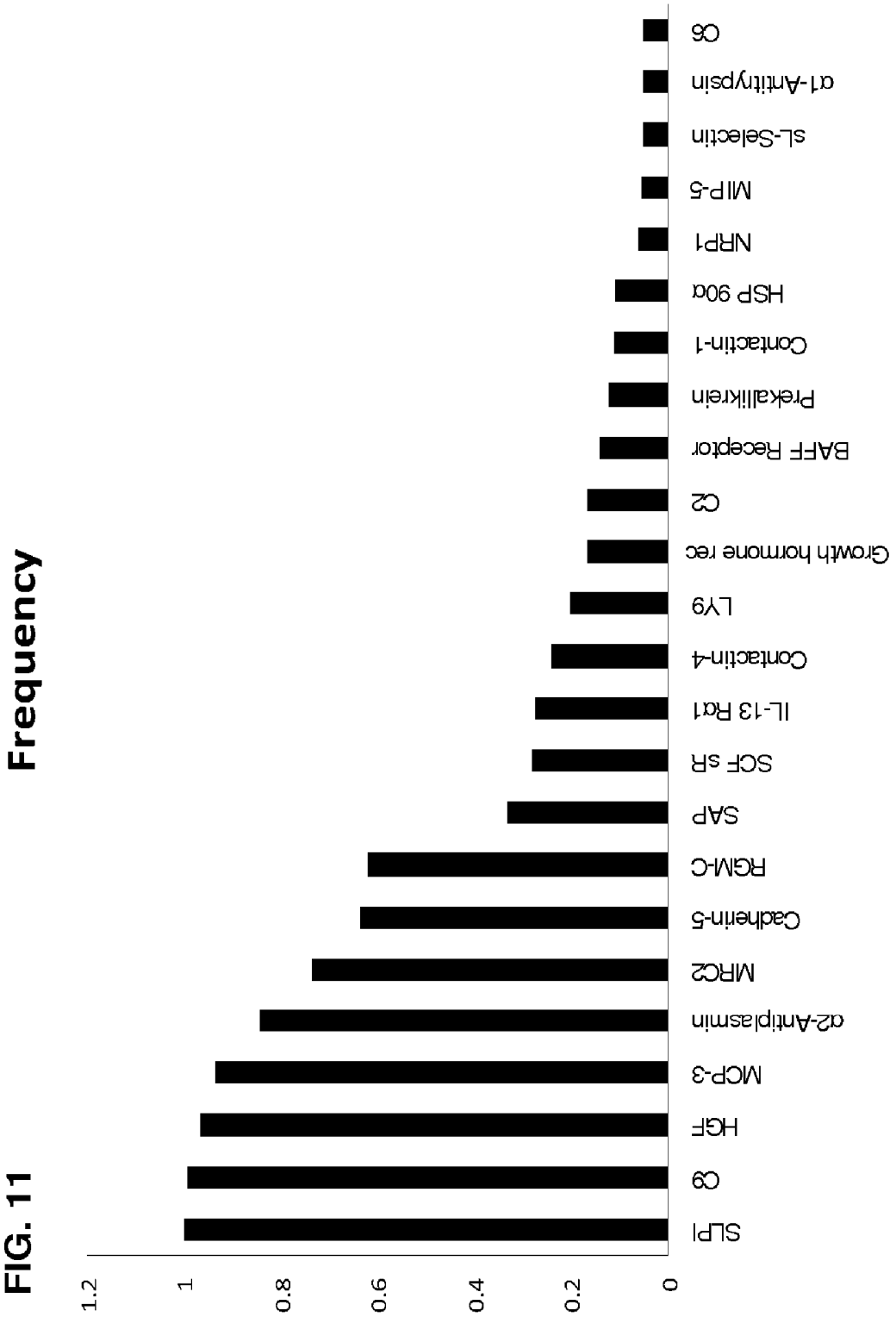

Frequency
1.2
1
0.8
0.6
0.4
0.2
0
SLPI
C9
HGF
MCP-3
α2-Antiplasmin
MRC2
Cadherin-5
RGM-C
SAP
SCF sR
IL-13 Ra1
Contactin-4
LY9
Growth hormone rec
C2
BAFF Receptor
Prekallikrein
Contactin-1
HSP 90α
NRP1
MIP-5
sL-Selectin
α1-Antitrypsin
C6

FIG. 12

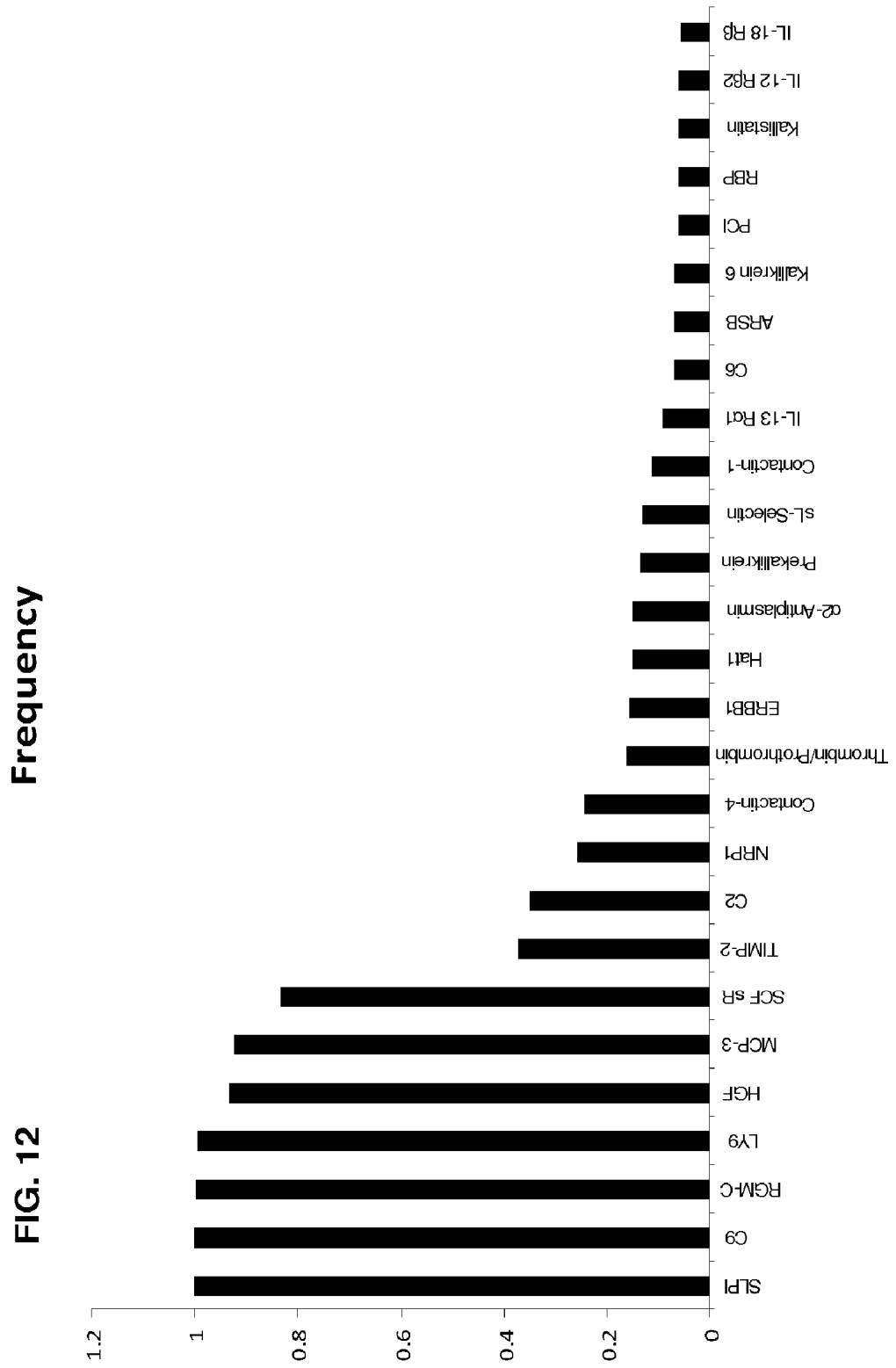

Frequency
1.2
1
0.8
0.6
0.4
0.2
0
SLPI
C9
RGMHC
LY9
HGF
MCP-3
SCF sR
TIMP-2
C2
NRP1
Contactin-4
Thrombin/Prothrombin
ERBB1
Hatl
α2-Antiplasmin
Prekallikrein
sL-Selectin
Contactin-1
IL-13 Rα1
C6
ARSB
Kallikrein 6
PCI
RBP
Kallistatin
IL-12 Rβ2
IL-18 Rβ

FIG. 13

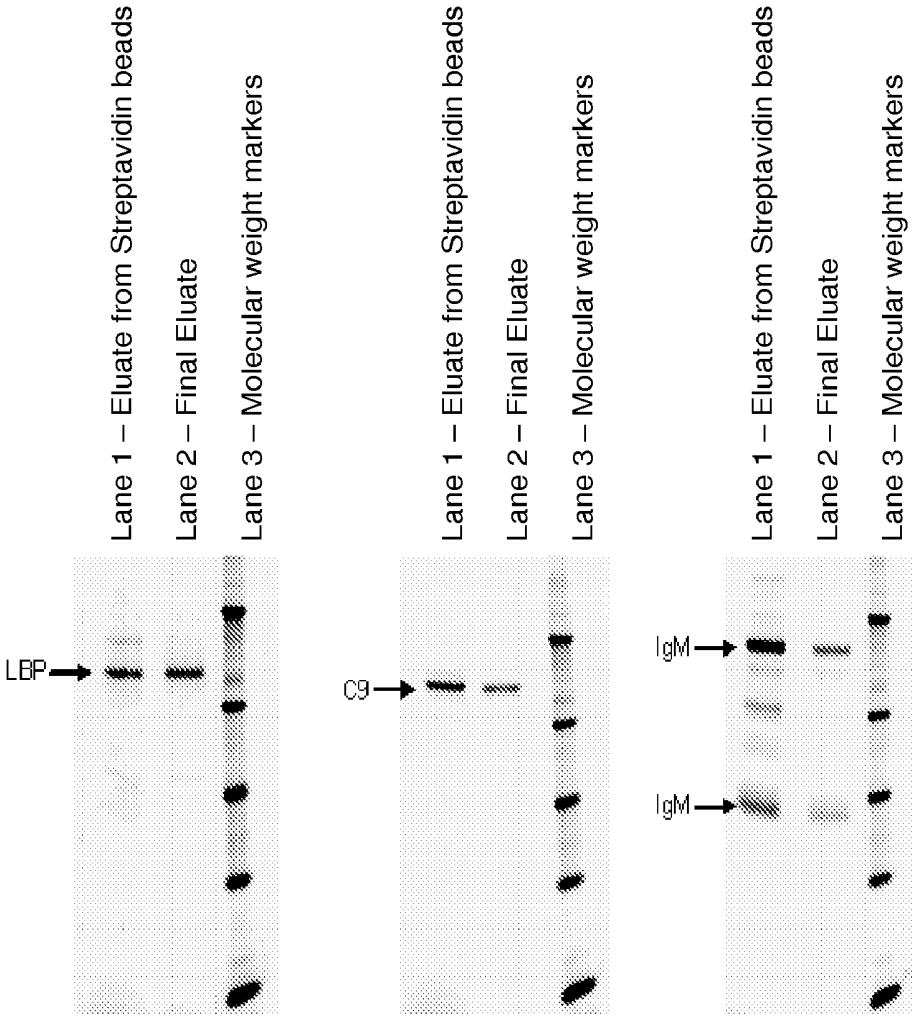

Lane 1 – Eluate from Streptavidin beads
Lane 2 – Final Eluate
Lane 3 – Molecular weight markers
LBP
Lane 1 – Eluate from Streptavidin beads
Lane 2 – Final Eluate
Lane 3 – Molecular weight markers
C9
Lane 1 – Eluate from Streptavidin beads
Lane 2 – Final Eluate
Lane 3 – Molecular weight markers
IgM
IgM

FIG. 14A

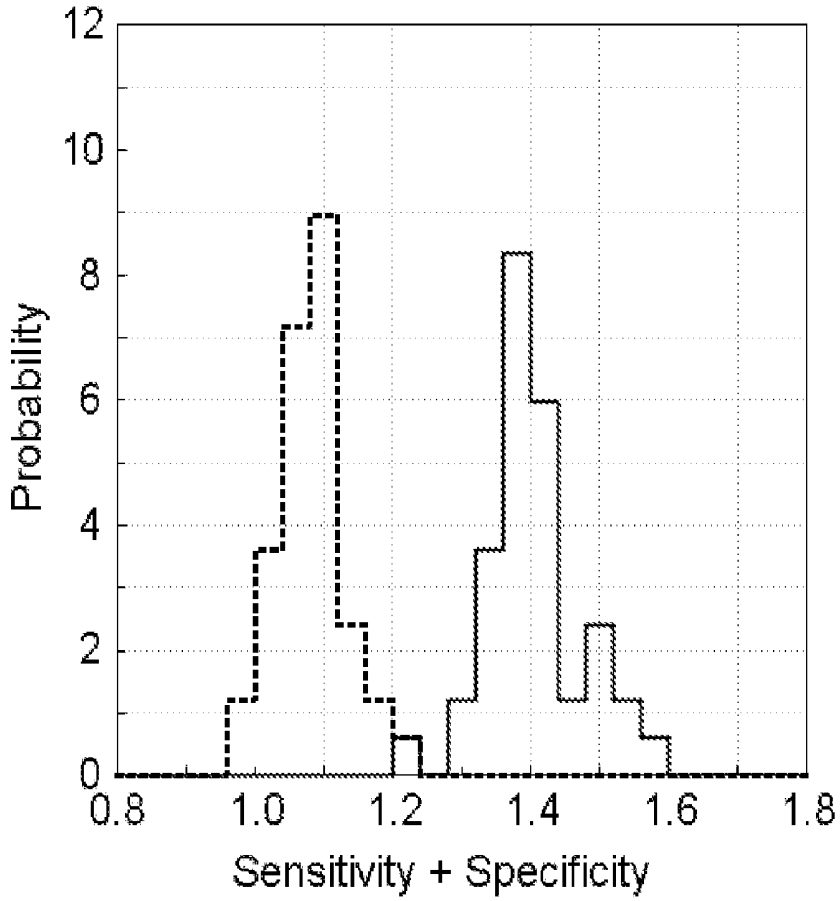

12
10
8
6
4
2
0
Probability
0.8
1.0
1.2
1.4
1.6
1.8
Sensitivity + Specificity

FIG. 14B

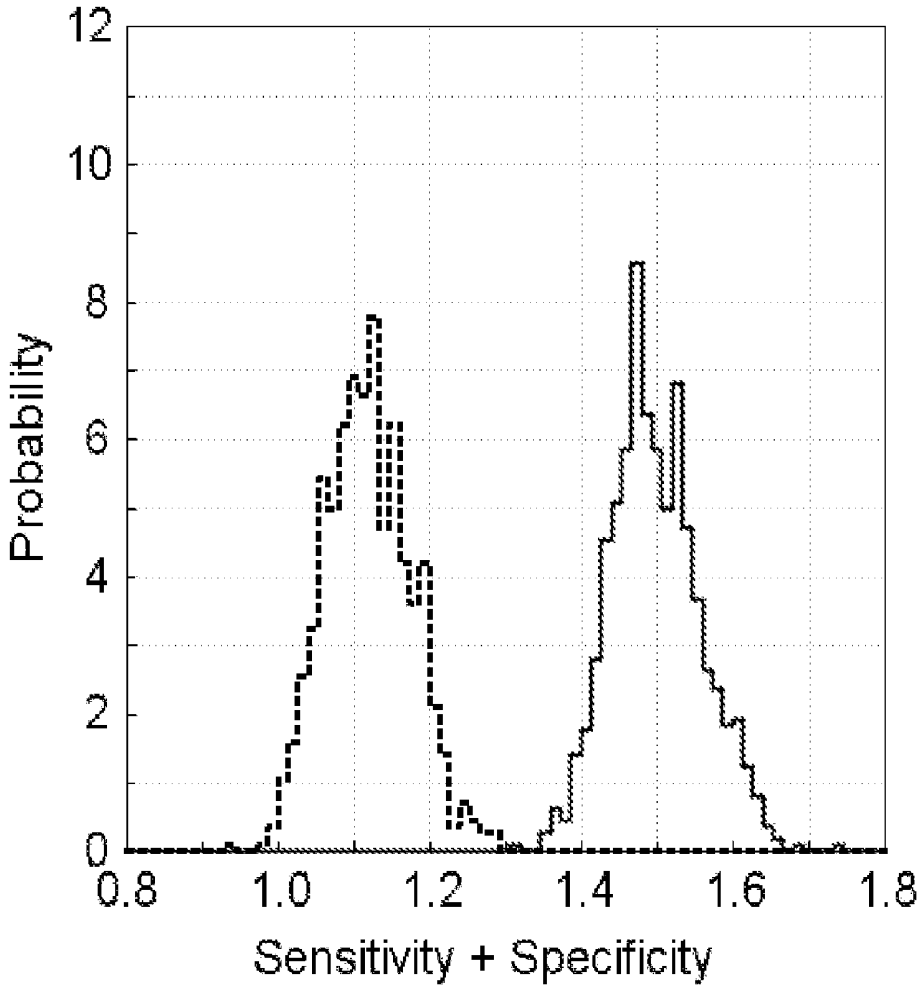

12
10
8
6
4
2
0
Probability
0.8
1.0
1.2
1.4
1.6
1.8
Sensitivity + Specificity

FIG. 14C

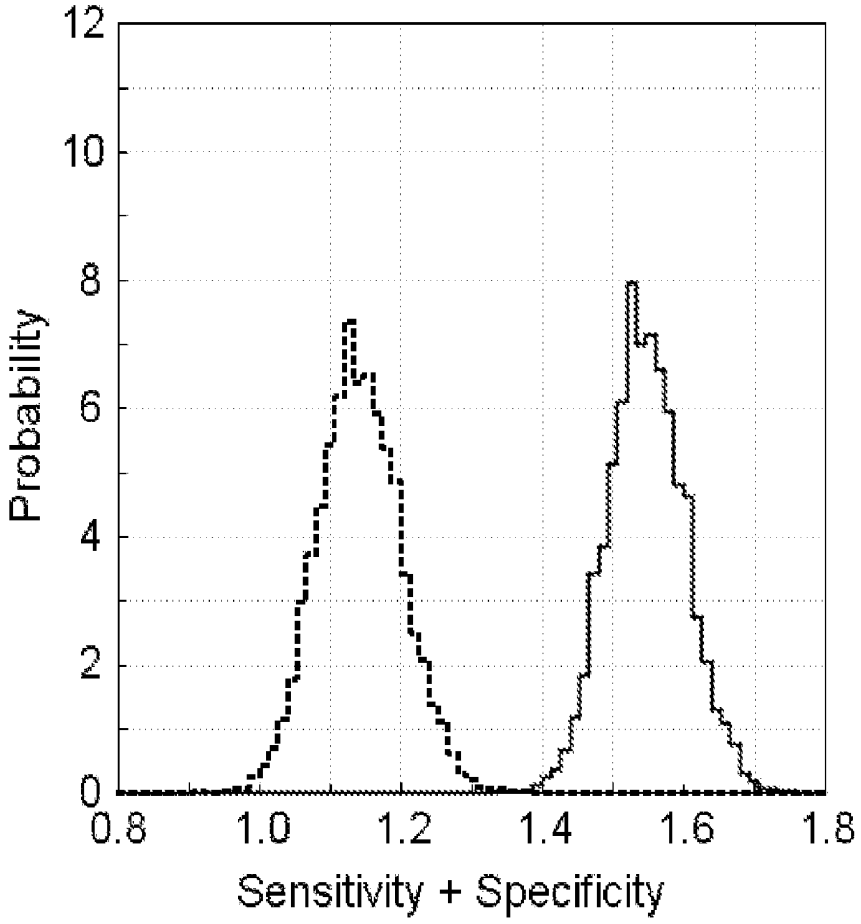

12
10
8
6
4
2
0
Probability
0.8
1.0
1.2
1.4
1.6
1.8
Sensitivity + Specificity

FIG. 15

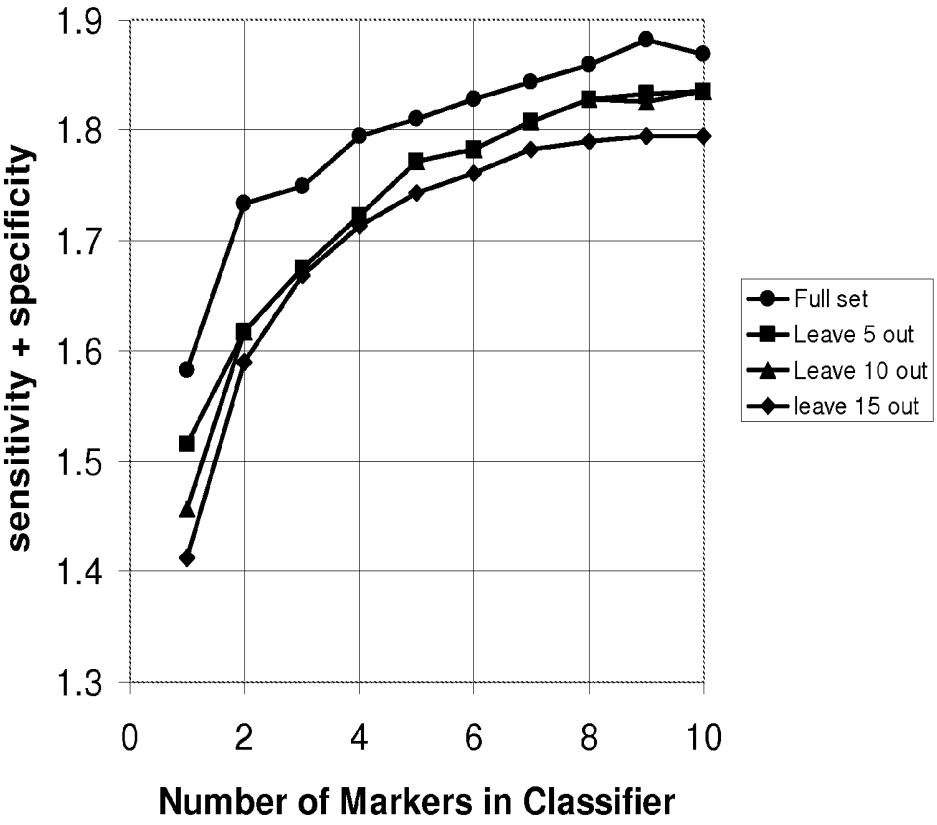

1.9
1.8
1.7
1.6
1.5
1.4
1.3
sensitivity + specificity
0
2
4
6
8
10
Number of Markers in Classifier
Full set
Leave 5 out
Leave 10 out
leave 15 out

FIG. 16A

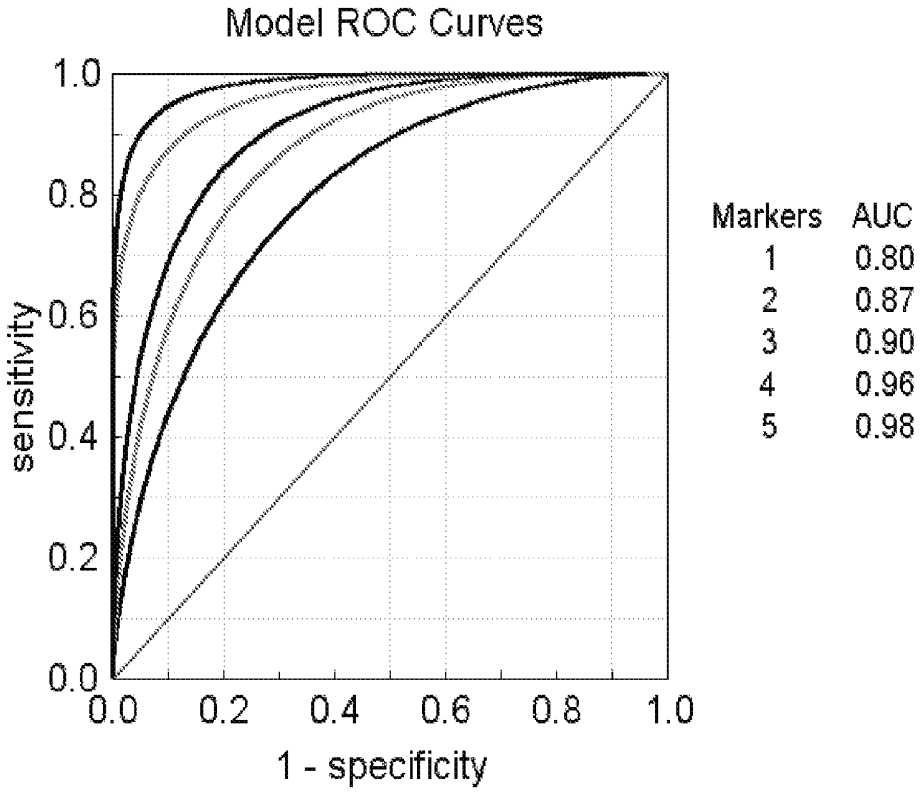
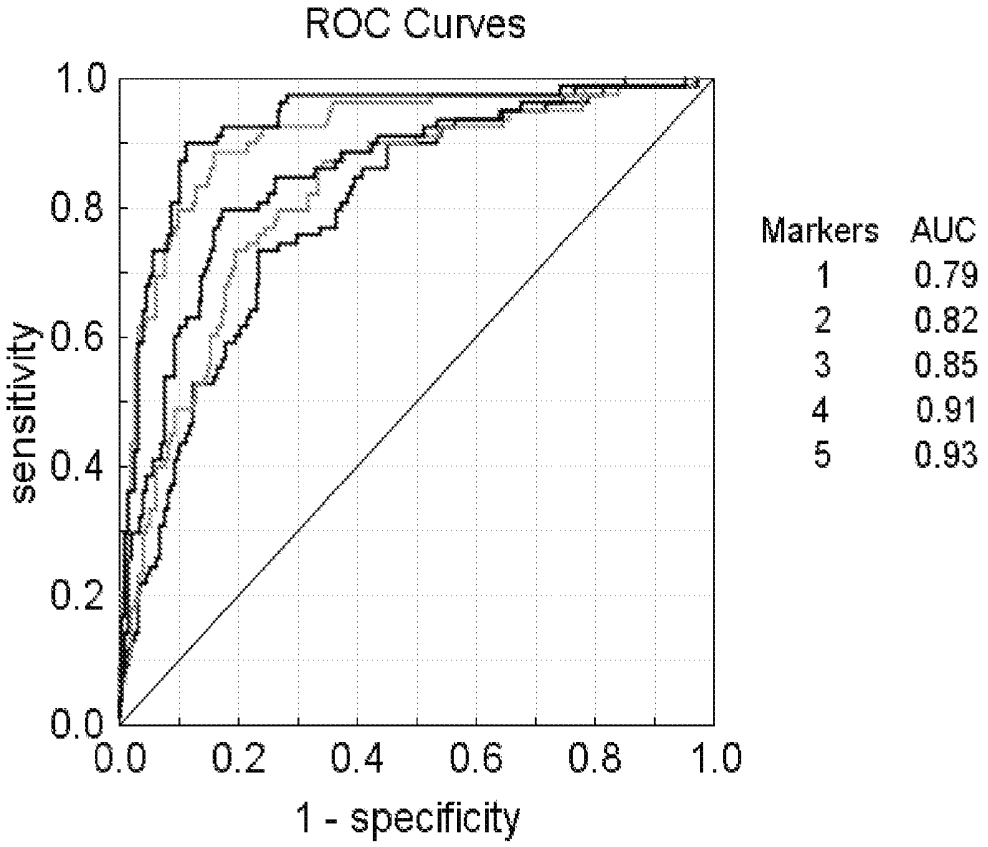

Model ROC Curves
sensitivity
1 - specificity
0.0
0.2
0.4
0.6
0.8
1.0
Markers AUC
1 0.80
2 0.87
3 0.90
4 0.96
5 0.98

FIG. 16B


ROC Curves
sensitivity
1 - specificity
0.0
0.2
0.4
0.6
0.8
1.0
Markers AUC
1 0.79
2 0.82
3 0.85
4 0.91
5 0.93

OVARIAN CANCER BIOMARKERS AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Ser. No. 61/103,149, filed Oct. 6, 2008, entitled "Multiplexed analyses of cancer samples", which is incorporated herein by reference in its entirety for all purposes.

FIELD OF THE INVENTION

[0002] The present application relates generally to the detection of biomarkers and the diagnosis of cancer in an individual and, more specifically, to one or more biomarkers, methods, devices, reagents, systems, and kits for diagnosing cancer, more particularly ovarian cancer, in an individual.

BACKGROUND

[0003] The following description provides a summary of information relevant to the present application and is not an admission that any of the information provided or publications referenced herein is prior art to the present application.

[0004] Ovarian cancer is the eighth most common cancer in women and the fifth leading cause of cancer-related deaths in women in the United States. Of all females born in the United States, one of every 70 will develop ovarian cancer and one of every 100 will die from this disease. The American Cancer Society estimates that approximately 21,550 women will be diagnosed with ovarian cancer in 2009 (American Cancer Society. Cancer Facts & Figures 2009. Atlanta: American Cancer Society; 2009). It is estimated that 14,600 women will die from this disease in 2009.

[0005] The survival rate and quality of patient life are improved the earlier ovarian cancer is detected. There is currently no sufficiently accurate screening test proven to be effective in the early detection of ovarian cancer. Thus, a pressing need exists for sensitive and specific methods for detecting ovarian cancer, particularly early-stage ovarian cancer.

[0006] Approximately 7% of the female population is at increased risk for ovarian cancer, based on genetic or family history. The risk for ovarian cancer increases with age. Women who have had breast cancer or who have a family history of breast or ovarian cancer are at increased risk. Inherited mutations in BRCA1 or BRCA2 genes increase risk. Ovarian cancer incidence rates are highest in Western industrialized countries.

[0007] Between 75% and 85% of ovarian cancers are diagnosed at an advanced stage. There is no consistent, reliable, non-invasive test to signal the presence of ovarian cancer. Pelvic examination only occasionally detects ovarian cancer, generally when the disease is advanced. Symptoms are often vague or nonexistent until late stages of the disease. Symptomatic women report frequent (>12 times/month) abdominal pain, bloating, increased girth, difficulty eating or feeling full quickly (Goff et al. Cancer 2007; 109:221). Trans-vaginal ultrasound and serum CA 125 levels have been tested as a screen for ovarian cancer and have not been found satisfactory. A laparotomy is required when ovarian cancer is suspected. The outcome of ovarian cancer patients operated on by a gynecology oncology surgical specialist is improved compared to a general gynecological surgeon, demonstrating that need for differential diagnosis of ovarian cancer from a suspicious pelvic mass prior to surgery. Goff reported on over 10,000 women in nine states undergoing surgery for a suspicious pelvic mass. Among the most important factors for receiving appropriate surgical management were surgeon specialty of gynecologic oncologist and the volume of cases performed by the surgeon annually. There are only 1000 board certified gynecologic oncologists in the United States, mostly in the larger medical centers across the country. Appropriately directing the women who are most likely to benefit from the care of such specialists can be critical for achieving good patient outcomes.

[0008] Currently, cancer antigen 125 (CA-125) is the most widely used serum biomarker for ovarian cancer. Serum concentrations of CA-125 are elevated (>35 U/ml) in 75-80% of patients with advanced-stage disease and this marker is routinely used to follow response to treatment and disease progression in patients from whom CA-125-secreting tumors have been resected. However, because the levels of CA-125 are correlated with tumor volume, only 50% of patients with early-stage disease have elevated levels, indicating that the sensitivity of CA-125 as a screening tool for early stage disease is limited. The utility of CA-125 screening is further limited by the high frequency of false-positive results associated with a variety of benign conditions, including endometriosis, pregnancy, menstruation, pelvic inflammatory disease, peritonitis, pancreatitis, and liver disease.

[0009] Classification of cancers determines appropriate treatment and helps determine the prognosis of the patient. Ovarian cancers are classified according to histology (i.e., "grading") and extent of the disease (i.e., "staging") using recognized grade and stage systems. In grade I, the tumor tissue is well differentiated. In grade II, tumor tissue is moderately well differentiated. In grade III, the tumor tissue is poorly differentiated. Grade III correlates with a less favorable prognosis than either grade I or II. Stage I is generally confined within the capsule surrounding one (stage IA) or both (stage IB) ovaries, although in some stage I (i.e. stage IC) cancers, malignant cells may be detected in ascites, in peritoneal rinse fluid, or on the surface of the ovaries. Stage II involves extension or metastasis of the tumor from one or both ovaries to other pelvic structures. In stage HA, the tumor extends or has metastasized to the uterus, the fallopian tubes, or both. Stage IIB involves metastasis of the tumor to the pelvis. Stage IIC is stage IIA or IIB with the added requirement that malignant cells may be detected in ascites, in peritoneal rinse fluid, or on the surface of the ovaries. In stage III, the tumor comprises at least one malignant extension to the small bowel or the omentum, has formed extra-pelvic peritoneal implants of microscopic (stage IIIA) or macroscopic (<2 centimeter diameter, stage IIIB; >2 centimeter diameter, stage IIIC) size, or has metastasized to a retroperitoneal or inguinal lymph node (an alternate indicator of stage IIIC). In stage IV, distant (i.e. non-peritoneal) metastases of the tumor can be detected.

[0010] Treatment options include surgery, chemotherapy, and occasionally radiation therapy. Surgery usually involves removal of one or both ovaries, fallopian tubes (salpingoophorectomy), and the uterus (hysterectomy). In younger women with very early stage tumors who wish to have children, only the involved ovary and fallopian tube may be removed. In more advanced disease, surgically removing all

abdominal metastases enhances the effect of chemotherapy and helps improve survival. For women with stage III ovarian cancer that has been optimally debulked (removal of as much of the cancerous tissue as possible), studies have shown that chemotherapy administered both intravenously and directly into the peritoneal cavity improves survival. Studies have found that women who are treated by a gynecologic oncologist have more successful outcomes.

[0011] Relative survival varies by age; women younger than 65 are about twice as likely to survive 5 years (57%) following diagnosis as women 65 and older (29%). Overall, the 1- and 5-year relative survival of ovarian cancer patients is 75% and 46%, respectively. If diagnosed at the localized stage, the 5-year survival rate is 93%; however, only 19% of all cases are detected at this stage, usually fortuitously during another medical procedure. The majority of cases (67%) are diagnosed at distant stage. For women with regional and distant disease, 5-year survival rates are 71% and 31%, respectively; the chance of recurrence in these women is 20-85%. The 10-year relative survival rate for all stages combined is 39%. Therefore, ovarian cancer tends to be diagnosed too late to save women's lives. Detecting recurrence and predicting and monitoring response to therapy is important for making informed decisions on appropriate treatment throughout the care of these patients.

[0012] A blood screening test that can reliably detect early stage ovarian cancer will save thousands of lives each year. Where methods of early diagnosis in cancer exist, the benefits are generally accepted by the medical community. Cancers for which widely utilized screening protocols exist have the highest 5-year survival rates, such as breast cancer (88%) and colon cancer (65%) versus 46% for ovarian cancer. However, fortuitous detection of early stage ovarian cancer is associated with a substantial increase in 5-year survival (>95%). Therefore, early detection could significantly impact long-term survival. This demonstrates the clear need for diagnostic methods that can reliably detect early-stage ovarian cancer.

[0013] Biomarker selection for a specific disease state involves first the identification of markers that have a measurable and statistically significant difference in a disease population compared to a control population for a specific medical application. Biomarkers can include secreted or shed molecules that parallel disease development or progression and readily diffuse into the blood stream from ovarian tissue or from surrounding tissues and circulating cells in response to a tumor. The biomarker or set of biomarkers identified are generally clinically validated or shown to be a reliable indicator for the original intended use for which it was selected. Biomarkers can include small molecules, peptides, proteins, and nucleic acids. Some of the key issues that affect the identification of biomarkers include over-fitting of the available data and bias in the data.

[0014] A variety of methods have been utilized in an attempt to identify biomarkers and diagnose disease. For protein-based markers, these include two-dimensional electrophoresis, mass spectrometry, and immunoassay methods. For nucleic acid markers, these include mRNA expression profiles, microRNA profiles, FISH, serial analysis of gene expression (SAGE), methylation profiles, and large scale gene expression arrays.

[0015] The utility of two-dimensional electrophoresis is limited by low detection sensitivity; issues with protein solubility, charge, and hydrophobicity; gel reproducibility; and the possibility of a single spot representing multiple proteins. For mass spectrometry, depending on the format used, limitations revolve around the sample processing and separation, sensitivity to low abundance proteins, signal to noise considerations, and inability to immediately identify the detected protein. Limitations in immunoassay approaches to biomarker discovery are centered on the inability of antibody-based multiplex assays to measure a large number of analytes. One might simply print an array of high-quality antibodies and, without sandwiches, measure the analytes bound to those antibodies. (This would be the formal equivalent of using a whole genome of nucleic acid sequences to measure by hybridization all DNA or RNA sequences in an organism or a cell. The hybridization experiment works because hybridization can be a stringent test for identity. Even very good antibodies are not stringent enough in selecting their binding partners to work in the context of blood or even cell extracts because the protein ensemble in those matrices have extremely different abundances.) Thus, one must use a different approach with immunoassay-based approaches to biomarker discovery—one would need to use multiplexed ELISA assays (that is, sandwiches) to get sufficient stringency to measure many analytes simultaneously to decide which analytes are indeed biomarkers. Sandwich immunoassays do not scale to high content, and thus biomarker discovery using stringent sandwich immunoassays is not possible using standard array formats. Lastly, antibody reagents are subject to substantial lot variability and reagent instability. The instant platform for protein biomarker discovery overcomes this problem.

[0016] Many of these methods rely on or require some type of sample fractionation prior to the analysis. Thus the sample preparation required to run a sufficiently powered study designed to identify and discover statistically relevant biomarkers in a series of well-defined sample populations is extremely difficult, costly, and time consuming. During fractionation, a wide range of variability can be introduced into the various samples. For example, a potential marker could be unstable to the process, the concentration of the marker could be changed, inappropriate aggregation or disaggregation could occur, and inadvertent sample contamination could occur and thus obscure the subtle changes anticipated in early disease.

[0017] It is widely accepted that biomarker discovery and detection methods using these technologies have serious limitations for the identification of diagnostic biomarkers. These limitations include an inability to detect low-abundance biomarkers, an inability to consistently cover the entire dynamic range of the proteome, irreproducibility in sample processing and fractionation, and overall irreproducibility and lack of robustness of the method. Further, these studies have introduced biases into the data and not adequately addressed the complexity of the sample populations, including appropriate controls, in terms of the distribution and randomization required to identify and validate biomarkers within a target disease population.

[0018] Although efforts aimed at the discovery of new and effective biomarkers have gone on for several decades, the efforts have been largely unsuccessful. Biomarkers for various diseases typically have been identified in academic laboratories, usually through an accidental discovery while doing basic research on some disease process. Based on the discov-

ery and with small amounts of clinical data, papers were published that suggested the identification of a new biomarker. Most of these proposed biomarkers, however, have not been confirmed as real or useful biomarkers; primarily because the small number of clinical samples tested provide only weak statistical proof that an effective biomarker has in fact been found. That is, the initial identification was not rigorous with respect to the basic elements of statistics. In each of the years 1994 through 2003, a search of the scientific literature shows that thousands of references directed to biomarkers were published. During that same time frame, however, the FDA approved for diagnostic use, at most, three new protein biomarkers a year, and in several years no new protein biomarkers were approved.

[0019] Based on the history of failed biomarker discovery efforts, mathematical theories have been proposed that further promote the general understanding that biomarkers for disease are rare and difficult to find. Biomarker research based on 2D gels or mass spectrometry supports these notions. Very few useful biomarkers have been identified through these approaches. However, it is usually overlooked that 2D gel and mass spectrometry measure proteins that are present in blood at approximately 1 nM concentrations and higher, and that this ensemble of proteins may well be the least likely to change with disease. Other than the instant biomarker discovery platform, proteomic biomarker discovery platforms that are able to accurately measure protein expression levels at much lower concentrations do not exist.

[0020] Much is known about biochemical pathways for complex human biology. Many biochemical pathways culminate in or are started by secreted proteins that work locally within the pathology, for example growth factors are secreted to stimulate the replication of other cells in the pathology, and other factors are secreted to ward off the immune system, and so on. While many of these secreted proteins work in a paracrine fashion, some operate distally in the body. One skilled in the art with a basic understanding of biochemical pathways would understand that many pathology-specific proteins ought to exist in blood at concentrations below (even far below) the detection limits of 2D gels and mass spectrometry. What must precede the identification of this relatively abundant number of disease biomarkers is a proteomic platform that can analyze proteins at concentrations below those detectable by 2D gels or mass spectrometry.

[0021] Accordingly, a need exists for biomarkers, methods, devices, reagents, systems, and kits that enable (a) the differentiation of benign pelvic masses from ovarian cancer; (b) referral to a gynecologic oncology surgeon rather than a general gynecologic surgeon to surgically treat cases of ovarian cancer; (c) the detection of ovarian cancer biomarkers; and (d) the diagnosis of ovarian cancer.

SUMMARY

[0022] The present application includes biomarkers, methods, reagents, devices, systems, and kits for the detection and diagnosis of cancer and more particularly, ovarian cancer. The biomarkers of the present application were identified using a multiplex aptamer-based assay, which is described in detail in Example 1. By using the aptamer-based biomarker identification method described herein, this application describes a surprisingly large number of ovarian cancer biomarkers that are useful for the detection and diagnosis of ovarian cancer. In identifying these biomarkers, over 800 proteins from hundreds of individual samples were measured, some of which were at concentrations in the low femtomolar range. This is about four orders of magnitude lower than biomarker discovery experiments done with 2D gels or mass spectrometry.

[0023] While certain of the described ovarian cancer biomarkers are useful alone for detecting and diagnosing ovarian cancer, methods are described herein for the grouping of multiple subsets of the ovarian cancer biomarkers that are useful as a panel of biomarkers. Once an individual biomarker or subset of biomarkers has been identified, the detection or diagnosis of ovarian cancer in an individual can be accomplished using any assay platform or format that is capable of measuring differences in the levels of the selected biomarker or biomarkers in a biological sample.

[0024] However, it was only by using the aptamer-based biomarker identification method described herein, wherein over 800 separate potential biomarker values were individually screened from a large number of individuals who were postoperatively diagnosed as either having or not having ovarian cancer that it was possible to identify the ovarian cancer biomarkers disclosed herein. This discovery approach is in stark contrast to biomarker discovery using conditioned media or lysed cells as it queries a more patient-relevant system that requires no translation to human pathology.

[0025] Thus, in one aspect of the instant application, one or more biomarkers are provided for use either alone or in various combinations to diagnose ovarian cancer or permit the differential diagnosis of pelvic masses as benign or malignant. Exemplary embodiments include the biomarkers provided in Table 1, which as noted above, were identified using a multiplex aptamer-based assay, as described in Examples 1 and 2. The markers provided in Table 1 are useful in distinguishing benign pelvic masses from ovarian cancer.

[0026] While certain of the described ovarian cancer biomarkers are useful alone for detecting and diagnosing ovarian cancer, methods are also described herein for the grouping of multiple subsets of the ovarian cancer biomarkers that are each useful as a panel of three or more biomarkers. Thus, various embodiments of the instant application provide combinations comprising N biomarkers, wherein N is at least two biomarkers. In other embodiments, N is selected to be any number from 2-42 biomarkers.

[0027] In yet other embodiments, N is selected to be any number from 2-7, 2-10, 2-15, 2-20, 2-25, 2-30, 2-35, 2-40, or 2-42. In other embodiments, N is selected to be any number from 3-7, 3-10, 3-15, 3-20, 3-25, 3-30, 3-35, 3-40, or 3-42. In other embodiments, N is selected to be any number from 4-7, 4-10, 4-15, 4-20, 4-25, 4-30, 4-35, 4-40, or 4-42. In other embodiments, N is selected to be any number from 5-7, 5-10, 5-15, 5-20, 5-25, 5-30, 5-35, 5-40, or 5-42. In other embodiments, N is selected to be any number from 6-10, 6-15, 6-20, 6-25, 6-30, 6-35, 6-40, or 6-42. In other embodiments, N is selected to be any number from 7-10, 7-15, 7-20, 7-25, 7-30, 7-35, 7-40, or 7-42. In other embodiments, N is selected to be any number from 8-10, 8-15, 8-20, 8-25, 8-30, 8-35, 8-40, or 8-42. In other embodiments, N is selected to be any number from 9-15, 9-20, 9-25, 9-30, 9-35, 9-40, or 9-42. In other embodiments, N is selected to be any number from 10-15, 10-20, 10-25, 10-30, 10-35, 10-40, or 10-42. It will be appreciated that N can be selected to encompass similar, but higher order, ranges.

[0028] In another aspect, a method is provided for diagnosing ovarian cancer in an individual, the method including detecting, in a biological sample from an individual, at least one biomarker value corresponding to at least one biomarker selected from the group of biomarkers provided in Table 1, wherein the individual is classified as having ovarian cancer based on the at least one biomarker value.

[0029] In another aspect, a method is provided for diagnosing ovarian cancer in an individual, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to one of at least N biomarkers selected from the group of biomarkers set forth in Table 1, wherein the likelihood of the individual having ovarian cancer is determined based on the biomarker values.

[0030] In another aspect, a method is provided for diagnosing ovarian cancer in an individual, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to one of at least N biomarkers selected from the group of biomarkers set forth in Table 1, wherein the individual is classified as having ovarian cancer based on the biomarker values, and wherein N=2-10.

[0031] In another aspect, a method is provided for diagnosing ovarian cancer in an individual, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to one of at least N biomarkers selected from the group of biomarkers set forth in Table 1, wherein the likelihood of the individual having ovarian cancer is determined based on the biomarker values, and wherein N=2-10.

[0032] In another aspect, a method is provided for differentiating an individual having a benign pelvic mass from an individual having ovarian cancer, the method including detecting, in a biological sample from an individual, at least one biomarker value corresponding to at least one biomarker selected from the group of biomarkers set forth in Table 1, wherein the individual is classified as having ovarian cancer, or the likelihood of the individual having ovarian cancer is determined, based on the at least one biomarker value.

[0033] In another aspect, a method is provided for differentiating an individual having a benign pelvic mass from an individual having ovarian cancer, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to one of at least N biomarkers selected from the group of biomarkers set forth in Table 1, wherein the individual is classified as having ovarian cancer, or the likelihood of the individual having ovarian cancer is determined, based on the biomarker values, wherein N=2-10.

[0034] In another aspect, a method is provided for diagnosing that an individual does not have ovarian cancer, the method including detecting, in a biological sample from an individual, at least one biomarker value corresponding to at least one biomarker selected from the group of biomarkers set forth in Table 1, wherein the individual is classified as not having ovarian cancer based on the at least one biomarker value.

[0035] In another aspect, a method is provided for diagnosing that an individual does not have ovarian cancer, the method including detecting, in a biological sample from an individual, biomarker values that each corresponding to one of at least N biomarkers selected from the group of biomarkers set forth in Table 1, wherein the individual is classified as not having ovarian cancer based on the biomarker values, and wherein N=2-10.

[0036] In another aspect, a method is provided for diagnosing ovarian cancer, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, wherein a classification of the biomarker values indicates that the individual has ovarian cancer, and wherein N=3-10.

[0037] In another aspect, a method is provided for diagnosing ovarian cancer, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, wherein a classification of the biomarker values indicates that the individual has ovarian cancer, and wherein N=3-15.

[0038] In another aspect, a method is provided for diagnosing ovarian cancer, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of biomarkers selected from the group of panels set forth in Tables 2-14, wherein a classification of the biomarker values indicates that the individual has ovarian cancer.

[0039] In another aspect, a method is provided for differentiating an individual having a benign pelvic mass from an individual having ovarian cancer, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, wherein the individual is classified as having ovarian cancer, or the likelihood of the individual having ovarian cancer is determined, based on the biomarker values, and wherein N=3-10.

[0040] In another aspect, a method is provided for differentiating an individual having a benign pelvic mass from an individual having ovarian cancer, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, wherein the individual is classified as having ovarian cancer, or the likelihood of the individual having ovarian cancer is determined, based on the biomarker values, and wherein N=3-15.

[0041] In another aspect, a method is provided for diagnosing an absence of ovarian cancer, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, wherein a classification of the biomarker values indicates an absence of ovarian cancer in the individual, and wherein N=3-10.

[0042] In another aspect, a method is provided for diagnosing an absence of ovarian cancer, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, wherein a classifi-

cation of the biomarker values indicates an absence of ovarian cancer in the individual, and wherein N=3-15.

[0043] In another aspect, a method is provided for diagnosing an absence of ovarian cancer, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of biomarkers selected from the group of panels provided in Tables 2-14, wherein a classification of the biomarker values indicates an absence of ovarian cancer in the individual.

[0044] In another aspect, a method is provided for diagnosing ovarian cancer in an individual, the method including detecting, in a biological sample from an individual, biomarker values that correspond to one of at least N biomarkers selected from the group of biomarkers set forth in Table 1, wherein the individual is classified as having ovarian cancer based on a classification score that deviates from a predetermined threshold, and wherein N=2-10.

[0045] In another aspect, a method is provided for differentiating an individual having a benign pelvic mass from an individual having ovarian cancer, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, wherein the individual is classified as having ovarian cancer, or the likelihood of the individual having ovarian cancer is determined, based on a classification score that deviates from a predetermined threshold, and wherein N=3-10.

[0046] In another aspect, a method is provided for differentiating an individual having a benign pelvic mass from an individual having ovarian cancer, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, wherein the individual is classified as having ovarian cancer, or the likelihood of the individual having ovarian cancer is determined, based on a classification score that deviates from a predetermined threshold, wherein N=3-15.

[0047] In another aspect, a method is provided for diagnosing an absence of ovarian cancer in an individual, the method including detecting, in a biological sample from an individual, biomarker values that correspond to one of at least N biomarkers selected from the group of biomarkers set forth in Table 1, wherein said individual is classified as not having ovarian cancer based on a classification score that deviates from a predetermined threshold, and wherein N=2-10.

[0048] In another aspect, a computer-implemented method is provided for indicating a likelihood of ovarian cancer. The method comprises: retrieving on a computer biomarker information for an individual, wherein the biomarker information comprises biomarker values that each correspond to one of at least N biomarkers, wherein N is as defined above, selected from the group of biomarkers set forth in Table 1; performing with the computer a classification of each of the biomarker values; and indicating a likelihood that the individual has ovarian cancer based upon a plurality of classifications.

[0049] In another aspect, a computer-implemented method is provided for classifying an individual as either having or not having ovarian cancer. The method comprises: retrieving on a computer biomarker information for an individual, wherein the biomarker information comprises biomarker values that each correspond to one of at least N biomarkers selected from the group of biomarkers provided in Table 1; performing with the computer a classification of each of the biomarker values; and indicating whether the individual has ovarian cancer based upon a plurality of classifications.

[0050] In another aspect, a computer program product is provided for indicating a likelihood of ovarian cancer. The computer program product includes a computer readable medium embodying program code executable by a processor of a computing device or system, the program code comprising: code that retrieves data attributed to a biological sample from an individual, wherein the data comprises biomarker values that each correspond to one of at least N biomarkers, wherein N is as defined above, in the biological sample selected from the group of biomarkers set forth in Table 1; and code that executes a classification method that indicates a likelihood that the individual has ovarian cancer as a function of the biomarker values.

[0051] In another aspect, a computer program product is provided for indicating an ovarian cancer status of an individual. The computer program product includes a computer readable medium embodying program code executable by a processor of a computing device or system, the program code comprising: code that retrieves data attributed to a biological sample from an individual, wherein the data comprises biomarker values that each correspond to one of at least N biomarkers in the biological sample selected from the group of biomarkers provided in Table 1; and code that executes a classification method that indicates an ovarian cancer status of the individual as a function of the biomarker values.

[0052] In another aspect, a computer-implemented method is provided for indicating a likelihood of ovarian cancer. The method comprises retrieving on a computer biomarker information for an individual, wherein the biomarker information comprises a biomarker value corresponding to a biomarker selected from the group of biomarkers set forth in Table 1; performing with the computer a classification of the biomarker value; and indicating a likelihood that the individual has ovarian cancer based upon the classification.

[0053] In another aspect, a computer-implemented method is provided for classifying an individual as either having or not having ovarian cancer. The method comprises retrieving, from a computer, biomarker information for an individual, wherein the biomarker information comprises a biomarker value corresponding to a biomarker selected from the group of biomarkers provided in Table 1; performing with the computer a classification of the biomarker value; and indicating whether the individual has ovarian cancer based upon the classification.

[0054] In still another aspect, a computer program product is provided for indicating a likelihood of ovarian cancer. The computer program product includes a computer readable medium embodying program code executable by a processor of a computing device or system, the program code comprising: code that retrieves data attributed to a biological sample from an individual, wherein the data comprises a biomarker value corresponding to a biomarker in the biological sample selected from the group of biomarkers set forth in Table 1; and code that executes a classification method that indicates a likelihood that the individual has ovarian cancer as a function of the biomarker value.

[0055] In still another aspect, a computer program product is provided for indicating an ovarian cancer status of an individual. The computer program product includes a computer readable medium embodying program code executable by a processor of a computing device or system, the program code comprising: code that retrieves data attributed to a biological sample from an individual, wherein the data comprises a biomarker value corresponding to a biomarker in the biological sample selected from the group of biomarkers provided in Table 1; and code that executes a classification method that indicates an ovarian cancer status of the individual as a function of the biomarker value.

BRIEF DESCRIPTION OF THE DRAWINGS

[0056] FIG. **1**A is a flowchart for an exemplary method for detecting ovarian cancer in a biological sample.

[0057] FIG. **1**B is a flowchart for an exemplary method for detecting ovarian cancer in a biological sample using a naïve Bayes classification method.

[0058] FIG. **2** shows a ROC curve for a single biomarker, BAFF Receptor, using a naïve Bayes classifier for a test that detects ovarian cancer in women with pelvis masses.

[0059] FIG. **3** shows ROC curves for biomarker panels of from one to ten biomarkers using naïve Bayes classifiers for a test that detects ovarian cancer in women with pelvis masses.

[0060] FIG. **4** illustrates the increase in the classification score (specificity+sensitivity) as the number of biomarkers is increased from one to ten using naïve Bayes classification for an ovarian cancer panel.

[0061] FIG. **5** shows the measured biomarker distributions for BAFF Receptor as a cumulative distribution function (cdf) in RFU for the benign control group (solid line) and the ovarian cancer disease group (dotted line) along with their curve fits to a normal cdf (dashed lines) used to train the naïve Bayes classifiers.

[0062] FIG. **6** illustrates an exemplary computer system for use with various computer-implemented methods described herein.

[0063] FIG. **7** is a flowchart for a method of indicating the likelihood that an individual has ovarian cancer in accordance with one embodiment.

[0064] FIG. **8** is a flowchart for a method of indicating the likelihood that an individual has ovarian cancer in accordance with one embodiment.

[0065] FIG. **9** illustrates an exemplary aptamer assay that can be used to detect one or more ovarian cancer biomarkers in a biological sample.

[0066] FIG. **10** shows a histogram of frequencies for which biomarkers were used in building classifiers to distinguish between ovarian cancer and benign pelvic masses from an aggregated set of potential biomarkers.

[0067] FIG. **11** shows a histogram of frequencies for which biomarkers were used in building classifiers to distinguish between ovarian cancer and benign pelvic masses from a site-consistent set of potential biomarkers.

[0068] FIG. **12** shows a histogram of frequencies for which biomarkers were used in building classifiers to distinguish between ovarian cancer and benign pelvic masses from a set of potential biomarkers resulting from a combination of aggregated and site-consistent markers.

[0069] FIG. **13** shows gel images resulting from pull-down experiments that illustrate the specificity of aptamers as capture reagents for the proteins LBP, C9 and IgM. For each gel, lane 1 is the eluate from the Streptavidin-agarose beads, lane 2 is the final eluate, and lane is a MW marker lane (major bands are at 110, 50, 30, 15, and 3.5 kDa from top to bottom).

[0070] FIG. **14**A shows a pair of histograms summarizing all possible single protein naïve Bayes classifier scores (sensitivity+specificity) using the biomarkers set forth in Table 1 (solid) and a set of random non-markers (dotted).

[0071] FIG. **14**B shows a pair of histograms summarizing all possible two-protein protein naïve Bayes classifier scores (sensitivity+specificity) using the biomarkers set forth in Table 1 (solid) and a set of random non-markers (dotted).

[0072] FIG. **14**C shows a pair of histograms summarizing all possible three-protein naïve Bayes classifier scores (sensitivity+specificity) using the biomarkers set forth in Table 1 (solid) and a set of non-random markers (dotted).

[0073] FIG. **15** shows the sensitivity+specificity score for naïve Bayes classifiers using from 2-10 markers selected from the full panel (●) and the scores obtained by dropping the best 5 (■), 10 (▲) and 15 (♦) markers during classifier generation.

[0074] FIG. **16**A shows a set of ROC curves modeled from the data in Table 18 for panels of from one to five markers.

[0075] FIG. **16**B shows a set of ROC curves computed from the training data for panels of from one to five markers as in FIG. **16**A.

DETAILED DESCRIPTION

[0076] Reference will now be made in detail to representative embodiments of the invention. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that the invention is not intended to be limited to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents that may be included within the scope of the present invention as defined by the claims.

[0077] One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in and are within the scope of the practice of the present invention. The present invention is in no way limited to the methods and materials described.

[0078] Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods, devices, and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods, devices and materials are now described.

[0079] All publications, published patent documents, and patent applications cited in this application are indicative of the level of skill in the art(s) to which the application pertains. All publications, published patent documents, and patent applications cited herein are hereby incorporated by reference to the same extent as though each individual publication,

published patent document, or patent application was specifically and individually indicated as being incorporated by reference.

[0080] As used in this application, including the appended claims, the singular forms "a,""an," and "the" include plural references, unless the content clearly dictates otherwise, and are used interchangeably with "at least one" and "one or more." Thus, reference to "an aptamer" includes mixtures of aptamers, reference to "a probe" includes mixtures of probes, and the like.

[0081] As used herein, the term "about" represents an insignificant modification or variation of the numerical value such that the basic function of the item to which the numerical value relates is unchanged.

[0082] As used herein, the terms "comprises,""comprising, ""includes,""including,""contains,""containing," and any variations thereof, are intended to cover a non-exclusive inclusion, such that a process, method, product-by-process, or composition of matter that comprises, includes, or contains an element or list of elements does not include only those elements but may include other elements not expressly listed or inherent to such process, method, product-by-process, or composition of matter.

[0083] The present application includes biomarkers, methods, devices, reagents, systems, and kits for the detection and diagnosis of ovarian cancer.

[0084] In one aspect, one or more biomarkers are provided for use either alone or in various combinations to diagnose ovarian cancer, permit the differential diagnosis of pelvic masses as benign or malignant, monitor ovarian cancer recurrence, or address other clinical indications. As described in detail below, exemplary embodiments include the biomarkers provided in Table 1, which were identified using a multiplex aptamer-based assay, as described generally in Example 1 and more specifically in Example 2.

[0085] Table 1 sets forth the findings obtained from analyzing blood samples from 142 individuals diagnosed with ovarian cancer and blood samples from 195 individuals diagnosed with a benign pelvic mass. The benign pelvic mass group was designed to match the population with which an ovarian cancer diagnostic test can have significant benefit. (These cases and controls were obtained from two clinical sites). The potential biomarkers were measured in individual samples rather than pooling the disease and control blood; this allowed a better understanding of the individual and group variations in the phenotypes associated with the presence and absence of disease (in this case ovarian cancer). Since over 800 protein measurements were made on each sample, and 337 samples from both the disease and the control populations were individually measured, Table 1 resulted from an analysis of an uncommonly large set of data. The measurements were analyzed using the methods described in the section, "Classification of Biomarkers and Calculation of Disease Scores" herein.

[0086] Table 1 lists the biomarkers found to be useful in distinguishing samples obtained from individuals with ovarian cancer from "control" samples obtained from individuals with benign pelvic masses. Using a multiplex aptamer assay, forty-two biomarkers were discovered that distinguished samples obtained from individuals with ovarian cancer from samples obtained from people who had benign pelvic masses (see Table 1).

[0087] While certain of the described ovarian cancer biomarkers are useful alone for detecting and diagnosing ovarian cancer, methods are also described herein for the grouping of multiple subsets of the ovarian cancer biomarkers, where each grouping or subset selection is useful as a panel of three or more biomarkers, interchangeably referred to herein as a "biomarker panel" and a panel. Thus, various embodiments of the instant application provide combinations comprising N biomarkers, wherein N is at least two biomarkers. In other embodiments, N is selected from 2-42 biomarkers.

[0088] In yet other embodiments, N is selected to be any number from 2-7, 2-10, 2-15, 2-20, 2-25, 2-30, 2-35, 2-40, or 2-42. In other embodiments, N is selected to be any number from 3-7, 3-10, 3-15, 3-20, 3-25, 3-30, 3-35, 3-40, or 3-42. In other embodiments, N is selected to be any number from 4-7, 4-10, 4-15, 4-20, 4-25, 4-30, 4-35, 4-40, or 4-42. In other embodiments, N is selected to be any number from 5-7, 5-10, 5-15, 5-20, 5-25, 5-30, 5-35, 5-40, or 5-42. In other embodiments, N is selected to be any number from 6-10, 6-15, 6-20, 6-25, 6-30, 6-35, 6-40, or 6-42. In other embodiments, N is selected to be any number from 7-10, 7-15, 7-20, 7-25, 7-30, 7-35, 7-40, or 7-42. In other embodiments, N is selected to be any number from 8-10, 8-15, 8-20, 8-25, 8-30, 8-35, 8-40, or 8-42. In other embodiments, N is selected to be any number from 9-15, 9-20, 9-25, 9-30, 9-35, 9-40, or 9-42. In other embodiments, N is selected to be any number from 10-15, 10-20, 10-25, 10-30, 10-35, 10-40, or 10-42. It will be appreciated that N can be selected to encompass similar, but higher order, ranges.

[0089] In one embodiment, the number of biomarkers useful for a biomarker subset or panel is based on the sensitivity and specificity value for the particular combination of biomarker values. The terms "sensitivity" and "specificity" are used herein with respect to the ability to correctly classify an individual, based on one or more biomarker values detected in their biological sample, as having ovarian cancer or not having ovarian cancer. "Sensitivity" indicates the performance of the biomarker(s) with respect to correctly classifying individuals that have ovarian cancer. "Specificity" indicates the performance of the biomarker(s) with respect to correctly classifying individuals who do not have ovarian cancer. For example, 85% specificity and 90% sensitivity for a panel of markers used to test a set of control samples and ovarian cancer samples indicates that 85% of the control samples were correctly classified as control samples by the panel, and 90% of the ovarian cancer samples were correctly classified as ovarian cancer samples by the panel. The desired or preferred minimum value can be determined as described in Example 3. Representative panels are set forth in Tables 2-14, which set forth a series of 100 different panels of 3-15 biomarkers, which have the indicated levels of specificity and sensitivity for each panel. The total number of occurrences of each marker in each of these panels is indicated at the bottom of each Table.

[0090] In one aspect, ovarian cancer is detected or diagnosed in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to at least one of the biomarkers SLPI, C9, HGF and RGM-C and at least N additional biomarkers selected from the list of biomarkers in Table 1, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15. In a further aspect, ovarian cancer is detected or diagnosed in an individual by conducting an assay on a biological sample from the

individual and detecting biomarker values that each correspond to the biomarkers SLPI, C9, HGF and RGM-C and one of at least N additional biomarkers selected from the list of biomarkers in Table 1, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13. In a further aspect, ovarian cancer is detected or diagnosed in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarker SLPI and one of at least N additional biomarkers selected from the list of biomarkers in Table 1, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15. In a further aspect, ovarian cancer is detected or diagnosed in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarker C9 and one of at least N additional biomarkers selected from the list of biomarkers in Table 1, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15. In a further aspect, ovarian cancer is detected or diagnosed in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarker HGF and one of at least N additional biomarkers selected from the list of biomarkers in Table 1, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15. In a further aspect, ovarian cancer is detected or diagnosed in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarker RGM-C and one of at least N additional biomarkers selected from the list of biomarkers in Table 1, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

[0091] The ovarian cancer biomarkers identified herein represent a relatively large number of choices for subsets or panels of biomarkers that can be used to effectively detect or diagnose ovarian cancer. Selection of the desired number of such biomarkers depends on the specific combination of biomarkers chosen. It is important to remember that panels of biomarkers for detecting or diagnosing ovarian cancer may also include biomarkers not found in Table 1, and that the inclusion of additional biomarkers not found in Table 1 may reduce the number of biomarkers in the particular subset or panel that is selected from Table 1. The number of biomarkers from Table 1 used in a subset or panel may also be reduced if additional biomedical information is used in conjunction with the biomarker values to establish acceptable sensitivity and specificity values for a given assay.

[0092] Another factor that can affect the number of biomarkers to be used in a subset or panel of biomarkers is the procedures used to obtain biological samples from individuals who are being evaluated for ovarian cancer. In a carefully controlled sample procurement environment, the number of biomarkers necessary to meet desired sensitivity and specificity values will be lower than in a situation where there can be more variation in sample collection, handling and storage. In developing the list of biomarkers set forth in Table 1, two sample collection sites were utilized to collect data for classifier training.

[0093] One aspect of the instant application can be described generally with reference to FIGS. 1A and B. A biological sample is obtained from an individual or individuals of interest. The biological sample is then assayed to detect the presence of one or more (N) biomarkers of interest and to determine a biomarker value for each of said N biomarkers (referred to in FIG. 1B as marker RFU (relative fluorescence units)). Once a biomarker has been detected and a biomarker value assigned each marker is scored or classified as described in detail herein. The marker scores are then combined to provide a total diagnostic score, which indicates the likelihood that the individual from whom the sample was obtained has ovarian cancer.

[0094] "Biological sample", "sample", and "test sample" are used interchangeably herein to refer to any material, biological fluid, tissue, or cell obtained or otherwise derived from an individual. This includes blood (including whole blood, leukocytes, peripheral blood mononuclear cells, buffy coat, plasma, and serum), sputum, tears, mucus, nasal washes, nasal aspirate, breath, urine, semen, saliva, meningeal fluid, amniotic fluid, glandular fluid, lymph fluid, nipple aspirate, bronchial aspirate, synovial fluid, joint aspirate, ascites, cells, a cellular extract, and cerebrospinal fluid. This also includes experimentally separated fractions of all of the preceding. For example, a blood sample can be fractionated into serum or into fractions containing particular types of blood cells, such as red blood cells or white blood cells (leukocytes). If desired, a sample can be a combination of samples from an individual, such as a combination of a tissue and fluid sample. The term "biological sample" also includes materials containing homogenized solid material, such as from a stool sample, a tissue sample, or a tissue biopsy, for example. The term "biological sample" also includes materials derived from a tissue culture or a cell culture. Any suitable methods for obtaining a biological sample can be employed; exemplary methods include, e.g., phlebotomy, swab (e.g., buccal swab), and a fine needle aspirate biopsy procedure. Samples can also be collected, e.g., by micro dissection (e.g., laser capture micro dissection (LCM) or laser micro dissection (LMD)), bladder wash, smear (e.g., a PAP smear), or ductal lavage. A "biological sample" obtained or derived from an individual includes any such sample that has been processed in any suitable manner after being obtained from the individual.

[0095] Further, it should be realized that a biological sample can be derived by taking biological samples from a number of individuals and pooling them or pooling an aliquot of each individual's biological sample. The pooled sample can be treated as a sample from a single individual and if the presence of cancer is established in the pooled sample, then each individual biological sample can be re-tested to determine which individuals have ovarian cancer.

[0096] For purposes of this specification, the phrase "data attributed to a biological sample from an individual" is intended to mean that the data in some form derived from, or were generated using, the biological sample of the individual. The data may have been reformatted, revised, or mathematically altered to some degree after having been generated, such as by conversion from units in one measurement system to units in another measurement system; but, the data are understood to have been derived from, or were generated using, the biological sample.

[0097] "Target", "target molecule", and "analyte" are used interchangeably herein to refer to any molecule of interest that may be present in a biological sample.

[0098] A "molecule of interest" includes any minor variation of a particular molecule, such as, in the case of a protein, for example, minor variations in amino acid sequence, disulfide bond formation, glycosylation, lipidation, acetylation,

phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component, which does not substantially alter the identity of the molecule. A "target molecule", "target", or "analyte" is a set of copies of one type or species of molecule or multi-molecular structure. "Target molecules", "targets", and "analytes" refer to more than one such set of molecules. Exemplary target molecules include proteins, polypeptides, nucleic acids, carbohydrates, lipids, polysaccharides, glycoproteins, hormones, receptors, antigens, antibodies, affybodies, antibody mimics, viruses, pathogens, toxic substances, substrates, metabolites, transition state analogs, cofactors, inhibitors, drugs, dyes, nutrients, growth factors, cells, tissues, and any fragment or portion of any of the foregoing.

[0099] As used herein, "polypeptide,""peptide," and "protein" are used interchangeably herein to refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), as well as other modifications known in the art. Polypeptides can be single chains or associated chains. Also included within the definition are preproteins and intact mature proteins; peptides or polypeptides derived from a mature protein; fragments of a protein; splice variants; recombinant forms of a protein; protein variants with amino acid modifications, deletions, or substitutions; digests; and post-translational modifications, such as glycosylation, acetylation, phosphorylation, and the like.

[0100] As used herein, "thrombin" refers to thrombin, prothrombin, or both thrombin and prothrombin.

[0101] As used herein, "marker" and "biomarker" are used interchangeably to refer to a target molecule that indicates or is a sign of a normal or abnormal process in an individual or of a disease or other condition in an individual. More specifically, a "marker" or "biomarker" is an anatomic, physiologic, biochemical, or molecular parameter associated with the presence of a specific physiological state or process, whether normal or abnormal, and, if abnormal, whether chronic or acute. Biomarkers are detectable and measurable by a variety of methods including laboratory assays and medical imaging. When a biomarker is a protein, it is also possible to use the expression of the corresponding gene as a surrogate measure of the amount or presence or absence of the corresponding protein biomarker in a biological sample or methylation state of the gene encoding the biomarker or proteins that control expression of the biomarker.

[0102] As used herein, "biomarker value", "value", "biomarker level", and "level" are used interchangeably to refer to a measurement that is made using any analytical method for detecting the biomarker in a biological sample and that indicates the presence, absence, absolute amount or concentration, relative amount or concentration, titer, a level, an expression level, a ratio of measured levels, or the like, of, for, or corresponding to the biomarker in the biological sample. The exact nature of the "value" or "level" depends on the specific design and components of the particular analytical method employed to detect the biomarker.

[0103] When a biomarker indicates or is a sign of an abnormal process or a disease or other condition in an individual, that biomarker is generally described as being either over-expressed or under-expressed as compared to an expression level or value of the biomarker that indicates or is a sign of a normal process or an absence of a disease or other condition in an individual. "Up-regulation", "up-regulated", "over-expression", "over-expressed", and any variations thereof are used interchangeably to refer to a value or level of a biomarker in a biological sample that is greater than a value or level (or range of values or levels) of the biomarker that is typically detected in similar biological samples from healthy or normal individuals. The terms may also refer to a value or level of a biomarker in a biological sample that is greater than a value or level (or range of values or levels) of the biomarker that may be detected at a different stage of a particular disease.

[0104] "Down-regulation", "down-regulated", "under-expression", "under-expressed", and any variations thereof are used interchangeably to refer to a value or level of a biomarker in a biological sample that is less than a value or level (or range of values or levels) of the biomarker that is typically detected in similar biological samples from healthy or normal individuals. The terms may also refer to a value or level of a biomarker in a biological sample that is less than a value or level (or range of values or levels) of the biomarker that may be detected at a different stage of a particular disease.

[0105] Further, a biomarker that is either over-expressed or under-expressed can also be referred to as being "differentially expressed" or as having a "differential level" or "differential value" as compared to a "normal" expression level or value of the biomarker that indicates or is a sign of a normal process or an absence of a disease or other condition in an individual. Thus, "differential expression" of a biomarker can also be referred to as a variation from a "normal" expression level of the biomarker.

[0106] The term "differential gene expression" and "differential expression" are used interchangeably to refer to a gene (or its corresponding protein expression product) whose expression is activated to a higher or lower level in a subject suffering from a specific disease, relative to its expression in a normal or control subject. The terms also include genes (or the corresponding protein expression products) whose expression is activated to a higher or lower level at different stages of the same disease. It is also understood that a differentially expressed gene may be either activated or inhibited at the nucleic acid level or protein level, or may be subject to alternative splicing to result in a different polypeptide product. Such differences may be evidenced by a variety of changes including mRNA levels, surface expression, secretion or other partitioning of a polypeptide. Differential gene expression may include a comparison of expression between two or more genes or their gene products; or a comparison of the ratios of the expression between two or more genes or their gene products; or even a comparison of two differently processed products of the same gene, which differ between normal subjects and subjects suffering from a disease; or between various stages of the same disease. Differential expression includes both quantitative, as well as qualitative, differences in the temporal or cellular expression pattern in a gene or its expression products among, for example, normal

and diseased cells, or among cells which have undergone different disease events or disease stages.

[0107] As used herein, "individual" refers to a test subject or patient. The individual can be a mammal or a non-mammal. In various embodiments, the individual is a mammal. A mammalian individual can be a human or non-human. In various embodiments, the individual is a human. A healthy or normal individual is an individual in which the disease or condition of interest (including, for example, ovarian diseases, ovarian-associated diseases, or other ovarian conditions) is not detectable by conventional diagnostic methods.

[0108] "Diagnose", "diagnosing", "diagnosis", and variations thereof refer to the detection, determination, or recognition of a health status or condition of an individual on the basis of one or more signs, symptoms, data, or other information pertaining to that individual. The health status of an individual can be diagnosed as healthy/normal (i.e., a diagnosis of the absence of a disease or condition) or diagnosed as ill/abnormal (i.e., a diagnosis of the presence, or an assessment of the characteristics, of a disease or condition). The terms "diagnose", "diagnosing", "diagnosis", etc., encompass, with respect to a particular disease or condition, the initial detection of the disease; the characterization or classification of the disease; the detection of the progression, remission, or recurrence of the disease; and the detection of disease response after the administration of a treatment or therapy to the individual. The diagnosis of ovarian cancer includes distinguishing individuals who have cancer from individuals who do not. It further includes distinguishing benign pelvic masses from ovarian cancer.

[0109] "Prognose", "prognosing", "prognosis", and variations thereof refer to the prediction of a future course of a disease or condition in an individual who has the disease or condition (e.g., predicting patient survival), and such terms encompass the evaluation of disease response after the administration of a treatment or therapy to the individual.

[0110] "Evaluate", "evaluating", "evaluation", and variations thereof encompass both "diagnose" and "prognose" and also encompass determinations or predictions about the future course of a disease or condition in an individual who does not have the disease as well as determinations or predictions regarding the likelihood that a disease or condition will recur in an individual who apparently has been cured of the disease. The term "evaluate" also encompasses assessing an individual's response to a therapy, such as, for example, predicting whether an individual is likely to respond favorably to a therapeutic agent or is unlikely to respond to a therapeutic agent (or will experience toxic or other undesirable side effects, for example), selecting a therapeutic agent for administration to an individual, or monitoring or determining an individual's response to a therapy that has been administered to the individual. Thus, "evaluating" ovarian cancer can include, for example, any of the following: prognosing the future course of ovarian cancer in an individual; predicting the recurrence of ovarian cancer in an individual who apparently has been cured of ovarian cancer; or determining or predicting an individual's response to an ovarian cancer treatment or selecting an ovarian cancer treatment to administer to an individual based upon a determination of the biomarker values derived from the individual's biological sample.

[0111] Any of the following examples may be referred to as either "diagnosing" or "evaluating" ovarian cancer: initially detecting the presence or absence of ovarian cancer; determining a specific stage, type or sub-type, or other classification or characteristic of ovarian cancer; determining whether a pelvic mass is benign or malignant; or detecting or monitoring ovarian cancer progression (e.g., monitoring ovarian tumor growth or metastatic spread), remission, or recurrence.

[0112] As used herein, "additional biomedical information" refers to one or more evaluations of an individual, other than using any of the biomarkers described herein, that are associated with ovarian cancer risk. "Additional biomedical information" includes any of the following: physical descriptors of an individual; physical descriptors of a pelvic mass observed by MRI, abdominal ultrasound, or CT imaging; the height and/or weight of an individual; change in weight; the ethnicity of an individual; occupational history; family history of ovarian cancer (or other cancer); the presence of a genetic marker(s) correlating with a higher risk of ovarian cancer in the individual or a family member; the presence of a pelvic mass; size of mass; location of mass; morphology of mass and associated pelvic region (e.g., as observed through imaging); clinical symptoms such as bloating, abdominal pain, or sudden weight gain or loss; and the like. Additional biomedical information can be obtained from an individual using routine techniques known in the art, such as from the individual themselves by use of a routine patient questionnaire or health history questionnaire, etc., or from a medical practitioner, etc. Alternately, additional biomedical information can be obtained from routine imaging techniques, including abdominal or transvaginal ultrasound, MRI, CT imaging, and PET-CT. Testing of biomarker levels in combination with an evaluation of any additional biomedical information, including other laboratory tests (e.g., CA-125 testing), may, for example, improve sensitivity, specificity, and/or AUC for detecting ovarian cancer (or other ovarian cancer-related uses) as compared to biomarker testing alone or evaluating any particular item of additional biomedical information alone (e.g., ultrasound imaging alone).

[0113] The term "area under the curve" or "AUC" refers to the area under the curve of a receiver operating characteristic (ROC) curve, both of which are well known in the art. AUC measures are useful for comparing the accuracy of a classifier across the complete data range. Classifiers with a greater AUC have a greater capacity to classify unknowns correctly between two groups of interest (e.g., ovarian cancer samples and normal or control samples). ROC curves are useful for plotting the performance of a particular feature (e.g., any of the biomarkers described herein and/or any item of additional biomedical information) in distinguishing between two populations (e.g., cases having ovarian cancer and controls without ovarian cancer). Typically, the feature data across the entire population (e.g., the cases and controls) are sorted in ascending order based on the value of a single feature. Then, for each value for that feature, the true positive and false positive rates for the data are calculated. The true positive rate is determined by counting the number of cases above the value for that feature and then dividing by the total number of cases. The false positive rate is determined by counting the number of controls above the value for that feature and then dividing by the total number of controls. Although this definition refers to scenarios in which a feature is elevated in cases compared to controls, this definition also applies to scenarios in which a feature is lower in cases compared to the controls (in such a scenario, samples below the value for that feature would be counted). ROC curves can be generated for a single feature as

well as for other single outputs, for example, a combination of two or more features can be mathematically combined (e.g., added, subtracted, multiplied, etc.) to provide a single sum value, and this single sum value can be plotted in a ROC curve. Additionally, any combination of multiple features, in which the combination derives a single output value, can be plotted in a ROC curve. These combinations of features may comprise a test. The ROC curve is the plot of the true positive rate (sensitivity) of a test against the false positive rate (1-specificity) of the test.

[0114] As used herein, "detecting" or "determining" with respect to a biomarker value includes the use of both the instrument required to observe and record a signal corresponding to a biomarker value and the material/s required to generate that signal. In various embodiments, the biomarker value is detected using any suitable method, including fluorescence, chemiluminescence, surface plasmon resonance, surface acoustic waves, mass spectrometry, infrared spectroscopy, Raman spectroscopy, atomic force microscopy, scanning tunneling microscopy, electrochemical detection methods, nuclear magnetic resonance, quantum dots, and the like.

[0115] "Solid support" refers herein to any substrate having a surface to which molecules may be attached, directly or indirectly, through either covalent or non-covalent bonds. A "solid support" can have a variety of physical formats, which can include, for example, a membrane; a chip (e.g., a protein chip); a slide (e.g., a glass slide or coverslip); a column; a hollow, solid, semi-solid, pore- or cavity-containing particle, such as, for example, a bead; a gel; a fiber, including a fiber optic material; a matrix; and a sample receptacle. Exemplary sample receptacles include sample wells, tubes, capillaries, vials, and any other vessel, groove or indentation capable of holding a sample. A sample receptacle can be contained on a multi-sample platform, such as a microtiter plate, slide, microfluidics device, and the like. A support can be composed of a natural or synthetic material, an organic or inorganic material. The composition of the solid support on which capture reagents are attached generally depends on the method of attachment (e.g., covalent attachment). Other exemplary receptacles include microdroplets and microfluidic controlled or bulk oil/aqueous emulsions within which assays and related manipulations can occur. Suitable solid supports include, for example, plastics, resins, polysaccharides, silica or silica-based materials, functionalized glass, modified silicon, carbon, metals, inorganic glasses, membranes, nylon, natural fibers (such as, for example, silk, wool and cotton), polymers, and the like. The material composing the solid support can include reactive groups such as, for example, carboxy, amino, or hydroxyl groups, which are used for attachment of the capture reagents. Polymeric solid supports can include, e.g., polystyrene, polyethylene glycol tetraphthalate, polyvinyl acetate, polyvinyl chloride, polyvinyl pyrrolidone, polyacrylonitrile, polymethyl methacrylate, polytetrafluoroethylene, butyl rubber, styrenebutadiene rubber, natural rubber, polyethylene, polypropylene, (poly)tetrafluoroethylene, (poly)vinylidenefluoride, polycarbonate, and polymethylpentene. Suitable solid support particles that can be used include, e.g., encoded particles, such as Luminex®-type encoded particles, magnetic particles, and glass particles.

Exemplary Uses of Biomarkers

[0116] In various exemplary embodiments, methods are provided for diagnosing ovarian cancer in an individual by detecting one or more biomarker values corresponding to one or more biomarkers that are present in the circulation of an individual, such as in serum or plasma, by any number of analytical methods, including any of the analytical methods described herein. These biomarkers are, for example, differentially expressed in individuals with ovarian cancer as compared to individuals without ovarian cancer. Detection of the differential expression of a biomarker in an individual can be used, for example, to permit the early diagnosis of ovarian cancer, to distinguish between a benign pelvic mass and ovarian cancer (such as, for example, a mass observed on an abdominal ultrasound or computed tomography (CT) scan), to monitor ovarian cancer recurrence, or for other clinical indications.

[0117] Any of the biomarkers described herein may be used in a variety of clinical indications for ovarian cancer, including any of the following: detection of ovarian cancer (such as in a high-risk individual or population); characterizing ovarian cancer (e.g., determining ovarian cancer type, sub-type, or stage), such as by determining whether a pelvic mass is benign or malignant; determining ovarian cancer prognosis; monitoring ovarian cancer progression or remission; monitoring for ovarian cancer recurrence; monitoring metastasis; treatment selection (e.g., pre- or post-operative chemotherapy selection); monitoring response to a therapeutic agent or other treatment; combining biomarker testing with additional biomedical information, such as CA-125 level, the presence of a genetic marker(s) indicating a higher risk for ovarian cancer, etc., or with mass size, morphology, presence of ascites, etc. (such as to provide an assay with increased diagnostic performance compared to CA-125 testing or other biomarker testing alone); facilitating the diagnosis of a pelvic mass as malignant or benign; facilitating clinical decision making once a pelvic mass is observed through imaging; and facilitating decisions regarding clinical follow-up (e.g., whether to refer an individual to a surgical specialist, such as a gynecologic oncology surgeon). Biomarker testing may improve positive predictive value (PPV) over CA-125 testing and imaging alone. Furthermore, the described biomarkers may also be useful in permitting certain of these uses before indications of ovarian cancer are detected by imaging modalities or other clinical correlates, or before symptoms appear.

[0118] As an example of the manner in which any of the biomarkers described herein can be used to diagnose ovarian cancer, differential expression of one or more of the described biomarkers in an individual who is not known to have ovarian cancer may indicate that the individual has ovarian cancer, thereby enabling detection of ovarian cancer at an early stage of the disease when treatment is most effective, perhaps before the ovarian cancer is detected by other means or before symptoms appear. Increased differential expression from "normal" (since some biomarkers may be down-regulated with disease) of one or more of the biomarkers during the course of ovarian cancer may be indicative of ovarian cancer progression, e.g., an ovarian tumor is growing and/or metastasizing (and thus indicate a poor prognosis), whereas a decrease in the degree to which one or more of the biomarkers is differentially expressed (i.e., in subsequent biomarker tests, the expression level in the individual is moving toward or approaching a "normal" expression level) may be indicative of ovarian cancer remission, e.g., an ovarian tumor is shrinking (and thus indicate a good or better prognosis). Similarly, an increase in the degree to which one or more of the biomarkers is differentially expressed (i.e., in subsequent biomar-

ker tests, the expression level in the individual is moving further away from a "normal" expression level) during the course of ovarian cancer treatment may indicate that the ovarian cancer is progressing and therefore indicate that the treatment is ineffective, whereas a decrease in differential expression of one or more of the biomarkers during the course of ovarian cancer treatment may be indicative of ovarian cancer remission and therefore indicate that the treatment is working successfully. Additionally, an increase or decrease in the differential expression of one or more of the biomarkers after an individual has apparently been cured of ovarian cancer may be indicative of ovarian cancer recurrence. In a situation such as this, for example, the individual can be restarted on therapy (or the therapeutic regimen modified such as to increase dosage amount and/or frequency, if the individual has maintained therapy) at an earlier stage than if the recurrence of ovarian cancer was not detected until later. Furthermore, a differential expression level of one or more of the biomarkers in an individual may be predictive of the individual's response to a particular therapeutic agent. In monitoring for ovarian cancer recurrence or progression, changes in the biomarker expression levels may indicate the need for repeat imaging, such as to determine ovarian cancer activity or to determine the need for changes in treatment.

[0119] Detection of any of the biomarkers described herein may be particularly useful following, or in conjunction with, ovarian cancer treatment, such as to evaluate the success of the treatment or to monitor ovarian cancer remission, recurrence, and/or progression (including metastasis) following treatment. Ovarian cancer treatment may include, for example, administration of a therapeutic agent to the individual, performance of surgery (e.g., surgical resection of at least a portion of a pelvic mass), administration of radiation therapy, or any other type of ovarian cancer treatment used in the art, and any combination of these treatments. For example, any of the biomarkers may be detected at least once after treatment or may be detected multiple times after treatment (such as at periodic intervals), or may be detected both before and after treatment. Differential expression levels of any of the biomarkers in an individual over time may be indicative of ovarian cancer progression, remission, or recurrence, examples of which include any of the following: an increase or decrease in the expression level of the biomarkers after treatment compared with the expression level of the biomarker before treatment; an increase or decrease in the expression level of the biomarker at a later time point after treatment compared with the expression level of the biomarker at an earlier time point after treatment; and a differential expression level of the biomarker at a single time point after treatment compared with normal levels of the biomarker.

[0120] As a specific example, the biomarker levels for any of the biomarkers described herein can be determined in pre-surgery and post-surgery (e.g., 2-8 weeks after surgery) serum or plasma samples. An increase in the biomarker expression level(s) in the post-surgery sample compared with the pre-surgery sample can indicate progression of ovarian cancer (e.g., unsuccessful surgery), whereas a decrease in the biomarker expression level(s) in the post-surgery sample compared with the pre-surgery sample can indicate regression of ovarian cancer (e.g., the surgery successfully removed the ovarian tumor). Similar analyses of the biomarker levels can be carried out before and after other forms of treatment, such as before and after radiation therapy or administration of a therapeutic agent or cancer vaccine.

[0121] In addition to testing biomarker levels as a standalone diagnostic test, biomarker levels can also be done in conjunction with determination of SNPs or other genetic lesions or variability that are indicative of increased risk of susceptibility of disease. (See, e.g., Amos et al., Nature Genetics 40, 616-622 (2009)).

[0122] In addition to testing biomarker levels as a standalone diagnostic test, biomarker levels can also be done in conjunction with relevant symptoms or abdominal ultrasound and CT imaging.

[0123] Detection of any of the biomarkers described herein may be useful after a pelvic mass has been observed through imaging to aid in the diagnosis of ovarian cancer and guide appropriate clinical care of the individual, including care by an appropriate surgical specialist.

[0124] In addition to testing biomarker levels in conjunction with relevant symptoms or abdominal ultrasound or CT imaging, information regarding the biomarkers can also be evaluated in conjunction with other types of data, particularly data that indicates an individual's risk for ovarian cancer (e.g., patient clinical history, symptoms, family history of cancer, risk factors such as the presence of a genetic marker(s), and/or status of other biomarkers, etc.). These various data can be assessed by automated methods, such as a computer program/software, which can be embodied in a computer or other apparatus/device.

[0125] Any of the described biomarkers may also be used in imaging tests. For example, an imaging agent can be coupled to any of the described biomarkers, which can be used to aid in ovarian cancer diagnosis, to monitor disease progression/remission or metastasis, to monitor for disease recurrence, or to monitor response to therapy, among other uses.

Detection and Determination of Biomarkers and Biomarker Values

[0126] A biomarker value for the biomarkers described herein can be detected using any of a variety of known analytical methods. In one embodiment, a biomarker value is detected using a capture reagent. As used herein, a "capture agent" or "capture reagent" refers to a molecule that is capable of binding specifically to a biomarker. In various embodiments, the capture reagent can be exposed to the biomarker in solution or can be exposed to the biomarker while the capture reagent is immobilized on a solid support. In other embodiments, the capture reagent contains a feature that is reactive with a secondary feature on a solid support. In these embodiments, the capture reagent can be exposed to the biomarker in solution, and then the feature on the capture reagent can be used in conjunction with the secondary feature on the solid support to immobilize the biomarker on the solid support. The capture reagent is selected based on the type of analysis to be conducted. Capture reagents include but are not limited to aptamers, antibodies, adnectins, ankyrins, other antibody mimetics and other protein scaffolds, autoantibodies, chimeras, small molecules, an $F(ab')_2$ fragment, a single chain antibody fragment, an Fv fragment, a single chain Fv fragment, a nucleic acid, a lectin, a ligand-binding receptor, affybodies, nanobodies, imprinted polymers, avimers, peptidomimetics, a hormone receptor, a cytokine receptor, and synthetic receptors, and modifications and fragments of these.

[0127] In some embodiments, a biomarker value is detected using a biomarker/capture reagent complex.

[0128] In other embodiments, the biomarker value is derived from the biomarker/capture reagent complex and is detected indirectly, such as, for example, as a result of a reaction that is subsequent to the biomarker/capture reagent interaction, but is dependent on the formation of the biomarker/capture reagent complex.

[0129] In some embodiments, the biomarker value is detected directly from the biomarker in a biological sample.

[0130] In one embodiment, the biomarkers are detected using a multiplexed format that allows for the simultaneous detection of two or more biomarkers in a biological sample. In one embodiment of the multiplexed format, capture reagents are immobilized, directly or indirectly, covalently or non-covalently, in discrete locations on a solid support. In another embodiment, a multiplexed format uses discrete solid supports where each solid support has a unique capture reagent associated with that solid support, such as, for example quantum dots. In another embodiment, an individual device is used for the detection of each one of multiple biomarkers to be detected in a biological sample. Individual devices can be configured to permit each biomarker in the biological sample to be processed simultaneously. For example, a microtiter plate can be used such that each well in the plate is used to uniquely analyze one of multiple biomarkers to be detected in a biological sample.

[0131] In one or more of the foregoing embodiments, a fluorescent tag can be used to label a component of the biomarker/capture complex to enable the detection of the biomarker value. In various embodiments, the fluorescent label can be conjugated to a capture reagent specific to any of the biomarkers described herein using known techniques, and the fluorescent label can then be used to detect the corresponding biomarker value. Suitable fluorescent labels include rare earth chelates, fluorescein and its derivatives, rhodamine and its derivatives, dansyl, allophycocyanin, PBXL-3, Qdot 605, Lissamine, phycoerythrin, Texas Red, and other such compounds.

[0132] In one embodiment, the fluorescent label is a fluorescent dye molecule. In some embodiments, the fluorescent dye molecule includes at least one substituted indolium ring system in which the substituent on the 3-carbon of the indolium ring contains a chemically reactive group or a conjugated substance. In some embodiments, the dye molecule includes an AlexFluor molecule, such as, for example, AlexaFluor 488, AlexaFluor 532, AlexaFluor 647, AlexaFluor 680, or AlexaFluor 700. In other embodiments, the dye molecule includes a first type and a second type of dye molecule, such as, e.g., two different AlexaFluor molecules. In other embodiments, the dye molecule includes a first type and a second type of dye molecule, and the two dye molecules have different emission spectra.

[0133] Fluorescence can be measured with a variety of instrumentation compatible with a wide range of assay formats. For example, spectrofluorimeters have been designed to analyze microtiter plates, microscope slides, printed arrays, cuvettes, etc. See Principles of Fluorescence Spectroscopy, by J. R. Lakowicz, Springer Science+Business Media, Inc., 2004. See Bioluminescence & Chemiluminescence: Progress & Current Applications; Philip E. Stanley and Larry J. Kricka editors, World Scientific Publishing Company, January 2002.

[0134] In one or more of the foregoing embodiments, a chemiluminescence tag can optionally be used to label a component of the biomarker/capture complex to enable the detection of a biomarker value. Suitable chemiluminescent materials include any of oxalyl chloride, Rodamin 6G, $Ru(bipy)_3^{2+}$, TMAE (tetrakis(dimethylamino)ethylene), Pyrogallol (1,2,3-trihydroxibenzene), Lucigenin, peroxyoxalates, Aryl oxalates, Acridinium esters, dioxetanes, and others.

[0135] In yet other embodiments, the detection method includes an enzyme/substrate combination that generates a detectable signal that corresponds to the biomarker value. Generally, the enzyme catalyzes a chemical alteration of the chromogenic substrate which can be measured using various techniques, including spectrophotometry, fluorescence, and chemiluminescence. Suitable enzymes include, for example, luciferases, luciferin, malate dehydrogenase, urease, horseradish peroxidase (HRPO), alkaline phosphatase, beta-galactosidase, glucoamylase, lysozyme, glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase, uricase, xanthine oxidase, lactoperoxidase, microperoxidase, and the like.

[0136] In yet other embodiments, the detection method can be a combination of fluorescence, chemiluminescence, radionuclide or enzyme/substrate combinations that generate a measurable signal. Multimodal signaling could have unique and advantageous characteristics in biomarker assay formats.

[0137] More specifically, the biomarker values for the biomarkers described herein can be detected using known analytical methods including, singleplex aptamer assays, multiplexed aptamer assays, singleplex or multiplexed immunoassays, mRNA expression profiling, miRNA expression profiling, mass spectrometric analysis, histological/cytological methods, etc. as detailed below.

Determination of Biomarker Values using Aptamer-Based Assays

[0138] Assays directed to the detection and quantification of physiologically significant molecules in biological samples and other samples are important tools in scientific research and in the health care field. One class of such assays involves the use of a microarray that includes one or more aptamers immobilized on a solid support. The aptamers are each capable of binding to a target molecule in a highly specific manner and with very high affinity. See, e.g., U.S. Pat. No. 5,475,096 entitled "Nucleic Acid Ligands"; see also, e.g., U.S. Pat. No. 6,242,246, U.S. Pat. No. 6,458,543, and U.S. Pat. No. 6,503,715, each of which is entitled "Nucleic Acid Ligand Diagnostic Biochip". Once the microarray is contacted with a sample, the aptamers bind to their respective target molecules present in the sample and thereby enable a determination of a biomarker value corresponding to a biomarker.

[0139] As used herein, an "aptamer" refers to a nucleic acid that has a specific binding affinity for a target molecule. It is recognized that affinity interactions are a matter of degree; however, in this context, the "specific binding affinity" of an aptamer for its target means that the aptamer binds to its target generally with a much higher degree of affinity than it binds to other components in a test sample. An "aptamer" is a set of copies of one type or species of nucleic acid molecule that has a particular nucleotide sequence. An aptamer can include any suitable number of nucleotides, including any number of chemically modified nucleotides. "Aptamers" refers to more

than one such set of molecules. Different aptamers can have either the same or different numbers of nucleotides. Aptamers can be DNA or RNA or chemically modified nucleic acids and can be single stranded, double stranded, or contain double stranded regions, and can include higher ordered structures. An aptamer can also be a photoaptamer, where a photoreactive or chemically reactive functional group is included in the aptamer to allow it to be covalently linked to its corresponding target. Any of the aptamer methods disclosed herein can include the use of two or more aptamers that specifically bind the same target molecule. As further described below, an aptamer may include a tag. If an aptamer includes a tag, all copies of the aptamer need not have the same tag. Moreover, if different aptamers each include a tag, these different aptamers can have either the same tag or a different tag.

[0140] An aptamer can be identified using any known method, including the SELEX process. Once identified, an aptamer can be prepared or synthesized in accordance with any known method, including chemical synthetic methods and enzymatic synthetic methods.

[0141] The terms "SELEX" and "SELEX process" are used interchangeably herein to refer generally to a combination of (1) the selection of aptamers that interact with a target molecule in a desirable manner, for example binding with high affinity to a protein, with (2) the amplification of those selected nucleic acids. The SELEX process can be used to identify aptamers with high affinity to a specific target or biomarker.

[0142] SELEX generally includes preparing a candidate mixture of nucleic acids, binding of the candidate mixture to the desired target molecule to form an affinity complex, separating the affinity complexes from the unbound candidate nucleic acids, separating and isolating the nucleic acid from the affinity complex, purifying the nucleic acid, and identifying a specific aptamer sequence. The process may include multiple rounds to further refine the affinity of the selected aptamer. The process can include amplification steps at one or more points in the process. See, e.g., U.S. Pat. No. 5,475,096, entitled "Nucleic Acid Ligands". The SELEX process can be used to generate an aptamer that covalently binds its target as well as an aptamer that non-covalently binds its target. See, e.g., U.S. Pat. No. 5,705,337 entitled "Systematic Evolution of Nucleic Acid Ligands by Exponential Enrichment: Chemi-SELEX."

[0143] The SELEX process can be used to identify high-affinity aptamers containing modified nucleotides that confer improved characteristics on the aptamer, such as, for example, improved in vivo stability or improved delivery characteristics. Examples of such modifications include chemical substitutions at the ribose and/or phosphate and/or base positions. SELEX process-identified aptamers containing modified nucleotides are described in U.S. Pat. No. 5,660,985, entitled "High Affinity Nucleic Acid Ligands Containing Modified Nucleotides", which describes oligonucleotides containing nucleotide derivatives chemically modified at the 5'- and 2'-positions of pyrimidines. U.S. Pat. No. 5,580,737, see supra, describes highly specific aptamers containing one or more nucleotides modified with 2'-amino (2'-NH2), 2'-fluoro (2'-F), and/or 2'-O-methyl (2'-OMe). See also, U.S. Patent Application Publication 20090098549, entitled "SELEX and PHOTOSELEX", which describes nucleic acid libraries having expanded physical and chemical properties and their use in SELEX and photoSELEX.

[0144] SELEX can also be used to identify aptamers that have desirable off-rate characteristics. See U.S. Patent Application Publication 20090004667, entitled "Method for Generating Aptamers with Improved Off-Rates", which describes improved SELEX methods for generating aptamers that can bind to target molecules. Methods for producing aptamers and photoaptamers having slower rates of dissociation from their respective target molecules are described. The methods involve contacting the candidate mixture with the target molecule, allowing the formation of nucleic acid-target complexes to occur, and performing a slow off-rate enrichment process wherein nucleic acid-target complexes with fast dissociation rates will dissociate and not reform, while complexes with slow dissociation rates will remain intact. Additionally, the methods include the use of modified nucleotides in the production of candidate nucleic acid mixtures to generate aptamers with improved off-rate performance.

[0145] A variation of this assay employs aptamers that include photoreactive functional groups that enable the aptamers to covalently bind or "photocrosslink" their target molecules. See, e.g., U.S. Pat. No. 6,544,776 entitled "Nucleic Acid Ligand Diagnostic Biochip". These photoreactive aptamers are also referred to as photoaptamers. See, e.g., U.S. Pat. No. 5,763,177, U.S. Pat. No. 6,001,577, and U.S. Pat. No. 6,291,184, each of which is entitled "Systematic Evolution of Nucleic Acid Ligands by Exponential Enrichment: Photoselection of Nucleic Acid Ligands and Solution SELEX"; see also, e.g., U.S. Pat. No. 6,458,539, entitled "Photoselection of Nucleic Acid Ligands". After the microarray is contacted with the sample and the photoaptamers have had an opportunity to bind to their target molecules, the photoaptamers are photoactivated, and the solid support is washed to remove any non-specifically bound molecules. Harsh wash conditions may be used, since target molecules that are bound to the photoaptamers are generally not removed, due to the covalent bonds created by the photoactivated functional group(s) on the photoaptamers. In this manner, the assay enables the detection of a biomarker value corresponding to a biomarker in the test sample.

[0146] In both of these assay formats, the aptamers are immobilized on the solid support prior to being contacted with the sample. Under certain circumstances, however, immobilization of the aptamers prior to contact with the sample may not provide an optimal assay. For example, pre-immobilization of the aptamers may result in inefficient mixing of the aptamers with the target molecules on the surface of the solid support, perhaps leading to lengthy reaction times and, therefore, extended incubation periods to permit efficient binding of the aptamers to their target molecules. Further, when photoaptamers are employed in the assay and depending upon the material utilized as a solid support, the solid support may tend to scatter or absorb the light used to effect the formation of covalent bonds between the photoaptamers and their target molecules. Moreover, depending upon the method employed, detection of target molecules bound to their aptamers can be subject to imprecision, since the surface of the solid support may also be exposed to and affected by any labeling agents that are used. Finally, immobilization of the aptamers on the solid support generally involves an aptamer-preparation step (i.e., the immobilization) prior to

exposure of the aptamers to the sample, and this preparation step may affect the activity or functionality of the aptamers.

[0147] Aptamer assays that permit an aptamer to capture its target in solution and then employ separation steps that are designed to remove specific components of the aptamer-target mixture prior to detection have also been described (see U.S. Patent Application Publication 20090042206, entitled "Multiplexed Analyses of Test Samples"). The described aptamer assay methods enable the detection and quantification of a non-nucleic acid target (e.g., a protein target) in a test sample by detecting and quantifying a nucleic acid (i.e., an aptamer). The described methods create a nucleic acid surrogate (i.e., the aptamer) for detecting and quantifying a non-nucleic acid target, thus allowing the wide variety of nucleic acid technologies, including amplification, to be applied to a broader range of desired targets, including protein targets.

[0148] Aptamers can be constructed to facilitate the separation of the assay components from an aptamer biomarker complex (or photoaptamer biomarker covalent complex) and permit isolation of the aptamer for detection and/or quantification. In one embodiment, these constructs can include a cleavable or releasable element within the aptamer sequence. In other embodiments, additional functionality can be introduced into the aptamer, for example, a labeled or detectable component, a spacer component, or a specific binding tag or immobilization element. For example, the aptamer can include a tag connected to the aptamer via a cleavable moiety, a label, a spacer component separating the label, and the cleavable moiety. In one embodiment, a cleavable element is a photocleavable linker. The photocleavable linker can be attached to a biotin moiety and a spacer section, can include an NHS group for derivatization of amines, and can be used to introduce a biotin group to an aptamer, thereby allowing for the release of the aptamer later in an assay method.

[0149] Homogenous assays, done with all assay components in solution, do not require separation of sample and reagents prior to the detection of signal. These methods are rapid and easy to use. These methods generate signal based on a molecular capture or binding reagent that reacts with its specific target. For ovarian cancer, the molecular capture reagents would be an aptamer or an antibody or the like and the specific target would be an ovarian cancer biomarker of Table 1.

[0150] In one embodiment, a method for signal generation takes advantage of anisotropy signal change due to the interaction of a fluorophore-labeled capture reagent with its specific biomarker target. When the labeled capture reacts with its target, the increased molecular weight causes the rotational motion of the fluorophore attached to the complex to become much slower changing the anisotropy value. By monitoring the anisotropy change, binding events may be used to quantitatively measure the biomarkers in solutions. Other methods include fluorescence polarization assays, molecular beacon methods, time resolved fluorescence quenching, chemiluminescence, fluorescence resonance energy transfer, and the like.

[0151] An exemplary solution-based aptamer assay that can be used to detect a biomarker value corresponding to a biomarker in a biological sample includes the following: (a) preparing a mixture by contacting the biological sample with an aptamer that includes a first tag and has a specific affinity for the biomarker, wherein an aptamer affinity complex is formed when the biomarker is present in the sample; (b) exposing the mixture to a first solid support including a first capture element, and allowing the first tag to associate with the first capture element; (c) removing any components of the mixture not associated with the first solid support; (d) attaching a second tag to the biomarker component of the aptamer affinity complex; (e) releasing the aptamer affinity complex from the first solid support; (f) exposing the released aptamer affinity complex to a second solid support that includes a second capture element and allowing the second tag to associate with the second capture element; (g) removing any non-complexed aptamer from the mixture by partitioning the non-complexed aptamer from the aptamer affinity complex; (h) eluting the aptamer from the solid support; and (i) detecting the biomarker by detecting the aptamer component of the aptamer affinity complex.

Determination of Biomarker Values Using Immunoassays

[0152] Immunoassay methods are based on the reaction of an antibody to its corresponding target or analyte and can detect the analyte in a sample depending on the specific assay format. To improve specificity and sensitivity of an assay method based on immuno-reactivity, monoclonal antibodies are often used because of their specific epitope recognition. Polyclonal antibodies have also been successfully used in various immunoassays because of their increased affinity for the target as compared to monoclonal antibodies Immunoassays have been designed for use with a wide range of biological sample matrices Immunoassay formats have been designed to provide qualitative, semi-quantitative, and quantitative results.

[0153] Quantitative results are generated through the use of a standard curve created with known concentrations of the specific analyte to be detected. The response or signal from an unknown sample is plotted onto the standard curve, and a quantity or value corresponding to the target in the unknown sample is established.

[0154] Numerous immunoassay formats have been designed. ELISA or EIA can be quantitative for the detection of an analyte. This method relies on attachment of a label to either the analyte or the antibody and the label component includes, either directly or indirectly, an enzyme. ELISA tests may be formatted for direct, indirect, competitive, or sandwich detection of the analyte. Other methods rely on labels such as, for example, radioisotopes (I^{125}) or fluorescence. Additional techniques include, for example, agglutination, nephelometry, turbidimetry, Western blot, immunoprecipitation, immunocytochemistry, immunohistochemistry, flow cytometry, Luminex assay, and others (see ImmunoAssay: A Practical Guide, edited by Brian Law, published by Taylor & Francis, Ltd., 2005 edition).

[0155] Exemplary assay formats include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay, fluorescent, chemiluminescence, and fluorescence resonance energy transfer (FRET) or time resolved-FRET (TR-FRET) immunoassays. Examples of procedures for detecting biomarkers include biomarker immunoprecipitation followed by quantitative methods that allow size and peptide level discrimination, such as gel electrophoresis, capillary electrophoresis, planar electrochromatography, and the like.

[0156] Methods of detecting and/or quantifying a detectable label or signal generating material depend on the nature

of the label. The products of reactions catalyzed by appropriate enzymes (where the detectable label is an enzyme; see above) can be, without limitation, fluorescent, luminescent, or radioactive or they may absorb visible or ultraviolet light. Examples of detectors suitable for detecting such detectable labels include, without limitation, x-ray film, radioactivity counters, scintillation counters, spectrophotometers, colorimeters, fluorometers, luminometers, and densitometers.

[0157] Any of the methods for detection can be performed in any format that allows for any suitable preparation, processing, and analysis of the reactions. This can be, for example, in multi-well assay plates (e.g., 96 wells or 384 wells) or using any suitable array or microarray. Stock solutions for various agents can be made manually or robotically, and all subsequent pipetting, diluting, mixing, distribution, washing, incubating, sample readout, data collection and analysis can be done robotically using commercially available analysis software, robotics, and detection instrumentation capable of detecting a detectable label.

Determination of Biomarker Values Using Gene Expression Profiling

[0158] Measuring mRNA in a biological sample may be used as a surrogate for detection of the level of the corresponding protein in the biological sample. Thus, any of the biomarkers or biomarker panels described herein can also be detected by detecting the appropriate RNA.

[0159] mRNA expression levels are measured by reverse transcription quantitative polymerase chain reaction (RT-PCR followed with qPCR). RT-PCR is used to create a cDNA from the mRNA. The cDNA may be used in a qPCR assay to produce fluorescence as the DNA amplification process progresses. By comparison to a standard curve, qPCR can produce an absolute measurement such as number of copies of mRNA per cell. Northern blots, microarrays, Invader assays, and RT-PCR combined with capillary electrophoresis have all been used to measure expression levels of mRNA in a sample. See Gene Expression Profiling: Methods and Protocols, Richard A. Shimkets, editor, Humana Press, 2004.

[0160] miRNA molecules are small RNAs that are non-coding but may regulate gene expression. Any of the methods suited to the measurement of mRNA expression levels can also be used for the corresponding miRNA. Recently many laboratories have investigated the use of miRNAs as biomarkers for disease. Many diseases involve wide-spread transcriptional regulation, and it is not surprising that miRNAs might find a role as biomarkers. The connection between miRNA concentrations and disease is often even less clear than the connections between protein levels and disease, yet the value of miRNA biomarkers might be substantial. Of course, as with any RNA expressed differentially during disease, the problems facing the development of an in vitro diagnostic product will include the requirement that the miRNAs survive in the diseased cell and are easily extracted for analysis, or that the miRNAs are released into blood or other matrices where they must survive long enough to be measured. Protein biomarkers have similar requirements, although many potential protein biomarkers are secreted intentionally at the site of pathology and function, during disease, in a paracrine fashion. Many potential protein biomarkers are designed to function outside the cells within which those proteins are synthesized.

Detection of Biomarkers Using In Vivo Molecular Imaging Technologies

[0161] Any of the described biomarkers (see Table 1) may also be used in molecular imaging tests. For example, an imaging agent can be coupled to any of the described biomarkers, which can be used to aid in ovarian cancer diagnosis, to monitor disease progression/remission or metastasis, to monitor for disease recurrence, or to monitor response to therapy, among other uses.

[0162] In vivo imaging technologies provide non-invasive methods for determining the state of a particular disease in the body of an individual. For example, entire portions of the body, or even the entire body, may be viewed as a three dimensional image, thereby providing valuable information concerning morphology and structures in the body. Such technologies may be combined with the detection of the biomarkers described herein to provide information concerning the cancer status, in particular the ovarian cancer status, of an individual.

[0163] The use of in vivo molecular imaging technologies is expanding due to various advances in technology. These advances include the development of new contrast agents or labels, such as radiolabels and/or fluorescent labels, which can provide strong signals within the body; and the development of powerful new imaging technology, which can detect and analyze these signals from outside the body, with sufficient sensitivity and accuracy to provide useful information. The contrast agent can be visualized in an appropriate imaging system, thereby providing an image of the portion or portions of the body in which the contrast agent is located. The contrast agent may be bound to or associated with a capture reagent, such as an aptamer or an antibody, for example, and/or with a peptide or protein, or an oligonucleotide (for example, for the detection of gene expression), or a complex containing any of these with one or more macromolecules and/or other particulate forms.

[0164] The contrast agent may also feature a radioactive atom that is useful in imaging. Suitable radioactive atoms include technetium-99m or iodine-123 for scintigraphic studies. Other readily detectable moieties include, for example, spin labels for magnetic resonance imaging (MRI) such as, for example, iodine-123 again, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron. Such labels are well known in the art and could easily be selected by one of ordinary skill in the art.

[0165] Standard imaging techniques include but are not limited to magnetic resonance imaging, contrast-enhanced abdominal or transvaginal ultrasound, computed tomography (CT) scanning, positron emission tomography (PET), single photon emission computed tomography (SPECT), and the like. For diagnostic in vivo imaging, the type of detection instrument available is a major factor in selecting a given contrast agent, such as a given radionuclide and the particular biomarker that it is used to target (protein, mRNA, and the like). The radionuclide chosen typically has a type of decay that is detectable by a given type of instrument. Also, when selecting a radionuclide for in vivo diagnosis, its half-life should be long enough to enable detection at the time of maximum uptake by the target tissue but short enough that deleterious radiation of the host is minimized.

[0166] Exemplary imaging techniques include but are not limited to PET and SPECT, which are imaging techniques in

which a radionuclide is synthetically or locally administered to an individual. The subsequent uptake of the radiotracer is measured over time and used to obtain information about the targeted tissue and the biomarker. Because of the high-energy (gamma-ray) emissions of the specific isotopes employed and the sensitivity and sophistication of the instruments used to detect them, the two-dimensional distribution of radioactivity may be inferred from outside of the body.

[0167] Commonly used positron-emitting nuclides in PET include, for example, carbon-11, nitrogen-13, oxygen-15, and fluorine-18. Isotopes that decay by electron capture and/or gamma-emission are used in SPECT and include, for example iodine-123 and technetium-99m. An exemplary method for labeling amino acids with technetium-99m is the reduction of pertechnetate ion in the presence of a chelating precursor to form the labile technetium-99m-precursor complex, which, in turn, reacts with the metal binding group of a bifunctionally modified chemotactic peptide to form a technetium-99m-chemotactic peptide conjugate.

[0168] Antibodies are frequently used for such in vivo imaging diagnostic methods. The preparation and use of antibodies for in vivo diagnosis is well known in the art. Labeled antibodies which specifically bind any of the biomarkers in Table 1 can be injected into an individual suspected of having a certain type of cancer (e.g., ovarian cancer), detectable according to the particular biomarker used, for the purpose of diagnosing or evaluating the disease status of the individual. The label used will be selected in accordance with the imaging modality to be used, as previously described. Localization of the label permits determination of the spread of the cancer. The amount of label within an organ or tissue also allows determination of the presence or absence of cancer in that organ or tissue.

[0169] Similarly, aptamers may be used for such in vivo imaging diagnostic methods. For example, an aptamer that was used to identify a particular biomarker described in Table 1 (and therefore binds specifically to that particular biomarker) may be appropriately labeled and injected into an individual suspected of having ovarian cancer, detectable according to the particular biomarker, for the purpose of diagnosing or evaluating the ovarian cancer status of the individual. The label used will be selected in accordance with the imaging modality to be used, as previously described. Localization of the label permits determination of the spread of the cancer. The amount of label within an organ or tissue also allows determination of the presence or absence of cancer in that organ or tissue. Aptamer-directed imaging agents could have unique and advantageous characteristics relating to tissue penetration, tissue distribution, kinetics, elimination, potency, and selectivity as compared to other imaging agents.

[0170] Such techniques may also optionally be performed with labeled oligonucleotides, for example, for detection of gene expression through imaging with antisense oligonucleotides. These methods are used for in situ hybridization, for example, with fluorescent molecules or radionuclides as the label. Other methods for detection of gene expression include, for example, detection of the activity of a reporter gene.

[0171] Another general type of imaging technology is optical imaging, in which fluorescent signals within the subject are detected by an optical device that is external to the subject. These signals may be due to actual fluorescence and/or to bioluminescence. Improvements in the sensitivity of optical detection devices have increased the usefulness of optical imaging for in vivo diagnostic assays.

[0172] The use of in vivo molecular biomarker imaging is increasing, including for clinical trials, for example, to more rapidly measure clinical efficacy in trials for new cancer therapies and/or to avoid prolonged treatment with a placebo for those diseases, such as multiple sclerosis, in which such prolonged treatment may be considered to be ethically questionable.

[0173] For a review of other techniques, see N. Blow, Nature Methods, 6, 465-469, 2009.

Determination of Biomarker Values Using Histology or Cytology Methods

[0174] For evaluation of ovarian cancer, a variety of tissue samples may be used in histological or cytological methods. Sample selection depends on the primary tumor location and sites of metastases. For example, fine needle aspirates, cutting needles, and core biopsies can be used for histology. Ascites can be used for cyotology. While cytological analysis is still used in the diagnosis of ovarian cancer, histological methods are known to provide better sensitivity for the detection of cancer. Any of the biomarkers identified herein that were shown to be up-regulated (see Table 15) in the individuals with ovarian cancer can be used to stain a histological specimen as an indication of disease.

[0175] In one embodiment, one or more capture reagents specific to the corresponding biomarker is used in a cytological evaluation of an ovarian cell sample and may include one or more of the following: collecting a cell sample, fixing the cell sample, dehydrating, clearing, immobilizing the cell sample on a microscope slide, permeabilizing the cell sample, treating for analyte retrieval, staining, destaining, washing, blocking, and reacting with one or more capture reagent/s in a buffered solution. In another embodiment, the cell sample is produced from a cell block.

[0176] In another embodiment, one or more capture reagents specific to the corresponding biomarker is used in a histological evaluation of an ovarian tissue sample and may include one or more of the following: collecting a tissue specimen, fixing the tissue sample, dehydrating, clearing, immobilizing the tissue sample on a microscope slide, permeabilizing the tissue sample, treating for analyte retrieval, staining, destaining, washing, blocking, rehydrating, and reacting with capture reagent/s in a buffered solution. In another embodiment, fixing and dehydrating are replaced with freezing.

[0177] In another embodiment, the one or more aptamers specific to the corresponding biomarker is reacted with the histological or cytological sample and can serve as the nucleic acid target in a nucleic acid amplification method. Suitable nucleic acid amplification methods include, for example, PCR, q-beta replicase, rolling circle amplification, strand displacement, helicase dependent amplification, loop mediated isothermal amplification, ligase chain reaction, and restriction and circularization aided rolling circle amplification.

[0178] In one embodiment, the one or more capture reagent/s specific to the corresponding biomarkers for use in the histological or cytological evaluation are mixed in a buffered solution that can include any of the following: blocking

materials, competitors, detergents, stabilizers, carrier nucleic acid, polyanionic materials, etc.

[0179] A "cytology protocol" generally includes sample collection, sample fixation, sample immobilization, and staining. "Cell preparation" can include several processing steps after sample collection, including the use of one or more slow off-rate aptamers for the staining of the prepared cells.

[0180] Sample collection can include directly placing the sample in an untreated transport container, placing the sample in a transport container containing some type of media, or placing the sample directly onto a slide (immobilization) without any treatment or fixation.

[0181] Sample immobilization can be improved by applying a portion of the collected specimen to a glass slide that is treated with polylysine, gelatin, or a silane. Slides can be prepared by smearing a thin and even layer of cells across the slide. Care is generally taken to minimize mechanical distortion and drying artifacts. Liquid specimens can be processed in a cell block method. Or, alternatively, liquid specimens can be mixed 1:1 with the fixative solution for about 10 minutes at room temperature.

[0182] Cell blocks can be prepared from residual effusions, sputum, urine sediments, gastrointestinal fluids, cell scraping, ascites, or fine needle aspirates. Cells are concentrated or packed by centrifugation or membrane filtration. A number of methods for cell block preparation have been developed. Representative procedures include the fixed sediment, bacterial agar, or membrane filtration methods. In the fixed sediment method, the cell sediment is mixed with a fixative like Bouins, picric acid, or buffered formalin and then the mixture is centrifuged to pellet the fixed cells. The supernatant is removed, drying the cell pellet as completely as possible. The pellet is collected and wrapped in lens paper and then placed in a tissue cassette. The tissue cassette is placed in a jar with additional fixative and processed as a tissue sample. Agar method is very similar but the pellet is removed and dried on paper towel and then cut in half. The cut side is placed in a drop of melted agar on a glass slide and then the pellet is covered with agar making sure that no bubbles form in the agar. The agar is allowed to harden and then any excess agar is trimmed away. This is placed in a tissue cassette and the tissue process completed. Alternatively, the pellet may be directly suspended in 2% liquid agar at 65° C. and the sample centrifuged. The agar cell pellet is allowed to solidify for an hour at 4° C. The solid agar may be removed from the centrifuge tube and sliced in half. The agar is wrapped in filter paper and then the tissue cassette. Processing from this point forward is as described above. Centrifugation can be replaced in any these procedures with membrane filtration. Any of these processes may be used to generate a "cell block sample".

[0183] Cell blocks can be prepared using specialized resin including Lowicryl resins, LR White, LR Gold, Unicryl, and MonoStep. These resins have low viscosity and can be polymerized at low temperatures and with ultra violet (UV) light. The embedding process relies on progressively cooling the sample during dehydration, transferring the sample to the resin, and polymerizing a block at the final low temperature at the appropriate UV wavelength.

[0184] Cell block sections can be stained with hematoxylin-eosin for cytomorphological examination while additional sections are used for examination for specific markers.

[0185] Whether the process is cytologoical or histological, the sample may be fixed prior to additional processing to prevent sample degradation. This process is called "fixation" and describes a wide range of materials and procedures that may be used interchangeably. The sample fixation protocol and reagents are best selected empirically based on the targets to be detected and the specific cell/tissue type to be analyzed. Sample fixation relies on reagents such as ethanol, polyethylene glycol, methanol, formalin, or isopropanol. The samples should be fixed as soon after collection and affixation to the slide as possible. However, the fixative selected can introduce structural changes into various molecular targets making their subsequent detection more difficult. The fixation and immobilization processes and their sequence can modify the appearance of the cell and these changes must be anticipated and recognized by the cytotechnologist. Fixatives can cause shrinkage of certain cell types and cause the cytoplasm to appear granular or reticular. Many fixatives function by crosslinking cellular components. This can damage or modify specific epitopes, generate new epitopes, cause molecular associations, and reduce membrane permeability. Formalin fixation is one of the most common cytological and histological approaches. Formalin forms methyl bridges between neighboring proteins or within proteins. Precipitation or coagulation is also used for fixation and ethanol is frequently used in this type of fixation. A combination of crosslinking and precipitation can also be used for fixation. A strong fixation process is best at preserving morphological information while a weaker fixation process is best for the preservation of molecular targets.

[0186] A representative fixative is 50% absolute ethanol, 2 mM polyethylene glycol (PEG), 1.85% formaldehyde. Variations on this formulation include ethanol (50% to 95%), methanol (20%-50%), and formalin (formaldehyde) only. Another common fixative is 2% PEG 1500, 50% ethanol, and 3% methanol. Slides are place in the fixative for about 10 to 15 minutes at room temperature and then removed and allowed to dry. Once slides are fixed they can be rinsed with a buffered solution like PBS.

[0187] A wide range of dyes can be used to differentially highlight and contrast or "stain" cellular, sub-cellular, and tissue features or morphological structures. Hematoylin is used to stain nuclei a blue or black color. Orange G-6 and Eosin Azure both stain the cell's cytoplasm. Orange G stains keratin and glycogen containing cells yellow. Eosin Y is used to stain nucleoli, cilia, red blood cells, and superficial epithelial squamous cells. Romanowsky stains are used for air dried slides and are useful in enhancing pleomorphism and distinguishing extracellular from intracytoplasmic material.

[0188] The staining process can include a treatment to increase the permeability of the cells to the stain. Treatment of the cells with a detergent can be used to increase permeability. To increase cell and tissue permeability, fixed samples can be further treated with solvents, saponins, or non-ionic detergents. Enzymatic digestion can also improve the accessibility of specific targets in a tissue sample.

[0189] After staining, the sample is dehydrated using a succession of alcohol rinses with increasing alcohol concentration. The final wash is done with xylene or a xylene substitute, such as a citrus terpene, that has a refractive index close to that of the coverslip to be applied to the slide. This final step is referred to as clearing. Once the sample is dehy-

drated and cleared, a mounting medium is applied. The mounting medium is selected to have a refractive index close to the glass and is capable of bonding the coverslip to the slide. It will also inhibit the additional drying, shrinking, or fading of the cell sample.

[0190] Regardless of the stains or processing used, the final evaluation of the ovarian cytological specimen is made by some type of microscopy to permit a visual inspection of the morphology and a determination of the marker's presence or absence. Exemplary microscopic methods include bright-field, phase contrast, fluorescence, and differential interference contrast.

[0191] If secondary tests are required on the sample after examination, the coverslip may be removed and the slide destained. Destaining involves using the original solvent systems used in staining the slide originally without the added dye and in a reverse order to the original staining procedure. Destaining may also be completed by soaking the slide in an acid alcohol until the cells are colorless. Once colorless the slides are rinsed well in a water bath and the second staining procedure applied.

[0192] In addition, specific molecular differentiation may be possible in conjunction with the cellular morphological analysis through the use of specific molecular reagents such as antibodies or nucleic acid probes or aptamers. This improves the accuracy of diagnostic cytology. Micro-dissection can be used to isolate a subset of cells for additional evaluation, in particular, for genetic evaluation of abnormal chromosomes, gene expression, or mutations.

[0193] Preparation of a tissue sample for histological evaluation involves fixation, dehydration, infiltration, embedding, and sectioning. The fixation reagents used in histology are very similar or identical to those used in cytology and have the same issues of preserving morphological features at the expense of molecular ones such as individual proteins. Time can be saved if the tissue sample is not fixed and dehydrated but instead is frozen and then sectioned while frozen. This is a more gentle processing procedure and can preserve more individual markers. However, freezing is not acceptable for long term storage of a tissue sample as subcellular information is lost due to the introduction of ice crystals. Ice in the frozen tissue sample also prevents the sectioning process from producing a very thin slice and thus some microscopic resolution and imaging of subcellular structures can be lost. In addition to formalin fixation, osmium tetroxide is used to fix and stain phospholipids (membranes).

[0194] Dehydration of tissues is accomplished with successive washes of increasing alcohol concentration. Clearing employs a material that is miscible with alcohol and the embedding material and involves a stepwise process starting at 50:50 alcohol:clearing reagent and then 100% clearing agent (xylene or xylene substitute). Infiltration involves incubating the tissue with a liquid form of the embedding agent (warm wax, nitrocellulose solution) first at 50:50 embedding agent: clearing agent and the 100% embedding agent. Embedding is completed by placing the tissue in a mold or cassette and filling with melted embedding agent such as wax, agar, or gelatin. The embedding agent is allowed to harden. The hardened tissue sample may then be sliced into thin section for staining and subsequent examination.

[0195] Prior to staining, the tissue section is dewaxed and rehydrated. Xylene is used to dewax the section, one or more changes of xylene may be used, and the tissue is rehydrated by successive washes in alcohol of decreasing concentration. Prior to dewax, the tissue section may be heat immobilized to a glass slide at about 80° C. for about 20 minutes.

[0196] Laser capture micro-dissection allows the isolation of a subset of cells for further analysis from a tissue section.

[0197] As in cytology, to enhance the visualization of the microscopic features, the tissue section or slice can be stained with a variety of stains. A large menu of commercially available stains can be used to enhance or identify specific features.

[0198] To further increase the interaction of molecular reagents with cytological or histological samples, a number of techniques for "analyte retrieval" have been developed. The first such technique uses high temperature heating of a fixed sample. This method is also referred to as heat-induced epitope retrieval or HIER. A variety of heating techniques have been used, including steam heating, microwaving, autoclaving, water baths, and pressure cooking or a combination of these methods of heating. Analyte retrieval solutions include, for example, water, citrate, and normal saline buffers. The key to analyte retrieval is the time at high temperature but lower temperatures for longer times have also been successfully used. Another key to analyte retrieval is the pH of the heating solution. Low pH has been found to provide the best immunostaining but also gives rise to backgrounds that frequently require the use of a second tissue section as a negative control. The most consistent benefit (increased immunostaining without increase in background) is generally obtained with a high pH solution regardless of the buffer composition. The analyte retrieval process for a specific target is empirically optimized for the target using heat, time, pH, and buffer composition as variables for process optimization. Using the microwave analyte retrieval method allows for sequential staining of different targets with antibody reagents. But the time required to achieve antibody and enzyme complexes between staining steps has also been shown to degrade cell membrane analytes. Microwave heating methods have improved in situ hybridization methods as well.

[0199] To initiate the analyte retrieval process, the section is first dewaxed and hydrated. The slide is then placed in 10 mM sodium citrate buffer pH 6.0 in a dish or jar. A representative procedure uses an 1100 W microwave and microwaves the slide at 100% power for 2 minutes followed by microwaving the slides using 20% power for 18 minutes after checking to be sure the slide remains covered in liquid. The slide is then allowed to cool in the uncovered container and then rinsed with distilled water. HIER may be used in combination with an enzymatic digestion to improve the reactivity of the target to immunochemical reagents.

[0200] One such enzymatic digestion protocol uses proteinase K. A 20 μg/ml concentration of proteinase K is prepared in 50 mM Tris Base, 1 mM EDTA, 0.5% Triton X-100, pH 8.0 buffer. The process first involves dewaxing sections in 2 changes of xylene, 5 minutes each. Then the sample is hydrated in 2 changes of 100% ethanol for 3 minutes each, 95% and 80% ethanol for 1 minute each, and then rinsed in distilled water. Sections are covered with Proteinase K working solution and incubated 10-20 minutes at 37° C. in humidified chamber (optimal incubation time may vary depending on tissue type and degree of fixation). The sections are cooled at room temperature for 10 minutes and then rinsed in PBS

Tween 20 for 2×2 min. If desired, sections can be blocked to eliminate potential interference from endogenous compounds and enzymes. The section is then incubated with primary antibody at appropriate dilution in primary antibody dilution buffer for 1 hour at room temperature or overnight at 4° C. The section is then rinsed with PBS Tween 20 for 2×2 min. Additional blocking can be performed, if required for the specific application, followed by additional rinsing with PBS Tween 20 for 3×2 min and then finally the immunostaining protocol completed.

[0201] A simple treatment with 1% SDS at room temperature has also been demonstrated to improve immunohistochemical staining. Analyte retrieval methods have been applied to slide mounted sections as well as free floating sections. Another treatment option is to place the slide in a jar containing citric acid and 0.1 Nonident P40 at pH 6.0 and heating to 95° C. The slide is then washed with a buffer solution like PBS.

[0202] For immunological staining of tissues it may be useful to block non-specific association of the antibody with tissue proteins by soaking the section in a protein solution like serum or non-fat dry milk.

[0203] Blocking reactions may include the need to do any of the following, either alone or in combination: reduce the level of endogenous biotin; eliminate endogenous charge effects; inactivate endogenous nucleases; and inactivate endogenous enzymes like peroxidase and alkaline phosphatase. Endogenous nucleases may be inactivated by degradation with proteinase K, by heat treatment, use of a chelating agent such as EDTA or EGTA, the introduction of carrier DNA or RNA, treatment with a chaotrope such as urea, thiourea, guanidine hydrochloride, guanidine thiocyanate, lithium perchlorate, etc, or diethyl pyrocarbonate. Alkaline phosphatase may be inactivated by treated with 0.1 N HCl for 5 minutes at room temperature or treatment with 1 mM levamisole. Peroxidase activity may be eliminated by treatment with 0.03% hydrogen peroxide. Endogenous biotin may be blocked by soaking the slide or section in an avidin (streptavidin, neutravidin may be substituted) solution for at least 15 minutes at room temperature. The slide or section is then washed for at least 10 minutes in buffer. This may be repeated at least three times. Then the slide or section is soaked in a biotin solution for 10 minutes. This may be repeated at least three times with a fresh biotin solution each time. The buffer wash procedure is repeated. Blocking protocols should be minimized to prevent damaging either the cell or tissue structure or the target or targets of interest but one or more of these protocols could be combined to "block" a slide or section prior to reaction with one or more slow off-rate aptamers. See Basic Medical Histology: the Biology of Cells, Tissues and Organs, authored by Richard G. Kessel, Oxford University Press, 1998.

Determination of Biomarker Values Using Mass Spectrometry Methods

[0204] A variety of configurations of mass spectrometers can be used to detect biomarker values. Several types of mass spectrometers are available or can be produced with various configurations. In general, a mass spectrometer has the following major components: a sample inlet, an ion source, a mass analyzer, a detector, a vacuum system, and instrument-control system, and a data system. Difference in the sample inlet, ion source, and mass analyzer generally define the type of instrument and its capabilities. For example, an inlet can be a capillary-column liquid chromatography source or can be a direct probe or stage such as used in matrix-assisted laser desorption. Common ion sources are, for example, electrospray, including nanospray and microspray or matrix-assisted laser desorption. Common mass analyzers include a quadrupole mass filter, ion trap mass analyzer and time-of-flight mass analyzer. Additional mass spectrometry methods are well known in the art (see Burlingame et al. Anal. Chem. 70:647 R-716R (1998); Kinter and Sherman, New York (2000)).

[0205] Protein biomarkers and biomarker values can be detected and measured by any of the following: electrospray ionization mass spectrometry (ESI-MS), ESI-MS/MS, ESI-MS/(MS)n, matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS), surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF-MS), desorption/ionization on silicon (DIOS), secondary ion mass spectrometry (SIMS), quadrupole time-of-flight (Q-TOF), tandem time-of-flight (TOF/TOF) technology, called ultraflex III TOF/TOF, atmospheric pressure chemical ionization mass spectrometry (APCI-MS), APCI-MS/MS, APCI-$(MS)^N$, atmospheric pressure photoionization mass spectrometry (APPI-MS), APPI-MS/MS, and APPI-$(MS)^N$, quadrupole mass spectrometry, Fourier transform mass spectrometry (FTMS), quantitative mass spectrometry, and ion trap mass spectrometry.

[0206] Sample preparation strategies are used to label and enrich samples before mass spectroscopic characterization of protein biomarkers and determination biomarker values. Labeling methods include but are not limited to isobaric tag for relative and absolute quantitation (iTRAQ) and stable isotope labeling with amino acids in cell culture (SILAC). Capture reagents used to selectively enrich samples for candidate biomarker proteins prior to mass spectroscopic analysis include but are not limited to aptamers, antibodies, nucleic acid probes, chimeras, small molecules, an $F(ab')_2$ fragment, a single chain antibody fragment, an Fv fragment, a single chain Fv fragment, a nucleic acid, a lectin, a ligand-binding receptor, affybodies, nanobodies, ankyrins, domain antibodies, alternative antibody scaffolds (e.g. diabodies etc) imprinted polymers, avimers, peptidomimetics, peptoids, peptide nucleic acids, threose nucleic acid, a hormone receptor, a cytokine receptor, and synthetic receptors, and modifications and fragments of these.

[0207] The foregoing assays enable the detection of biomarker values that are useful in methods for diagnosing ovarian cancer, where the methods comprise detecting, in a biological sample from an individual, at least N biomarker values that each correspond to a biomarker selected from the group consisting of the biomarkers provided in Table 1, wherein a classification, as described in detail below, using the biomarker values indicates whether the individual has ovarian cancer. While certain of the described ovarian cancer biomarkers are useful alone for detecting and diagnosing ovarian cancer, methods are also described herein for the grouping of multiple subsets of the ovarian cancer biomarkers that are each useful as a panel of three or more biomarkers. Thus, various embodiments of the instant application provide combinations comprising N biomarkers, wherein N is at least three biomarkers. In other embodiments, N is selected to be any number from 2-42 biomarkers. It will be appreciated that N can be selected to be any number from any of the above described

ranges, as well as similar, but higher order, ranges. In accordance with any of the methods described herein, biomarker values can be detected and classified individually or they can be detected and classified collectively, as for example in a multiplex assay format.

[0208] In another aspect, methods are provided for detecting an absence of ovarian cancer, the methods comprising detecting, in a biological sample from an individual, at least N biomarker values that each correspond to a biomarker selected from the group consisting of the biomarkers provided in Table 1, wherein a classification, as described in detail below, of the biomarker values indicates an absence of ovarian cancer in the individual. While certain of the described ovarian cancer biomarkers are useful alone for detecting and diagnosing the absence of ovarian cancer, methods are also described herein for the grouping of multiple subsets of the ovarian cancer biomarkers that are each useful as a panel of three or more biomarkers. Thus, various embodiments of the instant application provide combinations comprising N biomarkers, wherein N is at least three biomarkers. In other embodiments, N is selected to be any number from 2-42 biomarkers. It will be appreciated that N can be selected to be any number from any of the above described ranges, as well as similar, but higher order, ranges. In accordance with any of the methods described herein, biomarker values can be detected and classified individually or they can be detected and classified collectively, as for example in a multiplex assay format.

Classification of Biomarkers and Calculation of Disease Scores

[0209] A biomarker "signature" for a given diagnostic test contains a set of markers, each marker having different levels in the populations of interest. Different levels, in this context, may refer to different means of the marker levels for the individuals in two or more groups, or different variances in the two or more groups, or a combination of both. For the simplest form of a diagnostic test, these markers can be used to assign an unknown sample from an individual into one of two groups, either diseased or not diseased. The assignment of a sample into one of two or more groups is known as classification, and the procedure used to accomplish this assignment is known as a classifier or a classification method. Classification methods may also be referred to as scoring methods. There are many classification methods that can be used to construct a diagnostic classifier from a set of biomarker values. In general, classification methods are most easily performed using supervised learning techniques where a data set is collected using samples obtained from individuals within two (or more, for multiple classification states) distinct groups one wishes to distinguish. Since the class (group or population) to which each sample belongs is known in advance for each sample, the classification method can be trained to give the desired classification response. It is also possible to use unsupervised learning techniques to produce a diagnostic classifier.

[0210] Common approaches for developing diagnostic classifiers include decision trees; bagging+boosting+forests; rule inference based learning; Parzen Windows; linear models; logistic; neural network methods; unsupervised clustering; K-means; hierarchical ascending/descending; semi-supervised learning; prototype methods; nearest neighbor; kernel density estimation; support vector machines; hidden Markov models; Boltzmann Learning; and classifiers may be combined either simply or in ways which minimize particular objective functions. For a review, see, e.g., Pattern Classification, R. O. Duda, et al., editors, John Wiley & Sons, 2nd edition, 2001; see also, The Elements of Statistical Learning—Data Mining, Inference, and Prediction, T. Hastie, et al., editors, Springer Science+Business Media, LLC, 2nd edition, 2009; each of which is incorporated by reference in its entirety.

[0211] To produce a classifier using supervised learning techniques, a set of samples called training data are obtained. In the context of diagnostic tests, training data includes samples from the distinct groups (classes) to which unknown samples will later be assigned. For example, samples collected from individuals in a control population and individuals in a particular disease population can constitute training data to develop a classifier that can classify unknown samples (or, more particularly, the individuals from whom the samples were obtained) as either having the disease or being free from the disease. The development of the classifier from the training data is known as training the classifier. Specific details on classifier training depend on the nature of the supervised learning technique. For purposes of illustration, an example of training a naïve Bayesian classifier will be described below (see, e.g., Pattern Classification, R. O. Duda, et al., editors, John Wiley & Sons, 2nd edition, 2001; see also, The Elements of Statistical Learning—Data Mining, Inference, and Prediction, T. Hastie, et al., editors, Springer Science+Business Media, LLC, 2nd edition, 2009).

[0212] Since typically there are many more potential biomarker values than samples in a training set, care must be used to avoid over-fitting. Over-fitting occurs when a statistical model describes random error or noise instead of the underlying relationship. Over-fitting can be avoided in a variety of way, including, for example, by limiting the number of markers used in developing the classifier, by assuming that the marker responses are independent of one another, by limiting the complexity of the underlying statistical model employed, and by ensuring that the underlying statistical model conforms to the data.

[0213] An illustrative example of the development of a diagnostic test using a set of biomarkers includes the application of a naïve Bayes classifier, a simple probabilistic classifier based on Bayes theorem with strict independent treatment of the biomarkers. Each biomarker is described by a class-dependent probability density function (pdf) for the measured RFU values or log RFU (relative fluorescence units) values in each class. The joint pdfs for the set of markers in one class is assumed to be the product of the individual class-dependent pdfs for each biomarker. Training a naïve Bayes classifier in this context amounts to assigning parameters ("parameterization") to characterize the class dependent pdfs. Any underlying model for the class-dependent pdfs may be used, but the model should generally conform to the data observed in the training set.

[0214] Specifically, the class-dependent probability of measuring a value x_i for biomarker i in the disease class is written as $p(x_i \backslash d)$ and the overall naïve Bayes probability of

observing n markers with values $\underset{\sim}{x}=(x_1, x_2, \ldots x_n)$ is written as

$$p(\underset{\sim}{x} \mid d) = \prod_{i=1}^{n} p(x_i \mid d)$$

where the individual x_is are the measured biomarker levels in RFU or log RFU. The classification assignment for an unknown is facilitated by calculating the probability of being diseased $p(d\backslash\underset{\sim}{x})$ having measured $\underset{\sim}{x}$ compared to the probability of being disease free (control) $p(c\backslash\underset{\sim}{x})$ for the same measured values. The ratio of these probabilities is computed from the class-dependent pdfs by application of Bayes theorem, i.e.,

$$\frac{p(c \mid \underset{\sim}{x})}{p(d \mid \underset{\sim}{x})} = \frac{p(\underset{\sim}{x} \mid c)(1 - P(d))}{p(\underset{\sim}{x} \mid d)P(d)}$$

where P(d) is the prevalence of the disease in the population appropriate to the test. Taking the logarithm of both sides of this ratio and substituting the naïve Bayes class-dependent probabilities from above gives

$$\ln\frac{p(c \mid \underset{\sim}{x})}{p(d \mid \underset{\sim}{x})} = \sum_{i=1}^{n} \ln\frac{p(x_i \mid c)}{p(x_i \mid d)} + \ln\frac{(1 - P(d))}{P(d)}.$$

This form is known as the log likelihood ratio and simply states that the log likelihood of being free of the particular disease versus having the disease and is primarily composed of the sum of individual log likelihood ratios of the n individual biomarkers. In its simplest form, an unknown sample (or, more particularly, the individual from whom the sample was obtained) is classified as being free of the disease if the above ratio is greater than zero and having the disease if the ratio is less than zero.

[0215] In one exemplary embodiment, the class-dependent biomarker pdfs $p(x_i\backslash c)$ and $p(x_i\backslash d)$ are assumed to be normal or log-normal distributions in the measured RFU values x_i, i.e.

$$p(x_i \mid c) = \frac{1}{\sqrt{2\pi}\,\sigma_{c,i}} e^{\frac{(x_i-\mu_{c,i})^2}{2\sigma_{c,i}^2}}$$

with a similar expression for $p(x_i\backslash d)$ with $\mu_{d,i}$ and $\sigma_{d,i}^2$. Parameterization of the model requires estimation of two parameters for each class-dependent pdf, a mean μ and a variance σ^2, from the training data. This may be accomplished in a number of ways, including, for example, by maximum likelihood estimates, by least-squares, and by any other methods known to one skilled in the art. Substituting the normal distributions for $p(x_i\backslash c)$ and $p(x_i\backslash d)$ into the log-likelihood ratio defined above gives the following expression:

$$\ln\frac{p(c \mid \underset{\sim}{x})}{p(d \mid \underset{\sim}{x})} = \sum_{i=1}^{n} \ln\frac{\sigma_{d,i}}{\sigma_{c,i}} - \frac{1}{2}\sum_{i=1}^{n}\left[\left(\frac{x_i - \mu_{c,i}}{\sigma_{c,i}}\right)^2 - \left(\frac{x_i - \mu_{d,i}}{\sigma_{d,i}}\right)^2\right] + \ln\frac{(1 - P(d))}{P(d)}.$$

Once a set of μS and σ^2s have been defined for each pdf in each class from the training data and the disease prevalence in the population is specified, the Bayes classifier is fully determined and may be used to classify unknown samples with measured values $\underset{\sim}{x}$.

[0216] The performance of the naïve Bayes classifier is dependent upon the number and quality of the biomarkers used to construct and train the classifier. A single biomarker will perform in accordance with its KS-distance (Kolmogorov-Smirnov), as defined in Example 3, below. If a classifier performance metric is defined as the sum of the sensitivity (fraction of true positives, f_{TP}) and specificity (one minus the fraction of false positives, $1-f_{FP}$), a perfect classifier will have a score of two and a random classifier, on average, will have a score of one. Using the definition of the KS-distance, that value x* which maximizes the difference in the cdf functions can be found by solving

$$\frac{\partial KS}{\partial x} = \frac{\partial(cdf_c(x) - cdf_d(x))}{\partial x} = 0$$

for x which leads to $p(x^*\backslash c)=p(x^*\backslash d)$, i.e, the KS distance occurs where the class-dependent pdfs cross. Substituting this value of x* into the expression for the KS-distance yields the following definition for KS

$$\begin{aligned} KS &= cdf_c(x^*) - cdf_d(x^*) \\ &= \int_{-\infty}^{x^*} p(x \mid c)\,dx - \int_{-\infty}^{x^*} p(x \mid d)\,dx \\ &= 1 - \int_{x^*}^{\infty} p(x \mid c)\,dx - \int_{-\infty}^{x^*} p(x \mid d)\,dx \\ &= 1 - f_{FP} - f_{FN}, \end{aligned}$$

the KS distance is one minus the total fraction of errors using a test with a cut-off at x*, essentially a single analyte Bayesian classifier. Since we define a score of sensitivity+specificity= $2-f_{FP}-f_{FN}$, combining the above definition of the KS-distance we see that sensitivity+specificity=1+KS. We select biomarkers with a statistic that is inherently suited for building naïve Bayes classifiers.

[0217] The addition of subsequent markers with good KS distances (>0.3, for example) will, in general, improve the classification performance if the subsequently added markers are independent of the first marker. Using the sensitivity plus specificity as a classifier score, it is straightforward to generate many high scoring classifiers with a variation of a greedy algorithm. (A greedy algorithm is any algorithm that follows the problem solving metaheuristic of making the locally optimal choice at each stage with the hope of finding the global optimum.)

[0218] The algorithm approach used here is described in detail in Example 4. Briefly, all single analyte classifiers are generated from a table of potential biomarkers and added to a list. Next, all possible additions of a second analyte to each of the stored single analyte classifiers is then performed, saving a predetermined number of the best scoring pairs, say, for example, a thousand, on a new list. All possible three-marker classifiers are explored using this new list of the best two-marker classifiers, again saving the best thousand of these. This process continues until the score either plateaus or begins to deteriorate as additional markers are added. Those high scoring classifiers that remain after convergence can be evaluated for the desired performance for an intended use. For example, in one diagnostic application, classifiers with a high sensitivity and modest specificity may be more desirable than modest sensitivity and high specificity. In another diagnostic application, classifiers with a high specificity and a modest sensitivity may be more desirable. The desired level of performance is generally selected based upon a trade-off that must be made between the number of false positives and false negatives that can each be tolerated for the particular diagnostic application. Such trade-offs generally depend on the medical consequences of an error, either false positive or false negative.

[0219] Various other techniques are known in the art and may be employed to generate many potential classifiers from a list of biomarkers using a naïve Bayes classifier. In one embodiment, what is referred to as a genetic algorithm can be used to combine different markers using the fitness score as defined above. Genetic algorithms are particularly well suited to exploring a large diverse population of potential classifiers. In another embodiment, so-called ant colony optimization can be used to generate sets of classifiers. Other strategies that are known in the art can also be employed, including, for example, other evolutionary strategies as well as simulated annealing and other stochastic search methods. Metaheuristic methods, such as, for example, harmony search may also be employed.

[0220] Exemplary embodiments use any number of the ovarian cancer biomarkers listed in Table 1 in various combinations to produce diagnostic tests for detecting ovarian cancer (see Example 2 for a detailed description of how these biomarkers were identified). In one embodiment, a method for diagnosing ovarian cancer uses a naïve Bayes classification method in conjunction with any number of the ovarian cancer biomarkers listed in Table 1. In an illustrative example (see Example 3), the simplest test for detecting ovarian cancer from a population of women with pelvic masses can be constructed using a single biomarker, for example, BAFF Receptor which is down-regulated in ovarian cancer with a KS-distance of 0.39 (1+KS=1.39). Using the parameters $\mu_{c,i}$, $\sigma_{c,i}$, $\mu_{d,i}$ and $\sigma_{d,i}$ for BAFF Receptor from Table 16 and the equation for the log-likelihood described above, a diagnostic test with a sensitivity of 0.74 and specificity of 0.56 (sensitivity+specificity=1.31) can be produced, see Table 17. The ROC curve for this test is displayed in FIG. **2** and has an AUC of 0.70.

[0221] Addition of biomarker RGM-C, for example, with a KS-distance of 0.43, significantly improves the classifier performance to a sensitivity of 82% and specificity of 0.73% (sensitivity+specificity=1.51) and an AUC=0.81. Note that the score for a classifier constructed of two biomarkers is not a simple sum of the KS-distances; KS-distances are not additive when combining biomarkers, and it takes many more weak markers to achieve the same level of performance as a strong marker. Adding a third marker, HGF, for example, boosts the classifier performance to 83% sensitivity and 74% specificity and AUC=0.84. Adding additional biomarkers, such as, for example, SLPI, C9, α2-Antiplasmin, SAP, MMP-7, MCP-3, and HSP90α, produces a series of ovarian cancer tests summarized in Table 17 and displayed as a series of ROC curves in FIG. **3**. The score of the classifiers as a function of the number of analytes used in classifier construction is shown in FIG. **4**. This exemplary ten-marker classifier has a sensitivity of 97% and a specificity of 88% with an AUC of 0.94.

[0222] The markers listed in Table 1 can be combined in many ways to produce classifiers for diagnosing ovarian cancer. In some embodiments, panels of biomarkers are comprised of different numbers of analytes depending on a specific diagnostic performance criterion that is selected. For example, certain combinations of biomarkers will produce tests that are more sensitive (or more specific) than other combinations.

[0223] Once a panel is defined to include a particular set of biomarkers from Table 1 and a classifier is constructed from a set of training data, the definition of the diagnostic test is complete. In one embodiment, the procedure used to classify an unknown sample is outlined in FIG. **1**A. In another embodiment the procedure used to classify an unknown sample is outlined in FIG. **1**B. The biological sample is appropriately diluted and then run in one or more assays to produce the relevant quantitative biomarker levels used for classification. The measured biomarker levels are used as input for the classification method that outputs a classification and an optional score for the sample that reflects the confidence of the class assignment.

[0224] Table 1 identifies 42 biomarkers that are useful for diagnosing ovarian cancer. This is a surprisingly larger number than expected when compared to what is typically found during biomarker discovery efforts and may be attributable to the scale of the described study, which encompassed over 800 proteins measured in hundreds of individual samples, in some cases at concentrations in the low femtomolar range. Presumably, the large number of discovered biomarkers reflects the diverse biochemical pathways implicated in both tumor biology and the body's response to the tumor's presence; each pathway and process involves many proteins. The results show that no single protein of a small group of proteins is uniquely informative about such complex processes; rather, that multiple proteins are involved in relevant processes, such as apoptosis or extracellular matrix repair, for example.

[0225] Given the numerous biomarkers identified during the described study, one would expect to be able to derive large numbers of high-performing classifiers that can be used in various diagnostic methods. To test this notion, tens of thousands of classifiers were evaluated using the biomarkers in Table 1. As described in Example 4, many subsets of the biomarkers presented in Table 1 can be combined to generate useful classifiers. By way of example, descriptions are provided for classifiers containing 1, 2, and 3 biomarkers for the diagnosis of ovarian cancer, particularly, the diagnosis of ovarian cancer in individuals who have a pelvic mass that is detectable by CT. As described in Example 4, all classifiers

that were built using the biomarkers in Table 1 perform distinctly better than classifiers that were built using "non-markers".

[0226] The performance of ten-marker classifiers obtained by excluding the "best" individual markers from the ten-marker aggregation was tested. As described in Example 4, Part 3, classifiers constructed without the "best" markers in Table 1 performed well. Many subsets of the biomarkers listed in Table 1 performed close to optimally, even after removing the top 15 of the markers listed in the Table. This implies that the performance characteristics of any particular classifier are likely not due to some small core group of biomarkers and that the disease process likely impacts numerous biochemical pathways, which alters the expression level of many proteins.

[0227] The results from Example 4 suggest certain possible conclusions: First, the identification of a large number of biomarkers enables their aggregation into a vast number of classifiers that offer similarly high performance. Second, classifiers can be constructed such that particular biomarkers may be substituted for other biomarkers in a manner that reflects the redundancies that undoubtedly pervade the complexities of the underlying disease processes. That is to say, the information about the disease contributed by any individual biomarker identified in Table 1 overlaps with the information contributed by other biomarkers, such that it may be that no particular biomarker or small group of biomarkers in Table 1 must be included in any classifier.

[0228] Exemplary embodiments use naïve Bayes classifiers constructed from the data in Table 18 to classify an unknown sample. The procedure is outlined in FIGS. **1**A and B. In one embodiment, the biological sample is optionally diluted and run in a multiplexed aptamer assay. The data from the assay are normalized and calibrated as outlined in Example 3, and the resulting biomarker levels are used as input to a Bayes classification scheme. The log-likelihood ratio is computed for each measured biomarker individually and then summed to produce a final classification score, which is also referred to as a diagnostic score. The resulting assignment as well as the overall classification score can be reported. Optionally, the individual log-likelihood risk factors computed for each biomarker level can be reported as well. The details of the classification score calculation are presented in Example 3.

Kits

[0229] Any combination of the biomarkers of Table 1 (as well as additional biomedical information) can be detected using a suitable kit, such as for use in performing the methods disclosed herein. Furthermore, any kit can contain one or more detectable labels as described herein, such as a fluorescent moiety, etc.

[0230] In one embodiment, a kit includes (a) one or more capture reagents (such as, for example, at least one aptamer or antibody) for detecting one or more biomarkers in a biological sample, wherein the biomarkers include any of the biomarkers set forth in Table 1, and optionally (b) one or more software or computer program products for classifying the individual from whom the biological sample was obtained as either having or not having ovarian cancer or for determining the likelihood that the individual has ovarian cancer, as further described herein. Alternatively, rather than one or more computer program products, one or more instructions for manually performing the above steps by a human can be provided.

[0231] The combination of a solid support with a corresponding capture reagent and a signal generating material is referred to herein as a "detection device" or "kit". The kit can also include instructions for using the devices and reagents, handling the sample, and analyzing the data. Further the kit may be used with a computer system or software to analyze and report the result of the analysis of the biological sample.

[0232] The kits can also contain one or more reagents (e.g., solubilization buffers, detergents, washes, or buffers) for processing a biological sample. Any of the kits described herein can also include, e.g., buffers, blocking agents, mass spectrometry matrix materials, antibody capture agents, positive control samples, negative control samples, software and information such as protocols, guidance and reference data.

[0233] In one aspect, the invention provides kits for the analysis of ovarian cancer status. The kits include PCR primers for one or more biomarkers selected from Table 1. The kit may further include instructions for use and correlation of the biomarkers with ovarian cancer. The kit may also include any of the following, either alone or in combination: a DNA array containing the complement of one or more of the biomarkers selected from Table 1, reagents, and enzymes for amplifying or isolating sample DNA. The kits may include reagents for real-time PCR, such as, for example, TaqMan probes and/or primers, and enzymes.

[0234] For example, a kit can comprise (a) reagents comprising at least capture reagent for quantifying one or more biomarkers in a test sample, wherein said biomarkers comprise the biomarkers set forth in Table 1, or any other biomarkers or biomarkers panels described herein, and optionally (b) one or more algorithms or computer programs for performing the steps of comparing the amount of each biomarker quantified in the test sample to one or more predetermined cutoffs and assigning a score for each biomarker quantified based on said comparison, combining the assigned scores for each biomarker quantified to obtain a total score, comparing the total score with a predetermined score, and using said comparison to determine whether an individual has ovarian cancer. Alternatively, rather than one or more algorithms or computer programs, one or more instructions for manually performing the above steps by a human can be provided.

Computer Methods and Software

[0235] Once a biomarker or biomarker panel is selected, a method for diagnosing an individual can comprise the following: 1) collect or otherwise obtain a biological sample; 2) perform an analytical method to detect and measure the biomarker or biomarkers in the panel in the biological sample; 3) perform any data normalization or standardization required for the method used to collect biomarker values; 4) calculate the marker score; 5) combine the marker scores to obtain a total diagnostic score; and 6) report the individual's diagnostic score. In this approach, the diagnostic score may be a single number determined from the sum of all the marker calculations that is compared to a preset threshold value that is an indication of the presence or absence of disease. Or the diagnostic score may be a series of bars that each represent a biomarker value and the pattern of the responses may be compared to a pre-set pattern for determination of the presence or absence of disease.

[0236] At least some embodiments of the methods described herein can be implemented with the use of a computer. An example of a computer system **100** is shown in FIG. **6**. With reference to FIG. **6**, system **100** is shown comprised of hardware elements that are electrically coupled via bus **108**, including a processor **101**, input device **102**, output device **103**, storage device **104**, computer-readable storage media reader **105***a*, communications system **106** processing acceleration (e.g., DSP or special-purpose processors) **107** and memory **109**. Computer-readable storage media reader **105***a* is further coupled to computer-readable storage media **105***b*, the combination comprehensively representing remote, local, fixed and/or removable storage devices plus storage media, memory, etc. for temporarily and/or more permanently containing computer-readable information, which can include storage device **104**, memory **109** and/or any other such accessible system **100** resource. System **100** also comprises software elements (shown as being currently located within working memory **191**) including an operating system **192** and other code **193**, such as programs, data and the like.

[0237] With respect to FIG. **6**, system **100** has extensive flexibility and configurability. Thus, for example, a single architecture might be utilized to implement one or more servers that can be further configured in accordance with currently desirable protocols, protocol variations, extensions, etc. However, it will be apparent to those skilled in the art that embodiments may well be utilized in accordance with more specific application requirements. For example, one or more system elements might be implemented as sub-elements within a system **100** component (e.g., within communications system **106**). Customized hardware might also be utilized and/or particular elements might be implemented in hardware, software or both. Further, while connection to other computing devices such as network input/output devices (not shown) may be employed, it is to be understood that wired, wireless, modem, and/or other connection or connections to other computing devices might also be utilized.

[0238] In one aspect, the system can comprise a database containing features of biomarkers characteristic of ovarian cancer. The biomarker data (or biomarker information) can be utilized as an input to the computer for use as part of a computer implemented method. The biomarker data can include the data as described herein.

[0239] In one aspect, the system further comprises one or more devices for providing input data to the one or more processors.

[0240] The system further comprises a memory for storing a data set of ranked data elements.

[0241] In another aspect, the device for providing input data comprises a detector for detecting the characteristic of the data element, e.g., such as a mass spectrometer or gene chip reader.

[0242] The system additionally may comprise a database management system. User requests or queries can be formatted in an appropriate language understood by the database management system that processes the query to extract the relevant information from the database of training sets.

[0243] The system may be connectable to a network to which a network server and one or more clients are connected. The network may be a local area network (LAN) or a wide area network (WAN), as is known in the art. Preferably, the server includes the hardware necessary for running computer program products (e.g., software) to access database data for processing user requests.

[0244] The system may include an operating system (e.g., UNIX or Linux) for executing instructions from a database management system. In one aspect, the operating system can operate on a global communications network, such as the internet, and utilize a global communications network server to connect to such a network.

[0245] The system may include one or more devices that comprise a graphical display interface comprising interface elements such as buttons, pull down menus, scroll bars, fields for entering text, and the like as are routinely found in graphical user interfaces known in the art. Requests entered on a user interface can be transmitted to an application program in the system for formatting to search for relevant information in one or more of the system databases. Requests or queries entered by a user may be constructed in any suitable database language.

[0246] The graphical user interface may be generated by a graphical user interface code as part of the operating system and can be used to input data and/or to display inputted data. The result of processed data can be displayed in the interface, printed on a printer in communication with the system, saved in a memory device, and/or transmitted over the network or can be provided in the form of the computer readable medium.

[0247] The system can be in communication with an input device for providing data regarding data elements to the system (e.g., expression values). In one aspect, the input device can include a gene expression profiling system including, e.g., a mass spectrometer, gene chip or array reader, and the like.

[0248] The methods and apparatus for analyzing ovarian cancer biomarker information according to various embodiments may be implemented in any suitable manner, for example, using a computer program operating on a computer system. A conventional computer system comprising a processor and a random access memory, such as a remotely-accessible application server, network server, personal computer or workstation may be used. Additional computer system components may include memory devices or information storage systems, such as a mass storage system and a user interface, for example a conventional monitor, keyboard and tracking device. The computer system may be a stand-alone system or part of a network of computers including a server and one or more databases.

[0249] The ovarian cancer biomarker analysis system can provide functions and operations to complete data analysis, such as data gathering, processing, analysis, reporting and/or diagnosis. For example, in one embodiment, the computer system can execute the computer program that may receive, store, search, analyze, and report information relating to the ovarian cancer biomarkers. The computer program may comprise multiple modules performing various functions or operations, such as a processing module for processing raw data and generating supplemental data and an analysis module for analyzing raw data and supplemental data to generate an ovarian cancer status and/or diagnosis. Diagnosing ovarian cancer status may comprise generating or collecting any other information, including additional biomedical information,

regarding the condition of the individual relative to the disease, identifying whether further tests may be desirable, or otherwise evaluating the health status of the individual.

[0250] Referring now to FIG. **7**, an example of a method of utilizing a computer in accordance with principles of a disclosed embodiment can be seen. In FIG. **7**, a flowchart **3000** is shown. In block **3004**, biomarker information can be retrieved for an individual. The biomarker information can be retrieved from a computer database, for example, after testing of the individual's biological sample is performed. The biomarker information can comprise biomarker values that each correspond to one of at least N biomarkers selected from a group consisting of the biomarkers provided in Table 1, wherein N=2-42. In block **3008**, a computer can be utilized to classify each of the biomarker values. And, in block **3012**, a determination can be made as to the likelihood that an individual has ovarian cancer based upon a plurality of classifications. The indication can be output to a display or other indicating device so that it is viewable by a person. Thus, for example, it can be displayed on a display screen of a computer or other output device.

[0251] Referring now to FIG. **8**, an alternative method of utilizing a computer in accordance with another embodiment can be illustrated via flowchart **3200**. In block **3204**, a computer can be utilized to retrieve biomarker information for an individual. The biomarker information comprises a biomarker value corresponding to a biomarker selected from the group of biomarkers provided in Table 1. In block **3208**, a classification of the biomarker value can be performed with the computer. And, in block **3212**, an indication can be made as to the likelihood that the individual has ovarian cancer based upon the classification. The indication can be output to a display or other indicating device so that it is viewable by a person. Thus, for example, it can be displayed on a display screen of a computer or other output device.

[0252] Some embodiments described herein can be implemented so as to include a computer program product. A computer program product may include a computer readable medium having computer readable program code embodied in the medium for causing an application program to execute on a computer with a database.

[0253] As used herein, a "computer program product" refers to an organized set of instructions in the form of natural or programming language statements that are contained on a physical media of any nature (e.g., written, electronic, magnetic, optical or otherwise) and that may be used with a computer or other automated data processing system. Such programming language statements, when executed by a computer or data processing system, cause the computer or data processing system to act in accordance with the particular content of the statements. Computer program products include without limitation: programs in source and object code and/or test or data libraries embedded in a computer readable medium. Furthermore, the computer program product that enables a computer system or data processing equipment device to act in pre-selected ways may be provided in a number of forms, including, but not limited to, original source code, assembly code, object code, machine language, encrypted or compressed versions of the foregoing and any and all equivalents.

[0254] In one aspect, a computer program product is provided for indicating a likelihood of ovarian cancer. The computer program product includes a computer readable medium embodying program code executable by a processor of a computing device or system, the program code comprising: code that retrieves data attributed to a biological sample from an individual, wherein the data comprises biomarker values that each correspond to one of at least N biomarkers in the biological sample selected from the group of biomarkers provided in Table 1, wherein N=2-42; and code that executes a classification method that indicates an ovarian disease status of the individual as a function of the biomarker values.

[0255] In still another aspect, a computer program product is provided for indicating a likelihood of ovarian cancer. The computer program product includes a computer readable medium embodying program code executable by a processor of a computing device or system, the program code comprising: code that retrieves data attributed to a biological sample from an individual, wherein the data comprises a biomarker value corresponding to a biomarker in the biological sample selected from the group of biomarkers provided in Table 1; and code that executes a classification method that indicates an ovarian disease status of the individual as a function of the biomarker value.

[0256] While various embodiments have been described as methods or apparatuses, it should be understood that embodiments can be implemented through code coupled with a computer, e.g., code resident on a computer or accessible by the computer. For example, software and databases could be utilized to implement many of the methods discussed above. Thus, in addition to embodiments accomplished by hardware, it is also noted that these embodiments can be accomplished through the use of an article of manufacture comprised of a computer usable medium having a computer readable program code embodied therein, which causes the enablement of the functions disclosed in this description. Therefore, it is desired that embodiments also be considered protected by this patent in their program code means as well. Furthermore, the embodiments may be embodied as code stored in a computer-readable memory of virtually any kind including, without limitation, RAM, ROM, magnetic media, optical media, or magneto-optical media. Even more generally, the embodiments could be implemented in software, or in hardware, or any combination thereof including, but not limited to, software running on a general purpose processor, microcode, PLAs, or ASICs.

[0257] It is also envisioned that embodiments could be accomplished as computer signals embodied in a carrier wave, as well as signals (e.g., electrical and optical) propagated through a transmission medium. Thus, the various types of information discussed above could be formatted in a structure, such as a data structure, and transmitted as an electrical signal through a transmission medium or stored on a computer readable medium.

[0258] It is also noted that many of the structures, materials, and acts recited herein can be recited as means for performing a function or step for performing a function. Therefore, it should be understood that such language is entitled to cover all such structures, materials, or acts disclosed within this specification and their equivalents, including the matter incorporated by reference.

EXAMPLES

[0259] The following examples are provided for illustrative purposes only and are not intended to limit the scope of the

application as defined by the appended claims. All examples described herein were carried out using standard techniques, which are well known and routine to those of skill in the art. Routine molecular biology techniques described in the following examples can be carried out as described in standard laboratory manuals, such as Sambrook et al., Molecular Cloning: A Laboratory Manual, 3rd. ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (2001).

Example 1

Multiplexed Aptamer Analysis of Samples For Ovarian Cancer Biomarker Selection

[0260] This example describes the multiplex aptamer assay used to analyze the samples and controls for the identification of the biomarkers set forth in Table 1 (see FIG. 9). In this case, the multiplexed analysis utilized 811 aptamers, each unique to a specific target.

[0261] In this method, pipette tips were changed for each solution addition.

[0262] Also, unless otherwise indicated, most solution transfers and wash additions used the 96-well head of a Beckman Biomek Fx^P. Method steps manually pipetted used a twelve channel P200 Pipetteman (Rainin Instruments, LLC, Oakland, Calif.), unless otherwise indicated. A custom buffer referred to as SB17 was prepared in-house, comprising 40 mM HEPES, 100 mM NaCl, 5 mM KCl, 5 mM $MgCl_2$, 1 mM EDTA at pH7.5. All steps were performed at room temperature unless otherwise indicated.

[0263] 1. Preparation of Aptamer Stock Solution

[0264] For aptamers without a photo-cleavable biotin linker, custom stock aptamer solutions for 10%, 1% and 0.03% plasma were prepared at 8× concentration in 1×SB17, 0.05% Tween-20 with appropriate photo-cleavable, biotinylated primers, where the resultant primer concentration was 3 times the relevant aptamer concentration. The primers hybridized to all or part of the corresponding aptamer.

[0265] Each of the 3, 8× aptamer solutions were diluted separately 1:4 into 1×SB17, 0.05% Tween-20 (1500 μL of 8× stock into 4500 μL of 1×SB17, 0.05% Tween-20) to achieve a 2× concentration. Each diluted aptamer master mix was then split, 1500 μL each, into 4, 2 mL screw cap tubes and brought to 95° C. for 5 minutes, followed by a 37° C. incubation for 15 minutes. After incubation, the 4, 2 mL tubes corresponding to a particular aptamer master mix were combined into a reagent trough, and 55 μL of a 2× aptamer mix (for all three mixes) was manually pipetted into a 96-well Hybaid plate and the plate foil sealed. The final result was 3, 96-well, foil-sealed Hybaid plates. The individual aptamer concentration was 0.5 nM.

[0266] 2. Assay Sample Preparation

[0267] Frozen aliquots of 100% plasma, stored at −80° C., were placed in 25° C. water bath for 10 minutes. Thawed samples were placed on ice, gently vortexed (set on 4) for 8 seconds and then replaced on ice.

[0268] A 20% sample solution was prepared by transferring 16 μL of sample using a 50 μL 8-channel spanning pipettor into 96-well Hybaid plates, each well containing 64 μL of the appropriate sample diluent at 4° C. (0.8×SB17, 0.05% Tween-20, 2 μM Z-block_2, 0.6 mM $MgCl_2$ for plasma). This plate was stored on ice until the next sample dilution steps were initiated.

[0269] To commence sample and aptamer equilibration, the 20% sample plate was briefly centrifuged and placed on the Beckman FX where it was mixed by pipetting up and down with the 96-well pipettor. A 2% sample was then prepared by diluting 10 μL of the 20% sample into 90 μL of 1×SB17, 0.05% Tween-20. Next, dilution of 6 μL of the resultant 2% sample into 194 μL of 1×SB17, 0.05% Tween-20 made a 0.06% sample plate. Dilutions were done on the Beckman Biomek Fx^P. After each transfer, the solutions were mixed by pipetting up and down. The 3 sample dilution plates were then transferred to their respective aptamer solutions by adding 55 μL of the sample to 55 μL of the appropriate 2× aptamer mix. The sample and aptamer solutions were mixed on the robot by pipetting up and down.

[0270] 3. Sample Equilibration Binding

[0271] The sample/aptamer plates were foil sealed and placed into a 37° C. incubator for 3.5 hours before proceeding to the Catch 1 step.

[0272] 4. Preparation of Catch 2 Bead Plate

[0273] An 11 mL aliquot of MyOne (Invitrogen Corp., Carlsbad, Calif.) Streptavidin C1 beads was washed 2 times with equal volumes of 20 mM NaOH (5 minute incubation for each wash), 3 times with equal volumes of 1×SB17, 0.05% Tween-20 and resuspended in 11 mL 1×SB17, 0.05% Tween-20. Using a 12-span multichannel pipettor, 50 μL of this solution was manually pipetted into each well of a 96-well Hybaid plate. The plate was then covered with foil and stored at 4° C. for use in the assay.

[0274] 5. Preparation of Catch 1 Bead Plates

[0275] Three 0.45 μm Millipore HV plates (Durapore membrane, Cat# MAHVN4550) were equilibrated with 100 μL of 1×SB17, 0.05% Tween-20 for at least 10 minutes. The equilibration buffer was then filtered through the plate and 133.3 μL of a 7.5% Streptavidin-agarose bead slurry (in 1×SB17, 0.05% Tween-20) was added into each well. To keep the streptavidin-agarose beads suspended while transferring them into the filter plate, the bead solution was manually mixed with a 200 μL, 12-channel pipettor, 15 times. After the beads were distributed across the 3 filter plates, a vacuum was applied to remove the bead supernatant. Finally, the beads were washed in the filter plates with 200 μL 1×SB17, 0.05% Tween-20 and then resuspended in 200 μL 1×SB17, 0.05% Tween-20. The bottoms of the filter plates were blotted and the plates stored for use in the assay.

[0276] 6. Loading the Cytomat

[0277] The cytomat was loaded with all tips, plates, all reagents in troughs (except NHS-biotin reagent which was prepared fresh right before addition to the plates), 3 prepared catch 1 filter plates and 1 prepared MyOne plate.

[0278] 7. Catch 1

[0279] After a 3.5 hour equilibration time, the sample/aptamer plates were removed from the incubator, centrifuged for about 1 minute, foil removed, and placed on the deck of the Beckman Biomek Fx^P. The Beckman Biomek Fx^P program was initiated. All subsequent steps in Catch 1 were performed by the Beckman Biomek Fx^P robot unless other-

wise noted. Within the program, the vacuum was applied to the Catch 1 filter plates to remove the bead supernatant. One hundred microlitres of each of the 10%, 1% and 0.03% equilibration binding reactions were added to their respective Catch 1 filtration plates, and each plate was mixed using an on-deck orbital shaker at 800 rpm for 10 minutes.

[0280] Unbound solution was removed via vacuum filtration. The catch 1 beads were washed with 190 μL of 100 μM biotin in 1×SB17, 0.05% Tween-20 followed by 190 μL of 1×SB17, 0.05% Tween-20 by dispensing the solution and immediately drawing a vacuum to filter the solution through the plate.

[0281] Next, 190 μL 1×SB17, 0.05% Tween-20 was added to the Catch 1 plates. Plates were blotted to remove droplets using an on-deck blot station and then incubated with orbital shakers at 800 rpm for 10 minutes at 25° C.

[0282] The robot removed this wash via vacuum filtration and blotted the bottom of the filter plate to remove droplets using the on-deck blot station.

[0283] 8. Tagging

[0284] A NHS-PEO4-biotin aliquot was thawed at 37° C. for 6 minutes and then diluted 1:100 with tagging buffer (SB17 at pH=7.25 0.05% Tween-20). The NHS-PEO4-biotin reagent was dissolved at 100 mM concentration in anhydrous DMSO and had been stored frozen at −20° C. Upon a robot prompt, the diluted NHS-PEO4-biotin reagent was manually added to an on-deck trough and the robot program was manually re-initiated to dispense 100 μL of the NHS-PEO4-biotin into each well of each Catch 1 filter plate. This solution was allowed to incubate with Catch 1 beads shaking at 800 rpm for 5 minutes on the obital shakers.

[0285] 9. Kinetic Challenge and Photo-Cleavage

[0286] The tagging reaction was quenched by the addition of 150 μL of 20 mM glycine in 1×SB17, 0.05% Tween-20 to the Catch 1 plates while still containing the NHS tag. The plates were then incubated for 1 minute on orbital shakers at 800 rpm. The NHS-tag/glycine solution was removed via vacuum filtration. Next, 190 μL 20 mM glycine (1×SB17, 0.05% Tween-20) was added to each plate and incubated for 1 minute on orbital shakers at 800 rpm before removal by vacuum filtration.

[0287] 190 μL of 1×SB17, 0.05% Tween-20 was added to each plate and removed by vacuum filtration.

[0288] The wells of the Catch 1 plates were subsequently washed three times by adding 190 μL 1×SB17, 0.05% Tween-20, placing the plates on orbital shakers for 1 minute at 800 rpm followed by vacuum filtration. After the last wash the plates were placed on top of a 1 mL deep-well plate and removed from the deck. The Catch 1 plates were centrifuged at 1000 rpm for 1 minute to remove as much extraneous volume from the agarose beads before elution as possible.

[0289] The plates were placed back onto the Beckman Biomek Fx^P and 85 μL of 10 mM $DxSO_4$ in 1×SB17, 0.05% Tween-20 was added to each well of the filter plates.

[0290] The filter plates were removed from the deck, placed onto a Variomag Thermoshaker (Thermo Fisher Scientific, Inc., Waltham, Mass.) under the BlackRay (Ted Pella, Inc., Redding, Calif.) light sources, and irradiated for 10 minutes while shaking at 800 rpm.

[0291] The photocleaved solutions were sequentially eluted from each Catch 1 plate into a common deep well plate by first placing the 10% Catch 1 filter plate on top of a 1 mL deep-well plate and centrifuging at 1000 rpm for 1 minute. The 1% and 0.03% catch 1 plates were then sequentially centrifuged into the same deep well plate.

[0292] 10. Catch 2 Bead Capture

[0293] The 1 mL deep well block containing the combined eluates of catch 1 was placed on the deck of the Beckman Biomek Fx^P for catch 2.

[0294] The robot transferred all of the photo-cleaved eluate from the 1 mL deep-well plate onto the Hybaid plate containing the previously prepared catch 2 MyOne magnetic beads (after removal of the MyOne buffer via magnetic separation).

[0295] The solution was incubated while shaking at 1350 rpm for 5 minutes at 25° C. on a Variomag Thermoshaker (Thermo Fisher Scientific, Inc., Waltham, Mass.).

[0296] The robot transferred the plate to the on deck magnetic separator station. The plate was incubated on the magnet for 90 seconds before removal and discarding of the supernatant.

[0297] 11. 37° C. 30% Glycerol Washes

[0298] The catch 2 plate was moved to the on-deck thermal shaker and 75 μL of 1×SB17, 0.05% Tween-20 was transferred to each well. The plate was mixed for 1 minute at 1350 rpm and 37° C. to resuspend and warm the beads. To each well of the catch 2 plate, 75 μL of 60% glycerol at 37° C. was transferred and the plate continued to mix for another minute at 1350 rpm and 37° C. The robot transferred the plate to the 37° C. magnetic separator where it was incubated on the magnet for 2 minutes and then the robot removed and discarded the supernatant. These washes were repeated two more times.

[0299] After removal of the third 30% glycerol wash from the catch 2 beads, 150 μL of 1×SB17, 0.05% Tween-20 was added to each well and incubated at 37° C., shaking at 1350 rpm for 1 minute, before removal by magnetic separation on the 37° C. magnet.

[0300] The catch 2 beads were washed a final time using 150 μL 1×SB19, 0.05% Tween-20 with incubation for 1 minute while shaking at 1350 rpm, prior to magnetic separation.

[0301] 12. Catch 2 Bead Elution and Neutralization

[0302] The aptamers were eluted from catch 2 beads by adding 105 μL of 100 mM CAPSO with 1 M NaCl, 0.05% Tween-20 to each well. The beads were incubated with this solution with shaking at 1300 rpm for 5 minutes.

[0303] The catch 2 plate was then placed onto the magnetic separator for 90 seconds prior to transferring 90 μL of the eluate to a new 96-well plate containing 10 μL of 500 mM HCl, 500 mM HEPES, 0.05% Tween-20 in each well. After transfer, the solution was mixed robotically by pipetting 90 μL up and down five times.

[0304] 13. Hybridization

[0305] The Beckman Biomek Fx^P transferred 20 μL of the neutralized catch 2 eluate to a fresh Hybaid plate, and 5 μL of 10× Agilent Block, containing a 10× spike of hybridization

controls, was added to each well. Next, 25 μL of 2× Agilent Hybridization buffer was manually pipetted to the each well of the plate containing the neutralized samples and blocking buffer and the solution was mixed by manually pipetting 25 μL up and down 15 times slowly to avoid extensive bubble formation. The plate was spun at 1000 rpm for 1 minute.

[0306] A gasket slide was placed into an Agilent hybridization chamber and 40 μL of each of the samples containing hybridization and blocking solution was manually pipetted into each gasket. An 8-channel variable spanning pipettor was used in a manner intended to minimize bubble formation. Custom Agilent microarray slides (Agilent Technologies, Inc., Santa Clara, Calif.), with their Number Barcode facing up, were then slowly lowered onto the gasket slides (see Agilent manual for Detailed Description).

[0307] The top of the hybridization chambers were placed onto the slide/backing sandwich and clamping brackets slid over the whole assembly. These assemblies were tightly clamped by turning the screws securely.

[0308] Each slide/backing slide sandwich was visually inspected to assure the solution bubble could move freely within the sample. If the bubble did not move freely the hybridization chamber assembly was gently tapped to disengage bubbles lodged near the gasket.

[0309] The assembled hybridization chambers were incubated in an Agilent hybridization oven for 19 hours at 60° C. rotating at 20 rpm.

[0310] 14. Post Hybridization Washing

[0311] Approximately 400 mL Agilent Wash Buffer 1 was placed into each of two separate glass staining dishes. One of the staining dishes was placed on a magnetic stir plate and a slide rack and stir bar were placed into the buffer.

[0312] A staining dish for Agilent Wash 2 was prepared by placing a stir bar into an empty glass staining dish.

[0313] A fourth glass staining dish was set aside for the final acetonitrile wash.

[0314] Each of six hybridization chambers was disassembled. One-by-one, the slide/backing sandwich was removed from its hybridization chamber and submerged into the staining dish containing Wash 1. The slide/backing sandwich was pried apart using a pair of tweezers, while still submerging the microarray slide. The slide was quickly transferred into the slide rack in the Wash 1 staining dish on the magnetic stir plate.

[0315] The slide rack was gently raised and lowered 5 times. The magnetic stirrer was turned on at a low setting and the slides incubated for 5 minutes.

[0316] When one minute was remaining for Wash 1, Wash Buffer 2 pre-warmed to 37° C. in an incubator was added to the second prepared staining dish. The slide rack was quickly transferred to Wash Buffer 2 and any excess buffer on the bottom of the rack was removed by scraping it on the top of the stain dish. The slide rack was gently raised and lowered 5 times. The magnetic stirrer was turned on at a low setting and the slides incubated for 5 minutes.

[0317] The slide rack was slowly pulled out of Wash 2, taking approximately 15 seconds to remove the slides from the solution.

[0318] With one minute remaining in Wash 2 acetonitrile (ACN) was added to the fourth staining dish. The slide rack was transferred to the acetonitrile stain dish. The slide rack was gently raised and lowered 5 times. The magnetic stirrer was turned on at a low setting and the slides incubated for 5 minutes.

[0319] The slide rack was slowly pulled out of the ACN stain dish and placed on an absorbent towel. The bottom edges of the slides were quickly dried and the slide was placed into a clean slide box.

[0320] 15. Microarray Imaging

[0321] The microarray slides were placed into Agilent scanner slide holders and loaded into the Agilent Microarray scanner according to the manufacturer's instructions.

[0322] The slides were imaged in the Cy3-channel at 5 μm resolution at the 100% PMT setting and the XRD option enabled at 0.05. The resulting tiff images were processed using Agilent feature extraction software version 10.5.

Example 2

Biomarker Identification

[0323] The identification of potential ovarian cancer biomarkers was performed for diagnosis of ovarian cancer in women with pelvic masses. Enrollment criteria for this study were women scheduled for laparotomy or pelvic surgery for suspicion of ovarian cancer. The primary criteria for exclusion were women suffering from chronic infectious (e.g. hepatitis B, Hepatitis C or HIV), autoimmune, or inflammatory conditions or women being treated for malignancy (other than basal or squamous cell carcinomas of the skin) within the last two years. Plasma samples were collected from two different clinical sites and included 142 cases and 195 benign controls. Table 19 summarizes the site sample information. The multiplexed aptamer affinity assay was used to measure and report the RFU value for 811 analytes in each of these 337 samples. Since the plasma samples were obtained from two independent sites under similar protocols, an examination of site differences prior to the analysis for biomarkers discovery was performed. Each of the two populations, benign pelvic mass and ovarian cancer, was separately compared between sites by generating within-site, class-dependent cumulative distribution functions (cdfs) for each of the 811 analytes. The KS-test was then applied to each analyte between both site pairs within a common class to identify those analytes that differed not by class but rather by site. In both site comparisons among the two classes, statistically significant site-dependent differences were observed.

[0324] Such site-dependent effects tend to obscure the ability to identify specific control-disease differences. In order to minimize such effects and identify key disease dependent biomarkers, three distinct strategies were employed for biomarker discovery, namely (1) aggregated class-dependent cdfs across sites, (2) comparison of within-site class-dependent cdfs, and (3) blending methods (1) with (2). Details of these three methodologies and their results follow.

[0325] These three sets of potential biomarkers can be used to build classifiers that assign samples to either a control or disease group. In fact, many such classifiers were produced from these sets of biomarkers and the frequency with which any biomarker was used in good scoring classifiers deter-

mined. Those biomarkers that occurred most frequently among the top scoring classifiers were the most useful for creating a diagnostic test. In this example, Bayesian classifiers were used to explore the classification space but many other supervised learning techniques may be employed for this purpose. The scoring fitness of any individual classifier was gauged by summing the sensitivity and specificity of the classifier at the Bayesian surface assuming a disease prevalence of 0.5. This scoring metric varies from zero to two, with two being an error-free classifier. The details of constructing a Bayesian classifier from biomarker population measurements are described in Example 3.

[0326] By aggregating the class-dependent samples across all sites in method (1), those analyte measurements that showed large site-to-site variation, on average, failed to exhibit class-dependent differences due to the large site-to-site differences. Such analytes were automatically removed from further analysis. However, those analytes that did show class-dependent differences across the sites are robust biomarkers that were relatively insensitive to sample collection and sample handling variability. KS-distances were computed for all analytes using the class-dependent cdfs aggregated across all sites. Using a KS-distance threshold of 0.4, fifty-nine potential biomarkers for diagnosing malignant ovarian cancer from benign pelvic masses were identified.

[0327] Using the fifty-nine potential biomarkers identified above, a total of 1966 10-analyte classifiers were found with a score of 1.75 or better (>87.5% sensitivity and >87.5% specificity, on average) for diagnosing ovarian cancer from a control group with benign pelvic masses using measurements from both sites. From this set of classifiers, a total of twenty-five biomarkers were found to be present in 5.0% or more of the high scoring classifiers. Table 20 provides a list of these potential biomarkers and FIG. **10** is a frequency plot for the identified biomarkers. This completed the biomarker identification using method (1).

[0328] Method (2) focused on consistency of potential biomarker changes between the control and case groups among the individual sites. The class-dependent cdfs were constructed for all analytes within each site separately and from these cdfs the KS-distances were computed to identify potential biomarkers. Sixty-three analytes were found to have a KS-distance greater than 0.4 in all the sites. Using these Sixty-three analytes to build potential 10-analyte Bayesian classifiers, there were 2031 classifiers that had a score of 1.75 or better. Twenty-four analytes occurred with a frequency greater than 5% among these classifiers and are presented in Table 21 and shown in FIG. **11**.

[0329] Finally, by combining the criteria for potential biomarker selection described for method (1) and (2) above, a set of potential biomarkers were produced by requiring an analyte to have a KS distance of 0.4 or better in the aggregated set as well as the two site comparisons. Forty-five analytes satisfy these requirements and are referred to as a blended set of potential biomarkers. For a classification score of 1.75 or better, a total of 1563 Bayesian classifiers were built from this set of potential biomarkers and twenty-seven biomarkers were identified from this set of classifiers using a frequency cut-off of 5%. These analytes are displayed in Table 22 and FIG. **12** is a frequency plot for the identified biomarkers.

[0330] A final list of biomarkers is obtained by combining the three sets of biomarkers identified above with frequencies greater than 5% in high scoring classifiers, Tables 20-22. From these sets of twenty-five, twenty-four, and twenty-seven biomarkers, forty-two unique biomarkers were identified and are shown in Table 1. Table 15 includes a dissociation constant for the aptamer used to identify the biomarker, the limit of quantification for the marker in the multiplex aptamer assay, and whether the marker was up-regulated or down-regulated in the disease population relative to the control population.

Example 3

Naïve Bayesian Classification for Ovarian Cancer

[0331] From the list of biomarkers identified as useful for discriminating between benign pelvic masses and ovarian malignancies, a panel of ten biomarkers was selected and a naïve Bayes classifier was constructed, see Table 18. The class-dependent probability density functions (pdfs), $p(x_i|c)$ and $p(x_i|d)$, where x_i is the measured RFU value for biomarker i, and c and d refer to the control and disease populations, were modeled as normal distribution functions characterized by a mean μ and variance σ^2. The parameters for pdfs of the ten biomarkers are listed in Table 18 and an example of the raw data along with the model fit to a normal cdf is shown in FIG. **5** for biomarker BAFF Receptor. The underlying assumption appears to fit the data quite well as evidenced by FIG. **5**.

[0332] The naïve Bayes classification for such a model is given by the following equation, where P(d) is the prevalence of the disease in the population

$$\ln\frac{p(c\mid \underset{\sim}{x})}{p(d\mid \underset{\sim}{x})}=\sum_{i=1}^{n}\left(\ln\frac{\sigma_{d,i}}{\sigma_{c,i}}-\frac{1}{2}\left[\left(\frac{x_i-\mu_{c,i}}{\sigma_{c,i}}\right)^2-\left(\frac{x_i-\mu_{d,i}}{\sigma_{d,i}}\right)^2\right]\right)+\ln\frac{(1-P(d))}{P(d)}$$

appropriate to the test and n=10 here. Each of the terms in the summation is a log-likelihood ratio for an individual marker and the total log-likelihood ratio of a sample $\underset{\sim}{x}$ being free from the disease of interest versus having the disease (i.e. in this case, ovarian cancer) is simply the sum of these individual terms plus a term that accounts for the prevalence of the disease. For simplicity, we assume P(d)=0.5 so that

$$\frac{(1-P(d))}{P(d)}=0.$$

[0333] Given an unknown sample measurement in RFU for each of the ten biomarkers of $\underset{\sim}{x}$=(701, 34158, 182792, 19531, 170310, 896, 3207, 22545, 733, 12535), the calculation of the classification is detailed in Table 23. The individual components comprising the log likelihood ratio for control versus disease class are tabulated and can be computed from the parameters in Table 18 and the values of $\underset{\sim}{x}$. The sum of the individual log likelihood ratios is 1.965, or a likelihood of being free from the disease versus having the disease of 7:1, where likelihood=$e^{1.965}$==7.14. Four of the ten biomarker values have likelihoods more consistent with the disease group (log likelihood <0) while the remaining six biomarkers

favor the control group, the largest by a factor of 3.5:1. Multiplying the likelihoods together gives the same result as that shown above; an aggregate likelihood of 7:1 that the unknown sample is free from the disease. In fact, this sample came from the control population in the training set.

Example 4

Greedy Algorithm for Selecting Biomarker Panels for Classifiers

Part 1

[0334] This example describes the selection of biomarkers from Table 1 to form panels that can be used as classifiers in any of the methods described herein. Subsets of the biomarkers in Table 1 were selected to construct classifiers with good performance. This method was also used to determine which potential markers were included as biomarkers in Example 2.

[0335] The measure of classifier performance used here is the sum of the sensitivity and specificity; a performance of 1.0 is the baseline expectation for a random (coin toss) classifier, a classifier worse than random would score between 0.0 and 1.0, a classifier with better than random performance would score between 1.0 and 2.0. A perfect classifier with no errors would have a sensitivity of 1.0 and a specificity of 1.0, therefore a performance of 2.0 (1.0+1.0). One can apply other common measures of performance such as area under the ROC curve, the F-measure, or the product of sensitivity and specificity. Specifically one might want to treat sensitivity and specificity with differing weight, in order to select those classifiers that perform with higher specificity at the expense of some sensitivity, or to select those classifiers which perform with higher sensitivity at the expense of some specificity. Since the method described here only involves a measure of "performance", any weighting scheme which results in a single performance measure can be used. Different applications will have different benefits for true positive and true negative findings, and will have different costs associated with false positive findings from false negative findings. For example, screening and the differential diagnosis of benign pelvic masses will not in general have the same optimal trade-off between specificity and sensitivity. The different demands of the two tests will in general require setting different weighting to positive and negative misclassifications, which will be reflected in the performance measure. Changing the performance measure will in general change the exact subset of markers selected from Table 1 for a given set of data.

[0336] For the Bayesian approach to the discrimination of ovarian cancer samples from control samples described in Example 3, the classifier was completely parameterized by the distributions of biomarkers in the disease and non-disease training samples, and the list of biomarkers was chosen from Table 1; that is to say, the subset of markers chosen for inclusion determined a classifier in a one-to-one manner given a set of training data.

[0337] The greedy method employed here was used to search for the optimal subset of markers from Table 1. For small numbers of markers or classifiers with relatively few markers, every possible subset of markers was enumerated and evaluated in terms of the performance of the classifier constructed with that particular set of markers (see Example 4, Part 2). (This approach is well known in the field of statistics as "best subset selection"; see, e.g., Hastie et al, supra). However, for the classifiers described herein, the number of combinations of multiple markers can be very large, and it was not feasible to evaluate every possible set of 10 markers, for example, from the list of 42 markers (Table 1) (i.e., 1, 471, 442, 973 combinations). Because of the impracticality of searching through every subset of markers, the single optimal subset may not be found; however, by using this approach, many excellent subsets were found, and, in many cases, any of these subsets may represent an optimal one.

[0338] Instead of evaluating every possible set of markers, a "greedy" forward stepwise approach may be followed (see, e.g., Dabney A R, Storey J D (2007) Optimality Driven Nearest Centroid Classification from Genomic Data. PLoS ONE 2(10): e1002. doi:10.1371/journal.pone.0001002). Using this method, a classifier is started with the best single marker (based on KS-distance for the individual markers) and is grown at each step by trying, in turn, each member of a marker list that is not currently a member of the set of markers in the classifier. The one marker that scores the best in combination with the existing classifier is added to the classifier. This is repeated until no further improvement in performance is achieved. Unfortunately, this approach may miss valuable combinations of markers for which some of the individual markers are not all chosen before the process stops.

[0339] The greedy procedure used here was an elaboration of the preceding forward stepwise approach, in that, to broaden the search, rather than keeping just a single candidate classifier (marker subset) at each step, a list of candidate classifiers was kept. The list was seeded with every single marker subset (using every marker in the table on its own). The list was expanded in steps by deriving new classifiers (marker subsets) from the ones currently on the list and adding them to the list. Each marker subset currently on the list was extended by adding any marker from Table 1 not already part of that classifier, and which would not, on its addition to the subset, duplicate an existing subset (these are termed "permissible markers"). Every existing marker subset was extended by every permissible marker from the list. Clearly, such a process would eventually generate every possible subset, and the list would run out of space. Therefore, all the generated classifiers were kept only while the list was less than some predetermined size (often enough to hold all three marker subsets). Once the list reached the predetermined size limit, it became elitist; that is, only those classifiers which showed a certain level of performance were kept on the list, and the others fell off the end of the list and were lost. This was achieved by keeping the list sorted in order of classifier performance; new classifiers which were at least as good as the worst classifier currently on the list were inserted, forcing the expulsion of the current bottom underachiever. One further implementation detail is that the list was completely replaced on each generational step; therefore, every classifier on the list had the same number of markers, and at each step the number of markers per classifier grew by one.

[0340] Since this method produced a list of candidate classifiers using different combinations of markers, one may ask if the classifiers can be combined in order to avoid errors that might be made by the best single classifier, or by minority groups of the best classifiers. Such "ensemble" and "committee of experts" methods are well known in the fields of statistical and machine learning and include, for example, "Averaging", "Voting", "Stacking", "Bagging" and "Boosting" (see, e.g., Hastie et al., supra). These combinations of simple

classifiers provide a method for reducing the variance in the classifications due to noise in any particular set of markers by including several different classifiers and therefore information from a larger set of the markers from the biomarker table, effectively averaging between the classifiers. An example of the usefulness of this approach is that it can prevent outliers in a single marker from adversely affecting the classification of a single sample. The requirement to measure a larger number of signals may be impractical in conventional "one marker at a time" antibody assays but has no downside for a fully multiplexed aptamer assay. Techniques such as these benefit from a more extensive table of biomarkers and use the multiple sources of information concerning the disease processes to provide a more robust classification.

Part 2

[0341] The biomarkers selected in Table 1 gave rise to classifiers that perform better than classifiers built with "non-markers" (i.e., proteins having signals that did not meet the criteria for inclusion in Table 1 (as described in Example 2)).

[0342] For classifiers containing only one, two, and three markers, all possible classifiers obtained using the biomarkers in Table 1 were enumerated and examined for the distribution of performance compared to classifiers built from a similar table of randomly selected non-markers signals.

[0343] In FIG. **14**, the sum of the sensitivity and specificity was used as the measure of performance; a performance of 1.0 is the baseline expectation for a random (coin toss) classifier. The histogram of classifier performance was compared with the histogram of performance from a similar exhaustive enumeration of classifiers built from a "non-marker" table of 42 non-marker analytes; the 42 analytes were randomly chosen from 387 aptamer measurements that did not demonstrate differential signaling between control and disease populations (KS-distance <0.2).

[0344] FIG. **14** shows histograms of the performance of all possible one, two, and three-marker classifiers built from the biomarker parameters in Table 18 for biomarkers that can discriminate between benign pelvic masses and ovarian cancer and compares these classifiers with all possible one, two, and three-marker classifiers built using the 42 "non-marker" aptamer RFU signals. FIG. **14**A shows the histograms of single marker classifier performance, FIG. **14**B shows the histogram of two-marker classifier performance, and FIG. **14**C shows the histogram of three-marker classifier performance.

[0345] In FIG. **14**, the solid lines represent the histograms of the classifier performance of all one, two, and three-marker classifiers using the biomarker data for benign pelvic masses and ovarian cancer in Table 18. The dotted lines are the histograms of the classifier performance of all one, two, and three-marker classifiers using the data for benign pelvic masses and ovarian cancer but using the set of random non-marker signals.

[0346] The classifiers built from the markers listed in Table 1 form a distinct histogram, well separated from the classifiers built with signals from the "non-markers" for all one-marker, two-marker, and three-marker comparisons. The performance and AUC score of the classifiers built from the biomarkers in Table 1 also increase at a higher rate as markers are added than do the classifiers built from the non-markers. The separation of performance increases between the marker and non-marker classifiers as the number of markers per classifier increases. All classifiers built using the biomarkers listed in Table 1 perform distinctly better than classifiers built using the "non-markers".

Part 3

[0347] The distributions of classifier performance show that there are many possible multiple-marker classifiers that can be derived from the set of analytes in Table 1. Although some biomarkers are better than others on their own, as evidenced by the distribution of classifier scores and AUCs for single analytes, it was desirable to determine whether such biomarkers are required to construct high performing classifiers. To make this determination, the behavior of classifier performance was examined by leaving out some number of the best biomarkers. FIG. **15** compares the performance of classifiers built with the full list of biomarkers in Table 1 with the performance of classifiers built with subsets of biomarkers from Table 1 that excluded top-ranked markers.

[0348] FIG. **15** demonstrates that classifiers constructed without the best markers perform well, implying that the performance of the classifiers was not due to some small core group of markers and that the changes in the underlying processes associated with disease are reflected in the activities of many proteins. Many subsets of the biomarkers in Table 1 performed close to optimally, even after removing the top 15 of the 42 markers from Table 1. After dropping the 15 top-ranked markers (ranked by KS-distance) from Table 1, the classifier performance increased with the number of markers selected from the table to reach almost 1.80 (sensitivity+specificity), close to the performance of the optimal classifier score of 1.87 selected from the full list of biomarkers.

[0349] Finally, FIG. **16** shows how the ROC performance of typical classifiers constructed from the list of parameters in Table 18 according to Example 3. A five analyte classifier was constructed with TIMP-2, MCP-3, Cadherin-5, SLPI, and C9. FIG. **16**A shows the performance of the model, assuming independence of these markers, as in Example 3, and FIG. **16**B shows the empirical ROC curves generated from the study data set used to define the parameters in Table 18. It can be seen that the performance for a given number of selected markers was qualitatively in agreement, and that quantitative agreement was generally quite good, as evidenced by the AUCs, although the model calculation tends to overestimate classifier performance. This is consistent with the notion that the information contributed by any particular biomarker concerning the disease processes is redundant with the information contributed by other biomarkers provided in Table 1 while the model calculation assumes complete independence. FIG. **16** thus demonstrates that Table 1 in combination with the methods described in Example 3 enable the construction and evaluation of a great many classifiers useful for the discrimination of ovarian cancer from benign pelvic masses.

Example 5

Aptamer Specificity Demonstration in a Pull-down Assay

[0350] The final readout on the multiplex assay is based on the amount of aptamer recovered after the successive capture steps in the assay. The multiplex assay is based on the premise that the amount of aptamer recovered at the end of the assay

is proportional to the amount of protein in the original complex mixture (e.g., plasma). In order to demonstrate that this signal is indeed derived from the intended analyte rather than from non-specifically bound proteins in plasma, we developed a gel-based pull-down assay in plasma. This assay can be used to visually demonstrate that a desired protein is in fact pulled out from plasma after equilibration with an aptamer as well as to demonstrate that aptamers bound to their intended protein targets can survive as a complex through the kinetic challenge steps in the assay. In the experiments described in this example, recovery of protein at the end of this pull-down assay requires that the protein remain non-covalently bound to the aptamer for nearly two hours after equilibration Importantly, in this example we also provide evidence that non-specifically bound proteins dissociate during these steps and do not contribute significantly to the final signal. It should be noted that the pull-down procedure described in this example includes all of the key steps in the multiplex assay described above.

[0351] A. Plasma Pull-Down Assay

[0352] Plasma samples were prepared by diluting 50 μL EDTA-plasma to 100 μL in SB18 with 0.05% Tween-20 (SB18T) and 2 μM Z-Block. The plasma solution was equilibrated with 10 pmoles of a PBDC-aptamer in a final volume of 150 μL for 2 hours at 37° C. After equilibration, complexes and unbound aptamer were captured with 133 μL of a 7.5% Streptavidin-agarose bead slurry by incubating with shaking for 5 minutes at RT in a Durapore filter plate. The samples bound to beads were washed with biotin and with buffer under vacuum as described in Example 1. After washing, bound proteins were labeled with 0.5 mM NHS-S-S-biotin, 0.25 mM NHS-Alexa647 in the biotin diluent for 5 minutes with shaking at RT. This staining step allows biotinylation for capture of protein on streptavidin beads as well as highly sensitive staining for detection on a gel. The samples were washed with glycine and with buffer as described in Example 1. Aptamers were released from the beads by photocleavage using a Black Ray light source for 10 minutes with shaking at RT. At this point, the biotinylated proteins were captured on 0.5 mg MyOne Streptavidin beads by shaking for 5 minutes at RT. This step will capture proteins bound to aptamers as well as proteins that may have dissociated from aptamers since the initial equilibration. The beads were washed as described in Example 1. Proteins were eluted from the MyOne Streptavidin beads by incubating with 50 mM DTT in SB17T for 25 minutes at 37° C. with shaking. The eluate was then transferred to MyOne beads coated with a sequence complimentary to the 3' fixed region of the aptamer and incubated for 25 minutes at 37° C. with shaking. This step captures all of the remaining aptamer. The beads were washed 2× with 100 μL SB17T for 1 minute and 1× with 100 μL SB19T for 1 minute. Aptamer was eluted from these final beads by incubating with 45 μL 20 mM NaOH for 2 minutes with shaking to disrupt the hybridized strands. 40 μL of this eluate was neutralized with 10 μL 80 mM HCl containing 0.05% Tween-20. Aliquots representing 5% of the eluate from the first set of beads (representing all plasma proteins bound to the aptamer) and 20% of the eluate from the final set of beads (representing all plasma proteins remaining bound at the end of our clinical assay) were run on a NuPAGE 4-12% Bis-Tris gel (Invitrogen) under reducing and denaturing conditions. Gels were imaged on an Alpha Innotech FluorChem Q scanner in the Cy5 channel to image the proteins.

[0353] B. Pull-down gels for aptamers were selected against LBP (~1×10^{-7} M in plasma, polypeptide MW ~60 kDa), C9 (~1×10^{-6} M in plasma, polypeptide MW ~60 kDa), and IgM (~9×10^{-6} M in plasma, MW ~70 kDa and 23 kDa), respectively. (See FIG. **13**).

[0354] For each gel, lane 1 is the eluate from the Streptavidin-agarose beads, lane 2 is the final eluate, and lane 3 is a MW marker lane (major bands are at 110, 50, 30, 15, and 3.5 kDa from top to bottom). It is evident from these gels that there is a small amount non-specific binding of plasma proteins in the initial equilibration, but only the target remains after performing the capture steps of the assay. It is clear that the single aptamer reagent is sufficient to capture its intended analyte with no up-front depletion or fractionation of the plasma. The amount of remaining aptamer after these steps is then proportional to the amount of the analyte in the initial sample.

[0355] The foregoing embodiments and examples are intended only as examples. No particular embodiment, example, or element of a particular embodiment or example is to be construed as a critical, required, or essential element or feature of any of the claims. Further, no element described herein is required for the practice of the appended claims unless expressly described as "essential" or "critical." Various alterations, modifications, substitutions, and other variations can be made to the disclosed embodiments without departing from the scope of the present application, which is defined by the appended claims. The specification, including the figures and examples, is to be regarded in an illustrative manner, rather than a restrictive one, and all such modifications and substitutions are intended to be included within the scope of the application. Accordingly, the scope of the application should be determined by the appended claims and their legal equivalents, rather than by the examples given above. For example, steps recited in any of the method or process claims may be executed in any feasible order and are not limited to an order presented in any of the embodiments, the examples, or the claims. Further, in any of the aforementioned methods, one or more biomarkers of Table 1 can be specifically excluded either as an individual biomarker or as a biomarker from any panel.

TABLE 1

Biomarkers for Ovarian Cancer

Biomarker Designation	Alternate Protein Names	Gene Designation
α1-Antitrypsin	Alpha-1-antitrypsin API Alpha-1-protease inhibitor alpha 1 antitrypsin	SERPINA1

TABLE 1-continued

Biomarkers for Ovarian Cancer

Biomarker Designation	Alternate Protein Names	Gene Designation
	alpha1-protease inhibitor Serpin A1 AAT	
α2-Antiplasmin	alpha-2-plasmin inhibitor	SERPINF2
α2-HS-Glycoprotein	fetuin fetuin A alpha-2-HS glycoprotein AHSG Alpha2-Heremans Schmid glycoprotein Ba-alpha-2-glycoprotein Alpha-2-Z-globulin	AHSG
ADAM 9	Disintegrin and metalloproteinase domain-containing protein 9 Metalloprotease/disintegrin/cysteine-rich protein 9 Myeloma cell metalloproteinase Meltrin-gamma Cellular disintegrin-related protein	ADAM9
ARSB	Arylsulfatase B G4S N-acetylgalactosamine-4-sulfatase ASB G4S	ARSB
BAFF Receptor	B cell-activating factor receptor BLyS receptor 3 Tumor necrosis factor receptor superfamily member 13C TNFRSF13C CD268 antigen	TNFRSF13C
C2	Complement C2 C3/C5 convertase	C2
C5	Complement Factor C5 Complement C5 C3 and PZP-like alpha-2-macroglobulin domain-containing protein 4	C5
C6	Complement component C6	C6
C9	Complement Factor C9 Complement component C9	C9
Cadherin-5	VE-cadherin 7B4 antigen Vascular endothelial-cadherin CD144 antigen	CDH5
Coagulation Factor Xa	Activated factor Xa heavy chain	F10
Contactin-1	Neural cell surface protein F3 Glycoprotein gp135	CNTN1
Contactin-4	BIG-2 Brain-derived immunoglobulin superfamily protein 2 CNTN4	CNTN4
ERBB1	Epidermal growth factor receptor Receptor tyrosine-protein kinase ErbB-1 ErbB-1 EGFR HER1 Human EGF Receptor	EGFR
Growth hormone receptor	GH receptor Somatotropin receptor GHR	GHR
Hat1	Histone acetyltransferase type B catalytic subunit	HAT1
HGF	Hepatocyte growth factor Scatter factor Hepatopoeitin-A	HGF
HSP 90α	Heat shock protein HSP 90-alpha HSP 86 Renal carcinoma antigen NY-REN-38	HSP90AAl
IL-12 Rβ2	Interleukin-12 receptor beta-2 chain IL-12R-beta-2 IL-12 receptor beta-2 I12R2	IL12RB2

TABLE 1-continued

Biomarkers for Ovarian Cancer

Biomarker Designation	Alternate Protein Names	Gene Designation
IL-13 Rα1	Interleukin-13 receptor alpha-1 IL-13 receptor alpha-1 IL-13RA-1 IL-13R-alpha-1 Cancer/testis antigen 19 CT19 CD213a1 antigen IL13R	IL13RA1
IL-18 Rβ	Interleukin-18 receptor accessory protein IL-18 receptor accessory protein IL-18RacP Interleukin-18 receptor accessory protein-like IL-18Rbeta IL-1R accessory protein-like IL-1RAcPL IL-1R7 CD218 antigen-like family member B CDw218b antigen	IL18RAP
Kallikrein 6	Protease M Neurosin hK6 Zyme KLK6 SP59 Serine protease 9 Serine protease 18	KLK6
Kallistatin	Serpin A4 Kallikrein inhibitor Protease inhibitor 4	SERPINA4
LY9	T-lymphocyte surface antigen Ly-9 CD229 antigen Cell-surface molecule Ly-9 Lymphocyte antigen 9	LY9
MCP-3	Monocyte chemotactic protein 3 Small-inducible cytokine A7 Monocyte chemoattractant protein 3 NC28 CCL7	CCL7
MIP-5	C-C motif chemokine 15 Small-inducible cytokine A15 Macrophage inflammatory protein 5 Chemokine CC-2 HCC-2 NCC-3 MIP-1 delta Leukotactin-1 LKN-1 Mrp-2b	CCL15
MMP-7	Matrilysin Pump-1 protease Uterine metalloproteinase Matrix metalloproteinase-7 Matrin	MMP7
MRC2	Macrophage mannose receptor 2 CD280 antigen Endocytic receptor 180 Urokinase receptor-associated protein ENDO180	MRC2
NRP1	Neuropilin-1 CD304 antigen Vascular endothelial cell growth factor 165 receptor	NRP1
PCI	Protein C inhibitor Plasminogen activator inhibitor −3 PAI-3 Plasma serine protease inhibitor Serpin A5 Acrosomal serine protease inhibitor	SERPINA5
Prekallikrein	Plasma kallikrein Plasma prekallikrein Kininogenin	KLKB1

TABLE 1-continued

Biomarkers for Ovarian Cancer

Biomarker Designation	Alternate Protein Names	Gene Designation
	Fletcher factor	
Properdin	Complement factor P Factor P	CFP
RBP	Retinol Binding Protein Retinol-binding protein 4 RBP4 Plasma retinol-binding protein	RBP4
RGM-C	Hemojuvelin RGM domain family member C Hemochromatosis type 2 protein RGMC	HFE2
SAP	Serum Amyloid P Component 9.5S alpha-1-glycoprotein	APCS
SCF sR	Mast/stem cell growth factor receptor stem cell growth factor soluble receptor Proto-oncogene tyrosine-protein kinase Kit c-kit CD117	KIT
SLPI	Secretory leukocyte protease inhibitor Antileukoproteinase 1 HUSI-1 Seminal proteinase inhibitor BLPI Mucus proteinase inhibitor MPI WAP four-disulfide core domain protein 4 Protease inhibitor WAP4	SLPI
sL-Selectin	sL-Selectin Leukocyte adhesion molecule-1 Lymph node homing receptor LAM-1 L-Selectin L-Selectin, soluble Leukocyte surface antigen Leu-8 TQ1 gp90-MEL Leukocyte-endothelial cell adhesion molecule i LECAM1 CD62 antigen-like family m	SELL
Thrombin/ Prothrombin	Alpha Thrombin/Prothrombin Coagulation factor II	F2
TIMP-2	Tissue inhibitor of metalloproteinases-2 CSC-21K	TIMP2
Troponin T	troponin T cardiac muscle TnTc cTnT	TNNT2

[0356]

TABLE 2

100 Panels of 3 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers			Sensitivity	Specificity	Sensitivity + Specificity	AUC
1	ADAM 9	α1-Antitrypsin	α2-Antiplasmin	0.846	0.851	1.697	0.866
2	ARSB	SLPI	C9	0.846	0.856	1.703	0.913
3	BAFF Receptor	SLPI	C9	0.833	0.862	1.695	0.916
4	C2	LY9	SLPI	0.808	0.923	1.731	0.916
5	C5	Troponin T	C9	0.897	0.800	1.697	0.885
6	C6	ERBB1	SLPI	0.808	0.887	1.695	0.902
7	Cadherin-5	C9	SLPI	0.859	0.887	1.746	0.929
8	Coagulation Factor Xa	LY9	SLPI	0.821	0.882	1.703	0.911
9	Contactin-4	LY9	SLPI	0.833	0.872	1.705	0.906

TABLE 2-continued

10	Growth hormone receptor	SLPI	C9	0.859	0.859	1.715	0.916
11	HGF	Troponin T	C9	0.897	0.795	1.692	0.886
12	HSP 90α	LY9	SLPI	0.846	0.882	1.728	0.896
13	Hat1	SLPI	C9	0.846	0.867	1.713	0.914
14	IL-12 Rβ2	C9	SLPI	0.833	0.872	1.705	0.916
15	IL-13 Rα1	SLPI	C9	0.846	0.856	1.703	0.920
16	IL-18 Rβ	SLPI	C9	0.846	0.856	1.703	0.925
17	Kallikrein 6	SLPI	C9	0.821	0.851	1.672	0.921
18	LY9	Kallistatin	SLPI	0.795	0.897	1.692	0.912
19	MCP-3	SLPI	C9	0.833	0.882	1.715	0.924
20	MIP-5	C9	SLPI	0.821	0.846	1.667	0.919
21	MRC2	MMP-7	C9	0.859	0.846	1.705	0.898
22	SAP	NRP1	SLPI	0.821	0.887	1.708	0.917
23	LY9	PCI	SLPI	0.833	0.867	1.700	0.902
24	C2	Prekallikrein	SLPI	0.808	0.892	1.700	0.911
25	Properdin	LY9	SLPI	0.846	0.877	1.723	0.905
26	LY9	RBP	SLPI	0.782	0.903	1.685	0.897
27	SAP	RGM-C	SLPI	0.872	0.877	1.749	0.923
28	SCF sR	C9	SLPI	0.846	0.856	1.703	0.915
29	TIMP-2	C9	SLPI	0.885	0.856	1.741	0.926
30	MCP-3	Thrombin/ Prothrombin	C9	0.833	0.826	1.659	0.875
31	α2-HS-Glycoprotein	α2-Antiplasmin	SLPI	0.808	0.872	1.679	0.887
32	Contactin-1	LY9	SLPI	0.808	0.882	1.690	0.909
33	sL-Selectin	C9	SLPI	0.821	0.872	1.692	0.929
34	C2	ADAM 9	SLPI	0.795	0.897	1.692	0.879
35	Cadherin-5	ARSB	α1-Antitrypsin	0.769	0.897	1.667	0.867
36	BAFF Receptor	C6	SLPI	0.782	0.897	1.679	0.876
37	C5	RGM-C	SLPI	0.833	0.862	1.695	0.906
38	Coagulation Factor Xa	SLPI	C9	0.846	0.846	1.692	0.923
39	SAP	Contactin-4	SLPI	0.821	0.867	1.687	0.891
40	ERBB1	C9	SLPI	0.846	0.846	1.692	0.920
41	SAP	Growth hormone receptor	SLPI	0.808	0.892	1.700	0.917
42	HGF	MCP-3	C9	0.872	0.815	1.687	0.872
43	HSP 90α	SLPI	C9	0.859	0.862	1.721	0.927
44	SAP	Hat1	SLPI	0.808	0.903	1.710	0.902
45	IL-12 Rβ2	Prekallikrein	SLPI	0.821	0.856	1.677	0.889
46	IL-13 Rα1	RGM-C	C9	0.872	0.805	1.677	0.886
47	IL-18 Rβ	LY9	C9	0.859	0.826	1.685	0.870
48	Kallikrein 6	LY9	SLPI	0.795	0.872	1.667	0.896
49	Cadherin-5	Kallistatin	SLPI	0.769	0.903	1.672	0.910
50	MIP-5	RGM-C	C9	0.885	0.774	1.659	0.893
51	RGM-C	MMP-7	C9	0.885	0.815	1.700	0.908
52	MRC2	C9	SLPI	0.859	0.862	1.721	0.911
53	NRP1	LY9	SLPI	0.821	0.877	1.697	0.908
54	PCI	C9	SLPI	0.821	0.856	1.677	0.917
55	Cadherin-5	Properdin	SLPI	0.782	0.908	1.690	0.907
56	RBP	SLPI	C9	0.833	0.851	1.685	0.910
57	SCF sR	α1-Antitrypsin	SLPI	0.808	0.872	1.679	0.885
58	TIMP-2	α2-Antiplasmin	SLPI	0.821	0.882	1.703	0.900
59	NRP1	Thrombin/ Prothrombin	C9	0.846	0.805	1.651	0.873
60	SCF sR	α2-HS-Glycoprotein	SLPI	0.795	0.872	1.667	0.879
61	Contactin-1	NRP1	SLPI	0.782	0.897	1.679	0.906
62	RGM-C	sL-Selectin	C9	0.872	0.805	1.677	0.901
63	Cadherin-5	ADAM 9	α1-Antitrypsin	0.795	0.892	1.687	0.862
64	Properdin	ARSB	SLPI	0.769	0.892	1.662	0.889
65	BAFF Receptor	α2-Antiplasmin	SLPI	0.782	0.887	1.669	0.880
66	C5	Properdin	SLPI	0.808	0.882	1.690	0.898
67	C6	RGM-C	SLPI	0.821	0.872	1.692	0.908
68	SAP	Coagulation Factor Xa	SLPI	0.808	0.872	1.679	0.907
69	Contactin-4	Coagulation Factor Xa	MMP-7	0.808	0.867	1.674	0.868
70	C2	ERBB1	SLPI	0.795	0.892	1.687	0.904
71	Cadherin-5	Growth hormone receptor	α1-Antitrypsin	0.821	0.872	1.692	0.876
72	HGF	SLPI	C9	0.872	0.815	1.687	0.916
73	HSP 90α	C2	SLPI	0.808	0.872	1.679	0.900
74	Hat1	LY9	SLPI	0.808	0.877	1.685	0.903
75	IL-12 Rβ2	α2-Antiplasmin	SLPI	0.808	0.867	1.674	0.883

TABLE 2-continued

76	IL-13 Rα1	LY9	SLPI	0.795	0.877	1.672	0.900
77	IL-18 Rβ	Prekallikrein	C9	0.859	0.826	1.685	0.890
78	Kallikrein 6	SCF sR	C9	0.846	0.821	1.667	0.882
79	C2	Kallistatin	SLPI	0.782	0.887	1.669	0.903
80	MIP-5	Cadherin-5	SLPI	0.782	0.867	1.649	0.885
81	MRC2	Hat1	SLPI	0.782	0.897	1.679	0.889
82	PCI	α2-Antiplasmin	SLPI	0.795	0.867	1.662	0.891
83	SAP	RBP	SLPI	0.782	0.892	1.674	0.895
84	Cadherin-5	TIMP-2	SLPI	0.808	0.877	1.685	0.907
85	SCF sR	Thrombin/ Prothrombin	C9	0.859	0.790	1.649	0.865
86	Troponin T	SLPI	C9	0.833	0.851	1.685	0.923
87	α2-HS-Glycoprotein	C9	SLPI	0.808	0.851	1.659	0.915
88	Cadherin-5	Contactin-1	SLPI	0.808	0.867	1.674	0.897
89	Cadherin-5	sL-Selectin	SLPI	0.795	0.882	1.677	0.901
90	ADAM 9	SLPI	α2-Antiplasmin	0.782	0.892	1.674	0.883
91	ARSB	ADAM 9	α2-Antiplasmin	0.808	0.851	1.659	0.836
92	BAFF Receptor	α1-Antitrypsin	SLPI	0.769	0.897	1.667	0.889
93	C5	C9	SLPI	0.833	0.856	1.690	0.920
94	C6	LY9	SLPI	0.782	0.908	1.690	0.908
95	C5	Contactin-4	SLPI	0.808	0.862	1.669	0.883
96	ERBB1	α1-Antitrypsin	SLPI	0.808	0.877	1.685	0.893
97	C5	Growth hormone receptor	C9	0.872	0.810	1.682	0.881
98	HGF	Hat1	C9	0.872	0.810	1.682	0.871
99	HSP 90α	IL-18 Rβ	C9	0.859	0.815	1.674	0.885
100	IL-12 Rβ2	α1-Antitrypsin	SLPI	0.795	0.877	1.672	0.887

Marker	Count	Marker	Count
SLPI	77	Contactin-4	4
C9	41	Coagulation Factor Xa	4
LY9	15	C6	4
Cadherin-5	10	BAFF Receptor	4
α2-Antiplasmin	8	ARSB	4
α1-Antitrypsin	8	sL-Selectin	3
SAP	7	Contactin-1	3
RGM-C	7	α2-HS-Glycoprotein	3
C5	5	Troponin T	3
C2	6	Thrpmbin/Prothrombin	3
SCF sR	5	TIMP-2	3
Hat1	5	RBP	3
ADAM 9	5	Prekallikrein	3
Properdin	4	PCI	3
NRP1	4	MRC2	3
IL-18 Rβ	4	MMP-7	3
IL-12 Rβ2	4	MIP-5	3
HSP 90α	4	MCP-3	3
HGF	4	Kallistatin	3
Growth hormone receptor	4	Kallikrein 6	3
ERBB1	4	IL-13 Rα1	3

[0357]

TABLE 3

100 Panels of 4 Biomarkers for Daignosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers				Sensitivity	Specificity	Sensitivity + Specificity	AUC
1	LY9	ADAM 9	C9	SLPI	0.872	0.867	1.738	0.910
2	ARSB	LY9	C9	SLPI	0.872	0.877	1.749	0.920
3	BAFF Receptor	MCP-3	SLPI	C9	0.885	0.862	1.746	0.923
4	Cadherin-5	C2	SLPI	LY9	0.859	0.918	1.777	0.923
5	C5	C2	SLPI	LY9	0.846	0.897	1.744	0.907
6	C6	LY9	C9	SLPI	0.885	0.867	1.751	0.923
7	Coagulation Factor Xa	LY9	C9	SLPI	0.897	0.862	1.759	0.930
8	Hat1	LY9	Contactin-4	SLPI	0.872	0.897	1.769	0.910
9	IL-13 Rα1	LY9	ERBB1	SLPI	0.872	0.877	1.749	0.906

TABLE 3-continued

10	Cadherin-5	SAP	Growth hormone receptor	SLPI	0.885	0.892	1.777	0.924
11	HGF	MRC2	C9	SLPI	0.910	0.856	1.767	0.911
12	HSP 90α	LY9	C9	SLPI	0.897	0.897	1.795	0.924
13	Cadherin-5	IL-12 Rβ2	C9	SLPI	0.846	0.892	1.738	0.923
14	IL-18 Rβ	SLPI	RGM-C	C9	0.897	0.862	1.759	0.930
15	Cadherin-5	LY9	Kallikrein 6	SLPI	0.885	0.887	1.772	0.915
16	MMP-7	α2-Antitrypsin	Kallistatin	SLPI	0.859	0.882	1.741	0.921
17	MIP-5	LY9	C9	SLPI	0.872	0.877	1.749	0.925
18	NRP1	LY9	Cadherin-5	SLPI	0.859	0.908	1.767	0.924
19	LY9	PCI	C9	SLPI	0.872	0.867	1.738	0.917
20	LY9	Prekallikrein	C9	SLPI	0.897	0.856	1.754	0.925
21	SAP	Properdin	RGM-C	SLPI	0.859	0.903	1.762	0.931
22	LY9	RBP	C9	SLPI	0.897	0.862	1.759	0.917
23	SCF sR	LY9	C9	SLPI	0.885	0.867	1.751	0.923
24	MCP-3	TIMP-2	C9	SLPI	0.897	0.862	1.759	0.920
25	MMP-7	Thrombin/ Prothrombin	SLPI	C9	0.885	0.841	1.726	0.925
26	LY9	Troponin T	C9	SLPI	0.872	0.872	1.744	0.924
27	α2-Antitrypsin	C9	LY9	SLPI	0.885	0.862	1.746	0.919
28	Cadherin-5	α2-HS-Glycoprotein	SLPI	sL-Selectin	0.821	0.897	1.718	0.900
29	Contactin-1	LY9	C9	SLPI	0.885	0.882	1.767	0.927
30	Properdin	ADAM 9	C9	SLPI	0.872	0.862	1.733	0.907
31	Cadherin-5	ARSB	C9	SLPI	0.872	0.862	1.733	0.922
32	BAFF Receptor	LY9	C9	SLPI	0.885	0.856	1.741	0.915
33	Properdin	MCP-3	C5	SLPI	0.833	0.908	1.741	0.909
34	C6	C2	SLPI	LY9	0.833	0.918	1.751	0.922
35	SAP	C9	Coagulation Factor Xa	SLPI	0.885	0.867	1.751	0.929
36	Contactin-4	LY9	MCP-3	SLPI	0.859	0.892	1.751	0.914
37	LY9	ERBB1	C9	SLPI	0.872	0.872	1.744	0.923
38	Cadherin-5	Growth hormone receptor	C9	SLPI	0.872	0.877	1.749	0.926
39	HGF	RGM-C	α2-Anti-plasmin	C9	0.936	0.821	1.756	0.909
40	HSP 90α	Cadherin-5	C9	SLPI	0.859	0.892	1.751	0.928
41	Hat1	LY9	C9	SLPI	0.885	0.877	1.762	0.926
42	IL-12 Rβ2	C2	SLPI	LY9	0.833	0.903	1.736	0.907
43	IL-13 Rα1	SLPI	Cadherin-5	C9	0.885	0.882	1.767	0.928
44	MRC2	LY9	IL-18 Rβ	SLPI	0.833	0.908	1.741	0.913
45	Kallikrein 6	LY9	C9	SLPI	0.897	0.867	1.764	0.921
46	BAFF Receptor	LY9	Kallistatin	SLPI	0.833	0.903	1.736	0.900
47	MIP-5	SCF sR	SLPI	C9	0.872	0.862	1.733	0.914
48	NRP1	LY9	C9	SLPI	0.885	0.877	1.762	0.927
49	SAP	PCI	RGM-C	SLPI	0.872	0.862	1.733	0.916
50	BAFF Receptor	HGF	SLPI	Prekallikrein	0.897	0.841	1.738	0.893
51	RGM-C	RBP	MMP-7	C9	0.897	0.841	1.738	0.905
52	Cadherin-5	TIMP-2	C9	SLPI	0.872	0.882	1.754	0.931
53	C2	Thrombin/ Prothrombin	Growth hormone receptor	SLPI	0.859	0.862	1.721	0.904
54	RGM-C	Troponin T	C9	α1-Antitrypsin	0.872	0.867	1.738	0.908
55	sL-Selectin	α2-HS-Glycoprotein	C9	SLPI	0.833	0.882	1.715	0.920
56	Contactin-1	C2	SLPI	Cadherin-5	0.846	0.903	1.749	0.908
57	Cadherin-5	ADAM 9	C9	SLPI	0.833	0.897	1.731	0.916
58	Cadherin-5	Properdin	ARSB	SLPI	0.821	0.908	1.728	0.909
59	C5	LY9	α1-Antitrypsin	SLPI	0.859	0.882	1.741	0.909
60	RGM-C	LY9	C6	SLPI	0.859	0.887	1.746	0.920
61	NRP1	LY9	Coagulation Factor Xa	SLPI	0.872	0.872	1.744	0.915
62	RGM-C	Contactin-4	MCP-3	SLPI	0.846	0.897	1.744	0.919
63	MCP-3	LY9	ERBB1	SLPI	0.859	0.877	1.736	0.906
64	HSP 90α	MCP-3	C9	SLPI	0.897	0.851	1.749	0.922
65	Hat1	LY9	C2	SLPI	0.859	0.897	1.756	0.917
66	MRC2	IL-12 Rβ2	Properdin	SLPI	0.833	0.897	1.731	0.885
67	Cadherin-5	LY9	IL-13 Rα1	SLPI	0.872	0.887	1.759	0.917
68	IL-18 Rβ	SLPI	Cadherin-5	C9	0.859	0.882	1.741	0.933
69	Kallikrein 6	LY9	SCF sR	SLPI	0.859	0.887	1.746	0.898
70	Cadherin-5	LY9	Kallistatin	SLPI	0.833	0.903	1.736	0.921
71	MIP-5	Hat1	SLPI	C9	0.859	0.872	1.731	0.907
72	Cadherin-5	LY9	PCI	SLPI	0.846	0.887	1.733	0.909

TABLE 3-continued

73	Prekallikrein	α1-Antitrypsin	LY9	SLPI	0.846	0.887	1.733	0.911
74	SCF sR	RBP	SLPI	C9	0.872	0.856	1.728	0.908
75	RGM-C	TIMP-2	C9	SLPI	0.885	0.867	1.751	0.931
76	C2	LY9	Thrombin/ Prothrombin	SLPI	0.846	0.867	1.713	0.922
77	SAP	α1-Antitrypsin	Troponin T	SLPI	0.833	0.903	1.736	0.917
78	HGF	α2-Anti-plasmin	C9	SLPI	0.910	0.841	1.751	0.922
79	Cadherin-5	α2-HS-Glycoprotein	SLPI	LY9	0.833	0.882	1.715	0.908
80	Contactin-1	LY9	Growth hormone receptor	SLPI	0.859	0.887	1.746	0.914
81	sL-Selectin	LY9	C9	SLPI	0.885	0.867	1.751	0.926
82	Cadherin-5	Prekallikrein	ADAM 9	SLPI	0.846	0.882	1.728	0.897
83	Cadherin-5	ARSB	SLPI	LY9	0.846	0.882	1.728	0.907
84	Hat1	LY9	C5	SLPI	0.859	0.877	1.736	0.909
85	C6	MRC2	Hat1	SLPI	0.833	0.908	1.741	0.893
86	Cadherin-5	Coagulation Factor Xa	C9	SLPI	0.872	0.872	1.744	0.929
87	HSP 90α	Contactin-4	SLPI	LY9	0.872	0.872	1.744	0.902
88	Cadherin-5	ERBB1	C9	SLPI	0.846	0.887	1.733	0.926
89	Properdin	IL-12 Rβ2	MCP-3	SLPI	0.821	0.908	1.728	0.898
90	IL-13 Rα1	LY9	C9	SLPI	0.872	0.867	1.738	0.921
91	Cadherin-5	LY9	IL-18 Rβ	SLPI	0.846	0.882	1.728	0.918
92	RGM-C	Kallikrein 6	SLPI	C9	0.872	0.862	1.733	0.926
93	HSP 90α	LY9	Kallistatin	SLPI	0.833	0.903	1.736	0.911
94	MIP-5	RGM-C	SLPI	C9	0.872	0.856	1.728	0.930
95	MMP-7	SLPI	C9	LY9	0.897	0.877	1.774	0.935
96	Cadherin-5	NRP1	C9	SLPI	0.885	0.877	1.762	0.931
97	Coagulation Factor Xa	LY9	PCI	SLPI	0.833	0.892	1.726	0.909
98	Growth hormone receptor	RBP	C9	SLPI	0.859	0.867	1.726	0.907
99	Properdin	TIMP-2	C9	SLPI	0.872	0.872	1.744	0.927
100	Cadherin-5	Thrombin/ Prothrombin	Kallistatin	SLPI	0.821	0.892	1.713	0.908

Marker	Count	Marker	Count
SLPI	97	MRP1	4
C9	53	MRC2	4
LY9	51	MMP-7	4
Cadherin-5	26	MIP-5	4
RGM-C	11	Kallikrein 6	4
MCP-3	8	IL-18 Rβ	4
C2	8	IL-13 Rα1	4
Properdin	7	IL-12 Rβ2	4
Hat1	6	HGF	4
α1-Antitrypsin	5	ERBB1	4
SAP	5	Contactin-4	4
Kallistatin	5	C6	4
HSP 90α	5	C5	4
Growth hormone receptor	5	BAFF Receptor	4
Coagulation Factor Xa	5	ARSB	4
Thrombin/Prothrombin	4	ADAM 9	4
TIMP-2	4	sL-Selectin	3
SCF sR	4	Contactin-1	3
RBP	4	α2-HS-Glycoprotein	3
Prekallikrein	4	α2-Antiplasmin	3
PCI	4	Troponin T	3

[0358]

TABLE 4

100 Panels of 5 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
1	SCF sR	C9	SLPI	MCP-3	ADAM 9	0.897	0.882	1.779	0.916
2	IL-18 Rβ	C9	SLPI	Cadherin-5	ARSB	0.885	0.882	1.767	0.924

TABLE 4-continued

3	BAFF Receptor	SLPI	C9	LY9	MMP-7	0.885	0.877	1.762	0.924
4	C6	SLPI	LY9	RGM-C	C2	0.885	0.913	1.797	0.931
5	C5	SLPI	LY9	α1-Antitrypsin	RGM-C	0.885	0.892	1.777	0.919
6	SAP	Coagulation Factor Xa	SLPI	LY9	NRPI	0.897	0.892	1.790	0.932
7	Cadherin-5	SLPI	LY9	IL-13 Rα1	Contactin-4	0.910	0.887	1.797	0.919
8	Cadherin-5	C9	MCP-3	SLPI	ERBB1	0.859	0.908	1.767	0.928
9	Growth hormone receptor	SLPI	C9	LY9	Contactin-4	0.910	0.882	1.792	0.923
10	HGF	SLPI	C9	MMP-7	Cadherin-5	0.949	0.862	1.810	0.938
11	SLPI	NRP1	LY9	SAP	HSP 90α	0.923	0.887	1.810	0.923
12	Hat1	SLPI	C9	RGM-C	C2	0.910	0.877	1.787	0.925
13	SLPI	C9	Properdin	TIMP-2	IL-12 Rβ2	0.885	0.872	1.756	0.922
14	SLPI	NRP1	LY9	SAP	Kallikrein 6	0.910	0.887	1.797	0.918
15	LY9	α1-Antitrypsin	SLPI	Growth hormone receptor	Kallistatin	0.885	0.887	1.772	0.909
16	SLPI	NRP1	LY9	SAP	MIP-5	0.885	0.908	1.792	0.923
17	HGF	SLPI	C9	MMP-7	MRC2	0.923	0.862	1.785	0.932
18	RGM-C	SLPI	Cadherin-5	C9	PCI	0.897	0.877	1.774	0.926
19	LY9	C9	SLPI	Prekallikrein	MMP-7	0.923	0.862	1.785	0.933
20	RBP	C9	SLPI	LY9	RGM-C	0.897	0.877	1.774	0.923
21	RGM-C	SLPI	LY9	C9	Thrombin/ Prothrombin	0.910	0.862	1.772	0.930
22	Troponin T	C9	SLPI	LY9	NRP1	0.910	0.867	1.777	0.924
23	HGF	SLPI	C9	α2-Antiplasmin	HSP 90α	0.949	0.851	1.800	0.924
24	HSP 90α	C9	SLPI	LY9	α2-HS-Glycoprotein	0.885	0.882	1.767	0.920
25	SLPI	NRP1	Cadherin-5	LY9	Contactin-1	0.885	0.913	1.797	0.928
26	Cadherin-5	C9	SLPI	MMP-7	sL-Selectin	0.885	0.892	1.777	0.939
27	RGM-C	C9	MCP-3	SLPI	ADAM 9	0.897	0.872	1.769	0.923
28	ARSB	SLPI	C9	LY9	C2	0.885	0.882	1.767	0.923
29	SCF sR	C9	SLPI	MCP-3	BAFF Receptor	0.885	0.877	1.762	0.924
30	HGF	SLPI	C9	α2-Antitrypssin	C5	0.923	0.851	1.774	0.921
31	C6	SLPI	LY9	C9	Cadherin-5	0.897	0.882	1.779	0.928
32	LY9	SLPI	MMP-7	C2	Coagulation Factor Xa	0.885	0.897	1.782	0.942
33	ERBB1	SLPI	LY9	C9	IL-13 Rα1	0.897	0.867	1.764	0.919
34	Hat1	SLPI	LY9	C9	Contactin-4	0.885	0.897	1.782	0.922
35	Growth hormone receptor	SLPI	SAP	α1-Antitrypsin	IL-12 Rβ2	0.872	0.882	1.754	0.904
36	IL-18 Rβ	C9	SLPI	Cadherin-5	RGM-C	0.885	0.882	1.767	0.936
37	Cadherin-5	C9	SLPI	MMP-7	Kallikrein 6	0.897	0.887	1.785	0.940
38	Growth hormone receptor	SLPI	C9	LY9	Kallistatin	0.897	0.872	1.769	0.922
39	LY9	C9	SLPI	MIP-5	HSP 90α	0.897	0.877	1.774	0.923
40	MRC2	C9	SLPI	LY9	NRP1	0.897	0.887	1.785	0.926
41	LY9	C9	SLPI	PCI	Cadherin-5	0.885	0.887	1.772	0.923
42	SLPI	Contactin-4	LY9	MCP-3	Prekallikrein	0.872	0.903	1.774	0.916
43	SAP	SLPI	RGM-C	Properdin	Growth hormone receptor	0.897	0.882	1.779	0.926
44	RBP	C9	SLPI	LY9	MMP-7	0.897	0.872	1.769	0.927
45	LY9	SLPI	TIMP-2	C9	Kallikrein 6	0.910	0.872	1.782	0.919
46	Troponin T	C9	SLPI	LY9	RGM-C	0.897	0.872	1.769	0.931
47	Growth hormone receptor	SLPI	C9	LY9	Contactin-1	0.897	0.892	1.790	0.925
48	RGM-C	C9	MMP-7	SLPI	sL-Selectin	0.897	0.877	1.774	0.940
49	Growth hormone receptor	SLPI	SAP	α1-Antitrypsin	ADAM 9	0.872	0.892	1.764	0.899
50	C2	SLPI	LY9	C9	ARSB	0.885	0.882	1.767	0.923
51	SAP	SLPI	RGM-C	MCP-3	BAFF Receptor	0.885	0.877	1.762	0.924
52	SLPI	NRP1	LY9	C9	C5	0.897	0.877	1.774	0.924
53	IL-13 Rα1	C9	SLPI	Cadherin-5	C6	0.885	0.892	1.777	0.925
54	Coagulation Factor Xa	SLPI	C9	Cadherin-5	MMP-7	0.885	0.892	1.777	0.945
55	Cadherin-5	C9	SLPI	MMP-7	ERBB1	0.872	0.892	1.764	0.933
56	Hat1	SLPI	LY9	C2	SAP	0.872	0.908	1.779	0.922
57	SLPI	NRP1	LY9	C9	IL-12 Rβ2	0.872	0.882	1.754	0.919
58	IL-18 Rβ	C9	SLPI	RGM-C	Cadherin-5	0.885	0.882	1.767	0.936
59	Growth hormone receptor	SLPI	C9	Cadherin-5	Kallistatin	0.885	0.882	1.767	0.927
60	RGM-C	C9	MMP-7	MRC2	MIP-5	0.923	0.846	1.769	0.926
61	Cadherin-5	SLPI	LY9	C9	PCI	0.885	0.887	1.772	0.923
62	C2	SLPI	LY9	C9	Prekallikrein	0.897	0.877	1.774	0.931
63	SAP	SLPI	RGM-C	Properdin	MCP-3	0.859	0.918	1.777	0.932
64	LY9	SLPI	MMP-7	C9	RBP	0.897	0.872	1.769	0.927

TABLE 4-continued

65	SCF sR	C9	SLPI	MCP-3	Cadherin-5	0.885	0.897	1.782	0.930
66	LY9	SLPI	TIMP-2	C9	C2	0.897	0.877	1.774	0.928
67	RGM-C	SLPI	LY9	C9	Troponin T	0.897	0.872	1.769	0.931
68	α2-Antiplasmin	C9	SLPI	LY9	HGF	0.936	0.856	1.792	0.925
69	MCP-3	SLPI	C9	Contactin-1	Cadherin-5	0.872	0.908	1.779	0.930
70	sL-Selectin	C9	SLPI	LY9	HSP 90α	0.885	0.882	1.767	0.923
71	Cadherin-5	SLPI	LY9	C9	ADAM 9	0.872	0.892	1.764	0.917
72	LY9	α1-Antitrypsin	SLPI	Cadherin-5	ARSB	0.846	0.913	1.759	0.913
73	BAFF Receptor	SLPI	C9	LY9	MIP-5	0.897	0.862	1.759	0.915
74	RGM-C	C9	MCP-3	SLPI	C5	0.897	0.877	1.774	0.928
75	C6	SLPI	LY9	RGM-C	Cadherin-5	0.897	0.877	1.774	0.925
76	Coagulation	SLPI	C9	LY9	MMP-7	0.897	0.877	1.774	0.938
77	IL-13 Rα1	C9	SLPI	Cadherin-5	ERBB1	0.872	0.892	1.764	0.926
78	MCP-3	SLPI	C9	Contactin-1	Hat1	0.885	0.892	1.777	0.917
79	SAP	Coagulation	SLPI	LY9	IL-12 Rβ2	0.859	0.892	1.751	0.918
80	IL-18 Rβ	C9	SLPI	RGM-C	LY9	0.910	0.856	1.767	0.928
81	LY9	C9	SLPI	Kallikrein 6	Cadherin-5	0.897	0.877	1.774	0.928
82	Cadherin-5	SLPI	LY9	C9	Kallistatin	0.885	0.882	1.767	0.930
83	Growth hormone receptor	SLPI	C9	LY9	MRC2	0.885	0.897	1.782	0.925
84	LY9	C9	SLPI	PCI	Contactin-1	0.885	0.882	1.767	0.918
85	LY9	C9	SLPI	Prekallikrein	RGM-C	0.923	0.851	1.774	0.929
86	HSP 90α	C9	SLPI	LY9	Properdin	0.897	0.877	1.774	0.926
87	RBP	C9	SLPI	LY9	NRP1	0.885	0.877	1.762	0.916
88	SCF sR	C9	SLPI	LY9	C2	0.897	0.882	1.779	0.926
89	TIMP-2	SLPI	Cadherin-5	C9	MCP-3	0.885	0.887	1.772	0.927
90	SAP	SLPI	RGM-C	Properdin	Troponin T	0.859	0.908	1.767	0.933
91	α2-Antiplasmin	C9	SLPI	Cadherin-5	HGF	0.936	0.851	1.787	0.926
92	HSP 90α	C9	SLPI	LY9	sL-Selectin	0.885	0.882	1.767	0.923
93	SAP	SLPI	RGM-C	Properdin	ADAM 9	0.859	0.903	1.762	0.920
94	SCF sR	C9	SLPI	MCP-3	ARSB	0.872	0.887	1.759	0.918
95	LY9	C9	SLPI	MIP-5	BAFF Receptor	0.897	0.862	1.759	0.915
96	SCF sR	C9	SLPI	MCP-3	C5	0.897	0.867	1.764	0.922
97	SAP	SLPI	RGM-C	MCP-3	C6	0.872	0.903	1.774	0.926
98	SLPI	Comtactin-4	LY9	HSP 90α	NRP1	0.885	0.892	1.777	0.916
99	ERBB1	SLPI	LY9	C9	Cadherin-5	0.885	0.877	1.762	0.927
100	Hat1	SLPI	Cadherin-5	α1-Antitrypsin	MCP-3	0.872	0.903	1.774	0.902

Marker	Count	Marker	Count
SLPI	99	Coagulation Factor Xa	5
C9	75	C6	5
LY9	60	C5	5
Cadherin-5	29	BAFF Receptor	5
RGM-C	23	ARSB	5
MCP-3	16	ADAM 9	5
SAP	14	sL-Selectin	4
MMP-7	14	α2-Antiplasmin	4
NRP1	11	Troponin T	4
Growth hormon receptor	9	TIMP-2	4
C2	9	RBP	4
HSP 90α	8	Prekallikrein	4
α1-Antitrypsin	6	PCI	4
SCF sR	6	MRC2	4
Properdin	6	Kallistatin	4
HGF	6	Kallikrein 6	4
Contactin-1	5	IL-18 Rβ	4
MIP-5	5	IL-13 Rα1	4
Hat1	5	IL-12 Rβ2	4
ERBB1	5	α2-HS-Glycoprotein	1
Contactin-4	5	Thrombin/Prothrombin	1

[0359]

TABLE 5

100 Panels of 6 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
1	SCF sR	C9	SLPI	MCP-3		0.923	0.872	1.795	0.923
		ADAM 9	SAP						

TABLE 5-continued

2	SCF sR	C9 Cadherin-5	SLPI ARSB	MCP-3	0.897	0.892	1.790	0.923
3	LY9	C9 MMP-7	SLPI BAFF Receptor	Prekallikrein	0.923	0.867	1.790	0.922
4	LY9	SLPI Coagulation Factor Xa	MMP-7 Cadherin-5	C2	0.910	0.918	1.828	0.943
5	C5	SLPI RGM-C	LY9 Troponin T	α1-Antitrypsin	0.897	0.903	1.800	0.921
6	Cadherin-5	SLPI C9	LY9 C6	IL-13 Rα1	0.923	0.887	1.810	0.926
7	SLPI	Contactin-4 Prekallikrein	LY9 Cadherin-5	MCP-3	0.885	0.923	1.808	0.921
8	Cadherin-5	SLPI C9	LY9 ERBB1	IL-13 Rα1	0.910	0.897	1.808	0.924
9	Cadherin-5	C9 C2	SLPI Growth hormone receptor	MMP-7	0.923	0.887	1.810	0.941
10	HGF	SLPI MRC2	C9 α2-Antiplasmin	MMP-7	0.962	0.856	1.818	0.940
11	HGF	SLPI MRC2	C9 HSP 90α	MMP-7	0.949	0.856	1.805	0.934
12	HGF	SLPI MRC2	C9 Hat1	MMP-7	0.936	0.862	1.797	0.927
13	SLPI	Contactin-4 Prekallikrein	LY9 IL-12 Rβ2	MCP-3	0.859	0.923	1.782	0.910
14	MRC2	C9 NRP1	SLPI IL-18 Rβ	LY9	0.910	0.887	1.797	0.925
15	Growth hormone receptor	SLPI Contactin-4	C9 Kallikrein 6	LY9	0.923	0.882	1.805	0.916
16	RGM-C	C9 LY9	MMP-7 Kallistatin	SLPI	0.910	0.882	1.792	0.942
17	SLPI	NRP1 MIP-5	LY9 Cadherin-5	SAP	0.897	0.897	1.795	0.932
18	C6	SLPI Cadherin-5	LY9 PCI	C9	0.897	0.882	1.779	0.921
19	HGF	SLPI MRC2	C9 Properdin	MMP-7	0.923	0.877	1.800	0.936
20	RGM-C	C9 SAP	MMP-7 RBP	SLPI	0.936	0.862	1.797	0.940
21	HSP 90α	C9 IL-13 Rα1	SLPI TIMP-2	LY9	0.910	0.877	1.787	0.919
22	RGM-C	SLPI Thrombin/Prothrombin	LY9 NRP1	C9	0.897	0.877	1.774	0.932
23	RGM-C	C9 SAP	MMP-7 α2-HS-Glycoprotein	SLPI	0.923	0.856	1.779	0.941
24	RGM-C	SLPI NRP1	LY9 Contactin-1	SAP	0.910	0.903	1.813	0.932
25	Cadherin-5	C9 sL-Selectin	SLPI Growth hormone receptor	MMP-7	0.910	0.897	1.808	0.938
26	RGM-C	SLPI α1-Antitrypsin	LY9 ADAM 9	SAP	0.885	0.908	1.792	0.910
27	RGM-C	SLPI α1-Antitrypsin	LY9 ARSB	SAP	0.885	0.897	1.782	0.917
28	RGM-C	SLPI α1-Antitrypsin	LY9 BAFF Receptor	SAP	0.885	0.897	1.782	0.913
29	RGM-C	SLPI NRP1	LY9 C5	SAP	0.923	0.877	1.800	0.928
30	Coagulation Factor Xa	SLPI MMP-7	C9 RGM-C	Cadherin-5	0.923	0.892	1.815	0.949
31	Coagulation Factor Xa	SLPI MMP-7	C9 ERBB1	Cadherin-5	0.910	0.892	1.803	0.937
32	SLPI	NRP1 C2	Cadherin-5 Hat1	LY9	0.885	0.908	1.792	0.930
33	Growth hormon receptor	SLPI LY9	SAP IL-12 Rβ2	α1-Antitrypsin	0.885	0.897	1.782	0.910
34	HGF	SLPI MRC2	C9 IL-18 Rβ	MMP-7	0.949	0.846	1.795	0.931
35	RGM-C	C9 SAP	MMP-7 Kallikrein 6	SLPI	0.936	0.867	1.803	0.941
36	Growth hormone receptor	SLPI Contactin-1	C9 Kallistatin	LY9	0.885	0.903	1.787	0.923
37	RGM-C	SLPI NRP1	LY9 MIP-5	SAP	0.910	0.877	1.787	0.930
38	RGM-C	SLPI HSP 90α	LY9 PCI	C9	0.897	0.877	1.774	0.921

TABLE 5-continued

39	SAP	SLPI MCP-3	RGM-C Cadherin-5	Properdin	0.885	0.913	1.797	0.935
40	HGF	SLPI MRC2	C9 RBP	MMP-7	0.936	0.856	1.792	0.930
41	RGM-C	C9 SAP	MMP-7 TIMP-2	SLPI	0.923	0.862	1.785	0.942
42	RGM-C	C9 MRC2	MCP-3 Thrombin/Prothrombin	SLPI	0.885	0.887	1.772	0.928
43	HGF	SLPI MRC2	C9 Troponin T	MMP-7	0.949	0.846	1.795	0.936
44	α2-Antiplasmin	C9 HGF	SLPI MMP-7	Cadherin-5	0.949	0.862	1.810	0.943
45	HGF	SLPI MRC2	C9 α2-HS-Glycoprotein	MMP-7	0.923	0.856	1.779	0.934
46	Cadherin-5	C9 sL-Selectin	SLPI HGF	MMP-7	0.936	0.867	1.803	0.941
47	SAP	SLPI MCP-3	RGM-C ADAM 9	Properdin	0.885	0.903	1.787	0.926
48	Coagulation Factor Xa	SLPI MMP-7	C9 ARSB	LY9	0.897	0.882	1.779	0.932
49	LY9	SLPI Coagulation Factor Xa	MMP-7 BAFF Receptor	C2	0.872	0.908	1.779	0.926
50	SLPI	NRP1 C5	LY9 HSP 90α	C9	0.923	0.872	1.795	0.924
51	Growth hormone receptor	SLPI SAP	C2 C6	LY9	0.885	0.918	1.803	0.933
52	Cadherin-5	C9 SAP	SLPI ERBB1	MMP-7	0.910	0.887	1.797	0.939
53	Hat1	SLPI Contactin-4	LY9 NRP1	C9	0.897	0.892	1.790	0.925
54	SLPI	Contactin-4 NRP1	LY9 IL-12 Rβ2	HSP 90α	0.872	0.908	1.779	0.912
55	SCF sR	C9 Cadherin-5	SLPI IL-18 Rβ	MCP-3	0.885	0.897	1.782	0.928
56	SLPI	NRP1 Kallikrein 6	LY9 Cadherin-5	SAP	0.910	0.892	1.803	0.928
57	Growth hormone receptor	SLPI C2	C9 Kallistatin	LY9	0.885	0.892	1.777	0.927
58	SLPI	NRP1 MIP-5	LY9 RGM-C	SAP	0.910	0.877	1.787	0.930
59	C6	SLPI Cadherin-5	LY9 PCI	RGM-C	0.885	0.887	1.772	0.920
60	RBP	C9 RGM-C	SLPI NRP1	LY9	0.910	0.877	1.787	0.923
61	Growth hormone receptor	SLPI LY9	SAP TIMP-2	α1-Antitrypsin	0.885	0.897	1.782	0.915
62	HGF	SLPI MRC2	C9 Thrombin/Prothrombin	MMP-7	0.936	0.836	1.772	0.934
63	Growth hormone receptor	SLPI Cadherin-5	SAP Troponin T	α1-Antitrypsin	0.872	0.913	1.785	0.921
64	α2-Antiplasmin	C9 C2	SLPI Cadherin-5	LY9	0.919	0.897	1.808	0.938
65	Growth hormone receptor	SLPI MRC2	C9 α2-HS-Glycoprotein	LY9	0.885	0.892	1.777	0.920
66	Growth hormone receptor	SLPI C2	C9 Contactin-1	LY9	0.910	0.897	1.808	0.929
67	HGF	SLPI MRC2	C9 sL-Selectin	MMP-7	0.936	0.867	1.803	0.938
68	Growth hormone receptor	SLPI Cadherin-5	SAP ADAM 9	α1-Antitrypsin	0.872	0.913	1.785	0.904
69	SCF sR	C9 ADAM 9	SLPI ARSB	MCP-3	0.897	0.882	1.779	0.911
70	Cadherin-5	C9 MRC2	MCP-3 BAFF Receptor	SLPI	0.872	0.903	1.774	0.923
71	HGF	SLPI C5	C9 Cadherin-5	α2-Anti-plasmin	0.936	0.856	1.792	0.927
72	Cadherin-5	C9 C2	SLPI ERBB1	MMP-7	0.897	0.897	1.795	0.939
73	Cadherin-5	SLPI C2	LY9 Hat1	IL-13 Rα1	0.897	0.892	1.790	0.922
74	Cadherin-5	C9 SAP	SLPI IL-12 Rβ2	MMP-7	0.897	0.882	1.779	0.939
75	SLPI	NRP1 C2	LY9 IL-18 Rβ	SAP	0.885	0.897	1.782	0.932
76	Cadherin-5	C9 Kallikrein 6	SLPI HSP 90α	MMP-7	0.923	0.872	1.795	0.935

TABLE 5-continued

77	SLPI	NRP1 LY9	Cadherin-5 Kallistatin	C9	0.885	0.887	1.772	0.928
78	SLPI	NRP1 LY9	Cadherin-5 MIP-5	C9	0.897	0.887	1.785	0.931
79	Growth hormone receptor	SLPI Contactin-1	C9 PCI	LY9	0.885	0.887	1.772	0.918
80	LY9	C9 RGM-C	SLPI IL-13 Rα1	Prekallikrein	0.949	0.851	1.800	0.923
81	RGM-C	SLPI MMP-7	LY9 Properdin	SAP	0.910	0.882	1.792	0.939
82	Cadherin-5	C9 LY9	SLPI RBP	MMP-7	0.897	0.887	1.785	0.933
83	C5	SLPI RGM-C	LY9 TIMP-2	α1-Antitrypsin	0.897	0.882	1.779	0.915
84	RGM-C	SLPI Thrombin/Prothrombin	LY9 MCP-3	C9	0.897	0.872	1.769	0.926
85	SLPI	Contactin-4 Prekallikrein	LY9 Troponin T	MCP-3	0.885	0.897	1.782	0.911
86	HSP 90α	C9 LY9	SLPI α2-HS-Glycoprotein	Cadherin-5	0.885	0.887	1.772	0.922
87	RGM-C	C9 sL-Selectin	MMP-7 LY9	SLPI	0.910	0.887	1.797	0.941
88	Growth hormone receptor	SLPI Cadherin-5	SAP ARSB	α1-Antitrypsin	0.872	0.903	1.774	0.912
89	Growth hormone receptor	SLPI LY9	SAP BAFF Receptor	α1-Antitrypsin	0.885	0.887	1.772	0.907
90	Growth hormone receptor	SLPI Cadherin-5	SAP C6	LY9	0.897	0.903	1.800	0.929
91	RGM-C	SLPI NRP1	LY9 ERBB1	SAP	0.897	0.892	1.790	0.927
92	Hat1	SLPI SAP	LY9 Kallikrein 6	C2	0.885	0.897	1.782	0.913
93	SLPI	NRP1 C5	LY9 IL-12 Rβ2	C9	0.897	0.877	1.774	0.917
94	SLPI	NRP1 LY9	Cadherin-5 IL-18 Rβ	C9	0.897	0.877	1.774	0.930
95	Cadherin-5	SLPI C9	LY9 Kallistatin	IL-13 Rα1	0.897	0.872	1.769	0.926
96	Growth hormone receptor	SLPI MRC2	C9 MIP-5	LY9	0.897	0.887	1.785	0.927
97	RGM-C	SLPI PCI	Cadherin-5 LY9	C9	0.897	0.872	1.769	0.927
98	SAP	SLPI MCP-3	RGM-C Contactin-1	Properdin	0.859	0.928	1.787	0.932
99	RBP	C9 RGM-C	SLPI HGF	LY9	0.923	0.856	1.779	0.925
100	SCF sR	C9 Cadherin-5	SLPI IL-13 Rα1	MCP-3	0.897	0.903	1.800	0.926

Marker	Count	Marker	Count
SLPI	100	Properdin	5
C9	65	Prekallikrein	5
LY9	62	PCI	5
Cadherin-5	38	MIP-5	5
MMP-7	32	Kallistatin	5
SAP	31	Kallikrein 6	5
RGM-C	30	IL-18 Rβ	5
NRP1	19	IL-12 Rβ2	5
Growth hormone receptor	17	Hat1	5
MRC2	15	ERBB1	5
MCP-3	14	Coagulation Factor Xa	5
HGF	14	C6	5
C2	12	BAFF Receptor	5
α1-Antitrypsin	11	ARSB	5
IL-13 Rα1	7	ADAM 9	5
HSP 90α	7	sL-Selectin	4
Contactin-4	6	α2-HS-Glycoprotein	4
C5	6	α2-Antiplasmin	4
Contactin-1	5	Troponin T	4
SCF sR	5	Thrombin/Prothrombin	4
RBP	5	TIMP-2	4

[0360]

TABLE 6

100 Panels of 7 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers				Sensitivity	Specificity	Sensitivity + Specificity	AUC
1	SAP	SLPI	RGM-C	MCP-3	0.897	0.923	1.821	0.919
		α1-Antitrypsin	Cadherin-5	ADAM 9				
2	Cadherin-5	C9	SLPI	MMP-7	0.923	0.882	1.805	0.940
		LY9	RGM-C	ARSB				
3	HGF	SLPI	C9	MMP-7	0.936	0.887	1.823	0.928
		MRC2	Properdin	BAFF Receptor				
4	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.949	0.882	1.831	0.946
		HGF	C2	MMP-7				
5	LY9	C9	SLPI	Prekallikrein	0.936	0.872	1.808	0.932
		MMP-7	HSP 90α	C5				
6	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.936	0.887	1.823	0.945
		HGF	MMP-7	C6				
7	SLPI	NRP1	LY9	SAP	0.923	0.908	1.831	0.934
		MMP-7	Coagulation Factor Xa	MRC2				
8	HGF	SLPI	C9	α2-Antiplasmin	0.962	0.867	1.828	0.942
		SAP	MMP-7	Contactin-4				
9	HSP 90α	C9	SLPI	LY9	0.949	0.862	1.810	0.925
		HGF	C2	ERBB1				
10	HGF	SLPI	C9	α2-Antiplasmin	0.962	0.862	1.823	0.939
		SAP	MMP-7	Growth hormone receptor				
11	HGF	SLPI	C9	MMP-7	0.949	0.867	1.815	0.932
		MRC2	Hat1	LY9				
12	HGF	SLPI	C9	MMP-7	0.936	0.867	1.803	0.939
		MRC2	α2-Antiplasmin	IL-12 Rβ2				
13	SLPI	NRP1	Cadherin-5	C9	0.923	0.892	1.815	0.925
		LY9	Contactin-1	IL-13 Rα1				
14	HGF	SLPI	C9	MMP-7	0.949	0.856	1.805	0.937
		MRC2	Coagulation factor Xa	IL-18 Rβ				
15	Cadherin-5	C9	SLPI	MMP-7	0.936	0.882	1.818	0.940
		Kallikrein 6	HSP 90α	RGM-C				
16	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.936	0.872	1.808	0.946
		HGF	MMP-7	Kallistatin				
17	RGM-C	C9	MMP-7	SLPI	0.923	0.887	1.810	0.941
		sL-Selectin	LY9	MIP-5				
18	Cadherin-5	C9	SLPI	MMP-7	0.936	0.862	1.797	0.949
		SAP	RGM-C	PCI				
19	MRC2	C9	SLPI	LY9	0.923	0.897	1.821	0.925
		NRP1	MMP-7	RBP				
20	HGF	SLPI	C9	MMP-7	0.949	0.877	1.826	0.935
		MRC2	MCP-3	SCF sR				
21	HGF	SLPI	C9	MMP-7	0.949	0.867	1.815	0.942
		MRC2	α2-Antiplasmin	TIMP-2				
22	HGF	SLPI	C9	MMP-7	0.949	0.851	1.800	0.941
		MRC2	α2-Antiplasmin	Thrombin/Prothrombin				
23	HGF	SLPI	C9	MMP-7	0.949	0.872	1.821	0.941
		MRC2	Troponin T	α2-Antiplasmin				
24	Cadherin-5	C9	SLPI	MMP-7	0.910	0.887	1.797	0.946
		C2	RGM-C	α2-HS-Glycoprotein				
25	LY9	C9	SLPI	Prekallikrein	0.923	0.892	1.815	0.927
		MMP-7	SAP	ADAM 9				
26	Growth hormone receptor	SLPI	C9	LY9	0.910	0.887	1.797	0.911
		Contactin-4	Kallikrein 6	ARSB				
27	HGF	SLPI	C9	α2-Antiplasmin	0.962	0.856	1.818	0.931
		SAP	MMP-7	BAFF Receptor				
28	LY9	C9	SLPI	Prekallikrein	0.923	0.877	1.800	0.926
		RGM-C	MCP-3	C5				
29	SLPI	NRP1	Cadherin-5	C9	0.923	0.887	1.810	0.940
		LY9	MMP-7	C6				
30	Cadherin-5	C9	SLPI	MMP-7	0.910	0.897	1.808	0.939
		SAP	ERBB1	Growth hormone receptor				
31	HGF	SLPI	C9	MMP-7	0.949	0.862	1.810	0.933
		MRC2	Hat1	SAP				
32	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.936	0.862	1.797	0.941
		HGF	MMP-7	IL-12 Rβ2				
33	Cadherin-5	C9	SLPI	MMP-7	0.936	0.877	1.813	0.947
		C2	RGM-C	IL-13 Rα1				
34	HGF	SLPI	C9	MMP-7	0.949	0.856	1.805	0.941
		MRC2	IL-18 Rβ	RGM-C				

TABLE 6-continued

35	RGM-C	C9 SAP	MMP-7 LY9	SLPI Kallistatin	0.936	0.862	1.797	0.944
36	RGM-C	C9 SAP	MMP-7 MRC2	SLPI MIP-5	0.923	0.882	1.805	0.946
37	Coagulation Factor Xa	SLPI MMP-7	C9 RGM-C	Cadherin-5 PCI	0.910	0.887	1.797	0.945
38	HGF	SLPI MRC2	C9 Properdin	MMP-7 MCP-3	0.949	0.882	1.831	0.932
39	Cadherin-5	C9 LY9	SLPI RGM-C	MMP-7 RBP	0.923	0.892	1.815	0.940
40	HGF	SLPI Cadherin-5	C9 SCF sR	MMP-7 MCP-3	0.936	0.887	1.823	0.937
41	RGM-C	C9 SAP	MMP-7 MRC2	SLPI TIMP-2	0.936	0.867	1.803	0.942
42	SLPI	NRP1 RGM-C	LY9 MRC2	C9 Thrombin/Prothrombin	0.910	0.887	1.797	0.933
43	HGF	SLPI MRC2	C9 Troponin T	MMP-7 RGM-C	0.962	0.856	1.818	0.944
44	Growth hormone receptor	SLPI Cadherin-5	SAP LY9	α1-Antitrypsin HGF	0.936	0.872	1.808	0.921
45	Cadherin-5	C9 SAP	SLPI RGM-C	MMP-7 α2-HS-Glycoprotein	0.923	0.872	1.795	0.949
46	Cadherin-5	C9 SAP	SLPI HGF	MMP-7 Contactin-1	0.962	0.862	1.823	0.945
47	HGF	SLPI MRC2	C9 sL-Selectin	MMP-7 α2-Antiplasmin	0.962	0.867	1.828	0.942
48	Cadherin-5	C9 LY9	SLPI Prekallikrein	MMP-7 ADAM 9	0.910	0.897	1.808	0.927
49	Growth hormone receptor	SLPI Cadherin-5	SAP LY9	α1-Antitrypsin ARSB	0.885	0.908	1.792	0.916
50	α2-Antiplasmin	C9 HGF	SLPI MMP-7	Cadherin-5 BAFF Receptor	0.949	0.867	1.815	0.932
51	C5	SLPI RGM-C	LY9 Troponin T	α1-Antitrypsin Growth hormone receptor	0.910	0.887	1.797	0.916
52	LY9	SLPI Coagulation Factor Xa	MMP-7 Cadherin-5	C2 C6	0.897	0.913	1.810	0.942
53	RGM-C	C9 SAP	MMP-7 HGF	SLPI Contactin-4	0.962	0.856	1.818	0.946
54	Cadherin-5	C9 C2	SLPI ERBB1	MMP-7 HSP 90α	0.923	0.882	1.805	0.938
55	HGF	SLPI MRC2	C9 Hat1	MMP-7 α2-Antiplasmin	0.923	0.882	1.805	0.934
56	LY9	SLPI Coagulation Factor Xa	MMP-7 Cadherin-5	C2 IL-12 Rβ2	0.885	0.913	1.797	0.938
57	HGF	SLPI MRC2	C9 HSP 90α	MMP-7 IL-13 Rα1	0.962	0.851	1.813	0.936
58	HGF	SLPI MRC2	C9 IL-18 Rβ	MMP-7 LY9	0.936	0.867	1.803	0.932
59	HGF	SLPI MRC2	C9 Coagulation Factor Xa	MMP-7 Kallikrein 6	0.949	0.867	1.815	0.937
60	Cadherin-5	C9 Kallikrein 6	SLPI HSP 90α	MMP-7 Kallistatin	0.910	0.887	1.797	0.936
61	RGM-C	C9 LY9	MMP-7 HGF	SLPI MIP-5	0.962	0.841	1.803	0.939
62	RGM-C	C9 SAP	MMP-7 LY9	SLPI PCI	0.923	0.862	1.785	0.940
63	HGF	SLPI MRC2	C9 Properdin	MMP-7 RGM-C	0.949	0.877	1.826	0.945
64	C2	SLPI RGM-C	LY9 MMP-7	C9 RBP	0.923	0.892	1.815	0.943
65	RGM-C	C9 LY9	MMP-7 HGF	SLPI SCF sR	0.949	0.867	1.815	0.945
66	Growth hormone receptor	SLPI Cadherin-5	SAP C6	LY9 TIMP-2	0.897	0.897	1.795	0.927
67	Contactin-1	SLPI MMP-7	LY9 SAP	Growth hormone receptor Thrombin/Prothrombin	0.910	0.887	1.797	0.931
68	Cadherin-5	C9 LY9	SLPI RGM-C	MMP-7 α2-HS-Glycoprotein	0.923	0.872	1.795	0.944
69	Cadherin-5	C9 sL-Selectin	SLPI HGF	MMP-7 MRC2	0.936	0.887	1.823	0.943
70	RGM-C	C9 MRC2	MCP-3 α2-Antiplasmin	SLPI ADAM 9	0.897	0.908	1.805	0.928

TABLE 6-continued

71	Cadherin-5	C9 LY9	SLPI Prekallikrein	MMP-7 ARSB	0.897	0.892	1.790	0.932
72	HGF	SLPI MRC2	C9 MCP-3	MMP-7 BAFF Receptor	0.936	0.877	1.813	0.930
73	C5	SLPI RGM-C	LY9 Troponin T	α1-Antitrypsin C2	0.897	0.897	1.795	0.919
74	LY9	SLPI Coagulation Factor Xa	MMP-7 Cadherin-5	C2 Contactin-4	0.897	0.918	1.815	0.937
75	HGF	SLPI MRC2	C9 Properdin	MMP-7 ERBB1	0.923	0.882	1.805	0.935
76	HGF	SLPI MRC2	C9 α2-Antiplasmin	MMP-7 Hat1	0.923	0.882	1.805	0.934
77	Growth hormone receptor	SLPI Cadherin-5	SAP LY9	α1-Antitrypsin IL-12 Rβ2	0.897	0.897	1.795	0.913
78	HGF	SLPI MRC2	C9 LY9	MMP-7 IL-13 Rα1	0.949	0.862	1.810	0.932
79	HGF	SLPI MRC2	C9 LY9	MMP-7 IL-18 Rβ	0.936	0.867	1.803	0.932
80	SLPI	NRP1 LY9	Cadherin-5 MMP-7	C9 Kallistatin	0.910	0.887	1.797	0.940
81	Cadherin-5	C9 LY9	SLPI Prekallikrein	MMP-7 MIP-5	0.923	0.877	1.800	0.939
82	α2-Antiplasmin	C9 HGF	SLPI MMP-7	Cadherin-5 PCI	0.923	0.862	1.785	0.941
83	Cadherin-5	C9 sL-Selectin	SLPI Growth hormone receptor	MMP-7 RBP	0.923	0.892	1.815	0.931
84	SCF sR	C9 Cadherin-5	SLPI HGF	MCP-3 SAP	0.936	0.877	1.813	0.933
85	C2	SLPI RGM-C	LY9 MMP-7	C9 TIMP-2	0.923	0.872	1.795	0.943
86	α2-Antiplasmin	C9 HGF	SLPI MMP-7	Cadherin-5 Thrombin/Prothrombin	0.936	0.856	1.792	0.943
87	HGF	SLPI Cadherin-5	C9 SCF sR	MMP-7 α2-HS-Glycoprotein	0.923	0.867	1.790	0.942
88	RGM-C	C9 SAP	MMP-7 HGF	SLPI Contactin-1	0.962	0.856	1.818	0.948
89	C2	SLPI RGM-C	LY9 MMP-7	C9 ADAM 9	0.923	0.877	1.800	0.934
90	Cadherin-5	C9 SAP	SLPI NRP1	MMP-7 ARSB	0.897	0.892	1.790	0.940
91	RGM-C	C9 SAP	MMP-7 HGF	SLPI BAFF Receptor	0.949	0.862	1.810	0.936
92	C5	SLPI RGM-C	LY9 Troponin T	α1-Antitrypsin MCP-3	0.897	0.897	1.795	0.913
93	Growth hormone receptor	SLPI SAP	C2 C6	LY9 IL-13 Rα1	0.910	0.897	1.808	0.931
94	RGM-C	C9 LY9	MMP-7 HGF	SLPI Contactin-4	0.949	0.862	1.810	0.942
95	Cadherin-5	C9 SAP	SLPI ERBB1	MMP-7 HGF	0.949	0.856	1.805	0.943
96	HGF	SLPI MRC2	C9 Hat1	MMP-7 SCF sR	0.910	0.892	1.803	0.930
97	RGM-C	SLPI NRP1	LY9 Coagulation Factor Xa	SAP IL-12 Rβ2	0.897	0.897	1.795	0.926
98	HGF	SLPI MRC2	C9 IL-18 Rβ	MMP-7 Cadherin-5	0.936	0.862	1.797	0.939
99	Cadherin-5	C9 Kallikrein 6	SLPI HSP 90α	MMP-7 LY9	0.936	0.877	1.813	0.934
100	Cadherin-5	C9 SLPI LY9	MMP-7 Prekallikrein	0.910	0.882	1.792	0.937	Kallistatin

Marker	Count	Marker	Count
SLPI	100	Kallikrein 6	5
C9	85	IL-18 Rβ	5
MMP-7	83	IL-13 Rα1	5
HGF	49	IL-12 Rβ2	5
LY9	45	Hat1	5
Cadherin-5	44	ERBB1	5
RGM-C	34	Contactin-4	5
MRC2	32	C6	5
SAP	28	C5	5
α2-Antiplasmin	18	BAFF Receptor	5
C2	13	ARSB	5
Growth hormone receptor	11	ADAM 9	5

TABLE 6-continued

MCP-3	9	sL-Selectin	4
NRP1	8	Contactin-1	4
Coagulation Factor Xa	8	α2-HS-Glycoprotein	4
α1-Antitrypsin	7	Thrombin/Prothrombin	4
Prekallikrein	7	TIMP-2	4
HSP 90α	7	RBP	4
SCF sR	6	Preperdin	4
Troponin T	5	PCI	4
Kallistatin	5	MIP-5	4

[0361]

TABLE 7

100 Panels of Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers				Sensitivity	Specificity	Specificity + Specificity	AUC
1	HGF	SLPI	C9	MMP-7	0.962	0.872	1.833	0.935
	MRC2	Properdin	RGM-C	ADAM 9				
2	Cadherin-5	C9	SLPI	MMP-7	0.923	0.892	1.815	0.945
	C2	RGM-C	α2-Antiplasmin	ARSB				
3	HGF	SLPI	C9	MMP-7	0.962	0.897	1.859	0.938
	MRC2	MCP-3	BAFF Receptor	α2-Antiplasmin				
4	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.962	0.862	1.823	0.943
	HGF	MMP-7	Coagulation Factor Xa	C5				
5	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.962	0.872	1.833	0.944
	HGF	MMP-7	Coagulation Factor Xa	C6				
6	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.962	0.897	1.859	0.951
	RGM-C	MMP-7	HGF	Contactin-4				
7	Cadherin-5	C9	SLPI	MMP-7	0.949	0.882	1.831	0.942
	SAP	HGF	Kallikrein 6	ERBB1				
8	Cadherin-5	C9	SLPI	MMP-7	0.962	0.877	1.838	0.946
	SAP	HGF	Contactin-1	Growth hormone receptor				
9	HGF	SLPI	C9	MMP-7	0.962	0.887	1.849	0.939
	MRC2	HSP 90α	MCP-3	α2-Antiplasmin				
10	HGF	SLPI	C9	MMP-7	0.949	0.882	1.831	0.940
	MRC2	α2-Antiplasmin	RGM-C	Hat1				
11	HGF	SLPI	C9	MMP-7	0.936	0.887	1.823	0.942
	MRC2	Properdin	Cadherin-5	IL-12 Rβ2				
12	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.962	0.867	1.828	0.946
	RGM-C	MMP-7	HGF	IL-13 Rα1				
13	HGF	SLPI	C9	MMP-7	0.949	0.872	1.821	0.942
	MRC2	Properdin	Cadherin-5	IL-18 Rβ				
14	RGM-C	C9	MMP-7	SLPI	0.974	0.856	1.831	0.949
	SAP	HGF	HSP 90α	Kallistatin				
15	SLPI	NRP1	LY9	C9	0.949	0.892	1.841	0.941
	RGM-C	MRC2	MMP-7	HGF				
16	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.949	0.882	1.831	0.946
	HGF	MMP-7	MRC2	MIP-5				
17	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.962	0.862	1.823	0.949
	RGM-C	MMP-7	HGF	PCI				
18	RGM-C	C9	MMP-7	SLPI	0.962	0.862	1.823	0.950
	SAP	HGF	MRC2	Prekellikrein				
19	HGF	SLPI	C9	MMP-7	0.949	0.882	1.831	0.942
	MRC2	Properdin	RGM-C	RBP				
20	HGF	SLPI	C9	MMP-7	0.962	0.892	1.854	0.943
	Cadherin-5	SCF sR	MCP-3	RGM-C				
21	HGF	SLPI	C9	MMP-7	0.962	0.872	1.8333	0.945
	MRC2	α2-Antiplasmin	TIMP-2	SAP				
22	HGF	SLPI	C9	MMP-7	0.974	0.862	1.836	0.948
	MRC2	HSP 90α	RGM-C	Thrombin/Prothrombin				
23	HGF	SLPI	C9	MMP-7	0.962	0.872	1.833	0.948
	MRC2	Troponin T	RGM-C	α2-Antiplasmin				
24	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.936	0.877	1.813	0.939
	RGM-C	MMP-7	HGF	α1-Antitrypsin				
25	HGF	SLPI	C9	MMP-7	0.962	0.867	1.828	0.945
	MRC2	HSP 90α	RGM-C	α2-HS-Glycoprotein				
26	HGF	SLPI	C9	α2-Antiplasmin	0.974	0.877	1.851	0.949
	SAP	MMP-7	sL-Selectin	Cadherin-5				

TABLE 7-continued

27	RGM-C	C9	MMP-7	SLPI	0.949	0.877	1.826	0.937
	SAP	HGF	Contactin-4	ADAM 9				
28	HGF	SLPI	C9	MMP-7	0.936	0.877	1.813	0.939
	MRC2	sL-Selectin	α2-Antiplasmmin	ARSB				
29	HGF	SLPI	C9	MMP-7	0.962	0.872	1.833	0.939
	MRC2	α2-Antiplasmin	RGM-C	BAFF Receptor				
30	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.962	0.882	1.844	0.946
	HGF	MMP-7	Coagulation Factor Xa	C2				
31	HGF	SLPI	C9	MMP-7	0.949	0.872	1.821	0.945
	MRC2	Properdin	RGM-C	C5				
32	HGF	SLPI	C9	MMP-7	0.962	0.872	1.833	0.945
	MRC2	HSP 90α	RGM-C	C6				
33	Cadherin-5	C9	SLPI	MMP-7	0.949	0.877	1.826	0.944
	SAP	HGF	Properdin	ERBB1				
34	HGF	SLPI	C9	α2-Antiplasmin	0.974	0.862	1.836	0.942
	SAP	MMP-7	Contactin-1	Growth hormone receptor				
35	RGM-C	C9	MCP-3	SLPI	0.936	0.892	1.828	0.927
	MRC2	α2-Antiplasmin	HGF	Hat1				
36	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.936	0.887	1.823	0.945
	HGF	MMP-7	MRC2	IL-12 Rβ2				
37	HGF	SLPI	C9	MMP-7	0.962	0.867	1.828	0.944
	MRC2	Coagulation Factor Xa	RGM-C	IL-12 Rα1				
38	HGF	SLPI	C9	MMP-7	0.936	0.877	1.813	0.947
	MRC2	α2-Antiplasmin	RGM-C	IL-18 Rβ				
39	RGM-C	C9	MMP-7	SLPI	0.974	0.867	1.841	0.946
	SAP	HGF	MRC2	Kallikrein 6				
40	HGF	SLPI	C9	MMP-7	0.962	0.867	1.828	0.946
	MRC2	KSP 90α	RGM-C	Kallistatin				
41	Cadherin-5	C9	SLPI	MMP-7	0.936	0.903	1.838	0.942
	LY9	RGM-C	MRC2	NRP1				
42	HGF	SLPI	C9	MMP-7	0.962	0.862	1.823	0.942
	MRC2	HSP 90α	RGM-C	MIP-5				
43	Cadherin-5	C9	SLPI	MMP-7	0.910	0.897	1.808	0.947
	SAP	RGM-C	Prekallikrein	PCI				
44	Cadherin-5	C9	SLPI	MMP-7	0.936	0.892	1.828	0.941
	sL-Selectin	HGF	MRC2	RBP				
45	HGF	SLPI	C9	MMP-7	0.949	0.897	1.846	0.939
	MRC2	MCP-3	Cadherin-5	SCF sR				
46	RGM-C	C9	MCP-3	SLPI	0.949	0.877	1.826	0.938
	MRC2	HGF	MMP-7	TIMP-2				
47	RGM-C	C9	MMP-7	SLPI	0.962	0.862	1.823	0.945
	LY9	HGF	MRC2	Thrombin/Prothrombin				
48	HGF	SLPI	C9	MMP-7	0.962	0.862	1.823	0.947
	MRC2	Troponin T	RGM-C	sL-Selectin				
49	HGF	SLPI	C9	MMP-7	0.923	0.887	1.810	0.925
	MRC2	MCP-3	BAFF Receptor	α1-Antitrypsin				
50	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.949	0.877	1.826	0.944
	HGF	MMP-7	Contactin-1	α2-HS-Glycoprotein				
51	RGM-C	C9	MMP-7	SLPI	0.962	0.862	1.823	0.935
	SAP	Coagulation Factor Xa	HGF	ADAM 9				
52	HGF	SLPI	C9	MMP-7	0.936	0.872	1.808	0.945
	MRC2	α2-Antiplasmin	RGM-C	ARSB				
53	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.962	0.882	1.844	0.948
	HGF	C2	MMP-7	HSP 90α				
54	RGM-C	C9	MMP-7	SLPI	0.962	0.851	1.813	0.943
	SAP	HGF	Contactin-4	C5				
55	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.949	0.877	1.826	0.945
	HGF	MMP-7	Contactin-1	C6				
56	LY9	SLPI	MMP-7	C2	0.949	0.867	1.8115	0.933
	Coagulation Factor Xa	Cadherin-5	HGF	ERBB1				
57	RGM-C	C9	MMP-7	SLPI	0.974	0.862	1.836	0.944
	SAP	HGF	Contactin-4	Growth hormone receptor				
58	HGF	SLPI	C9	MMP-7	0.949	0.877	1.826	0.934
	MRC2	Hat1	LY9	C2				
59	Cadherin-5	C9	SLPI	MMP-7	0.936	0.877	1.813	0.944
	SAP	HGF	Properdin	IL-12 Rβ2				
60	Cadherin-5	C9	SLPI	MMP-7	0.936	0.887	1.823	0.949
	C2	RGM-C	IL-13 Rα1	Coagulation Factor Xa				
61	Cadherin-5	C9	SLPI	MMP-7	0.949	0.862	1.810	0.944
	SAP	HGF	Contactin-1	IL-18 Rβ				
62	HGF	SLPI	C9	MMP-7	0.974	0.862	1.836	0.942
	MRC2	HSP 90α	RGM-C	Kallikrein 6				
63	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.949	0.877	1.826	0.953
	RGM-C	MMP-7	HGF	Kallistatin				

TABLE 7-continued

64	HGF	SLPI	C9	MMP-7	0.923	0.892	1.815	0.942
	MRC2	Properdin	Cadherin-5	MIP-5				
65	RGM-C	C9	MMP-7	SLPI	0.974	0.872	1.846	0.947
	SAP	HGF	Contactin-4	NRP1				
66	Coagulation Factor Xa	SLPI	C9	Cadherin-5	0.910	0.897	1.808	0.946
	MMP-7	RGM-C	sL-Selectin	PCI				
67	Cadherin-5	C9	SLPI	MMP-7	0.936	0.887	1.823	0.938
	SAP	RGM-C	Prekallikrein	ADAM 9				
68	RGM-C	C9	MMP-7	SLPI	0.949	0.877	1.826	0.944
	SAP	HGF	MRC2	RBP				
69	HGF	SLPI	C9	MMP-7	0.949	0.892	1.841	0.938
	Cadherin-5	SCF sR	MCP-3	Coagulaation Factor Xa				
70	HGF	SLPI	C9	MMP-7	0.949	0.877	1.826	0.941
	MRC2	α2-Antiplasmin	TIMP-2	NRP1				
71	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.962	0.862	1.823	0.950
	RGM-C	MMP-7	HGF	Thrombin/Prothrombin				
72	HGF	SLPI	C9	MMP-7	0.949	0.872	1.821	0.947
	MRC2	Troponin T	RGM-C	Properdin				
73	RGM-C	C9	MMP-7	SLPI	0.949	0.862	1.810	0.940
	SAP	HGF	HSP 90α	α1-Antitrypsin				
74	SLPI	NRP1	LY9	C9	0.923	0.897	1.821	0.938
	RGM-C	MRC2	MMP-7	α2-HS-Glycoprotein				
75	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.936	0.872	1.808	0.945
	RGM-C	MMP-7	HGF	ARSB				
76	HGF	SLPI	C9	MMP-7	0.949	0.882	1.831	0.935
	MRC2	MCP-3	BAFF Receptor	sL-Selectin				
77	RGM-C	C9	MMP-7	SLPI	0.962	0.851	1.813	0.939
	LY9	HGF	MRC2	C5				
78	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.949	0.877	1.826	0.945
	HGF	MMP-7	C6	Contactin-1				
79	Cadherin-5	C9	SLPI	MMP-7	0.949	0.867	1.815	0.935
	Kallikrein 6	HSP 90α	RGM-C	ERBB1				
80	HGF	SLPI	C9	α2-Antiplasmin	0.962	0.872	1.833	0.946
	SAP	MMP-7	Growth hormone receptor	Cadherin-5				
81	Cadherin-5	C9	SLPI	MMP-7	0.923	0.897	1.821	0.940
	SAP	HGF	Contactin-1	Hat1				
82	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.936	0.877	1.813	0.947
	RGM-C	MMP-7	HGF	IL-12 Rβ2				
83	SLPI	NRP1	Cadherin-5	C9	0.923	0.897	1.821	0.929
	LY9	Contactin-1	IL-13 Rα1	SAP				
84	HGF	SLPI	C9	MMP-7	0.936	0.867	1.803	0.942
	MRC2	Coagulation Factor Xa	Cadherin-5	IL-18 Rβ				
85	α2-Antiplasmmin	C9	SLPI	Cadherin-5	0.949	0.872	1.821	0.948
	HGF	MMP-7	MRC2	Kallistatin				
86	HGF	SLPI	C9	MMP-7	0.949	0.867	1.815	0.942
	MRC2	Coagulation Factor Xa	Cadherin-5	MIP-5				
87	HGF	SLPI	C9	MMP-7	0.949	0.856	1.805	0.939
	MRC2	α2-Antiplasmin	TIMP-2	PCI				
88	LY9	C9	SLPI	Prekallikrein	0.936	0.887	1.823	0.933
	MMP-7	SAP	ADAM 9	C2				
89	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.936	0.887	1.823	0.943
	HGF	MMP-7	MRC2	RBP				
90	RGM-C	C9	MCP-3	SLPI	0.949	0.887	1.836	0.942
	MRC2	HGF	MMP-7	SCF sR				
91	SLPI	NRP1	LY9	SAP	0.949	0.872	1.821	0.935
	MMP-7	MRC2	HGF	Thrombin/Prothrombin				
92	HGF	SLPI	C9	MMP-7	0.949	0.872	1.821	0.947
	MRC2	Properdin	RGM-C	Troponin T				
93	SCF sR	C9	SLPI	MCP-3	0.910	0.897	1.808	0.920
	Cadherin-5	HGF	SAP	α1-Antitrypsin				
94	HGF	SLPI	C9	MMP-7	0.949	0.872	1.821	0.930
	MRC2	HSP 90α	MCP-3	α2-HS-Glycoprotein				
95	Cadherin-5	C9	SLPI	MMP-7	0.923	0.882	1.805	0.940
	C2	RGM-C	IL-13 Rα1	ARSB				
96	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.949	0.882	1.831	0.937
	HGF	MMP-7	BAFF Receptor	SAP				
97	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.949	0.862	1.810	0.950
	RGM-C	MMP-7	HGF	C5				
98	α2-Antiplasmin	C9	SLPI	Cadherin-5	0.949	0.877	1.826	0.945
	HGF	MMP-7	C6	Contactin-4				
99	MRC2	C9	SLPI	LY9	0.949	0.867	1.815	0.931
	NRP1	MMP-7	HGF	ERBB1				
100	RGM-C	C9	MMP-7	SLPI	0.962	0.872	1.833	0.943
	SAP	HGF	MRC2	Growth hormone receptor				

TABLE 7-continued

Marker	Count	Marker	Count
SLPI	100	Growth hormone receptor	5
C9	98	ERBB1	5
MMP-7	97	C6	5
HGF	89	C5	5
RGM-C	54	BAFF Receptor	5
MRC2	53	ARSB	5
Cadherin-5	50	ADAM 9	5
α2-Antiplasmin	38	α2-HS-Glycoprotein	4
SAP	28	α1-Antitrypsin	4
MCP-3	12	Troponin T	4
HSP 90α	12	Thrombin/Prothrombin	4
LY9	11	TIMP-2	4
Coagulation Factor Xa	11	RBP	4
Properdin	10	Prekallikrein	4
Contactin-1	8	PCI	4
NRP1	8	MIP-5	4
C2	8	Kallistatin	4
sL-Selectin	6	Kallikrein 6	4
Contactin-4	6	IL-18 Rβ	4
SCF sR	5	IL-12 Rβ2	4
IL-13 Rα1	5	Hat1	4

[0362]

TABLE 8

100 Panels of 9 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
1	RGM-C	C9 HGF	MCP-3 MMP-7	SLPI sL-Selectin	MRC2 ADAM 9	0.962	0.897	1.859	0.939
2	RGM-C	C9 HGF	MMP-7 MRC2	SLPI NRP1	SAP ARSB	0.962	0.877	1.838	0.945
3	HGF	SLPI α2-Antiplas-min	C9 RGM-C	MMP-7 BAFF Receptor	MRC2 MCP-3	0.962	0.897	1.859	0.942
4	α2-Antiplas-min	C9 C2	SLPI MMP-7	Cadherin-5 Contactin-4	HGF RGM-C	0.962	0.903	1.864	0.952
5	α2-Antiplas-min	SLPI MMP-7	Cadherin-5 HGF	RGM-C Contactin-4	0.962 C5	0.887	1.849	0.951	
6	α2-Antiplas-min	C9 MMP-7	SLPI HGF	Cadherin-5 SAP	RGM-C C6	0.962	0.892	1.854	0.954
7	RGM-C	C9 HGF	MMP-7 Contactin-4	SLPI MCP-3	SAP Coagulation Factor Xa	0.974	0.882	1.856	0.942
8	RGM-C	C9 HGF	MMP-7 HSP 90α	SLPI α2-Antiplasmin	SAP ERBB1	0.974	0.877	1.851	0.947
9	RGM-C	C9 HGF	MMP-7 Contactin-4	SLPI Growth hormone receptor	SAP Contactin-1	0.974	0.872	1.846	0.947
10	HGF	SLPI α2-Antiplas-min	C9 RGM-C	MMP-7 Hat1	MRC2 SAP	0.949	0.892	1.841	0.944
11	α2-Antiplas-min MMP-7	C9 HGF	SLPI SAP	Cadherin-5 IL-12 Rβ2	RGM-C	0.962	0.877	1.838	0.952
12	α2-Antiplas-min	C9 C2	SLPI MMP-7	Cadherin-5 HSP 90α	HGF IL-13 Rα1	0.962	0.877	1.838	0.945
13	HGF	SLPI Properdin	C9 RGM-C	MMP-7 RBP	MRC2 IL-18 Rβ	0.962	0.872	1.833	0.942
14	Cadherin-5	C9 HGF	SLPI Kallikrein 6	MMP-7 RGM-C	SAP MRC2	0.962	0.882	1.844	0.949
15	α2-Antiplas-min	C9 MMP-7	SLPI HGF	Cadherin-5 Contactin-4	RGM-C Kallistatin	0.962	0.882	1.844	0.952
16	RGM-C	C9 HGF	MMP-7 MRC2	SLPI C2	LY9 NRP1	0.949	0.897	1.846	0.944
17	α2-Antiplas-min	C9 MMP-7	SLPI HGF	Cadherin-5 SAP	RGM-C MIP-5	0.974	0.882	1.856	0.953

TABLE 8-continued

18	α2-Antiplas-min	C9 MMP-7	SLPI HGF	Cadherin-5 Contactin-4	RGM-C PCI	0.962	0.882	1.844	0.949
19	RGM-C	C9 HGF	MCP-3 MMP-7	SLPI SAP	MRC2 Prekallikrein	0.962	0.887	1.849	0.946
20	RGM-C	C9 HGF	MCP-3 MMP-7	SLPI Cadherin-5	MRC2 SCF sR	0.949	0.908	1.856	0.944
21	RGM-C	C9 HGF	MCP-3 MMP-7	SLPI SAP	MRC2 TIMP-2	0.962	0.877	1.838	0.942
22	HGF	SLPI α2-Antiplas-min	C9 RGM-C	MMP-7 sL-Selectin	MRC2 Thrombin/Prothrombin	0.962	0.882	1.844	0.950
23	RGM-C	C9 HGF	MMP-7 MRC2	SLPI MRP1	SAP Troponin T	0.962	0.877	1.838	0.947
24	HGF	SLPI SCF sR	C9 MCP-3	MMP-7 Coagulation Factor Xa	Cadherin-5 α1-Antitrypsin	0.936	0.887	1.823	0.929
25	HGF	SLPI MCP-3	C9 Cadherin-5	MMP-7 SCF sR	MRC2 α2-HS-Glycoprotein	0.936	0.913	1.849	0.939
26	HGF	SLPI Properdin	C9 RGM-C	MMP-7 ADAM 9	MRC2 SAP	0.962	0.892	1.854	0.939
27	RGM-C	C9 HGF	MMP-7 Contactin-4	SLPI α2-Antiplasmin	SAP ARSB	0.962	0.877	1.838	0.945
28	HGF	SLPI MMP-7	C9 BAFF Receptor	α2-Antiplasmin RGM-C	SAP Contactin-4	0.974	0.882	1.856	0.940
29	α2-Antiplas-min	C9 MMP-7	SLPI HGF	Cadherin-5 SAP	RGM-C C5	0.962	0.882	1.844	0.952
30	α2-Antiplas-min	C9 MMP-7	SLPI HGF	Cadherin-5 Contactin-4	RGM-C C6	0.962	0.887	1.849	0.952
31	Cadherin-5	C9 HGF	SLPI Coagulation Factor Xa	MMP-7 MCP-3	SAP ERBB1	0.949	0.887	1.836	0.938
32	HGF	SLPI α2-Antiplas-min	C9 Growth hormone receptor	MMP-7 Cadherin-5	MRC2 C6	0.949	0.892	1.841	0.946
33	HGF	SLPI α2-Antiplas-min	C9 RGM-C	MMP-7 Hat1	MRC2 NRP1	0.949	0.887	1.836	0.939
34	α2-Antiplas-min	C9 MMP-7	SLPI Coagulation Factor Xa	Cadherin-5 SAP	HGF IL-12 Rβ2	0.962	0.872	1.833	0.946
35	HGF	SLPI MCP-3	C9 Cadherin-5	MMP-7 SCF sR	MRC2 IL-13 Rα1	0.936	0.903	1.838	0.938
36	HGF	SLPI Properdin	C9 RGM-C	MMP-7 HSP 90α	MRC2 IL-18 Rβ	0.962	0.867	1.828	0.945
37	RGM-C	C9 HGF	MMP-7 MRC2	SLPI Kallikrein 6	SAP sL-Selectin	0.974	0.867	1.841	0.948
38	HGF	SLPI α2-Antiplas-min	C9 RGM-C	MMP-7 Cadherin-5	MRC2 Kallistatin	0.949	0.892	1.841	0.953
39	RGM-C	C9 HGF	MMP-7 MRC2	SLPI C2	LY9 MIP-5	0.962	0.882	1.844	0.945
40	HGF	SLPI SCF sR	C9 MCP-3	MMP-7 RGM-C	Cadherin-5 PCI	0.949	0.892	1.841	0.941
41	HGF	SLPI MCP-3	C9 Cadherin-5	MMP-7 SCF sR	MRC2 Prekallikrein	0.936	0.913	1.849	0.941
42	HGF	SLPI MCP-3	C9 Cadherin-5	MMP-7 SCF sR	MRC2 RBP	0.949	0.897	1.846	0.936
43	HGF	SLPI α2-Antiplas-min	C9 TIMP-2	MMP-7 SAP	MRC2 sL-Selectin	0.936	0.897	1.833	0.947
44	HGF	SLPI HSP 90α	C9 RGM-C	MMP-7 Thrombin/Pro-thrombin	MRC2 α2-Antiplasmin	0.974	0.867	1.841	0.950
45	RGM-C	C9 HGF	MCP-3 MMP-7	SLPI sL-Selectin	MRC2 Tropinin T	0.949	0.887	1.836	0.941
46	α2-Antiplas-min	C9 MMP-7	SLPI BAFF Receptor	Cadherin-5 SAP	HGF α1-Antitrypsin	0.949	0.872	1.821	0.929
47	Cadherin-5	C9 RGM-C	SLPI α2-Antiplasmin	MMP-7 HGF	C2 α2-HS-Glycoprotein	0.962	0.882	1.844	0.951
48	α2-Antiplas-min	C9 MMP-7	SLPI Contactin-1	Cadherin-5 RGM-C	HGF SAP	0.974	0.892	1.867	0.955
49	HGF	SLPI HSP 90α	C9 Cadherin-5	MMP-7 MCP-3	MRC2 ADAM 9	0.949	0.897	1.846	0.935
50	HGF	SLPI MMP-7	C9 Contactin-4	α2-Antiplasmin Cadherin-5	SAP ARSB	0.949	0.887	1.836	0.943

TABLE 8-continued

51	RGM-C	C9 HGF	MMP-7 HSP 90α	SLPI α2-Antiplasmin	SAP C5	0.987	0.851	1.838	0.950
52	RGM-C	C9 HGF	MMP-7 HSP 90α	SLPI Kallistatin	SAP ERBB1	0.962	0.872	1.833	0.947
53	HGF	SLPI MMP-7	C9 Growth hormone receptor	α2-Antiplasmin Cadherin-5	SAP Contactin-1	0.962	0.877	1.838	0.947
54	α2-Antiplas-min	C9 MMP-7	SLPI MRC2	Cadherin-5 SAP	HGF Hat1	0.936	0.897	1.833	0.941
55	HGF	SLPI α2-Antiplas-min	C9 RGM-C	MMP-7 Cadherin-5	MRC2 IL-12 Rβ2	0.936	0.897	1.833	0.950
56	α2-Antiplas-min	C9 MMP-7	SLPI HGF	Cadherin-5 Contactin-4	RGM-C IL-12 Rα1	0.962	0.877	1.838	0.948
57	HGF	SLPI HSP 90α	C9 RGM-C	MMP-7 C2	MRC2 IL-18 Rβ	0.962	0.862	1.823	0.946
58	Cadherin-5	C9 HGF	SLPI Kallikrein 6	MMP-7 RGM-C	SAP Contactin-1	0.962	0.877	1.838	0.951
59	Cadherin-5	C9 RGM-C	SLPI MRC2	MMP-7 NRP1	LY9 RBP	0.936	0.908	1.844	0.938
60	α2-Antiplas-min	C9 MMP-7	SLPI HGF	Cadherin-5 Contactin-4	RGM-C MIP-5	0.962	0.887	1.849	0.949
61	α2-Antiplas-min	C9 MMP-7	SLPI Coagulation Factor Xa	Cadherin-5 C2	HGF PCI	0.962	0.877	1.838	0.944
62	HGF	SLPI HSP 90α	C9 SAP	MMP-7 NRP1	MRC2 Prekallikrein	0.962	0.882	1.844	0.941
63	HGF	SLPI α2-Antiplas-min	C9 TIMP-2	MMP-7 SAP	MRC2 RGM-C	0.949	0.882	1.831	0.951
64	Cadherin-5	C9 RGM-C	SLPI MRC2	MMP-7 NRP1	LY9 Thrombin/Prothrombin	0.923	0.913	1.836	0.946
65	RGM-C	C9 HGF	MMP-7 Contactin-4	SLPI MCP-3	SAP Troponin T	0.962	0.872	1.833	0.938
66	Cadherin-5	C9 HGF	SLPI Coagulation Factor Xa	MMP-7 MCP-3	SAP α1-Antitrypsin	0.949	0.872	1.821	0.929
67	HGF	SLPI SCF sR	C9 MCP-3	MMP-7 Coagulation Factor Xa	Cadherin-5 α2-HS-Glycoprotein	0.949	0.892	1.841	0.937
68	HGF	SLPI Properdin	C9 RGM-C	MMP-7 ADAM 9	MRC2 HSP 90α	0.962	0.882	1.844	0.935
69	α2-Antiplas-min	C9 C2	SLPI MMP-7	Cadherin-5 Contactin-4	HGF ARSB	0.936	0.887	1.823	0.941
70	α2-Antiplas-min	C9 MMP-7	SLPI BAFF Receptor	Cadherin-5 SAP	HGF C2	0.962	0.887	1.849	0.940
71	HGF	SLPI HSP 90α	C9 MCP-3	MMP-7 α2-Antiplasmin	MRC2 C5	0.962	0.877	1.838	0.938
72	α2-Antiplas-min	C9 C2	SLPI MMP-7	Cadherin-5 HSP 90α	HGF C6	0.962	0.877	1.838	0.948
73	HGF	SLPI HSP 90α	C9 RGM-C	MMP-7 C2	MRC2 ERBB1	0.962	0.872	1.833	0.945
74	RGM-C	C9 HGF	MMP-7 MRC2	SLPI Growth hormone receptor	SAP α2-Antiplasmin	0.962	0.877	1.838	0.947
75	RGM-C	C9 HGF	MCP-3 MMP-7	SLPI Contactin-1	MRC2 Hat1	0.936	0.892	1.828	0.933
76	HGF	SLPI MCP-3	C9 Cadherin-5	MMP-7 SCF sR	MRC2 IL-12 Rβ2	0.923	0.908	1.831	0.939
77	RGM-C	C9 HGF	MMP-7 HSP 90α	SLPI Kallistatin	SAP IL-13 Rα1	0.974	0.856	1.831	0.945
78	RGM-C	C9 HGF	MMP-7 MRC2	SLPI NRP1	SAP IL-18 Rβ	0.949	0.872	1.821	0.944
79	Cadherin-5	C9 HGF	SLPI Kallikrein 6	MMP-7 RGM-C	SAP Properdin	0.974	0.862	1.836	0.950
80	HGF	SLPI SCF sR	C9 MCP-3	MMP-7 RGM-C	Cadherin-5 MIP-5	0.962	0.877	1.838	0.938
81	α2-Antiplas-min	C9 MMP-7	SLPI HGF	Cadherin-5 SAP	RGM-C PCI	0.962	0.872	1.833	0.952
82	RGM-C	C9 HGF	MMP-7 MRC2	SLPI Properdin	SAP Prekallikrein	0.949	0.892	1.841	0.953
83	RGM-C	C9 HGF	MCP-3 MMP-7	SLPI SAP	MRC2 RBP	0.962	0.882	1.844	0.939
84	RGM-C	C9 HGF	MCP-3 MMP-7	SLPI sL-Selectin	MRC2 TIMP-2	0.949	0.882	1.831	0.943

TABLE 8-continued

85	HGF	SLPI HSP 90α	C9 NRP1	MMP-7 Thrombin/Pro-thrombin	MRC2 RGM-C	0.962	0.872	1.833	0.946
86	RGM-C	C9 HGF	MMP-7 Contactin-4	SLPI α2-Antiplasmin	SAP Troponin T	0.962	0.867	1.828	0.947
87	α2-Antiplas-min	C9 MMP-7	SLPI HGF	Cadherin-5 SAP	RGM-C α2-Antitrypsin	0.949	0.872	1.821	0.942
88	RGM-C	C9 HGF	MCP-3 MMP-7	SLPI SCF sR	MRC2 α2-HS-Glycoprotein	0.949	0.887	1.836	0.943
89	RGM-C	C9 HGF	MMP-7 Contactin-4	SLPI MCP-3	SAP ADAM 9	0.949	0.892	1.841	0.939
90	Cadherin-5	C9 HGF	SLPI Contactin-1	MMP-7 MCP-3	SAP ARSB	0.936	0.887	1.823	0.937
91	RGM-C	C9 HGF	MCP-3 MMP-7	SLPI Cadherin-5	MRC2 BAFF Receptor	0.949	0.897	1.846	0.942
92	RGM-C	C9 HGF	MMP-7 Contactin-1	SLPI MCP-3	SAP C5	0.962	0.872	1.833	0.940
93	HGF	SLPI MCP-3	C9 Cadherin-5	MMP-7 SCF sR	MRC2 C6	0.936	0.903	1.838	0.938
94	Cadherin-5	C9 HGF	SLPI Contactin-1	MMP-7 MCP-3	SAP ERBB1	0.936	0.897	1.833	0.940
95	RGM-C	C9 HGF	MMP-7 MRC2	SLPI Growth hormone receptor	SAP Contactin-4	0.962	0.877	1.838	0.944
96	HGF	SLPI α2-Antiplas-min	C9 RGM-C	MMP-7 Hat1	MRC2 IL-13 Rα1	0.962	0.867	1.828	0.937
97	α2-Antiplas-min	C9 MMP-7	SLPI Contactin-1	Cadherin-5 RGM-C	HGF IL-12 Rβ2	0.936	0.887	1.823	0.948
98	HGF	SLPI SCF sR	C9 MCP-3	MMP-7 RGM-C	Cadherin-5 IL-18 Rβ	0.949	0.872	1.821	0.940
99	HGF	SLPI HSP 90α	C9 Cadherin-5	MMP-7 MCP-3	MRC2 Kallikrein 6	0.949	0.887	1.836	0.937
100	HGF	SLPI SCF sR	C9 MCP-3	MMP-7 RGM-C	Cadherin-5 Kallistatin	0.949	0.892	1.841	0.944

Marker	Count	Marker	Count
SLPI	100	IL-18 Rβ	5
MMP-7	100	IL-13 Rα1	5
C9	100	IL-12 Rβ2	5
HGF	98	Hat1	5
RGM-C	72	Growth hormone receptor	5
Cadherin-5	54	ERBB1	5
MRC2	51	C6	5
SAP	47	C5	5
α2-Antiplasmin	44	BAFF Receptor	5
MCP-3	34	ARSB	5
Contactin-4	17	ADAM 9	5
HSP 90α	16	α2-HS-Glycoprotein	4
SCF sR	14	α1-Antitrypsin	4
C2	11	Troponin T	4
Contactin-1	9	Thrombin/Prothrombin	4
NRP1	9	TIMP-2	4
Coagulation Factor Xa	7	RBP	4
sL-Selectin	6	Prekallikrein	4
Properdin	6	PCI	4
Kallistatin	5	MIP-5	4
Kallikrein 6	5	LY9	4

[0363]

TABLE 9

100 Panels of 10 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
1	RGM-C HGF	C9 MMP-7	MCP-3 Cadherin-5	SLPI SCF sR	MRC2 ADAM 9	0.949	0.918	1.867	0.943

TABLE 9-continued

2	HGF MMP-7	SLPI Contactin-4	C9 Cadherin-5	α2-Antiplas-min RGM-C	SAP ARSB	0.949	0.897	1.846	0.950
3	HGF MMP-7	SLPI BAFF Receptor	C9 RGM-C	α2-Antiplas-min MCP-3	SAP MRC2	0.962	0.908	1.869	0.946
4	HGF MMP-7	SLPI sL-Selectin	C9 RGM-C	α2-Antiplas-min Cadherin-5	SAP C2	0.962	0.903	1.864	0.955
5	α2-Antiplas-min MMP-7	C9 HGF	SLPI SAP	Cadherin-5 BAFF Receptor	RGM-C C5	0.962	0.887	1.849	0.944
6	α2-Antiplas-min MMP-7	C9 HGF	SLPI Contactin-4	Cadherin-5 α2-HS-Glyco-protein	RGM-C C6	0.962	0.892	1.854	0.951
7	RGM-C HGF	C9 Contactin-4	MMP-7 MCP-3	SLPI Coagulation Factor Xa	SAP sL-Selectin	0.974	0.892	1.867	0.945
8	Cadherin-5 RGM-C	C9 α2-Antiplas-min	SLPI HGF	MMP-7 SAP	C2 ERBB1	0.962	0.903	1.864	0.952
9	RGM-C HGF	C9 Contactin-4	MMP-7 Growth hormone receptor	SLPI Contactin-1	SAP Coagulation Factor Xa	0.962	0.882	1.844	0.947
10	RGM-C HGF	C9 HSP 90α	MMP-7 α2-Antiplasmin	SLPI Contactin-1	SAP Cadherin-5	0.962	0.897	1.859	0.954
11	RGM-C HGF	C9 MMP-7	MCP-3 sL-Selectin	SLPI SAP	MRC2 Hat1	0.949	0.892	1.841	0.937
12	α2-Antiplas-min MMP-7	C9 HGF	SLPI SAP	Cadherin-5 IL-12 Rβ2	RGM-C Contactin-4	0.962	0.892	1.854	0.952
13	α2-Antiplas-min MMP-7	C9 HGF	SLPI Contactin-4	Cadherin-5 IL-13 Rα1	RGM-C SAP	0.962	0.892	1.854	0.952
14	HGF Properdin	SLPI RGM-C	C9 HSP 90α	MMP-7 α2-Antiplas-min	MRC2 IL-18 Rβ	0.962	0.877	1.838	0.948
15	HGF MCP-3	SLPI BAFF Receptor	C9 α2-Antiplasmin	MMP-7 SAP	MRC2 Kallikrein 6	0.962	0.887	1.849	0.940
16	α2-Antiplas-min MMP-7	C9 HGF	SLPI SAP	Cadherin-5 Kallistatin	RGM-C sL-Selectin	0.974	0.887	1.862	0.955
17	RGM-C HGF	C9 MRC2	MMP-7 C2	SLPI NRP1	LY9 SAp	0.962	0.892	1.854	0.946
18	α2-Antiplas-min MMP-7	C9 HGF	SLPI SAp	Cadherin-5 MIP-5	RGM-C Contactin-1	0.974	0.892	1.867	0.954
19	α2-Antiplas-min MMP-7	C9 HGF	SLPI SAP	Cadherin-5 PCI	RGM-C Contactin-1	0.962	0.892	1.854	0.952
20	RGM-C HGF	C9 MMP-7	MCP-3 Cadherin-5	SLPI BAFF Receptor	MRC2 Prekallikrein	0.962	0.897	1.859	0.944
21	HGF MCP-3	SLPI Cadherin-5	C9 SCF sR	MMP-7 RBP	MRC2 RGM-C	0.949	0.913	1.862	0.942
22	RGM-C HGF	C9 MMP-7	MCP-3 sL-Selectin	SLPI SAP	MRC2 TIMP-2	0.962	0.887	1.849	0.945
23	RGM-C HGF	C9 MRC2	MMP-7 NRP1	SOLPI sL-Selectin	SAP Thrombin/Prothrombin	0.974	0.882	1.856	0.951
24	HGF MMP-7	SLPI BAFF Receptor	C9 RGM-C	α2-Antiplas-min MCP-3	SAP Troponin T	0.962	0.887	1.849	0.937
25	HGF SCF sR	SLPI MCP-3	C9 RGM-C	MMP-7 SAp	Cadherin-5 α2-Antitrypsin	0.936	0.897	1.833	0.936
26	RGM-C HGF	C9 MMP-7	MCP-3 SAP	SLPI Prekallikrein	MRC2 ADAM 9	0.962	0.892	1.854	0.943
27	α2-Antiplas-min MMP-7	C9 HGF	SLPI SAp	Cadherin-5 C5	RGM-C ARSB	0.949	0.892	1.841	0.950
28	α2-Antiplas-min MMP-7	C9 HGF	SLPI SAp	Cadherin-5 Properdin	RGM-C C6	0.962	0.892	1.854	0.954
29	HGF SCF sR	SLPI MCP-3	C9 RGM-C	MMP-7 SAP	Cadherin-5 ERBB1	0.962	0.897	1.859	0.946
30	RGM-C HGF	C9 Contactin-4	MMP-7 Growth hormone receptor	SLPI Contactin-1	SAP MCP-3	0.962	0.882	1.844	0.942

TABLE 9-continued

31	RGM-C HGF	C9 MRC2	MMP-7 C2	SLPI NRP1	LY9 Hat1	0.949	0.887	1.836	0.938
32	α2-Antiplas- min MMP-7	C9 HGF	SLPI SAP	Cadherin-5 IL-12 Rβ2	RGM-C C5	0.962	0.887	1.849	0.949
33	α2-Antiplas- min MMP-7	C9 HGF	SLPI Contactin-4	Cadherin-5 IL-13 Rα1	RGM-C C2	0.962	0.887	1.849	0.949
34	HGF SCF sR	SLPI MCP-3	C9 Coagulation Factor Xa	MMP-7 MRC2	Cadherin-5 IL-18 Rβ	0.936	0.903	1.838	0.940
35	HGF SCF sR	SLPI MCP-3	C9 RGM-C	MMP-7 SAp	Cadherin-5 Kallikrein 6	0.962	0.887	1.849	0.946
36	HGF SCF sR	SLPI MCP-3	C9 RGM-C	MMP-7 Kallistatin	Cadherin-5 SAP	0.962	0.887	1.849	0.947
37	α2-Antiplas- min MMP-7	C9 HGF	SLPI Contactin-4	Cadherin-5 MIP-5	RGM-C SAP	0.962	0.897	1.859	0.953
38	α2-Antiplas- min MMP-7	C9 HGF	SLPI SAP	Cadherin-5 PCI	RGM-C C6	0.962	0.882	1.844	0.951
39	HGF MMP-7	SLPI BAFF Receptor	C9 RGM-C	α2-Antiplas- min MCP-3	SAP RBP	0.962	0.887	1.849	0.939
40	α2-Antiplas- min MMP-7	C9 HGF	SLPI SAP	Cadherin-5 C6	RGM-C TIMP-2	0.962	0.887	1.849	0.952
41	HGF MMP-7	SLPI BAFF Receptor	C9 RGM-C	α2-Antiplas- min MCP-3	SAp Thrombin/Prothrombin	0.974	0.877	1.851	0.940
42	HGF MCP-3	SLPI BAFF Receptor	C9 α2-Antiplasmin	MMP-7 SAP	MRC2 Troponin T	0.949	0.887	1.836	0.938
43	Cadherin-5 HGF	C9 Coagulation Factor Xa	SLPI MCP-3	MMP-7 SCF sR	SAP α2-Antitrypsin	0.936	0.897	1.833	0.932
44	Cadherin-5 RGM-C	C9 α2-Antiplas- min	SLPI HGF	MMP-7 α2-HS-Glyco- protein	C2 Contactin-1	0.962	0.897	1.859	0.951
45	HGF Properdin	SLPI RGM-C	C9 ADAM 9	MMP-7 SAp	MRC2 MCP-3	0.962	0.892	1.854	0.941
46	RGM-C HGF	C9 MRC2	MMP-7 NRP1	SLPI sL-Selectin	SAP ARSB	0.949	0.892	1.841	0.947
47	RGM-C HGF	C9 HSP 90α	MMP-7 α2-Antiplasmin	SLPI Contactin-1	SAP ERBB1	0.974	0.877	1.851	0.947
48	HGF SCF sR	SLPI MCP-3	C9 RGM-C	MMP-7 SAP	Cadherin-5 Growth hormone receptor	0.962	0.882	1.844	0.945
49	Cadherin-5 RGM-C	C9 α2-Antiplas- min	SLPI HGF	MMP-7 SAP	C2 Hat1	0.936	0.897	1.833	0.947
50	α2-Antiplas- min MMP-7	C9 HGF	SLPI SAP	Cadherin-5 IL-12 Rβ2	RGM-C Contactin-1	0.949	0.897	1.846	0.952
51	RGM-C HGF	C9 MMP-7	MCP-3 sL-Selectin	SLPI SAP	MRC2 IL-13 Rα1	0.962	0.887	1.849	0.945
52	HGF Properdin	SLPI RGM-C	C9 HSP 90α	MMP-7 Cadherin-5	MRC2 IL-18 Rβ	0.962	0.877	1.838	0.948
53	RGM-C HGF	C9 MMP-7	MCP-3 Cadherin-5	SLPI SXCF sR	MRC2 Kallikrein 6	0.949	0.897	1.846	0.945
54	RGM-C HGF	C9 MMP-7	MCP-3 Cadherin-5	SLPI sL-Selectin	MRC2 Kallistatin	0.949	0.897	1.846	0.946
55	RGM-C HGF	C9 MMP-7	MCP-3 Cadherin-5	SLPI SCF sR	MRC2 LY9	0.936	0.913	1.849	0.942
56	HGF SCF sR	SLPI MCP-3	C9 RGM-C	MMP-7 MIP-5	Cadherin-5 SAp	0.962	0.892	1.854	0.944
57	α2-Antiplas- min MMP-7	C9 HGF	SLPI SAP	Cadherin-5 PCI	RGM-C Properdin	0.949	0.892	1.841	0.952
58	HGF SCF sR	SLPI MCP-3	C9 RGM-C	MMP-7 SAP	Cadherin-5 Prekallikrein	0.962	0.897	1.859	0.949
59	α2-Antiplas- min MMP-7	C9 HGF	SLPI SAP	Cadherin-5 Properdin	RGM-C RBP	0.949	0.897	1.846	0.952
60	α2-Antiplas- min MMP-7	C9 Contactin-1	SLPI RGM-C	Cadherin-5 C2	HGF TIMP-2	0.962	0.882	1.844	0.950
61	RGM-C HGF	C9 MMP-7	MCP-3 Cadherin-5	SLPI SCF sR	MRC2 Thrombin/Prothrombin	0.949	0.903	1.851	0.946

TABLE 9-continued

62	α2-Antiplas-min MMP-7	C9 HGF	SLPI SAP	Cadherin-5 Kallistatin	RGM-C Troponin T	0.949	0.882	1.831	0.952
63	α2-Antiplas-min MMP-7	C9 HGF	SLPI SAP	Cadherin-5 Properdin	RGM-C α1-Antitrypsin	0.949	0.877	1.826	0.942
64	HGF MCP-3	SLPI Cadherin-5	C9 SCF sR	MMP-7 α2-HS-Glyco-protein	MRC2 RGM-C	0.949	0.908	1.856	0.945
65	HGF Properdin	SLPI RGM-C	C9 ADAM 9	MMP-7 HSP 90α	MRC2 Cadherin-5	0.949	0.903	1.851	0.939
66	HGF MCP-3	SLPI Cadherin-5	C9 SCF sR	MMP-7 NRP1	MRC2 ARSB	0.936	0.903	1.838	0.938
67	α2-Antiplas-min MMP-7	C9 HGF	SLPI Contactin-4	Cadherin-5 MRC2	RGM-C C5	0.949	0.897	1.846	0.948
68	HGF MMP-7	SLPI BAFF Receptor	C9 RGM-C	α2-Antiplas-min MCP-3	SAP ERBB1	0.962	0.882	1.844	0.939
69	Cadherin-5 RGM-C	C9 α2-Antiplas-min	SLPI HGF	MMP-7 SAp	C2 Growth hormone receptor	0.962	0.882	1.844	0.951
70	HGF MCP-3	SLPI BAFF Receptor	C9 α2-Antiplasmin	MMP-7 SAp	MRC2 Hat1	0.936	0.892	1.828	0.932
71	α2-Antiplas-min MMP-7	C9 Contactin-1	SLPI RGM-C	Cadherin-5 SAp	HGF IL-12 Rβ2	0.949	0.897	1.846	0.952
72	α2-Antiplas-min MMP-7 C2	C9 Contactin-4	SLPI RGM-C	Cadherin-5 IL-13 Rα1	HGF	0.962	0.887	1.849	0.949
73	α2-Antiplas-min MMP-7	C9 Contactin-1	SLPI RGM-C	Cadherin-5 Contactin-4	HGF IL-18 Rβ	0.949	0.887	1.836	0.948
74	HGF HSP 90α	SLPI MCP-3	C9 SAP	MMP-7 α2-Antiplas-min	MRC2 Kallikrein 6	0.962	0.882	1.844	0.941
75	α2-Antiplas-min MMP-7	C9 MRC2	SLPI SAp	Cadherin-5 RGM-C	HGF LY9	0.949	0.897	1.846	0.949
76	HGF MMP-7	SLPI sL-Selectin	C9 RGM-C	α2-Antiplas-min Cadherin-5	SAp MIP-5	0.962	0.892	1.854	0.953
77	α2-Antiplas-min MMP-7	C9 HGF	SLPI SAP	Cadherin-5 PCI	RGM-C sL-Selectin	0.949	0.892	1.841	0.953
78	RGM-C HGF	C9 MMP-7	1.854 SAp	0.950 Prekallikrein	α2-Antiplasmin				
79	RGM-C HGF	C9 MMP-7	MCP-3 SAp	SLPI RBP	MRC2 sL-Selectin	0.949	0.897	1.846	0.943
80	α2-Antiplas-min MMP-7	C9 HGF	SLPI SAP	Cadherin-5 Kallistatin	RGM-C TIMP-2	0.962	0.877	1.838	0.953
81	RGM-C HGF	C9 MMP-7	MCP-3 Contactin-1	SLPI BAFF Receptor	MRC2 Thrombin/Prothrombin	0.962	0.887	1.849	0.942
82	RGM-C HGF	C9 MMP-7	MCP-3 Contactin-1	SLPI HSP 90α	MRC2 Troponin T	0.949	0.882	1.831	0.940
83	α2-Antiplas-min MMP-7	C9 HGF	SLPI Contactin-4	Cadherin-5 MRC2	RGM-C α1-Antitrypsin	0.936	0.887	1.823	0.937
84	α2-Antiplas-min MMP-7	C9 HGF	SLPI Contactin-4	Cadherin-5 α2-HS-Glyco-protein	RGM-C C2	0.962	0.892	1.854	0.951
85	RGM-C HGF	C9 MMP-7	MCP-3 Cadherin-5	SLPI BAFF Receptor	MRC2 ADAM 9	0.949	0.903	1.851	0.941
86	RGM-C HGF	C9 MMP-7	MCP-3 Cadherin-5	SLPI SCF sR	MRC2 ARSB	0.936	0.903	1.838	0.942
87	α2-Antiplas-min MMP-7	C9 HGF	SLPI Contactin-4	Cadherin-5 C5	RGM-C MRC2	0.949	0.897	1.846	0.948
88	α2-Antiplas-min MMP-7	C9 HGF	SLPI SAp	Cadherin-5 C6	RGM-C sL-Selectin	0.962	0.892	1.854	0.954
89	Cadherin-5 HGF	C9 Coagulation Factor Xa	SLPI MCP-3	MMP-7 SCF sR	SAP Contactin-1	0.962	0.897	1.859	0.943

TABLE 9-continued

90	RGM-C HGF	C9 Contactin-4	MMP-7 MCP-3	SLPI Coagulation Factor Xa	SAP ERBB1	0.962	0.882	1.844	0.943
91	α2-Antiplasmin MMP-7	C9 SLPI Contactin-1	Cadherin-5 RGM-C	HGF SAP	0.962 Growth hormone receptor	0.882	1.844	0.951	
92	RGM-C HGF	C9 MRC2	MMP-7 C2	SLPI MIP-5	LY9 Hat1	0.949	0.877	1.826	0.938
93	α2-Antiplasmin MMP-7	C9 HGF	SLPI SAP	Cadherin-5 IL-12 Rβ2	RGM-C sL-Selectin	0.962	0.882	1.844	0.951
94	α2-Antiplasmin MMP-7	C9 Contactin-1	SLPI RGM-C	Cadherin-5 SAP	HGF IL-13 Rα1	0.962	0.887	1.849	0.952
95	RGM-C HGF	C9 MRC2	MMP-7 C2	SLPI NRP1	LY9 IL-18 Rβ	0.949	0.887	1.836	0.944
96	HGF Properdin	SLPI RGM-C	C9 HSP 90α	MMP-7 Cadherin-5	MRC2 Kallikrein 6	0.962	0.882	1.844	0.947
97	RGM-C HGF	C9 MMP-7	MCP-3 sL-Selectin	SLPI SAP	MRC2 PCI	0.949	0.892	1.841	0.944
98	RGM-C HGF	C9 MMP-7	MCP-3 SAP	SLPI Prekallikrein	MRC2 BAFF Receptor	0.962	0.887	1.849	0.945
99	HGF α2-Antiplasmin	SLPI RGM-C	C9 BAFF Receptor	MMP-7 MCP-3	MRC2 RBP	0.949	0.897	1.846	0.940
100	α2-Antiplasmin MMP-7	C9 HGF	SLPI SAP	Cadherin-5 Properdin	RGM-C TIMP-2	0.962	0.877	1.838	0.952

Marker	Count	Marker	Count
SLPI	100	TIMP-2	5
MMP-7	100	RBP	5
HGF	100	Prekallikrein	5
C9	100	PCI	5
RGM-C	92	MIP-5	5
SAP	68	Kallistatin	5
Cadherin-5	67	Kallikrein 6	5
α2-Antiplasmin	56	IL-18 Rβ	5
MCP-3	45	IL-13 Rα1	5
MRC2	43	IL-12 Rβ2	5
SCF sR	18	Hat1	5
Contactin-1	16	Growth hormone receptor	5
Contactin-4	16	ERBB1	5
sL-Selectin	15	C6	5
BAFF Receptor	14	C5	5
C2	13	ARSB	5
Properdin	10	ADAM 9	5
HSP 90α	8	α2-HS-Glycoprotein	4
NRP1	6	α1-Antitrypsin	4
LY9	6	Tropinin T	4
Coagulation Factor Xa	6	Thrombin/Prothrombin	4

[0364]

TABLE 10

100 Panels of Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers						Sensitivity	Specificity	Sensitivity + Specificity	AUC
1	SAP	MRC2 Cadherin-05	SLPI HGF	RGM-C Prekallikrein	MMP-7 MCP-3	Properdin ADAM 9	0.949	0.928	1.877	0.946
2	SAP	MMP-7 MRC2	SLPI RGM-C	Cadherin-5 NRP1	HGF ARSB	C9 MCP-3	0.962	0.892	1.854	0.946
3	SAP	C9 BAFF Receptor	SLPI Properdin	MMP-7 Cadherin-5	HGF MCP-3	RGM-C MRC2	0.962	0.918	1.879	0.945
4	RGM-C	MRC2 α2-Antiplasmin	SLPI BAFF Receptor	C9 HGF	MMP-7 C2	MCP-3 SAP	0.962	0.908	1.869	0.946

TABLE 10-continued

5	Cadherin-5	HGF MRC2	SLPI BAFF Receptor	C9 MCP-3	MMP-7 C5	Properdin RGM-C	0.949	0.913	1.862	0.942
6	HGF	SCF sR SAP	C9 sL-Selectin	SLPI MMP-7	MCP-3 Coagulation Factor Xa	RGM-C C6	0.962	0.903	1.864	0.945
7	HGF	SLPI MCP-3	C9 Contactin-4	Coagulation Factor Xa RGM-C	MMP-7 Properdin	SAP Contactin-1	0.962	0.913	1.874	0.945
8	Cadherin-5	HGF SAP	SLPI α2-Antiplas-min	C9 RGM-C	MMP-7 PCI	C2 ERBB1	0.962	0.897	1.859	0.951
9	HGF	LY9 MMP-7	SLPI SAP	C9 Growth hor-mone receptor	C2 Contactin-1	RGM-C Contactin-4	0.974	0.887	1.862	0.945
10	Contactin-4	MCP-3 MMP-7	SLPI SAP	C9 Cadherin-5	HGF α2-Antiplas-min	HSP 90α RGM-C	0.974	0.892	1.867	0.947
11	SAP	C9 α2-Antiplas-min	SLPI RGM-C	MMP-7 LY9	HGF Hat1	MRC2 MCP-3	0.962	0.892	1.854	0.939
12	Cadherin-5	MMP-7 MRC2	C9 HSP 90α	RGM-C ADAM 9	SLPI IL-12 Rβ2	HGF BAFF Receptor	0.962	0.897	1.859	0.936
13	SAP	C9 BAFF Receptor	SLPI Properdin	MMP-7 sL-Selectin	HGF MRC2	RGM-C IL-13 Rα1	0.962	0.897	1.859	0.940
14	MMP-7	SLPI α2-Antiplas-min	C9 MRC2	HSP 90α RGM-C	HGF MCP-3	Cadherin-5 IL-18 Rβ	0.962	0.892	1.854	0.945
15	SAP	C9 Kallikrein 6	SLPI Contactin-4	MMP-7 Cadherin-5	HGF MCP-3	RGM-C Kallistatin	0.974	0.887	1.862	0.945
16	Cadherin-5	HGF MRC2	SLPI Prekallikrein	C9 SCF sR	MMP-7 MIP-5	MCP-3 RGM-C	0.949	0.913	1.862	0.945
17	SAP	C9 MCP-3	SLPI HSP 90α	MMP-7 Cadherin-5	HGF ADAM 9	MRC2 RBP	0.962	0.903	1.864	0.936
18	SAP	C9 MCP-3	SLPI RGM-C	MMP-7 α2-Antiplas-min	HGF BAFF Receptor	MRC2 TIMP-2	0.962	0.903	1.864	0.944
19	RGM-C	MRC2 HGF	SLPI BAFF Receptor	C9 Cadherin-5	MMP-7 Thrombin/Pro-thrombin	MCP-3 Contactin-1	0.962	0.903	1.864	0.944
20	SAP	S9 MCP-3	SLPI Properdin	MMP-7 RGM-C	HGF Troponin T	MRC2 Contactin-1	0.949	0.908	1.856	0.944
21	RGM-C	MRC2 ADAM 9	SLPI SAP	C9 BAFF Receptor	MMP-7 α1-Antitrypsin	HGF MCP-3	0.962	0.903	1.864	0.931
22	RGM-C	MCP-3 HGF	C9 Contactin-4	MMP-7 SAP	SLPI BAFF Receptor	Contactin-1 α2-HS-Glycoprotein	0.974	0.892	1.867	0.941
23	Cadherin-5	MMP-7 RGM-C	SLPI HGF	MRC2 MCP-3	C9 ARSB	sL-Selectin	0.949	0.903	1.851	0.940
24	SAP	C9 MCP-3	SLPI BAFF Receptor	MMP-7 Prekallikrein	HGF C5	MRC2 ADAM 9	0.962	0.897	1.859	0.936
25	MMP-7	SLPI SAP	C9 RGM-C	HSP 90α MCP-3	α2-Antiplas-min Contactin-4	HGF C6	0.974	0.887	1.862	0.944
26	HGF	MMP-7 RGM-C	α2-Antiplas-min Cadherin-5	C9 HSP 90α	SLPI SAP	C2 ERBB1	0.962	0.897	1.859	0.952
27	MMP-7	SLPI Contactin-4	Contactin-1 MCP-3	Growth hor-mone receptor ADAM 9	SAP C9	HGF RGM-C	0.962	0.897	1.859	0.940
28	SAP	C9 MCP-3	SLPI Contactin-1	MMP-7 Hat1	HGF RGM-C	MRC2 Kallistatin	0.949	0.897	1.846	0.936
29	SAP	MRC2 HSP 90α	SLPI HGF	RGM-C Cadherin-5	MMP-7 MCP-3	Properdin IL-12 Rβ2	0.936	0.923	1.859	0.941
30	SAP	C9 MCP-3	SLPI RGM-C	MMP-7 α2-Antiplas-min	HGF BAFF Receptor	MRC2 IL-13 Rα1	0.962	0.897	1.859	0.943
31	RGM-C	MRC2 SCF sR	SLPI MCP-3	C9 ADAM 9	MMP-7 SAP	HGF IL-18 Rβ	0.962	0.892	1.854	0.941
32	SAP	C9 MCP-3	SLPI RGM-C	MMP-7 Contactin-4	HGF sL-Selectin	MRC2 Kallikrein 6	0.962	0.897	1.859	0.945
33	Contactin-4	MCP-3 MMP-7	SLPI SAP	C9 Cadherin-5	HGF RGM-C	HSP 90α MIP-5	0.974	0.887	1.862	0.943
34	SAP	C9 MCP-3	SLPI RGM-C	MMP-7 Contactin-4	HGF NRP1	MRC2 ADAM 9	0.962	0.903	1.864	0.939

TABLE 10-continued

35	Cadherin-5	HGF RGM-C	SLPI α2-Antiplas-min	C9 PCI	MMP-7 SAP	Properdin Contactin-1	0.962	0.897	1.859	0.952
36	SAP	C9 RBP	SLPI RGM-C	MMP-7 Properdin	HGF ADAM 9	MRC2 MCP-3	0.962	0.897	1.859	0.939
37	SAP	C9 MCP-3	SLPI BAFF Receptor	MMP-7 sL-Selectin	HGF NRP1	MRC2 TIMP-2	0.962	0.897	1.859	0.936
338	SAP	C9 NRP1	SLPI MRC2	MMP-7 Thrombin/Pro-thrombin	HGF sL-Selectin	RGM-C Properdin	0.962	0.903	1.864	0.952
39	Cadherin-5	MMP-7 MRC2	C9 Troponin T	RGM-C BAFF Receptor	SLPI SAP	HGF Properdin	0.949	0.908	1.856	0.943
40	SAP	C9 MCP-3	SLPI RGM-C	MMP-7 HSP 90α	HGF α2-Antitrypsin	MRC2 ADAM 9	0.962	0.892	1.854	0.931
41	SAP	MRC2 HSP 90α	SLPI HGF	RGM-C Cadherin-5	MMP-7 MCP-3	Properdin α2-HS-Gly-coprotein	0.949	0.918	1.867	0.942
42	MRC2	NRP1 RGM-C	SLPI MCP-3	C9 Contactin-4	HGF SCF sR	MMP-7 ARSB	0.949	0.903	1.851	0.939
43	SAP	C9 MCP-3	SLPI BAFF Receptor	MMP-7 Prekallikrein	HGF C5	MRC2 Properdin	0.962	0.897	1.859	0.938
44	HGF	SCF sR α2-Antiplas-min	C9 SAP	SLPI RGM-C	MMP-7 MCP-3	Cadherin-5 C6	0.962	0.897	1.859	0.947
45	HGF	SLPI MCP-3	C9 Contactin-4	Coagulation Factor Xa RGM-C	MMP-7 Cadherin-5	SAP SCF sR	0.962	0.908	1.869	0.946
46	SAP	C9 MCP-3	SLPI ERBB1	MMP-7 RGM-C	HGF ADAM 9	MRC2 C2	0.962	0.897	1.859	0.942
47	RGM-C	Contactin-4 C9	SLPI HGF	SAP MCP-3	MMP-7 Contactin-1	Growth hor-mone re-ceptor C6	0.962	0.897	1.859	0.942
48	SAP	C9 α2-Antiplas-min	SLPI RGM-C	MMP-7 LY9	HGF Hat1	MRC2 C5	0.949	0.897	1.846	0.945
49	HGF	SCF sR SAP	C9 MCP-3	SLPI Coagulation Factor Xa	MMP-7 IL-12 Rβ2	Cadherin-5 Contactin-1	0.949	0.903	1.851	0.942
50	IL-13 Rα1	RGM-C Cadherin-5	SLPI HGF	C9 BAFF Receptor	MMP-7 SAP	Contactin-4 MCP-3	0.974	0.882	1.856	0.941
51	MRC2	NRP1 Thrombin/Pro-thrombin	SLPI RGM-C	C9 Contactin-1	HGF Properdin	MMP-7 IL-18 Rβ	0.962	0.892	1.854	0.946
52	SAP	C9 Kallikrein 6	SLPI Contactin-4	MMP-7 Cadherin-5	HGF MCP-3	RGM-C BAFF Re-ceptor	0.974	0.882	1.856	0.943
53	Contactin-4	MCP-3 MMP-7	SLPI SAP	C9 Cadherin-5	HGF RGM-C	HSP 90α Kallistatin	0.974	0.892	1.867	0.945
54	Cadherin-5	HGF RGM-C	SLPI BAFF Receptor	C9 Contactin-4	MMP-7 MIP-5	MCP-3 SAP	0.974	0.887	1.862	0.943
55	SAP	MMP-7 HGF	SLPI ERBB1	C2 RGM-C	Coagulation Factor Xa PCI	Cadherin-5 Properdin	0.962	0.897	1.859	0.947
56	SAP	C9 MCP-3	SLPI BAFF Receptor	MMP-7 Properdin	HGF RBP	MRC2 Cadherin-5	0.949	0.908	1.856	0.938
57	Cadherin-5	MMP-7 SAP	C9 α2-Antiplas-min	RGM-C ERBB1	SLPI C9	HGF TIMP-2	0.962	0.887	1.849	0.949
58	MRC2	NRP1 RGM-C	SLPI MCP-3	C9 Contactin-4	HGF SCF sR	MMP-7 Troponin T	0.949	0.908	1.856	0.941
59	SAP	C9 MCP-3	SLPI RGM-C	MMP-7 HSP 90α	HGF α1-Antitrypsin	MRC2 BAFF Re-ceptor	0.962	0.887	1.849	0.931
60	Cadherin-5	HGF RGM-C	SLPI α2-Antiplas-min	C9 α2-HS-Glyco-protein	MMP-7 C2	Properdsin Contactin-1	0.962	0.903	1.864	0.951
61	SAP	MMP-7 MRC2	SLPI RGM-C	Cadherin-5 NRP1	HGF ARSB	C9 Troponin T	0.962	0.887	1.849	0.950
62	Cadherin-5	HGF RGM-C	SLPI Contactin-1	C9 SCF sR	MMP-7 Contactin-4	MCP-3 Growth hor-mone re-aceptor	0.949	0.908	1.856	0.943
63	Cadherin-5	HGF SAP	SLPI α2-Antiplas-min	C9 RGM-C	MMP-7 Hat1	C2 Contactin-1	0.936	0.908	1.844	0.947

TABLE 10-continued

64	RGM-C	MRC2 HGF	SLPI BAFF Receptor	C9 Cadherin-5	MMP-7 IL-12 Rβ2	MCP-3 Properdin	0.936	0.913	1.849	0.942
65	HGF	SCF sR RGM-C	C9 MCP-3	SLPI SAP	MMP-7 Contactin-1	HSP 90α IL-13 Rα1	0.962	0.892	1.854	0.942
66	HGF	SCF sR SAP	C9 MCP-3	SLPI Contactin-1	MMP-7 RGM-C	Cadherin-5 IL-18 Rβ	0.949	0.903	1.851	0.946
67	SAP	C9 SCF sR	SLPI MCP-3	MMP-7 Contactin-4	HGF Kallikrein 6	RGM-C ADAM 9	0.962	0.892	1.854	0.941
68	Contactin-4	MCP-3 MMP-7	SLPI SAP	C9 RGM-C	HGF Contactin-1	HSP 90α Kallistatin	0.974	0.887	1.862	0.943
69	SAP	MRC2 sL-Selectin	SLPI HGF	RGM-C ADAM 9	MCP-3 α2-HS-Glycoprotein	MMP-7 LY9	0.949	0.913	1.862	0.939
70	RGM-C	MRC2 MIP-5	SLPI HGF	C9 BAFF Receptor	MMP-7 Cadherin-5	SAP MCP-3	0.962	0.897	1.859	0.944
71	HGF	SCF sR SAP	C9 MCP-3	SLPI RGM-C	MMP-7 PCI	Cadherin-5 BAFF Receptor	0.962	0.892	1.854	0.943
72	Cadherin-5	HGF α2-Antiplasmin	SLPI Contactin-1	C9 SAP	MMP-7 RBP	MCP-3 MRC2	0.936	0.918	1.854	0.943
73	SAP	MMP-7 C6	SLPI α2-Antiplasmin	Cadherin-5 RGM-C	HGF Contactin-1	C9 TIMP-2	0.949	0.897	1.846	0.952
74	SAP	C9 MCP-3	SLPI RGM-C	MMP-7 Thrombin/Prothrombin	HGF Properdin	MRC2 Prekallikrein	0.949	0.913	1.862	0.949
75	HGF	SLPI MCP-3	C9 Contactin-4	Coagulation Factor Xa RGM-C	MMP-7 Cadherin-5	SAP α1-Antitrypsin	0.949	0.897	1.846	0.934
76	SAP	C9 SCF sR	SLPI MCP-3	MMP-7 Contactin-4	HGF ADAM 9	RGM-C ARSB	0.962	0.887	1.849	0.938
77	Cadherin-5	HGF α2-Antiplasmin	SLPI Contactin-1	C9 RGM-C	MMP-7 C2	α2-HS-Glycoprotein C5	0.962	0.897	1.859	0.950
78	Cadherin-5	MMP-7 MRC2	C9 α2-Antiplasmin	RGM-C Growth hormone receptor	SLPI SAP	HGF C2	0.949	0.908	1.856	0.951
79	SAP	C9 MCP-3	SLPI RGM-C	MMP-7 α2-Antiplasmin	HGF Hat1	MRC2 C2	0.936	0.908	1.844	0.940
80	RGM-C	MRC2 HGF	SLPI HSP 90α	C9 Cadherin-5	MMP-7 IL-12 Rβ2	MCP-3 Properdin	0.949	0.897	1.846	0.944
81	RGM-C	MRC2 α2-Antiplasmin	SLPI BAFF Receptor	C9 HGF	MMP-7 Contactin-4	MCP-3 IL-13 Rα1	0.962	0.892	1.854	0.941
82	RGM-C	MRC2 α2-Antiplasmin	SLPI BAFF Receptor	C9 HGF	MMP-7 Cadherin-5	MCP-3 IL-18 Rβ	0.962	0.887	1.849	0.943
83	SAP	C9 MCP-3	ARSB RGM-C	MMP-7 HSP 90α	HGF SCF sR	MRC2 Kallikrein 6	0.962	0.892	1.854	0.945
84	HSP 90α	SLPI HGF	C9 Kallistatin	RGM-C MCP-3	MMP-7 Cadherin-5	SAP BAFF Receptor	0.974	0.887	1.862	0.942
85	MMP-7	LY9 SAP	SLPI ADAM 9	RGM-C Kallistatin	MRC2 MCP-3	HGF BAFF Receptor	0.949	0.913	1.862	0.937
86	RGM-C	MRC2 MIP-5	SLPI HGF	C9 BAFF Receptor	MMP-7 Cadherin-5	SAP NRP1	0.962	0.897	1.859	0.942
87	MMP-7	SLPI sL-Selectin	C9 HGF	α2-Antiplasmin Coagulation Factor Xa	RGM-C C2	Cadherin-5 PCI	0.962	0.892	1.854	0.950
88	MMP-7	SLPI BAFF Receptor	C9 ADAM 9	MCP-3 SAP	MRC2 RBP	HGF α2-Antiplasmin	0.962	0.892	1.854	0.938
89	SAP	C9 MCP-3	SLPI RGM-C	MMP-7 C6	HGF SCF sR	MRC2 TIMP-2	0.949	0.897	1.846	0.943
90	MRC2	NRP1 RGM-C	SLPI Properdin	C9 SAP	HGF BAFF Receptor	MMP-7 Thrombin/Prothrombin	0.962	0.897	1.859	0.942
91	Contactin-4	MCP-3 MRC2	SLPI RGM-C	C9 Troponin T	HGF C2	MMP-7 SAP	0.962	0.892	1.854	0.942
92	Cadherin-5	HGF RGM-C	SLPI BAFF Receptor	C9 SAP	MMP-7 α1-Antitrypsin	MCP-3 Troponin T	0.949	0.892	1.841	0.931

TABLE 10-continued

93	SAP	C9 NRP1	SLPI MRC2	MMP-7 Contactin-1	HGF MCP-3	RGM-C ARSB	0.949	0.897	1.846	0.942
94	SAP	C9 MCP-3	SLPI Contactin-4	MMP-7 Kallistatin	HGF BAFF Receptor	RGM-C C5	0.974	0.882	1.856	0.939
95	SAP	C9 MCP-3	SLPI RGM-C	MMP-7 Thrombin/Pro-thrombin	HGF ERBB1	MRC2 NRP1	0.962	0.892	1.854	0.943
96	Cadherin-5	HGF α2-Antiplas-min	SLPI SAP	C9 RGM-C	MMP-7 Growth hor-mone receptor	Contactin-4 C6	0.962	0.892	1.854	0.950
97	HGF	MMP-7 RGM-C	α2-Antiplas-min Contactin-1	C9 Cadherin-5	SLPI SAP	C2 Hat1	0.936	0.908	1.844	0.947
98	Contactin-4	MCP-3 MRC2	SLPI RGM-C	C9 Troponin T	HGF Cadherin-5	MMP-7 IL-12 Rβ2	0.949	0.897	1.846	0.942
99	MMP-7	SLPI Contactin-1	C9 RGM-C	HSP 90α MCP-3	α2-Antiplas-min MRC2	HGF IL-13 Rα1	0.962	0.892	1.854	0.944
100	SAP	C9 MCP-3	SLPI RGM-C	MMP-7 HSP 90α	HGF SCF sR	MRC2 IL-18 Rβ	0.962	0.887	1.849	0.943

Marker	Count	Marker	Count
SLPI	100	Troponin T	7
MMP-7	100	Kallistatin	7
HGF	100	Coagulation Factor Xa	7
C9	94	Thrombin/Prothrombin	6
RGM-C	92	IL-18 Rβ	6
SAP	81	IL-13 Rα1	6
MCP-3	77	IL-12 Rβ2	6
MRC2	60	Hat1	6
Cadherin-5	51	Growth hormone receptor	6
BAFF Receptor	31	ERBB1	6
Contactin-4	28	C5	6
α2-Antiplasmin	27	ARSB	6
Contactin-1	23	α2-HS-Glycoprotein	5
Properdin	21	α1-Antitrypsin	5
HSP 90α	19	TIMP-2	5
SCF sR	17	RBP	5
ADAM 9	17	Prekallikrein	5
C2	14	PCI	5
NRP1	12	MIP-5	5
sL-Selectin	8	LY9	5
C6	8	Kallikrein 6	5

[0365]

TABLE 11

100 Panels of 12 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers						Sensitivity	Specificity	Sensitivity + Specificity	AUC
1	Cadherin-5 RGM-C	HGF MRC2	SLPI MCP-3	C9 BAFF Receptor	MMP-7 ADAM 9	Properdin SAP	0.962	0.918	1.879	0.944
2	SAP MCP-3	C9 RGM-C	SLPI α2-Antiplas-min	MMP-7 BAFF Receptor	HGF ARSB	MRC2 C2	0.949	0.908	1.856	0.942
3	SAP MCP-3	C9 BAFF Receptor	SLPI Properdin	MMP-7 RGM-C	HGF C5	MRC2 ADAM 9	0.962	0.908	1.869	0.942
4	SAP MCP-3	C9 BAFF Receptor	SLPI Properdin	MMP-7 RGM-C	HGF C6	MRC2 ADAM 9	0.949	0.918	1.867	0.940
5	HGF MCP-3	SLPI Contactin-4	C9 RGM-C	Coagulation Factor Xa MIP-5	MMP-7 BAFF Receptor	SAP Contactin-1	0.974	0.897	1.872	0.941
6	Cadherin-5 SAP	MMP-7 Coagulation Factor Xa	C9 C2	RGM-C α2-Antiplas-min	SLPI ERBB1	HGF NRP1	0.962	0.897	1.859	0.951
7	Cadherin-5 SAP	HGF Contactin-1	SLPI RGM-C	C9 MCP-3	MMP-7 BAFF Receptor	Growth hor-mone re-ceptor	0.974	0.892	1.867	0.943

TABLE 11-continued

						Kallistatin				
8	RGM-C	MCP-3	C9	MMP-7	SLPI	Contactin-1	0.974	0.897	1.872	0.944
	HGF	BAFF Receptor	Kallistatin	SAP	HSP 90α	Cadherin-5				
9	MMP-7	LY9	SLPI	RGM-C	MRC2	HGF	0.962	0.897	1.859	0.940
	SAP	Cadherin-5	MCP-3	α2-Antiplas-min	C9	Hat1				
10	HGF	SLPI	C9	Coagulation	MMP-7	SAP	0.949	0.908	1.856	0.946
	MCP-3	Contactin-4	RGM-C	Factor Xa	SCF sR	IL-12 Rβ2				
				Cadherin-5						
11	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.962	0.897	1.859	0.940
	MCP-3	BAFF Receptor	Properdin	RGM-C	IL-13 Rα1	Contactin-4				
12	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.962	0.897	1.859	0.944
	MCP-3	RGM-C	α2-Antiplas-min	BAFF Receptor	IL-18 Rβ	C2				
13	Cadherin-5	α2-Antiplas-min	C9	SLPI	MCP-3	HGF	0.962	0.903	1.864	0.948
	RGM-C	Contactin-4	MMP-7	SAP	Kallikrein 6	MRC2				
14	RGM-C	MRC2	SLPI	C9	MMP-7	MCP-3	0.962	0.897	1.859	0.940
	sL-Selectin	HGF	ADAM 9	BAFF Receptor	SAP	PCI				
15	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.962	0.913	1.874	0.945
	MCP-3	RGM-C	Cadherin-5	Prekallikrein	BAFF Receptor	ADAM 9				
16	RGM-C	MRC2	SLPI	C9	MMP-7	SAP	0.962	0.913	1.874	0.939
	BAFF Receptor	HGF	Properdin	ADAM 9	Cadherin-5	RBP				
17	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.949	0.913	1.862	0.940
	MCP-3	BAFF Receptor	Prekallikrein	HSP 90α	Cadherin-5	TIMP-2				
18	Cadherin-5	HGF	SLPI	C9	MMP-7	Properdin	0.962	0.918	1.879	0.947
	RGM-C	MRC2	MCP-3	BAFF Receptor	Thrombin/Pro-thrombin	SAP				
19	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.962	0.903	1.864	0.943
	MCP-3	RGM-C	Contactin-4	SCF sR	Troponin T					
20	RGM-C	MRC2	SLPI	C9	MMP-7	HGF	0.949	0.913	1.862	0.934
	ADAM 9	SAP	BAFF Receptor	Cadherin-5	α1-Antitrypsin					
21	SAP	MRC2	SLPI	RGM-C	MCP-3	MMP-7	0.949	0.918	1.8670.942	
	sL-Selectin	HGF	ADAM 9	α2-HS-Gly-coprotein	HSP 90α	Cadherin-5				
22	SAP	C9	SLPI	MMP-7	HGF	RGM-C	0.962	0.892	1.854	0.938
	SCF sR	MCP-3	Contactin-4	ADAM 9	ARSB	Properdin				
23	RGM-C	MRC2	SLPI	C9	MMP-7	HGF	0.962	0.903	1.864	0.943
	ADAM 9	SAP	BAFF Receptor	Cadherin-5	MCP-3	C5				
24	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.949	0.918	1.867	0.946
	MCP-3	RGM-C	α2-Antiplas-min	BAFF Receptor	C6	sL-Selectin				
25	SAP	C9	SLPI	MMP-7	HGF	RGM-C	0.962	0.897	1.859	0.946
	NRP1	MRC2	Thrombin/Pro-thrombin	sL-Selectin	ERBB1	MCP-3				
26	RGM-C	MCP-3	C9	MMP-7	SLPI	Contactin-1	0.962	0.903	1.864	0.940
	HGF	Contactin-4	SAP	BAFF Receptor	Growth hor-mone receptor	ADAM 9				
27	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.949	0.903	1.851	0.939
	MCP-3	RGM-C	α2-Antiplas-min	BAFF Receptor	Hat1	Cadherin-5				
28	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.949	0.903	1.851	0.942
	MCP-3	BAFF Receptor	Properdin	RGM-C	IL-12 Rβ2	Coagulation Factor Xa				
29	RGM-C	MRC2	SLPI	C9	MMP-7	MCP-3	0.962	0.897	1.859	0.941
	α2-Antiplas-min	BAFF Receptor	HGF	ADAM 9	SAP	IL-13 Rα1				
30	Cadherin-5	HGF	SLPI	C9	MMP-7	α2-HS-Gly-coprotein	0.962	0.892	1.854	0.947
	α2-Antiplas-min	Contactin-1	RGM-C	C2	IL-18 Rβ	Properdin				
31	RGM-C	MRC2	SLPI	C9	MMP-7	MCP-3	0.962	0.903	1.864	0.947
	α2-Antiplas-min	BAFF Receptor	HGF	Cadherin-5	SAP	Kallikrein 6				
32	NRP1	LY9	C9	SLPI	MMP-7	RGM-C	0.962	0.903	1.864	0.945
	MRC2	HGF	Contactin-1	Thrombin/Pro-thrombin	SAP	Growth hor-mone re-ceptor				
33	RGM-C	MCP-3	C9	MMP-7	SLPI	Contactin-1	0.974	0.892	1.867	0.943
	HGF	BAFF Receptor	Cadherin-5	SAP	MIP-5	Contactin-4				
34	Cadherin-5	HGF	SLPI	C9	MMP-7	MCP-3	0.949	0.908	1.856	0.944
	RGM-C	Contactin-1	SCF sR	PCI	SAP	Coagulation Factor Xa				
35	RGM-C	SLPI	RBP	C9	MMP-7	SAP	0.962	0.908	1.869	0.942
	HGF	sL-Selectin	MRC2	MCP-3	BAFF Receptor	Properdin				
36	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.962	0.897	1.859	0.941
	MCP-3	RGM-C	α2-Antiplas-	BAFF Receptor	IL-13 Rα1	TIMP-2				

TABLE 11-continued

			min							
37	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.962	0.897	1.859	0.943
	MCP-3	RGM-C	α2-Antiplas-min	BAFF Receptor	Kallistatin	Troponin T				
38	MMP-7	C9	Contactin-1	SLPI	HGF	SAP	0.962	0.892	1.854	0.931
	HSP 90α	MCP-3	RGM-C	ADAM 9	MRC2	α1-Antitryp-sin				
39	SAP	C9	SLPI	MMP-7	HGF	RGM-C	0.949	0.903	1.851	0.939
	SCF sR	MCP-3	Contactin-4	ADAM 9	ARSB	LY9				
40	RGM-C	MRC2	SLPI	C9	MMP-7	MCP-3	0.962	0.903	1.864	0.941
	HGF	BAFF Receptor	SAP	Kallistatin	ADAM 9	C5				
41	Cadherin-5	α2-Antiplas-min	C9	SLPI	MCP-3	HGF	0.949	0.913	1.862	0.949
	RGM-C	Contactin-4	MMP-7	SAP	Properdin	C6				
42	HGF	SLPI	C9	Coagulation	MMP-7	SAP	0.962	0.892	1.854	0.942
	MCP-3	RGM-C	MRC2	Factor Xa	ERBB1	C2				
				ADAM 9						
43	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.962	0.887	1.849	0.934
	α2-Antiplas-min	RGM-C	LY9	Hat1	MCP-3	ADAM 9				
44	MRC2	LY9	SLPI	MMP-7	SAP	HGF	0.949	0.903	1.851	0.940
	NRP1	Thrombin/Pro-thrombin	Contactin-4	RGM-C	Growth hor-mone receptor	IL-12 Rβ2				
45	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.949	0.903	1.851	0.946
	MCP-3	RGM-C	α2-Antiplas-min	BAFF Receptor	IL-18 Rβ	Cadherin-5				
46	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.962	0.903	1.864	0.944
	MCP-3	RGM-C	Contactin-4	NRP1	SCF sR	Kallikrein 6				
47	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.962	0.903	1.864	0.944
	MCP-3	BAFF Receptor	Properdin	RGM-C	MIP-5	Cadherin-5				
48	HGF	SLPI	C9	Coagulation	MMP-7	SAP	0.949	0.908	1.856	0.945
	MCP-3	Contactin-4	RGM-C	Factor Xa	SCF sR	PCI				
				Cadherin-5						
49	Cadherin-5	Prekallikrein	MCP-3	SLPI	MMP-7	0.962	0.908	1.869	0.946	
	C9	HSP 90α	HGF	Kallistatin	RGM-C	Contactin-4				
50	RGM-C	MRC2	SLPI	C9	MMP-7	HGF	0.949	0.918	1.867	0.942
	SCF sR	MCP-3	ADAM 9	SAP	Properdin	RBP				
51	MRC2	NRP1	SLPI	C9	HGF	MMP-7	0.949	0.908	1.856	0.942
	RGM-C	Properdin	SAP	BAFF Receptor	Cadherin-5	TIMP-2				
52	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.962	0.897	1.859	0.945
	MCP-3	RGM-C	α2-Antiplas-min	BAFF Receptor	Troponin T	C2				
53	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.962	0.892	1.854	0.929
	MCP-3	RGM-C	HSP 90α	α1-Antitrypsin	BAFF Receptor	MIP-5				
54	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.962	0.903	1.864	0.942
	MCP-3	HSP 90α	Cadherin-5	α2-HS-Gly-coprotein	RGM-C	BAFF Re-ceptor				
55	Contactin-4	MCP-3	SLPI	C9	HGF	MMP-7	0.949	0.903	1.851	0.938
	MRC2	RGM-C	ADAM 9	Properdin	SAP	ARSB				
56	HGF	SLPI	C9	Coagulation	MMP-7	SAP	0.962	0.903	1.864	0.946
	MCP-3	Contactin-4	RGM-C	Factor Xa	SCF sR	C5				
				Cadherin-5						
57	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.936	0.923	1.859	0.943
	MCP-3	BAFF Receptor	Properdin	RGM-C	C6	SCF sR				
58	HGF	SLPI	C9	Coagulation	MMP-7	SAP	0.962	0.892	1.854	0.939
	MCP-3	RGM-C	MRC2	Factor Xa	ERBB1	MIP-5				
				ADAM 9						
59	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.936	0.913	1.849	0.939
	α2-Antiplas-min	RGM-C	LY9	Hat1	MCP-3	SCF sR				
60	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.949	0.903	1.851	0.942
	MCP-3	RGM-C	HSP 90α	Contactin-1	Properdin	IL-12 Rβ2				
61	HGF	Contactin-4	SLPI	C9	α2-Antiplas-min	MMP-7	0.962	0.897	1.859	0.943
	RGM-C	BAFF Receptor	SAP	MRC2	MCP-3	IL-13 Rα1				
62	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.949	0.903	1.851	0.944
	MCP-3	RGM-C	α2-Antiplas-min	BAFF Receptor	IL-18 Rβ	Contactin-1				
63	Cadherin-5	α2-Antiplas-min	C9	SLPI	MCP-3	HGF	0.962	0.897	1.859	0.947
	RGM-C	Contactin-4	MMP-7	SAP	Kallikrein 6	Contactin-1				
64	Contactin-4	MCP-3	SLPI	C9	HGF	HSP 90α	0.962	0.892	1.854	0.941
	MMP-7	SAP	Cadherin-5	BAFF Receptor	RGM-C	PCI				
65	RGM-C	MRC2	SLPI	C9	MMP-7	SAP	0.962	0.908	1.869	0.943
	BAFF Receptor	HGF	Properdin	ADAM 9	Prekallikrein	Cadherin-5				
66	Cadherin-5	HGF	SLPI	C9	MMP-7	Properdin	0.962	0.903	1.864	0.942

TABLE 11-continued

	RGM-C	MRC2	MCP-3	BAFF Receptor	RBP	SAP				
67	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.962	0.892	1.854	0.938
	MCP-3	RGM-C	Contactin-4	NRP1	BAFF Receptor	TIMP-2				
68	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.962	0.897	1.859	0.945
	MCP-3	RGM-C	Cadherin-5	C2	BAFF Receptor	Troponin T				
69	MMP-7	Coagulation	C9	RGM-C	Cadherin-5	SLPI	0.949	0.903	1.851	0.936
	SCF sR	Factor Xa	SAP	MCP-3	Prekallikrein	α1-Antitryp-				
		HGF				sin				
70	RGM-C	MCP-3	C9	MMP-7	SLPI	Contactin-1	0.962	0.903	1.864	0.944
	HGF	BAFF Receptor	Cadherin-5	SAP	α2-HS-Gly-	Contactin-4				
					coprotein					
71	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.949	0.903	1.851	0.941
	MCP-3	RGM-C	Contactin-4	NRP1	SCF sR	ARSB				
72	HGF	SLPI	C9	Coagulation	MMP-7	SAP	0.974	0.887	1.862	0.940
	MCP-3	Contactin-4	RGM-C	Factor Xa	BAFF Receptor	C5				
				Kallistatin						
73	HGF	Contactin-4	SLPI	C9	α2-Antiplas-	MMP-7	0.962	0.897	1.859	0.944
	RGM-C	C6	Cadherin-5	BAFF Receptor	min	MIP-5				
					SAP					
74	Cadherin-5	MMP-7	C9	RGM-C	SLPI	HGF	0.962	0.892	1.854	0.951
	SAP	Coagulation	C2	α2-Antiplas-	ERBB1	Properdin				
		Factor Xa		min						
75	HGF	SCF sR	C9	SLPI	MCP-3	RGM-C	0.962	0.903	1.864	0.942
	SAP	Growth hor-	Contactin-1	MMP-7	Contactin-4	ADAM 9				
		mone receptor								
76	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.949	0.897	1.846	0.937
	MCP-3	RGM-C	α2-Antiplas-	BAFF Receptor	Hat1	Kallistatin				
			min							
77	RGM-C	MRC2	SLPI	C9	MMP-7	MCP-3	0.949	0.903	1.851	0.940
	HGF	BAFF Receptor	Contactin-4	Cadherin-5	IL-13 Rα1	IL-12 Rβ2				
78	SAP	MRC2	SLPI	RGM-C	MMP-7	Properdin	0.949	0.903	1.851	0.942
	Cadherin-5	HGF	Prekallikrein	MCP-3	BAFF Receptor	IL-18 Rβ				
79	MRC2	α2-Antiplas-	C9 SLPI	MCP-3	HGF	0.962	0.897	1.859	0.946	
	MMP-7	min	SAP	HSP 90α	RGM-C	Contactin-1				
		Kallikrein 6								
80	Contactin-4	MCP-3	SLPI	C9	HGF	MMP-7	0.962	0.892	1.854	0.938
	MRC2	RGM-C	ADAM 9	BAFF Receptor	SAP	PCI				
81	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.962	0.903	1.864	0.938
	MCP-3	HSP 90α	Cadherin-5	ADAM 9	RBP	Properdin				
82	RGM-C	MRC2	SLPI	C9	MMP-7	HGF	0.962	0.892	1.854	0.941
	ADAM 9	SAP	BAFF Receptor	Cadherin-5	MCP-3	TIMP-2				
83	Contactin-4	MCP-3	SLPI	C9	HGF	MMP-7	0.949	0.918	1.867	0.946
	MRC2	RGM-C	Thrombin/Pro-	NRP1	Cadherin-5	SAP				
			thrombin							
84	Cadherin-5	HGF	SLPI	C9	MMP-7	MCP-3	0.962	0.897	1.859	0.941
	RGM-C	Contactin-1	MRC2	ADAM 9	HSP 90α	Troponin T				
85	RGM-C	MRC2	SLPI	C9	MMP-7	HGF	0.949	0.903	1.851	0.931
	ADAM 9	SAP	BAFF Receptor	α1-Antitrypsin	MCP-3	C5				
86	Cadherin-5	HGF	SLPI	C9	MMP-7	Properdin	0.949	0.913	1.862	0.944
	RGM-C	MRC2	MCP-3	BAFF Receptor	α2-HS-Gly-	SAP				
					coprotein					
87	SAP	C9	SLPI	MMP-7	HGF	RGM-C	0.962	0.887	1.849	0.937
	SCF sR	MCP-3	Contactin-4	ADAM 9	ARSB	Kallikrein 6				
88	SAP	MMP-7	α2-Antiplas-	SLPI	RGM-C	C9	0.962	0.897	1.859	0.945
	HGF	BAFF Receptor	min	C6	SCF sR	MCP-3				
			Cadherin-5							
89	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.962	0.892	1.854	0.939
	MCP-3	ERBB1	RGM-C	ADAM 9	α2-HS-Gly-	Contactin-1				
					coprotein					
90	RGM-C	Contactin-4	SLPI	SAP	MMP-7	Growth hor-	0.949	0.913	1.862	0.946
	C9	HGF	NRP1	MRC2	α2-Antiplas-	mone re-				
					min	ceptor				
						MCP-3				
91	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.949	0.897	1.846	0.934
	MCP-3	RGM-C	Cadherin-5	LY9	ADAM 9	Hat1				
92	Contactin-4	MCP-3	SLPI	C9	HGF	MMP-7	0.949	0.903	1.851	0.940
	MRC2	RGM-C	ADAM 9	BAFF Receptor	SAP	IL-12 Rβ2				
93	MMP-7	SLPI	C9	HSP 90α	α2-Antiplas-	HGF	0.962	0.897	1.859	0.946
	Contactin-1	RGM-C	MCP-3	MRC2	min	SAP				
					IL-13 Rα1					
94	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.949	0.903	1.851	0.943
	MCP-3	RGM-C	Contactin-4	NRP1	SCF sR	IL-18 Rβ				
95	RGM-C	MCP-3	C9	MMP-7	SLPI	Contactin-1	0.962	0.892	1.854	0.941
	HGF	BAFF Receptor	Cadherin-5	SAP	HSP 90α	PCI				
96	SAP	C9	SLPI	MMP-7	HGF	MRC2	0.962	0.903	1.864	0.940
	MCP-3	HSP 90α	Cadherin-5	ADAM 9	RBP	RGM-C				

TABLE 11-continued

97	SAP MCP-3	C9 RGM-C	SLPI α2-Antiplas-min	MMP-7 BAFF Receptor	HGF Kallistatin	MRC2 TIMP-2	0.949	0.903	1.851	0.945
98	SAP NRP1	C9 MRC2	SLPI Contactin-1	MMP-7 MCP-3	HGF Thrombin/Pro-thrombin	RGM-C sL-Selectin	0.962	0.903	1.864	0.946
99	SAP MCP-3	C9 RGM-C	SLPI α2-Antiplas-min	MMP-7 BAFF Receptor	HGF Troponin T	MRC2 Cadherin-5	0.949	0.908	1.856	0.946
100	RGM-C ADAM 9	MRC2 SAP	SLPI BAFF Receptor	C9 α1-Antitrypsin	MMP-7 MCP-3	HGF Coagulation Factor Xa	0.949	0.903	1.851	0.932

Marker	Count	Marker	Count
SLPI	100	LY9	7
MMP-7	100	sL-Selectin	6
HGF	100	α2-HS-Glycoprotin	6
RGM-C	98	α1-Antitrypsin	6
SAP	97	Troponin T	6
C9	97	Thrombin/Prothrombin	6
MCP-3	91	TIMP-2	6
MRC2	74	RBP	6
BAFF Receptor	57	Prekallikrein	6
Cadherin-5	48	PCI	6
ADAM 9	33	MIP-5	6
Contactin-4	32	Kallikrein 6	6
α2-Antiplasmin	29	IL-18 Rβ	6
Properdin	23	IL-13 Rα1	6
Contactin-1	20	IL-12 Rβ2	6
SCF sR	17	Hat1	6
HSP 90α	15	Growth hormone receptor	6
NRP1	13	ERBB1	6
Coagulation Factor Xa	13	C6	6
Kallistatin	8	C5	6
C2	8	ARSB	6

[0366]

TABLE 12

100 Panels of 13 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
1	SAP	C9 MRC2 C2	SLPI MCP-3 BAFF Receptor	MMP-7 RGM-C ADAM 9	HGF Cadherin-5 Prekallikrein	0.962	0.918	1.879	0.946
2	SAP	C9 MRC2 BAFF Receptor	SLPI MCP-3 ARSB	MMP-7 RGM-C C2	HGF α2-Antiplasmin C5	0.962	0.903	1.864	0.943
3	RGM-C	MRC2 HGF Prekellikrein	SLPI ADAM 9 C5	C9 SAP BAFF Receptor	MMP-7 MCP-3 C6	0.962	0.908	1.869	0.941
4	RGM-C	MCP-3 Contactin-1 BAFF Receptor	C9 HGF Coagulation Factor Xa	MMP-7 Contactin-4 HSP 90α	SLPI SAP Cadherin-5	0.974	0.892	1.867	0.943
5	HGF	SCF sR Cadherin-5 Growth hormone receptor	C9 SAP sL-Selectin	SLPI MCP-3 C2	MMP-7 RGM-C ERBB1	0.949	0.913	1.862	0.945
6	SAP	C9 MRC2 BAFF Receptor	SLPI MCP-3 Hat1	MMP-7 RGM-C Cadherin-5	HGF α2-Antiplasmin LY9	0.962	0.897	1.859	0.936
7	MMP-7	SLPI HGF Prekallikrein	C9 BAFF Receptor Cadherin-5	MCP-3 ADAM 9 IL-12 Rβ2	MRC2 SAP RGM-C	0.949	0.918	1.867	0.945
8	SAP	C9 MRC2 BAFF Receptor	SLPI MCP-3 IL-13 Rα1	MMP-7 RGM-C Cadherin-5	HGF α2-Antiplasmin ADAM 9	0.962	0.908	1.869	0.943

TABLE 12-continued

9	RGM-C	MRC2 MCP-3 BAFF Receptor	SLPI sL-Selectin SAP	C9 HGF Cadherin-5	MMP-7 ADAM 9 IL-18 Rβ	0.962	0.892	1.854	0.942
10	RGM-C	Contactin-4 Growth hormone receptor Cadherin-5	SLPI C9 ADAM 9	SAP HGF SCF sR	MMP-7 MCP-3 Kallikrein 6	0.962	0.908	1.869	0.942
11	Contactin-4	MCP-3 HSP 90α RGM-C	SLPI MMP-7 Kallistatin	C9 SAP C5	HGF Cadherin-5 BAFF Receptor	0.974	0.897	1.872	0.943
12	SAP	C9 MRC2 BAFF Receptor	SLPI MCP-3 IL-13 Rα1	MMP-7 RGM-C Cadherin-5	HGF α2-Antiplasmin MIP-5	0.962	0.908	1.869	0.945
13	SAP	C9 MRC2 RGM-C	SLPI MCP-3 HSP 90α	MMP-7 BAFF Receptor Cadherin-5	HGF Properdin NRP1	0.962	0.913	1.874	0.942
14	MMP-7	SLPI HGF Contactin-1	C9 BAFF Receptor RGM-C	MCP-3 ADAM 9 PCI	MRC2 SAP sL-Selectin	0.962	0.897	1.859	0.942
15	RGM-C	MRC2 MCP-3 ADAM 9	SLPI HGF SAP	C9 BAFF Receptor RBP	MMP-7 Properdin Cadherin-5	0.962	0.913	1.874	0.942
16	SAP	C9 MRC2 BAFF Receptor	SLPI MCP-3 Kallistatin	MMP-7 RGM-C TIMP-2	HGF α2-Antiplasmin LY9	0.962	0.903	1.864	0.941
17	RGM-C	MRC2 MCP-3 Thrombin/Pro-thrombin	SLPI HGF Contactin-1	C9 BAFF Receptor IL-13 Rα1	MMP-7 Cadherin-5 SAP	0.962	0.908	1.869	0.944
18	SAP	C9 MRC2 BAFF Receptor	SLPI MCP-3 Tropinin T	MMP-7 RGM-C C2	HGF α2-Antiplasmin C5	0.962	0.903	1.864	0.945
19	RGM-C	MRC2 HGF Cadherin-5	SLPI ADAM 9 MCP-3	C9 SAP HSP 90α	MMP-7 BAFF Receptor α1-Antitrypsin	0.949	0.903	1.851	0.932
20	SAP	C9 MRC2 α2-HS-Glyco-protein	SLPI MCP-3 RGM-C	MMP-7 BAFF Receptor ADAM 9	HGF Prekallikrein Cadherin-5	0.962	0.913	1.874	0.944
21	HGF	SCF sR RGM-C MMP-7	C9 SAP receptor Contactin-4	SLPI Growth hormone ADAM 9	MCP-3 Contactin-1 ARSB	0.962	0.903	1.864	0.938
22	SAP	C9 MRC2 RGM-C	SLPI MCP-3 C6	MMP-7 BAFF Receptor ADAM 9	HGF Properdin C5	0.962	0.908	1.869	0.941
23	SAP	C9 RGM-C MCP-3	SLPI BAFF Receptor MRC2	MMP-7 Properdin Coagulation Factor Xa	HGF Cadherin-5 ADAM 9	0.962	0.903	1.864	0.945
24	SAP	C9 MRC2 BAFF Receptor	SLPI MCP-3 LY9	MMP-7 RGM-C C2	HGF α2-Antiplasmin ERBB1	0.962	0.897	1.859	0.940
25	MMP-7	LY9 HGF α2-Antiplasmin	SLPI SAP C9	RGM-C Cadherin-5 MIP-5	MRC2 MCP-3 Hat1	0.962	0.892	1.854	0.939
26	Cadherin-5	MMP-7 HGF IL-12 Rβ2	C9 MRC2 BAFF Receptor	RGM-C HSP 90α MCP-3	SLPI ADAM 9 Contactin-4	0.949	0.913	1.862	0.940
27	SAP	C9 MRC2 BAFF Receptor	SLPI MCP-3 IL-18 Rβ	MMP-7 RGM-C Cadherin-5	HGF α2-Antiplasmin sL-Selectin	0.949	0.903	1.851	0.946
28	Cadherin-5	HGF MCP-3 MRC2	SLPI RGM-C α2-Antiplasmin	C9 Contactin-1 BAFF Receptor	MMP-7 SAP Kallikrein 6	0.962	0.908	1.869	0.946
29	SAP	C9 RGM-C MCP-3	SLPI BAFF Receptor MRC2	MMP-7 Properdin sL-Selectin	HGF Cadherin-5 NRP1	0.962	0.908	1.869	0.945
30	HGF	SLPI SAP Cadherin-5	C9 MCP-3 BAFF Receptor	Coagulation Factor Xa Contactin-4 PCI	MMP-7 RGM-C HSP 90α	0.962	0.897	1.859	0.940
31	Cadherin-5	MMP-7 HGF MCP-3	C9 SAP MRC2	RGM-C Properdin RBP	SLPI HSP 90α ADAM 9	0.962	0.908	1.869	0.940
32	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.897	1.859	0.943

TABLE 12-continued

		MCP-3	HGF	BAFF Receptor	ADAM 9				
		Coagulation Factor Xa	Cadherin-5	SAP	TIMP-2				
33	SAP	C9	SLPI	MMP-7	HGF	0.949	0.918	1.867	0.945
		MRC2	MCP-3	RGM-C	Cadherin-5				
		Properdin	NRP1	Thrombin/Pro-thrombin	BAFF Receptor				
34	SAP	C9	SLPI	MMP-7	HGF	0.949	0.913	1.862	0.939
		MRC2	MCP-3	HSP 90α	Cadherin-5				
		ADAM 9	RBP	Contactin-1	Troponin T				
35	SAP	C9	SLPI	MMP-7	HGF	0.949	0.903	1.851	0.932
		MRC2	MCP-3	RGM-C	HSP 90α				
		α1-Antitrypsin	BAFF Receptor	MIP-5	Cadherin-5				
36	SAP	C9	SLPI	MMP-7	HGF	0.962	0.908	1.869	0.944
		MRC2	MCP-3	Contactin-1	RGM-C				
		α2-HS-Glyco-protein	BAFF Receptor	α2-Antiplasmin	MIP-5				
37	SAP	C9	SLPI	MMP-7	HGF	0.949	0.908	1.856	0.939
		RGM-C	SCF sR	MCP-3	Contactin-4				
		ADAM 9	ARSB	LY9	Properdin				
38	Cadherin-5	α2-Antiplasmin	C9	SLPI	MCP-3	0.949	0.918	1.867	0.949
		HGF	RGM-C	Contactin-4	MMP-7				
		Contactin-1	SAP	Properdin	C6				
39	Cadherin-5	MMP-7	C9	RGM-C	SLPI	0.962	0.897	1.859	0.951
		HGF	SAP	Coagulation	C2				
		α2-Antiplasmin	ERBB1	Factor Xa	NRP1				
				Properdin					
40	SAP	C9	SLPI	MMP-7	HGF	0.949	0.903	1.851	0.939
		MRC2	MCP-3	RGM-C	α2-Antiplasmin				
		BAFF Receptor	Hat1	Cadherin-5	C5				
41	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.897	1.859	0.942
		HGF	ADAM 9	SAP	BAFF Receptor				
		Cadherin-5	MCP-3	HSP 90α	IL-12 Rβ2				
42	HGF	Contactin-4	SLPI	C9	α2-Antiplasmin	0.949	0.903	1.851	0.946
		MMP-7	RGM-C	C6	Cadherin-5				
		MCP-3	SAP	C2	IL-18 Rβ				
43	MMP-7	LY9	SLPI	RGM-C	MRC2	0.962	0.903	1.864	0.938
		HGF	SAP	ADAM 9	Kallistatin				
		MCP-3	BAFF Receptor	Cadherin-5	Kallikrein 6				
44	SAP	C9	SLPI	MMP-7	HGF	0.949	0.908	1.856	0.941
		RGM-C	BAFF Receptor	Properdin	Cadherin-5				
		MCP-3	MRC2	PCI	HSP 90α				
45	SAP	C9	SLPI	MMP-7	HGF	0.962	0.897	1.859	0.942
		MRC2	MCP-3	RGM-C	α2-Antiplasmin				
		BAFF Receptor	TIMP-2	Contactin-1	IL-13 Rα1				
46	SAP	C9	SLPI	MMP-7	HGF	0.962	0.9033	1.864	0.941
		RGM-C	NRP1	MRC2	Contactin-1				
		MCP-3	Thrombin/Pro-thrombin	Contactin-4	ADAM 9				
47	SAP	C9	SLPI	MMP-7	HGF	0.949	0.913	1.862	0.946
		RGM-C	BAFF Receptor	Properdin	Cadherin-5				
		MCP-3	MRC2	α2-Antiplasmin	Troponin T				
48	SAP	C9	SLPI	MMP-7	HGF	0.949	0.903	1.851	0.931
		MRC2	MCP-3	BAFF Receptor	Prekallikrein				
		α2-HS-Glyco-protein	RGM-C	ADAM 9	α1-Antitrypsin				
49	Contactin-4	MCP-3	SLPI	C9	HGF	0.949	0.908	1.856	0.940
		MMP-7	MRC2	RGM-C	ADAM 9				
		Properdin	SAP	ARSB	C5				
50	SAP	C9	SLPI	MMP-7	HGF	0.962	0.897	1.859	0.943
		MRC2	MCP-3	RGM-C	Thrombin/Pro-thrombin				
		ERBB1	NRP1	ADAM 9	Cadherin-5				
51	HGF	MMP-7	α2-Antiplasmin	C9	SLPI	0.962	0.908	1.869	0.952
		C2	RGM-C	Contactin-1	Cadherin-5				
		sL-Selectin	NRP1	SAP	Growth hormone receptor				
52	SAP	C9	SLPI	MMP-7	HGF	0.949	0.903	1.851	0.936
		MRC2	MCP-3	RGM-C	α2-Antiplasmin				
		BAFF Receptor	Growth hormone receptor	Contactin-1	Hat1				
53	Cadherin-5	MMP-7	C9	RGM-C	SLPI	0.949	0.908	1.856	0.942
		HGF	SAP	Properdin	HSP 90α				
		MCP-3	MRC2	IL-12 Rβ2	BAFF Receptor				
54	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.887	1.849	0.943
		MCP-3	HGF	BAFF Receptor	SAP				

TABLE 12-continued

		Coagulation Factor Xa	C2	IL-18 Rβ	α2-Antiplasmin				
55	MRC2	α2-Antiplasmin HGF HSP 90α	C9 MMP-7 RGM-C	SLPI Kallikrein 6 Cadherin-5	MCP-3 SAP MIP-5	0.974	0.887	1.862	0.947
56	HSP 90α	SLPI SAP Cadherin-5	C9 HGF BAFF Receptor	RGM-C Kallistatin Prekallikrein	MMP-7 MCP-3 Contactin-1	0.962	0.908	1.869	0.944
57	HGF	SLPI SAP Cadherin-5	C9 MCP-3 C2	Coagulation Factor Xa Contactin-4 sL-Selectin	MMP-7 RGM-C PCI	0.949	0.908	1.856	0.945
58	Cadherin-5	MMP-7 HGF MCP-3	C9 SAP MRC2	RGM-C Properdin RBP	SLPI HSP 90α BAFF Receptor	0.962	0.908	1.869	0.941
59	SAP	C9 MRC2 HSP 90α	SLPI MCP-3 Cadherin-5	MMP-7 BAFF Receptor RGM-C	HGF Prekallikrein RIMP-2	0.949	0.908	1.856	0.943
60	SAP	C9 MRC2 α2-HS-Glyco-protein	SLPI MCP-3 BAFF Receptor	MMP-7 Contactin-1 α2-Antiplasmin	HGF RGM-C Troponin T	0.962	0.897	1.859	0.942
61	RGM-C	MRC2 HGF Cadherin-5	SLPI ADAM 9 MCP-3	C9 SAP α1-Antitrypsin	MMP-7 BAFF Receptor HSP 90α	0.949	0.903	1.851	0.932
62	SAP	C9 MRC2 SCF sR	SLPI MCP-3 ADAM 9	MMP-7 RGM-C C2	HGF HSP 90α ARSB	0.949	0.908	1.856	0.939
63	MMP-7	Coagulation Factor Xa SLPI Kallistatin	C9 SCF sR SAP	RGM-C HGF sL-Selectin	Cadherin-5 MCP-3 C6	0.962	0.903	1.864	0.947
64	Cadherin-5	MMP-7 HGF α2-Antiplasmin	C9 SAP ERBB1	RGM-C Coagulation Factor Xa NRP1	SLPI C2 sL-Selectin	0.962	0.897	1.859	0.951
65	MMP-7	MY9 HGF α2-Antiplasmin	SLPI SAP C9	RGM-C Cadherin-5 Hat1	MRC2 MCP-3 ADAM 9	0.949	0.903	1.851	0.936
66	Contactin-4	MCP-3 HSP 90α RGM-C	SLPI MMP-7 Contactin-1	C9 SAP Prekallikrein	HGF Cadherin-5 IL-12 Rβ2	0.949	0.908	1.856	0.946
67	SAP	C9 RGM-C MCP-3	SLPI BAFF Receptor MRC2	MMP-7 Contactin-1 ADAM 9	HGF α2-Antiplasmin IL-13 Rα1	0.962	0.908	1.869	0.942
68	RGM-C	MRC2 MCP-3 C2	SLPI α2-Antiplasmin SAP	C9 BAFF Receptor HSP 90α	MMP-7 HGF IL-18 Rβ	0.962	0.887	1.849	0.943
69	MMP-7	SLPI HGF Contactin-1	C9 BAFF Receptor RGM-C	MCP-3 ADAM 9 Kallikrein 6	MRC2 SAP Coagulation Factor Xa	0.962	0.897	1.859	0.942
70	HGF	SCF sR Cadherin-5 Properdin	C9 SAP Coagulation Factor Xa	SLPI MCP-3 PCI	MMP-7 RGM-C Contactin-1	0.949	0.908	1.856	0.945
71	HGF	SCF sR Cadherin-5 Properdin	C9 SAP MRC2	SLPI MCP-3 RBP	MMP-7 RGM-C ADAM 9	0.949	0.918	1.867	0.943
72	RGM-C	MRC2 MCP-3 Kallistatin	SLPI HGF ADAM 9	C9 BAFF Receptor Prekallikrein	MMP-7 SAP TIMP-2	0.949	0.908	1.856	0.943
73	SAP	C9 MRC2 Prekallikrein	SLPI MCP-3 BAFF Receptor	MMP-7 RGM-C Thrombin/Pro-thrombin	HGF Cadherin-5 ADAM 9	0.962	0.903	1.864	0.947
74	SAP	C9 MRC2 NRP1	SLPI MCP-3 ADAM 9	MMP-7 RGM-C Thrombin/Pro-thrombin	HGF Contactin-4 Troponin T	0.962	0.897	1.859	0.940
75	RGM-C	MRC2 HGF α1-Antitrypsin	SLPI ADAM 9 MCP-3	C9 SAP Coagulation Factor Xa	MMP-7 BAFF Receptor Troponin T	0.9449	0.897	1.846	0.931
76	RGM-C	SLPI MCP-3	C9 α2-Antiplasmin	MMP-7 BAFF Receptor	0.962 HGF	0.908	1.869	0.945	

TABLE 12-continued

		Cadherin-5	SAP	MIP-5	α2-HS-Glyco-protein				
77	SAP	C9	SLPI	MMP-7	HGF	0.949	0.908	1.856	0.943
		MRC2	MCP-3	RGM-C	α2-Antiplasmin				
		BAFF Receptor	ARSB	C2	Contactin-1				
78	SAP	MMP-7	α2-Antiplasmin	SLPI	RGM-C	0.949	0.913	1.862	0.947
		Contactin-4	MCP-3	C9	HGF				
		BAFF Receptor	C6	Contactin-1	Cadherin-5				
79	Contactin-4	MCP-3	SLPI	C9	HGF	0.949	0.908	1.856	0.945
		MMP-7	MRC2	RGM-C	Thrombin/Pro-thrombin				
		NRP1	Cadherin-5	SAP	ERBB1				
80	Cadherin-5	SLPI	C9	MMP-7	0.962	0.903	1.864	0.942	
		MCP-3	RGM-C	BAFF Receptor	Contactin-4				
		Kallistatin	SAP	Growth hormone receptor	Properdin				
81	Cadherin-5	HGF	SLPI	C9	MMP-7	0.936	0.913	1.849	0.937
		MCP-3	RGM-C	Contactin-1	SAP				
		MRC2	NRP1	Contactin-4	Hat1				
82	MMP-7	SLPI	C9	MCP-3	MRC2	0.949	0.908	1.856	0.943
		HGF	BAFF Receptor	ADAM 9	SAP				
		Prekallikrein	Cadherin-5	IL-12 Rβ2	Coagulation Factor Xa				
83	MMP-7	LY9	SLPI	RGM-C	MRC2	0.962	0.908	1.869	0.937
		HGF	SAP	ADAM 9	Kallistatin				
		MCP-3	BAFF Receptor	IL-13 Rα1	Cadherin-5				
84	SAP	C9	SLPI	MMP-7	HGF	0.962	0.887	1.849	0.939
		MRC2	MCP-3	RGM-C	α2-Antiplasmin				
		BAFF Receptor	LY9	Contactin-4	IL-18 Rβ				
85	SAP	C9	SLPI	MMP-7	HGF	0.962	0.897	1.859	0.947
		MRC2	MCP-3	RGM-C	α2-Antiplasmin				
		sL-Selectin	BAFF Receptor	Kallikrein 6	Cadherin-5				
86	SAP	C9	SLPI	MMP-7	HGF	0.949	0.908	1.856	0.942
		MRC2	MCP-3	RGM-C	α2-Antiplasmin				
		BAFF Receptor	Growth hormone receptor	Contactin-1	PCI				
87	SAP	C9	SLPI	MMP-7	HGF	0.962	0.903	1.864	0.939
		MRC2	MCP-3	RGM-C	Contactin-4				
		NRP1	ADAM 9	RBP	SCF sR				
88	SAP	C9	SLPI	MMP-7	HGF	0.949	0.908	1.856	0.940
		MRC2	MCP-3	RGM-C	Contactin-4				
		NRP1	SCF sR	ADAM 9	TIMP-2				
89	RGM-C	MCP-3	C9	MMP-7	SLPI	0.949	0.897	1.846	0.931
		Contactin-1	HGF	Contactin-4	SAP				
		BAFF Receptor	Growth hormone receptor	ADAM 9	α1-Antitrypsin				
90	SAP	C9	SLPI	MMP-7	HGF	0.962	0.903	1.864	0.940
		MRC2	MCP-3	RGM-C	HSP 90α				
		SCF sR	ADAM 9	α2-HS-Glyco-protein	NRP1				
91	SAP	C9	SLPI	MMP-7	HGF	0.949	0.908	1.856	0.943
		MRC2	MCP-3	HSP 90α	Cadherin-5				
		ADAM 9	Prekallikrein	RGM-C	ARSB				
92	MMP-7	SLPI	C9	MCP-3	MRC2	0.949	0.913	1.862	0.945
		HGF	BAFF Receptor	ADAM 9	SAP				
		Prekallikrein	Cadherin-5	C6	RGM-C				
93	SAP	C9	SLPI	MMP-7	HGF	0.9622	0.892	1.854	0.940
		RGM-C	NRP1	MCR2	Contactin-1				
		MCP-3	Thrombin/Pro-thrombin	ADAM 9	ERBB1				
94	SAP	C9	SLPI	MMP-7	HGF	0.949	0.897	1.846	0.936
		MRC2	MCP-3	RGM-C	α2-Antiplasmin				
		BAFF Receptor	IL-13 Rα1	Cadherin-5	Hat1				
95	SAP	C9	SLPI	MMP-7	HGF	0.949	0.908	1.856	0.939
		MRC2	MCP-3	BAFF Receptor	Prekallikrein				
		HSP 90α	Cadherin-5	NRP1	IL-12 Rβ2				
96	MMP-7	SLPI	C9	HSP 90α	HGF	0.962	0.887	1.849	0.947
		MRC2	C2	MCP-3	RGM-C				
		α2-Antiplasmin	SAP	sL-Selectin	IL-18 Rβ				
97	SAP	C9	SLPI	MMP-7	HGF	0.962	0.897	1.859	0.939
		MRC2	MCP-3	RGM-C	α2-Antiplasmin				
		BAFF Receptor	LY9	Contactin-4	Kallikrein 6				
98	Cadherin-5	HGF	SLPI	C9	MMP-7	0.962	0.908	1.869	0.944
		MCP-3	RGM-C	Contactin-1	SAP				
		MRC2	NRP1	BAFF Receptor	MIP-5				
99	MMP-7	SLPI	C9	MCP-3	MRC2	0.962	0.892	1.854	0.939

TABLE 12-continued

100	SAP	HGF Contactin-1 C9 MRC2 α2-HS-Glyco-protein	BAFF Receptor RGM-C SLPI MCP-3 RGM-C	ADAM 9 PCI MMP-7 HSP 90α BAFF Receptor	SAP HSP 90α HGF Cadherin-5 RBP	0.962	0.903	1.864	0.940

Marker	Count	Marker	Count
SLPI	100	SCF sR	11
MMP-7	100	LY9	10
HGF	100	Thrombin/Prothrombin	8
SAP	99	Kallistatin	8
C9	98	Growth hormone receptor	8
RGM-C	97	α2-HS-Glycoprotein	7
MCP-3	97	RBP	7
MRC2	80	PCI	7
BAFF Receptor	68	MIP-5	7
Cadherin-5	65	Kallikrein 6	7
ADAM 9	44	IL-18 Rβ	7
α2-Antiplasmin	35	IL-13 Rα1	7
Contactin-1	26	IL-12 Rβ2	7
HSP 90α	26	Hat1	7
Contactin-4	23	ERBB1	7
Properdin	18	C6	7
NRP1	17	C5	7
C2	15	ARSB	7
Prekallikrein	14	α1-Antitrypsin	6
Coagulation Factor Xa	13	Troponin T	6
sL-Selectin	11	TIMP-2	6

[0367]

TABLE 18

100 Panels of 14 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
1	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.913	1.874	0.943
	SAP	BAFF Receptor	HGF	Properdin	ADAM 9				
		Cadherin-5	NRP1	Contactin-4	MCP-3				
2	MMP-7	SLPI	C9	Properdin	MRC2	0.949	0.913	1.862	0.940
	HGF	MCP-3	HSP 90α	RGM-C	C5				
		SAP	ADAM 9	SCF sR	ARSB				
3	MMP-7	SLPI	C9	MCP-3	MRC2	0.962	0.913	1.874	0.945
	HGF	BAFF Receptor	ADAM 9	SAP	Prekallikrein				
		Cadherin-5	HSP 90α	C2	RGM-C				
4	Cadherin-5	α2-Antiplasmin	C9	SLPI	MCP-3	0.949	0.923	1.872	0.948
	HGF	RGM-C	Contactin-4	MMP-7	Contactin-1				
		SAP	Properdin	C6	α2-HS-Glycoprotein				
5	RGM-C	MRC2	SLPI	C9	MMP-7	0.974	0.897	1.872	0.944
	MCP-3	α2-Antiplasmin	BAFF Receptor	HGF	C2				
		SAP	HSP 90α	Coagulation Factor Xa	MIP-5				
6	HGF	SCF sR	C9	SLPI	MMP-7	0.949	0.913	1.862	0.943
	Cadherin-5	SAP	MCP-3	RGM-C	Growth hormone receptor				
		sL-Selectin	C2	ERBB1	MIP-5				
7	SAP	C9	SLPI	MMP-7	HGF	0.962	0.903	1.864	0.937
	MRC2	MCP-3	RGM-C	α2-Antiplasmin	BAFF Receptor				
		Kallistatin	LY9	Cadherin-5	Hat1				
8	SAP	C9	SLPI	MMP-7	HGF	0.962	0.908	1.869	0.943
	MRC2	MCP-3	RGM-C	Cadherin-5	Prekallikrein				
		BAFF Receptor	ADAM 9	RBP	IL-12 Rβ2				
9	MRC2	α2-Antiplasmin	C9	SLPI	MCP-3	0.974	0.892	1.867	0.943
	HGF	MMP-7	HSP 90α	BAFF Receptor	RGM-C				
		SAP	IL-13 Rα1	MIP-5	Cadherin-5				
10	MRC2	α2-Antiplasmin	C9	SLPI	MCP-3	0.962	0.892	1.854	0.940
	HGF	MMP-7	HSP 90α	BAFF Receptor	RGM-C				
		SAP	IL-13 Rα1	Contactin-1	IL-18 Rβ				
11	Cadherin-5	HGF	SLPI	C9	MMP-7	0.962	0.908	1.869	0.945
	MCP-3	RGM-C	Contactin-1	SAP	MRC2				
		α2-Antiplasmin	BAFF Receptor	MIP-5	Kallikrein 6				
12	HGF	SLPI	C9	Coagulation Factor Xa	MMP-7	0.949	0.913	1.862	0.945
	SAP	MCP-3	Contactin-4	RGM-C	Cadherin-5				
		C2	sL-Selectin	Contactin-1	PCI				
13	Contactin-4	MCP-3	SLPI	C9	HGF	0.962	0.897	1.859	0.941
	HSP 90α	MMP-7	SAP	Cadherin-5	RGM-C				
		Kallistatin	C5	BAFF Receptor	TIMP-2				
14	Cadherin-5	HGF	SLPI	C9	MMP-7	0.962	0.913	1.874	0.944
	MCP-3	RGM-C	Contactin-1	SAP	MRC2				
		NRP1	ADAM 9	Thrombin/Prothrombin	BAFF Receptor				
15	SAP	C9	SLPI	MMP-7	HGF	0.962	0.908	1.869	0.941
	MRC2	MCP-3	HSP 90α	Cadherin-5	ADAM 9				
		RBP	RGM-C	Contactin-1	Troponin T				
16	RGM-C	MRC2	SLPI	C9	MMP-7	0.949	0.897	1.846	0.929

TABLE 18-continued

100 Panels of 14 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
	HGF	ADAM 9	SAP	BAFF Receptor	Cadherin-5				
		MCP-3	α1-Antitrypsin	HSP 90α	LY9				
17	Contactin-4	MCP-3	SLPI	C9	HGF	0.962	0.897	1.859	0.943
	HSP 90α	MMP-7	SAP	Cadherin-5	RGM-C				
		Kallistatin	C5	Contactin-1	ARSB				
18	SAP	C9	SLPI	MMP-7	HGF	0.949	0.918	1.867	0.944
	MRC2	MCP-3	HSP 90α	Cadherin-5	ADAM 9				
		Prekallikrein	RGM-C	MIP-5	C6				
19	MMP-7	SLPI	C9	HSP 90α	HGF	0.962	0.897	1.859	0.945
	MRC2	C2	MCP-3	RGM-C	α2-Antiplasmin				
		SAP	LY9	Kallistatin	ERBB1				
20	RGM-C	MCP-3	C9	MMP-7	SLPI	0.962	0.908	1.869	0.943
	Contactin-1	HGF	Contactin-4	SAP	BAFF Receptor				
		Growth hormone receptor	Cadherin-5	Kallistatin	ADAM 9				
21	SAP	C9	SLPI	MMP-7	HGF	0.962	0.903	1.864	0.937
	MRC2	MCP-3	RGM-C	α2-Antiplasmin	BAFF Receptor				
		LY9	Contactin-1	Cadherin-5	Hat1				
22	SAP	C9	SLPI	MMP-7	HGF	0.962	0.908	1.869	0.944
	MRC2	MCP-3	BAFF Receptor	Prekallikrein	HSP 90α				
		Cadherin-5	C2	RGM-C	IL-12 Rβ2				
23	RGM-C	MRC2	SLPI	C9	MMP-7	0.949	0.903	1.851	0.945
	MCP-3	α2-Antiplasmin	BAFF Receptor	HGF	C2				
		SAP	Cadherin-5	MIP-5	IL-18 Rβ				
24	RGM-C	Contactin-4	SLPI	SAP	MMP-7	0.962	0.903	1.864	0.942
	Growth hormone receptor	C9	HGF	MCP-3	Cadherin-5				
		ADAM 9	SCF sR	Contactin-1	Kallikrein 6				
25	Cadherin-5	HGF	SLPI	C9	MMP-7	0.962	0.897	1.859	0.950
	C2	SAP	α2-Antiplasmin	RGM-C	PCI				
		ERBB1	HSP 90α	NRP1	Contactin-1				
26	RGM-C	MCP-3	C9	MMP-7	SLPI	0.949	0.908	1.856	0.941
	Contactin-1	HGF	Contactin-4	SAP	BAFF Receptor				
		Growth hormone receptor	Cadherin-5	Kallistatin	TIMP-2				
27	Contactin-4	MCP-3	SLPI	C9	HGF	0.962	0.908	1.869	0.943
	MMP-7	MRC2	RGM-C	Thrombin/Prothrombin	MRP1				
		Cadherin-5	SAP	ADAM 9	HSP 90α				
28	SAP	C9	SLPI	MMP-7	HGF	0.962	0.903	1.864	0.945
	MRC2	MCP-3	RGM-C	Cadherin-5	Prekallikrein				
		BAFF Receptor	ADAM 9	Troponin T	Contactin-1				
29	RGM-C	MRC2	SLPI	C9	MMP-7	0.949	0.897	1.846	0.933
	HGF	ADAM 9	SAP	BAFF Receptor	Cadherin-5				
		MCP-3	α1-Antitrypsin	HSP 90α	Thrombin/Prothrombin				
30	MRC2	α2-Antiplamsmin	C9	SLPI	MCP-3	0.974	0.897	1.872	0.943
	HGF	MMP-7	HSP 90α	BAFF Receptor	RGM-C				
		SAP	α2-HS-Glycoprotein	MIP-5	Contactin-1				
31	SAP	C9	SLPI	MMP-7	HGF	0.962	0.897	1.859	0.936
	RGM-C	SCF sR	MCP-3	Contactin-4	Kallikrein 6				
		Growth hormone receptor	Contactin-1	ADAM 9	ARSB				

TABLE 18-continued

100 Panels of 14 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
32	SAP	C9	SLPI	MMP-7	HGF	0.962	0.903	1.864	0.942
	MRC2	MCP-3	BAFF Receptor	sL-Selectin	NRP1				
		RGM-C	Thrombin/Prothrombin	C6	Contactin-4				
33	Contactin-4	MCP-3	SLPI	C9	HGF	0.974	0.892	1.867	0.942
	HSP 90α	MMP-7	SAP	Cadherin-5	BAFF Receptor				
		RGM-C	Coagulation Factor Xa	C5	Kallistatin				
34	SAP	C9	SLPI	MMP-7	HGF	0.962	0.903	1.864	0.937
	MRC2	MCP-3	RGM-C	α2-Antiplasmin	BAFF Receptor				
		Hat1	Cadherin-5	LY9	C5				
35	SAP	C9	SLPI	MMP-7	HGF	0.962	0.903	1.864	0.945
	MRC2	MCP-3	RGM-C	Cadherin-5	Prekallikrein				
		ADAM 9	Thrombin/Prothrombin	HSP 90α	IL-12 Rβ2				
36	Contactin-4	MCP-3	SLPI	C9	HGF	0.974	0.892	1.867	0.940
	HSP 90α	MMP-7	SAP	Cadherin-5	RGM-C				
		Kallistatin	C5	BAFF Receptor	IL-13 Rα1				
37	SAP	C9	SLPI	MMP-7	HGF	0.949	0.903	1.851	0.941
	MRC2	MCP-3	BAFF Receptor	Properdin	RGM-C				
		IL-13 Rα1	Contactin-1	α2-Antiplasmin	IL-18 Rβ				
38	Cadherin-5	MMP-7	C9	RGM-C	SLPI	0.962	0.897	1.859	0.950
	HGF	SAP	Coagulation Factor Xa	C2	α2-Antiplasmin				
		ERBB1	NRP1	sL-Selectin	PCI				
39	Cadherin-5	HGF	SLPI	C9	MMP-7	0.962	0.913	1.874	0.942
	MCP-3	RGM-C	Contactin-1	SAP	MRC2				
		NRP1	BAFF Receptor	RBP	MIP-5				
40	HGF	SCF sR	C9	SLPI	MCP-3	0.949	0.908	1.856	0.939
	RGM-C	SAP	Growth hormone receptor	Contactin-1	MMP-7				
		Contactin-4	ADAM 9	TIMP-2	LY9				
41	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.903	1.864	0.945
	MCP-3	α2-Antiplasmin	BAFF Receptor	HGF	C2				
		SAP	Cadherin-5	Troponin T	ADAM 9				
42	HGF	SCF sR	C9	SLPI	MMP-7	0.936	0.908	1.844	0.934
	Cadherin-5	SAP	MCP-3	RGM-C	Growth hormone receptor				
		sL-Selectin	C2	Contactin-4	α1-Antitrypsin				
43	Contactin-4	MCP-3	SLPI	C9	HGF	0.974	0.897	1.872	0.941
	HSP 90α	MMP-7	SAP	Cadherin-5	RGM-C				
		Kallistatin	C5	BAFF Receptor	α2-HS-Glycoprotein				
44	SAP	C9	SLPI	MMP-7	HGF	0.949	0.908	1.856	0.939
	MRC2	MCP-3	RGM-C	Contactin-4	NRP1				
		SCF sR	ADAM 9	Properdin	ARSB				
45	SAP	C9	SLPI	MMP-7	HGF	0.962	0.903	1.864	0.941
	MRC2	MCP-3	RGM-C	α2-Antiplasmin	BAFF Receptor				
		Growth hormone receptor	Contactin-1	C6	IL-13 Rα1				
46	SAP	C9	SLPI	MMP-7	HGF	0.949	0.903	1.851	0.937
	MRC2	MCP-3	RGM-C	α2-Antiplasmin	BAFF Receptor				
		Growth hormone receptor	Cadherin-5	Kallistatin	Hat1				
47	MMP-7	SLPI	C9	HSP 90α	HGF	0.962	0.903	1.864	0.941
	MRC2	C2	MCP-3	RGM-C	BAFF Receptor				

TABLE 18-continued

100 Panels of 14 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
		SAP	Prekallikrein	α2-HS-Glycoprotein	IL-12 Rβ2				
48	HSP 90α	SLPI	C9	RGM-C	MMP-7	0.962	0.887	1.849	0.943
	SAP	HGF	Kallistatin	MCP-3	Cadherin-5				
		BAFF Receptor	MIP-5	MRC2	IL-18 Rβ				
49	MRC2	α2-Antiplasmin	C9	SLPI	MCP-3	0.962	0.903	1.864	0.946
	HGF	MMP-7	Kallikrein 6	SAP	HSP 90α				
		RGM-C	Cadherin-5	Contactin-1	BAFF Receptor				
50	RGM-C	MCP-3	C9	MMP-7	SLPI	0.949	0.908	1.856	0.943
	Contactin-1	HGF	BAFF Receptor	Cadherin-5	SAP				
		HSP 90α	C2	Prekallikrein	PCI				
51	SAP	C9	SLPI	MMP-7	HGF	0.962	0.908	1.869	0.943
	MRC2	MCP-3	RGM-C	Cadherin-5	Prekallikrein				
		BAFF Receptor	MIP-5	RBP	ADAM 9				
52	SAP	C9	SLPI	MMP-7	HGF	0.949	0.908	1.856	0.941
	MRC2	MCP-3	BAFF Receptor	Prekallikrein	HSP 90α				
		Cadherin-5	RGM-C	α2-HS-Glycoprotein	TIMP-2				
53	SAP	C9	SLPI	MMP-7	HGF	0.949	0.913	1.862	0.945
	MRC2	MCP-3	RGM-C	Cadherin-5	Prekallikrein				
		BAFF Receptor	ADAM 9	Troponin T	Kallistatin				
54	SAP	C9	SLPI	MMP-7	HGF	0.936	0.908	1.844	0.933
	MRC2	MCP-3	BAFF Receptor	sL-Selectin	NRP1				
		RGM-C	Thrombin/Prothrombin	Cadherin-5	α1-Antitrypsin				
55	SAP	C9	SLPI	MMP-7	HGF	0.949	0.908	1.856	0.939
	MRC2	MCP-3	RGM-C	Contactin-4	NRP1				
		SCF sR	ADAM 9	ARSB	C2				
56	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.903	1.864	0.942
	HGF	ADAM 9	SAP	BAFF Receptor	Cadherin-5				
		MCP-3	HSP 90α	C5	C6				
57	RGM-C	Contactin-4	SLPI	SAP	MMP-7	0.949	0.918	1.867	0.946
	Coagulation Factor Xa	MCP-3	C2	HGF	C9				
		Properdin	Cadherin-5	Contactin-1	C5				
58	Cadherin-5	HGF	SLPI	C9	MMP-7	0.962	0.897	1.859	0.941
	Contactin-1	SAP	MCP-3	Kallistatin	BAFF Receptor				
		C5	RGM-C	α2-HS-Glycoprotein	ERBB1				
59	NRP1	LY9	C9	SLPI	MMP-7	0.936	0.913	1.849	0.934
	RGM-C	MRC2	HGF	Contactin-1	Thrombin/Prothrombin				
		SAP	Cadherin-5	ADAM 9	Hat1				
60	MMP-7	SLPI	C9	MCP-3	MRC2	0.962	0.903	1.864	0.944
	HGF	BAFF Receptor	ADAM 9	SAP	Prekallikrein				
		Cadherin-5	HSP 90α	IL-12 Rβ2	RGM-C				
61	MMP-7	SLPI	C9	HSP 90α	α2-Antiplasmin	0.962	0.887	1.849	0.944
	HGF	Contactin-1	RGM-C	MCP-3	MRC2				
		IL-13 Rα1	SAP	C2	IL-18 Rβ				
62	MMP-7	LY9	SLPI	RGM-C	MRC2	0.962	0.903	1.864	0.937
	HGF	SAP	ADAM 9	Kallistatin	MCP-3				
		BAFF Receptor	Cadherin-5	Kallikrein 6	Contactin-1				
63	Cadherin-5	HGF	SLPI	C9	MMP-7	0.936	0.918	1.854	0.943

TABLE 18-continued

100 Panels of 14 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
	MCP-3	RGM-C	BAFF Receptor	SAP	Contactin-4				
		Prekallikrein	ADAM 9	MRC2	PCI				
64	Contactin-4	MCP-3	SLPI	C9	HGF	0.962	0.903	1.864	0.941
	MMP-7	MRC2	RGM-C	ADAM 9	BAFF Receptor				
		Cadherin-5	RBP	SAP	MIP-5				
65	RGM-C	MRC2	SLPI	C9	MMP-7	0.949	0.908	1.856	0.940
	MCP-3	HGF	BAFF Receptor	ADAM 9	Cadherin-5				
		Kallistatin	SAP	RBP	TIMP-2				
66	SAP	C9	SLPI	MMP-7	HGF	0.949	0.913	1.862	0.947
	MRC2	MCP-3	RGM-C	Cadherin-5	Properdin				
		NRP1	Thrombin/Prothrombin	Contactin-4	Troponin T				
67	RGM-C	MRC2	SLPI	C9	MMP-7	0.949	0.892	1.841	0.932
	HGF	ADAM 9	SAP	BAFF Receptor	Cadherin-5				
		MCP-3	α1-Antitrypsin	HSP 90α	C5				
68	RGM-C	MRC2	SLPI	C9	MMP-7	0.949	0.908	1.856	0.941
	HGF	ADAM 9	SAP	sL-Selectin	MCP-3				
		Properdin	Growth hormone receptor	Cadherin-5	ARSB				
69	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.903	1.864	0.942
	MCP-3	HGF	BAFF Receptor	SAP	C2				
		ADAM 9	Prekallikrein	HSP 90α	C6				
70	RGM-C	MCP-3	C9	MMP-7	SLPI	0.962	0.903	1.864	0.940
	Contactin-1	HGF	Contactin-4	SAP	BAFF Receptor				
		Coagulation Factor Xa	Growth hormone receptor	ADAM 9	Kallistatin				
71	SAP	C9	SLPI	MMP-7	HGF	0.962	0.897	1.859	0.942
	MRC2	MCP-3	RGM-C	Cadherin-5	C2				
		BAFF Receptor	ADAM 9	NRP1	ERBB1				
72	Cadherin-5	HGF	SLPI	C9	MMP-7	0.936	0.913	1.849	0.938
	MCP-3	RGM-C	Contactin-1	SAP	MRC2				
		NRP1	BAFF Receptor	Properdin	Hat1				
73	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.903	1.864	0.936
	SAP	BAFF Receptor	HGF	Properdin	ADAM 9				
		Cadherin-5	HSP 90α	RBP	IL-12 Rβ2				
74	HGF	MMP-7	α2-Antiplasmin	C9	SLPI	0.962	0.887	1.849	0.949
	C2	RGM-C	Contactin-1	Cadherin-5	sL-Selectin				
		NRP1	SAP	Growth hormone receptor	IL-18 Rβ				
75	Cadherin-5	HGF	SLPI	C9	MMP-7	0.949	0.913	1.862	0.943
	Properdin	RGM-C	MRC2	MCP-3	BAFF Receptor				
		ADAM 9	SAP	SCF sR	Kallikrein 6				
76	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.892	1.854	0.938
	MCP-3	HGF	BAFF Receptor	SAP	Kallistatin				
		ADAM 9	C5	HSP 90α	PCI				
77	RGM-C	MRC2	SLPI	C9	MMP-7	0.949	0.908	1.856	0.944
	MCP-3	HGF	BAFF Receptor	SAP	Kallistatin				
		ADAM 9	Prekallikrein	TIMP-2	Cadherin-5				
78	RGM-C	MRC2	SLPI	C9	MMP-7	0.949	0.913	1.862	0.939
	SAP	BAFF Receptor	HGF	Properdin	ADAM 9				
		Cadherin-5	HSP 90α	RBP	Troponin T				

TABLE 18-continued

100 Panels of 14 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
79	RGM-C	MRC2	SLPI	C9	MMP-7	0.949	0.892	1.841	0.931
	HGF	ADAM 9	SAP	BAFF Receptor	Cadherin-5				
		MCP-3	α1-Antitrypsin	HSP 90α	NRP1				
80	RGM-C	Contactin-4	SLPI	SAP	MMP-7	0.949	0.908	1.856	0.940
	Growth hormone receptor	C9	HGF	MCP-3	Cadherin-5				
		ADAM 9	SCF sR	Contactin-1	ARSB				
81	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.903	1.864	0.941
	HGF	ADAM 9	SAP	MCP-3	Prekallikrein				
		C5	HSP 90α	BAFF Receptor	C6				
82	SAP	C9	SLPI	MMP-7	HGF	0.962	0.903	1.864	0.943
	MRC2	MCP-3	HSP 90α	Cadherin-5	α2-HS-Glycoprotein				
		RGM-C	BAFF Receptor	MIP-5	Coagulation Factor Xa				
83	HGF	SCF sR	C9	SPLI	MMP-7	0.949	0.908	1.856	0.945
	Cadherin-5	SAP	MCP-3	RGM-C	Growth hormone receptor				
		sL-Selectin	C2	Contactin-4	ERBB1				
84	SAP	C9	SLPI	MMP-7	HGF	0.949	0.897	1.846	0.935
	MRC2	MCP-3	RGM-C	α2-Antiplasmin	BAFF Receptor				
		Kallistatin	LY9	C5	Hat1				
85	SAP	C9	SLPI	MMP-7	HGF	0.949	0.913	1.862	0.944
	RGM-C	BAFF Receptor	Properdin	Cadherin-5	MCP-3				
		MRC2	IL-12 Rβ2	ADAM 9	Prekallikrein				
86	Cadherin-5	MMP-7	C9	RGM-C	SLPI	0.962	0.903	1.864	0.945
	HGF	SAP	HSP 90α	α2-Antiplasmin	BAFF Receptor				
		MCP-3	Contactin-1	IL-13 Rα1	MRC2				
87	Cadherin-5	HGF	SLPI	C9	MMP-7	0.949	0.897	1.846	0.943
	MCP-3	RGM-C	Contactin-1	SAP	MRC2				
		NRP1	BAFF Receptor	Properdin	IL-18 Rβ				
88	RGM-C	MRC2	SLPI	C9	MMP-7	0.974	0.887	1.862	0.937
	MCP-3	HGF	BAFF Receptor	SAP	Kallistatin				
		ADAM 9	C5	IL-13 Rα1	Kallikrein 6				
89	Contactin-4	MCP-3	SLPI	C9	HGF	0.962	0.892	1.854	0.941
	HSP 90α	MMP-7	SAP	Cadherin-5	RGM-C				
		Kallistatin	C5	BAFF Receptor	PCI				
90	Cadherin-5	HGF	SLPI	C9	MMP-7	0.962	0.892	1.854	0.939
	MCP-3	RGM-C	BAFF Receptor	Contactin-4	Kallistatin				
		SAP	Growth hormone receptor	TIMP-2	HSP 90α				
91	MMP-7	SLPI	C9	MCP-3	MRC2	0.962	0.897	1.859	0.939
	HGF	BAFF Receptor	ADAM 9	SAP	Contactin-1				
		RGM-C	NRP1	HSP 90α	Troponin T				
92	SAP	C9	SLPI	MMP-7	HGF	0.949	0.892	1.841	0.931
	RGM-C	NRP1	MRC2	Contactin-1	MCP-3				
		HSP 90α	Thrombin/Prothrombin	BAFF Receptor	α1-Antitrypsin				
93	HGF	SCF sR	C9	SLPI	MCP-3	0.962	0.892	1.854	0.940
	RGM-C	SAP	Growth hormone receptor	Contactin-1	MMP-7				
		Contactin-4	ADAM 9	ARSB	C5				
94	SAP	C9	SLPI	MMP-7	HGF	0.962	0.903	1.864	0.941
	MRC2	MCP-3	BAFF Receptor	Properdin	RGM-C				

TABLE 18-continued

100 Panels of 14 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
		C6	ADAM 9	C5	MIP-5				
95	MMP-7	SLPI	C9	MCP-3	MRC2	0.962	0.903	1.864	0.942
	HGF	BAFF Receptor	ADAM 9	SAP	Contactin-1				
		RGM-C	IL-13 Rα1	Coagulation Factor Xa	Prekallikrein				
96	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.892	1.854	0.939
	MCP-3	HGF	BAFF Receptor	SAP	C2				
		ADAM 9	RBP	C5	ERBB1				
97	MMP-7	LY9	SLPI	RGM-C	MRC2	0.949	0.897	1.846	0.937
	HGF	SAP	Cadherin-5	MCP-3	α2-Antiplasmin				
		C9	Hat1	ADAM 9	C5				
98	SAP	C9	SLPI	MMP-7	HGF	0.949	0.913	1.862	0.945
	MRC2	MCP-3	HSP 90α	Cadherin-5	ADAM 9				
		Prekallikrein	RGM-C	IL-12 Rβ2	C2				
99	Cadherin-5	MMP-7	C9	RGM-C	SLPI	0.949	0.897	1.846	0.947
	HGF	SAP	Properdin	HSP 90α	MCP-3				
		MRC2	C2	Prekallikrein	IL-18 Rβ				
100	RGM-C	MRC2	SLPI	C9	MMP-7	0.949	0.913	1.862	0.941
	HGF	SCF sR	MCP-3	ADAM 9	SAP				
		Properdin	Kallikrein 6	sL-Selectin	BAFF Receptor				

Marker	Count	Marker	Count
SLPI	100	Growth hormone receptor	16
SAP	100	SCF sR	13
RGM-C	100	MIP-5	13
MMP-7	100	sL-Selectin	10
HGF	100	LY9	10
C9	99	Thrombin/Prothrombin	9
MCP-3	94	RBP	9
MRC2	74	IL-13 Rα1	9
Cadherin-5	73	Kallikrein 6	8
BAFF Receptor	70	IL-18 Rβ	8
ADAM 9	51	IL-12 Rβ2	8
HSP 90α	43	Hat 1	8
Contactin-1	36	ERBB1	8
Contactin-4	28	Coagulation Factor Xa	8
α2-Antiplasmin	23	C6	8
C2	23	ARSB	8
Kallistatin	22	α2-HS-Glycoprotein	7
Prekallikrein	20	α1-Antitrypsin	7
C5	20	Troponin T	7
NRP1	19	TIMP-2	7
Properdin	17	PCI	7

[0368]

TABLE 14

100 Panels of 15 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
1	SAP	C9	SLPI	MMP-7	HGF	0.962	0.918	1.879	0.943
	MRC2	MCP-3	RGM-C	Cadherin-5	Prekallikrein				
	BAFF Receptor	MIP-5	ADAM 9	NRP1	Contactin-4				
2	SAP	C9	SLPI	MMP-7	HGF	0.949	0.913	1.862	0.944
	RGM-C	BAFF Receptor	Properdin	Cadherin-5	MCP-3				
	MRC2	Kallistatin	ADAM 9	Prekallikrein	ARSB				
3	SAP	C9	SLPI	MMP-7	HGF	0.962	0.913	1.874	0.945
	MRC2	MCP-3	BAFF Receptor	Prekallikrein	HSP 90α				
	Cadherin-5	C2	RGM-C	C5	ADAM 9				
4	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.908	1.869	0.945
	MCP-3	α2-Antiplasmin	BAFF Receptor	HGF	Cadherin-5				
	SAP	Kallikrein 6	Kallistatin	HSP 90α	C6				
5	Cadherin-5	HGF	SLPI	C9	MMP-7	0.974	0.897	1.872	0.943
	MCP-3	RGM-C	Contactin-1	SAP	Coagulation Factor Xa				
	BAFF Receptor	Kallistatin	C5	ADAM 9	HSP 90α				
6	Cadherin-5	MMP-7	C9	RGM-C	SLPI	0.962	0.903	1.864	0.945
	HGF	MRC2	α2-Antiplasmin	Growth hormone receptor	SAP				
	C2	Kallistatin	LY9	C5	ERBB1				
7	SAP	C9	SLPI	MMP-7	HGF	0.962	0.903	1.864	0.937
	MRC2	MCP-3	RGM-C	α2-Antiplasmin	BAFF Receptor				
	LY9	Contactin-1	Cadherin-5	Hat1	C5				
8	SAP	C9	SLPI	MMP-7	HGF	0.962	0.908	1.869	0.944
	MRC2	MCP-3	RGM-C	Cadherin-5	C2				
	BAFF Receptor	ADAM 9	Prekallikrein	IL-12 Rβ2	HSP 90α				
9	HSP 90α	SLPI	C9	RGM-C	MMP-7	0.974	0.897	1.872	0.942
	SAP	HGF	Kallistatin	MCP-3	Cadherin-5				
	BAFF Receptor	MIP-5	MRC2	IL-13 Rα1	Coagulation Factor Xa				
10	SAP	C9	SLPI	MMP-7	HGF	0.949	0.908	1.856	0.944
	MRC2	MCP-3	RGM-C	Cadherin-5	C2				
	BAFF Receptor	ADAM 9	Prekallikrein	IL-18 Rβ	Contactin-1				
11	Cadherin-5	HGF	SLPI	C9	MMP-7	0.949	0.908	1.856	0.941
	MCP-3	RGM-C	Contactin-1	MRC2	ADAM 9				
	BAFF Receptor	SAP	IL-12 Rβ2	HSP 90α	PCI				
12	SAP	C9	SLPI	MMP-7	HGF	0.962	0.913	1.874	0.944
	MRC2	MCP-3	Contactin-1	RGM-C	BAFF Receptor				
	RBP	ADAM 9	Prekallikrein	Cadherin-5	MIP-5				
13	SAP	C9	SLPI	MMP-7	HGF	0.962	0.908	1.869	0.944
	MRC2	MCP-3	RGM-C	α2-Antiplasmin	BAFF Receptor				
	IL-13 Rα1	Cadherin-5	SCF sR	MIP-5	C6				
14	SAP	C9	SLPI	MMP-7	HGF	0.949	0.918	1.867	0.943
	MRC2	MCP-3	BAFF Receptor	Prekallikrein	HSP 90α				
	Cadherin-5	C2	RGM-C	TIMP-2	C5				
15	Cadherin-5	HGF	SLPI	C9	MMP-7	0.949	0.918	1.867	0.944
	MCP-3	RGM-C	Contactin-1	SAP	MRC2				
	NRP1	BAFF Receptor	Properdin	MIP-5	Thrombin/Prothrombin				
16	SAP	C9	SLPI	MMP-7	HGF	0.962	0.913	1.874	0.943

TABLE 14-continued

100 Panels of 15 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
	MRC2	MCP-3	BAFF Receptor	Properdin	RGM-C				
	MIP-5	Cadherin-5	Troponin T	Contactin-1	C5				
17	HGF	SCF sR	C9	SLPI	MCP-3	0.936	0.908	1.844	0.932
	RGM-C	SAP	Growth hormone receptor	Contactin-1	MMP-7				
	Contactin-4	ADAM 9	sL-Selectin	Cadherin-5	α1-Antitrypsin				
18	SAP	C9	SLPI	MMP-7	HGF	0.962	0.913	1.874	0.943
	MRC2	MCP-3	BAFF Receptor	Prekallikrein	α2-HS-Glycoprotein				
	RGM-C	ADAM 9	Contactin-1	HSP 90α	Cadherin-5				
19	Contactin-4	MCP-3	SLPI	C9	HGF	0.962	0.897	1.859	0.939
	HSP 90α	MMP-7	SAP	Cadherin-5	RGM-C				
	Kallistatin	C5	BAFF Receptor	ARSB	α2-HS-Glycoprotein				
20	HGF	SCF sR	C9	SLPI	MMP-7	0.949	0.913	1.862	0.943
	Cadherin-5	SAP	MCP-3	RGM-C	Growth hormone receptor				
	sL-Selectin	C2	Contactin-4	ERBB1	MIP-5				
21	SAP	C9	SLPI	MMP-7	HGF	0.962	0.897	1.859	0.935
	MRC2	MCP-3	RGM-C	α2-Antiplasmin	BAFF Receptor				
	Hat1	Cadherin-5	LY9	C5	MIP-5				
22	MRC2	α2-Antiplasmin	C9	SLPI	MCP-3	0.962	0.892	1.854	0.941
	HGF	MMP-7	HSP 90α	BAFF Receptor	RGM-C				
	SAP	IL-13 Rα1	Contactin-1	IL-18 Rβ	C6				
23	MMP-7	SLPI	C9	MCP-3	MRC2	0.962	0.903	1.864	0.940
	HGF	BAFF Receptor	ADAM 9	SAP	Contactin-1				
	RGM-C	Kallikrein 6	Cadherin-5	RBP	HSP 90α				
24	Cadherin-5	HGF	SLPI	C9	MMP-7	0.949	0.908	1.856	0.945
	C2	SAP	α2-Antiplasmin	RGM-C	MCP-3				
	Contactin-4	Coagulation Factor Xa	C6	sL-Selectin	PCI				
25	Cadherin-5	HGF	SLPI	C9	MMP-7	0.949	0.913	1.862	0.943
	MCP-3	RGM-C	Contactin-1	SAP	MRC2				
	NRP1	BAFF Receptor	MIP-5	TIMP-2	Prekallikrein				
26	SAP	C9	SLPI	MMP-7	HGF	0.962	0.903	1.864	0.944
	MRC2	MCP-3	BAFF Receptor	sL-Selectin	NRP1				
	RGM-C	Thrombin/Prothrombin	Cadherin-5	HSP 90α	C5				
27	SAP	C9	SLPI	MMP-7	HGF	0.962	0.908	1.869	0.945
	MRC2	MCP-3	RGM-C	Cadherin-5	C2				
	BAFF Receptor	ADAM 9	Prekallikrein	IL-12 Rβ2	Troponin T				
28	MMP-7	SLPI	C9	MCP-3	MRC2	0.949	0.892	1.841	0.929
	HGF	BAFF Receptor	ADAM 9	SAP	Contactin-1				
	RGM-C	NRP1	HSP 90α	α2-HS-Glycoprotein	α1-Antitrypsin				
29	Contactin-4	MSP-3	SLPI	C9	HGF	0.962	0.897	1.859	0.941
	HSP 90α	MMP-7	SAP	Cadherin-5	RGM-C				
	Kallistatin	C5	BAFF Receptor	ARSB	Properdin				
30	MMP-7	SLPI	C9	HSP 90α	HGF	0.962	0.892	1.854	0.945
	MRC2	C2	MCP-3	RGM-C	α2-Antiplasmin				
	SAP	LY9	Contactin-1	C5	ERBB1				
31	SAP	C9	SLPI	MMP-7	HGF	0.949	0.903	1.851	0.936
	MRC2	MCP-3	RGM-C	α2-Antiplasmin	BAFF Receptor				
	Growth hormone receptor	Cadherin-5	Kallistatin	C5	Hat1				

TABLE 14-continued

100 Panels of 15 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
32	SAP	C9	SLPI	MMP-7	HGF	0.949	0.903	1.851	0.943
	MRC2	MCP-3	RGM-C	Cadherin-5	C2				
	BAFF Receptor	ADAM 9	Properdin	C5	IL-18 Rβ				
33	RGM-C	Contactin-4	SLPI	SAP	MMP-7	0.949	0.913	1.862	0.942
	Growth hormone receptor	C9	HGF	MCP-3	Cadherin-5				
	ADAM 9	SCF sR	Kallikrein 6	Properdin	C5				
34	SAP	C9	SLPI	MMP-7	HGF	0.949	0.908	1.856	0.941
	MRC2	MCP-3	RGM-C	α2-Antiplasmin	BAFF Receptor				
	Growth hormone receptor	Cadherin-5	Kallistatin	C5	PCI				
35	Cadherin-5	HGF	SLPI	C9	MMP-7	0.962	0.908	1.869	0.942
	MCP-3	RGM-C	Contactin-1	MRC2	ADAM 9				
	BAFF Receptor	SAP	IL-12 Rβ2	HSP 90α	RBP				
36	HSP 90α	SLPI	C9	RGM-C	MMP-7	0.962	0.897	1.859	0.939
	SAP	HGF	Kallistatin	MCP-3	Cadherin-5				
	BAFF Receptor	MIP-5	MRC2	NRP1	TIMP-2				
37	SAP	C9	SLPI	MMP-7	HGF	0.962	0.903	1.864	0.943
	RGM-C	NRP1	MRC2	Contactin-1	MCP-3				
	HSP 90α	Thrombin/Prothrombin	sL-Selectin	α2-HS-Glycoprotein	BAFF Receptor				
38	SAP	C9	SLPI	MMP-7	HGF	0.962	0.908	1.869	0.944
	MRC2	MCP-3	BAFF Receptor	Prekallikrein	HSP 90α				
	Cadherin-5	C2	RGM-C	Troponin T	IL-12 Rβ2				
39	SAP	C9	SLPI	MMP-7	HGF	0.936	0.903	1.838	0.933
	MRC2	MCP-3	RGM-C	Cadherin-5	Prekallikrein				
	BAFF Receptor	MIP-5	ADAM 9	HSP 90α	α1-Antitrypsin				
40	HGF	SCF sR	C9	SLPI	MCP-3	0.962	0.897	1.859	0.937
	RGM-C	SAP	Growth hormone receptor	Contactin-1	MMP-7				
	Contactin-4	ADAM 9	Kallistatin	Kallikrein 6	ARSB				
41	SAP	C9	SLPI	MMP-7	HGF	0.962	0.908	1.869	0.942
	MRC2	MCP-3	RGM-C	α2-Antiplasmin	BAFF Receptor				
	LY9	Contactin-4	Cadherin-5	ADAM 9	Coagulation Factor Xa				
42	Cadherin-5	MMP-7	C9	RGM-C	SLPI	0.962	0.892	1.854	0.941
	HGF	MRC2	NRP1	BAFF Receptor	C2				
	SAP	HSP 90α	MCP-3	MIP-5	ERBB1				
43	SAP	C9	SLPI	MMP-7	HGF	0.949	0.903	1.851	0.935
	MRC2	MCP-3	RGM-C	α2-Antiplasmin	BAFF Receptor				
	Kallistatin	LY9	C5	ADAM 9	Hat1				
44	Cadherin-5	HGF	SLPI	C9	MMP-7	0.974	0.897	1.872	0.944
	MCP-3	RGM-C	Contactin-1	SAP	MRC2				
	α2-Antiplasmin	BAFF Receptor	MIP-5	IL-13 Rα1	HSP 90α				
45	MMP-7	LY9	SLPI	RGM-C	MRC2	0.949	0.903	1.851	0.939
	HGF	SAP	ADAM 9	Kallistatin	MCP-3				
	BAFF Receptor	Cadherin-5	Prekallikrein	C2	IL-18 Rβ				
46	Cadherin-5	HGF	SLPI	C9	MMP-7	0.949	0.908	1.856	0.940
	MCP-3	RGM-C	Contactin-1	SAP	MRC2				
	NRP1	BAFF Receptor	MIP-5	HSP 90α	PCI				
47	Cadherin-5	HGF	SLPI	C9	MMP-7	0.962	0.908	1.869	0.940
	MCP-3	RGM-C	Contactin-1	MRC2	ADAM 9				

TABLE 14-continued

100 Panels of 15 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
	BAFF Receptor	SAP	HSP 90α	RBP	MIP-5				
48	SAP	C9	SLPI	MMP-7	HGF	0.949	0.908	1.856	0.939
	MRC2	MCP-3	BAFF Receptor	Properdin	RGM-C				
	C6	ADAM 9	C5	RBP	TIMP-2				
49	SAP	C9	SLPI	MMP-7	HGF	0.962	0.903	1.864	0.944
	MRC2	MCP-3	BAFF Receptor	Prekallikrein	HSP 90α				
	Cadherin-5	NRP1	Thrombin/Prothrombin	RGM-C	IL-12 Rβ2				
50	SAP	C9	SLPI	MMP-7	HGF	0.949	0.918	1.867	0.945
	MRC2	MCP-3	RGM-C	Cadherin-5	Prekallikrein				
	BAFF Receptor	ADAM 9	Troponin T	IL-12 Rβ2	Kallistatin				
51	MMP-7	LY9	SLPI	RGM-C	MRC2	0.936	0.903	1.838	0.928
	HGF	SAP	ADAM 9	Kallistatin	MCP-3				
	BAFF Receptor	Cadherin-5	Prekallikrein	C5	α1-Antitrypsin				
52	SAP	C9	SLPI	MMP-7	HGF	0.949	0.908	1.856	0.940
	MRC2	MCP-3	RGM-C	HSP 90α	SCF sR				
	ADAM 9	C2	NRP1	ARSB	Kallistatin				
53	MMP-7	SLPI	C9	MCP-3	MRC2	0.962	0.908	1.869	0.945
	HGF	BAFF Receptor	ADAM 9	SAP	Contactin-1				
	RGM-C	NRP1	Coagulation Factor Xa	sL-Selectin	Cadherin-5				
54	SAP	C9	SLPI	MMP-7	HGF	0.949	0.903	1.851	0.941
	MRC2	MCP-3	RGM-C	Contactin-4	Prekallikrein				
	ADAM 9	MIP-5	HSP 90α	C2	ERBB1				
55	SAP	C9	SLPI	MMP-7	HGF	0.949	0.903	1.851	0.937
	MRC2	MCP-3	RGM-C	α2-Antiplasmin	BAFF Receptor				
	Kallistatin	LY9	Cadherin-5	Hat1	C5				
56	MRC2	α2-Antiplasmin	C9	SLPI	MCP-3	0.974	0.897	1.872	0.943
	HGF	MMP-7	HSP 90α	BAFF Receptor	RGM-C				
	SAP	IL-13 Rα1	C5	Cadherin-5	MIP-5				
57	HGF	MMP-7	α2-Antiplasmin	C9	SLPI	0.962	0.887	1.849	0.948
	C2	RGM-C	Contactin-1	Cadherin-5	sL-Selectin				
	NRP1	SAP	Growth hormone receptor	IL-18 Rβ	α2-HS-Glycoprotein				
58	RGM-C	MRC2	SLPI	C9	MMP-7	0.974	0.887	1.862	0.939
	MCP-3	HGF	BAFF Receptor	SAP	Kallistatin				
	ADAM 9	C5	Kallikrein 6	Coagulation Factor Xa	MIP-5				
59	HSP 90α	SLPI	C9	RGM-C	MMP-7	0.949	0.908	1.856	0.940
	SAP	HGF	Kallistatin	MCP-3	Cadherin-5				
	BAFF Receptor	MIP-5	MRC2	NRP1	PCI				
60	Cadherin-5	HGF	SLPI	C9	MMP-7	0.949	0.908	1.856	0.940
	MCP-3	RGM-C	BAFF Receptor	Contactin-4	Kallistatin				
	SAP	Growth hormone receptor	TIMP-2	HSP 90α	Contactin-1				
61	MRC2	NRP1	SPLI	C9	HGF	0.962	0.903	1.864	0.945
	MMP-7	RGM-C	Properdin	SAP	BAFF Receptor				
	Cadherin-5	HSP 90α	Thrombin/Prothrombin	MCP-3	Kallistatin				
62	SAP	C9	SLPI	MMP-7	HGF	0.962	0.903	1.864	0.942
	MRC2	MCP-3	RGM-C	Cadherin-5	C2				
	BAFF Receptor	ADAM 9	Prekallikrein	IL-13 Rα1	Troponin T				
63	RGM-C	Contactin-4	SLPI	SAP	MMP-7	0.936	0.903	1.838	0.932

TABLE 14-continued

100 Panels of 15 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
	Growth hormone receptor	C9	HGF	MCP-3	Cadherin-5				
	ADAM 9	SCF sR	sL-Selectin	C5	α1-Antitrypsin				
64	SAP	C9	SLPI	MMP-7	HGF	0.949	0.908	1.856	0.944
	MRC2	MCP-3	RGM-C	Cadherin-5	Prekallikrein				
	ADAM 9	C5	BAFF Receptor	Thrombin/Prothrombin	ARSB				
65	HGF	SCF sR	C9	SLPI	MMP-7	0.949	0.918	1.867	0.947
	Cadherin-5	SAP	MCP-3	Coagulation Factor Xa	C2				
	Contactin-1	RGM-C	Properdin	C6	C5				
66	MMP-7	SLPI	C9	HSP 90α	HGF	0.949	0.903	1.851	0.941
	MRC2	C2	MCP-3	RGM-C	α2-Antiplasmin				
	SAP	LY9	Kallistatin	ERBB1	ADAM 9				
67	SAP	C9	SLPI	MMP-7	HGF	0.949	0.903	1.851	0.936
	MRC2	MCP-3	RGM-C	α2-Antiplasmin	BAFF Receptor				
	Hat1	Cadherin-5	LY-9	C5	Contactin-4				
68	SAP	C9	SLPI	MMP-7	HGF	0.962	0.887	1.849	0.941
	MRC2	MCP-3	HSP 90α	Cadherin-5	ADAM 9				
	RBP	RGM-C	BAFF Receptor	Kallistatin	IL-18 Rβ				
69	Cadherin-5	HGF	SLPI	C9	MMP-7	0.962	0.897	1.859	0.945
	MCP-3	RGM-C	Contactin-1	SAP	MRC2				
	α2-Antiplasmin	BAFF Receptor	Kallikrein 6	C5	HSP 90α				
70	Cadherin-5	HGF	SLPI	C9	MMP-7	0.936	0.918	1.854	0.942
	MCP-3	RGM-C	α2-Antiplasmin	MRC2	SCF sR				
	LY9	Contactin-1	SAP	α2-HS-Glycoprotein	PCI				
71	RGM-C	MRC2	SLPI	C9	MMP-7	0.949	0.908	1.856	0.939
	MCP-3	HGF	BAFF Receptor	ADAM 9	Cadherin-5				
	Kallistatin	SAP	RBP	TIMP-2	LY9				
72	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.903	1.864	0.944
	HGF	ADAM 9	SAP	MCP-3	Prekallikrein				
	C5	HSP 90α	BAFF Receptor	Troponin T	Cadherin-5				
73	Cadherin-5	HGF	SLPI	C9	MMP-7	0.923	0.913	1.836	0.932
	Properdin	MRC2	BAFF Receptor	MCP-3	C5				
	RGM-C	ADAM 9	SAP	Troponin T	α1-Antitrypsin				
74	MMP-7	LY9	SLPI	RGM-C	MRC2	0.949	0.908	1.856	0.938
	HGF	SAP	ADAM 9	Kallistatin	MCP-3				
	BAFF Receptor	Cadherin-5	Prekallikrein	C5	ARSB				
75	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.903	1.864	0.940
	HGF	ADAM 9	SAP	MCP-3	Prekallikrein				
	C5	BAFF Receptor	C6	MIP-5	HSP 90α				
76	RGM-C	MCP-3	C9	MMP-7	SLPI	0.949	0.903	1.851	0.940
	Contactin-1	HGF	Contactin-4	SAP	BAFF Receptor				
	Growth hormone receptor	Cadherin-5	C2	ADAM 9	ERBB1				
77	NRP1	LY9	C9	SLPI	MMP-7	0.936	0.913	1.849	0.936
	RGM-C	MRC2	HGF	Contactin-1	Thrombin/Prothrombin				
	SAP	Cadherin-5	ADAM 9	MCP-3	Hat1				
78	MRC2	α2-Antiplasmin	C9	SLPI	MCP-3	0.962	0.908	1.869	0.943
	HGF	MMP-7	HSP 90α	BAFF Receptor	RGM-C				
	SAP	IL-13 Rα1	C5	Contactin-4	Cadherin-5				

TABLE 14-continued

100 Panels of 15 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
79	SAP	C9	SLPI	MMP-7	HGF	0.949	0.897	1.846	0.941
	MRC2	MCP-3	RGM-C	Cadherin-5	C2				
	BAFF Receptor	ADAM 9	Prekallikrein	IL-18 Rβ	RBP				
80	SAP	C9	SLPI	MMP-7	HGF	0.962	0.897	1.859	0.940
	MRC2	MCP-3	RGM-C	α2-Antiplasmin	BAFF Receptor				
	LY9	Contactin-1	Cadherin-5	Kallikrein 6	MIP-5				
81	Cadherin-5	HGF	SLPI	C9	MMP-7	0.949	0.903	1.851	0.942
	Properdin	MRC2	BAFF Receptor	MCP-3	C5				
	RGM-C	ADAM 9	SAP	Troponin T	PCI				
82	RGM-C	MRC2	SLPI	C9	MMP-7	0.949	0.908	1.856	0.942
	MCP-3	HGF	BAFF Receptor	SAP	Kallistatin				
	ADAM 9	Prekallikrein	TIMP-2	Cadherin-5	HSP 90α				
83	Cadherin-5	HGF	SLPI	C9	MMP-7	0.923	0.913	1.836	0.930
	Properdin	RGM-C	MRC2	MCP-3	BAFF Receptor				
	ADAM 9	SAP	Contactin-4	Growth hormone receptor	α1-Antitrypsin				
84	Cadherin-5	HGF	SLPI	C9	MMP-7	0.962	0.908	1.869	0.942
	Properdin	MRC2	BAFF Receptor	MCP-3	C5				
	RGM-C	ADAM 9	SAP	α2-HS-Glycoprotein	HSP 90α				
85	SAP	C9	SLPI	MMP-7	HGF	0.949	0.908	1.856	0.941
	MRC2	MCP-3	BAFF Receptor	sL-Selectin	NRP1				
	RGM-C	Contactin-4	Cadherin-5	ADAM 9	ARSB				
86	SAP	C9	SLPI	MMP-7	HGF	0.962	0.903	1.864	0.940
	MRC2	MCP-3	HSP 90α	Cadherin-5	ADAM 9				
	RBP	RGM-C	BAFF Receptor	sL-Selectin	C6				
87	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.908	1.869	0.942
	MCP-3	HGF	BAFF Receptor	SAP	Kallistatin				
	ADAM 9	sL-Selectin	C5	NRP1	Coagulation Factor Xa				
88	HGF	SCF sR	C9	SLPI	MMP-7	0.949	0.903	1.851	0.943
	Cadherin-5	SAP	MCP-3	RGM-C	Growth hormone receptor				
	sL-Selectin	C2	ERBB1	MIP-5	Kallistatin				
89	SAP	MRC2	SLPI	RGM-C	MMP-7	0.923	0.923	1.846	0.936
	Properdin	Cadherin-5	HGF	Prekallikrein	MCP-3				
	ADAM 9	C5	HSP 90α	C2	Hat1				
90	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.908	1.869	0.941
	HGF	ADAM 9	SAP	BAFF Receptor	Cadherin-5				
	MCP-3	HSP 90α	IL-12 Rβ2	Kallistatin	RBP				
91	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.903	1.864	0.941
	HGF	ADAM 9	SAP	BAFF Receptor	Cadherin-5				
	MCP-3	C5	IL-13 Rα1	Contactin-1	HSP 90α				
92	SAP	C9	SLPI	MMP-7	HGF	0.949	0.897	1.846	0.941
	MRC2	MCP-3	BAFF Receptor	Prekallikrein	α2-HS-Glycoprotein				
	RGM-C	ADAM 9	Cadherin-5	Coagulation Factor Xa	IL-18 Rβ				
93	HSP 90α	SLPI	C9	RGM-C	MMP-7	0.962	0.897	1.859	0.939
	SAP	HGF	Kallistatin	MCP-3	Cadherin-5				
	BAFF Receptor	C2	MRC2	Kallikrein 6	LY9				
94	RGM-C	MCP-3	C9	MMP-7	SLPI	0.949	0.903	1.851	0.941
	Contactin-1	HGF	BAFF Receptor	Cadherin-5	SAP				

TABLE 14-continued

100 Panels of 15 Biomarkers for Diagnosing Ovarian Cancer from Benign Pelvic Masses

	Biomarkers					Sensitivity	Specificity	Sensitivity + Specificity	AUC
	HSP 90α	C2	Prekallilrein	Coagulation Factor Xa	PCI				
95	SAP	C9	SLPI	MMP-7	HGF	0.949	0.908	1.856	0.942
	MRC2	MCP-3	RGM-C	α2-Antiplasmin	BAFF Receptor				
	Kallistatin	LY9	C5	ADAM 9	TIMP-2				
96	HSP 90α	SLPI	C9	RGM-C	MMP-7	0.962	0.903	1.864	0.944
	SAP	HGF	Kallistatin	MCP-3	Cadherin-5				
	bAFF Receptor	MIP-5	MRC2	NRP1	Thrombin/Prothrombin				
97	Cadherin-5	HGF	SLPI	C9	MMP-7	0.923	0.913	1.836	0.933
	MCP-3	RGM-C	α2-Antiplasmin	MRC2	SCF sR				
	LY9	Contactin-1	SAP	α2-HS-Glycoprotein	α1-Antitrypsin				
98	Cadherin-5	HGF	SLPI	C9	MMP-7	0.949	0.908	1.856	0.941
	NRP1	MRC2	BAFF Receptor	ADAM 9	RGM-C				
	SAP	sL-Selectin	MCP-3	Kallistatin	ARSB				
99	RGM-C	MRC2	SLPI	C9	MMP-7	0.962	0.903	1.864	0.941
	MCP-3	sL-Selectin	HGF	ADAM 9	BAFF Receptor				
	SAP	Cadherin-5	C6	NRP-1	Contactin-4				
100	Cadherin-5	HGF	SLPI	C9	MMP-7	0.949	0.903	1.851	0.941
	Properdin	RGM-C	MRC2	MCP-3	BAFF Receptor				
	ADAM 9	SAP	MIP-5	C5	ERBB1				

Marker	Aount	Marker	Control
SLPI	100	Contactin-4	18
SAP	100	Properdin	15
RGM-C	100	sL-Selectin	14
MMP-7	100	Growth hormone receptor	13
HGF	100	SCF sR	11
MCP-3	98	RBP	10
C9	96	Coagulation Factor Xa	10
Cadherin-5	86	α2-HS-Glycoprotein	9
MRC2	85	ERBB1	9
BAFF Receptor	82	C6	9
ADAM 9	57	ARSB	9
HSP 90α	46	α1-Antitrypsin	8
C5	38	Troponin T	8
Kallistatin	33	Thrombin/Prothrombin	8
Contactin-1	32	TIMP-2	8
Prekallikrein	27	PCI	8
C2	25	Kallikrein 6	8
α2-Antiplasmin	24	IL-18 Rβ	8
MIP-5	24	IL-13 Rα1	8
NRP1	21	IL-12 Rβ2	8
LY9	19	Hat1	8

[0369]

TABLE 15

Biomarker Designation	Solution K_d(M)	Assay LLOQ (M)	Up or Down Regulated
α1-Antitrypsin	2×10^{-9}	2×10^{-11}	Up
α2-Antiplasmin	8×10^{-9}	6×10^{-13}	Down
α2-HS-Glycoprotein	1×10^{-8}	4×10^{-13}	Down
ADAM 9	4×10^{-9} (pool)	NM	Down
ARSB	3×10^{-9}	NM	Down
BAFF Receptor	5×10^{-9} (pool)	NM	Down
C2	1×10^{-10}	5×10^{-14}	Up
C5	1×10^{-9}	4×10^{-12}	Up
C6	7×10^{-12} (pool)	1×10^{-12}	Up
C9	1×10^{-9}	1×10^{-14}	Up
Cadherin-5	2×10^{-9}	4×10^{-12}	Down
Coagulation Factor Xa	2×10^{-10}	4×10^{-13}	Down
Contactin-1	5×10^{-11}	8×10^{-14}	Down
Contactin-4	3×10^{-10}	8×10^{-13}	Down
ERBB1	1×10^{-10}	1×10^{-14}	Down
Growth hormone receptor	3×10^{-9}	5×10^{-12}	Down
Hat1	1×10^{-9}	NM	Down
HGF	4×10^{-10}	NM	Up
HSP 90α	1×10^{-10}	1×10^{-12}	Up
IL-12 Rβ2	2×10^{-9} (pool)	NM	Down
IL-13 Rα1	3×10^{-9}	NM	Up
IL-18 Rα	6×10^{-11}	NM	Up
Kallikrein 6	4×10^{-9} (pool)	NM	Up
Kallistatin	2×10^{-11} (pool)	7×10^{-14}	Down
LY9	1×10^{-9}	NM	Down
MCP-3	6×10^{-9}	2×10^{-12}	Down
MIP-5	9×10^{-9} (pool)	2×10^{-10}	Up
MMP-7	7×10^{-11}	3×10^{-13}	Up
MRC2	2×10^{-9}	1×10^{-13}	Down
NRP1	9×10^{-11}	1×10^{-14}	Up
PCI	1×10^{-10}	1×10^{-12}	Down
Prekallikrein	2×10^{-11} (pool)	3×10^{-13}	Down
Properdin	2×10^{-11}	2×10^{-12}	Down
RBP	1×10^{-11} (pool)	9×10^{-11}	Down
RGM-C	3×10^{-11}	NM	Down
SAP	7×10^{-10}	3×10^{-13}	Up
SCF sR	5×10^{-11}	3×10^{-12}	Down
SLPI	2×10^{-11}	9×10^{-13}	Up
sL-Selectin	2×10^{-10} (pool)	2×10^{-13}	Down
Thrombin/Prothrombin	5×10^{-11}	7×10^{-13}	Down
TIMP-2	1×10^{-10}	6×10^{-11}	Down
Troponin T	2×10^{-10}	5×10^{-11}	Down

[0370]

TABLE 16

Aptamer Designation	μ_c	σ_c^2	μ_d	σ_d^2	KS	p-value	AUC
α1-Antitrypsin	3386	7.20E+05	5948	5.92E+06	0.62	2.03E−19	0.86
α2-Antiplasmin	19115	3.68E+06	16103	5.43E+06	0.54	3.02E−15	0.80
α2-HS-Glycoprotein	1747	6.19E+04	1474	8.61E+04	0.44	3.51E−10	0.75
ADAM 9	1844	2.17E+04	1685	1.71E+04	0.47	2.39E−11	0.78
ARSB	6297	2.92E+05	5808	2.21E+05	0.42	3.47E−09	0.76
BAFF Receptor	3265	6.02E+04	3079	3.34E+04	0.38	7.61E−08	0.71
C2	107229	9.91E+07	117783	1.89E+08	0.43	1.64E−09	0.73
C5	14468	4.15E+06	16477	5.22E+06	0.40	1.89E−08	0.74
C6	92660	1.73E+08	107328	2.82E+08	0.41	9.22E−09	0.76
C9	161177	9.17E+08	208251	9.01E+08	0.61	6.01E−19	0.86
Cadherin-5	9561	2.58E+06	8221	1.89E+06	0.35	1.96E−06	0.74
Coagulation Factor Xa	18670	1.12E+07	15407	9.80E+06	0.43	7.64E−10	0.76
contactin-1	37472	4.81E+07	29895	7.16E+07	0.41	7.23E−09	0.75
Contactin-4	14963	9.29E+06	12268	8.16E+06	0.41	9.22E−09	0.73
ERBB1	52741	6.94E+07	41543	6.56E+07	0.53	1.08E−14	0.81
Growth hormone receptor	1057	1.90E+04	942	7.06E+03	0.39	3.02E−08	0.76
Hat1	1019	1.07E+04	928	6.33E+03	0.42	2.11E−09	0.75
HGF	668	4.07E+03	735	4.67E+03	0.41	5.67E−09	0.75
HSP 90α	40733	3.01E+08	55087	3.31E+08	0.38	7.61E−08	0.71
IL-12 Rβ2	1217	1.42E+04	1099	1.56E+04	0.41	9.22E−09	0.75
IL-13 Rα1	614	6.40E+03	697	8.92E+03	0.42	3.47E−09	0.74
IL-18 Rβ	449	1.30E+03	488	1.48E+03	0.44	3.51E−10	0.76
Kallikrein 6	256	1.67E+03	298	2.15E+03	0.42	2.11E−09	0.75
Kallistatin	111611	3.01E+08	85665	5.64E+08	0.48	5.89E−12	0.82
LY9	983	2.19E+04	845	1.46E+04	0.43	9.86E−10	0.75
MCP-3	703	4.88E+03	642	2.71E+03	0.43	9.86E−10	0.75
MIP-5	1531	4.55E+05	2123	7.95E+05	0.33	5.35E−06	0.72
MMP-7	3057	2.61E+06	5936	1.74E+07	0.44	2.70E−10	0.74
MRC2	16105	1.78E+07	12716	1.09E+07	0.39	3.82E−08	0.72
NRP1	5314	1.41E+06	6450	9.96E+05	0.43	9.86E−10	0.74
PCI	31852	4.29E+07	22140	8.05E+07	0.53	1.48E−14	0.80
Prekallikrein	122660	3.23E+08	100877	2.99E+08	0.52	7.01E−14	0.80
Properdin	65527	1.10E+08	55599	1.25E+08	0.41	1.17E−08	0.74
RBP	5193	1.21E+06	4088	1.36E+06	0.45	1.22E−10	0.73
RGM-C	21625	2.11E+07	17527	9.18E+06	0.43	1.64E−09	0.78
SAP	142805	7.07E+08	167146	7.28E+08	0.38	7.61E−08	0.75
SCF sR	12432	1.09E+07	9472	5.69E+06	0.44	2.70E−10	0.76
SLPI	25007	2.07E+07	35986	1.22E+08	0.59	1.02E−17	0.85
sL-Selectin	30048	3.31E+07	24163	2.50E+07	0.43	9.86E−10	0.79
Thrombin/Prothrombin	62302	1.67E+07	58099	1.80E+07	0.45	1.59E−10	0.75

TABLE 16-continued

Aptamer Designation	μ_c	σ_c^2	μ_d	σ_d^2	KS	p-value	AUC
TIMP-2	15793	3.16E+06	113796	2.64E+06	0.49	1.04E−12	0.79
Troponin T	1972	3.68E+04	1767	2.58E+04	0.47	1.81E−11	0.78

[0371]

TABLE 17

Sensitivity & Specificity for Exemplary Combinations of BAFF Receptors

#										Sensitivity	Specificity	Sensitivity + Specificity	AUC
1	BAFF Receptor									0.744	0.564	1.308	0.7
2	BAFF Receptor	RGM-C								0.821	0.733	1.554	0.81
3	BAFF Receptor	RGM-C	HGF							0.833	0.744	1.577	0.84
4	BAFF Receptor	RGM-C	HGF	SLPI						0.846	0.8	1.646	0.89
5	BAFF Receptor	RGM-C	HGF	SLPI	C9					0.885	0.81	1.695	0.92
6	BAFF Receptor	RGM-C	HGF	SLPI	C9	α2-Antiplasmin				0.91	0.846	1.756	0.92
7	BAFF Receptor	RGM-C	HGF	SLPI	C9	α2-Antiplasmin	SAP			0.923	0.846	1.769	0.93
8	BAFF Receptor	RGM-C	HGF	SLPI	C9	α2-Antiplasmin	SAP	MMP-7		0.974	0.856	1.83	0.94
9	BAFF Receptor	RGM-C	HGF	SLPI	C9	α2-Antiplasmin	SAP	MMP-7	MCP-3	0.962	0.882	1.844	0.94
10	BAFF Receptor	RGM-C	HGF	SLPI	C9	α2-Antiplasmin	SAP	MMP-7	MCP-3	HSP 90α	0.974	0.882	1.856	0.94

[0372]

TABLE 18

Parameters derived from training set for naïve Bayes classifier.

Biomarker	μ_c	σ_c^2	μ_d	σ_d^2
HGF	668	4.07E+03	735	4.67E+03
SLPI	25007	2.07E+07	35986	1.22E+08
C9	161177	9.17E+08	208251	9.01E+08
α2-Antiplasmin	19115	3.68E+06	16103	5.43E+06
SAP	142805	7.07E+08	167146	7.28E+08
MMP-7	3057	2.61E+06	5936	1.74E+07
BAFF Receptor	3265	6.02E+04	3079	3.34E+04
RGM-C	21625	2.11E+07	17527	9.18E+06
MCP-3	703	4.88E+03	642	2.71E+03
MRC2	16105	1.78E+07	12716	1.09E+07

[0373]

TABLE 19

Number of Samples by Site

	Benign	Cancer
Site 1	114	87
Site 2	81	55
TOTAL	195	142

[0374]

TABLE 20

Biomarkers of Ovarian Cancer from All Site Analysis (Aggregated Data)

α2-Antiplasmin	Contactin-4	NRP1
α2-HS-Glycoprotein	ERBB1	Properdin
ADAM 9	HGF	RGM-C
C2	IL-12R132	SCFsR
C5	Kallistatin	SLPI
C6	LY9	sL-Selectin
C9	MCP-3	Thrombin/Prothrombin
Coagulation Factor Xa	MMP-7	Troponin T
Contactin- 1		

[0375]

TABLE 21

Biomarkers of Ovarian Cancer Within Sites

α1-Antitrypsin	Contactin-4	MRC2
α-Antiplasmin	Growth hormone receptor	NRP1
BAFF Receptor	HGF	Prekallikrein
C2	HSP 90α	RGM-C
C6	IL-13 Rα1	SAP
C9	LY9	SCF sR
Cadherin-5	MCP-3	SLPI
Contactin-1	MIP-5	sL-Selectin

[0376]

TABLE 22

Biomarkers of Ovarian Cancer from Blended Data Analysis

α2-Antiplasmin	HGF	PCI
ARSB	IL-12 Rβ2	Prekallikrein
C2	IL-13 Rα1	RBP
C6	IL-18 Rβ	RGM-C
C9	Kallikrein 6	SCF sR
Contactin-1	Kallistatin	SLPI
Contactin-4	LY9	sL-Selectin
ERBB1	MCP-3	Thrombin/Prothrombin
Hat1	NRP1	TIMP-2

[0377]

TABLE 23

Calculation details for naïve Bayes classifier.

Biomarker	RFU	$-\frac{1}{2}\left(\frac{x_i-\mu_{c,i}}{\sigma_{c,i}}\right)^2$	$-\frac{1}{2}\left(\frac{x_i-\mu_{d,i}}{\sigma_{d,i}}\right)^2$	$\ln\left(\frac{x_i-\mu_{c,i}}{\sigma_{c,i}}\right)^2$	Ln(likelihood)	likelihood
HGF	701	−0.134	−0.125	0.069	0.060	1.062
SLPI	34158	−2.018	−0.014	0.886	−1.118	0.327
C9	182792	−0.255	−0.360	−0.009	0.096	1.101
α2-Antiplasmin	19531	−0.023	−1.081	0.195	1.253	3.500
SAP	170310	−0.535	−0.007	0.015	−0.513	0.599
MMP-7	896	−0.894	−0.730	0.948	0.784	2.190
BAFF Receptor	3207	−0.028	−0.242	−0.294	−0.079	0.924
RGM-C	22545	−0.020	−1.371	−0.415	0.936	2.550
MCP-3	733	−0.095	−1.537	−0.294	1.148	3.152
MRC2	12535	−0.357	−0.001	−0.246	−0.601	0.548

What is claimed is:

1. A method for diagnosing that an individual does or does not have ovarian cancer, the method comprising:

detecting, in a biological sample from an individual, biomarker values that each correspond to one of at least N biomarkers selected from Table 1, wherein said individual is classified as having or not having ovarian cancer based on said biomarker values, and wherein N=2-42.

2. The method of claim 1, wherein detecting the biomarker values comprises performing an in vitro assay.

3. The method of claim 2, wherein said in vitro assay comprises at least one capture reagent corresponding to each of said biomarkers, and further comprising selecting said at least one capture reagent from the group consisting of aptamers, antibodies, and a nucleic acid probe.

4. The method of claim 3, wherein said at least one capture reagent is an aptamer.

5. The method of claim 2, wherein the in vitro assay is selected from the group consisting of an immunoassay, an aptamer-based assay, a histological or cytological assay, and an mRNA expression level assay.

6. The method of claim 1, wherein each biomarker value is evaluated based on a predetermined value or a predetermined range of values.

7. The method claim 1, wherein the biological sample is ovarian tissue and wherein the biomarker values derive from a histological or cytological analysis of said ovarian tissue.

8. The method of claim 1, wherein the biological sample is selected from the group consisting of whole blood, plasma, and serum.

9. The method of claim 1, wherein the biological sample is plasma.

10. The method of claim 1, wherein the individual is a human.

11. The method of claim 1, wherein N=2-15.

12. The method of claim 1, wherein N=2-10.

13. The method of claim 1, wherein N=3-10.

14. The method of claim 1, wherein N=4-10.

15. The method of claim 1, wherein N=5-10.

16. The method of claim 1, wherein the individual has a pelvic mass.

17. A computer-implemented method for indicating a likelihood of ovarian cancer, the method comprising:

retrieving on a computer biomarker information for an individual, wherein the biomarker information comprises biomarker values that each correspond to one of at least N biomarkers selected from Table 1;

performing with the computer a classification of each of said biomarker values; and

indicating a likelihood that said individual has ovarian cancer based upon a plurality of classifications, and wherein N=2-42.

18. A computer program product for indicating a likelihood of ovarian cancer, the computer program product comprising:

a computer readable medium embodying program code executable by a processor of a computing device or system, the program code comprising:

code that retrieves data attributed to a biological sample from an individual, wherein the data comprises biomarker values that each correspond to one of at least N biomarkers selected from Table 1, wherein said biomarkers were detected in the biological sample; and

code that executes a classification method that indicates an ovarian cancer status of the individual as a function of said biomarker values; and wherein N=2-42.

19. The computer program product of claim 18, wherein said classification method uses a probability density function.

20. The computer program product of claim 19, wherein said classification method uses two or more classes.

21. The method of claim 17, wherein indicating the likelihood that the individual has ovarian cancer comprises displaying the likelihood on a computer display.

22. A method for diagnosing that an individual does or does not have ovarian cancer, the method comprising:

detecting, in a biological sample from an individual, biomarker values that each correspond to a panel of biomarkers selected from Table 1, wherein said individual is classified as having or not having ovarian cancer, and wherein the panel of biomarkers has a sensitivity+specificity value of 1.64 or greater.

23. The method of claim 22, wherein the panel has a sensitivity+specificity value of 1.69 or greater.

24. The method of claim 22, wherein the individual has a pelvic mass.

* * * * *

专利名称(译)	卵巢癌生物标志物及其用途		
公开(公告)号	US20100221752A2	公开(公告)日	2010-09-02
申请号	US12/574341	申请日	2009-10-06
[标]申请(专利权)人(译)	私募蛋白质体公司		
申请(专利权)人(译)	SOMALOGIC INC.		
当前申请(专利权)人(译)	SOMALOGIC INC.		
[标]发明人	GOLD LARRY STANTON MARTY BRODY EDWARD OSTROFF RACHEL ZICHI DOMINIC STEWART ALEX		
发明人	GOLD, LARRY STANTON, MARTY BRODY, EDWARD OSTROFF, RACHEL ZICHI, DOMINIC STEWART, ALEX		
IPC分类号	G01N33/567 G01N33/53 G06F19/00 G06F17/18		
CPC分类号	G01N33/57449 Y10T436/143333 G06F19/24 G16B40/00		
优先权	61/103149 2008-10-06 US		
其他公开文献	US20100086948A1		
外部链接	Espacenet USPTO		

摘要(译)

本申请包括用于检测和诊断卵巢癌的生物标记物，方法，装置，试剂，系统和试剂盒。在一个方面，本申请提供了可以单独使用或以各种组合使用以诊断卵巢癌或允许将盆腔肿块鉴别诊断为良性或恶性的生物标记物。另一方面，提供了用于诊断个体卵巢癌的方法，其中所述方法包括在来自个体的生物样品中检测至少一种生物标志物值，所述生物标志物值对应于选自表1中提供的生物标志物组的至少一种生物标志物。其中，基于至少一种生物标记值，确定个体被分类为患有卵巢癌，或者确定患有卵巢癌的个体的可能性。