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(54) METHODS FOR IDENTIFYING PATIENTS WITH AN INCREASED LIKELIHOOD OF HAVING OVARIAN CANCER AND COMPOSITIONS THEREFOR

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G01N 33/53	(2006.01)

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(57) ABSTRACT

Screening methods for identifying patients with an increased likelihood of having ovarian cancer are provided. The screening methods involve the detection of expression of a plurality of biomarkers in a body sample, wherein overexpression of the biomarkers is indicative of an increased likelihood of having ovarian cancer. The screening methods may further comprise a two-step analysis. Biomarkers of interest include genes and proteins that are, for example, involved in defects in DNA replication/cell cycle control, cell growth and proliferation, escape from apoptosis, angiogenesis or lymphogenesis, or the mechanisms of cancer cell motility and invasion. In some aspects of the invention, expression of a biomarker is detected at the protein level using a biomarker-specific antibody or at the nucleic acid level using nucleic acid hybridization techniques. Methods for detecting ovarian cancer in patients are further disclosed herein. Kits for practicing the methods of the invention are further provided.

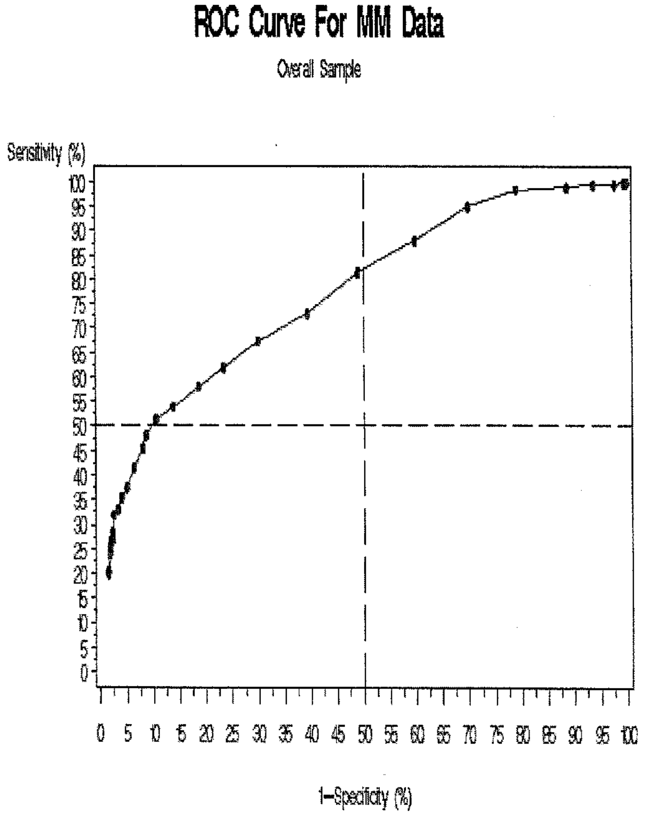


FIG. 1

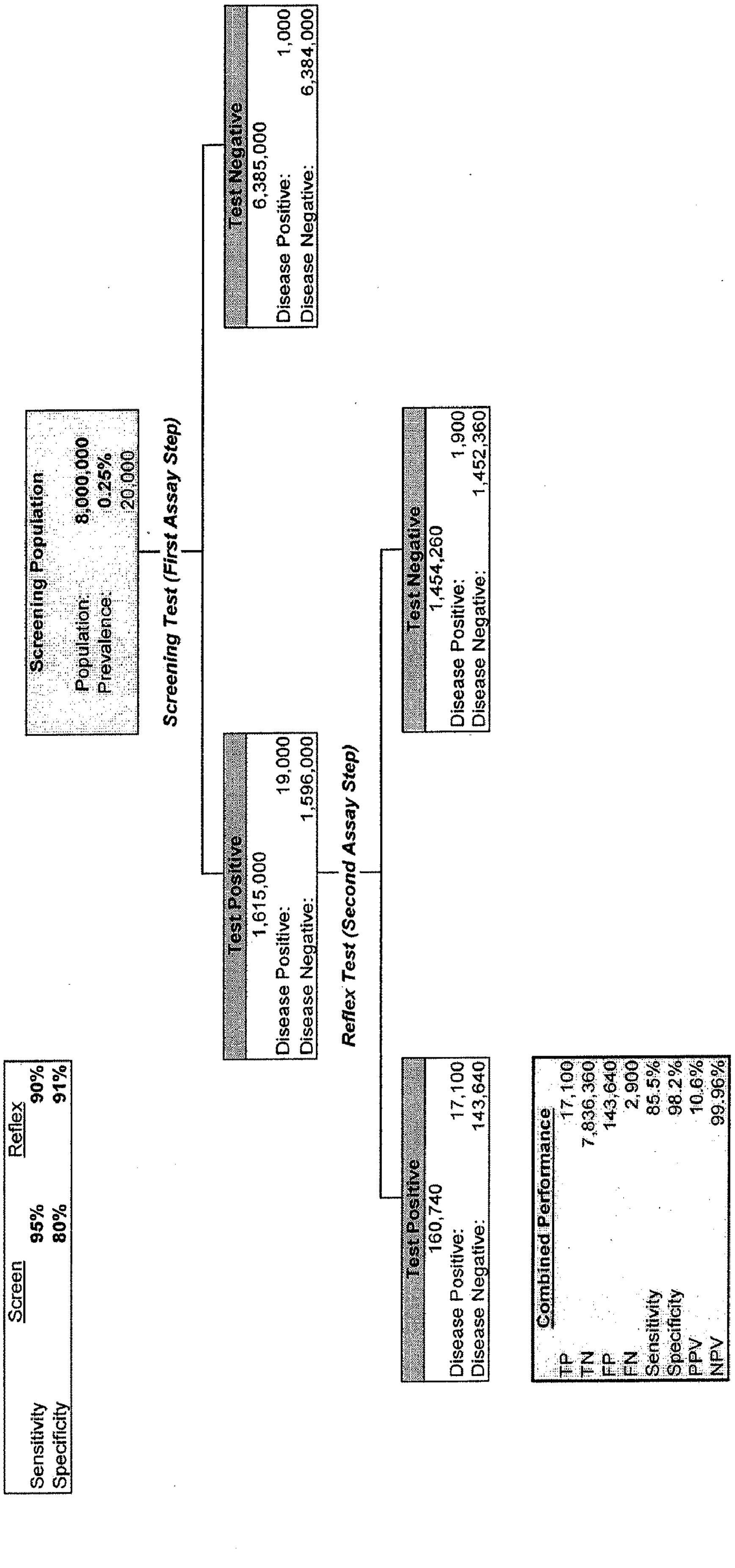

Screen
Reflex
Sensitivity 95% 90%
Specificity 80% 91%
Screening Population
Population: 8,000,000
Prevalence: 0.25%
20,000
Screening Test (First Assay Step)
Test Positive
1,615,000
Disease Positive: 19,000
Disease Negative: 1,596,000
Test Negative
6,385,000
Disease Positive: 1,000
Disease Negative: 6,384,000
Reflex Test (Second Assay Step)
Test Positive
160,740
Disease Positive: 17,100
Disease Negative: 143,640
Test Negative
1,454,260
Disease Positive: 1,900
Disease Negative: 1,452,360
Combined Performance
TP 17,100
TN 7,836,360
FP 143,640
FN 2,900
Sensitivity 85.5%
Specificity 98.2%
PPV 10.6%
NPV 99.96%

FIG. 2

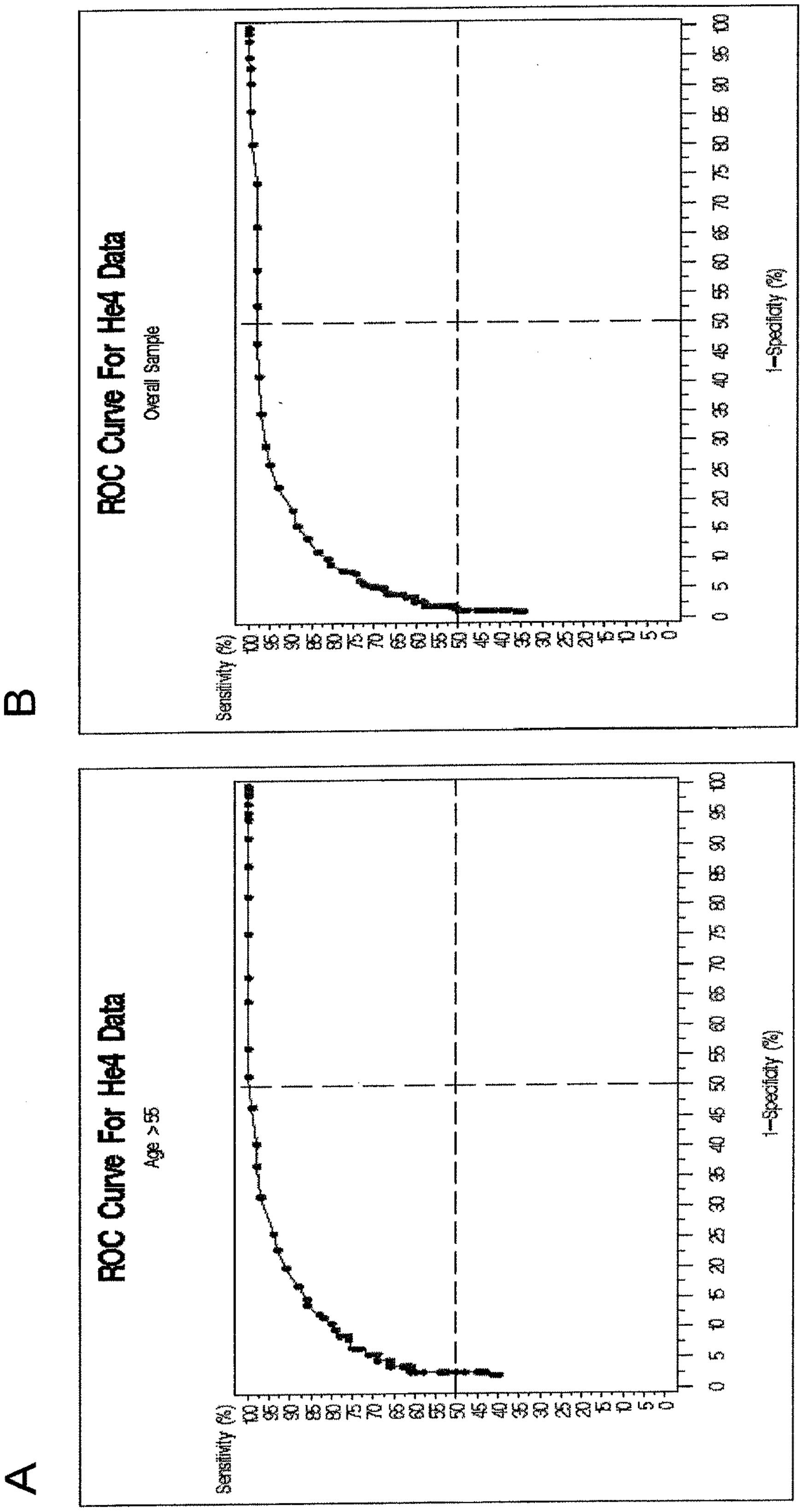
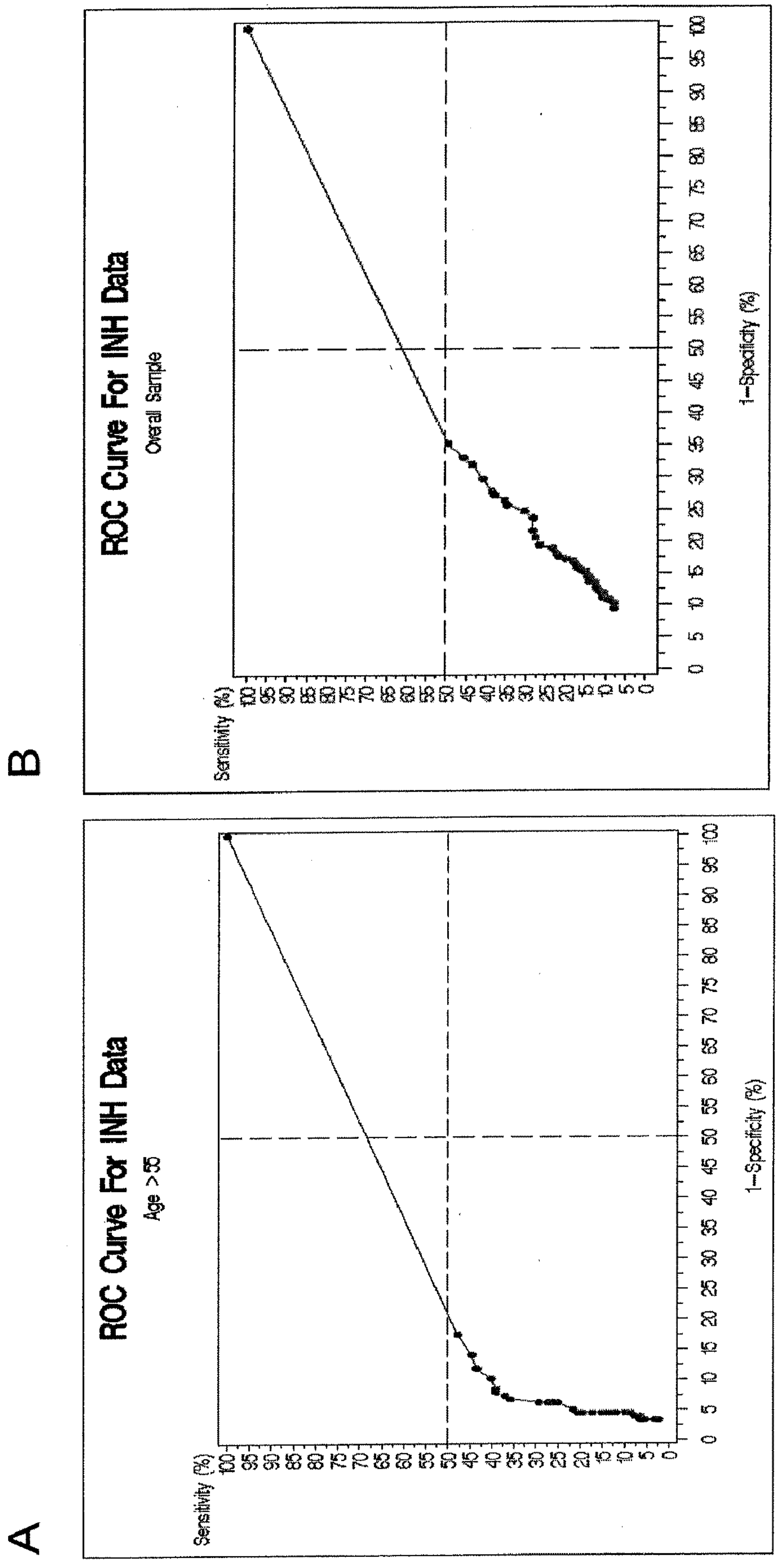

A
ROC Curve For He4 Data
Age >55
Sensitivity (%)
100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
1−Specificity (%)
B
ROC Curve For He4 Data
Overall Sample
Sensitivity (%)
100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
1−Specificity (%)

FIG. 3


A
ROC Curve For INH Data
Age > 55
Sensitivity (%)
1−Specificity (%)
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
B
ROC Curve For INH Data
Overall Sample
Sensitivity (%)
1−Specificity (%)
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

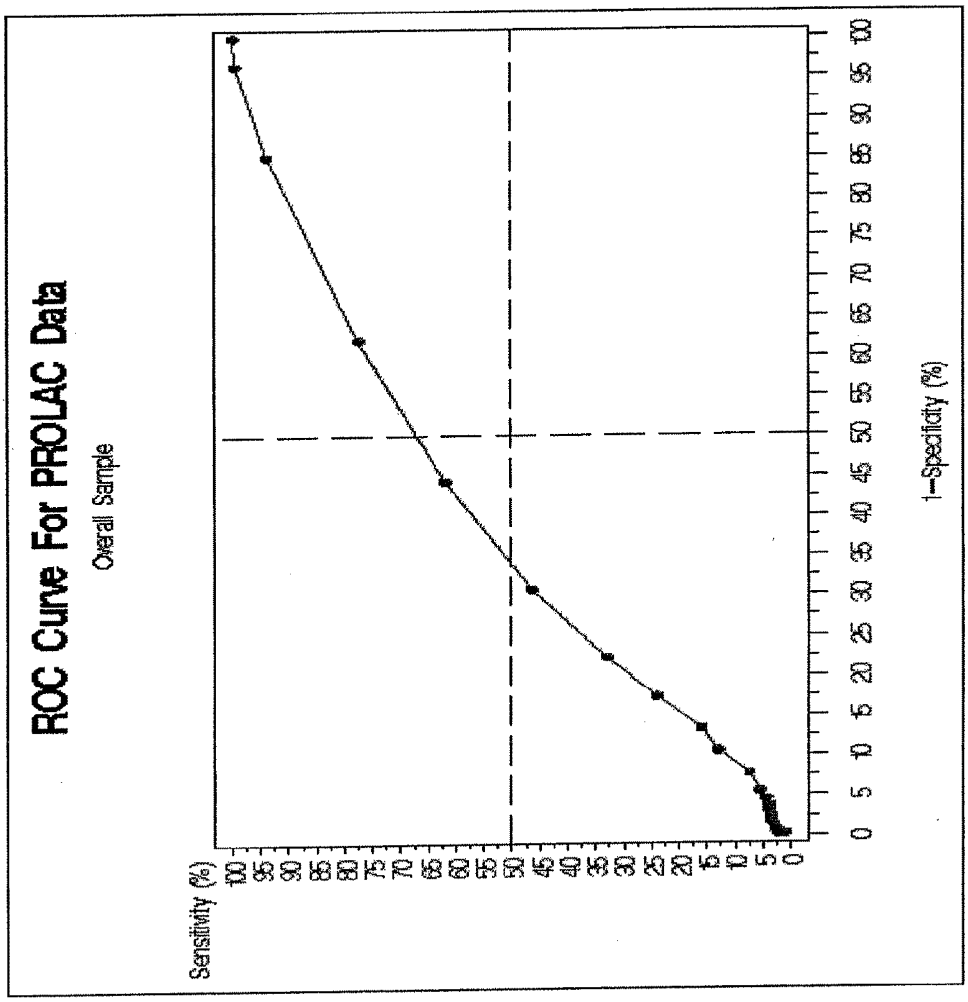

ROC Curve For PROLAC Data
Overall Sample
Sensitivity (%)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
1—Specificity (%)
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100

FIG. 4

FIG. 5

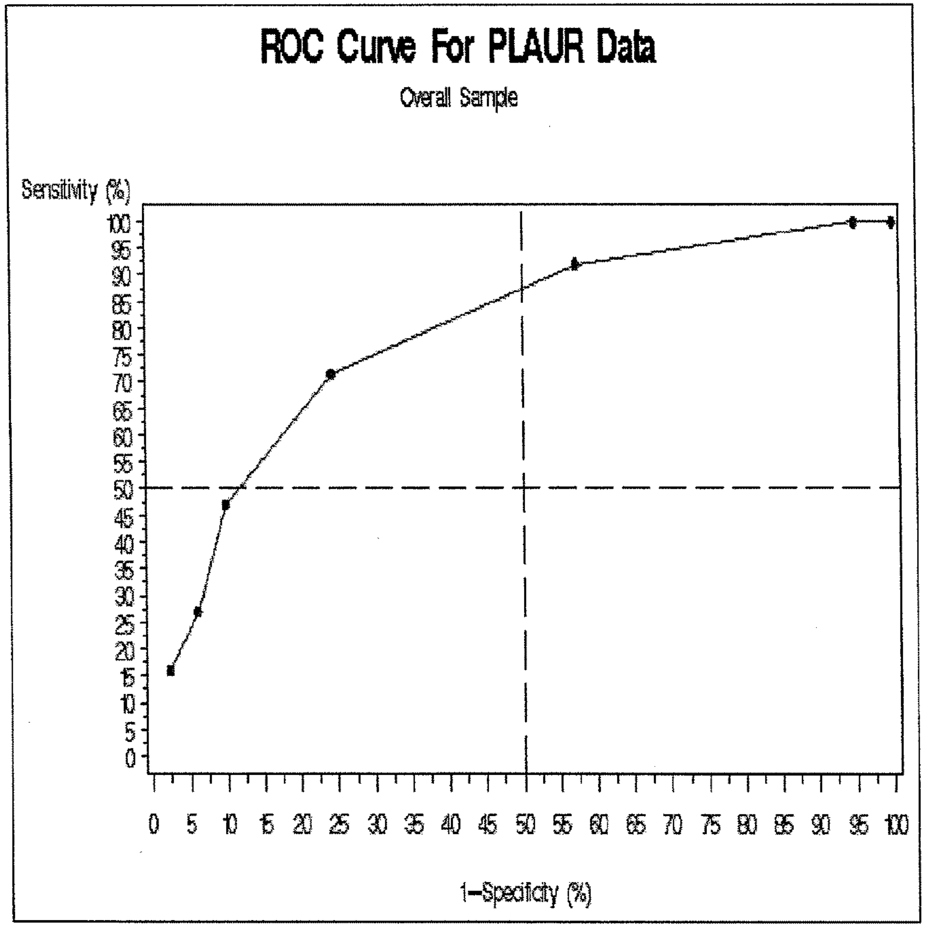
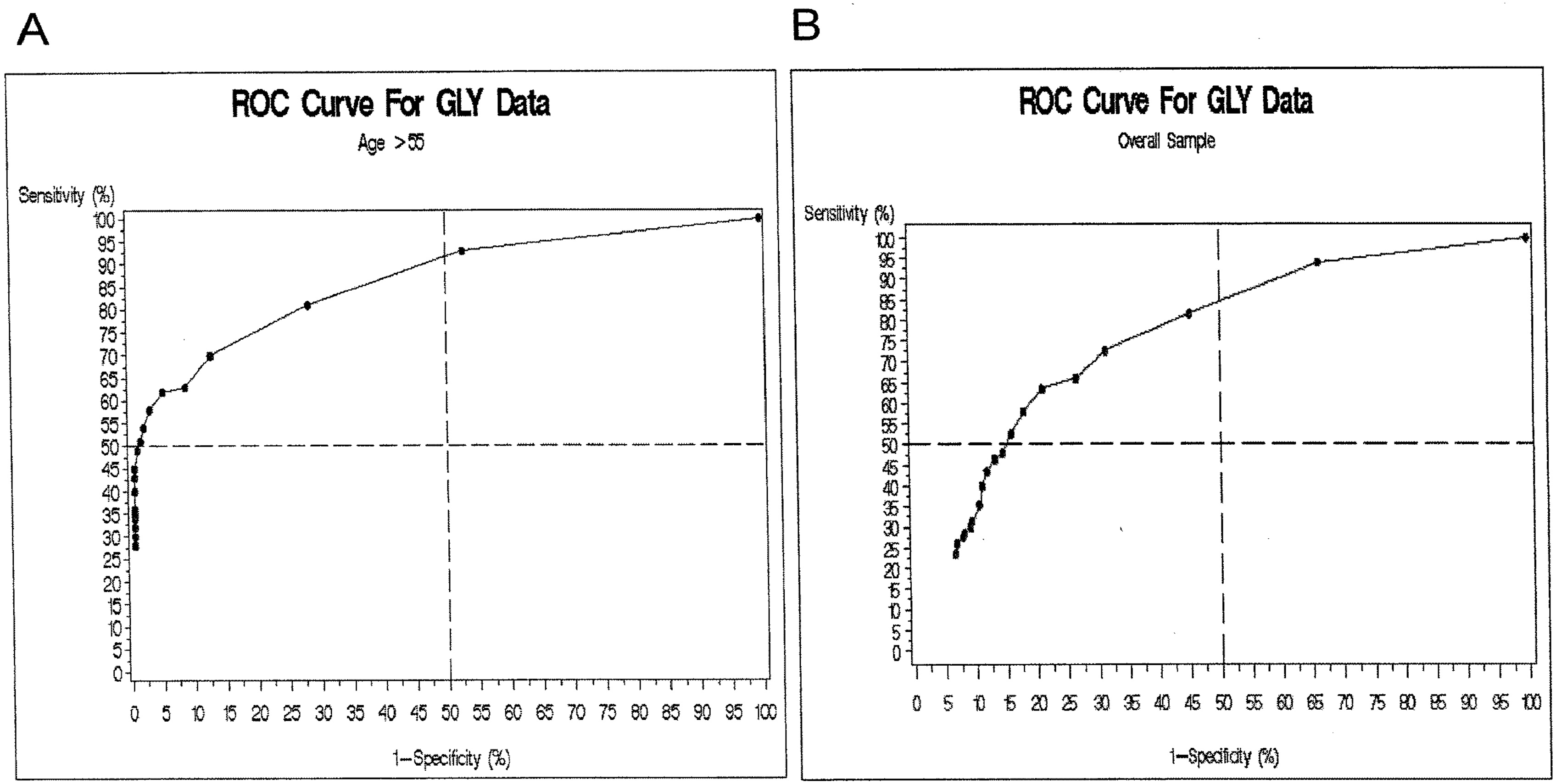

ROC Curve For PLAUR Data
Overall Sample
Sensitivity (%)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
1–Specificity (%)

FIG. 6


A
ROC Curve For GLY Data
Age >55
Sensitivity (%)
100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
1−Specificity (%)
B
ROC Curve For GLY Data
Overall Sample
Sensitivity (%)
100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
1−Specificity (%)

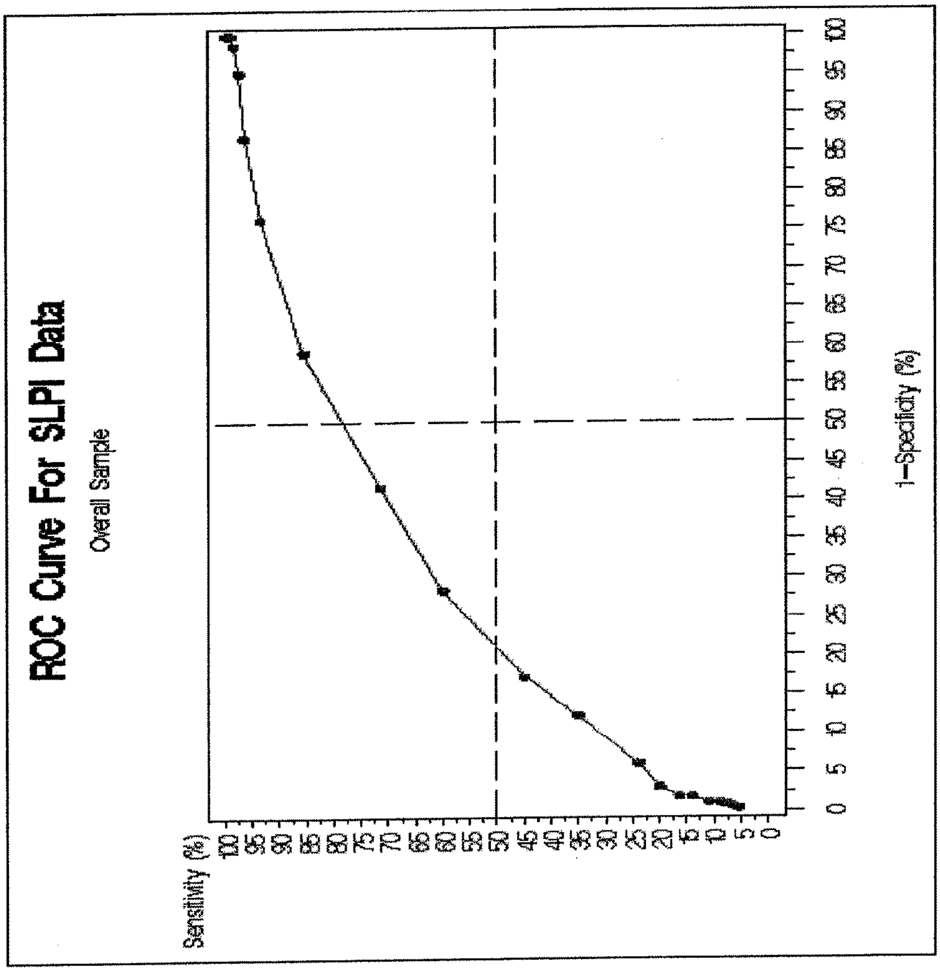

ROC Curve For SLPI Data
Overall Sample
Sensitivity (%)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
1−Specificity (%)

FIG. 7

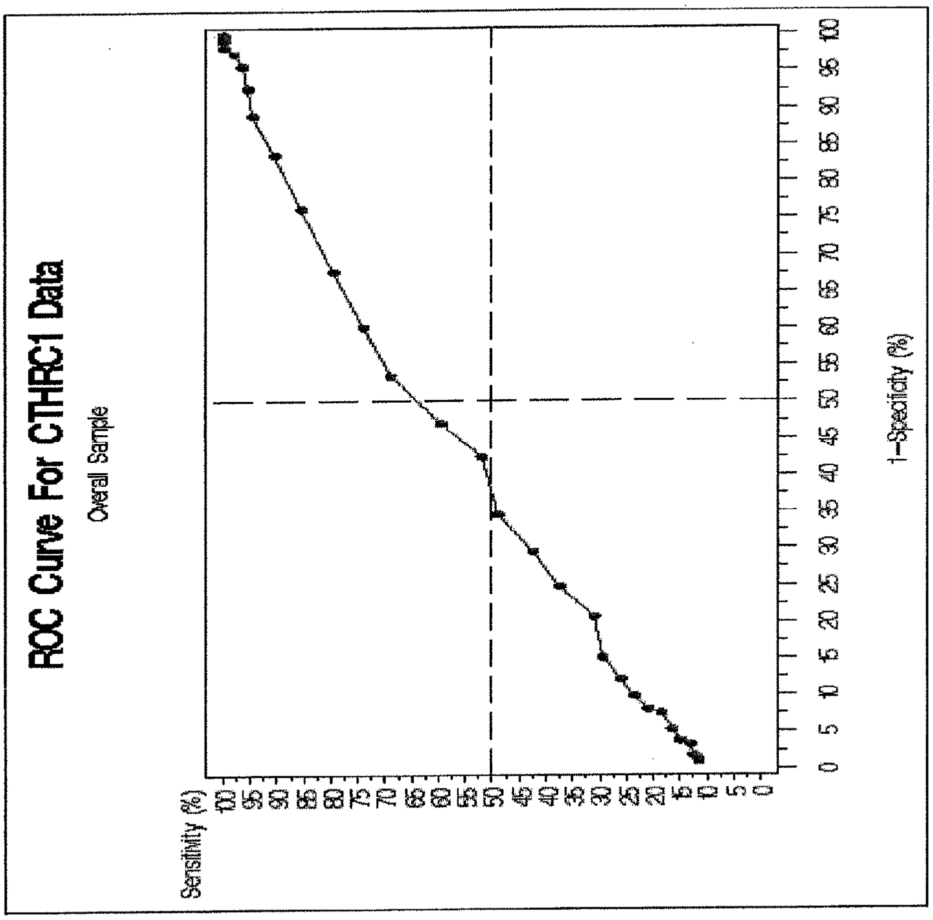

ROC Curve For CTHRC1 Data
Overall Sample
Sensitivity (%)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
1–Specificity (%)
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100

FIG. 8

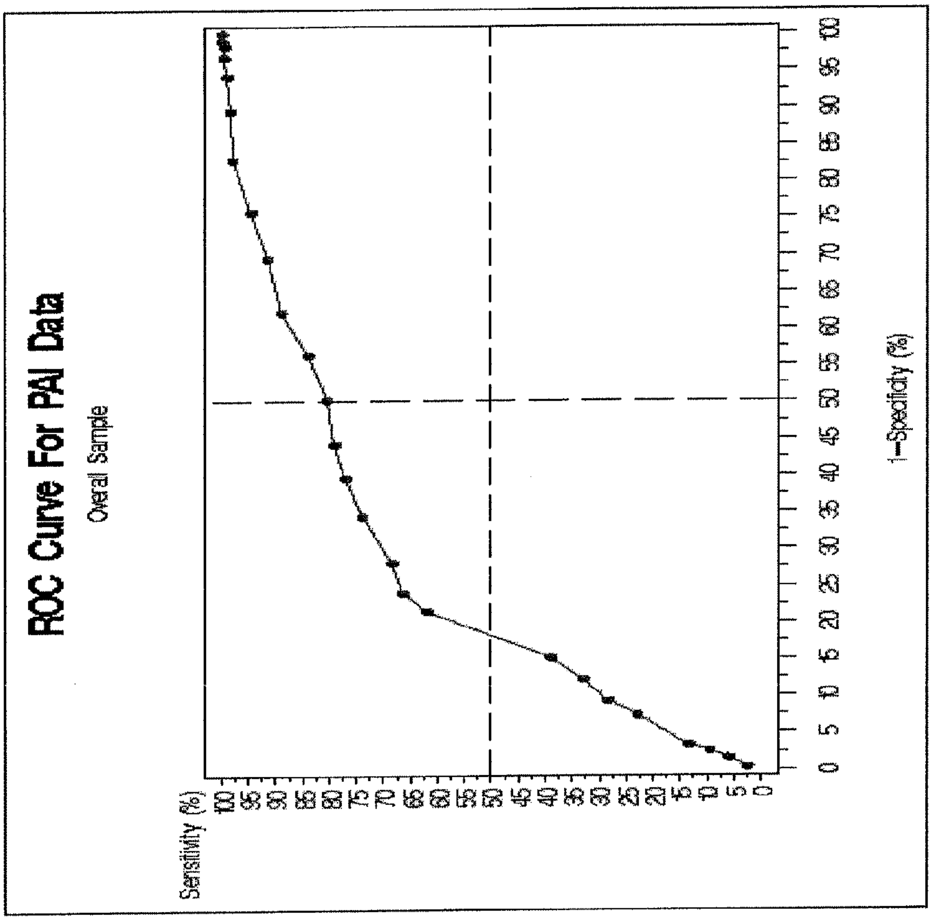

ROC Curve For PAI Data
Overall Sample
Sensitivity (%)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
1−Specificity (%)
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100

FIG. 9

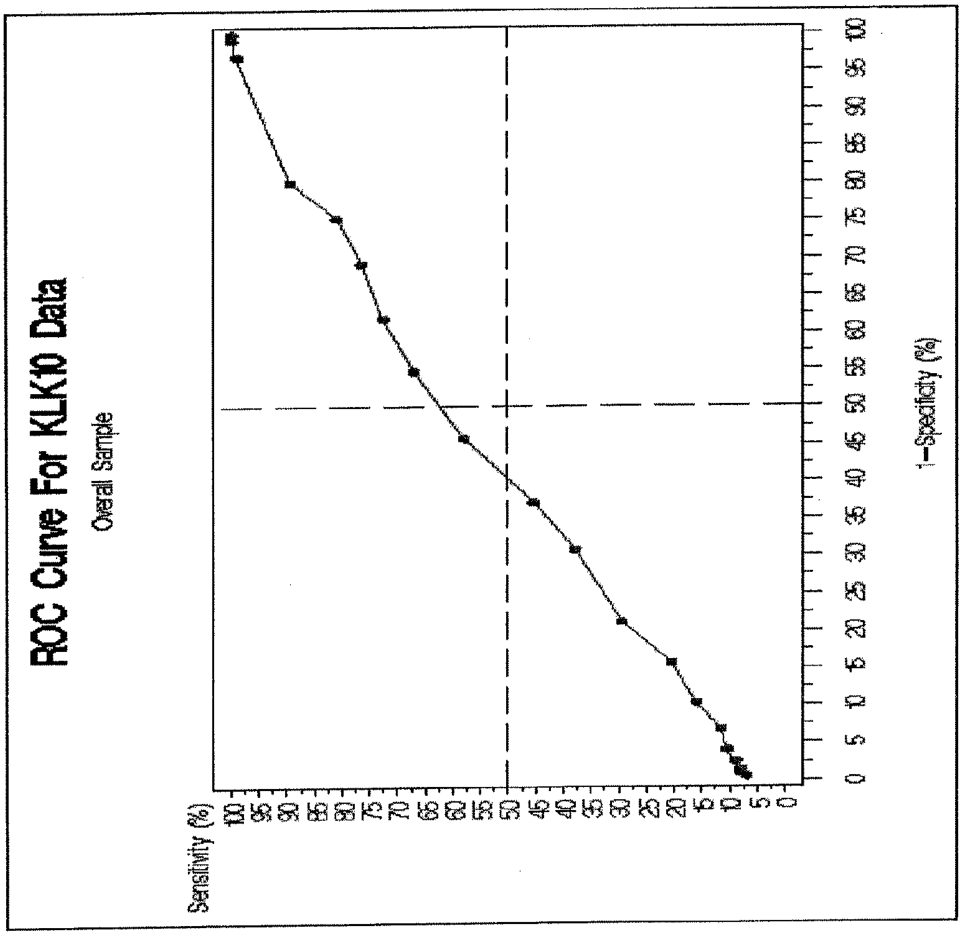

ROC Curve For KLK10 Data
Overall Sample
Sensitivity (%)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
1−Specificity (%)
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100

FIG. 10

FIG. 11

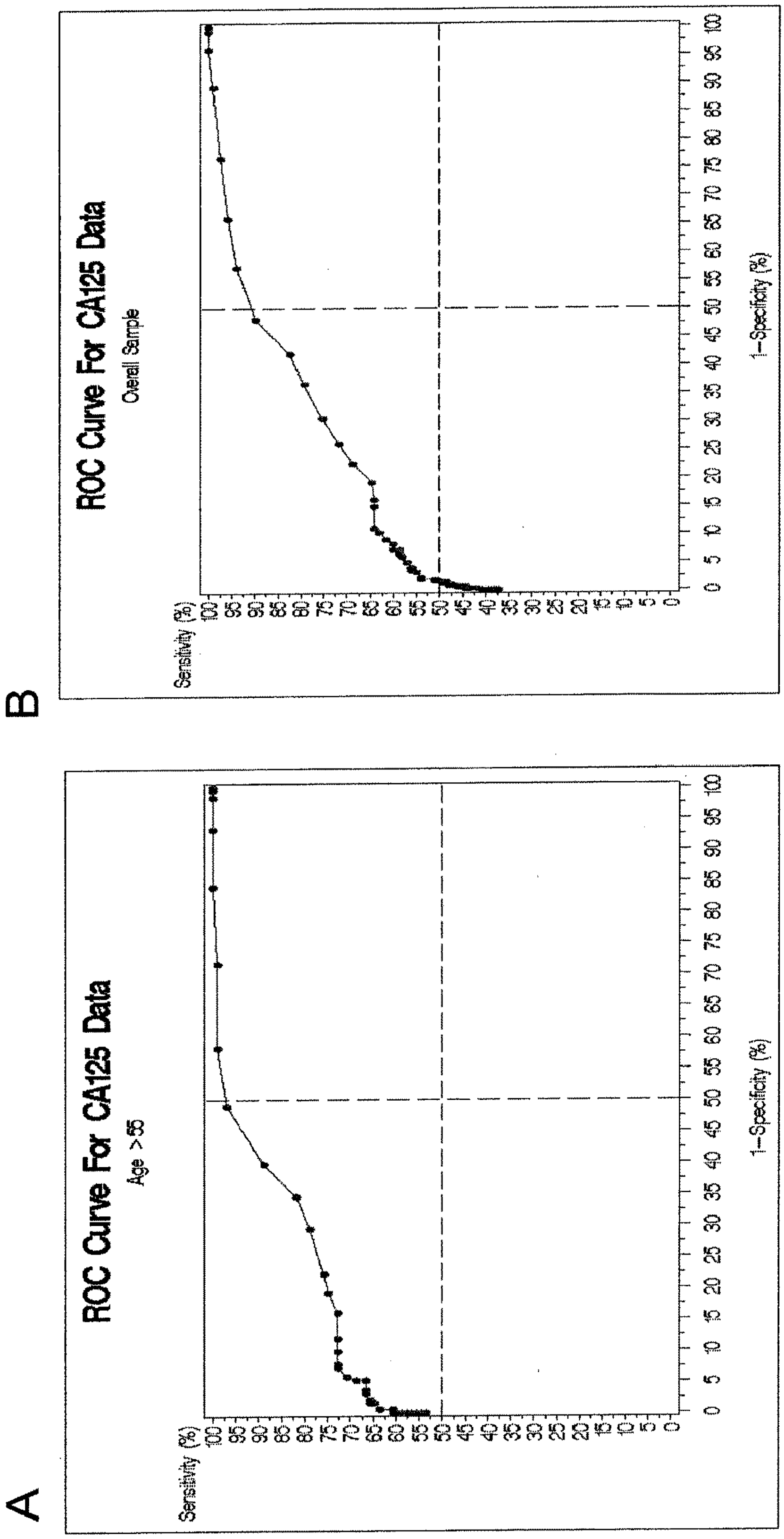
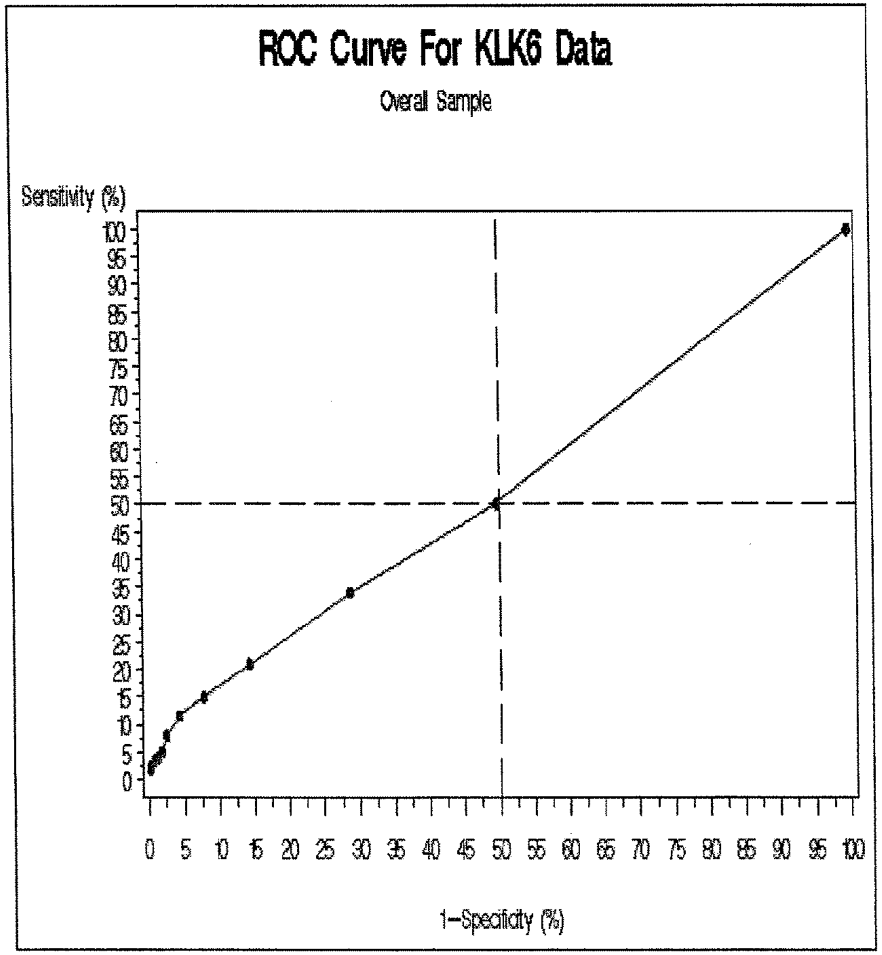

A
ROC Curve For CA125 Data
Age >55
Sensitivity (%)
100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
1-Specificity (%)
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
B
ROC Curve For CA125 Data
Overall Sample
Sensitivity (%)
100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
1-Specificity (%)
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

FIG. 12


ROC Curve For KLK6 Data
Overall Sample
Sensitivity (%)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
1−Specificity (%)

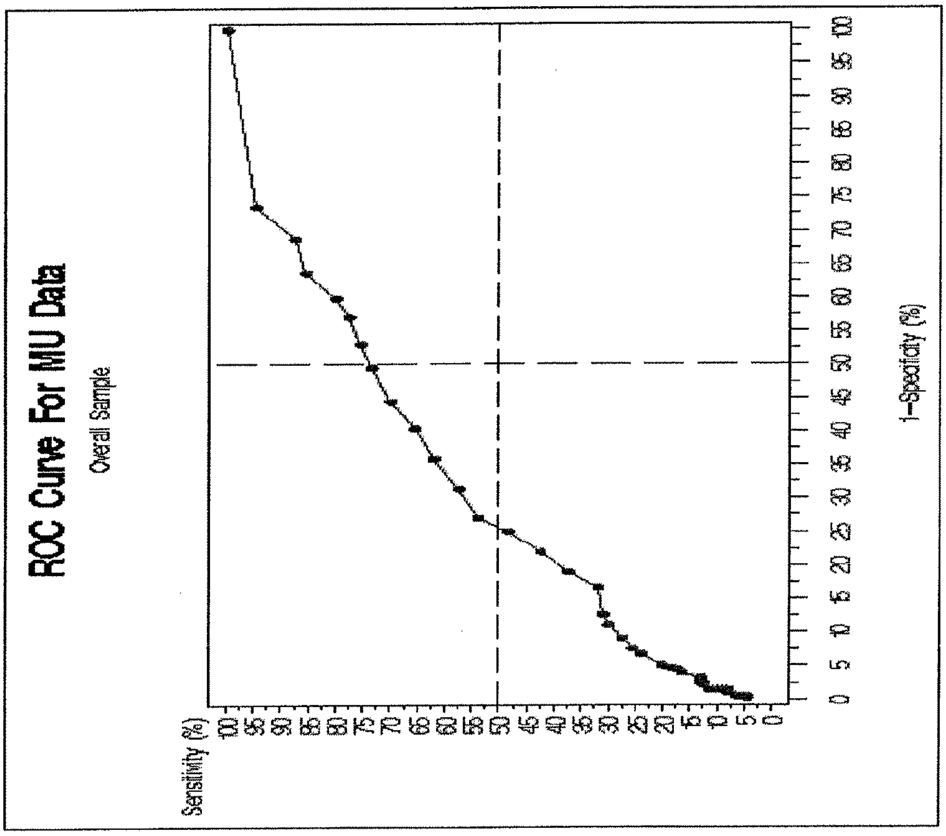
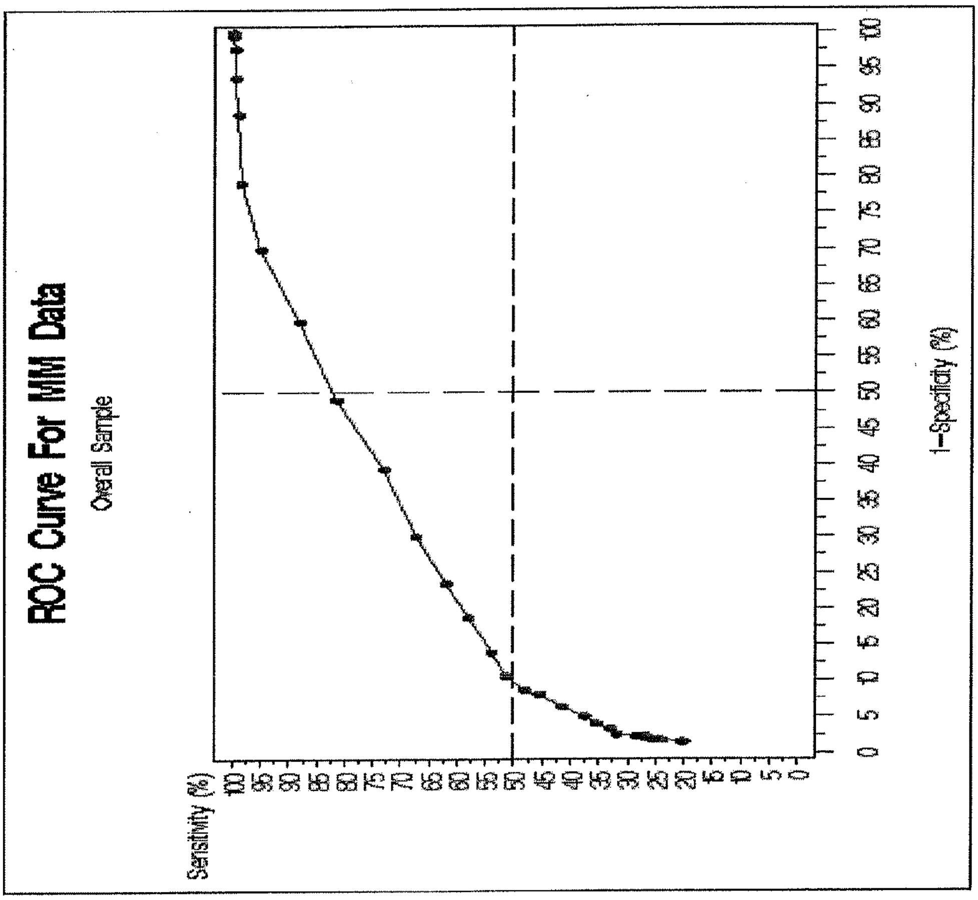

ROC Curve For MU Data
Overall Sample
Sensitivity (%)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
1−Specificity (%)
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100

FIG. 13

FIG. 14


ROC Curve For MM Data
Overall Sample
Sensitivity (%)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
1–Specificity (%)
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100

METHODS FOR IDENTIFYING PATIENTS WITH AN INCREASED LIKELIHOOD OF HAVING OVARIAN CANCER AND COMPOSITIONS THEREFOR

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. application Ser. No. 11/699,229, filed Jan. 29, 2007, which claims the benefit of U.S. Provisional Application Ser. No. 60/762,760, filed on Jan. 27, 2006, both of which are incorporated herein by reference in their entirety.

REFERENCE TO A SEQUENCE LISTING SUBMITTED AS A TEXT FILE VIA EFS-WEB

[0002] The official copy of the sequence listing is submitted concurrently with the specification as a text file via EFS-Web, in compliance with the American Standard Code for Information Interchange (ASCII), with a file name of 364717SequenceListing.txt, a creation date of Oct. 29, 2008, and a size of 284 KB. The sequence listing filed via EFS-Web is part of the specification and is hereby incorporated in its entirety by reference herein.

FIELD OF THE INVENTION

[0003] The present invention relates to methods and compositions for identifying women having an increased likelihood of having ovarian cancer.

BACKGROUND OF THE INVENTION

[0004] Ovarian cancer represents a heterogeneous group of diseases that affect women on a global basis. There are several forms of ovarian cancer which include epithelial cancer, germ-line cancer of the ovaries and ovarian stromal cancer. Epithelial ovarian cancer represents the most common form of the disease. Approximately 5-10% of epithelial ovarian cancer represents a hereditary form of the disease and three common patterns are recognized: ovarian cancer alone; ovarian and breast cancer linked to BRAC1 and BRCA2 genetic linkage on chromosomes 17q21 and 13q12 respectively; and ovarian and colon cancer. The most important risk factor for ovarian cancer is a first degree relative with the disease (e.g., a mother, sister or daughter with ovarian cancer). See, for example, Patridge et al. (1999) *CA-A Cancer Journal for Clinicians* 49:297-320In 2005, there were an estimated 22,000 new cases of ovarian cancer diagnoses and 16,000 deaths from ovarian cancer. See generally American Cancer Society website at www.cancer.org; National Cancer Institute website at www.cancer.gov. Ovarian cancer is a disease that primarily affects post-menopausal women with the median age for diagnosis at 63 years of age. However, the disease can affect women at all age groups. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program at www.seer.cancer.gov.

[0005] The classification of ovarian cancer stage is based upon the extent of localization versus spread of the disease beyond the ovaries. Stage 1 ovarian cancer is confined to one or both of the ovaries. Stage 2 disease involves a tumor in one or both ovaries with pelvic extension. In Stage 3 ovarian cancer, a tumor is present in or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis. Stage 4 ovarian cancer is characterized by distant metastasis beyond the peritoneal cavity. Ovarian cancer is generally diagnosed in an advance stage of the disease due to the lack of specific clinical symptoms that would indicate the presence of small tumors. For women under the age of 50, less than 40% of ovarian cancers are detected when tumors are localized to one or both ovaries and when disease prognosis is best. For women over the age of 50, that number drops to less than 15%. Approximately 68% of women of all age groups afflicted with ovarian cancer are not diagnosed until distant metastasis is present. See generally National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program at www.seer.cancer.gov.

[0006] Ovarian cancer spreads via local shedding from the ovarian epithelium into the peritoneal cavity followed by implantation on the peritoneum and local invasion of the bowel and bladder. The presence of lymph node involvement in ovarian cancer is evident in all stages of diagnosed ovarian cancer. The percentage of positive lymph nodes increases significantly with progression of the disease (i.e., Stage 1, 24%; Stage 2, 50%, Stage 3, 74%; Stage 4, 73%). Id.

[0007] The survival of patients with ovarian cancer is a function of the stage at which the disease is diagnosed, with the 5-year survival decreasing with advanced disease. More than 90% of women diagnosed with ovarian cancer in Stage 1 survive for at least 5 years following diagnosis. The 5-year survival rate drops to less than 30% when the disease is not diagnosed until Stage 4 (i.e., distant metastasis). Id.

[0008] Epithelial ovarian cancer is the most common form of the disease. There are four recognized major histological classes of epithelial ovarian cancer and include serous, endometrioid, clear cell, and mucinous subtypes. The pathogenesis of ovarian cancer is poorly understood but is believed to arise from ovarian surface epithelium. See Bell (2005) *Mod. Pathol.* 18 (Suppl 2):S19-32. Life factors that provide the greatest reduction in risk of ovarian cancer include multiparity, use of oral contraceptives, and breast feeding, all of which prevent ovulation. Because ovulation results in epithelial damage, followed by repair and possible inflammatory responses, repetition of this process throughout a woman's reproductive life without interruption appears to lead to cell damage and to increase the risk of ovarian cancer. See, for example, Ness et al. (1999) *J. Natl. Cancer Inst.* 91:1459-1467. However, there is no recognized, stepwise progression of ovarian cancer through defined precursor lesions, such as those recognized for both cervical carcinoma and colon cancer. Hence, considerable research has been directed at understanding the molecular basis for ovarian cancer and to understand the basic differences between the various histological subtypes of ovarian cancer. These studies have utilized gene expression analysis to provide this understanding and have identified a series of potential biomarkers for evaluation in diagnostic applications. See for example Ono et al. (2000) *Cancer Res.* 60:5007-11; Welsh et al. (2001)*Proc. Natl. Acad. Sci. USA* 98:1176-1181; Donninger et al. (2004)*Oncogene* 23:8065-8077; and Lee et al. (2004) *Int. J. Oncol.* 24(4):847-851.

[0009] Ovarian cancer is often detected with the presentation of overt clinical symptoms, most notably the presentation of abdominal pain, an adnexal mass, abdominal bloating, and urinary urgency. As such, the detection of ovarian cancer is often detected at an advanced stage, where the prognosis and clinical outcome is poor. Detection of ovarian cancer at an early stage (i.e., Stage 1) results in approximately 90% cure rate using standard surgery and chemotherapy; hence there is a clinical need to detect ovarian cancer at an early stage where treatment will be most effective. Unfortunately, current screening methods to detect early stage ovarian cancer are insufficient. The current practice for ovarian cancer screening employs the use of CA 125 and transvaginal ultrasound (sonography). Rising serum levels of CA125 are associated with ovarian cancer and subsequent utilization of transvaginal ultrasound helps detect the presence of ovarian cancer. Confirmation of ovarian disease is based upon invasive procedures such as laprotomy. However, the use of CA125 is ineffective for general population screening due to issues of limited sensitivity, limited specificity, and a poor positive predictive value of <3%. Bast (2003) *J Clin Oncol.* 21 (10 Suppl):200-205. As a result, there is no consensus on the recommendations for generally screening for ovarian cancer in the asymptomatic patient population. See National Cancer Institute Web Site at www.cancer.gov. For high risk patients, the generally accepted procedures for the detection of ovarian cancer include the use of pelvic examinations, the use of CA125 serum testing, and transvaginal ultrasound (sonography). Patridge et al. (1999) *CA-A Cancer Journal for Clinicians* 49:297-320.

[0010] CA125 is a well characterized tumor marker normally expressed on the surface of epithelial cells and is often detected in the serum of normal patients at 35 U/mL. Elevated serum levels of CA125 (>35 U/mL) are often detected in approximately 85% of ovarian cancer patients; the remaining 15% of ovarian cancer patients have normal serum levels of CA125. Furthermore, Calif. 125 is elevated in only 50% of stage 1 ovarian cancer patients, thereby limiting its clinical utility in the early detection of ovarian cancer. However, elevated serum levels of CA125 are used for the monitoring of disease recurrence following therapeutic intervention and this represents the currently approved use for CA125 by the FDA. In addition, elevated serum levels of CA125 are predictive of future detectable ovarian cancer.

[0011] The low prevalence rates of ovarian cancer in the general population create significant challenges for the development of a screening test that would promote early detection of the disease. Screening methods for diseases with low prevalence rates such as ovarian cancer often result in a high ratio of false positives to true positives that limits the clinical utility of such screening programs. Given the significant risks associated with surgical exploration for possible ovarian cancer, a clinically useful screening test should refer to surgery no more than 10 women for every woman who actually has ovarian cancer (i.e., a positive predictive value (PPV) of at least 10%). Skates et al. (2004) *J. Clin. Oncol.* 22:4059-4066. PPV is highly dependent upon the prevalence rates for a particular disease or condition and will shift dramatically as a result of differences in disease prevalence. Therefore, with low-prevalence diseases, such as ovarian cancer, screening diagnostic tests with a relatively low PPV still have significant clinical utility. Potential ovarian cancer screening programs must be adjusted for the low prevalence of ovarian cancer and assessed for biomarker performance and clinical need. See, for example, Skates et al. (2004) *J. Clin. Oncol.* 22:4059-4066; Bast et al. (2005) *Int. J. Gynecol. Cancer* 15:274-281; and Rosen et al. (2005) *Gyn. Oncol.* 99:267-277. Despite efforts to identify a biomarker or panel of biomarkers for the detection, particularly early detection, of ovarian cancer, no adequate screening or diagnostic test that satisfies clinical needs currently exists. Currently available methods, such as detection of CA125, exhibit unacceptably high false-positive rates.

[0012] The current recommendations from the National Cancer Institute state that "there is insufficient evidence to establish that screening for ovarian cancer with serum markers such as CA 125, transvaginal ultrasound or pelvic examinations would result in a decrease in mortality from ovarian cancer" (NCI Summary of Evidence (Level 4, 5); dated February 2005). In light of the serious risk of false-positives with currently available screening techniques, the NCI has not supported institution of general screening procedures for ovarian cancer. As such, no standardized screening test exists for ovarian cancer, despite the fact that early diagnosis significantly improves 5-year survival rates.

[0013] Therefore, a significant need exists in the art for reliable methods and compositions that are capable of specifically identifying women that have ovarian cancer. In particular, screening methods for identifying patients with an increased likelihood of having ovarian cancer are needed. Women identified as having an increased likelihood of having ovarian cancer could be selected for more aggressive diagnostic methods to definitively determine if they presently have the disease. Moreover, such screening methods could be performed in the general female patient population on a routine basis to facilitate the detection of ovarian cancer in the early stages of the disease when prognosis and disease outcome are best.

BRIEF SUMMARY OF THE INVENTION

[0014] Screening methods for identifying patients with an increased likelihood of having ovarian cancer are provided. The methods of the invention generally comprise detecting in a patient body sample expression of a plurality of biomarkers that are selectively overexpressed in ovarian cancer. Overexpression of the biomarkers is indicative of an increased likelihood that the patient has ovarian cancer. The methods of the invention may comprise, for example, a "two-step" analysis, wherein a first assay step is performed to detect the expression of a first biomarker or panel of biomarkers. If the first biomarker or panel of biomarkers is overexpressed, a second assay step is performed to detect the expression of a second biomarker or panel of biomarkers. Overexpression of the first and second biomarkers or panels of biomarkers is indicative of an increased likelihood that the patient has ovarian cancer. The first assay step may be designed to enrich the patient population under review by eliminating a large percentage of women that are "true negatives." The second assay step is typically intended to rule out those patients in the enriched population that do not presently have ovarian cancer by eliminating additional true negative patients from the enriched population. These assay steps may be performed as a single test encompassing both assay steps or as two distinct tests, wherein each test comprises one of the assay steps. A single biomarker or panel of biomarkers may be used in each analysis step to achieve the desired values for sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV). Algorithms may be developed to combine particular biomarkers in the different assay steps to achieve the desired sensitivity, specificity, NPV, and PPV.

[0015] In other aspects of the invention, a screening method for identifying patients with an increased likelihood of having ovarian cancer comprises performing a "single-step" or "one-step" assay in which the overexpression of a plurality of biomarkers that are selectively overexpressed in ovarian cancer is assessed in a patient body sample. Overexpression of these biomarkers is indicative of an increased likelihood of the patient having ovarian cancer. In contrast to the two-step screening method described above, the single-step screening assay does not require performing a first assay step to detect overexpression of a particular biomarker(s) followed by a second assay step to assess if a second biomarker(s) is also overexpressed in order to identify a patient with an increased likelihood of having ovarian cancer.

[0016] A patient that is identified by the screening methods of the invention as having an increased likelihood of having ovarian cancer may be subjected to further diagnostic tests to definitively determine if the patient has ovarian cancer. Patients that are classified as having an increased likelihood of having ovarian cancer in accordance with the methods disclosed herein, but that are determined not to currently have the disease, are generally monitored on a regular basis for the development of ovarian cancer. Moreover, the present methods may be used to screen the general female patient population for ovarian cancer on a routine basis. Thus, the screening methods of the invention may permit the diagnosis of ovarian cancer at earlier stages of the disease when prognosis is significantly better. Kits for practicing the screening methods of the invention are also provided.

[0017] Biomarker expression can be assessed at the protein or nucleic acid level. In some embodiments, biomarker expression is detected at the protein level using biomarker-specific antibodies. Expression of the biomarkers of the invention can also be detected by nucleic acid-based techniques, including, for example, hybridization and RT-PCR. Biomarker expression can be assessed in a variety of body samples, including but not limited to blood (e.g., whole blood, blood serum, blood having platelets removed, etc.), lymph, ascitic fluids, urine, gynecological fluids (e.g., ovarian, fallopian, and uterine secretion, menses, etc.), biopsies, and fluids obtained during laparoscopy.

[0018] Methods for diagnosing ovarian cancer in a patient are also encompassed by the present invention. The diagnostic methods generally comprise detecting in a body sample the expression of a plurality of biomarkers that are selectively overexpressed in ovarian cancer. Overexpression of the plurality of biomarkers is indicative of the presence of ovarian cancer. Kits for practicing the diagnostic methods of the invention are also provided.

[0019] Methods for assessing the efficacy of a particular therapy for ovarian cancer in a patient are also disclosed herein. The invention is further directed to a method for monitoring the regression or progression of ovarian cancer in a patient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] FIG. **1** provides a schematic representation of an exemplary "two-step" screening test for identifying patients with an increased likelihood of having ovarian cancer. The 8 million female patients screened in this example represent the high-risk, asymptomatic U.S. patient population, as defined herein below. In the first assay step, a significant number of true negatives are eliminated from further testing, thereby leaving an enriched population for further analysis in the second assay step. The second assay step further rules out additional patients that are true negatives in order to identify those women with the highest risk of having ovarian cancer. Additional details regarding the two-step screening method are provided in the text.

[0021] FIG. **2** provides the Receiver Operating Characteristic (ROC) plots for HE4 obtained with samples from patients over the age of 55 (A) and with all patient samples. Additional experimental details are provided in Example 2.

[0022] FIG. **3** provides the ROC plots for inhibin A (INH) obtained with samples from patients over the age of 55 (A) and with all patient samples. Additional experimental details are provided in Example 2.

[0023] FIG. **4** provides the ROC plot for prolactin obtained with all patient samples. Additional experimental details are provided in Example 2.

[0024] FIG. **5** provides the ROC plot for PLAU-R obtained with all patient samples. Additional experimental details are provided in Example 2.

[0025] FIG. **6** provides the ROC plots for glycodelin (GLY) obtained with samples from patients over the age of 55 (A) and with all patient samples. Additional experimental details are provided in Example 2.

[0026] FIG. **7** provides the ROC plot for SLPI obtained with all patient samples. Additional experimental details are provided in Example 2.

[0027] FIG. **8** provides the ROC plot for CTHRC1 obtained with all patient samples. Additional experimental details are provided in Example 2.

[0028] FIG. **9** provides the ROC plot for PAI-1 obtained with all patient samples. Additional experimental details are provided in Example 2.

[0029] FIG. **10** provides the ROC plot for KLK-10 obtained with all patient samples. Additional experimental details are provided in Example 2.

[0030] FIG. **11** provides the ROC plots for CA125 obtained with samples from patients over the age of 55 (A) and with all patient samples. Additional experimental details are provided in Example 2.

[0031] FIG. **12** provides the ROC plot for KLK-6 obtained with all patient samples. Additional experimental details are provided in Example 2.

[0032] FIG. **13** provides the ROC plot for Muc-1 (MU) obtained with all patient samples. Additional experimental details are provided in Example 2.

[0033] FIG. **14** provides the ROC plot for MMP-7 (MM) obtained with all patient samples. Additional experimental details are provided in Example 2.

DETAILED DESCRIPTION OF THE INVENTION

[0034] The present invention provides screening methods and compositions for identifying patients with ovarian cancer. The screening methods generally comprise detecting the expression of a plurality of biomarkers in a body sample, particularly a blood sample, more particularly a serum sample, from the patient. Overexpression of the biomarkers used in the practice of the invention is indicative of an increased likelihood of the presence of ovarian cancer. In particular screening methods of the invention, a two-step analysis is used to identify patients having an increased likelihood of having ovarian cancer. The first assay step is performed to detect the expression of a first biomarker or panel of biomarkers in a patient body sample. If the first biomarker or panel of biomarkers is determined to be overexpressed in the sample, a second assay step is performed to detect the expression of a second biomarker or panel of biomarkers. Overexpression of the first and second biomarkers or panels of biomarkers is indicative of an increased likelihood that the patient has ovarian cancer. In certain embodiments, antibodies are used to detect biomarker protein expression. In other aspects of the invention, when the expression of a panel of biomarkers is detected, overexpression of only a subset of the biomarkers analyzed may be sufficient to be indicative of an increased likelihood of the patient having ovarian cancer.

[0035] Although the invention is not limited to a particular mechanism, the first assay step is generally designed to enrich the true-positive patient population (i.e., on a percentage basis) by eliminating a large number of true negatives from further testing. The first assay step may employ a higher sensitivity and negative predictive value (NPV) in order to achieve the desired enrichment of the true-positive patient population. The second assay step is typically intended to rule out those patients in the enriched population that do not presently have ovarian cancer, that is, to eliminate additional true negatives from the enriched population. The second assay step may employ a higher specificity and positive predictive value (PPV), while maintaining a reasonable sensitivity, to further eliminate true negatives from the enriched population of true-positive patients. A schematic representation of the two-step screening test and the results that can be obtained with this method is provided in FIG. **1**.

[0036] One of skill in the art will recognize that these assay steps may be performed as a single screening test encompassing both assay steps or as two distinct tests, wherein each test encompasses one of the assay steps. A single biomarker or panel of biomarkers may be used in each assay step to achieve the desired values for sensitivity, specificity, NPV, and PPV. Algorithms may be developed to select particular biomarkers or combinations of biomarkers to achieve the desired sensitivity, specificity, NPV, and PPV for each assay step and the combined screening test comprising both assay steps.

[0037] In addition to the two-step analysis described herein above, a screening method for identifying patients with an increased likelihood of having ovarian cancer comprises performing a “single-step” or “one-step” screening method or assay in which the expression of a plurality of biomarkers that are selectively overexpressed in ovarian cancer is assessed in a patient body sample. Overexpression of at least one biomarker(s) is indicative of an increased likelihood of the patient having ovarian cancer. In particular aspects of the invention, the single or one-step screening method comprises detecting expression of a plurality of biomarkers, including, for example, HE4, CA 125, glycodelin, MMP-7, Muc-1, PAI-1, CTHRC1, inhibin A, PLAU-R, prolactin, KLK-10, KLK-6, SLPI, and alpha-1 anti-trypsin, in a body sample, wherein overexpression of at least one, particularly two, more particularly three, of the biomarkers is indicative of an increased likelihood of having ovarian cancer. In particular embodiments of the single-step screening method of the invention, expression of glycodelin, HE4, and CA125 is assessed and overexpression of at least one, two, or three of the biomarkers is indicative of an increased likelihood of having ovarian cancer. See, for example, Table 54 and Experimental Example 4. One of skill in the art will appreciate that in contrast to the two-step screening method described above, the single-step screening assay does not require performing a first assay step to detect overexpression of a particular biomarker or panel of biomarkers followed by a second assay step to assess if a second biomarker or panel of biomarkers is also overexpressed in order to identify a patient with an increased likelihood of having ovarian cancer. As such, a first assay step to enrich the population for “true-positive” patients and a second assay step to rule out those patients from the enriched population that do not actually have ovarian cancer (“false positives”) is not required in the single-step screening method described herein.

[0038] The level of expression of a particular biomarker that is sufficient to constitute “overexpression” will vary depending on the specific biomarker used. In particular embodiments of the invention, a “threshold level” of expression is established for a particular biomarker, wherein expression levels above this value are deemed overexpression. A variety of statistical and mathematical methods for establishing the threshold level of expression are known in the art. A threshold expression level for a particular biomarker may be selected, for example, based on data from Receiver Operating Characteristic (ROC) plots, as described in Examples 2 and 3, or on compilations of data from normal patient samples (i.e., a normal patient population). For example, the threshold expression level may be established at the mean expression level plus two times the standard deviation, based on analysis of samples from normal patients not afflicted with ovarian cancer. One of skill in the art will appreciate that these threshold expression levels can be varied, for example, by moving along the ROC plot for a particular biomarker, to obtain different values for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), thereby affecting overall assay performance.

[0039] A patient that is identified as having an increased likelihood of having ovarian cancer in accordance with the disclosed methods may be subjected to further diagnostic testing to definitively determine if the patient has ovarian cancer. “Further diagnostic testing” includes but is not limited to pelvic examination, transvaginal ultrasound, CT scan, MRI, laparotomy, laparoscopy, and biopsy. Such diagnostic methods are well known in the art. Moreover, patients classified as having an increased likelihood of having ovarian cancer that are determined by further diagnostic testing not to currently have ovarian cancer may be closely monitored on a regular basis for the development of ovarian cancer. Monitoring of such patients may include but is not limited to periodic pelvic examination, transvaginal ultrasound, CT scan, and MRI. A physician of ordinary skill in the art will appreciate appropriate techniques for monitoring patients for the development of ovarian cancer. By identifying and monitoring patients having an increased likelihood of having ovarian cancer, the screening methods of the invention may permit the detection of ovarian cancer at an earlier stage of the disease, particularly Stage 1 or Stage 2, when prognosis and disease outcome are greatly improved.

[0040] In particular embodiments, antibodies are used to detect biomarker expression at the protein level. In other aspects of the invention, biomarker expression is detected at the nucleic acid level. Kits for practicing the screening methods of the invention, including the two-step screening method, are further provided.

[0041] By “ovarian cancer” is intended those conditions classified by post-exploratory laparotomy as premalignant pathology, malignant pathology, and cancer (FIGO Stages 1-4). Staging and classification of ovarian cancer are described in detail above. “Early-stage ovarian cancer” refers to those disease states classified as Stage 1 or Stage 2 carcinoma. Early detection of ovarian cancer significantly increases 5-year survival rates. The term “screening method” refers to strategies to identify patients that have an increased likelihood of having ovarian cancer so that such patients can be selected for more aggressive diagnostic methods to definitively determine if the patients have ovarian cancer. The "screening methods" or "diagnostic screening methods" of the invention are generally not intended to definitively diagnose a patient as having or not having ovarian cancer. Rather, such methods are intended to identify women having an increased likelihood of having ovarian cancer so that these women may be definitively diagnosed using other methods (e.g., pelvic examination, transvaginal ultrasound, CT scan, MRI, laparotomy, laparoscopy, and biopsy of tissue samples). Regimens may also be instituted for monitoring patients identified as having an increased likelihood of having ovarian cancer by the present methods but that are determined not to currently have the disease.

[0042] The screening methods of the invention may be performed on a case-by-case basis or as a periodic routine screening test for the general female population. In some embodiments, the screening methods for identifying patients with an increased likelihood of having ovarian cancer may be viewed as comparable to Pap smears for the identification of patients having an increased likelihood of having cervical cancer. As used herein, "identifying patients with an increased likelihood of having ovarian cancer" is intended methods for detecting those females that are more likely to have ovarian cancer. An "increased likelihood of having ovarian cancer" is intended to mean that patients who are determined in accordance with the present methods to exhibit overexpression of particular biomarkers are more likely to have ovarian cancer than those patients who do not.

[0043] "Diagnosing ovarian cancer" is intended to include, for example, diagnosing or detecting the presence of ovarian cancer, monitoring the progression of the disease, and identifying or detecting cells or samples that are indicative of ovarian cancer. The terms diagnosing, detecting, and identifying ovarian cancer are used interchangeably herein. Definitive diagnosis of ovarian cancer will generally comprise performing a biopsy on a tissue sample from the patient.

[0044] The methods of the present invention permit superior assessment of the likelihood of having ovarian cancer when compared with proposed screening methods currently known in the art (e.g., measurement of CA125 levels). As used herein, "specificity" refers to the level at which a method of the invention can accurately identify samples that have been confirmed as nonmalignant by exploratory laparotomy (i.e., true negatives). That is, specificity is the proportion of disease negatives that are test-negative. In a clinical study, specificity is calculated by dividing the number of true negatives by the sum of true negatives and false positives. By "sensitivity" is intended the level at which a method of the invention can accurately identify samples that have been laparotomy-confirmed as positive for ovarian cancer (i.e., true positives). Thus, sensitivity is the proportion of disease positives that are test-positive. Sensitivity is calculated in a clinical study by dividing the number of true positives by the sum of true positives and false negatives. The sensitivity of the disclosed methods for the detection of ovarian cancer is at least about 70%, particularly at least about 80%, more particularly at least about 90, 91, 92, 93, 94, 95, 96, 97, 98, 99% or more. Furthermore, the specificity of the present methods is at least about 70%, particularly at least about 80%, most particularly at least about 90, 91, 92, 93, 94, 95, 96, 97, 98, 99% or more.

[0045] The term "positive predictive value" or "PPV" refers to the percentage of patients with a positive test result in the methods of the invention who actually have ovarian cancer. PPV is calculated in a clinical study by dividing the number of true positives by the sum of true positives and false positives. PPV is highly dependent upon the prevalence rates for a particular disease or condition and will shift dramatically as a result of differences in disease prevalence. Therefore, with low-prevalence diseases, such as ovarian cancer, screening tests with a relatively low PPV still have significant clinical utility. In contrast, a disease with high prevalence rates would require a higher PPV to be clinically useful. See, for example, Skates et al. (2004) *J. Clin. Oncol.* 22:4059-4066; Bast et al. (2005) *Int. J. Gynecol. Cancer* 15:274-281; Rosen et al. (2005) *Gyn. Oncol.* 99:267-277; and Pepe (2004) *The Statistical Evaluation of Medical Tests for Classification and Prediction* (Oxford University Press), all of which are herein incorporated by reference in their entirety. The PPV for the present methods of identifying patients with an increased likelihood of having ovarian cancer is generally at least about 7, 8, 9, 10, 15, 20, 25, 30% or more. In some embodiments, the PPV of a method of the invention is at least about 10%. A PPV of at least about 10% for a diagnostic screening method is considered in the art to be of clinical utility. See Skates et al., supra. The "negative predictive value" or "NPV" of a test is the percentage of patients with a negative test result who actually do not have ovarian cancer. NPV is calculated in a clinical study by dividing the number of true negatives by the sum of true negatives and false negatives. The NPV for the present methods of identifying patients with an increased likelihood of having ovarian cancer is generally at least about 80%, particularly at least about 90%, more particularly at least about 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9% or more. In some embodiments, the NPV of a method of the invention for is at least about 99%. One of skill in the art will appreciate that the PPV and NPV values for the methods of the invention are based on a prevalence-adjusted population and are reflective of the prevalence rates of ovarian cancer within the U.S. female population.

[0046] A "biomarker" is any gene or protein whose level of expression in a tissue or cell is altered compared to that of a normal or healthy cell or tissue. Biomarkers of the invention are selective for ovarian cancer. By "selectively overexpressed in ovarian cancer" is intended that the biomarker of interest is overexpressed in ovarian cancer but is not overexpressed in conditions classified as nonmalignant, benign, and other conditions that are not considered to be clinical disease. Thus, detection of the biomarkers of the invention permits the differentiation of samples indicative of an increased likelihood of having ovarian cancer or the presence of ovarian cancer from normal samples (i.e., samples from patients that are ovarian-cancer free) and samples that are indicative of nonmalignant and benign proliferation. Biomarkers of the invention may be referred to herein interchangeably as "ovarian cancer biomarkers," "markers," or "ovarian cancer markers."

[0047] The biomarkers of the invention include genes and proteins. Such biomarkers include DNA comprising the entire or partial sequence of the nucleic acid sequence encoding the biomarker, or the complement of such a sequence. The biomarker nucleic acids also include RNA comprising the entire or partial sequence of any of the nucleic acid sequences of interest. A biomarker protein is a protein encoded by or corresponding to a DNA biomarker of the invention. A biomarker protein comprises the entire or partial amino acid sequence of any of the biomarker proteins or polypeptides. Fragments and variants of biomarker genes and proteins are also encompassed by the present invention. By "fragment" is intended a portion of the polynucleotide or a portion of the amino acid sequence and hence protein encoded thereby. Polynucleotides that are fragments of a biomarker nucleotide sequence generally comprise at least 10, 15, 20, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 800, 900, 1,000, 1,100, 1,200, 1,300, or 1,400 contiguous nucleotides, or up to the number of nucleotides present in a full-length biomarker polynucleotide disclosed herein. A fragment of a biomarker polynucleotide will generally encode at least 15, 25, 30, 50, 100, 150, 200, or 250 contiguous amino acids, or up to the total number of amino acids present in a full-length biomarker protein of the invention. "Variant" is intended to mean substantially similar sequences. Generally, variants of a particular biomarker of the invention will have at least about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to that biomarker as determined by sequence alignment programs.

[0048] The biomarkers of the invention include any gene or protein that is selectively overexpressed in ovarian cancer, as defined herein above, and may comprise known biomarkers as well as those presently unknown in the art. In particular embodiments, biomarkers are secreted proteins or proteins that are predicted to encode membranous proteins with transmembrane segments and extracellular domains. Biomarkers of interest include HE4, CA125, glycodelin, MMP-7, Muc-1, PAI-1, CTHRC1, inhibin, PLAU-R, prolactin, KLK-10, KLK-6, and SLPI, alpha-1 anti-trypsin (AAT), Imp-2, FLJ10546, FLJ23499, MGC13057, SPON1, S100A1, SLC39A4, TACSTD2, MBG2, HETKL27 (MAL2), Cox-1, protein kinase C-iota, cadherin-6, ADPRT, matriptase, folate receptor, claudin 4, mesothelin, aquaporin 5, cofilin 1, gelsolin, clusterin, alpha tetranectin, vitronectin. pregnancy-associated plasma protein-A (PAPP-A), and folistatin. Biomarkers of particular interest include but are not limited to HE4, CA125, Glycodelin, MMP-7, Muc-1, PAI-1, CTHRC1, inhibin, PLAU-R, prolactin, KLK-10, KLK-6, SLPI, and alpha-1 anti-trypsin (AAT). Biomarkers of more particular interest include HE4, glycodelin, MMP-7, SLPI, PLAU-R, Muc-1, inhibin A, and PAI-1.

[0049] HE4 is a protein that was first observed in human epididymis tissue, and the name "HE4" is an abbreviation of "Human Epididymis Protein 4". Subsequent studies have shown that HE4 protein is also present in the female reproductive tract and other epithelial tissues. The HE4 gene resides on human chromosome 20q12-13.1, and the 20q12 chromosome region has been found to be frequently amplified in ovarian carcinomas. Studies have shown that HE4 is expressed by ovarian carcinoma cells. The protein is N-glycosylated and is secreted extracellularly. See, for example, Drapin et al. (2005) Cancer Research 65(6): 2162-9; Hellström et al. (2003) *Cancer Research* 63: 3695-3700; and Bingle et al. (2002) *Oncogene* 21: 2768-2773.

[0050] CA-125 is a high molecular weight, cell surface glycoprotein detected in the serum of a large proportion of patients with ovarian epithelial cancer (OEC). However, while the percentage is high (75-90%) in advanced stages of this disease, it is only elevated in 50% of the patients with Stage 1 disease. Use of CA-125 as a marker for OEC is problematic because the molecule is also expressed in a number of normal and pathological conditions including menstruation, pregnancy, endometriosis, inflammatory diseases and other types of cancer. Improved sensitivity and specificity for OEC has been reported among post menopausal women. See, for example, Bast et al. (1998) *Int'l J Biological Markers* 13:170-187; and Moss et al. (2005) *J. Clin. Pathol.* 58:308-312.

[0051] Glycodelin is a member of the lipocalin superfamily with several distinctive actions in cell recognition and differentiation principally in the reproductive axis. Previously, this glycoprotein has been named progesterone-associated endometrial protein (PAEP) and placental protein 14 (PP-14). The name change was in part initiated because glycodelin is not synthesized by the endometrium or placenta. Glycodelin has been purified from amniotic fluid as 28 kDa molecule in SDS gels and reported to be synthesized by the normal ovary and by malignant ovarian tumors. Its presence has been reported in serum. See generally Seppala et al. (2002) *Endocrine Reviews* 23:401-430; Pala et al. (1997) *J. Chromatography B* 704:25-34; Meerit Kamarainen et al. (1996) *Amer. J Pathology* 148:1435-1443.

[0052] Proteins of the matrix metalloproteinase (MMP) family are involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling, as well as in disease processes, such as arthritis and metastasis. Most MMP's are secreted as inactive proproteins which are activated when cleaved by extracellular proteinases. The enzyme encoded by the MMP-7 (matrilysin) gene degrades proteoglycans, fibronectin, elastin and casein and differs from most MMP family members in that it lacks a conserved C-terminal protein domain. The enzyme is involved in wound healing, and studies in mice suggest that it regulates the activity of defensins in intestinal mucosa. The MMP-7 gene is part of a cluster of MMP genes which localize to chromosome 11q22.3. MMP-7 is expressed in epithelial cells of normal and diseased tissue. It is known to be expressed in tumors of the breast, colon, and prostate, among others. It is abundant in ovarian carcinoma cells, but not detectable by IHC in normal ovarian epithelial tissue.

[0053] Muc-1 (mucin1, EMA, PEM, episialin) is a large cell surface mucin glycoprotein expressed by most glandular and ductal epithelial cells and some hematopoietic cell lineages. Functionally, Muc-1 is believed be involved with cell protection and lubrication, and may play a role in cell adhesion, and/or cell signaling. The Muc-1 gene contains seven exons and produces several different alternatively spliced variants. The major expressed form of Muc-1 uses all seven exons and is a type 1 transmembrane protein with a large extracellular tandem repeat domain. The tandem repeat domain is highly O-glycosylated and alterations in glycosylation have been shown in epithelial cancer cells. Muc-1 has been found to be elevated in many types of cancer, most notably with advanced breast cancer. Standing alone as a serum-based marker, it would have little specificity, but could be utilized as a prognostic aid, in conjunction with other, more specific markers.

[0054] PAI-1 (i.e., plasminogen activator inhibitor type 1) is a serine or cysteine proteinase inhibitor. The PAI-1 mRNA is 2876 bp in length, and the encoded protein is 402 amino acids long. The calculated molecular weight is 42,769 Da, whereas the affinity-purified protein is reported to be approximately 50,000 Da, as determined by SDS gel electrophoresis. PAI-1 plays a role in inhibiting extracellular matrix degradation by PLAU and is a putative unregulated c-Myc target gene. PAI-1 also plays a key role in controlling coagulation and tissue remodeling. PAI-1 limits the production of plasmin and serves to keep fibrinolysis in check. Some physiological functions involving the inhibition of plasmin by PAI-1 include ovulation, cell migration, and epithelial cell differentiation. High PAI-1 levels in cancer indicates poor prognosis for survival of many human cancers, including breast and lung cancers. Pappot et al. Nov. 29, 2005) *Lung Cancer* [Epub ahead of print]; Chazaud et al. (2002) *American Journal of Pathology* 160:237-246.

[0055] Collagen triple helix repeat containing 1 (CTHRC1) was identified in a screen for differentially expressed sequences in balloon-injured versus normal arteries. In studies by Pyagay et al., CTHRC1 expression was not detectable in normal arteries. However, on injury it was transiently expressed by fibroblasts of the remodeling adventitia and by smooth muscle cells of the neointima. It was also found in the matrix of calcifying human atherosclerotic plaques. CTHRC1 is a secreted 28-kDa protein that is glycosylated and highly conserved from lower chordates to mammals. A short collagen motif with 12 Gly-X-Y repeats appears to be responsible for trimerization of the protein and this renders the molecule susceptible to cleavage by collagenase. Cthrc1 mRNA expression levels are increased in response to transforming growth factor-beta and bone morphogenetic protein-4. Cell migration assays performed with CTHRC1-overexpressing fibroblasts and smooth muscle cells demonstrate that increased CTHRC1 levels are associated with enhanced migratory ability. Furthermore, CTHRC1 overexpression caused a dramatic reduction in collagen type I mRNA and protein levels. The data of Pyagay et al. indicate that the novel molecule CTHRC1 is transiently expressed in the arterial wall in response to injury where it may contribute to vascular remodeling by limiting collagen matrix deposition and promoting cell migration. Pyagay et al. (2005) *Circ. Res.* 96(2): 261-8.

[0056] Inhibins are protein hormones that belong to the transforming growth factor β superfamily and are heterodimers consisting of α and β subunits joined by disulfide bonds. The 2 forms of inhibins (i.e., A and B) differ in the type of β subunit (i.e., βA or βB) linked to the α subunit. In women of reproductive age, inhibins are known to be secreted by granulosa cells of the ovary and circulate in blood. Inhibins vary in concentration through the menstrual cycle and during pregnancy, and impact pituitary FSH production, gametogenesis and gestational events. In post menopausal women inhibins fall to very low levels. Recent publications indicate that inhibins are diagnostic markers for ovarian cancer. See for example Robertson et al. (2002)*Mol. Cell Endocrinol.* 191:97-103; El-Shalakany et al. (2004) *J. Obstet. Gynaecol. Res.* 30: 155-161.

[0057] Plasminogen activator urokinase-receptor (PLAU-R or UPAR) is a cell surface glycoprotein with a molecular weight of approximately 60 kDa that is attached by its carboxy-terminal end to the cell membrane by GPI linkage. PLAU-R serves as a specific receptor for the serine protease urokinase plasminogen activator (uPA) that is involved in basement membrane/extracellular matrix remodeling in both normal and pathological processes. Soluble PLAU-R, released from the cell surface, has been reported to be at elevated concentrations in serum in several types of human cancer including colorectal, breast and ovarian cancer. See for example Sier et al. (1998) *Cancer Res.* 58:1843-1849; and Begum et al. (2004) *Anticancer Research* 24:1981-1986.

[0058] Prolactin is a 198-amino acid, 23 kDa protein hormone secreted in significant quantities by the anterior pituitary gland. In concert with estrogen, prolactin plays an important role in the initiation of mammary gland growth and in lactation. In addition, prolactin is thought to have a significant role in cell growth and immune function. A recent report using a commercially available ELISA kit reported that prolactin levels in serum were significantly elevated in ovarian cancer. See generally Mor et al. (2005) *Proc. Natl Acad. Sci.* 102: 7677-7682.

[0059] Kallikreins are a subgroup of serine proteases having diverse physiological functions. They are clustered as a group on chromosome 19q13. Growing evidence suggests that many kallikreins are implicated in carcinogenesis and some have potential as novel cancer and other disease biomarkers.

[0060] KLK-6 is one of the fifteen kallikrein subfamily members located in a cluster on chromosome 19. The encoded enzyme is regulated by steroid hormones. In tissue culture, the enzyme has been found to generate amyloidogenic fragments from the amyloid precursor protein, suggesting a potential for involvement in Alzheimer's disease. KLK-6 has been verified as a secreted protein, and found to be elevated in ovarian cancer patients. Thus, it has been hypothesized to have value as a serological marker for this disease.

[0061] The human kallikrein 10 gene (KLK10, also known as normal epithelial cell specific 1 gene (NES-1)) is a member of the kallikrein gene family. The gene product is a secreted serine protease whose concentration in various biological fluids is known to be altered in some disease states. In particular, KLK10 is expressed in epithelial cells of the ovary and this expression has been reported to be elevated in serum of patients with ovarian cancer. Thus, KLK10 may serve as a serum biomarker for ovarian cancer. See for example Liu-Ying et al. (2003) *Cancer Res.* 63:807-811; Yousef and Diamandis (2003) *Thromb Haemost.* 90:7-16.

[0062] Secretory Leukocyte Protease Inhibitor (SLPI) is a protein that was first isolated in human parotid gland secretions. Subsequent studies have shown that the SLPI protein is also present in saliva and numerous mucosal surfaces such as those of the lung, nasal passages, cervix, and seminal vesicles.

[0063] SLPI is believed to act as a defense against chronic lung ailments because it is a potent inhibitor of neutrophil elastase, whose presence is heightened in chronic inflammatory lung diseases and which can destroy many of the components of lung tissue. SLPI also inhibits the release of histamine from mast cells, so it is also active in the allergic response. Protection of fetal membranes and cervical tissue is also thought to be a function of SLPI.

[0064] The gene which encodes the SLPI protein has been found to be up-regulated in ovarian cancer, and a significant difference has been found between the elevated levels of SLPI in the serum of patients with malignant ovarian cancer as opposed to the levels found in patients with benign ovarian cysts or normal patients. The SLPI protein has a mass of 12 kDa, is non-glycosylated, hydrophobic, and cationic. See generally Hollander et al. (2003) *Cancer Cell International* 3:14; Helmig et al. (1995) *Eur. J. Obstet. Gynecol. Reprod.*

Biol. 59(1):95-101; Hough et al. (2001) *Cancer Research* 61: 3869-3876; and Tsukishiro et al. (2005) *Gynecologic Oncology* 96: 516-519.

[0065] Alpha-1 anti-trypsin (AAT) is an acute phase protein synthesized by the liver and the principal serum inhibitor of proteolytic enzymes such as trypsin, chymotrypsin, plasmin and thrombin. In an inflammatory reaction the serum concentration of AAT may be elevated as much as 3-4 fold. The molecule exists as a number of genetic variants with a monomer molecular weight of 40-50 kDa. The mean normal serum concentration (mg/ml) has been reported to be 2.21±0.35 and 2.14±0.37. Interest in AAT as an ovarian cancer biomarker resulted from an in-house 2D gel electrophoresis/mass spec. study that indicated that AAT was elevated in the serum of ovarian cancer patients. See for example Song et al. (1994) *J. Affect. Disorders* 30:283-288; Ledue et al. (1993) *Clin. Chim. Acta.* 223: 73-28.

[0066] Although the above biomarkers have been discussed in detail, any biomarker whose overexpression is selective for ovarian cancer can be used to practice the invention, including biomarkers known in the art and those not yet identified. Such biomarkers include genes and proteins that are, for example, involved in defects in DNA replication/cell cycle control, cell growth and proliferation, escape from apoptosis, angiogenesis or lymphogenesis, or the mechanisms of cancer cell motility and invasion.

[0067] Of particular interest are biomarkers that are selectively overexpressed in early-stage ovarian cancer. By "selectively overexpressed in early-stage ovarian cancer" is intended that the biomarker of interest is overexpressed in stage 1 or stage 2 ovarian cancer states but is not overexpressed in normal samples or in conditions classified as non-malignant, benign, and other conditions that are not considered to be clinical disease. One of skill in the art will appreciate that early-stage ovarian cancer biomarkers include those genes and proteins specific for ovarian cancer that are initially overexpressed in stage 1 or stage 2 and whose overexpression persists throughout the advanced stages of the disease, as well as biomarkers that are only overexpressed in stage 1 or stage 2 ovarian cancer. Detection of expression of biomarkers that are selectively overexpressed in early-stage ovarian cancer may permit the earlier detection and diagnosis of ovarian cancer and, accordingly, improve patient prognosis.

[0068] The methods of the invention comprise detecting the expression of a plurality of biomarkers. As used herein, a "plurality" of biomarkers refers to 2, 3, 4, 5, 6, 7, 8, 9, 10 or more biomarkers. In particular, when the two-step screening method of the invention is used to identify patients having an increased likelihood of having ovarian cancer, a plurality of biomarkers may refer to the detection of at least one biomarker during the first assay step and at least one additional biomarker during the second assay step. One of skill in the art will also recognize that a panel of biomarkers can be used to identify patients with an increased likelihood of having ovarian cancer in accordance with the present methods. A panel of biomarkers may comprise any number or combination of biomarkers of interest. In some embodiments, a panel comprising a plurality of biomarkers selected from the group consisting of HE4, CA125, Glycodelin, MMP-7, Muc-1, PAI-1, CTHRC1, inhibin, PLAU-R, prolactin, KLK-10, KLK-6, and SLPI, alpha-1 anti-trypsin (AAT). In other embodiments, a panel of biomarkers selected from the subset of biomarkers comprising CA125, HE4, glycodelin, MMP-7, SLPI, PLAU-R, Muc-1, inhibin A, and PAI-1 is provided.

[0069] Any female patient or patient population may be assessed using the screening and diagnostic methods of the invention. For example, the methods disclosed herein may be performed on the general female patient population, as well as on the narrower population of post-menopausal women. The term "post-menopausal" is understood by those of skill in the art. In particular embodiments, post-menopausal generally refers to, for example, women over the age of 55. In particular embodiments, the screening methods are performed routinely (e.g., annually, every two years, etc.) on the general female population. Regular screening of patients may begin, for example, at the onset of menses, at age 30, or at the beginning of menopause. Screening of the high-risk patient population, as defined herein below, will typically be performed on a routine basis independent of patient age. Patients who are both asymptomatic and symptomatic (i.e., displaying characteristic symptoms of ovarian cancer, such as pelvic or abdominal pain or swelling) can be assessed for an increased likelihood of having ovarian using the screening and diagnostic methods of the invention. Women that are at a low-risk of developing ovarian and those that are considered high-risk based on clinical and family history risk factors may also be assessed using the present methods. Patients considered "high-risk" based on such clinical and family history risk factors include but are not limited to patients living with breast cancer, colon cancer, or breast/ovarian syndrome, women with a first-degree relative with ovarian cancer (e.g., mother, daughter, or sister), patients positive for at least one breast cancer gene (BRCA 1 or 2), and women suffering from HNPCC (i.e., Hereditary non-polyposis colorectal cancer).

[0070] In one aspect of the invention, the target population for the screening and diagnostic methods is the group of asymptomatic patients classified as high-risk on the basis of, for example, the above-referenced clinical and familial risk factors. This high-risk, asymptomatic population represents more than 8 million women in the U.S. It is recognized that the methods, compositions, and kits of the invention will be of particular utility to patients having an enhanced risk of developing ovarian cancers and to their physicians. Patients recognized in the art as having an increased risk of developing ovarian cancers include, for example, patients having a familial history of ovarian cancer and patients of advancing age (i.e., typically women over 55 years of age).

[0071] A number of clinical conditions or characteristics not directly related to ovarian cancer may exist in the patient populations tested in accordance with the methods of the invention, thereby interfering with the results of the screening and diagnostic methods disclosed herein. Such clinical conditions and characteristics are referred to herein as "interfering substances and pathologies" and include but are not limited to pregnancy (first trimester), breast cancer, chronic hepatitis, colon cancer, oral contraceptive therapy, coronary artery disease, deep vein thrombosis, diabetes, endometriosis, hormone replacement therapy, menstruation, multiple myeloma, ovarian cysts/polycystic disease, polymyalgia, polymyositis, rectal cancer, rheumatoid arthritis, systemic lupus rythematosus (SLE), and warfarin treatment. Additional exemplary interfering pathologies include uterine conditions (e.g., myomas, adenomyosis, and endometrial cancer), ovarian conditions (e.g., benign growths such as functional cysts, theca-lutein cysts, pregnancy luteoma, sclerocystic ovaries, serous cystadenoma, mucinous cystadenoma, cystic teratoma, fibroma, thecoma, and Brenner tumor; neoplasms; and malignant conditions such as cystadenocarcinoma and adenocarcinoma), fallopian tube conditions (e.g., tubo-ovarian abscess, hydrosaplinx, parovarian cyst, ectopic pregnancy, and cancer of the fallopian tubes), bowel conditions (e.g., distention with gas and/or feces, diverticulitis, ileitis, appendicitis, and colon cancer), and other miscellaneous conditions (e.g., distended bladder, pelvic kidney, urachal cyst, abdominal wall hematoma, abdominal wall abscess, and retroperitoneal neoplasms, such as lymphoma, sarcoma, and teratoma. In particular embodiments, the biomarkers, threshold expression levels, and mathematical models used in the screening and diagnostic methods described herein will be selected so as to minimize the effects of interfering substances and pathologies on the performance (i.e., the specificity, sensitivity, PPV, and NPV) of the claimed methods.

[0072] By "body sample" is intended any sampling of cells, tissues, or bodily fluids from a patient in which expression of a biomarker can be detected. Examples of such body samples include but are not limited to blood (e.g., whole blood, blood serum, blood having platelets removed, etc.), lymph, ascitic fluids, urine, gynecological fluids (e.g., ovarian, fallopian, and uterine secretion, menses, etc.), biopsies, and fluids obtained during laparoscopy. Body samples may be obtained from a patient by a variety of techniques including, for example, by venipuncture, by scraping or swabbing an area, or by using a needle to aspirate bodily fluids or tissues. Methods for collecting various body samples are well known in the art. In particular embodiments, the body sample comprises blood or serum. The present inventors have recognized that the methods for the collection and storage of blood samples, more particularly serum samples, affect the performance of the methods disclosed herein. Several studies indicate that body sample, particularly serum sample, collection and storage methods are critical to achieve acceptable assay performance. See, for example, Diamandis (2004) *J. Natl. Cancer Institute* 95:353-356 and Thavasu et al. (1992) *J. Immunol. Meth.* 153:115-124. which is herein incorporated reference in its entirety. An exemplary method for serum collection and storage is provided in Example 1.

[0073] Any methods available in the art for the detection biomarker expression can be used to practice the invention. The expression of a biomarker of the invention can be detected on a nucleic acid level or a protein level. In order to determine overexpression, the body sample to be examined may be compared with a corresponding body sample that originates from a healthy person. That is, the "normal" level of expression is the level of expression of the biomarker in a body sample from a patient that is not afflicted with ovarian cancer. Such a sample can be present in standardized form. In some embodiments, determination of biomarker overexpression requires no comparison between the body sample and a corresponding body sample that originates from a normal person.

[0074] Any biomarker or combination of biomarkers of the invention, as well as any known ovarian cancer biomarkers, may be used in the methods, compositions, and kits of the present invention. In general, it is preferable to use biomarkers for which the difference between the level of expression of the biomarker in a body sample from a patient afflicted with ovarian cancer and the level of expression of the same biomarker in a "normal" body sample (i.e., from an ovarian cancer free patient) is as great as possible. Although this difference can be as small as the limit of detection of the method for assessing expression of the biomarker, it is preferred that the difference be at least greater than the standard error of the assessment method, and optimally a difference of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25-fold or greater than the level of expression of the same biomarker in a normal body sample. The "normal" level of expression of a biomarker of the invention may be determined by assessing expression of the biomarker in a body sample obtained from a non-ovarian cancer afflicted patient. Alternatively, and particularly as further information becomes available as a result of the routine performance of the methods described herein, average values for biomarker expression levels may be used.

[0075] As described above, in some aspects of the invention, a threshold level of expression of a particular biomarker, above which the biomarker is considered to be overexpressed in a patient sample, may be established. Methods for selecting the threshold value include but are not limited to analysis of the ROC plot for the biomarker or analysis of the biomarker expression level for a normal patient population. Exemplary threshold or "cutoff" values include (1) the mean expression level plus two times the standard deviation, as determined from a population of normal patient samples and (2) expression levels selected from the ROC curve that represent the highest value of sensitivity plus specificity. The threshold level of expression for a particular biomarker may be determined relative to the expression level in a normal patient population. Persons of skill in the art will appreciate that other methods for selecting appropriate threshold expression values can be used to practice the invention.

[0076] Methods for detecting biomarkers of the invention comprise any methods that determine the quantity or the presence of the biomarkers either at the nucleic acid or protein level. Such methods are well known in the art and include but are not limited to western blots, northern blots, southern blots, ELISA, immunoprecipitation, immunofluorescence, flow cytometry, immunocytochemistry, multiplex bead-based immunoassays, nucleic acid hybridization techniques, nucleic acid reverse transcription methods, and nucleic acid amplification methods. In particular embodiments, overexpression of a biomarker is detected on a protein level using, for example, antibodies that are directed against specific biomarker proteins. These antibodies can be used in various methods such as Western blot, ELISA, multiplex bead-based immunoassay, immunoprecipitation, or immunocytochemistry techniques. The multiplex bead-based assays used to practice the present invention include but are not limited to the Luminex technology described in U.S. Pat. Nos. 6,599,331, 6,592,822, and 6,268,222, all of which are herein incorporated by reference in their entirety. In particular embodiments, the Luminex LabMAP® system is utilized, as described in International Publication No. WO 2005/016126, which is herein incorporated by reference it its entirety.

[0077] In some embodiments of the invention, antibodies specific for biomarker proteins are utilized to detect the expression of a plurality of biomarker proteins in a body sample in order to identify patients with an increased likelihood of having ovarian cancer. The method comprises obtaining a body sample from a patient, particularly a serum sample, contacting the body sample with antibodies directed to a plurality of biomarkers that are selectively overexpressed in ovarian cancer, and detecting antibody binding to determine if the biomarkers are overexpressed in the patient sample. In the screening methods of the invention, overexpression of the biomarkers is indicative of an increased likelihood of having ovarian cancer. Patients classified by the present screening methods as having an increased likelihood of having ovarian cancer are subjected to further diagnostic testing to detect the presence of ovarian cancer. Female patients identified by the present screening methods for ovarian cancer that are determined to not be currently suffering from ovarian cancer are regularly monitored in order to potentially detect ovarian cancer at an earlier stage.

[0078] As described above, in particular aspects of the invention, the screening methods for identifying patients with an increased likelihood of having ovarian cancer may comprise a two-step analysis. That is, the method comprises performing a first assay step comprising detecting the expression of a first biomarker or a first panel of biomarkers in a body sample and determining if the first biomarker or panel of biomarkers is overexpressed. If a positive result is obtained in the first assay step (i.e., the first biomarker or panel of biomarkers is overexpressed in the body sample), the method further comprises performing a second assay step comprising detecting the expression of a second biomarker or a second panel of biomarkers and determining if the second biomarker or panel of biomarkers is overexpressed. Overexpression of both the first and second biomarkers or panels of biomarkers (i.e., a positive result in both assay steps) is indicative of an increased likelihood of having ovarian cancer. In particular embodiments, detection of expression of the biomarkers in the first and second assay steps is performed at the protein level and comprises contacting the body sample, more particularly a serum sample, with antibodies specific for the particular biomarkers of interest and detecting antibody binding. In certain methods, biomarker protein expression is detected using an ELISA or multiplex bead-based immunoassay format.

[0079] In the "two-step" screening methods of the invention, the biomarker or panel of biomarkers used in the first step may be employed to maximize sensitivity and NPV. That is, the first screening step may be designed to maximize the number of true negatives classified as negative by the methods of the invention, thereby eliminating a significant percentage of true negatives from further analysis. Therefore, the patient population classified as positive by the first assay step will be enriched in true positive patients. The second screening step in the two-step methods may be designed to maximize PPV and specificity, while maintaining a reasonable sensitivity, in order to identify women with the highest likelihood of having ovarian cancer. Specificity, sensitivity, PPV, and NPV values may be determined for each individual assay step in the method, as described above. When a two-step screening method is used, combined sensitivity, specificity, PPV, and NPV values may determined for the method as a whole. In particular embodiments, the two-step method for identifying patients having an increased likelihood of having ovarian cancer will have a combined sensitivity of at least 90%, a combined specificity of at least 98%, a combined PPV of at least 10%, and a combined NPV of at least 99.9%. One of skill in the art will further appreciate that while two-step screening methods have been described in detail, similar screening methods comprising 3, 4, 5, or more assay steps are also encompassed by the present invention. Such follow-on assay steps may rule out other diseases, such as cardiovascular conditions, from the presence of ovarian cancer.

[0080] In some embodiments of the invention, algorithms or mathematical models may be applied to develop "test rules" for determining when a patient sample is "positive" (i.e., indicative of an increased likelihood of having ovarian cancer). For example, when expression of HE4, CA125, PLAU-R, glycodelin, Muc-1, and PAI-1 is detected, the screening test is considered positive if (1) any three of HE4, CA 125, glycodelin, PAI-1, and PLAU-R are positive (i.e., overexpressed) or if (2) HE4 and CA125 are both overexpressed; otherwise, the test is considered negative. In a further example, the test is considered positive if (1) any three of HE4, CA125, glycodelin, MMP-7, and PLAU-R are positive (i.e., overexpressed) or if (2) HE4 is overexpressed and also any one of CA125, glycodelin, MMP-7, or PLAU-R is positive; otherwise, the test is deemed negative. One of skill in the art will appreciate that a variety of such test rules can be developed and applied in the present methods for identifying patients with an increased likelihood of having ovarian cancer such as logistical regression. Other mathematical models that can be applied are described in Zhou et al. (2002) *Statistical Methods in Diagnostic Medicine* (Wiley, New York), which is herein incorporated by reference in its entirety.

[0081] In other aspects of the invention, methods for diagnosing ovarian cancer in a patient comprise obtaining a body sample from a patient, contacting the body sample with antibodies directed to a plurality of biomarkers that are selectively overexpressed in ovarian cancer, and detecting antibody binding to determine if the biomarkers are overexpressed in the patient sample. In the diagnostic methods of the invention, overexpression of the biomarkers is indicative of the presence of ovarian cancer.

[0082] In still other embodiments of the invention, methods for assessing the efficacy of a therapy for treating ovarian cancer in a patient are provided. Such methods typically comprise comparing the level of expression of a plurality of biomarkers of the invention in a first patient body sample procured prior to the initiation of therapy with that from a second sample obtained following administration of at least a portion of the therapy. A significantly lower level of expression of the biomarkers in the second patient sample relative to that of the first sample obtained prior to the initiation of the therapy is a positive indication of the efficacy of the therapy for treating ovarian cancer in the patient, whereas a significantly higher level of expression of the biomarkers in the second sample is a negative indication of the efficacy of the therapy. As used herein, a "positive indication of the efficacy of the therapy" means that the therapy is producing beneficial results in the treatment of ovarian cancer (e.g., tumor regression, etc.). A "negative indication of the efficacy of the therapy" is intended to mean that the therapy is not having beneficial effects with respect to treatment of ovarian cancer. A negative indication of the efficacy of the particular treatment may be related to, for example, the dosage. At higher dosages, the therapy may be efficacious.

[0083] One of skill in the art will recognize that in these methods the term "therapy" includes any therapy for treating ovarian cancer, including but not limited to chemotherapy, radiation therapy, surgical removal of tumor tissue, gene therapy, and biologic therapy. The methods of the invention may be used to evaluate a patient before, during, and after therapy to evaluate, for example, a reduction in tumor burden.

[0084] The invention additionally provides a monitoring method for assessing the regression or progression of ovarian cancer in a patient comprising detecting in a first patient sample at a first time point the level of expression of a plurality of biomarkers of the invention, repeating this analysis with a second patient sample obtained at a later time point, and comparing the level of expression of the biomarkers at the two time points. A significantly higher level of expression of the biomarkers in the patient body sample at the later time point indicates that the ovarian cancer has progressed, whereas a significantly lower level of expression is an indication that the ovarian cancer has regressed. As used herein, "regression of ovarian cancer" is intended to mean that the condition of the patient with respect to ovarian cancer has improved, as characterized by, for example, decreased tumor size. "Progression of ovarian cancer" means that the condition of the patient with respect to ovarian cancer has worsened, as characterized by, for example, increased tumor size, metastasis, etc. The meanings of the terms "regression" and "progression" with respect to disease states will be understood by those of skill in the art.

[0085] In certain aspects of the invention, biomarker expression is detected at the protein level using antibodies. The terms "antibody" and "antibodies" broadly encompass naturally occurring forms of antibodies and recombinant antibodies such as single-chain antibodies, chimeric and humanized antibodies and multi-specific antibodies as well as fragments and derivatives of all of the foregoing, which fragments and derivatives have at least an antigenic binding site. Antibody derivatives may comprise a protein or chemical moiety conjugated to the antibody.

[0086] "Antibodies" and "immunoglobulins" (Igs) are glycoproteins having the same structural characteristics. While antibodies exhibit binding specificity to an antigen, immunoglobulins include both antibodies and other antibody-like molecules that lack antigen specificity. Polypeptides of the latter kind are, for example, produced at low levels by the lymph system and at increased levels by myelomas.

[0087] The term "antibody" is used in the broadest sense and covers fully assembled antibodies, antibody fragments that can bind antigen (e.g., Fab', F'(ab)$_2$, Fv, single chain antibodies, diabodies), and recombinant peptides comprising the foregoing.

[0088] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts.

[0089] "Antibody fragments" comprise a portion of an intact antibody, preferably the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')2, and Fv fragments; diabodies; linear antibodies (Zapata et al. (1995) *Protein Eng.* 8(10):1057-1062); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments. Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize 35 readily. Pepsin treatment yields an F(ab')2 fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

[0090] "Fv" is the minimum antibody fragment that contains a complete antigen recognition and binding site. In a two-chain Fv species, this region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. In a single-chain Fv species, one heavy- and one light-chain variable domain can be covalently linked by flexible peptide linker such that the light and heavy chains can associate in a "dimeric" structure analogous to that in a two-chain Fv species. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

[0091] The Fab fragment also contains the constant domain of the light chain and the first constant domain (CHI) of the heavy chain. Fab fragments differ from Fab' fragments by the addition of a few residues at the carboxy terminus of the heavy-chain C_H1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')2 antibody fragments originally were produced as pairs of Fab' fragments that have hinge cysteines between them.

[0092] Polyclonal antibodies can be prepared by immunizing a suitable subject (e.g., rabbit, goat, mouse, or other mammal) with a biomarker protein immunogen. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized biomarker protein. At an appropriate time after immunization, e.g., when the antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497, the human B cell hybridoma technique (Kozbor et al. (1983) *Immunol. Today* 4:72), the EBV-hybridoma technique (Cole et al. (1985) in *Monoclonal Antibodies and Cancer Therapy, ed. Reisfeld and Sell* (Alan R. Liss, Inc., New York, N.Y.), pp. 77-96) or trioma techniques. The technology for producing hybridomas is well known (see generally Coligan et al., eds. (1994) *Current Protocols in Immunology* (John Wiley & Sons, Inc., New York, N.Y.); Galfre et al. (1977) *Nature* 266:550-52; Kenneth (1980) in *Monoclonal Antibodies: A New Dimension In Biological Analyses* (Plenum Publishing Corp., NY); and Lerner (1981) *Yale J. Biol. Med.,* 54:387-402).

[0093] Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with a biomarker protein to thereby isolate immunoglobulin library members that bind the biomarker protein. Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the *Stratagene SurfZAP* θ *Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Pat. No. 5,223,409; PCT Publication Nos. WO 92/18619; WO 91/17271; WO 92/20791; WO 92/15679; 93/01288; WO 92/01047; 92/09690; and 90/02809; Fuchs et al. (1991) *Bio/Technology* 9:1370-1372; Hay et al. (1992) *Hum. Antibod Hybridomas* 3:81-85; Huse et al. (1989) *Science* 246:1275-1281; Griffiths et al. (1993) *EMBO J.* 12:725-734.

[0094] The compositions of the invention further comprise monoclonal antibodies and variants and fragments thereof that specifically bind to biomarker proteins of interest. The monoclonal antibodies may be labeled with a detectable substance as described below to facilitate biomarker protein detection in the sample. Such antibodies find use in practicing the methods of the invention. Monoclonal antibodies having the binding characteristics of the antibodies disclosed herein are also encompassed by the present invention. Compositions further comprise antigen-binding variants and fragments of the monoclonal antibodies, hybridoma cell lines producing these antibodies, and isolated nucleic acid molecules encoding the amino acid sequences of these monoclonal antibodies.

[0095] Antibodies having the binding characteristics of a monoclonal antibody of the invention are also provided. "Binding characteristics" or "binding specificity" when used in reference to an antibody means that the antibody recognizes the same or similar antigenic epitope as a comparison antibody. Examples of such antibodies include, for example, an antibody that competes with a monoclonal antibody of the invention in a competitive binding assay. One of skill in the art could determine whether an antibody competitively interferes with another antibody using standard methods.

[0096] By "epitope" is intended the part of an antigenic molecule to which an antibody is produced and to which the antibody will bind. Epitopes can comprise linear amino acid residues (i.e., residues within the epitope are arranged sequentially one after another in a linear fashion), nonlinear amino acid residues (referred to herein as "nonlinear epitopes"; these epitopes are not arranged sequentially), or both linear and nonlinear amino acid residues. Typically epitopes are short amino acid sequences, e.g. about five amino acids in length. Systematic techniques for identifying epitopes are known in the art and are described, for example, in U.S. Pat. No. 4,708,871. Briefly, a set of overlapping oligopeptides derived from the antigen may be synthesized and bound to a solid phase array of pins, with a unique oligopeptide on each pin. The array of pins may comprise a 96-well microtiter plate, permitting one to assay all 96 oligopeptides simultaneously, e.g., for binding to a biomarker-specific monoclonal antibody. Alternatively, phage display peptide library kits (New England BioLabs) are currently commercially available for epitope mapping. Using these methods, the binding affinity for every possible subset of consecutive amino acids may be determined in order to identify the epitope that a given antibody binds. Epitopes may also be identified by inference when epitope length peptide sequences are used to immunize animals from which antibodies are obtained. Epitopes may also be defined by carbohydrate side chains present as either N-linked or O-linked oligosaccharides present on glycoproteins.

[0097] Antigen-binding fragments and variants of the monoclonal antibodies disclosed herein are further provided. Such variants will retain the desired binding properties of the parent antibody. Methods for making antibody fragments and variants are generally available in the art. For example, amino acid sequence variants of a monoclonal antibody described herein, can be prepared by mutations in the cloned DNA sequence encoding the antibody of interest. Methods for mutagenesis and nucleotide sequence alterations are well known in the art. See, for example, Walker and Gaastra, eds. (1983) Techniques in Molecular Biology (MacMillan Publishing Company, New York); Kunkel (1985) Proc. Natl. Acad. Sci. USA 82:488-492; Kunkel et al. (1987) Methods Enzymol. 154:367-382; Sambrook et al. (1989) Molecular Cloning: A Laboratory Manual (Cold Spring Harbor, N.Y.); U.S. Pat. No. 4,873,192; and the references cited therein; herein incorporated by reference. Guidance as to appropriate amino acid substitutions that do not affect biological activity of the polypeptide of interest may be found in the model of Dayhoff et al. (1978) in Atlas of Protein Sequence and Structure (Natl. Biomed. Res. Found., Washington, D.C.), herein incorporated by reference. Conservative substitutions, such as exchanging one amino acid with another having similar properties, may be preferred. Examples of conservative substitutions include, but are not limited to, Gly<Ala, ValrIlerLeu, Asp>Glu, LysrArg, Asn¢Gln, and Phe<Trp<=Tyr.

[0098] In constructing variants of the antibody polypeptide of interest, modifications are made such that variants continue to possess the desired activity, i.e., similar binding affinity to the biomarker. Obviously, any mutations made in the DNA encoding the variant polypeptide must not place the sequence out of reading frame and preferably will not create complementary regions that could produce secondary mRNA structure. See EP Patent Application Publication No. 75,444.

[0099] Preferably, variants of a reference biomarker antibody have amino acid sequences that have at least 70% or 75% sequence identity, preferably at least 80% or 85% sequence identity, more preferably at least 90%, 91%, 92%, 93%, 94% or 95% sequence identity to the amino acid sequence for the reference antibody molecule, or to a shorter portion of the reference antibody molecule. More preferably, the molecules share at least 96%, 97%, 98% or 99% sequence identity. For purposes of the present invention, percent sequence identity is determined using the Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 2, BLOSUM matrix of 62. The Smith-Waterman homology search algorithm is taught in Smith and Waterman (1981) *Adv. Appl. Math.* 2:482-489. A variant may, for example, differ from the reference antibody by as few as 1 to 15 amino acid residues, as few as 1 to 10 amino acid residues, such as 6-10, as few as 5, as few as 4, 3, 2, or even 1 amino acid residue.

[0100] With respect to optimal alignment of two amino acid sequences, the contiguous segment of the variant amino acid sequence may have additional amino acid residues or deleted amino acid residues with respect to the reference amino acid sequence. The contiguous segment used for comparison to the reference amino acid sequence will include at least 20 contiguous amino acid residues, and may be 30, 40, 50, or more amino acid residues. Corrections for sequence identity associated with conservative residue substitutions or gaps can be made (see Smith-Waterman homology search algorithm).

[0101] One of skill in the art will recognize that optimization of reagents and conditions, for example, antibody titer and parameters for detection of antigen-antibody binding, is needed to maximize the signal to noise ratio for a particular antibody. Antibody concentrations that maximize specific binding to the biomarkers of the invention and minimize non-specific binding (or "background") will be determined. In particular embodiments, appropriate antibody titers are determined by initially testing various antibody dilutions on patient serum samples. The design of assays to optimize antibody titer and detection conditions is standard and well within the routine capabilities of those of ordinary skill in the art. Some antibodies require additional optimization to reduce background and/or to increase specificity and sensitivity.

[0102] Furthermore, one of skill in the art will recognize that the concentration of a particular antibody used to practice the methods of the invention will vary depending on such factors as time for binding, level of specificity of the antibody for the biomarker protein, and method of body sample preparation. Moreover, when multiple antibodies are used in a single sample, the required concentration may be affected by the order in which the antibodies are applied to the sample, i.e., simultaneously as a cocktail or sequentially as individual antibody reagents. Furthermore, the detection chemistry used to visualize antibody binding to a biomarker of interest must also be optimized to produce the desired signal to noise ratio.

[0103] Detection of antibody binding can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S, or ^{3}H.

[0104] The antibodies used to practice the invention are selected to have high specificity for the biomarker proteins of interest. Methods for making antibodies and for selecting appropriate antibodies are known in the art. See, for example, Celis, ed. (in press) *Cell Biology & Laboratory Handbook,* 3rd edition (Academic Press, New York), which is herein incorporated in its entirety by reference. In some embodiments, commercial antibodies directed to specific biomarker proteins may be used to practice the invention. The antibodies of the invention may be selected on the basis of desirable staining of cytological, rather than histological, samples. That is, in particular embodiments the antibodies are selected with the end sample type (i.e., serum samples) in mind and for binding specificity.

[0105] In other embodiments, the expression of a biomarker of interest is detected at the nucleic acid level. Nucleic acid-based techniques for assessing expression are well known in the art and include, for example, determining the level of biomarker mRNA in a body sample. Many expression detection methods use isolated RNA. Any RNA isolation technique that does not select against the isolation of mRNA can be utilized for the purification of RNA from serum samples (see, e.g., Ausubel et al., ed., (1987-1999) *Current Protocols in Molecular Biology* (John Wiley & Sons, New York). Additionally, large numbers of blood, serum, or tissue samples can readily be processed using techniques well known to those of skill in the art, such as, for example, the single-step RNA isolation process of Chomczynski (1989, U.S. Pat. No. 4,843,155).

[0106] The term "probe" refers to any molecule that is capable of selectively binding to a specifically intended target biomolecule, for example, a nucleotide transcript or a protein encoded by or corresponding to a biomarker. Probes can be synthesized by one of skill in the art, or derived from appropriate biological preparations. Probes may be specifically designed to be labeled. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

[0107] Isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or Northern analyses, polymerase chain reaction analyses and probe arrays. One method for the detection of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to the mRNA encoded by the gene being detected. The nucleic acid probe can be, for example, a full-length cDNA, or a portion thereof, such as an oligonucleotide of at least 7, 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to an mRNA or genomic DNA encoding a biomarker of the present invention. Hybridization of an mRNA with the probe indicates that the biomarker in question is being expressed.

[0108] In one embodiment, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative embodiment, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in detecting the level of mRNA encoded by the biomarkers of the present invention.

[0109] An alternative method for determining the level of biomarker mRNA in a sample involves the process of nucleic acid amplification, e.g., by RT-PCR (the experimental embodiment set forth in Mullis, 1987, U.S. Pat. No. 4,683, 202), ligase chain reaction (Barany (1991) *Proc. Natl. Acad. Sci. USA* 88:189-193), self sustained sequence replication (Guatelli et al. (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh et al. (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi et al. (1988) *Bio/Technology* 6:1197), rolling circle replication (Lizardi et al., U.S. Pat. No. 5,854,033) or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. In particular aspects of the invention, biomarker expression is assessed by quantitative fluorogenic RT-PCR (i.e., the TaqMan® System). Such methods typically utilize pairs of oligonucleotide primers that are specific for the biomarker of interest. Methods for designing oligonucleotide primers specific for a known sequence are well known in the art.

[0110] Biomarker expression levels of RNA may be monitored using a membrane blot (such as used in hybridization analysis such as Northern, Southern, dot, and the like), or microwells, sample tubes, gels, beads or fibers (or any solid support comprising bound nucleic acids). See U.S. Pat. Nos. 5,770,722, 5,874,219, 5,744,305, 5,677,195 and 5,445,934, which are incorporated herein by reference. The detection of biomarker expression may also comprise using nucleic acid probes in solution.

[0111] In one embodiment of the invention, microarrays are used to detect biomarker expression. Microarrays are particularly well suited for this purpose because of the reproducibility between different experiments. DNA microarrays provide one method for the simultaneous measurement of the expression levels of large numbers of genes. Each array consists of a reproducible pattern of capture probes attached to a solid support. Labeled RNA or DNA is hybridized to complementary probes on the array and then detected by laser scanning. Hybridization intensities for each probe on the array are determined and converted to a quantitative value representing relative gene expression levels. See, U.S. Pat. Nos. 6,040,138, 5,800,992 and 6,020,135, 6,033,860, and 6,344,316, which are incorporated herein by reference. High-density oligonucleotide arrays are particularly useful for determining the gene expression profile for a large number of RNA's in a sample.

[0112] Techniques for the synthesis of these arrays using mechanical synthesis methods are described in, e.g., U.S. Pat. No. 5,384,261, incorporated herein by reference in its entirety for all purposes. Although a planar array surface is preferred, the array may be fabricated on a surface of virtually any shape or even a multiplicity of surfaces. Arrays may be peptides or nucleic acids on beads, gels, polymeric surfaces, fibers such as fiber optics, glass or any other appropriate substrate, see U.S. Pat. Nos. 5,770,358, 5,789,162, 5,708,153, 6,040,193 and 5,800,992, each of which is hereby incorporated in its entirety for all purposes. Arrays may be packaged in such a manner as to allow for diagnostics or other manipulation of an all-inclusive device. See, for example, U.S. Pat. Nos. 5,856,174 and 5,922,591 herein incorporated by reference.

[0113] In one approach, total mRNA isolated from the sample is converted to labeled cRNA and then hybridized to an oligonucleotide array. Each sample is hybridized to a separate array. Relative transcript levels may be calculated by reference to appropriate controls present on the array and in the sample.

[0114] Kits for practicing the screening and diagnostic methods of the invention are further provided. By "kit" is intended any manufacture (e.g., a package or a container) comprising at least one reagent, e.g., an antibody, a nucleic acid probe, etc. for specifically detecting the expression of a biomarker of the invention. The kit may be promoted, distributed, or sold as a unit for performing the methods of the present invention. Additionally, the kits may contain a package insert describing the kit and methods for its use.

[0115] In particular embodiments, kits for use in screening methods for identifying patients with an increased likelihood of having ovarian cancer comprise a plurality of antibodies directed to biomarker proteins of interest, particularly wherein the biomarkers are selected from the group consisting of HE4, CA 125, glycodelin, MMP-7, Muc-1, PAI-1, CTHRC 1, inhibin A, PLAU-R, prolactin, KLK-10, KLK-6, SLPI, and alpha-1 anti-trypsin. Chemicals for the detection of antibody binding to the biomarker may also be included in the kit. Other reagents for detecting expression of biomarkers using antibodies in an ELISA or multiplex bead-based immunoassay format may be further included in a kit of the invention. In other embodiments, kits for use in the screening methods disclosed herein comprise nucleic acid probes for the detection of expression of a plurality of biomarkers of interest in a body sample, particularly wherein the biomarkers are selected from the group consisting of HE4, CA125, glycodelin, MMP-7, Muc-1, PAI-1, CTHRC1, inhibin A, PLAU-R, prolactin, KLK-10, KLK-6, SLPI, and alpha-1 anti-trypsin.

[0116] In certain aspects of the invention, kits for performing the two-step screening method for identifying patients having an increased likelihood of having ovarian cancer are provided. Kits may be designed to perform the two-step screening method as two separate tests. Such kits include reagents for performing a single assay step (i.e., the first or second assay step). In other embodiments, the kits comprise reagents so that the two-step method may be performed as a single test (i.e., include reagents for both the first and second assay steps). Further kits encompassed by the invention find use in practicing the single-step screening method described herein above. The kits may further comprise descriptions of algorithms or mathematical models to be applied with the one-step or two-step screening methods, as well as automated platforms that implement the algorithms/mathematical models with little or no human intervention. The kits may be further provided such that each step in the two-step method is performed in an automated, semi-automated, or manual fashion.

[0117] Kits for diagnosing ovarian cancer are also provided. Such kits may include antibodies or nucleic acid probes that are specific for detection of a plurality of biomarkers that are selectively overexpressed in ovarian cancer, more particularly HE4, CA125, glycodelin, MMP-7, Muc-1, PAI-1, CTHRC1, inhibin A, PLAU-R, prolactin, KLK-10, KLK-6, SLPI, and alpha-1 anti-trypsin.

[0118] One of skill in the art will further appreciate that any or all steps in the screening and diagnostic methods of the invention could be implemented by personnel or, alternatively, performed in an automated fashion. That is, the methods can be performed in an automated, semi-automated, or manual fashion. Furthermore, the methods disclosed herein can also be combined with other methods known or later developed to permit a more accurate identification of patients having an increased likelihood of having ovarian cancer or a more reliable diagnosis of ovarian cancer.

[0119] The article "a" and "an" are used herein to refer to one or more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one or more element.

[0120] Throughout the specification the word "comprising," or variations such as "comprises" or "comprising," will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

[0121] The following examples are offered by way of illustration and not by way of limitation:

EXPERIMENTAL

Example 1

Exemplary Method for Collection of Blood, Processing of Blood Into Serum, Serum Storage Conditions, and Serum Shipping Conditions

Blood Collection

[0122] A sufficient quantity of blood was drawn by venipuncture into a Becton Dickinson Vacutainer red-topped collection tubes containing no additive (catalog number 366430). The lot number of the blood collection tube was recorded. Whole blood was not refrigerated or frozen. Processing of the whole blood to serum began immediately after collection of the blood.

Serum Preparation Procedure

[0123] Blood collection tubes were placed upright in a rack and stored at room temperature. The blood was allowed to clot for a minimum of 60 minutes and a maximum of 90 minutes from time of collection. Blood was thoroughly clotted before centrifugation. The time required for complete clotting for each sample was recorded.

[0124] After blood was thoroughly clotted, the samples were centrifuged at 1300×g for 10 minutes using either a swing-head or fixed-angle centrifuge rotor. Tubes were carefully removed from the centrifuge to avoid disturbing the red blood cells on the bottom.

[0125] The stopper was removed from each tube without disturbing the cell pellet. The serum from each donor was combined into a labeled tube using a disposable transfer pipette without disturbing the cell layer or allowing any cells into the pipette. If cells were disturbed during transfer, the samples were re-centrifuged as described above.

[0126] Serum samples from each donor were mixed by gently inverting the tube five times. One mL aliquots were placed in labeled tubes and frozen at −20° C. to −80° C. Serum was not stored at room temperature for more than two hours or at 2-8° C. for more than eight hours prior to freezing.

Example 2

Ovarian Biomarker Selection Study

Individual Biomarker Analysis

[0127] The purpose of the biomarker selection study was to evaluate the initial clinical utility of a set of fourteen candidate ovarian cancer biomarkers. The premise of the study was to be able to identify and quantitate the amount of each biomarker in a patient's serum. Biomarker protein expression in serum samples was detected using commercial or novel biomarker-specific antibodies in an ELISA format. Fourteen target biomarkers were analyzed, as described below in Table 1:

TABLE 1

Candidate markers	
HE4	CA125
SLPI	Glycodelin
KLK6	MMP7
KLK10	PLAU-R
CTHRC1	Inhibin
PAI-1	Prolactin
MUC1	Alpha-1 anti-trypsin

Target Population and Demographics of the Study

[0128] In evaluations of this type, it is essential that the samples tested are representative of the target clinical population and that normal controls are demographically matched. A total of 900 patient serum samples were analyzed in this study. 200 of the samples were from ovarian cancer patients in various stages of the disease (i.e., the 200 samples were evenly split among Stage 1, 2, 3 ovarian cancer samples). A total of 500 normal sera were used in the study. 104 of the normal serum samples were from post-menopausal women (set as women over the age of 55 for the present study) to establish the baseline levels of each biomarker and to calculate the appropriate threshold cut-off values. The remaining 396 normal serum samples were evenly split between pre-menopausal women under the age of 55 and post-menopausal women over the age of 55. This distribution permitted the investigation of any age or hormone-related patient distributions. The remaining 200 samples in the study were collected from donors with various conditions/diseases, as described herein above (i.e., "interfering conditions" or "interfering pathologies"). The inclusion of these samples allowed for the analysis of any interfering pathologies that may affect individual biomarker performance. Summaries of the patient populations analyzed and study demographics are provided in Tables 2-4.

TABLE 2

Demographics of sample cases in the study

Characteristics	Ovarian Cancer	Study Normals	Interfering Pathologies	Threshold Normals
Total number of samples	200	396	200	104
Age at diagnosis (years)				
Mean (std)	55.5 (11.5)	55.3 (9.7)	57.0 (18.3)	63.0 (6.9)
Range	19-81	40-84	20-97	41-80
Age group distribution				
<=55	100 (50%)	201 (50.8%)	92 (46%)	2 (1.9%)
>55	100 (50%)	195 (49.2%)	108 (54%)	102 (98.1%)
Race, n				
African-American	10 (5%)	3 (1%)	12 (6%)	0
Caucasian	183 (92%)	389 (99%)	185 (92.5%)	98 (100%)
Other	6 (3%)	1 (<1%)	3 (1.5%)	0
Missing	1	3	0	6

TABLE 3

Clinical Characteristics of Ovarian Cancer Patients in Study

	Frequency	Percent
Ovarian Cancer Stage, n	200	
1	67	33.5%
2	66	33%
3	67	33.5%

TABLE 3-continued

Clinical Characteristics of Ovarian Cancer Patients in Study

	Frequency	Percent
Histological Classification, n	197	
Clear Cell	10	5%
Endometrioid	39	19%
Serous	23	12%
Mucinous	36	18%
Adenocarcinoma	49	25%
Papillary	25	13%
Unclassified	13	7%
Stromal Sarcoma	2	1%

TABLE 4

Distribution of Interfering Substances/Pathologies

	Category	Number	Percent
Hormonal	1st trimester pregnancy	10	5.0
	Contraceptive Pills	5	2.5
	Hormone Replacement Therapy	9	4.5
	Menstruation	9	4.5
Cancer	Breast Cancer	27	13.5
	Colon Cancer	15	7.5
	Rectal Cancer	2	1.0
	Multiple Myeloma	1	0.5
Vascular	Coronary Artery Disease	9	4.5
	Deep Vein Thrombosis	1	0.5
	Warfarin Treatment	15	7.5
Metabolic	Diabetes	10	5.0
	Chronic Hepatitis	10	5.0
Gyn	Endometriosis	25	12.5
	Ovarian cysts/polycystic	10	5.0
Inflammatory	Polymyalgia	10	5.0
	Polymyositis	3	1.5
	Rheumatoid Arthritis	27	13.5
	SLE	2	1.0

General Description of Automation and Validation Analysis for the Study

[0129] All 900 sera samples were processed in duplicate for each of the 14 markers. An automated assay system with barcode tracking was utilized in generating the marker selection data. The assays run in this marker selection study were all completed using a Tecan Evo automated robotic liquid handler. The use of this platform allowed all 900 samples to be processed for each marker in a single experimental run (one run per day). The precision of the automated platform was verified before any study samples were processed.

[0130] All of the ELISA assays were processed for this study using a buffered solution as the diluent for the standard curve. This was done to standardize, as much as possible, the protocols for each of the assays.

[0131] The normal sera used in this study were obtained from community blood collection centers compliant with local IRB customs, While these sera can be considered 'normal' it must be noted that these donors were not screened by a medical professional to confirm their disease free or normal status

Detection of Expression of HE4 in Serum Samples (A Representative Example)

Materials and Methods

[0132] A. Coating of Assay Plates:

[0133] ELISA 96-well plates were coated with 100 µl/well of the primary antibody, anti-HE4 monoclonal 90.1 #6, at 2 µg/ml in PBS, then the plates were incubated at 4° C. overnight. The next day, the plates were washed once with PBS, then 250 µl/well of PBS-3% BSA was added to all wells, and the plates were incubated for 2 hours at 30° C. The plates were then emptied and dried in a vacuum oven for 2 hours at room temperature. Then they were heat-sealed inside a mylar foil bag along with a desiccant pack and stored at 4° C. until used in an assay.

[0134] B. Assay Methods

[0135] The foil bags containing the assay plates were warmed to room temperature immediately prior to use in the assay. The serum samples were diluted 1:4 into PBS-1% bovine Serum-0.05% Tween 20-1 mg/ml mouse IgG. The HE4 antigen protein was diluted to 100 ng/ml, then serially diluted two-fold into PBS-1% Bovine Serum-0.05% Tween 20-1 mg/ml Mouse IgG, then all the individual standard curve samples were further diluted 1:4 into the buffer so that they would be diluted the same as the serum samples.

[0136] The diluted sera samples and standard curve samples were added to the anti-HE4 coated assay plates in 100 µl/well volumes. Then the plates were incubated for 2 hours at 30° C. The plates were next washed 5× with 250 µl/well of PBS-0.05% Tween 20.

[0137] The secondary antibody, anti-HE4 monoclonal 71.1#1.13-HRP, was diluted 1:16,000 into PBS-1% bovine IgG-0.05% Tween 20-1 mg/ml mouse IgG. The secondary antibody solution was then added to the aspirated plates in 100 µl/well volumes. The plates were incubated for 1 hour at 30° C.

[0138] The plates were washed 5× with 250 µl/well of PBS-0.05% Tween 20. The developing solution, TMB (3,3',5,5'-Tetramethylbenzidine) was warmed to room temperature prior to use, and then the TMB was added to the aspirated plates in 100 µl/well volumes.

[0139] The plates were incubated for 10 minutes at room temperature and then the Stop solution, 2N H2SO4, was added to the plates (containing the TMB) in 100 µl/well volumes.

[0140] The plates were incubated for 10 minutes at room temperature, and then they were read on the Molecular Devices SpectraMax plate reader at 450 nm, with a reference wavelength of 650 nm, using SoftMax Pro software.

[0141] The data was saved as SoftMax Pro files, and also exported as Text files for use with MS Excel.

[0142] Controls: Serum used as the High Control: Uniglobe # 72372

[0143] Serum used as the Low Control: Uniglobe # 72404

[0144] Buffer Control used was PBS-1% Bovine Serum-0.05% Tween 20-1 mg/ml Mouse IgG

[0145] The CV's for the controls across all 25 plates are summarized in Table 5.

TABLE 5

The CV's for the Controls Across All 25 Plates

Standards point-per-point CV % across all 25 plates			
ng/ml	Mean OD	SD	CV %
100	2.614	0.145	5.6
50	1.681	0.101	6.0
25	0.931	0.075	8.1
12.5	0.510	0.043	8.4
6.25	0.263	0.027	10.4
3.13	0.139	0.014	10.0
1.56	0.076	0.008	10.5
0.78	0.044	0.012	27.6

Results (Standard Curves)

[0146] A standard curve for HE4 was prepared by diluting the HE4 protein in PBS/1% bovine serum/0.05% Tween 20-1 mg/mL of mouse IgG. Preparation of such standard curves is well known in the art. Standard curves and the levels or concentrations of the biomarkers in all serum samples were produced for the remaining biomarkers, essentially as described above for HE4, with variations that could be appreciated and implemented by one of skill in the art. Standard curve ranges and curve fit equations for the biomarkers analyzed (i.e., HE4, glycodelin, SLPI, PLAU-R, MUC-1, PAI-1, MMP-7, inhibin, CA125, CTHRC1, KLK-6, KLK-10, alpha-1 anti-trypsin, and prolactin) are presented below:

HE4

[0147] Standard Curve experimental range=0.78 ng/ml to 100 ng/ml, in serial two-fold dilutions

[0148] Curve fit=third order polynomial, $y=-1E-07x^3-0.0001x^2+0.0402x+0.0157$; $R^2=0.9999$

[0149] The standard curve samples and the serum samples were then both diluted 1:4 to run in the assay; since both the serum samples and the standard curve samples were diluted in the same manner there was no need to use a dilution factor during data analysis to determine the concentrations of the unknown serum samples.

Glycodelin

[0150] Standard Curve experimental range=3 ng/ml to 100 ng/ml, in serial two-fold dilutions

[0151] Curve fit=quadratic, $y=-0.0003x^2+0.0478x+0.0952$; $R^2=0.9851$

[0152] The serum samples were run in the assay undiluted, so no dilution factor was used in the data analysis.

SLPI

[0153] Standard Curve experimental range=2.38 ng/ml to 305 ng/ml, in serial two-fold dilutions

[0154] Curve fit=third order polynomial, $y=7E-08x^3-7E-05x^2+0.0237x-0.039$; $R^2=0.9997$

[0155] The serum samples were diluted 1:6.1 in an early step of the automated sample preparation technique. Then those diluted serum samples were further diluted 1:6.6 in another automated step in order to achieve a total dilution of 1:40. Those 1:40 diluted samples were then run in the assay.

[0156] The standard curve samples were prepared at the concentrations stated above (experimental range), then those standard curve samples were all further diluted 1:6.1, and those 1:6.1 diluted samples were then run in the assay.

[0157] Since there was a discrepancy between the dilution of the serum samples (1:40) as compared to the dilution of the standard curve samples (1:6.1), all the serum sample concentration values obtained from the standard curve were multiplied by a dilution factor of "6.6" to correct for the discrepancy (1:40=1:6.1×1:6.6).

uPar (PLAU-R)

[0158] Standard Curve experimental range=62.5 pg/ml to 4000 pg/ml, in serial two-fold dilutions

[0159] Curve fit=linear, $y=0.0006x+0.0522$; $R^2=0.9977$

[0160] The serum samples were diluted 1:6 in an early step of the automated sample preparation technique. Then those diluted serum samples were further diluted 1:3 in another automated step in order to achieve a total dilution of 1:18. Those 1:18 diluted samples were then run in the assay.

[0161] The standard curve samples were prepared at the concentrations stated above (experimental range), then those standard curve samples were all further diluted 1:3, and those 1:3 diluted samples were then run in the assay.

[0162] Since there was a discrepancy between the dilution of the serum samples (1:18) as compared to the dilution of the standard curve samples (1:3), all the serum sample concentration values obtained from the standard curve were multiplied by a dilution factor of "6" to correct for the discrepancy (1:18=1:3×1:6).

MUC-1

[0163] Standard Curve experimental range=0.3 U/ml to 600 U/ml, in serial three-fold dilutions

[0164] Curve fit=third order polynomial, $y=3E-07x^3-0.00001x^2+0.0236x+0.0371$; $R^2=1.0$

[0165] The standard curve samples and the serum samples were then both diluted 1:2 to run in the assay; since both the serum samples and the standard curve samples were diluted in the same manner there was no need to use a dilution factor during data analysis to determine the concentrations of the unknown serum samples.

PAI-1

[0166] Standard Curve experimental range=0.78 ng/ml to 100 ng/ml, in serial two-fold dilutions

[0167] Curve fit=linear, $y=0.0139x+0.0151$; $R^2=0.9996$

[0168] The standard curve samples and the serum samples were then both diluted 1:4 to run in the assay; since both the serum samples and the standard curve samples were diluted in the same manner there was no need to use a dilution factor during data analysis to determine the concentrations of the unknown serum samples.

MMP-7

[0169] Standard Curve experimental range=0.16 ng/ml to 20 ng/ml, in serial two-fold dilutions

[0170] Curve fit=third order polynomial, $y=0.0001x^3-0.0046x^2+0.1578x+0.0936$; $R^2=0.9999$

[0171] The standard curve samples and the serum samples were then both diluted 1:2 to run in the assay; since both the serum samples and the standard curve samples were diluted in the same manner there was no need to use a dilution factor during data analysis to determine the concentrations of the unknown serum samples.

Inhibin

[0172] Standard Curve experimental range=10 pg/ml to 1000 pg/ml, in serial two-fold dilutions

[0173] Curve fit=linear, $y=0.0007x+0.0136$; $R^2=0.9997$

[0174] The standard curve samples and the serum samples were then both diluted 1:3 to run in the assay; since both the serum samples and the standard curve samples were diluted in the same manner there was no need to use a dilution factor during data analysis to determine the concentrations of the unknown serum samples.

CA125

[0175] Standard Curve experimental range=15 U/ml to 400 U/ml, in serial two-fold dilutions

[0176] Curve fit=linear, $y=0.0021x+0.0892$; $R^2=0.9986$

[0177] The serum samples were run in the assay undiluted, so no dilution factor was used in the data analysis.

CTHRC1

[0178] Standard Curve experimental range=0.78 ng/ml to 100 ng/ml, in serial two-fold dilutions

[0179] Curve fit=linear, $y=0.0261x+0.042$; $R^2=0.9991$

[0180] The standard curve samples and the serum samples were then both diluted 1:2 to run in the assay; since both the serum samples and the standard curve samples were diluted in the same manner there was no need to use a dilution factor during data analysis to determine the concentrations of the unknown serum samples.

KLK-6

[0181] Standard Curve experimental range=0.78 ng/ml to 100 ng/ml, in serial two-fold dilutions

[0182] Curve fit=third order polynomial, $y=-4E\text{-}07x^3+0.00001x^2+0.0133x+0.0662$; $R^2=1.0$

[0183] The standard curve samples and the serum samples were then both diluted 1:2 to run in the assay; since both the serum samples and the standard curve samples were diluted in the same manner there was no need to use a dilution factor during data analysis to determine the concentrations of the unknown serum samples.

KLK-10

[0184] Standard Curve experimental range=1 ng/ml to 80 ng/ml, in serial two-fold dilutions

[0185] Curve fit=linear, $y=0.0758\times-0.0312$; R^2 0.9976

[0186] The standard curve samples and the serum samples were then both diluted 1:4 to run in the assay; since both the serum samples and the standard curve samples were diluted in the same manner there was no need to use a dilution factor during data analysis to determine the concentrations of the unknown serum samples.

Alpha 1 anti-trypsin

[0187] Standard Curve experimental range=3.3 ng/ml to 90 ng/ml, in serial two-fold dilutions

[0188] Curve fit=quadratic, $y=-0.0002x^2+0.0412x+0.0592$; $R^2=0.9997$

[0189] The serum samples were diluted 1:250,000, and then those diluted samples were run in the assay. The standard curve samples were serially diluted as stated above (experimental range), and then those samples were run in the assay.

[0190] Since there was a discrepancy between the dilution of the serum samples (1:250,000) as compared to the dilution of the standard curve samples (undiluted beyond the serial dilutions), all the serum sample concentration values obtained from the standard curve were multiplied by a dilution factor of "250,000" to correct for the discrepancy.

Prolactin

[0191] Standard Curve experimental range=2 ng/ml to 240 ng/ml, in serial two-fold dilutions

[0192] Curve fit=linear, $y=0.0049x+0.0363$; $R^2=0.9917$

[0193] The standard curve samples and the serum samples were then both diluted 1:5 to run in the assay; since both the serum samples and the standard curve samples were diluted in the same manner there was no need to use a dilution factor during data analysis to determine the concentrations of the unknown serum samples.

Results—Individual Marker Performance

[0194] Among the 500 normal cases used in the present study, 104 normal cases were used as control group to select the threshold cutoff point. Table 6 provides the mean, standard deviation, range, mean+2*std, mean+3*std based on these 104 threshold normal cases for each marker. Table 7 and Table 8 provide the mean standard deviation, range, mean+2*std in all normal study cases (396 cases) and with normal study cases from patients over the age of 55 (195 or less). The mean and standard deviations were very similar between the normal threshold control cases and normal study cases for patients over the age of 55 for each biomarker except for markers HE4 and Inhibin. See Tables 6 and 8.

TABLE 6

Mean and STD of Each Biomarker in 104 Normal Control Cases

Variable	N	Mean	Std Dev	Min	Max	Mean + 2 * std	Mean + 3 * std	Best Cutoff
HE4	104	1.7	0.91	0.5	6.6	3.5	4.4	2.2
CA125	104	6.9	6.42	0.6	42.6	19.7	26.1	20
GLY	104	1.8	2.75	0.0	18.6	7.4	10.1	5
MMP	104	3.4	1.05	1.9	7.0	5.5	6.5	4

TABLE 6-continued

Mean and STD of Each Biomarker in 104 Normal Control Cases

Variable	N	Mean	Std Dev	Min	Max	Mean + 2 * std	Mean + 3 * std	Best Cutoff
Mucl	104	12.5	10.71	0.1	51.8	33.9	44.6	12
PAI	104	74.8	24.92	16.4	143.2	124.7		95
CTRHC1	104	3.2	1.16	1.2	6.2	5.5		4
INH	104	0.6	2.80	0.0	26.9	6.2	9.0	2
Plau-R	104	1945.4	534.03	1056.00	4248.0	3013.4	3547.5	2399.9
PROLAC	104	10.2	10.94	3.1	102.2	32.0	43.0	11
KLK10	104	0.8	0.51	0.3	2.3	1.8		0.9
KLK6	104	2.2	2.39	0.3	16.3	7.0	9.4	5
SLPI	104	65.7	14.38	40.2	134.5	94.5	108.9	65

TABLE 7

Mean and STD of Each Biomarker in 396 Normal Study Cases

Variable	N	Mean	Std Dev	Min	Max	Mean + 2 * std
HE4	396	1.6	2.1	0.2	36.4	5.8*
CA125	396	10.4	14.2	1.7	212.4	38.7*
GLY	396	5.0	10.2	0.0	98.4	25.3*
MMP	396	3.0	1.1	0.8	10.4	5.1
Mucl	396	8.3	8.2	0.0	52.1	24.7
PAI	396	73.2	28.0	18.8	145.7	129.2
CTRHC1	396	2.9	1.2	0.4	8.7	5.2
INH	360	11.3	28.1	0.0	265.4	67.5*
PLAUR	396	2086.0	782.0	822.0	6384.00	3650
PROLAC	396	11.6	9.5	2.0	138.0	30.7
KLK10	396	0.9	0.4	0.2	2.5	1.7
KLK6	396	1.7	1.7	0.1	18.0	5.1
SLPI	396	59.6	18.0	31.3	305.0	95.6

*The values in normal cases were very different from the values in normal control cases, which means these markers might be sensitive due to age effect.

TABLE 8

Mean and STD of Each Biomarker in Normal Study Cases
(Patients Over the Age of 55)

Variable	N	Mean	Std Dev	Min	Max	Mean + 2 * std
HE4	195	2.0	2.8	0.2	36.4	7.6*
CA125	194	10.6	5.6	2.3	35.7	21.9
GLY	195	1.7	2.3	0.0	24.8	6.3
MMP	195	3.2	1.2	0.8	10.4	5.6
Mucl	195	8.9	8.4	0.0	36.6	25.7
PAI	195	75.6	27.9	19.1	145.7	131.3
CTRHC1	195	3.2	1.1	1.2	7.1	5.4
INH	177	5.2	26.6	0.0	265.4	58.5**
PLAUR	195	2209.5	752.1	1122.0	5100.0	3713.7
PROLAC	195	10.8	11.1	2.0	138.0	32.9
KLK10	195	0.9	0.4	0.2	2.4	1.7
KLK6	195	1.8	2.0	0.1	18.0	5.7
SLPI	195	60.3	14.2	31.3	126.9	88.6

*The standard deviation was larger in the normal study cases than in the normal control cases for patients over the age of 55

**The mean and standard deviation were larger in the normal study cases than in the normal control cases for patients over the age of 55

[0195] For each individual marker, the ROC curve was obtained. The ROC curve only consists of the 396 normal cases and the 200 ovarian cancer cases. The 104 normal cases as control and 200 interfering substance/pathology cases were not included in this analysis. The ROC curves for HE4, inhibin A, prolactin, PLAU-R, glycodelin, SLPI, CTHRC1, PAI-1, KLK-10, CA125, KLK-6, MUC-1, and MMP-7 are presented in FIGS. **2-14**, respectively.

[0196] Also, the percentage of positive and negative samples were determined for each marker by age group, by cancer stage, and by interfering substance/pathology category. These determinations were based on two kinds of cutoff points: (1) mean+2*std, and (2) the best cutoff from the ROC curve. The best cutoff points were selected from the ROC curve with the highest value of sensitivity plus specificity. The best cutoff point was listed in Table 6. Summaries of the positive results for each biomarker by age group, cancer stage, and interfering substance/pathology category are presented in tables 9 to 47.

Biomarker: HE4

[0197]

TABLE 9

Summary by Age Group for HE4

		Best Cutoff from ROC plot				Mean + 2 * std			
		Age <= 55		Age > 55		Age <= 55		Age > 55	
Group	Result	N	%	N	%	N	%	N	%
IP	Positive	57	63.33	98	90.74	41	45.56	81	75.00
	Negative	33	36.67	10	9.26	49	54.44	27	25.00
	Total	90	100.00	108	100.00	90	100.00	108	100.00
NORMAL	Positive	15	7.46	39	20.00	3	1.49	13	6.67
	Negative	186	92.54	156	80.00	198	98.51	182	93.33
	Total	201	100.00	195	100.00	201	100.00	195	100.00
OvCA	Positive	81	81.00	91	91.00	58	58.00	75	75.00
	Negative	19	19.00	9	9.00	42	42.00	25	25.00
	Total	100	100.00	100	100.00	100	100.00	100	100.00

TABLE 10

Summary by Interfering Substance/Pathology Category for HE4

		Best Cutoff from ROC plot		Mean + 2 * std	
Group	Result	N	%	N	%
Tumors	Positive	38	84.44	27	60.00
	Negative	7	15.56	18	40.00
	Total	45	100.00	45	100.00
Metabolic Disorder	Positive	20	100.00	20	100.00
	Negative	0	0.00	0	0.00
	Total	20	100.00	20	100.00
Hormonal Fluctuation	Positive	23	69.70	16	48.48
	Negative	10	30.30	17	51.52
	Total	33	100.00	33	100.00
Gynecologic Disorder	Positive	17	48.57	12	34.29
	Negative	18	51.43	23	65.71
	Total	35	100.00	35	100.00
Vascular Disorder	Positive	22	88.00	19	76.00
	Negative	3	12.00	6	24.00
	Total	25	100.00	25	100.00
Chronic Immuno. Disorder	Positive	37	88.10	29	69.05
	Negative	5	11.90	13	30.95
	Total	42	100.00	42	100.00

TABLE 11

Summary by Cancer Stage for HE4

		Best Cutoff from ROC plot		Mean + 2 * std	
Stage	Result	N	%	N	%
1	Positive	57	85.07	42	62.69
	Negative	10	14.93	25	37.31
	Total	67	100.00	67	100.00
2	Positive	53	80.30	41	62.12
	Negative	13	19.70	25	37.88
	Total	66	100.00	66	100.00
3	Positive	62	92.54	50	74.63
	Negative	5	7.46	17	25.37

Biomarker Muc-1

[0198]

TABLE 12

Summary by Age Group for Muc-1

		Best Cutoff from ROC plot				Mean + 2 * std			
		Age <= 55		Age > 55		Age <= 55		Age > 55	
Group	Result	N	%	N	%	N	%	N	%
IP	Positive	38	42.22	53	49.07	4	4.44	9	8.33
	Negative	52	57.78	55	50.93	86	95.56	99	91.67
	Total	90	100.00	108	100.00	90	100.00	108	100.00
NORMAL	Positive	49	24.38	58	29.74	2	1.00	4	2.05
	Negative	152	75.62	137	70.26	199	99.00	191	97.95
	Total	201	100.00	195	100.00	201	100.00	195	100.00
OvCA	Positive	56	56.00	52	52.00	4	4.00	12	12.00
	Negative	44	44.00	48	48.00	96	96.00	88	88.00
	Total	100	100.00	100	100.00	100	100.00	100	100.00

TABLE 13

Summary by Interfering Substance/Pathology Category for Muc-1

		Best Cutoff from ROC plot		Mean + 2 * std	
Group	Result	N	%	N	%
Tumors	Positive	20	44.44	3	6.67
	Negative	25	55.56	42	93.33
	Total	45	100.00	45	100.00
Metabolic Disorder	Positive	8	40.00	1	5.00
	Negative	12	60.00	19	95.00
	Total	20	100.00	20	100.00
Hormonal Fluctuation	Positive	14	42.42	1	3.03
	Negative	19	57.58	32	96.97
	Total	33	100.00	33	100.00
Gynecologic Disorder	Positive	17	48.57	1	2.86
	Negative	18	51.43	34	97.14
	Total	35	100.00	35	100.00
Vascular Disorder	Positive	11	44.00	2	8.00
	Negative	14	56.00	23	92.00
	Total	25	100.00	25	100.00
Chronic Immuno. Disorder	Positive	22	52.38	5	11.90
	Negative	20	47.62	37	88.10
	Total	42	100.00	42	100.00

TABLE 14

Summary by Cancer Stage for Muc-1

		Best Cutoff from ROC plot		Mean + 2 * std	
Stage	Result	N	%	N	%
1	Positive	44	65.67	6	8.96
	Negative	23	34.33	61	91.04
	Total	67	100.00	67	100.00
2	Positive	27	40.91	3	4.55
	Negative	39	59.09	63	95.45
	Total	66	100.00	66	100.00
3	Positive	37	55.22	7	10.45
	Negative	30	44.78	60	89.55
	Total	67	100.00	67	100.00

Biomarker. KLK-6

TABLE 15

		Summary by Age Group for KLK-6							
		Best Cutoff from ROC plot				Mean + 2 * std			
		Age <= 55		Age > 55		Age <= 55		Age > 55	
Group	Result	N	%	N	%	N	%	N	%
IP	Positive	5	5.56	8	7.41	4	4.44	4	3.70
	Negative	85	94.44	100	92.59	86	95.56	104	96.30
	Total	90	100.00	108	100.00	90	100.00	108	100.00
NORMAL	Positive	6	2.99	11	5.64	2	1.00	5	2.56
	Negative	195	97.01	184	94.36	199	99.00	190	97.44
	Total	201	100.00	195	100.00	201	100.00	195	100.00
OvCA	Positive	10	10.00	13	13.00	4	4.00	6	6.00
	Negative	90	90.00	87	87.00	96	96.00	94	94.00
	Total	100	100.00	100	100.00	100	100.00	100	100.00

TABLE 16

		Summary by Interfering Substance/Pathology Category for KLK-6			
		Best Cutoff from ROC plot		Mean + 2 * std	
Group	Result	N	%	N	%
Tumors	Positive	5	11.11	4	8.89
	Negative	40	88.89	41	91.11
	Total	45	100.00	45	100.00
Metabolic Disorder	Positive	0	0.00	0	0.00
	Negative	20	100.00	20	100.00
	Total	20	100.00	20	100.00
Hormonal Fluctuation	Positive	0	0.00	0	0.00
	Negative	33	100.00	33	100.00
	Total	33	100.00	33	100.00
Gynecologic Disorder	Positive	3	8.57	2	5.71
	Negative	32	91.43	33	94.29
	Total	35	100.00	35	100.00
Vascular Disorder	Positive	3	12.00	1	4.00
	Negative	22	88.00	24	96.00
	Total	25	100.00	25	100.00
Chronic Immuno. Disorder	Positive	2	4.76	1	2.38
	Negative	40	95.24	41	97.62
	Total	42	100.00	42	100.00

TABLE 17

		Summary by Cancer Stage Group for KLK-6			
		Best Cutoff from ROC plot		Mean + 2 * std	
Stage	Result	N	%	N	%
1	Positive	10	14.93	4	5.97
	Negative	57	85.07	63	94.03
	Total	67	100.00	67	100.00
2	Positive	7	10.61	3	4.55
	Negative	59	89.39	63	95.45
	Total	66	100.00	66	100.00
3	Positive	6	8.96	3	4.48
	Negative	61	91.04	64	95.52
	Total	67	100.00	67	100.00

Biomarker: KLK-10

[0199]

TABLE 18

		Summary by Age Group for KLK-10							
		Best Cutoff from ROC plot				Mean + 2 * std			
		Age <= 55		Age > 55		Age <= 55		Age > 55	
Group	Result	N	%	N	%	N	%	N	%
IP	Positive	56	62.22	51	47.22	7	7.78	6	5.56
	Negative	34	37.78	57	52.78	83	92.22	102	94.44
	Total	90	100.00	108	100.00	90	100.00	108	100.00
NORMAL	Positive	92	45.77	89	45.64	4	1.99	2	1.03
	Negative	109	54.23	106	54.36	197	98.01	193	98.97
	Total	201	100.00	195	100.00	201	100.00	195	100.00
OvCA	Positive	63	63.00	53	53.00	9	9.00	7	7.00
	Negative	37	37.00	47	47.00	91	91.00	93	93.00
	Total	100	100.00	100	100.00	100	100.00	100	100.00

TABLE 19

		Summary by Interfering Substance/Pathology Group for KLK-10			
		Best Cutoff from ROC plot		Mean + 2 * std	
Group	Result	N	%	N	%
Tumors	Positive	28	62.22	3	6.67
	Negative	17	37.78	42	93.33
	Total	45	100.00	45	100.00
Metabolic Disorder	Positive	10	50.00	0	0.00
	Negative	10	50.00	20	100.00
	Total	20	100.00	20	100.00
Hormonal Fluctuation	Positive	14	42.42	0	0.00
	Negative	19	57.58	33	100.00
	Total	33	100.00	33	100.00
Gynecologic Disorder	Positive	23	65.71	3	8.57
	Negative	12	34.29	32	91.43
	Total	35	100.00	35	100.00
Vascular Disorder	Positive	11	44.00	1	4.00
	Negative	14	56.00	24	96.00
	Total	25	100.00	25	100.00
Chronic Immuno. Disorder	Positive	23	54.76	6	14.29
	Negative	19	45.24	36	85.71
	Total	42	100.00	42	100.00

TABLE 20

		Summary by Cancer Stage Group for KLK-10			
		Best Cutoff from ROC plot		Mean + 2 * std	
Stage	Result	N	%	N	%
1	Positive	37	55.22	8	11.94
	Negative	30	44.78	59	88.06
	Total	67	100.00	67	100.00
2	Positive	37	56.06	3	4.55
	Negative	29	43.94	63	95.45
	Total	66	100.00	66	100.00
3	Positive	42	62.69	5	7.46
	Negative	25	37.31	62	92.54
	Total	67	100.00	67	100.00

Biomarker. PAI-1

TABLE 21

Summary by Age Group for PAI-1

		Best Cutoff from ROC plot				Mean + 2 * std			
		Age <= 55		Age > 55		Age <= 55		Age > 55	
Group	Result	N	%	N	%	N	%	N	%
IP	Positive	52	57.78	67	62.04	12	13.33	10	9.26
	Negative	38	42.22	41	37.96	78	86.67	98	90.74
	Total	90	100.00	108	100.00	90	100.00	108	100.00
NORMAL	Positive	43	21.39	52	26.67	5	2.49	10	5.13
	Negative	158	78.61	143	73.33	196	97.51	185	94.87
	Total	201	100.00	195	100.00	201	100.00	195	100.00
OvCA	Positive	71	71.00	62	62.00	19	19.00	11	11.00
	Negative	29	29.00	38	38.00	81	81.00	89	89.00
	Total	100	100.00	100	100.00	100	100.00	100	100.00

TABLE 22

Summary by Interfering Substance/Pathology Group for PAI-1

		Best Cutoff from ROC plot		Mean + 2 * std	
Group	Result	N	%	N	%
Tumors	Positive	17	37.78	4	8.89
	Negative	28	62.22	41	91.11
	Total	45	100.00	45	100.00
Metabolic Disorder	Positive	16	80.00	4	20.00
	Negative	4	20.00	16	80.00
	Total	20	100.00	20	100.00
Hormonal Fluctuation	Positive	24	72.73	5	15.15
	Negative	9	27.27	28	84.85
	Total	33	100.00	33	100.00
Gynecologic Disorder	Positive	17	48.57	2	5.71
	Negative	18	51.43	33	94.29
	Total	35	100.00	35	100.00
Vascular Disorder	Positive	17	68.00	1	4.00
	Negative	8	32.00	24	96.00
	Total	25	100.00	25	100.00
Chronic Immuno. Disorder	Positive	30	71.43	6	14.29
	Negative	12	28.57	36	85.71
	Total	42	100.00	42	100.00

TABLE 23

Summary by Cancer Stage Group for PAI-1

		Best Cutoff from ROC plot		Mean + 2 * std	
Stage	Result	N	%	N	%
1	Positive	54	80.60	15	22.39
	Negative	13	19.40	52	77.61
	Total	67	100.00	67	100.00
2	Positive	33	50.00	4	6.06
	Negative	33	50.00	62	93.94
	Total	66	100.00	66	100.00
3	Positive	46	68.66	11	16.42
	Negative	21	31.34	56	83.58
	Total	67	100.00	67	100.0

Biomarker: CTHRC1
[0200]

TABLE 24

Summary by Age Group for CTHRC1

		Best Cutoff from ROC plot				Mean + 2 * std			
		Age <= 55		Age > 55		Age <= 55		Age > 55	
Group	Result	N	%	N	%	N	%	N	%
IP	Positive	12	13.33	35	32.41	6	6.67	11	10.19
	Negative	78	86.67	73	67.59	84	93.33	97	89.81
	Total	90	100.00	108	100.00	90	100.00	108	100.00
NORMAL	Positive	20	9.95	40	20.51	4	1.99	4	2.05
	Negative	181	90.05	155	79.49	197	98.01	191	97.95
	Total	201	100.00	195	100.00	201	100.00	195	100.00
OvCA	Positive	24	24.00	35	35.00	10	10.00	15	15.00
	Negative	76	76.00	65	65.00	90	90.00	85	85.00
	Total	100	100.00	100	100.00	100	100.00	100	100.00

TABLE 25

Summary by Interfering Substance/Pathology Group for CTHRC1

		Best Cutoff from ROC plot		Mean + 2 * std	
Group	Result	N	%	N	%
Tumors	Positive	13	28.89	7	15.56
	Negative	32	71.11	38	84.44
	Total	45	100.00	45	100.00
Metabolic Disorder	Positive	2	10.00	0	0.00
	Negative	18	90.00	20	100.00
	Total	20	100.00	20	100.00
Hormonal Fluctuation	Positive	1	3.03	1	3.03
	Negative	32	96.97	32	96.97
	Total	33	100.00	33	100.00
Gynecologic Disorder	Positive	2	5.71	0	0.00
	Negative	33	94.29	35	100.00
	Total	35	100.00	35	100.00
Vascular Disorder	Positive	11	44.00	5	20.00
	Negative	14	56.00	20	80.00
	Total	25	100.00	25	100.00
Chronic Immuno. Disorder	Positive	18	42.86	4	9.52
	Negative	24	57.14	38	90.48
	Total	42	100.00	42	100.00

TABLE 26

Summary by Cancer Stage Group for CTHRC1

		Best Cutoff from ROC plot		Mean + 2 * std	
Stage	Result	N	%	N	%
1	Positive	16	23.88	7	10.45
	Negative	51	76.12	60	89.55
	Total	67	100.00	67	100.00
2	Positive	19	28.79	8	12.12
	Negative	47	71.21	58	87.88
	Total	66	100.00	66	100.00
3	Positive	24	35.82	10	14.93
	Negative	43	64.18	57	85.07
	Total	67	100.00	67	100.00

Biomarker: SLPI

[0201]

TABLE 27

Summary by Age Group for SLPI

		Best Cutoff from ROC plot				Mean + 2 * std			
		Age <= 55		Age > 55		Age <= 55		Age > 55	
Group	Result	N	%	N	%	N	%	N	%
IP	Positive	27	30.00	61	56.48	4	4.44	23	21.30
	Negative	63	70.00	47	43.52	86	95.56	85	78.70
	Total	90	100.00	108	100.00	90	100.00	108	100.00
NORMAL	Positive	49	24.38	63	32.31	4	1.99	3	1.54
	Negative	152	75.62	132	67.69	197	98.01	192	98.46
	Total	201	100.00	195	100.00	201	100.00	195	100.00
OvCA	Positive	53	53.00	67	67.00	14	14.00	16	16.00
	Negative	47	47.00	33	33.00	86	86.00	84	84.00
	Total	100	100.00	100	100.00	100	100.00	100	100.00

TABLE 28

Summary by Interfering Substance/Pathology Group for SLPI

		Best Cutoff from ROC plot		Mean + 2 * std	
Group	Result	N	%	N	%
Tumors	Positive	20	44.44	7	15.56
	Negative	25	55.56	38	84.44
	Total	45	100.00	45	100.00
Metabolic Disorder	Positive	10	50.00	1	5.00
	Negative	10	50.00	19	95.00
	Total	20	100.00	20	100.00
Hormonal Fluctuation	Positive	6	18.18	0	0.00
	Negative	27	81.82	33	100.00
	Total	33	100.00	33	100.00
Gynecologic Disorder	Positive	12	34.29	4	11.43
	Negative	23	65.71	31	88.57
	Total	35	100.00	35	100.00
Vascular Disorder	Positive	16	64.00	9	36.00
	Negative	9	36.00	16	64.00
	Total	25	100.00	25	100.00
Chronic Immuno. Disorder	Positive	26	61.90	7	16.67
	Negative	16	38.10	35	83.33
	Total	42	100.00	42	100.00

TABLE 29

Summary by Cancer Stage Group for SLPI

		Best Cutoff from ROC plot		Mean + 2 * std	
Stage	Result	N	%	N	%
1	Positive	34	50.75	9	13.43
	Negative	33	49.25	58	86.57
	Total	67	100.00	67	100.00
2	Positive	38	57.58	4	6.06
	Negative	28	42.42	62	93.94
	Total	66	100.00	66	100.00
3	Positive	48	71.64	17	25.37
	Negative	19	28.36	50	74.63
	Total	67	100.00	67	100.00

Biomarker: Inhibin A

[0202]

TABLE 30

		Summary by Age Group for Inhibin							
		Best Cutoff from ROC plot				Mean + 2 * std			
		Age <= 55		Age > 55		Age <= 55		Age > 55	
Group	Result	N	%	N	%	N	%	N	%
IP	Positive	53	58.89	11	10.19	48	53.33	7	6.48
	Negative	37	41.11	97	89.81	42	46.67	101	93.52
	Total	90	100.00	108	100.00	90	100.00	108	100.00
NORMAL	Positive	94	46.77	25	12.82	83	41.29	14	7.18
	Negative	107	53.23	170	87.18	118	58.71	181	92.82
	Total	201	100.00	195	100.00	201	100.00	195	100.00
OvCA	Positive	42	42.00	41	41.00	32	32.00	36	36.00
	Negative	58	58.00	59	59.00	68	68.00	64	64.00
	Total	100	100.00	100	100.00	100	100.00	100	100.00

TABLE 31

		Summary by Interfering Substance/Pathology Group for Inhibin			
		Best Cutoff from ROC plot		Mean + 2 * std	
Group	Result	N	%	N	%
Tumors	Positive	4	8.89	2	4.44
	Negative	41	91.11	43	95.56
	Total	45	100.00	45	100.00
Metabolic Disorder	Positive	8	40.00	8	40.00
	Negative	12	60.00	12	60.00
	Total	20	100.00	20	100.00
Hormonal Fluctuation	Positive	16	48.48	16	48.48
	Negative	17	51.52	17	51.52
	Total	33	100.00	33	100.00
Gynecologic Disorder	Positive	27	77.14	25	71.43
	Negative	8	22.86	10	28.57
	Total	35	100.00	35	100.00
Vascular Disorder	Positive	3	12.00	2	8.00
	Negative	22	88.00	23	92.00
	Total	25	100.00	25	100.00
Chronic Immuno. Disorder	Positive	8	19.05	4	9.52
	Negative	34	80.95	38	90.48
	Total	42	100.00	42	100.00

TABLE 32

		Summary by Cancer Stage Group for Inhibin			
		Best Cutoff from ROC plot		Mean + 2 * std	
Stage	Result	N	%	N	%
1	Positive	25	37.31	20	29.85
	Negative	42	62.69	47	70.15
	Total	67	100.00	67	100.00
2	Positive	35	53.03	32	48.48
	Negative	31	46.97	34	51.52
	Total	66	100.00	66	100.00
3	Positive	23	34.33	16	23.88
	Negative	44	65.67	51	76.12
	Total	67	100.00	67	100.00

Biomarker: Glycodelin

[0203]

TABLE 33

		Summary by Age Group for Glycodelin							
		Best Cutoff from ROC plot				Mean + 2 * std			
		Age <= 55		Age > 55		Age <= 55		Age > 55	
Group	Result	N	%	N	%	N	%	N	%
IP	Positive	53	58.89	18	16.67	36	40.00	10	9.26
	Negative	37	41.11	90	83.33	54	60.00	98	90.74
	Total	90	100.00	108	100.00	90	100.00	108	100.00
NORMAL	Positive	73	36.32	10	5.13	56	27.86	3	1.54
	Negative	128	63.68	185	94.87	145	72.14	192	98.46
	Total	201	100.00	195	100.00	201	100.00	195	100.00
OvCA	Positive	65	65.00	62	62.00	49	49.00	52	52.00
	Negative	35	35.00	38	38.00	51	51.00	48	48.00
	Total	100	100.00	100	100.00	100	100.00	100	100.00

TABLE 34

		Summary by Interfering Substance/Pathology Group for Glycodelin			
		Best Cutoff from ROC plot		Mean + 2 * std	
Group	Result	N	%	N	%
Tumors	Positive	13	28.89	6	13.33
	Negative	32	71.11	39	86.67
	Total	45	100.00	45	100.00
Metabolic Disorder	Positive	9	45.00	5	25.00
	Negative	11	55.00	15	75.00
	Total	20	100.00	20	100.00
Hormonal Fluctuation	Positive	18	54.55	15	45.45
	Negative	15	45.45	18	54.55
	Total	33	100.00	33	100.00
Gynecologic Disorder	Positive	21	60.00	14	40.00
	Negative	14	40.00	21	60.00
	Total	35	100.00	35	100.00
Vascular Disorder	Positive	1	4.00	1	4.00
	Negative	24	96.00	24	96.00
	Total	25	100.00	25	100.00
Chronic Immuno. Disorder	Positive	9	21.43	5	11.90
	Negative	33	78.57	37	88.10
	Total	42	100.00	42	100.00

TABLE 35

		Summary by Cancer Stage Group for Glycodelin			
		Best Cutoff from ROC plot		Mean + 2 * std	
Stage	Result	N	%	N	%
1	Positive	43	64.18	34	50.75
	Negative	24	35.82	33	49.25
	Total	67	100.00	67	100.00
2	Positive	41	62.12	37	56.06
	Negative	25	37.88	29	43.94
	Total	66	100.00	66	100.00
3	Positive	43	64.18	30	44.78
	Negative	24	35.82	37	55.22
	Total	67	100.00	67	100.00

Biomarker: MMP-7

[0204]

TABLE 36

Summary by Age Group for MMP-7									
		Best Cutoff from ROC plot				Mean + 2 * std			
		Age <= 55		Age > 55		Age <= 55		Age > 55	
Group	Result	N	%	N	%	N	%	N	%
IP	Positive	19	21.11	78	72.22	9	10.00	44	40.74
	Negative	71	78.89	30	27.78	81	90.00	64	59.26
	Total	90	100.00	108	100.00	90	100.00	108	100.00
NORMAL	Positive	12	5.97	30	15.38	2	1.00	7	3.59
	Negative	189	94.03	165	84.62	199	99.00	188	96.41
	Total	201	100.00	195	100.00	201	100.00	195	100.00
OvCA	Positive	50	50.00	53	53.00	28	28.00	33	33.00
	Negative	50	50.00	47	47.00	72	72.00	67	67.00
	Total	100	100.00	100	100.00	100	100.00	100	100.00

TABLE 37

Summary by Interfering Substance/Pathology Group for MMP-7					
		Best Cutoff from ROC plot		Mean + 2 * std	
Group	Result	N	%	N	%
Tumors	Positive	27	60.00	15	33.33
	Negative	18	40.00	30	66.67
	Total	45	100.00	45	100.00
Metabolic Disorder	Positive	8	40.00	5	25.00
	Negative	12	60.00	15	75.00
	Total	20	100.00	20	100.00
Hormonal Fluctuation	Positive	3	9.09	0	0.00
	Negative	30	90.91	33	100.00
	Total	33	100.00	33	100.00
Gynecologic Disorder	Positive	8	22.86	3	8.57
	Negative	27	77.14	32	91.43
	Total	35	100.00	35	100.00
Vascular Disorder	Positive	22	88.00	10	40.00
	Negative	3	12.00	15	60.00
	Total	25	100.00	25	100.00
Chronic Immuno. Disorder	Positive	29	69.05	20	47.62
	Negative	13	30.95	22	52.38
	Total	42	100.00	42	100.00

TABLE 38

Summary by Cancer Stage Group for MMP-7					
		Best Cutoff from ROC plot		Mean + 2 * std	
Stage	Result	N	%	N	%
1	Positive	33	49.25	20	29.85
	Negative	34	50.75	47	70.15
	Total	67	100.00	67	100.00
2	Positive	28	42.42	11	16.67
	Negative	38	57.58	55	83.33
	Total	66	100.00	66	100.00
3	Positive	42	62.69	30	44.78
	Negative	25	37.31	37	55.22
	Total	67	100.00	67	100.00

Biomarker: PLAU-R

[0205]

TABLE 39

Summary by Age Group for PLAU-R

		Best Cutoff from ROC plot				Mean + 2 * std			
		Age <= 55		Age > 55		Age <= 55		Age > 55	
Group	Result	N	%	N	%	N	%	N	%
IP	Positive	50	55.56	71	65.74	24	26.67	56	51.85
	Negative	40	44.44	37	34.26	66	73.33	52	48.15
	Total	90	100.00	108	100.00	90	100.00	108	100.00
NORMAL	Positive	35	17.41	61	31.28	16	7.96	23	11.79
	Negative	166	82.59	134	68.72	185	92.04	172	88.21
	Total	201	100.00	195	100.00	201	100.00	195	100.00
OvCA	Positive	71	71.00	72	72.00	44	44.00	50	50.00
	Negative	29	29.00	28	28.00	56	56.00	50	50.00
	Total	100	100.00	100	100.00	100	100.00	100	100.00

TABLE 40

Summary by Interfering Substance/Pathology Group for PLAU-R

		Best Cutoff from ROC plot		Mean + 2 * std	
Group	Result	N	%	N	%
Tumors	Positive	30	66.67	20	44.44
	Negative	15	33.33	25	55.56
	Total	45	100.00	45	100.00
Metabolic Disorder	Positive	13	65.00	11	55.00
	Negative	7	35.00	9	45.00
	Total	20	100.00	20	100.00
Hormonal Fluctuation	Positive	13	39.39	1	3.03
	Negative	20	60.61	32	96.97
	Total	33	100.00	33	100.00
Gynecologic Disorder	Positive	15	42.86	9	25.71
	Negative	0	57.14	26	74.29
	Total	35	100.00	35	100.00
Vascular Disorder	Positive	18	72.00	11	44.00
	Negative	7	28.00	14	56.00
	Total	25	100.00	25	100.00

TABLE 40-continued

Summary by Interfering Substance/Pathology Group for PLAU-R

		Best Cutoff from ROC plot		Mean + 2 * std	
Group	Result	N	%	N	%
Chronic Immuno. Disorder	Positive	32	76.19	28	66.67
	Negative	10	23.81	14	33.33
	Total	42	100.00	42	100.00

TABLE 41

Summary by Cancer Stage Group for PLAU-R

		Best Cutoff from ROC plot		Mean + 2 * std	
Stage	Result	N	%	N	%
1	Positive	53	79.10	30	44.78
	Negative	14	20.90	37	55.22
	Total	67	100.00	67	100.00
2	Positive	40	60.61	29	43.94
	Negative	26	39.39	37	56.06
	Total	66	100.00	66	100.00
3	Positive	50	74.63	35	52.24
	Negative	17	25.37	32	47.76
	Total	67	100.00	67	100.00

Biomarker: Prolactin

[0206]

TABLE 42

		Summary by Age Group for Prolactin							
		Best Cutoff from ROC plot				Mean + 2 * std			
		Age <= 55		Age > 55		Age <= 55		Age > 55	
Group	Result	N	%	N	%	N	%	N	%
IP	Positive	50	55.56	49	45.37	9	10.00	6	5.56
	Negative	40	44.44	59	54.63	81	90.00	102	94.44
	Total	90	100.00	108	100.00	90	100.00	108	100.00
NORMAL	Positive	92	45.77	54	27.69	6	2.99	3	1.54
	Negative	109	54.23	141	72.31	195	97.01	192	98.46
	Total	201	100.00	195	100.00	201	100.00	195	100.00
OvCA	Positive	64	64.00	48	48.00	5	5.00	2	2.00
	Negative	36	36.00	52	52.00	95	95.00	98	98.00
	Total	100	100.00	100	100.00	100	100.00	100	100.00

TABLE 43

		Summary by Interfering Substance/Pathology Group for Prolactin			
		Best Cutoff from ROC plot		Mean + 2 * std	
Group	Result	N	%	N	%
Tumors	Positive	17	37.78	3	6.67
	Negative	28	62.22	42	93.33
	Total	45	100.00	45	100.00
Metabolic Disorder	Positive	4	20.00	2	10.00
	Negative	16	80.00	18	90.00
	Total	20	100.00	20	100.00
Hormonal Fluctuation	Positive	23	69.70	4	12.12
	Negative	10	30.30	29	87.88
	Total	33	100.00	33	100.00
Gynecologic Disorder	Positive	18	51.43	3	8.57
	Negative	17	48.57	32	91.43
	Total	35	100.00	35	100.00
Vascular Disorder	Positive	13	52.00	2	8.00
	Negative	12	48.00	23	92.00
	Total	25	100.00	25	100.00
Chronic Immuno. Disorder	Positive	26	61.90	2	4.76
	Negative	16	38.10	40	95.24
	Total	42	100.00	42	100.00

TABLE 44

		Summary by Cancer Stage Group for Prolactin			
		Best Cutoff from ROC plot		Mean + 2 * std	
Stage	Result	N	%	N	%
1	Positive	42	62.69	2	2.99
	Negative	25	37.31	65	97.01
	Total	67	100.00	67	100.00
2	Positive	30	45.45	2	3.03
	Negative	36	54.55	64	96.97
	Total	66	100.00	66	100.00
3	Positive	40	59.70	3	4.48
	Negative	27	40.30	64	95.52
	Total	67	100.00	67	100.00

Biomarker: CA125 (Lab Corp Data)

[0207]

TABLE 45

		Summary by Age Group for CA125 (LabCorp Data)			
		Cutoff at 35			
		Age <= 55		Age > 55	
Group	Result	N	%	N	%
IP	Positive	13	14.94	6	5.66
	Negative	74	85.06	100	94.34
	Total	87	100.00	106	100.00

TABLE 45-continued

Summary by Age Group for CA125 (LabCorp Data)

		Cutoff at 35			
		Age <= 55		Age > 55	
Group	Result	N	%	N	%
NORMAL	Positive	5	2.51	1	0.52
	Negative	194	97.49	193	99.48
	Total	199	100.00	194	100.00
OvCA	Positive	39	39.39	60	60.61
	Negative	60	60.61	39	39.39
	Total	99	100.00	99	100.00

TABLE 46

Summary by Interfering Substance/Pathology Group for CA125 (LabCorp data)

		Cutoff at 35	
Group	Result	N	%
Tumors	Positive	5	11.11
	Negative	40	88.89
	Total	45	100.00
Metabolic Disorder	Positive	1	5.56
	Negative	17	94.44
	Total	18	100.00
Hormonal Fluctuation	Positive	7	21.21
	Negative	26	78.79
	Total	33	100.00
Gynecologic Disorder	Positive	4	12.50
	Negative	28	87.50
	Total	32	100.00
Vascular Disorder	Positive	0	0.00
	Negative	25	100.00
	Total	25	100.00
Chronic Immuno. Disorder	Positive	2	4.76
	Negative	40	95.24
	Total	42	100.00

TABLE 47

Summary by Cancer Stage Group for CA 125 (LabCorp data)

		Cutoff at 35	
Stage	Result	N	%
1	Positive	24	35.82
	Negative	43	64.18
	Total	67	100.00
2	Positive	37	56.06
	Negative	29	43.94
	Total	66	100.00
3	Positive	38	58.46
	Negative	27	41.54
	Total	65	100.00

[0208] Summaries of the sensitivity of the thirteen biomarkers analyzed are presented in Tables 48-50, based on tumor stage, normal 2-standard deviation limits, or "best fit," respectively.

TABLE 48

Individual marker sensitivity summary by tumor stage (Based on best cutoff)

Marker	Stage 1 % pos	Stage 2 % pos	Stage 3 % pos
HE4	85.1	80.3	92.5
Glycodelin	64.2	62.1	64.2
MMP7	49.3	42.4	62.7
SLPI	50.8	57.6	71.6
PAI-1	80.6	50.0	68.7
MUC-1	65.7	40.9	55.2
CA125	35.8	56.1	58.5
Plau-R	79.1	60.6	74.6
Inhibin A	37.3	53.0	34.3
CTHRC1	23.9	28.8	35.8
KLK6	14.9	10.6	9.0
KLK10	55.2	56.1	62.7
Prolactin	62.7	45.5	59.7

TABLE 49

Individual Marker Sensitivity Summary (based on Normal 2SD limit)

Marker	Sensitivity	Specificity
HE4	66.5	96
Glycodelin	50.5	85.3
MMP7	30.5	97.7
SLPI	15.0	98.3
Plau-R	47.0	90.1
MUC1	8.0	98.5
Inhibin A	34.0	75.8
PAI-1	15.0	96.2
CA125 (>=35 u/ml)	50.0	98.5
CTHRC1	12.5	98.0
KLK6	5.0	98.2
KLK10	8.0	98.5
Prolactin	3.5	97.7

TABLE 50

Individual Marker Sensitivity Summary (based on best cutoff)

Marker	Sensitivity	Specificity
HE4	86.0	86.3
Glycodelin	63.5	79.0
MMP7	51.5	89.4
SLPI	60.0	71.7

TABLE 50-continued

Individual Marker Sensitivity Summary (based on best cutoff)		
Marker	Sensitivity	Specificity
Plau-R	71.5	77.2
MUC1	54.0	73.0
Inhibin A	40.7	70.3
PAI-1	66.5	76.0
CA125 (>=35 u/ml)	50.5	98.2
CTHRC1	29.5	84.8
KLK6	11.5	95.7
KLK10	58.0	54.3
Prolactin	56.0	63.1

Example 3

Ovarian Biomarker Selection Study

Multiple Biomarker Analysis

[0209] The logistic regression method was used for selection of optimal biomarkers for this study. Using logistic regression, stepwise selection starts off by finding the biomarker that produces the largest R-square value with the dependent variable. Then, given that the 'best' biomarker is in the model, logistic regression finds that next best biomarker in terms of adding to the R-square. This process of finding a set of biomarkers that adds to the R-square is stopped when biomarkers can no longer add to the R-square, in accordance with certain statistical criteria. These sets of biomarkers are not unique because some of the biomarkers have the same predictive performance.

[0210] Based on one selected model, a ROC plot can be produced, which provides the relationship between the sensitivity and specificity rates. Therefore, an appropriate specificity and sensitivity can be chosen in order to obtain an expected PPV with accepted sensitivity.

[0211] Tables 51 and 52 provide several examples involving selection of a set of biomarkers with a higher specificity and an appropriate sensitivity with a PPV of approximately 10% and a combined sensitivity rate around 70%-80%, under the assumption that the population is 8,000,000 and the disease prevalence is 0.25%. Different target values for sensitivity, specificity, NPV and PPV can be obtained by selecting different assay cutoffs, different biomarker combinations, and different rules for combining the biomarkers. Biomarker performance was analyzed using the biomarker values as continuous variables (Table 51) and as categorical variables (Table 52).

[0212] By way of definition, when two assay steps are performed, the first assay step may be referred to as the "screen test," and the second step may be referred to as the "reflex test." "Best cutoff point" refers to the value obtained from the ROC plot for a particular biomarker that produces the best sensitivity and specificity. "Mean+2*std" refers to the average expression level plus twice the standard deviation, based on analysis of normal samples from patients not afflicted with ovarian cancer.

Biomarker Performance as Continuous Variables

[0213]

TABLE 51

Estimated Sensitivity, Specificity, PPV, and NPV Adjusted by Disease Prevalence for Different Models (Biomarker values as continuous variables)

Example	Marker Selected and rule	Screen/Reflex Test Sensitivity	Screen/Reflex Test Specificity	Combined Performance* Sensitivity	Combined Performance* Specificity	Combined Performance* PPV	Combined Performance* NPV
			Age > 55				
1	Screen Test: If HE4 <= 1.8 then test is negative	90.2%	62.2%				
	Reflex Test: If HE4 > 1.8 then the following marker selected: CA125, GLY, PAI, Plau-R (actual value used**)	87%	96%	78.474%	98.4880%	11.5105%	99.9453%
2†	Marker selected: HE4, CA125, GLY, MMP-7, PAI, Plau-R (actual value used)	81.7%	98%	81.7%	98%	9.2873%	99.9532%

*Assume the population = 8,000,000; prevalence = 0.25%, estimated cancer cases = 20,000 in the population.

**Actual value refers to the actual biomarker expression level obtained in the test

†Although all listed biomarkers were assayed in a single step, additional algorithms were applied to obtain the values for sensitivity, specificity, PPV, and NPV indicated in the table.

Biomarker Performance as Categorical Variables

[0214]

TABLE 52

Estimated Sensitivity, Specificity, PPV, and NPV Adjusted by Disease Prevalence for Different Models (Biomarker Values as Categorical Variables)

Example	Marker Selected and rule	Screen/Reflex Test Sensitivity	Screen/Reflex Test Specificity	Combined Performance* Sensitivity	Combined Performance* Specificity	Combined Performance* PPV	Combined Performance* NPV
			Overall Sample				
1	Screen Test: If HE4 <= 1.8 then test is negative	91.9%	73%				
	Reflex Test: If HE4 > 1.8 then the following marker selected: CA125, MUC1, GLY, PAI-1, Plau-R (Best cutoff points used)	80%	92.5%	73.52%	98.704%	12.4479%	99.9328%
			Age > 55				
1	Screen Test: If HE4 <= 1.8 then test is negative	90.2%	62.2%				
	Reflex Test: If HE4 > 1.8 then the following marker selected (best cutoff points used): CA125, MUC-1, MMP-7, Plau-R, GLY	78%	95.9%	70.356%	98.4502%	10.2154%	99.9246%
2	Screen Test: If HE4 <= 1.8 then test is negative	90.2%	62.2%				
	Reflex Test: If HE4 > 1.8 then the following marker selected (Mean + 2 * std cutoff points used): CA125, MUC-1, MMP-7, Plau-R, Inhibin	82%	95.8%	73.964%	98.4124%	10.4555%	99.9337%
3†	Marker selected: PLAU-R, GLY, HE4, CA125, MMP-7, PAI-1 (Best cutoff points used)	80.8%	98.5%	80.8%	98.5%	11.8946%	99.9512%
4†	Marker selected: PLAU-R, GLY, HE4, CA125, MMP-7 (Mean + 2 * std cutoff points used)	75%	99%	75%	99%	15.8228%	99.9368%

*CA125 cutoff >= 35 in either best cutoff or mean + 2std cases

**Assume the population = 8,000,000; prevalence = 0.25%, the estimate cancer cases = 20,000 in the population.

†Although all listed biomarkers were assayed in a single step, additional algorithms were applied to obtain the values for sensitivity, specificity, PPV, and NPV indicated in the table.

Sensitivity, Specificity, PPV, and NPV Results Obtained with Application of "Test Rules"

[0215] In the current study, the biomarkers HE4, CA125, PLAU-R, glycodelin, Muc-1, PAI-1, MMP-7, and inhibin were the most frequently selected markers based on marker performance either as continuous or categorical variables. In contrast to the statistical methods described above, Table 53 provides the estimated sensitivity, specificity, PPV, and NPV (adjusted by disease prevalence) based on two test rules: (1) if any two of the above biomarkers are positive (i.e., overexpressed), then the test is declared positive or (2) if any 3 of the above biomarkers are positive (i.e., overexpressed), the test is declared positive. Contrary to the results presented above in Tables 51 and 52, though, the application of either test rule did not produce a high specificity rate, which in turn lead to an unacceptably low PPV (<1.5%) when adjusted for the low prevalence rate of ovarian cancer. The application of "test rules," such as those described herein, is representative of the current state of the art in the identification of patients having an increased risk of ovarian cancer.

TABLE 53

Estimated Sensitivity, Specificity, PPV, and NPV Adjusted by Disease Prevalence Based on Test Rules

		Performance*			
Example	Marker Selected and rule	Sensitivity	Specificity	PPV	NPV
	Overall Sample				
1	Any of two following markers are positive: HE4, CA125, Plau-R, GLY, MUC-1, PAI-1, MMP-7, Inhibin (best cutoff points used)	97.475%	51.654%	0.5028%	99.9878%
2	Any of 3 following markers are positive: HE4, CA125, Plau-R, GLY, MUC-1, PAI-1, MMP-7, Inhibin (best cutoff points used)	91.414%	78.372%	1.0482%	99.9726%
	Age > 55 Year Older				
1	Any of two following markers are positive: HE4, CA125, Plau-R, GLY, MUC-1, PAI-1, MMP-7, Inhibin (best cutoff points used)	96.970%	56.186%	0.5516%	99.9865%
2	Any of 3 following markers are positive: HE4, CA125, Plau-R, GLY, MUC-1, PAI-1, MMP-7, Inhibin (best cutoff points used)	94.949%	78.866%	1.1135%	99.9840%

*CA125 cutoff >= 35 in either best cutoff or mean + 2std cases

**Assume the population = 8,000,000; prevalence = 0.25%, estimated cancer cases = 20,000 in the population.

Example 4

Ovarian Biomarker Selection Study

Multiple Biomarker Analysis Using One-Step Screening Method

[0216] Expression of the biomarkers HE4, CA125, and glycodelin and combinations thereof for all patients and patient age over 55 was assessed using a one-step screening method, as described herein above. In particular, Table 54 provides the results for a one-step algorithm for patients over age 55. The test algorithm was based on a linear logistic regression model, and the actual value of each marker was used in the model. Linear logistic regression models (and other algorithms) are routine and well known in the art. See, for example, Fleiss (2003) Statistical Methods for Rates and Proportions (3^{rd} Ed.), which is herein incorporated by reference in its entirety. The algorithm offered 76.8% sensitivity at 96.4% specificity. A test outcome defined as positive was based on the following linear logistic regression model: $\ln(P/(1-P))=-4.2391+0.0888*CA125+0.1790*HE4+0.2349*GLY$, where P is the conditional probability of ovarian cancer given CA 125, HE4, and glycodelin being overexpressed in the patient body sample. A similar result was obtained with CA 125 determined using manufacture's recommended cutoff value of >35u/mL.

TABLE 54

Sensitivity and specificity of single-step screening assay to distinguish ovarian cancer (all stages) from controls in patients over age 55

Marker	Variable	Algorithm	Sensitivity	Specificity
HE4, CA125, GLYCODELIN	Actual value	1 Step: based on linear logistic model	76.8%	96.4%
HE4, CA125, GLYCODELIN	Actual value, except CA125	1 Step: based on linear logistic model	71.4%	95.4%

Example 5

Bootstrap Method of Analysis

Validation of Study Methods

[0217] A bootstrap method of analysis was also conducted to assure a robust estimate of sensitivity and specificity for the above studies given that an independent and unique set of cancer sera was not available to validate the model. The bootstrap method consisted of artificially creating 1000 random datasets with replacement selection from the study sample set. A set of the most frequently selected markers in the study based on optimal performance was selected: HE4, CA125, PLAU-R, Glycodelin, MUC1 and PAI-1. A "test" was defined as follows: Test is positive if either (1) HE4 is positive and any one of CA125, Glycodelin, MMP-7, PLAU-R is positive or (2) HE4 is negative but CA125, Glycodelin, MMP-7, PLAU-R are all positive; otherwise, the "test" is negative. From the 1000 random samples, the mean/standard deviation and 95% confidence interval of the sensitivity/specificity of this defined test were obtained.

[0218] All publications and patent applications mentioned in the specification are indicative of the level of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

[0219] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended embodiments.

TABLE 55

	Biomarker Sequence Information			
	Amino Acid Sequence		Nucleotide Sequence	
Biomarker Name	Accession No.	Sequence Identifier	Accession No.	Sequence Identifier
HE4 (Isoform 1)	NP_006094	SEQ ID NO: 1	NM_006103	SEQ ID NO: 2
HE4 (Isoform 3)	NP_542771	SEQ ID NO: 3	NM_080733	SEQ ID NO: 4
HE4 (Isoform 4)	NP_542772	SEQ ID NO: 5	NM_080734	SEQ ID NO: 6
HE4 (Isoform 2)	NP_542774	SEQ ID NO: 7	NM_080736	SEQ ID NO: 8
HE4 (Isoform 5)	NP_542773	SEQ ID NO: 9	NM_080735	SEQ ID NO: 10
KLK6 (Variant A)	NP_002765	SEQ ID NO: 11	NM_002774	SEQ ID NO: 12
KLK6 (Variant B)	NP_001012982	SEQ ID NO: 13	NM_001012964	SEQ ID NO: 14
KLK6 (Variant C)	NP_001012983	SEQ ID NO: 15	NM_001012965	SEQ ID NO: 16
KLK (Variant D)	NP_001012984	SEQ ID NO: 17	NM_001012966	SEQ ID NO: 18
KLK10 (Variant 1)	NP_002767	SEQ ID NO: 19	NM_002776	SEQ ID NO: 20
KLK10 (Variant 2)	NP_665895	SEQ ID NO: 21	NM_145888	SEQ ID NO: 22
Glycodelin (Variant 1)	NP_001018059	SEQ ID NO: 23	NM_001018409	SEQ ID NO: 24
Glycodelin (Variant 2)	NP_002562	SEQ ID NO: 25	NM_002571	SEQ ID NO: 26
PAI-1	NP_000593	SEQ ID NO: 27	NM_000602	SEQ ID NO: 28
Muc-1 (Variant 1)	NP_002447	SEQ ID NO: 29	NM_002456	SEQ ID NO: 30
Muc-1 (Variant 2)	NP_001018016	SEQ ID NO: 31	NM_001018016	SEQ ID NO: 32
Muc-1 (Variant 3)	NP_001018017	SEQ ID NO: 33	NM_001018017	SEQ ID NO: 34
Muc-1 (Variant 4)	NP_001018021	SEQ ID NO: 35	NM_001018021	SEQ ID NO: 36
Alpha-1 anti-trypsin	NP_000286	SEQ ID NO: 37	NM_000295	SEQ ID NO: 38
Alpha-1 anti-trypsin	NP_001002235	SEQ ID NO: 39	NM_001002235	SEQ ID NO: 40
Alpha-1 anti-trypsin	NP_001002236	SEQ ID NO: 41	NM_001002236	SEQ ID NO: 42
PLAUR (Variant 1)	NP_002650	SEQ ID NO: 43	NM_002659	SEQ ID NO: 44
PLAUR (Variant 2)	NP_001005376	SEQ ID NO: 45	NM_001005376	SEQ ID NO: 46
PLAUR (Variant 3)	NP_001005377	SEQ ID NO: 47	NM_001005377	SEQ ID NO: 48
CTHRC1	NP_612464	SEQ ID NO: 49	NM_138455	SEQ ID NO: 50
Inhibin (INHA)	NP_002182	SEQ ID NO: 51	NM_002191	SEQ ID NO: 52
Inhibin (INHBB)	NP_002184	SEQ ID NO: 53	NM_002193	SEQ ID NO: 54
Inhibin (INHBA)	NP_002183	SEQ ID NO: 55	NM_002192	SEQ ID NO: 56
CA125 (Muc-16)	NP_078966	SEQ ID NO: 57	NM_024690	SEQ ID NO: 58
MMP-7	NP_002414	SEQ ID NO: 59	NM_002423	SEQ ID NO: 60
Prolactin	NP_000939	SEQ ID NO: 61	NM_000948	SEQ ID NO: 62
SLPI	NP_003055	SEQ ID NO: 63	NM_003064	SEQ ID NO: 64

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                                SEQUENCE LISTING


<160> NUMBER OF SEQ ID NOS: 64

<210> SEQ ID NO 1
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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Met Pro Ala Cys Arg Leu Gly Pro Leu Ala Ala Ala Leu Leu Leu Ser
1               5                   10                  15

Leu Leu Leu Phe Gly Phe Thr Leu Val Ser Gly Thr Gly Ala Glu Lys
            20                  25                  30

Thr Gly Val Cys Pro Glu Leu Gln Ala Asp Gln Asn Cys Thr Gln Glu
        35                  40                  45

Cys Val Ser Asp Ser Glu Cys Ala Asp Asn Leu Lys Cys Cys Ser Ala
    50                  55                  60

Gly Cys Ala Thr Phe Cys Ser Leu Pro Asn Asp Lys Glu Gly Ser Cys
65                  70                  75                  80

Pro Gln Val Asn Ile Asn Phe Pro Gln Leu Gly Leu Cys Arg Asp Gln
                85                  90                  95

Cys Gln Val Asp Ser Gln Cys Pro Gly Gln Met Lys Cys Cys Arg Asn
            100                 105                 110

Gly Cys Gly Lys Val Ser Cys Val Thr Pro Asn Phe
        115                 120


<210> SEQ ID NO 2
<211> LENGTH: 570
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

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cgccctcctc ctcagcctgc tgctgttcgg cttcacccta gtctcaggca caggagcaga     120

gaagactggc gtgtgccccg agctccaggc tgaccagaac tgcacgcaag agtgcgtctc     180

ggacagcgaa tgcgccgaca acctcaagtg ctgcagcgcg ggctgtgcca ccttctgctc     240

tctgcccaat gataaggagg gttcctgccc ccaggtgaac attaactttc cccagctcgg     300

cctctgtcgg gaccagtgcc aggtggacag ccagtgtcct ggccagatga aatgctgccg     360

caatggctgt gggaaggtgt cctgtgtcac tcccaatttc tgagctccag ccaccaccag     420

gctgagcagt gaggagagaa agtttctgcc tggccctgca tctggttcca gcccacctgc     480

cctccccttt ttcgggactc tgtattccct cttgggctga ccacagcttc tccctttccc     540

aaccaataaa gtaaccactt tcagcaaaaa                                      570


<210> SEQ ID NO 3
<211> LENGTH: 79
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

Met Pro Ala Cys Arg Leu Gly Pro Leu Ala Ala Ala Leu Leu Leu Ser
1               5                   10                  15

Leu Leu Leu Phe Gly Phe Thr Leu Val Ser Gly Thr Gly Ala Glu Lys
```

-continued

20 25 30

Thr Gly Val Cys Pro Glu Leu Gln Ala Asp Gln Asn Cys Thr Gln Glu
35 40 45

Cys Val Ser Asp Ser Glu Cys Ala Asp Asn Leu Lys Cys Cys Ser Ala
50 55 60

Gly Cys Ala Thr Phe Cys Ser Leu Pro Asn Gly Gln Leu Ala Glu
65 70 75

<210> SEQ ID NO 4
<211> LENGTH: 694
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

cacctgcacc ccgcccgggc atagcaccat gcctgcttgt cgcctaggcc cgctagccgc 60

cgccctcctc ctcagcctgc tgctgttcgg cttcacccta gtctcaggca caggagcaga 120

gaagactggc gtgtgccccg agctccaggc tgaccagaac tgcacgcaag agtgcgtctc 180

ggacagcgaa tgcgccgaca acctcaagtg ctgcagcgcg ggctgtgcca ccttctgctc 240

tctgcccaat ggccaactgg ctgagtgatt cgaagaaagt gaggaatcct ccctggacac 300

tgtatcgccc ttcgtcgtct ttcagtcaat ctcttccact ctaaggattg agtgagcgcg 360

agctggggac tctctcaaag ataaggaggg ttcctgcccc caggtgaaca ttaactttcc 420

ccagctcggc ctctgtcggg accagtgcca ggtggacagc cagtgtcctg gccagatgaa 480

atgctgccgc aatggctgtg ggaaggtgtc ctgtgtcact cccaatttct gaggtccagc 540

caccaccagg ctgagcagtg aggagagaaa gtttctgcct ggccctgcat ctggttccag 600

cccacctgcc ctcccctttt tcgggactct gtattccctc ttgggctgac cacagcttct 660

ccctttccca accaataaag taaccacttt cagc 694

<210> SEQ ID NO 5
<211> LENGTH: 76
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

Met Pro Ala Cys Arg Leu Gly Pro Leu Ala Ala Ala Leu Leu Leu Ser
1 5 10 15

Leu Leu Leu Phe Gly Phe Thr Leu Val Ser Asp Lys Glu Gly Ser Cys
20 25 30

Pro Gln Val Asn Ile Asn Phe Pro Gln Leu Gly Leu Cys Arg Asp Gln
35 40 45

Cys Gln Val Asp Ser Gln Cys Pro Gly Gln Met Lys Cys Cys Arg Asn
50 55 60

Gly Cys Gly Lys Val Ser Cys Val Thr Pro Asn Phe
65 70 75

<210> SEQ ID NO 6
<211> LENGTH: 421
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

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cgccctcctc ctcagcctgc tgctgttcgg cttcacccta gtctcagata aggagggttc    120

ctgcccccag gtgaacatta actttcccca gctcggcctc tgtcgggacc agtgccaggt    180

ggacagccag tgtcctggcc agatgaaatg ctgccgcaat ggctgtggga aggtgtcctg    240

tgtcactccc aatttctgag gtccagccac caccaggctg agcagtgagg agagaaagtt    300

tctgcctggc cctgcatctg gttccagccc acctgccctc cccttttcg ggactctgta     360

ttccctcttg ggctgaccac agcttctccc tttcccaacc aataaagtaa ccactttcag    420

c                                                                    421
```

<210> SEQ ID NO 7
<211> LENGTH: 102
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

```
Met Pro Ala Cys Arg Leu Gly Pro Leu Ala Ala Ala Leu Leu Leu Ser
1               5                   10                  15

Leu Leu Leu Phe Gly Phe Thr Leu Val Ser Gly Thr Gly Ala Glu Lys
            20                  25                  30

Thr Gly Val Cys Pro Glu Leu Gln Ala Asp Gln Asn Cys Thr Gln Glu
        35                  40                  45

Cys Val Ser Asp Ser Glu Cys Ala Asp Asn Leu Lys Cys Cys Ser Ala
    50                  55                  60

Gly Cys Ala Thr Phe Cys Ser Leu Pro Asn Ala Leu Phe His Trp His
65                  70                  75                  80

Leu Lys Thr Arg Arg Leu Trp Glu Ile Ser Gly Pro Arg Pro Arg Arg
                85                  90                  95

Pro Thr Trp Asp Ser Ser
            100
```

<210> SEQ ID NO 8
<211> LENGTH: 358
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

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cacctgcacc ccgcccgggc atagcaccat gcctgcttgt cgcctaggcc cgctagccgc     60

cgccctcctc ctcagcctgc tgctgttcgg cttcacccta gtctcaggca caggagcaga    120

gaagactggc gtgtgccccg agctccaggc tgaccagaac tgcacgcaag agtgcgtctc    180

ggacagcgaa tgcgccgaca acctcaagtg ctgcagcgcg ggctgtgcca ccttctgctc    240

tctgcccaat gcactgttcc actggcacct aaagacacgg aggctctggg agatttctgg    300

ccctaggcca cgaaggccca cttgggactc aagctgaggt cctgtgattc catttggg      358
```

<210> SEQ ID NO 9
<211> LENGTH: 73
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

```
Met Leu Gln Val Gln Val Asn Leu Pro Val Ser Pro Leu Pro Thr Tyr
1               5                   10                  15

Pro Tyr Ser Phe Phe Tyr Pro Asp Lys Glu Gly Ser Cys Pro Gln Val
            20                  25                  30
```

-continued

```
Asn Ile Asn Phe Pro Gln Leu Gly Leu Cys Arg Asp Gln Cys Gln Val
        35                  40                  45

Asp Ser Gln Cys Pro Gly Gln Met Lys Cys Cys Arg Asn Gly Cys Gly
    50                  55                  60

Lys Val Ser Cys Val Thr Pro Asn Phe
65                  70


<210> SEQ ID NO 10
<211> LENGTH: 411
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

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cctctgccca cttaccctta ctcctttttc tacccagata aggagggttc ctgcccccag    120

gtgaacatta actttcccca gctcggcctc tgtcgggacc agtgccaggt ggacagccag    180

tgtcctggcc agatgaaatg ctgccgcaat ggctgtggga aggtgtcctg tgtcactccc    240

aatttctgag gtccagccac caccaggctg agcagtgagg agagaaagtt tctgcctggc    300

cctgcatctg gttccagccc acctgccctc cccttttttcg ggactctgta ttccctcttg    360

ggctgaccac agcttctccc tttcccaacc aataaagtaa ccactttcag c             411


<210> SEQ ID NO 11
<211> LENGTH: 244
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

Met Lys Lys Leu Met Val Val Leu Ser Leu Ile Ala Ala Ala Trp Ala
1               5                   10                  15

Glu Glu Gln Asn Lys Leu Val His Gly Gly Pro Cys Asp Lys Thr Ser
            20                  25                  30

His Pro Tyr Gln Ala Ala Leu Tyr Thr Ser Gly His Leu Leu Cys Gly
        35                  40                  45

Gly Val Leu Ile His Pro Leu Trp Val Leu Thr Ala Ala His Cys Lys
    50                  55                  60

Lys Pro Asn Leu Gln Val Phe Leu Gly Lys His Asn Leu Arg Gln Arg
65                  70                  75                  80

Glu Ser Ser Gln Glu Gln Ser Ser Val Val Arg Ala Val Ile His Pro
                85                  90                  95

Asp Tyr Asp Ala Ala Ser His Asp Gln Asp Ile Met Leu Leu Arg Leu
            100                 105                 110

Ala Arg Pro Ala Lys Leu Ser Glu Leu Ile Gln Pro Leu Pro Leu Glu
        115                 120                 125

Arg Asp Cys Ser Ala Asn Thr Thr Ser Cys His Ile Leu Gly Trp Gly
    130                 135                 140

Lys Thr Ala Asp Gly Asp Phe Pro Asp Thr Ile Gln Cys Ala Tyr Ile
145                 150                 155                 160

His Leu Val Ser Arg Glu Glu Cys Glu His Ala Tyr Pro Gly Gln Ile
                165                 170                 175

Thr Gln Asn Met Leu Cys Ala Gly Asp Glu Lys Tyr Gly Lys Asp Ser
            180                 185                 190
```

-continued

Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Gly Asp His Leu Arg
195 200 205

Gly Leu Val Ser Trp Gly Asn Ile Pro Cys Gly Ser Lys Glu Lys Pro
210 215 220

Gly Val Tyr Thr Asn Val Cys Arg Tyr Thr Asn Trp Ile Gln Lys Thr
225 230 235 240

Ile Gln Ala Lys

<210> SEQ ID NO 12
<211> LENGTH: 1527
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

ggcggacaaa gcccgattgt tcctgggccc tttccccatc gcgcctgggc ctgctcccca 60

gcccggggca ggggcggggg ccagtgtggt gacacacgct gtagctgtct ccccggctgg 120

ctggctcgct ctctcctggg gacacagagg tcggcaggca gcacacagag ggacctacgg 180

gcagctgttc cttcccccga ctcaagaatc cccggaggcc cggaggcctg cagcaggagc 240

ggccatgaag aagctgatgg tggtgctgag tctgattgct gcagcctggg cagaggagca 300

gaataagttg gtgcatggcg gaccctgcga caagacatct cacccctacc aagctgccct 360

ctacacctcg ggccacttgc tctgtggtgg ggtccttatc catccactgt gggtcctcac 420

agctgcccac tgcaaaaaac cgaatcttca ggtcttcctg gggaagcata accttcggca 480

aagggagagt tcccaggagc agagttctgt tgtccgggct gtgatccacc ctgactatga 540

tgccgccagc catgaccagg acatcatgct gttgcgcctg gcacgcccag ccaaactctc 600

tgaactcatc cagcccttc ccctggagag ggactgctca gccaacacca ccagctgcca 660

catcctgggc tggggcaaga cagcagatgg tgatttccct gacaccatcc agtgtgcata 720

catccacctg gtgtcccgtg aggagtgtga gcatgcctac cctggccaga tcacccagaa 780

catgttgtgt gctggggatg agaagtacgg gaaggattcc tgccagggtg attctggggg 840

tccgctggta tgtggagacc acctccgagg ccttgtgtca tggggtaaca tcccctgtgg 900

atcaaaggag aagccaggag tctacaccaa cgtctgcaga tacacgaact ggatccaaaa 960

aaccattcag gccaagtgac cctgacatgt gacatctacc tcccgaccta ccaccccact 1020

ggctggttcc agaacgtctc tcacctagac cttgcctccc ctcctctcct gcccagctct 1080

gaccctgatg cttaataaac gcagcgacgt gagggtcctg attctccctg gttttacccc 1140

agctccatcc ttgcatcact ggggaggacg tgatgagtga ggacttgggt cctcggtctt 1200

acccccacca ctaagagaat acaggaaaat cccttctagg catctcctct ccccaaccct 1260

tccacacgtt tgatttcttc ctgcagaggc ccagccacgt gtctggaatc ccagctccgc 1320

tgcttactgt cggtgtcccc ttgggatgta cctttcttca ctgcagattt ctcacctgta 1380

agatgaagat aaggatgata cagtctccat aaggcagtgg ctgttggaaa gatttaaggt 1440

ttcacaccta tgacatacat ggaatagcac ctgggccacc atgcactcaa taaagaatga 1500

attttattat gaaaaaaaaa aaaaaaa 1527

<210> SEQ ID NO 13
<211> LENGTH: 244
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 13

Met Lys Lys Leu Met Val Val Leu Ser Leu Ile Ala Ala Ala Trp Ala
1               5                   10                  15

Glu Glu Gln Asn Lys Leu Val His Gly Gly Pro Cys Asp Lys Thr Ser
            20                  25                  30

His Pro Tyr Gln Ala Ala Leu Tyr Thr Ser Gly His Leu Leu Cys Gly
        35                  40                  45

Gly Val Leu Ile His Pro Leu Trp Val Leu Thr Ala Ala His Cys Lys
    50                  55                  60

Lys Pro Asn Leu Gln Val Phe Leu Gly Lys His Asn Leu Arg Gln Arg
65                  70                  75                  80

Glu Ser Ser Gln Glu Gln Ser Ser Val Val Arg Ala Val Ile His Pro
                85                  90                  95

Asp Tyr Asp Ala Ala Ser His Asp Gln Asp Ile Met Leu Leu Arg Leu
            100                 105                 110

Ala Arg Pro Ala Lys Leu Ser Glu Leu Ile Gln Pro Leu Pro Leu Glu
        115                 120                 125

Arg Asp Cys Ser Ala Asn Thr Thr Ser Cys His Ile Leu Gly Trp Gly
    130                 135                 140

Lys Thr Ala Asp Gly Asp Phe Pro Asp Thr Ile Gln Cys Ala Tyr Ile
145                 150                 155                 160

His Leu Val Ser Arg Glu Glu Cys Glu His Ala Tyr Pro Gly Gln Ile
                165                 170                 175

Thr Gln Asn Met Leu Cys Ala Gly Asp Glu Lys Tyr Gly Lys Asp Ser
            180                 185                 190

Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Gly Asp His Leu Arg
        195                 200                 205

Gly Leu Val Ser Trp Gly Asn Ile Pro Cys Gly Ser Lys Glu Lys Pro
    210                 215                 220

Gly Val Tyr Thr Asn Val Cys Arg Tyr Thr Asn Trp Ile Gln Lys Thr
225                 230                 235                 240

Ile Gln Ala Lys


<210> SEQ ID NO 14
<211> LENGTH: 1527
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

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ggctctgcca ctgcatctga gtgtcttctc tcctcacggc tccccgcatt tctaactctt     180

tctgcctcct cgtctcaaag ctgttccttc ccccgactca agaatccccg gaggcccgga     240

ggcctgcagc aggagcggcc atgaagaagc tgatggtggt gctgagtctg attgctgcag     300

cctgggcaga ggagcagaat aagttggtgc atggcggacc ctgcgacaag acatctcacc     360

cctaccaagc tgccctctac acctcgggcc acttgctctg tggtggggtc cttatccatc     420

cactgtgggt cctcacagct gcccactgca aaaaaccgaa tcttcaggtc ttcctgggga     480

agcataacct tcggcaaagg gagagttccc aggagcagag ttctgttgtc cgggctgtga     540
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tccaccctga ctatgatgcc gccagccatg accaggacat catgctgttg cgcctggcac    600

gcccagccaa actctctgaa ctcatccagc cccttcccct ggagagggac tgctcagcca    660

acaccaccag ctgccacatc ctgggctggg gcaagacagc agatggtgat ttccctgaca    720

ccatccagtg tgcatacatc cacctggtgt cccgtgagga gtgtgagcat gcctaccctg    780

gccagatcac ccagaacatg ttgtgtgctg ggatgagaa gtacgggaag gattcctgcc     840

agggtgattc tgggggtccg ctggtatgtg gagaccacct ccgaggcctt gtgtcatggg    900

gtaacatccc ctgtggatca aaggagaagc caggagtcta caccaacgtc tgcagataca    960

cgaactggat ccaaaaaacc attcaggcca agtgaccctg acatgtgaca tctacctccc   1020

gacctaccac cccactggct ggttccagaa cgtctctcac ctagaccttg cctcccctcc   1080

tctcctgccc agctctgacc ctgatgctta ataaacgcag cgacgtgagg gtcctgattc   1140

tccctggttt taccccagct ccatccttgc atcactgggg aggacgtgat gagtgaggac   1200

ttgggtcctc ggtcttaccc ccaccactaa gagaatacag gaaaatccct tctaggcatc   1260

tcctctcccc aacccttcca cacgtttgat ttcttcctgc agaggcccag ccacgtgtct   1320

ggaatcccag ctccgctgct tactgtcggt gtccccttgg gatgtacctt tcttcactgc   1380

agatttctca cctgtaagat gaagataagg atgatacagt ctccataagg cagtggctgt   1440

tggaaagatt taaggtttca cacctatgac atacatggaa tagcacctgg gccaccatgc   1500

actcaataaa gaatgaattt tattatg                                       1527
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<210> SEQ ID NO 15
<211> LENGTH: 137
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

Met Leu Leu Arg Leu Ala Arg Pro Ala Lys Leu Ser Glu Leu Ile Gln
1               5                   10                  15

Pro Leu Pro Leu Glu Arg Asp Cys Ser Ala Asn Thr Thr Ser Cys His
            20                  25                  30

Ile Leu Gly Trp Gly Lys Thr Ala Asp Gly Asp Phe Pro Asp Thr Ile
        35                  40                  45

Gln Cys Ala Tyr Ile His Leu Val Ser Arg Glu Glu Cys Glu His Ala
    50                  55                  60

Tyr Pro Gly Gln Ile Thr Gln Asn Met Leu Cys Ala Gly Asp Glu Lys
65                  70                  75                  80

Tyr Gly Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys
                85                  90                  95

Gly Asp His Leu Arg Gly Leu Val Ser Trp Gly Asn Ile Pro Cys Gly
            100                 105                 110

Ser Lys Glu Lys Pro Gly Val Tyr Thr Asn Val Cys Arg Tyr Thr Asn
        115                 120                 125

Trp Ile Gln Lys Thr Ile Gln Ala Lys
    130                 135


<210> SEQ ID NO 16
<211> LENGTH: 1495
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16
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ggctctgcca ctgcatctga gtgtcttctc tcctcacggc tccccgcatt tctaactctt 180

tctgcctcct cgtctcaaag ctgttccttc ccccgactca agaatccccg gaggcccgga 240

ggcctgcagc agcctgggca gaggagcaga ataagttggt gcatggcgga ccctgcgaca 300

agacatctca cccctaccaa gctgccctct acacctcggg ccacttgctc tgtggtgggg 360

tccttatcca tccactgtgg gtcctcacag ctgcccactg caaaaaaccg aatcttcagg 420

tcttcctggg gaagcataac cttcggcaaa gggagagttc ccaggagcag agttctgttg 480

tccgggctgt gatccaccct gactatgatg ccgccagcca tgaccaggac atcatgctgt 540

tgcgcctggc acgcccagcc aaactctctg aactcatcca gccccttccc ctggagaggg 600

actgctcagc caacaccacc agctgccaca tcctgggctg ggcaagaca gcagatggtg 660

atttccctga caccatccag tgtgcataca tccacctggt gtcccgtgag gagtgtgagc 720

atgcctaccc tggccagatc acccagaaca tgttgtgtgc tggggatgag aagtacggga 780

aggattcctg ccagggtgat tctgggggtc cgctggtatg tggagaccac ctccgaggcc 840

ttgtgtcatg ggggtaacatc ccctgtggat caaaggagaa gccaggagtc tacaccaacg 900

tctgcagata cacgaactgg atccaaaaaa ccattcaggc caagtgaccc tgacatgtga 960

catctacctc ccgacctacc accccactgg ctggttccag aacgtctctc acctagacct 1020

tgcctcccct cctctcctgc ccagctctga ccctgatgct taataaacgc agcgacgtga 1080

gggtcctgat tctccctggt tttaccccag ctccatcctt gcatcactgg ggaggacgtg 1140

atgagtgagg acttgggtcc tcggtcttac ccccaccact aagagaatac aggaaaatcc 1200

cttctaggca tctcctctcc ccaacccttc cacacgtttg atttcttcct gcagaggccc 1260

agccacgtgt ctggaatccc agctccgctg cttactgtcg gtgtcccctt gggatgtacc 1320

tttcttcact gcagatttct cacctgtaag atgaagataa ggatgataca gtctccataa 1380

ggcagtggct gttggaaaga tttaaggttt cacacctatg acatacatgg aatagcacct 1440

gggccaccat gcactcaata aagaatgaat tttattatga aaaaaaaaaa aaaaa 1495

<210> SEQ ID NO 17
<211> LENGTH: 40
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

Met Lys Lys Leu Met Val Val Leu Ser Leu Ile Ala Ala Gly Ile Phe
1 5 10 15

Arg Ser Ser Trp Gly Ser Ile Thr Phe Gly Lys Gly Arg Val Pro Arg
20 25 30

Ser Arg Val Leu Leu Ser Gly Leu
35 40

<210> SEQ ID NO 18
<211> LENGTH: 1386
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

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aggacgttcc agaagcatct ggggacagaa ccagcctctt ccagggaggc ctgggagctg     60

ggggtgtgtg tctggcagtc cctgcagccc tgggctctgc ggcccctgcg tcctccgctt    120

ggctctgcca ctgcatctga gtgtcttctc tcctcacggc tccccgcatt tctaactctt    180

tctgcctcct cgtctcaaag ctgttccttc ccccgactca agaatccccg gaggcccgga    240

ggcctgcagc aggagcggcc atgaagaagc tgatggtggt gctgagtctg attgctgcag    300

gaatcttcag gtcttcctgg ggaagcataa ccttcggcaa agggagagtt cccaggagca    360

gagttctgtt gtccgggctg tgatccaccc tgactatgat gccgccagcc atgaccagga    420

catcatgctg ttgcgcctgg cacgcccagc caaactctct gaactcatcc agccccttcc    480

cctggagagg gactgctcag ccaacaccac cagctgccac atcctgggct ggggcaagac    540

agcagatggt gatttccctg acaccatcca gtgtgcatac atccacctgg tgtcccgtga    600

ggagtgtgag catgcctacc ctggccagat cacccagaac atgttgtgtg ctggggatga    660

gaagtacggg aaggattcct gccagggtga ttctgggggt ccgctggtat gtggagacca    720

cctccgaggc cttgtgtcat ggggtaacat cccctgtgga tcaaaggaga agccaggagt    780

ctacaccaac gtctgcagat acacgaactg gatccaaaaa accattcagg ccaagtgacc    840

ctgacatgtg acatctacct cccgacctac caccccactg gctggttcca gaacgtctct    900

cacctagacc ttgcctcccc tcctctcctg cccagctctg accctgatgc ttaataaacg    960

cagcgacgtg agggtcctga ttctccctgg ttttacccca gctccatcct tgcatcactg   1020

gggaggacgt gatgagtgag gacttgggtc ctcggtctta cccccaccac taagagaata   1080

caggaaaatc ccttctaggc atctcctctc cccaaccctt ccacacgttt gatttcttcc   1140

tgcagaggcc cagccacgtg tctggaatcc cagctccgct gcttactgtc ggtgtcccct   1200

tgggatgtac ctttcttcac tgcagatttc tcacctgtaa gatgaagata aggatgatac   1260

agtctccata aggcagtggc tgttggaaag atttaaggtt tcacacctat gacatacatg   1320

gaatagcacc tgggccacca tgcactcaat aaagaatgaa ttttattatg aaaaaaaaaa   1380

aaaaaa                                                              1386


<210> SEQ ID NO 19
<211> LENGTH: 276
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

Met Arg Ala Pro His Leu His Leu Ser Ala Ala Ser Gly Ala Arg Ala
1               5                   10                  15

Leu Ala Lys Leu Leu Pro Leu Leu Met Ala Gln Leu Trp Ala Ala Glu
            20                  25                  30

Ala Ala Leu Leu Pro Gln Asn Asp Thr Arg Leu Asp Pro Glu Ala Tyr
        35                  40                  45

Gly Ser Pro Cys Ala Arg Gly Ser Gln Pro Trp Gln Val Ser Leu Phe
    50                  55                  60

Asn Gly Leu Ser Phe His Cys Ala Gly Val Leu Val Asp Gln Ser Trp
65                  70                  75                  80

Val Leu Thr Ala Ala His Cys Gly Asn Lys Pro Leu Trp Ala Arg Val
                85                  90                  95

Gly Asp Asp His Leu Leu Leu Leu Gln Gly Glu Gln Leu Arg Arg Thr
            100                 105                 110
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Thr Arg Ser Val Val His Pro Lys Tyr His Gln Gly Ser Gly Pro Ile
        115                 120                 125

Leu Pro Arg Arg Thr Asp Glu His Asp Leu Met Leu Leu Lys Leu Ala
    130                 135                 140

Arg Pro Val Val Leu Gly Pro Arg Val Arg Ala Leu Gln Leu Pro Tyr
145                 150                 155                 160

Arg Cys Ala Gln Pro Gly Asp Gln Cys Gln Val Ala Gly Trp Gly Thr
                165                 170                 175

Thr Ala Ala Arg Arg Val Lys Tyr Asn Lys Gly Leu Thr Cys Ser Ser
            180                 185                 190

Ile Thr Ile Leu Ser Pro Lys Glu Cys Glu Val Phe Tyr Pro Gly Val
        195                 200                 205

Val Thr Asn Asn Met Ile Cys Ala Gly Leu Asp Arg Gly Gln Asp Pro
    210                 215                 220

Cys Gln Ser Asp Ser Gly Gly Pro Leu Val Cys Asp Glu Thr Leu Gln
225                 230                 235                 240

Gly Ile Leu Ser Trp Gly Val Tyr Pro Cys Gly Ser Ala Gln His Pro
                245                 250                 255

Ala Val Tyr Thr Gln Ile Cys Lys Tyr Met Ser Trp Ile Asn Lys Val
            260                 265                 270

Ile Arg Ser Asn
        275


<210> SEQ ID NO 20
<211> LENGTH: 1580
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

catcctgcca cccctagcct tgctggggac gtgaaccctc tccccgcgcc tgggaagcct      60

tcttggcacc gggacccgga gaatccccac ggaagccagt tccaaaaggg atgaaaaggg     120

ggcgtttcgg gcactgggag aagcctgtat tccagggccc ctcccagagc aggaatctgg     180

gacccaggag tgccagcctc acccacgcag atcctggcca tgagagctcc gcacctccac     240

ctctccgccg cctctggcgc ccgggctctg gcgaagctgc tgccgctgct gatggcgcaa     300

ctctgggccg cagaggcggc gctgctcccc caaaacgaca cgcgcttgga ccccgaagcc     360

tatggctccc cgtgcgcgcg cggctcgcag ccctggcagg tctcgctctt caacggcctc     420

tcgttccact gcgcgggtgt cctggtggac cagagttggg tgctgacggc cgcgcactgc     480

ggaaacaagc cactgtgggc tcgagtaggg gatgaccacc tgctgcttct tcagggagag     540

cagctccgcc ggaccactcg ctctgttgtc catcccaagt accaccaggg ctcaggcccc     600

atcctgccaa ggcgaacgga tgagcacgat ctcatgttgc tgaagctggc caggcccgta     660

gtgctggggc cccgcgtccg ggccctgcag cttccctacc gctgtgctca gcccggagac     720

cagtgccagg ttgctggctg ggggcaccacg gccgcccgga gagtgaagta caacaagggc     780

ctgacctgct ccagcatcac tatcctgagc cctaaagagt gtgaggtctt ctaccctggc     840

gtggtcacca acaacatgat atgtgctgga ctggaccggg gccaggaccc ttgccagagt     900

gactctggag gcccccctggt ctgtgacgag accctccaag gcatcctctc gtggggtgtt     960

tacccctgtg gctctgccca gcatccagct gtctacaccc agatctgcaa atacatgtcc    1020
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                                -continued

tggatcaata aagtcatacg ctccaactga tccagatgct acgctccagc tgatccagat   1080

gttatgctcc tgctgatcca gatgcccaga ggctccatcg tccatcctct tcctccccag   1140

tcggctgaac tctccccttg tctgcactgt tcaaacctct gccgccctcc acacctctaa   1200

acatctcccc tctcacctca ttcccccacc tatccccatt ctctgcctgt actgaagctg   1260

aaatgcagga agtggtggca aaggtttatt ccagagaagc caggaagccg gtcatcaccc   1320

agcctctgag agcagttact ggggtcaccc aacctgactt cctctgccac tccctgctgt   1380

gtgactttgg gcaagccaag tgccctctct gaacctcagt ttcctcatct gcaaaatggg   1440

aacaatgacg tgcctacctc ttagacatgt tgtgaggaga ctatgatata acatgtgtat   1500

gtaaatcttc atggtgattg tcatgtaagg cttaacacag tgggtggtga gttctgacta   1560

aaggttacct gttgtcgtga                                               1580


<210> SEQ ID NO 21
<211> LENGTH: 276
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

Met Arg Ala Pro His Leu His Leu Ser Ala Ala Ser Gly Ala Arg Ala
1               5                   10                  15

Leu Ala Lys Leu Leu Pro Leu Leu Met Ala Gln Leu Trp Ala Ala Glu
            20                  25                  30

Ala Ala Leu Leu Pro Gln Asn Asp Thr Arg Leu Asp Pro Glu Ala Tyr
        35                  40                  45

Gly Ser Pro Cys Ala Arg Gly Ser Gln Pro Trp Gln Val Ser Leu Phe
    50                  55                  60

Asn Gly Leu Ser Phe His Cys Ala Gly Val Leu Val Asp Gln Ser Trp
65                  70                  75                  80

Val Leu Thr Ala Ala His Cys Gly Asn Lys Pro Leu Trp Ala Arg Val
                85                  90                  95

Gly Asp Asp His Leu Leu Leu Leu Gln Gly Glu Gln Leu Arg Arg Thr
            100                 105                 110

Thr Arg Ser Val Val His Pro Lys Tyr His Gln Gly Ser Gly Pro Ile
        115                 120                 125

Leu Pro Arg Arg Thr Asp Glu His Asp Leu Met Leu Leu Lys Leu Ala
    130                 135                 140

Arg Pro Val Val Leu Gly Pro Arg Val Arg Ala Leu Gln Leu Pro Tyr
145                 150                 155                 160

Arg Cys Ala Gln Pro Gly Asp Gln Cys Gln Val Ala Gly Trp Gly Thr
                165                 170                 175

Thr Ala Ala Arg Arg Val Lys Tyr Asn Lys Gly Leu Thr Cys Ser Ser
            180                 185                 190

Ile Thr Ile Leu Ser Pro Lys Glu Cys Glu Val Phe Tyr Pro Gly Val
        195                 200                 205

Val Thr Asn Asn Met Ile Cys Ala Gly Leu Asp Arg Gly Gln Asp Pro
    210                 215                 220

Cys Gln Ser Asp Ser Gly Gly Pro Leu Val Cys Asp Glu Thr Leu Gln
225                 230                 235                 240

Gly Ile Leu Ser Trp Gly Val Tyr Pro Cys Gly Ser Ala Gln His Pro
                245                 250                 255
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Ala Val Tyr Thr Gln Ile Cys Lys Tyr Met Ser Trp Ile Asn Lys Val
260 265 270

Ile Arg Ser Asn
275

<210> SEQ ID NO 22
<211> LENGTH: 1443
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

accagcggca gaccacaggc agggcagagg cacgtctggg tcccctccct ccttcctatc 60

ggcgactccc aggatcctgg ccatgagagc tccgcacctc cacctctccg ccgcctctgg 120

cgcccgggct ctggcgaagc tgctgccgct gctgatggcg caactctggg ccgcagaggc 180

ggcgctgctc ccccaaaacg acacgcgctt ggaccccgaa gcctatggct ccccgtgcgc 240

gcgcggctcg cagccctggc aggtctcgct cttcaacggc ctctcgttcc actgcgcggg 300

tgtcctggtg gaccagagtt gggtgctgac ggccgcgcac tgcggaaaca agccactgtg 360

ggctcgagta ggggatgacc acctgctgct tcttcaggga gagcagctcc gccggaccac 420

tcgctctgtt gtccatccca agtaccacca gggctcaggc cccatcctgc caaggcgaac 480

ggatgagcac gatctcatgt tgctgaagct ggccaggccc gtagtgctgg ggccccgcgt 540

ccgggccctg cagcttccct accgctgtgc tcagcccgga gaccagtgcc aggttgctgg 600

ctggggcacc acggccgccc ggagagtgaa gtacaacaag ggcctgacct gctccagcat 660

cactatcctg agccctaaag agtgtgaggt cttctaccct ggcgtggtca ccaacaacat 720

gatatgtgct ggactggacc ggggccagga cccttgccag agtgactctg gaggccccct 780

ggtctgtgac gagaccctcc aaggcatcct ctcgtggggt gtttacccct gtggctctgc 840

ccagcatcca gctgtctaca cccagatctg caaatacatg tcctggatca ataaagtcat 900

acgctccaac tgatccagat gctacgctcc agctgatcca gatgttatgc tcctgctgat 960

ccagatgccc agaggctcca tcgtccatcc tcttcctccc cagtcggctg aactctcccc 1020

ttgtctgcac tgttcaaacc tctgccgccc tccacacctc taaacatctc ccctctcacc 1080

tcattccccc acctatcccc attctctgcc tgtactgaag ctgaaatgca ggaagtggtg 1140

gcaaaggttt attccagaga agccaggaag ccggtcatca cccagcctct gagagcagtt 1200

actggggtca cccaacctga cttcctctgc cactccctgc tgtgtgactt tgggcaagcc 1260

aagtgccctc tctgaacctc agtttcctca tctgcaaaat gggaacaatg acgtgcctac 1320

ctcttagaca tgttgtgagg agactatgat ataacatgtg tatgtaaatc ttcatggtga 1380

ttgtcatgta aggcttaaca cagtgggtgg tgagttctga ctaaaggtta cctgttgtcg 1440

tga 1443

<210> SEQ ID NO 23
<211> LENGTH: 180
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

Met Leu Cys Leu Leu Leu Thr Leu Gly Val Ala Leu Val Cys Gly Val
1 5 10 15

Pro Ala Met Asp Ile Pro Gln Thr Lys Gln Asp Leu Glu Leu Pro Lys

-continued

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            20                  25                  30

Leu Ala Gly Thr Trp His Ser Met Ala Met Ala Thr Asn Asn Ile Ser
        35                  40                  45

Leu Met Ala Thr Leu Lys Ala Pro Leu Arg Val His Ile Thr Ser Leu
    50                  55                  60

Leu Pro Thr Pro Glu Asp Asn Leu Glu Ile Val Leu His Arg Trp Glu
65                  70                  75                  80

Asn Asn Ser Cys Val Glu Lys Lys Val Leu Gly Glu Lys Thr Glu Asn
                85                  90                  95

Pro Lys Lys Phe Lys Ile Asn Tyr Thr Val Ala Asn Glu Ala Thr Leu
            100                 105                 110

Leu Asp Thr Asp Tyr Asp Asn Phe Leu Phe Leu Cys Leu Gln Asp Thr
        115                 120                 125

Thr Thr Pro Ile Gln Ser Met Met Cys Gln Tyr Leu Ala Arg Val Leu
    130                 135                 140

Val Glu Asp Asp Glu Ile Met Gln Gly Phe Ile Arg Ala Phe Arg Pro
145                 150                 155                 160

Leu Pro Arg His Leu Trp Tyr Leu Leu Asp Leu Lys Gln Met Glu Glu
                165                 170                 175

Pro Cys Arg Phe
            180


<210> SEQ ID NO 24
<211> LENGTH: 857
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

catccctctg gctccagagc tcagagccac ccacagccgc agccatgctg tgcctcctgc     60

tcaccctggg cgtggccctg gtctgtggtg tcccggccat ggacatcccc cagaccaagc    120

aggacctgga gctcccaaag ttggcaggga cctggcactc catggccatg gcgaccaaca    180

acatctccct catggcgaca ctgaaggccc ctctgagggt ccacatcacc tcactgttgc    240

ccacccccga ggacaacctg gagatcgttc tgcacagatg ggagaacaac agctgtgttg    300

agaagaaggt ccttggagag aagactgaga atccaaagaa gttcaagatc aactatacgg    360

tggcgaacga ggccacgctg ctcgatactg actacgacaa tttcctgttt ctctgcctac    420

aggacaccac cacccccatc cagagcatga tgtgccagta cctggccaga gtcctggtgg    480

aggacgatga gatcatgcag ggattcatca gggctttcag gcccctgccc aggcacctat    540

ggtacttgct ggacttgaaa cagatggaag agccgtgccg tttctaggtg agctcctgcc    600

tggtcctgcc tcctggctca cctccgcctc caggaagacc agactcccac ccttccacac    660

ctccagagca gtgggacttc ctcctgccct ttcaaagaat aaccacagct cagaagacga    720

tgacgtggtc atctgtgtcg ccatcccctt cctgctgcac acctgcacca cggccatggg    780

gaggctgctc cctgggggca gagtctctgg cagaggttat taataaaccc ttggagcatg    840

aaaaaaaaaa aaaaaaa                                                   857


<210> SEQ ID NO 25
<211> LENGTH: 180
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 25

Met Leu Cys Leu Leu Leu Thr Leu Gly Val Ala Leu Val Cys Gly Val
1               5                   10                  15

Pro Ala Met Asp Ile Pro Gln Thr Lys Gln Asp Leu Glu Leu Pro Lys
            20                  25                  30

Leu Ala Gly Thr Trp His Ser Met Ala Met Ala Thr Asn Asn Ile Ser
        35                  40                  45

Leu Met Ala Thr Leu Lys Ala Pro Leu Arg Val His Ile Thr Ser Leu
    50                  55                  60

Leu Pro Thr Pro Glu Asp Asn Leu Glu Ile Val Leu His Arg Trp Glu
65                  70                  75                  80

Asn Asn Ser Cys Val Glu Lys Lys Val Leu Gly Glu Lys Thr Glu Asn
                85                  90                  95

Pro Lys Lys Phe Lys Ile Asn Tyr Thr Val Ala Asn Glu Ala Thr Leu
            100                 105                 110

Leu Asp Thr Asp Tyr Asp Asn Phe Leu Phe Leu Cys Leu Gln Asp Thr
        115                 120                 125

Thr Thr Pro Ile Gln Ser Met Met Cys Gln Tyr Leu Ala Arg Val Leu
    130                 135                 140

Val Glu Asp Asp Glu Ile Met Gln Gly Phe Ile Arg Ala Phe Arg Pro
145                 150                 155                 160

Leu Pro Arg His Leu Trp Tyr Leu Leu Asp Leu Lys Gln Met Glu Glu
                165                 170                 175

Pro Cys Arg Phe
            180


<210> SEQ ID NO 26
<211> LENGTH: 828
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

catccctctg gctccagagc tcagagccac ccacagccgc agccatgctg tgcctcctgc      60

tcaccctggg cgtggccctg gtctgtggtg tcccggccat ggacatcccc cagaccaagc     120

aggacctgga gctcccaaag ttggcaggga cctggcactc catggccatg gcgaccaaca     180

acatctccct catggcgaca ctgaaggccc ctctgagggt ccacatcacc tcactgttgc     240

ccacccccga ggacaacctg gagatcgttc tgcacagatg ggagaacaac agctgtgttg     300

agaagaaggt ccttggagag aagactgaga atccaaagaa gttcaagatc aactatacgg     360

tggcgaacga ggccacgctg ctcgatactg actacgacaa tttcctgttt ctctgcctac     420

aggacaccac cacccccatc cagagcatga tgtgccagta cctggccaga gtcctggtgg     480

aggacgatga gatcatgcag ggattcatca gggctttcag gcccctgccc aggcacctat     540

ggtacttgct ggacttgaaa cagatggaag agccgtgccg tttctagctc acctccgcct     600

ccaggaagac cagactccca cccttccaca cctccagagc agtgggactt cctcctgccc     660

tttcaaagaa taaccacagc tcagaagacg atgacgtggt catctgtgtc gccatcccct     720

tcctgctgca cacctgcacc acggccatgg ggaggctgct ccctgggggc agagtctctg     780

gcagaggtta ttaataaacc cttggagcat gaaaaaaaaa aaaaaaaa                  828


<210> SEQ ID NO 27
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<211> LENGTH: 402
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

Met Gln Met Ser Pro Ala Leu Thr Cys Leu Val Leu Gly Leu Ala Leu
1               5                   10                  15

Val Phe Gly Glu Gly Ser Ala Val His His Pro Pro Ser Tyr Val Ala
            20                  25                  30

His Leu Ala Ser Asp Phe Gly Val Arg Val Phe Gln Gln Val Ala Gln
        35                  40                  45

Ala Ser Lys Asp Arg Asn Val Val Phe Ser Pro Tyr Gly Val Ala Ser
    50                  55                  60

Val Leu Ala Met Leu Gln Leu Thr Thr Gly Gly Glu Thr Gln Gln Gln
65                  70                  75                  80

Ile Gln Ala Ala Met Gly Phe Lys Ile Asp Asp Lys Gly Met Ala Pro
                85                  90                  95

Ala Leu Arg His Leu Tyr Lys Glu Leu Met Gly Pro Trp Asn Lys Asp
            100                 105                 110

Glu Ile Ser Thr Thr Asp Ala Ile Phe Val Gln Arg Asp Leu Lys Leu
        115                 120                 125

Val Gln Gly Phe Met Pro His Phe Phe Arg Leu Phe Arg Ser Thr Val
    130                 135                 140

Lys Gln Val Asp Phe Ser Glu Val Glu Arg Ala Arg Phe Ile Ile Asn
145                 150                 155                 160

Asp Trp Val Lys Thr His Thr Lys Gly Met Ile Ser Asn Leu Leu Gly
                165                 170                 175

Lys Gly Ala Val Asp Gln Leu Thr Arg Leu Val Leu Val Asn Ala Leu
            180                 185                 190

Tyr Phe Asn Gly Gln Trp Lys Thr Pro Phe Pro Asp Ser Ser Thr His
        195                 200                 205

Arg Arg Leu Phe His Lys Ser Asp Gly Ser Thr Val Ser Val Pro Met
    210                 215                 220

Met Ala Gln Thr Asn Lys Phe Asn Tyr Thr Glu Phe Thr Thr Pro Asp
225                 230                 235                 240

Gly His Tyr Tyr Asp Ile Leu Glu Leu Pro Tyr His Gly Asp Thr Leu
                245                 250                 255

Ser Met Phe Ile Ala Ala Pro Tyr Glu Lys Glu Val Pro Leu Ser Ala
            260                 265                 270

Leu Thr Asn Ile Leu Ser Ala Gln Leu Ile Ser His Trp Lys Gly Asn
        275                 280                 285

Met Thr Arg Leu Pro Arg Leu Leu Val Leu Pro Lys Phe Ser Leu Glu
    290                 295                 300

Thr Glu Val Asp Leu Arg Lys Pro Leu Glu Asn Leu Gly Met Thr Asp
305                 310                 315                 320

Met Phe Arg Gln Phe Gln Ala Asp Phe Thr Ser Leu Ser Asp Gln Glu
                325                 330                 335

Pro Leu His Val Ala Gln Ala Leu Gln Lys Val Lys Ile Glu Val Asn
            340                 345                 350

Glu Ser Gly Thr Val Ala Ser Ser Ser Thr Ala Val Ile Val Ser Ala
        355                 360                 365

Arg Met Ala Pro Glu Glu Ile Ile Met Asp Arg Pro Phe Leu Phe Val
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-continued

370 375 380

Val Arg His Asn Pro Thr Gly Thr Val Leu Phe Met Gly Gln Val Met
385 390 395 400

Glu Pro

<210> SEQ ID NO 28
<211> LENGTH: 2876
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

gaattcctgc agctcagcag ccgccgccag agcaggacga accgccaatc gcaaggcacc 60

tctgagaact tcaggatgca gatgtctcca gccctcacct gcctagtcct gggcctggcc 120

cttgtctttg gtgaagggtc tgctgtgcac catcccccat cctacgtggc ccacctggcc 180

tcagacttcg ggtgagggt gtttcagcag gtggcgcagg cctccaagga ccgcaacgtg 240

gttttctcac cctatggggt ggcctcggtg ttggccatgc tccagctgac aacaggagga 300

gaaacccagc agcagattca agcagctatg ggattcaaga ttgatgacaa gggcatggcc 360

cccgccctcc ggcatctgta caaggagctc atggggccat ggaacaagga tgagatcagc 420

accacagacg cgatcttcgt ccagcgggat ctgaagctgg tccagggctt catgccccac 480

ttcttcaggc tgttccggag cacggtcaag caagtggact tttcagaggt ggagagagcc 540

agattcatca tcaatgactg ggtgaagaca cacacaaaag gtatgatcag caacttgctt 600

gggaaaggag ccgtggacca gctgacacgg ctggtgctgg tgaatgccct ctacttcaac 660

ggccagtgga agactccctt ccccgactcc agcacccacc gccgcctctt ccacaaatca 720

gacggcagca ctgtctctgt gcccatgatg gctcagacca acaagttcaa ctatactgag 780

ttcaccacgc ccgatggcca ttactacgac atcctggaac tgccctacca cggggacacc 840

ctcagcatgt tcattgctgc cccttatgaa aaagaggtgc ctctctctgc cctcaccaac 900

attctgagtg cccagctcat cagccactgg aaaggcaaca tgaccaggct gccccgcctc 960

ctggttctgc ccaagttctc cctggagact gaagtcgacc tcaggaagcc cctagagaac 1020

ctgggaatga ccgacatgtt cagacagttt caggctgact tcacgagtct ttcagaccaa 1080

gagcctctcc acgtcgcgca ggcgctgcag aaagtgaaga tcgaggtgaa cgagagtggc 1140

acggtggcct cctcatccac agctgtcata gtctcagccc gcatggcccc cgaggagatc 1200

atcatggaca gacccttcct ctttgtggtc cggcacaacc ccacaggaac agtccttttc 1260

atgggccaag tgatggaacc ctgaccctgg ggaaagacgc cttcatctgg gacaaaactg 1320

gagatgcatc gggaaagaag aaactccgaa gaaaagaatt ttagtgttaa tgactctttc 1380

tgaaggaaga gaagacattt gccttttgtt aaaagatggt aaaccagatc tgtctccaag 1440

accttggcct ctccttggag gacctttagg tcaaactccc tagtctccac ctgagaccct 1500

gggagagaag tttgaagcac aactccctta aggtctccaa accagacggt gacgcctgcg 1560

ggaccatctg gggcacctgc ttccacccgt ctctctgccc actcgggtct gcagacctgg 1620

ttcccactga ggccctttgc aggatggaac tacggggctt acaggagctt ttgtgtgcct 1680

ggtagaaact atttctgttc cagtcacatt gccatcactc ttgtactgcc tgccaccgcg 1740

gaggaggctg gtgacaggcc aaaggccagt ggaagaaaca ccctttcatc tcagagtcca 1800

ctgtggcact ggccacccct ccccagtaca ggggtgctgc aggtggcaga gtgaatgtcc 1860

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cccatcatgt ggcccaactc tcctggcctg gccatctccc tccccagaaa cagtgtgcat   1920

gggttatttt ggagtgtagg tgacttgttt actcattgaa gcagatttct gcttcctttt   1980

atttttatag gaatagagga agaaatgtca gatgcgtgcc cagctcttca ccccccaatc   2040

tcttggtggg gaggggtgta cctaaatatt tatcatatcc ttgcccttga gtgcttgtta   2100

gagagaaaga gaactactaa ggaaaataat attatttaaa ctcgctccta gtgtttcttt   2160

gtggtctgtg tcaccgtatc tcaggaagtc cagccacttg actggcacac acccctccgg   2220

acatccagcg tgacggagcc cacactgcca ccttgtggcc gcctgagacc ctcgcgcccc   2280

ccgcgccccc cgcgcccctc tttttcccct tgatggaaat tgaccataca atttcatcct   2340

ccttcagggg atcaaaagga cggagtgggg ggacagagac tcagatgagg acagagtggt   2400

ttccaatgtg ttcaatagat ttaggagcag aaatgcaagg ggctgcatga cctaccagga   2460

cagaactttc cccaattaca gggtgactca cagccgcatt ggtgactcac ttcaatgtgt   2520

catttccggc tgctgtgtgt gagcagtgga cacgtgaggg gggggtgggt gagagagaca   2580

ggcagctcgg attcaactac cttagataat atttctgaaa acctaccagc cagagggtag   2640

ggcacaaaga tggatgtaat gcactttggg aggccaaggc gggaggattg cttgagccca   2700

ggagttcaag accagcctgg gcaacatacc aagacccccg tctctttaaa aatatatata   2760

ttttaaatat acttaaatat atatttctaa tatctttaaa tatatatata tattttaaag   2820

accaatttat gggagaattg cacacagatg tgaaatgaat gtaatctaat agaagc       2876


<210> SEQ ID NO 29
<211> LENGTH: 273
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr
1               5                   10                  15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly
            20                  25                  30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
        35                  40                  45

Thr Glu Lys Asn Ala Leu Ser Thr Gly Val Ser Phe Phe Phe Leu Ser
    50                  55                  60

Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu Asp Pro Ser
65                  70                  75                  80

Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met Phe Leu
                85                  90                  95

Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe
            100                 105                 110

Arg Pro Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg Glu Gly
        115                 120                 125

Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr
    130                 135                 140

Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser
145                 150                 155                 160

Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val Pro Gly
                165                 170                 175
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Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala Leu Ala
            180                 185                 190

Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg Lys Asn
        195                 200                 205

Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met
    210                 215                 220

Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser
225                 230                 235                 240

Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly
                245                 250                 255

Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn
            260                 265                 270

Leu
```

<210> SEQ ID NO 30
<211> LENGTH: 1209
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

```
acctctcaag cagccagcgc ctgcctgaat ctgttctgcc ccctccccac ccatttcacc      60

accaccatga caccgggcac ccagtctcct ttcttcctgc tgctgctcct cacagtgctt     120

acagttgtta cgggttctgg tcatgcaagc tctaccccag gtggagaaaa ggagacttcg     180

gctacccaga gaagttcagt gcccagctct actgagaaga atgctttgtc tactggggtc     240

tctttctttt tcctgtcttt tcacatttca aacctccagt ttaattcctc tctggaagat     300

cccagcaccg actactacca agagctgcag agagacattt ctgaaatgtt tttgcagatt     360

tataaacaag gggtttttct gggcctctcc aatattaagt tcaggccagg atctgtggtg     420

gtacaattga ctctggcctt ccgagaaggt accatcaatg tccacgacgt ggagacacag     480

ttcaatcagt ataaaacgga agcagcctct cgatataacc tgacgatctc agacgtcagc     540

gtgagtgatg tgccatttcc tttctctgcc cagtctgggg ctggggtgcc aggctggggc     600

atcgcgctgc tggtgctggt ctgtgttctg gttgcgctgg ccattgtcta tctcattgcc     660

ttggctgtct gtcagtgccg ccgaaagaac tacgggcagc tggacatctt tccagcccgg     720

gatacctacc atcctatgag cgagtacccc acctaccaca cccatgggcg ctatgtgccc     780

cctagcagta ccgatcgtag cccctatgag aaggtttctg caggtaatgg tggcagcagc     840

ctctcttaca caaacccagc agtggcagcc acttctgcca acttgtaggg gcacgtcgcc     900

cgctgagctg agtggccagc cagtgccatt ccactccact caggttcttc agggccagag     960

cccctgcacc ctgtttgggc tggtgagctg ggagttcagg tgggctgctc acagcctcct    1020

tcagaggccc caccaatttc tcggacactt ctcagtgtgt ggaagctcat gtgggcccct    1080

gagggctcat gcctgggaag tgttgtggtg gggggctccca ggaggactgg cccagagagc    1140

cctgagatag cggggatcct gaactggact gaataaaacg tggtctccca ctgcgccaaa    1200

aaaaaaaaa                                                            1209
```

<210> SEQ ID NO 31
<211> LENGTH: 264
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 31

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr
1               5                   10                  15

Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly
            20                  25                  30

Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala
        35                  40                  45

Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Phe Asn
    50                  55                  60

Ser Ser Leu Glu Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg
65                  70                  75                  80

Asp Ile Ser Glu Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu
                85                  90                  95

Gly Leu Ser Asn Ile Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu
            100                 105                 110

Thr Leu Ala Phe Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr
        115                 120                 125

Gln Phe Asn Gln Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr
    130                 135                 140

Ile Ser Asp Val Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln
145                 150                 155                 160

Ser Gly Ala Gly Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val
                165                 170                 175

Cys Val Leu Val Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val
            180                 185                 190

Cys Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala
        195                 200                 205

Arg Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His
    210                 215                 220

Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys
225                 230                 235                 240

Val Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala
                245                 250                 255

Val Ala Ala Thr Ser Ala Asn Leu
            260


<210> SEQ ID NO 32
<211> LENGTH: 1182
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

acctctcaag cagccagcgc ctgcctgaat ctgttctgcc ccctccccac ccatttcacc     60

accaccatga caccgggcac ccagtctcct ttcttcctgc tgctgctcct cacagtgctt    120

acagctacca cagcccctaa acccgcaaca gttgttacgg gttctggtca tgcaagctct    180

accccaggtg gagaaaagga gacttcggct acccagagaa gttcagtgcc cagctctact    240

gagaagaatg cttttaattc ctctctggaa gatcccagca ccgactacta ccaagagctg    300

cagagagaca tttctgaaat gtttttgcag atttataaac aagggggttt tctgggcctc    360

tccaatatta agttcaggcc aggatctgtg gtggtacaat tgactctggc cttccgagaa    420

ggtaccatca atgtccacga cgtggagaca cagttcaatc agtataaaac ggaagcagcc    480
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tctcgatata acctgacgat ctcagacgtc agcgtgagtg atgtgccatt tcctttctct     540

gcccagtctg gggctggggt gccaggctgg ggcatcgcgc tgctggtgct ggtctgtgtt     600

ctggttgcgc tggccattgt ctatctcatt gccttggctg tctgtcagtg ccgccgaaag     660

aactacgggc agctggacat ctttccagcc cgggatacct accatcctat gagcgagtac     720

cccacctacc acacccatgg gcgctatgtg ccccctagca gtaccgatcg tagcccctat     780

gagaaggttt ctgcaggtaa tggtggcagc agcctctctt acacaaaccc agcagtggca     840

gccacttctg ccaacttgta ggggcacgtc gcccgctgag ctgagtggcc agccagtgcc     900

attccactcc actcaggttc ttcagggcca gagcccctgc accctgtttg ggctggtgag     960

ctgggagttc aggtgggctg ctcacagcct ccttcagagg ccccaccaat ttctcggaca    1020

cttctcagtg tgtggaagct catgtgggcc cctgagggct catgcctggg aagtgttgtg    1080

gtgggggctc ccaggaggac tggcccagag agccctgaga tagcggggat cctgaactgg    1140

actgaataaa acgtggtctc ccactgcgcc aaaaaaaaaa aa                       1182
```

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<210> SEQ ID NO 33
<211> LENGTH: 255
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr
1               5                   10                  15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly
            20                  25                  30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
        35                  40                  45

Thr Glu Lys Asn Ala Phe Asn Ser Ser Leu Glu Asp Pro Ser Thr Asp
    50                  55                  60

Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met Phe Leu Gln Ile
65                  70                  75                  80

Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe Arg Pro
                85                  90                  95

Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg Glu Gly Thr Ile
            100                 105                 110

Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr Glu Ala
        115                 120                 125

Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser Asp Val
    130                 135                 140

Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val Pro Gly Trp Gly
145                 150                 155                 160

Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala Leu Ala Ile Val
                165                 170                 175

Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly
            180                 185                 190

Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu
        195                 200                 205

Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr
    210                 215                 220

Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser
```

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225                 230                 235                 240

Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu
                245                 250                 255


<210> SEQ ID NO 34
<211> LENGTH: 1155
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

acctctcaag cagccagcgc ctgcctgaat ctgttctgcc ccctccccac ccatttcacc      60

accaccatga caccgggcac ccagtctcct ttcttcctgc tgctgctcct cacagtgctt     120

acagttgtta cgggttctgg tcatgcaagc tctaccccag gtggagaaaa ggagacttcg     180

gctacccaga gaagttcagt gcccagctct actgagaaga atgcttttaa ttcctctctg     240

gaagatccca gcaccgacta ctaccaagag ctgcagagag acatttctga aatgtttttg     300

cagatttata aacaaggggg ttttctgggc ctctccaata ttaagttcag gccaggatct     360

gtggtggtac aattgactct ggccttccga gaaggtacca tcaatgtcca cgacgtggag     420

acacagttca atcagtataa aacggaagca gcctctcgat ataacctgac gatctcagac     480

gtcagcgtga gtgatgtgcc atttcctttc tctgcccagt ctggggctgg ggtgccaggc     540

tggggcatcg cgctgctggt gctggtctgt gttctggttg cgctggccat tgtctatctc     600

attgccttgg ctgtctgtca gtgccgccga aagaactacg ggcagctgga catctttcca     660

gcccgggata cctaccatcc tatgagcgag taccccacct accacaccca tgggcgctat     720

gtgcccccta gcagtaccga tcgtagcccc tatgagaagg tttctgcagg taatggtggc     780

agcagcctct cttacacaaa cccagcagtg gcagccactt ctgccaactt gtaggggcac     840

gtcgcccgct gagctgagtg gccagccagt gccattccac tccactcagg ttcttcaggg     900

ccagagcccc tgcaccctgt ttgggctggt gagctgggag ttcaggtggg ctgctcacag     960

cctccttcag aggccccacc aatttctcgg acacttctca gtgtgtggaa gctcatgtgg    1020

gcccctgagg gctcatgcct gggaagtgtt gtggtggggg ctcccaggag gactggccca    1080

gagagccctg agatagcggg gatcctgaac tggactgaat aaaacgtggt ctcccactgc    1140

gccaaaaaaa aaaaa                                                     1155


<210> SEQ ID NO 35
<211> LENGTH: 96
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr
1               5                   10                  15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly
            20                  25                  30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
        35                  40                  45

Thr Glu Lys Asn Ala Ile Pro Ala Pro Thr Thr Thr Lys Ser Cys Arg
    50                  55                  60

Glu Thr Phe Leu Lys Cys Phe Cys Arg Phe Ile Asn Lys Gly Val Phe
65                  70                  75                  80
```

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```
Trp Ala Ser Pro Ile Leu Ser Ser Gly Gln Asp Leu Trp Trp Tyr Asn
                85                  90                  95
```

<210> SEQ ID NO 36
<211> LENGTH: 1136
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

```
acctctcaag cagccagcgc ctgcctgaat ctgttctgcc ccctccccac ccatttcacc     60

accaccatga caccgggcac ccagtctcct ttcttcctgc tgctgctcct cacagtgctt    120

acagttgtta cgggttctgg tcatgcaagc tctaccccag gtggagaaaa ggagacttcg    180

gctacccaga gaagttcagt gcccagctct actgagaaga atgctatccc agcaccgact    240

actaccaaga gctgcagaga gacatttctg aaatgttttt gcagatttat aaacaagggg    300

gttttctggg cctctccaat attaagttca ggccaggatc tgtggtggta caattgactc    360

tggccttccg agaaggtacc atcaatgtcc acgacgtgga gacacagttc aatcagtata    420

aaacggaagc agcctctcga tataacctga cgatctcaga cgtcagcgtg agtgatgtgc    480

catttccttt ctctgcccag tctggggctg gggtgccagg ctggggcatc gcgctgctgg    540

tgctggtctg tgttctggtt gcgctggcca ttgtctatct cattgccttg gctgtctgtc    600

agtgccgccg aaagaactac gggcagctgg acatctttcc agcccgggat acctaccatc    660

ctatgagcga gtaccccacc taccacaccc atgggcgcta tgtgcccccct agcagtaccg    720

atcgtagccc ctatgagaag gtttctgcag gtaatggtgg cagcagcctc tcttacacaa    780

acccagcagt ggcagccact tctgccaact tgtaggggca cgtcgcccgc tgagctgagt    840

ggccagccag tgccattcca ctccactcag gttcttcagg gccagagccc ctgcaccctg    900

tttgggctgg tgagctggga gttcaggtgg gctgctcaca gcctccttca gaggccccac    960

caatttctcg gacacttctc agtgtgtgga agctcatgtg ggcccctgag ggctcatgcc   1020

tgggaagtgt tgtggtgggg gctcccagga ggactggccc agagagccct gagatagcgg   1080

ggatcctgaa ctggactgaa taaaacgtgg tctcccactg cgccaaaaaa aaaaaa       1136
```

<210> SEQ ID NO 37
<211> LENGTH: 418
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

```
Met Pro Ser Ser Val Ser Trp Gly Ile Leu Leu Leu Ala Gly Leu Cys
1               5                   10                  15

Cys Leu Val Pro Val Ser Leu Ala Glu Asp Pro Gln Gly Asp Ala Ala
            20                  25                  30

Gln Lys Thr Asp Thr Ser His His Asp Gln Asp His Pro Thr Phe Asn
        35                  40                  45

Lys Ile Thr Pro Asn Leu Ala Glu Phe Ala Phe Ser Leu Tyr Arg Gln
    50                  55                  60

Leu Ala His Gln Ser Asn Ser Thr Asn Ile Phe Phe Ser Pro Val Ser
65                  70                  75                  80

Ile Ala Thr Ala Phe Ala Met Leu Ser Leu Gly Thr Lys Ala Asp Thr
                85                  90                  95

His Asp Glu Ile Leu Glu Gly Leu Asn Phe Asn Leu Thr Glu Ile Pro
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            100                 105                 110

Glu Ala Gln Ile His Glu Gly Phe Gln Glu Leu Leu Arg Thr Leu Asn
        115                 120                 125

Gln Pro Asp Ser Gln Leu Gln Leu Thr Thr Gly Asn Gly Leu Phe Leu
    130                 135                 140

Ser Glu Gly Leu Lys Leu Val Asp Lys Phe Leu Glu Asp Val Lys Lys
145                 150                 155                 160

Leu Tyr His Ser Glu Ala Phe Thr Val Asn Phe Gly Asp Thr Glu Glu
                165                 170                 175

Ala Lys Lys Gln Ile Asn Asp Tyr Val Glu Lys Gly Thr Gln Gly Lys
            180                 185                 190

Ile Val Asp Leu Val Lys Glu Leu Asp Arg Asp Thr Val Phe Ala Leu
        195                 200                 205

Val Asn Tyr Ile Phe Phe Lys Gly Lys Trp Glu Arg Pro Phe Glu Val
    210                 215                 220

Lys Asp Thr Glu Glu Glu Asp Phe His Val Asp Gln Val Thr Thr Val
225                 230                 235                 240

Lys Val Pro Met Met Lys Arg Leu Gly Met Phe Asn Ile Gln His Cys
                245                 250                 255

Lys Lys Leu Ser Ser Trp Val Leu Leu Met Lys Tyr Leu Gly Asn Ala
            260                 265                 270

Thr Ala Ile Phe Phe Leu Pro Asp Glu Gly Lys Leu Gln His Leu Glu
        275                 280                 285

Asn Glu Leu Thr His Asp Ile Ile Thr Lys Phe Leu Glu Asn Glu Asp
    290                 295                 300

Arg Arg Ser Ala Ser Leu His Leu Pro Lys Leu Ser Ile Thr Gly Thr
305                 310                 315                 320

Tyr Asp Leu Lys Ser Val Leu Gly Gln Leu Gly Ile Thr Lys Val Phe
                325                 330                 335

Ser Asn Gly Ala Asp Leu Ser Gly Val Thr Glu Glu Ala Pro Leu Lys
            340                 345                 350

Leu Ser Lys Ala Val His Lys Ala Val Leu Thr Ile Asp Glu Lys Gly
        355                 360                 365

Thr Glu Ala Ala Gly Ala Met Phe Leu Glu Ala Ile Pro Met Ser Ile
    370                 375                 380

Pro Pro Glu Val Lys Phe Asn Lys Pro Phe Val Phe Leu Met Ile Glu
385                 390                 395                 400

Gln Asn Thr Lys Ser Pro Leu Phe Met Gly Lys Val Val Asn Pro Thr
                405                 410                 415

Gln Lys


<210> SEQ ID NO 38
<211> LENGTH: 1607
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

aatgactcct ttcggtaagt gcagtggaag ctgtacactg cccaggcaaa gcgtccgggc      60

agcgtaggcg ggcgactcag atcccagcca gtggacttag cccctgtttg ctcctccgat     120

aactggggtg accttggtta atattcacca gcagcctccc ccgttgcccc tctggatcca     180

ctgcttaaat acggacgagg acagggccct gtctcctcag cttcaggcac caccactgac     240
```

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```
ctgggacagt gaatcgacaa tgccgtcttc tgtctcgtgg ggcatcctcc tgctggcagg    300

cctgtgctgc ctggtccctg tctccctggc tgaggatccc cagggagatg ctgcccagaa    360

gacagataca tcccaccatg atcaggatca cccaaccttc aacaagatca cccccaacct    420

ggctgagttc gccttcagcc tataccgcca gctggcacac cagtccaaca gcaccaatat    480

cttcttctcc ccagtgagca tcgctacagc ctttgcaatg ctctccctgg ggaccaaggc    540

tgacactcac gatgaaatcc tggagggcct gaatttcaac ctcacggaga ttccggaggc    600

tcagatccat gaaggcttcc aggaactcct ccgtaccctc aaccagccag acagccagct    660

ccagctgacc accggcaatg gcctgttcct cagcgagggc ctgaagctag tggataagtt    720

tttggaggat gttaaaaagt tgtaccactc agaagccttc actgtcaact tcggggacac    780

cgaagaggcc aagaaacaga tcaacgatta cgtggagaag ggtactcaag ggaaaattgt    840

ggatttggtc aaggagcttg acagagacac agtttttgct ctggtgaatt acatcttctt    900

taaaggcaaa tgggagagac cctttgaagt caaggacacc gaggaagagg acttccacgt    960

ggaccaggtg accaccgtga aggtgcctat gatgaagcgt ttaggcatgt ttaacatcca   1020

gcactgtaag aagctgtcca gctgggtgct gctgatgaaa tacctgggca atgccaccgc   1080

catcttcttc ctgcctgatg aggggaaact acagcacctg gaaaatgaac tcacccacga   1140

tatcatcacc aagttcctgg aaaatgaaga cagaaggtct gccagcttac atttacccaa   1200

actgtccatt actggaacct atgatctgaa gagcgtcctg ggtcaactgg gcatcactaa   1260

ggtcttcagc aatggggctg acctctccgg ggtcacagag gaggcacccc tgaagctctc   1320

caaggccgtg cataaggctg tgctgaccat cgacgagaaa gggactgaag ctgctggggc   1380

catgttttta gaggccatac ccatgtctat ccccccccgag gtcaagttca acaaaccctt   1440

tgtcttctta atgattgaac aaaataccaa gtctcccctc ttcatgggaa aagtggtgaa   1500

tcccacccaa aaataactgc ctctcgctcc tcaacccctc ccctccatcc ctggccccct   1560

ccctggatga cattaaagaa gggttgagct ggtccctgcc tgcaaaa                 1607
```

```
<210> SEQ ID NO 39
<211> LENGTH: 418
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

Met Pro Ser Ser Val Ser Trp Gly Ile Leu Leu Leu Ala Gly Leu Cys
1               5                   10                  15

Cys Leu Val Pro Val Ser Leu Ala Glu Asp Pro Gln Gly Asp Ala Ala
            20                  25                  30

Gln Lys Thr Asp Thr Ser His His Asp Gln Asp His Pro Thr Phe Asn
        35                  40                  45

Lys Ile Thr Pro Asn Leu Ala Glu Phe Ala Phe Ser Leu Tyr Arg Gln
    50                  55                  60

Leu Ala His Gln Ser Asn Ser Thr Asn Ile Phe Phe Ser Pro Val Ser
65                  70                  75                  80

Ile Ala Thr Ala Phe Ala Met Leu Ser Leu Gly Thr Lys Ala Asp Thr
                85                  90                  95

His Asp Glu Ile Leu Glu Gly Leu Asn Phe Asn Leu Thr Glu Ile Pro
            100                 105                 110
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Glu Ala Gln Ile His Glu Gly Phe Gln Glu Leu Leu Arg Thr Leu Asn
        115                 120                 125

Gln Pro Asp Ser Gln Leu Gln Leu Thr Thr Gly Asn Gly Leu Phe Leu
    130                 135                 140

Ser Glu Gly Leu Lys Leu Val Asp Lys Phe Leu Glu Asp Val Lys Lys
145                 150                 155                 160

Leu Tyr His Ser Glu Ala Phe Thr Val Asn Phe Gly Asp Thr Glu Glu
            165                 170                 175

Ala Lys Lys Gln Ile Asn Asp Tyr Val Glu Lys Gly Thr Gln Gly Lys
                180                 185                 190

Ile Val Asp Leu Val Lys Glu Leu Asp Arg Asp Thr Val Phe Ala Leu
        195                 200                 205

Val Asn Tyr Ile Phe Phe Lys Gly Lys Trp Glu Arg Pro Phe Glu Val
    210                 215                 220

Lys Asp Thr Glu Glu Glu Asp Phe His Val Asp Gln Val Thr Thr Val
225                 230                 235                 240

Lys Val Pro Met Met Lys Arg Leu Gly Met Phe Asn Ile Gln His Cys
            245                 250                 255

Lys Lys Leu Ser Ser Trp Val Leu Leu Met Lys Tyr Leu Gly Asn Ala
                260                 265                 270

Thr Ala Ile Phe Phe Leu Pro Asp Glu Gly Lys Leu Gln His Leu Glu
        275                 280                 285

Asn Glu Leu Thr His Asp Ile Ile Thr Lys Phe Leu Glu Asn Glu Asp
    290                 295                 300

Arg Arg Ser Ala Ser Leu His Leu Pro Lys Leu Ser Ile Thr Gly Thr
305                 310                 315                 320

Tyr Asp Leu Lys Ser Val Leu Gly Gln Leu Gly Ile Thr Lys Val Phe
            325                 330                 335

Ser Asn Gly Ala Asp Leu Ser Gly Val Thr Glu Glu Ala Pro Leu Lys
                340                 345                 350

Leu Ser Lys Ala Val His Lys Ala Val Leu Thr Ile Asp Glu Lys Gly
        355                 360                 365

Thr Glu Ala Ala Gly Ala Met Phe Leu Glu Ala Ile Pro Met Ser Ile
    370                 375                 380

Pro Pro Glu Val Lys Phe Asn Lys Pro Phe Val Phe Leu Met Ile Glu
385                 390                 395                 400

Gln Asn Thr Lys Ser Pro Leu Phe Met Gly Lys Val Val Asn Pro Thr
            405                 410                 415

Gln Lys


<210> SEQ ID NO 40
<211> LENGTH: 1588
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

tgggcaggaa ctgggcactg tgcccagggc atgcactgcc tccacgcagc aaccctcaga     60

gtcctgagct gaaccaagaa ggaggagggg gtcgggcctc cgaggaaggc ctagccgctg    120

ctgctgccag gaattccagg ttggaggggc ggcaacctcc tgccagcctt caggccactc    180

tcctgtgcct gccagaagag acagagcttg aggagagctt gaggagagca ggaaaggaca    240

atgccgtctt ctgtctcgtg gggcatcctc ctgctggcag gcctgtgctg cctggtccct    300
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gtctccctgg ctgaggatcc ccagggagat gctgcccaga agacagatac atcccaccat 360

gatcaggatc acccaacctt caacaagatc acccccaacc tggctgagtt cgccttcagc 420

ctataccgcc agctggcaca ccagtccaac agcaccaata tcttcttctc cccagtgagc 480

atcgctacag cctttgcaat gctctccctg gggaccaagg ctgacactca cgatgaaatc 540

ctggagggcc tgaatttcaa cctcacggag attccggagg ctcagatcca tgaaggcttc 600

caggaactcc tccgtaccct caaccagcca gacagccagc tccagctgac caccggcaat 660

ggcctgttcc tcagcgaggg cctgaagcta gtggataagt tttggaggaa tgttaaaaag 720

ttgtaccact cagaagcctt cactgtcaac ttcggggaca ccgaagaggc caagaaacag 780

atcaacgatt acgtggagaa gggtactcaa gggaaaattg tggatttggt caaggagctt 840

gacagagaca cagtttttgc tctggtgaat tacatcttct ttaaaggcaa atgggagaga 900

ccctttgaag tcaaggacac cgaggaagag gacttccacg tggaccaggt gaccaccgtg 960

aaggtgccta tgatgaagcg tttaggcatg tttaacatcc agcactgtaa gaagctgtcc 1020

agctgggtgc tgctgatgaa atacctgggc aatgccaccg ccatcttctt cctgcctgat 1080

gaggggaaac tacagcacct ggaaaatgaa ctcacccacg atatcatcac caagttcctg 1140

gaaaatgaag acagaaggtc tgccagctta catttaccca aactgtccat tactggaacc 1200

tatgatctga agagcgtcct gggtcaactg ggcatcacta aggtcttcag caatggggct 1260

gacctctccg gggtcacaga ggaggcaccc ctgaagctct ccaaggccgt gcataaggct 1320

gtgctgacca tcgacgagaa agggactgaa gctgctgggg ccatgttttt agaggccata 1380

cccatgtcta tcccccccga ggtcaagttc aacaaaccct ttgtcttctt aatgattgaa 1440

caaaatacca agtctcccct cttcatggga aaagtggtga atcccaccca aaaataactg 1500

cctctcgctc ctcaacccct cccctccatc cctggccccc tccctggatg acattaaaga 1560

agggttgagc tggtccctgc ctgcaaaa 1588

<210> SEQ ID NO 41
<211> LENGTH: 418
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

Met Pro Ser Ser Val Ser Trp Gly Ile Leu Leu Leu Ala Gly Leu Cys
1 5 10 15

Cys Leu Val Pro Val Ser Leu Ala Glu Asp Pro Gln Gly Asp Ala Ala
20 25 30

Gln Lys Thr Asp Thr Ser His His Asp Gln Asp His Pro Thr Phe Asn
35 40 45

Lys Ile Thr Pro Asn Leu Ala Glu Phe Ala Phe Ser Leu Tyr Arg Gln
50 55 60

Leu Ala His Gln Ser Asn Ser Thr Asn Ile Phe Phe Ser Pro Val Ser
65 70 75 80

Ile Ala Thr Ala Phe Ala Met Leu Ser Leu Gly Thr Lys Ala Asp Thr
85 90 95

His Asp Glu Ile Leu Glu Gly Leu Asn Phe Asn Leu Thr Glu Ile Pro
100 105 110

Glu Ala Gln Ile His Glu Gly Phe Gln Glu Leu Leu Arg Thr Leu Asn
115 120 125

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Gln Pro Asp Ser Gln Leu Gln Leu Thr Thr Gly Asn Gly Leu Phe Leu
    130                 135                 140

Ser Glu Gly Leu Lys Leu Val Asp Lys Phe Leu Glu Asp Val Lys Lys
145                 150                 155                 160

Leu Tyr His Ser Glu Ala Phe Thr Val Asn Phe Gly Asp Thr Glu Glu
                165                 170                 175

Ala Lys Lys Gln Ile Asn Asp Tyr Val Glu Lys Gly Thr Gln Gly Lys
            180                 185                 190

Ile Val Asp Leu Val Lys Glu Leu Asp Arg Asp Thr Val Phe Ala Leu
        195                 200                 205

Val Asn Tyr Ile Phe Phe Lys Gly Lys Trp Glu Arg Pro Phe Glu Val
    210                 215                 220

Lys Asp Thr Glu Glu Glu Asp Phe His Val Asp Gln Val Thr Thr Val
225                 230                 235                 240

Lys Val Pro Met Met Lys Arg Leu Gly Met Phe Asn Ile Gln His Cys
                245                 250                 255

Lys Lys Leu Ser Ser Trp Val Leu Leu Met Lys Tyr Leu Gly Asn Ala
            260                 265                 270

Thr Ala Ile Phe Phe Leu Pro Asp Glu Gly Lys Leu Gln His Leu Glu
        275                 280                 285

Asn Glu Leu Thr His Asp Ile Ile Thr Lys Phe Leu Glu Asn Glu Asp
    290                 295                 300

Arg Arg Ser Ala Ser Leu His Leu Pro Lys Leu Ser Ile Thr Gly Thr
305                 310                 315                 320

Tyr Asp Leu Lys Ser Val Leu Gly Gln Leu Gly Ile Thr Lys Val Phe
                325                 330                 335

Ser Asn Gly Ala Asp Leu Ser Gly Val Thr Glu Glu Ala Pro Leu Lys
            340                 345                 350

Leu Ser Lys Ala Val His Lys Ala Val Leu Thr Ile Asp Glu Lys Gly
        355                 360                 365

Thr Glu Ala Ala Gly Ala Met Phe Leu Glu Ala Ile Pro Met Ser Ile
    370                 375                 380

Pro Pro Glu Val Lys Phe Asn Lys Pro Phe Val Phe Leu Met Ile Glu
385                 390                 395                 400

Gln Asn Thr Lys Ser Pro Leu Phe Met Gly Lys Val Val Asn Pro Thr
                405                 410                 415

Gln Lys


<210> SEQ ID NO 42
<211> LENGTH: 1902
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

tgggcaggaa ctgggcactg tgcccagggc atgcactgcc tccacgcagc aaccctcaga     60

gtcctgagct gaaccaagaa ggaggagggg gtcgggcctc cgaggaaggc ctagccgctg    120

ctgctgccag gaattccagg ttggaggggc ggcaacctcc tgccagcctt caggccactc    180

tcctgtgcct gccagaagag acagagcttg aggagagctt gaggagagca ggaaagggcg    240

gcagtaagtc ttcagcatca ggcattttgg ggtgactcag taaatggtag atcttgctac    300

cagtggaaca gccactaagg attctgcagt gagagcagag ggccagctaa gtggtactct    360
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cccagagact gtctgactca cgccaccccc tccaccttgg acacaggacg ctgtggtttc    420

tgagccaggt acaatgactc ctttcgcagc ctccccgtt gcccctctgg atccactgct    480

taaatacgga cgaggacagg gccctgtctc ctcagcttca ggcaccacca ctgacctggg    540

acagtgaatc gacaatgccg tcttctgtct cgtggggcat cctcctgctg gcaggcctgt    600

gctgcctggt ccctgtctcc ctggctgagg atccccaggg agatgctgcc cagaagacag    660

atacatccca ccatgatcag gatcacccaa ccttcaacaa gatcaccccc aacctggctg    720

agttcgcctt cagcctatac cgccagctgg cacaccagtc caacagcacc aatatcttct    780

tctccccagt gagcatcgct acagcctttg caatgctctc cctggggacc aaggctgaca    840

ctcacgatga aatcctggag ggcctgaatt tcaacctcac ggagattccg gaggctcaga    900

tccatgaagg cttccaggaa ctcctccgta ccctcaacca gccagacagc cagctccagc    960

tgaccaccgg caatggcctg ttcctcagcg agggcctgaa gctagtggat aagtttttgg   1020

aggatgttaa aaagttgtac cactcagaag ccttcactgt caacttcggg gacaccgaag   1080

aggccaagaa acagatcaac gattacgtgg agaagggtac tcaagggaaa attgtggatt   1140

tggtcaagga gcttgacaga gacacagttt ttgctctggt gaattacatc ttctttaaag   1200

gcaaatggga gagacccttt gaagtcaagg acaccgagga agaggacttc cacgtggacc   1260

aggtgaccac cgtgaaggtg cctatgatga agcgtttagg catgtttaac atccagcact   1320

gtaagaagct gtccagctgg gtgctgctga tgaaatacct gggcaatgcc accgccatct   1380

tcttcctgcc tgatgagggg aaactacagc acctggaaaa tgaactcacc cacgatatca   1440

tcaccaagtt cctggaaaat gaagacagaa ggtctgccag cttacattta cccaaactgt   1500

ccattactgg aacctatgat ctgaagagcg tcctgggtca actgggcatc actaaggtct   1560

tcagcaatgg ggctgacctc tccggggtca cagaggaggc acccctgaag ctctccaagg   1620

ccgtgcataa ggctgtgctg accatcgacg agaaagggac tgaagctgct ggggccatgt   1680

ttttagaggc catacccatg tctatccccc ccgaggtcaa gttcaacaaa ccctttgtct   1740

tcttaatgat tgaacaaaat accaagtctc ccctcttcat gggaaaagtg gtgaatccca   1800

cccaaaaata actgcctctc gctcctcaac cctcccctc catccctggc cccctccctg   1860

gatgacatta aagaagggtt gagctggtcc ctgcctgcaa aa                     1902


<210> SEQ ID NO 43
<211> LENGTH: 335
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

Met Gly His Pro Pro Leu Leu Pro Leu Leu Leu Leu Leu His Thr Cys
1               5                   10                  15

Val Pro Ala Ser Trp Gly Leu Arg Cys Met Gln Cys Lys Thr Asn Gly
            20                  25                  30

Asp Cys Arg Val Glu Glu Cys Ala Leu Gly Gln Asp Leu Cys Arg Thr
        35                  40                  45

Thr Ile Val Arg Leu Trp Glu Glu Gly Glu Glu Leu Glu Leu Val Glu
    50                  55                  60

Lys Ser Cys Thr His Ser Glu Lys Thr Asn Arg Thr Leu Ser Tyr Arg
65                  70                  75                  80
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Thr Gly Leu Lys Ile Thr Ser Leu Thr Glu Val Val Cys Gly Leu Asp
                85                  90                  95

Leu Cys Asn Gln Gly Asn Ser Gly Arg Ala Val Thr Tyr Ser Arg Ser
            100                 105                 110

Arg Tyr Leu Glu Cys Ile Ser Cys Gly Ser Ser Asp Met Ser Cys Glu
        115                 120                 125

Arg Gly Arg His Gln Ser Leu Gln Cys Arg Ser Pro Glu Glu Gln Cys
    130                 135                 140

Leu Asp Val Val Thr His Trp Ile Gln Glu Gly Glu Glu Gly Arg Pro
145                 150                 155                 160

Lys Asp Asp Arg His Leu Arg Gly Cys Gly Tyr Leu Pro Gly Cys Pro
                165                 170                 175

Gly Ser Asn Gly Phe His Asn Asn Asp Thr Phe His Phe Leu Lys Cys
            180                 185                 190

Cys Asn Thr Thr Lys Cys Asn Glu Gly Pro Ile Leu Glu Leu Glu Asn
        195                 200                 205

Leu Pro Gln Asn Gly Arg Gln Cys Tyr Ser Cys Lys Gly Asn Ser Thr
    210                 215                 220

His Gly Cys Ser Ser Glu Glu Thr Phe Leu Ile Asp Cys Arg Gly Pro
225                 230                 235                 240

Met Asn Gln Cys Leu Val Ala Thr Gly Thr His Glu Pro Lys Asn Gln
                245                 250                 255

Ser Tyr Met Val Arg Gly Cys Ala Thr Ala Ser Met Cys Gln His Ala
            260                 265                 270

His Leu Gly Asp Ala Phe Ser Met Asn His Ile Asp Val Ser Cys Cys
        275                 280                 285

Thr Lys Ser Gly Cys Asn His Pro Asp Leu Asp Val Gln Tyr Arg Ser
    290                 295                 300

Gly Ala Ala Pro Gln Pro Gly Pro Ala His Leu Ser Leu Thr Ile Thr
305                 310                 315                 320

Leu Leu Met Thr Ala Arg Leu Trp Gly Gly Thr Leu Leu Trp Thr
                325                 330                 335


<210> SEQ ID NO 44
<211> LENGTH: 1548
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

cagggccgag ccagcccctt caccaccagc cggccgcgcc ccgggaaggg aagtttgtgg     60

cggaggaggt tcgtacggga ggagggggag gcgcccacgc atctggggct gactcgctct    120

ttcgcaaaac gtctgggagg agtccctggg gccacaaaac tgcctccttc ctgaggccag    180

aaggagagaa gacgtgcagg gaccccgcgc acaggagctg ccctcgcgac atgggtcacc    240

cgccgctgct gccgctgctg ctgctgctcc acacctgcgt cccagcctct tggggcctgc    300

ggtgcatgca gtgtaagacc aacggggatt gccgtgtgga agagtgcgcc ctgggacagg    360

acctctgcag gaccacgatc gtgcgcttgt gggaagaagg agaagagctg gagctggtgg    420

agaaaagctg tacccactca gagaagacca acaggaccct gagctatcgg actggcttga    480

agatcaccag ccttaccgag gttgtgtgtg ggttagactt gtgcaaccag ggcaactctg    540

gccgggctgt cacctattcc cgaagccgtt acctcgaatg catttcctgt ggctcatcag    600
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acatgagctg tgagaggggc cggcaccaga gcctgcagtg ccgcagccct gaagaacagt    660

gcctggatgt ggtgacccac tggatccagg aaggtgaaga agggcgtcca aaggatgacc    720

gccacctccg tggctgtggc taccttcccg gctgcccggg ctccaatggt ttccacaaca    780

acgacacctt ccacttcctg aaatgctgca acaccaccaa atgcaacgag ggcccaatcc    840

tggagcttga aaatctgccg cagaatggcc gccagtgtta cagctgcaag ggaacagca     900

cccatggatg ctcctctgaa gagactttcc tcattgactg ccgaggcccc atgaatcaat    960

gtctggtagc caccggcact cacgaaccga aaaaccaaag ctatatggta agaggctgtg   1020

caaccgcctc aatgtgccaa catgcccacc tgggtgacgc cttcagcatg aaccacattg   1080

atgtctcctg ctgtactaaa agtggctgta accacccaga cctggatgtc cagtaccgca   1140

gtggggctgc tcctcagcct ggccctgccc atctcagcct caccatcacc ctgctaatga   1200

ctgccagact gtggggaggc actctcctct ggacctaaac ctgaaatccc cctctctgcc   1260

ctggctggat ccgggggacc cctttgccct tccctcggct cccagcccta cagacttgct   1320

gtgtgacctc aggccagtgt gccgacctct ctgggcctca gttttcccag ctatgaaaac   1380

agctatctca caaagttgtg tgaagcagaa gagaaaagct ggaggaaggc cgtgggccaa   1440

tgggagagct cttgttatta ttaatattgt tgccgctgtt gtgttgttgt tattaattaa   1500

tattcatatt atttatttta tacttacata aagattttgt accagtgg                1548
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<210> SEQ ID NO 45
<211> LENGTH: 281
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

Met Gly His Pro Pro Leu Leu Pro Leu Leu Leu Leu Leu His Thr Cys
1               5                   10                  15

Val Pro Ala Ser Trp Gly Leu Arg Cys Met Gln Cys Lys Thr Asn Gly
            20                  25                  30

Asp Cys Arg Val Glu Glu Cys Ala Leu Gly Gln Asp Leu Cys Arg Thr
        35                  40                  45

Thr Ile Val Arg Leu Trp Glu Glu Gly Glu Glu Leu Glu Leu Val Glu
    50                  55                  60

Lys Ser Cys Thr His Ser Glu Lys Thr Asn Arg Thr Leu Ser Tyr Arg
65                  70                  75                  80

Thr Gly Leu Lys Ile Thr Ser Leu Thr Glu Val Val Cys Gly Leu Asp
                85                  90                  95

Leu Cys Asn Gln Gly Asn Ser Gly Arg Ala Val Thr Tyr Ser Arg Ser
            100                 105                 110

Arg Tyr Leu Glu Cys Ile Ser Cys Gly Ser Ser Asp Met Ser Cys Glu
        115                 120                 125

Arg Gly Arg His Gln Ser Leu Gln Cys Arg Ser Pro Glu Glu Gln Cys
    130                 135                 140

Leu Asp Val Val Thr His Trp Ile Gln Glu Gly Glu Glu Gly Arg Pro
145                 150                 155                 160

Lys Asp Asp Arg His Leu Arg Gly Cys Gly Tyr Leu Pro Gly Cys Pro
                165                 170                 175

Gly Ser Asn Gly Phe His Asn Asn Asp Thr Phe His Phe Leu Lys Cys
            180                 185                 190
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Cys Asn Thr Thr Lys Cys Asn Glu Gly Pro Ile Leu Glu Leu Glu Asn
        195                 200                 205

Leu Pro Gln Asn Gly Arg Gln Cys Tyr Ser Cys Lys Gly Asn Ser Thr
    210                 215                 220

His Gly Cys Ser Ser Glu Glu Thr Phe Leu Ile Asp Cys Arg Gly Pro
225                 230                 235                 240

Met Asn Gln Cys Leu Val Ala Thr Gly Thr His Glu Arg Ser Leu Trp
                245                 250                 255

Gly Ser Trp Leu Pro Cys Lys Ser Thr Thr Ala Leu Arg Pro Pro Cys
            260                 265                 270

Cys Glu Glu Ala Gln Ala Thr His Val
        275                 280


<210> SEQ ID NO 46
<211> LENGTH: 1437
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

cagggccgag ccagcccctt caccaccagc cggccgcgcc ccgggaaggg aagtttgtgg      60

cggaggaggt tcgtacggga ggagggggag gcgcccacgc atctggggct gactcgctct     120

ttcgcaaaac gtctgggagg agtccctggg gccacaaaac tgcctccttc ctgaggccag     180

aaggagagaa gacgtgcagg gaccccgcgc acaggagctg ccctcgcgac atgggtcacc     240

cgccgctgct gccgctgctg ctgctgctcc acacctgcgt cccagcctct tggggcctgc     300

ggtgcatgca gtgtaagacc aacggggatt gccgtgtgga agagtgcgcc ctgggacagg     360

acctctgcag gaccacgatc gtgcgcttgt gggaagaagg agaagagctg gagctggtgg     420

agaaaagctg tacccactca gagaagacca acaggaccct gagctatcgg actggcttga     480

agatcaccag ccttaccgag gttgtgtgtg ggttagactt gtgcaaccag ggcaactctg     540

gccgggctgt cacctattcc cgaagccgtt acctcgaatg catttcctgt ggctcatcag     600

acatgagctg tgagaggggc cggcaccaga gcctgcagtg ccgcagccct gaagaacagt     660

gcctggatgt ggtgacccac tggatccagg aaggtgaaga agggcgtcca aaggatgacc     720

gccacctccg tggctgtggc taccttcccg gctgcccggg ctccaatggt ttccacaaca     780

acgacacctt ccacttcctg aaatgctgca acaccaccaa atgcaacgag ggcccaatcc     840

tggagcttga aaatctgccg cagaatggcc gccagtgtta cagctgcaag ggaacagca      900

cccatggatg ctcctctgaa gagactttcc tcattgactg ccgaggcccc atgaatcaat     960

gtctggtagc caccggcact cacgaacgct cactctgggg aagctggttg ccatgtaaaa    1020

gtactactgc cctgagacca ccatgctgtg aggaagccca agctactcat gtataaatgc    1080

catgtggaga tagagcccca gatgtttcag ccatctcagc ccaggcacca gacaagtggg    1140

tgaagaagcc accttggaca tgtagcccca gcagatgtga tatagagaag aaacaggaaa    1200

cttggctata ttagtttcct agggctgcct gtgataaatt attacaaact ttataaacta    1260

acacattgtg tgcctatatc aaaacatcat ggaaggacag gcacagtggc tcatgcctgt    1320

agtcctagca ctttgggagg gtgagaaagg aagatctctt gagctcagga gttcaagatc    1380

agcctgggca acacagtgag acctcatctc cactaaaaat aaaaaaaaat tggctgg       1437


<210> SEQ ID NO 47
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<211> LENGTH: 290
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

Met Gly His Pro Pro Leu Leu Pro Leu Leu Leu Leu Leu His Thr Cys
1               5                   10                  15

Val Pro Ala Ser Trp Gly Leu Arg Cys Met Gln Cys Lys Thr Asn Gly
            20                  25                  30

Asp Cys Arg Val Glu Glu Cys Ala Leu Gly Gln Asp Leu Cys Arg Thr
        35                  40                  45

Thr Ile Val Arg Leu Trp Glu Glu Gly Glu Glu Leu Glu Leu Val Glu
    50                  55                  60

Lys Ser Cys Thr His Ser Glu Lys Thr Asn Arg Thr Leu Ser Tyr Arg
65                  70                  75                  80

Thr Gly Leu Lys Ile Thr Ser Leu Thr Glu Val Val Cys Gly Leu Asp
                85                  90                  95

Leu Cys Asn Gln Gly Asn Ser Gly Arg Ala Val Thr Tyr Ser Arg Ser
            100                 105                 110

Arg Tyr Leu Glu Cys Ile Ser Cys Gly Ser Ser Asp Met Ser Cys Glu
        115                 120                 125

Arg Gly Arg His Gln Ser Leu Gln Cys Arg Ser Pro Glu Glu Gln Cys
    130                 135                 140

Leu Asp Val Val Thr His Trp Ile Gln Glu Gly Glu Glu Val Leu Glu
145                 150                 155                 160

Leu Glu Asn Leu Pro Gln Asn Gly Arg Gln Cys Tyr Ser Cys Lys Gly
                165                 170                 175

Asn Ser Thr His Gly Cys Ser Ser Glu Glu Thr Phe Leu Ile Asp Cys
            180                 185                 190

Arg Gly Pro Met Asn Gln Cys Leu Val Ala Thr Gly Thr His Glu Pro
        195                 200                 205

Lys Asn Gln Ser Tyr Met Val Arg Gly Cys Ala Thr Ala Ser Met Cys
    210                 215                 220

Gln His Ala His Leu Gly Asp Ala Phe Ser Met Asn His Ile Asp Val
225                 230                 235                 240

Ser Cys Cys Thr Lys Ser Gly Cys Asn His Pro Asp Leu Asp Val Gln
                245                 250                 255

Tyr Arg Ser Gly Ala Ala Pro Gln Pro Gly Pro Ala His Leu Ser Leu
            260                 265                 270

Thr Ile Thr Leu Leu Met Thr Ala Arg Leu Trp Gly Gly Thr Leu Leu
        275                 280                 285

Trp Thr
    290


<210> SEQ ID NO 48
<211> LENGTH: 1360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

cagggccgag ccagcccctt caccaccagc cggccgcgcc ccgggaaggg aagtttgtgg      60

cggaggaggt tcgtacggga ggagggggag gcgcccacgc atctggggct gactcgctct     120

ttcgcaaaac gtctgggagg agtccctggg gccacaaaac tgcctccttc ctgaggccag     180
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aaggagagaa gacgtgcagg gaccccgcgc acaggagctg ccctcgcgac atgggtcacc    240

cgccgctgct gccgctgctg ctgctgctcc acacctgcgt cccagcctct tggggcctgc    300

ggtgcatgca gtgtaagacc aacggggatt gccgtgtgga agagtgcgcc ctgggacagg    360

acctctgcag gaccacgatc gtgcgcttgt gggaagaagg agaagagctg gagctggtgg    420

agaaaagctg tacccactca gagaagacca acaggaccct gagctatcgg actggcttga    480

agatcaccag ccttaccgag gttgtgtgtg ggttagactt gtgcaaccag ggcaactctg    540

gccgggctgt cacctattcc cgaagccgtt acctcgaatg catttcctgt ggctcatcag    600

acatgagctg tgagaggggc cggcaccaga gcctgcagtg ccgcagccct gaagaacagt    660

gcctggatgt ggtgacccac tggatccagg aaggtgaaga agtcctggag cttgaaaatc    720

tgccgcagaa tggccgccag tgttacagct gcaaggggaa cagcacccat ggatgctcct    780

ctgaagagac tttcctcatt gactgccgag gccccatgaa tcaatgtctg gtagccaccg    840

gcactcacga accgaaaaac caaagctata tggtaagagg ctgtgcaacc gcctcaatgt    900

gccaacatgc ccacctgggt gacgccttca gcatgaacca cattgatgtc tcctgctgta    960

ctaaaagtgg ctgtaaccac ccagacctgg atgtccagta ccgcagtggg gctgctcctc   1020

agcctggccc tgcccatctc agcctcacca tcaccctgct aatgactgcc agactgtggg   1080

gaggcactct cctctggacc taaacctgaa atcccccctct ctgccctggc tggatccggg   1140

ggacccccttt gcccttccct cggctcccag ccctacagac ttgctgtgtg acctcaggcc   1200

agtgtgccga cctctctggg cctcagtttt cccagctatg aaaacagcta tctcacaaag   1260

ttgtgtgaag cagaagagaa aagctggagg aaggccgtgg gccaatggga gagctcttgt   1320

tattattaat attgttgccg ctgttgtgtt gttgttatta                         1360
```

<210> SEQ ID NO 49
<211> LENGTH: 243
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

```
Met Arg Pro Gln Gly Pro Ala Ala Ser Pro Gln Arg Leu Arg Gly Leu
1               5                   10                  15

Leu Leu Leu Leu Leu Leu Gln Leu Pro Ala Pro Ser Ser Ala Ser Glu
            20                  25                  30

Ile Pro Lys Gly Lys Gln Lys Ala Gln Leu Arg Gln Arg Glu Val Val
        35                  40                  45

Asp Leu Tyr Asn Gly Met Cys Leu Gln Gly Pro Ala Gly Val Pro Gly
    50                  55                  60

Arg Asp Gly Ser Pro Gly Ala Asn Gly Ile Pro Gly Thr Pro Gly Ile
65                  70                  75                  80

Pro Gly Arg Asp Gly Phe Lys Gly Glu Lys Gly Glu Cys Leu Arg Glu
                85                  90                  95

Ser Phe Glu Glu Ser Trp Thr Pro Asn Tyr Lys Gln Cys Ser Trp Ser
            100                 105                 110

Ser Leu Asn Tyr Gly Ile Asp Leu Gly Lys Ile Ala Glu Cys Thr Phe
        115                 120                 125

Thr Lys Met Arg Ser Asn Ser Ala Leu Arg Val Leu Phe Ser Gly Ser
    130                 135                 140
```

-continued

```
Leu Arg Leu Lys Cys Arg Asn Ala Cys Cys Gln Arg Trp Tyr Phe Thr
145                 150                 155                 160

Phe Asn Gly Ala Glu Cys Ser Gly Pro Leu Pro Ile Glu Ala Ile Ile
                165                 170                 175

Tyr Leu Asp Gln Gly Ser Pro Glu Met Asn Ser Thr Ile Asn Ile His
            180                 185                 190

Arg Thr Ser Ser Val Glu Gly Leu Cys Glu Gly Ile Gly Ala Gly Leu
        195                 200                 205

Val Asp Val Ala Ile Trp Val Gly Thr Cys Ser Asp Tyr Pro Lys Gly
    210                 215                 220

Asp Ala Ser Thr Gly Trp Asn Ser Val Ser Arg Ile Ile Ile Glu Glu
225                 230                 235                 240

Leu Pro Lys
```

<210> SEQ ID NO 50
<211> LENGTH: 1236
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

```
ctgcggcggc ctcggagcgc ggcggagcca gacgctgacc acgttcctct cctcggtctc     60

ctccgcctcc agctccgcgc tgcccggcag ccgggagcca tgcgaccccа gggccccgcc    120

gcctccccgc agcggctccg cggcctcctg ctgctcctgc tgctgcagct gcccgcgccg    180

tcgagcgcct ctgagatccc caaggggaag caaaaggcgc agctccggca gagggaggtg    240

gtggacctgt ataatggaat gtgcttacaa gggccagcag gagtgcctgg tcgagacggg    300

agccctgggg ccaatggcat tccgggtaca cctgggatcc caggtcggga tggattcaaa    360

ggagaaaagg gggaatgtct gagggaaagc tttgaggagt cctggacacc caactacaag    420

cagtgttcat ggagttcatt gaattatggc atagatcttg ggaaaattgc ggagtgtaca    480

tttacaaaga tgcgttcaaa tagtgctcta agagttttgt tcagtggctc acttcggcta    540

aaatgcagaa atgcatgctg tcagcgttgg tatttcacat tcaatggagc tgaatgttca    600

ggacctcttc ccattgaagc tataatttat ttggaccaag gaagccctga aatgaattca    660

acaattaata ttcatcgcac ttcttctgtg gaaggacttt gtgaaggaat tggtgctgga    720

ttagtggatg ttgctatctg ggttggcact tgttcagatt acccaaaagg agatgcttct    780

actggatgga attcagtttc tcgcatcatt attgaagaac taccaaaata aatgctttaa    840

ttttcatttg ctacctcttt ttttattatg ccttggaatg gttcacttaa atgacatttt    900

aaataagttt atgtatacat ctgaatgaaa agcaaagcta aatatgttta cagaccaaag    960

tgtgatttca cactgttttt aaatctagca ttattcattt tgcttcaatc aaaagtggtt   1020

tcaatatttt ttttagttgg ttagaatact ttcttcatag tcacattctc tcaacctata   1080

atttggaata ttgttgtggt cttttgtttt ttctcttagt atagcatttt taaaaaaata   1140

taaaagctac caatctttgt acaatttgta aatgttaaga attttttta tatctgttaa   1200

ataaaaatta tttccaacaa aaaaaaaaaa aaaaaa                             1236
```

<210> SEQ ID NO 51
<211> LENGTH: 366
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

-continued

```
<400> SEQUENCE: 51

Met Val Leu His Leu Leu Leu Phe Leu Leu Leu Thr Pro Gln Gly Gly
1               5                   10                  15

His Ser Cys Gln Gly Leu Glu Leu Ala Arg Glu Leu Val Leu Ala Lys
            20                  25                  30

Val Arg Ala Leu Phe Leu Asp Ala Leu Gly Pro Pro Ala Val Thr Arg
        35                  40                  45

Glu Gly Gly Asp Pro Gly Val Arg Arg Leu Pro Arg Arg His Ala Leu
    50                  55                  60

Gly Gly Phe Thr His Arg Gly Ser Glu Pro Glu Glu Glu Glu Asp Val
65                  70                  75                  80

Ser Gln Ala Ile Leu Phe Pro Ala Thr Asp Ala Ser Cys Glu Asp Lys
                85                  90                  95

Ser Ala Ala Arg Gly Leu Ala Gln Glu Ala Glu Glu Gly Leu Phe Arg
            100                 105                 110

Tyr Met Phe Arg Pro Ser Gln His Thr Arg Ser Arg Gln Val Thr Ser
        115                 120                 125

Ala Gln Leu Trp Phe His Thr Gly Leu Asp Arg Gln Gly Thr Ala Ala
    130                 135                 140

Ser Asn Ser Ser Glu Pro Leu Leu Gly Leu Leu Ala Leu Ser Pro Gly
145                 150                 155                 160

Gly Pro Val Ala Val Pro Met Ser Leu Gly His Ala Pro Pro His Trp
                165                 170                 175

Ala Val Leu His Leu Ala Thr Ser Ala Leu Ser Leu Leu Thr His Pro
            180                 185                 190

Val Leu Val Leu Leu Leu Arg Cys Pro Leu Cys Thr Cys Ser Ala Arg
        195                 200                 205

Pro Glu Ala Thr Pro Phe Leu Val Ala His Thr Arg Thr Arg Pro Pro
    210                 215                 220

Ser Gly Gly Glu Arg Ala Arg Arg Ser Thr Pro Leu Met Ser Trp Pro
225                 230                 235                 240

Trp Ser Pro Ser Ala Leu Arg Leu Leu Gln Arg Pro Pro Glu Glu Pro
                245                 250                 255

Ala Ala His Ala Asn Cys His Arg Val Ala Leu Asn Ile Ser Phe Gln
            260                 265                 270

Glu Leu Gly Trp Glu Arg Trp Ile Val Tyr Pro Pro Ser Phe Ile Phe
        275                 280                 285

His Tyr Cys His Gly Gly Cys Gly Leu His Ile Pro Pro Asn Leu Ser
    290                 295                 300

Leu Pro Val Pro Gly Ala Pro Pro Thr Pro Ala Gln Pro Tyr Ser Leu
305                 310                 315                 320

Leu Pro Gly Ala Gln Pro Cys Cys Ala Ala Leu Pro Gly Thr Met Arg
                325                 330                 335

Pro Leu His Val Arg Thr Thr Ser Asp Gly Gly Tyr Ser Phe Lys Tyr
            340                 345                 350

Glu Thr Val Pro Asn Leu Leu Thr Gln His Cys Ala Cys Ile
        355                 360                 365


<210> SEQ ID NO 52
<211> LENGTH: 1424
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
```

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```
<400> SEQUENCE: 52

gaaggactgg ggaagactgg atgagaaggg tagaagaggg tgggtgtggg atggggaggg      60

gagagtggaa aggccctggg cagaccctgg cagaaggggc acggggcagg gtgtgagttc     120

cccactagca gggccaggtg agctatggtg ctgcacctac tgctcttctt gctgctgacc     180

ccacagggtg ggcacagctg ccaggggctg gagctggccc gggaacttgt tctggccaag     240

gtgagggccc tgttcttgga tgccttgggg ccccccgcgg tgaccaggga aggtggggac     300

cctggagtca ggcggctgcc ccgaagacat gccctggggg gcttcacaca caggggctct     360

gagcccgagg aagaggagga tgtctcccaa gccatccttt tcccagccac agatgccagc     420

tgtgaggaca agtcagctgc cagagggctg gcccaggagg ctgaggaggg cctcttcaga     480

tacatgttcc ggccatccca gcatacacgc agccgccagg tgacttcagc ccagctgtgg     540

ttccacaccg ggctggacag gcagggcaca gcagcctcca atagctctga gcccctgcta     600

ggcctgctgg cactgtcacc gggaggaccc gtggctgtgc ccatgtcttt gggccatgct     660

cccccctcact gggccgtgct gcacctggcc acctctgctc tctctctgct gacccacccc     720

gtcctggtgc tgctgctgcg ctgtcccctc tgtacctgct cagcccggcc tgaggccacg     780

cccttcctgg tggcccacac tcggaccaga ccacccagtg gaggggagag agcccgacgc     840

tcaactcccc tgatgtcctg gccttggtct ccctctgctc tgcgcctgct gcagaggcct     900

ccggaggaac cggctgccca tgccaactgc cacagagtag cactgaacat ctccttccag     960

gagctgggct gggaacggtg gatcgtgtac cctcccagtt tcatcttcca ctactgtcat    1020

ggtggttgtg ggctgcacat cccaccaaac ctgtcccttc cagtccctgg ggctcccccct    1080

accccagccc agccctactc cttgctgcca ggggcccagc cctgctgtgc tgctctccca    1140

gggaccatga ggcccctaca tgtccgcacc acctcggatg gaggttactc tttcaagtat    1200

gagacagtgc ccaaccttct cacgcagcac tgtgcttgta tctaagggtg gggggtcttc    1260

cttcttaatc ccatggctgg tggccacgcc cccaccatca tcagctggga ggaaaggcag    1320

agttgggaaa tagatggctc ccactcctcc ctcctttcac ttctctgcct atgggctacc    1380

ctccccaccc cacttctatc tcaataaaga acacagtgca tatg                     1424


<210> SEQ ID NO 53
<211> LENGTH: 407
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

Met Asp Gly Leu Pro Gly Arg Ala Leu Gly Ala Ala Cys Leu Leu Leu
1               5                   10                  15

Leu Ala Ala Gly Trp Leu Gly Pro Glu Ala Trp Gly Ser Pro Thr Pro
            20                  25                  30

Pro Pro Thr Pro Ala Ala Pro Pro Pro Pro Pro Pro Pro Gly Ala Pro
        35                  40                  45

Gly Gly Ser Gln Asp Thr Cys Thr Ser Cys Gly Gly Phe Arg Arg Pro
    50                  55                  60

Glu Glu Leu Gly Arg Val Asp Gly Asp Phe Leu Glu Ala Val Lys Arg
65                  70                  75                  80

His Ile Leu Ser Arg Leu Gln Met Arg Gly Arg Pro Asn Ile Thr His
                85                  90                  95
```

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```
Ala Val Pro Lys Ala Ala Met Val Thr Ala Leu Arg Lys Leu His Ala
            100                 105                 110

Gly Lys Val Arg Glu Asp Gly Arg Val Glu Ile Pro His Leu Asp Gly
        115                 120                 125

His Ala Ser Pro Gly Ala Asp Gly Gln Glu Arg Val Ser Glu Ile Ile
    130                 135                 140

Ser Phe Ala Glu Thr Asp Gly Leu Ala Ser Ser Arg Val Arg Leu Tyr
145                 150                 155                 160

Phe Phe Ile Ser Asn Glu Gly Asn Gln Asn Leu Phe Val Val Gln Ala
                165                 170                 175

Ser Leu Trp Leu Tyr Leu Lys Leu Leu Pro Tyr Val Leu Glu Lys Gly
            180                 185                 190

Ser Arg Arg Lys Val Arg Val Lys Val Tyr Phe Gln Glu Gln Gly His
        195                 200                 205

Gly Asp Arg Trp Asn Met Val Glu Lys Arg Val Asp Leu Lys Arg Ser
    210                 215                 220

Gly Trp His Thr Phe Pro Leu Thr Glu Ala Ile Gln Ala Leu Phe Glu
225                 230                 235                 240

Arg Gly Glu Arg Arg Leu Asn Leu Asp Val Gln Cys Asp Ser Cys Gln
                245                 250                 255

Glu Leu Ala Val Val Pro Val Phe Val Asp Pro Gly Glu Glu Ser His
            260                 265                 270

Arg Pro Phe Val Val Val Gln Ala Arg Leu Gly Asp Ser Arg His Arg
        275                 280                 285

Ile Arg Lys Arg Gly Leu Glu Cys Asp Gly Arg Thr Asn Leu Cys Cys
    290                 295                 300

Arg Gln Gln Phe Phe Ile Asp Phe Arg Leu Ile Gly Trp Asn Asp Trp
305                 310                 315                 320

Ile Ile Ala Pro Thr Gly Tyr Tyr Gly Asn Tyr Cys Glu Gly Ser Cys
                325                 330                 335

Pro Ala Tyr Leu Ala Gly Val Pro Gly Ser Ala Ser Ser Phe His Thr
            340                 345                 350

Ala Val Val Asn Gln Tyr Arg Met Arg Gly Leu Asn Pro Gly Thr Val
        355                 360                 365

Asn Ser Cys Cys Ile Pro Thr Lys Leu Ser Thr Met Ser Met Leu Tyr
    370                 375                 380

Phe Asp Asp Glu Tyr Asn Ile Val Lys Arg Asp Val Pro Asn Met Ile
385                 390                 395                 400

Val Glu Glu Cys Gly Cys Ala
                405


<210> SEQ ID NO 54
<211> LENGTH: 3516
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

ggatcctgga gacaactttg ccgtgtgacg cgccgggagg actgcagggc ccgcggccga      60

gggctcggcg ccgcctgtga gcgggcccgc gcggccggct ctcccgggca ccaagcttgc     120

tccgcgccac tgcccgccgg cccgcggcga ggacgacctg cccgtctccg ccgccggcgg     180

cccttcctgg cgcgaggcag tgagggcgag gcgctcaggt gcgagcgcgg ggccccgccg     240
```

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```
cagcgcccgc cgcagcgccg cgccaagccg cgcccggctc cgctccgggg ggctccagcg    300

ccttcgcttc cgtctcagcc aagttgcgtg gacccgctct ttcgccacct tccccagccg    360

ccggccgaac cgccgctccc actgacgctg ctttcgcttc acccgaaccg gggctgcggg    420

gcccccgacg cggaaaggat ggggagaagg ctgcagatgc cgaggcgccc cgagacgccc    480

gtgcggcagt gacccgcgac ctccgccccg cccggcgcgc ccctcgggcc cccggggccc    540

tcggcgcccc ttccctgccg cgcgggaacc cccgaggccc ggccggcccc ctccccctgc    600

gagccggcgg cagccctccc ggcgggcggg cgggcggagg cccgggcggg cgcgggcgcg    660

ggcgggggcg gggcggggcg gcgcgcccgg agcccggagc ccggccctgc gctcggctcg    720

actcggctcg cctcgcggcg ggcgccctcg tcgccagcgg cgcaccatgg acgggctgcc    780

cggtcgggcg ctgggggccg cctgccttct gctgctggcg gccggctggc tggggcctga    840

ggcctggggc tcacccacgc ccccgccgac gcctgccgcg ccgccgccac ccccgccacc    900

cggagccccg ggtggctcgc aggacacctg tacgtcgtgc ggcggcttcc ggcggccaga    960

ggagctcggc cgagtggacg gcgacttcct ggaggcggtg aagcggcaca tcttgagccg   1020

cctgcagatg cggggccggc ccaacatcac gcacgccgtg cctaaggccg ccatggtcac   1080

ggccctgcgc aagctgcacg cgggcaaggt gcgcgaggac ggccgcgtgg agatcccgca   1140

cctcgacggc cacgccagcc cgggcgccga cggccaggag cgcgtttccg aaatcatcag   1200

cttcgccgag acagatggcc tcgcctcctc ccgggtccgc ctatacttct tcatctccaa   1260

cgaaggcaac cagaacctgt ttgtggtcca ggccagcctg tggctttacc tgaaactcct   1320

gccctacgtc ctggagaagg gcagccggcg gaaggtgcgg gtcaaagtgt acttccagga   1380

gcagggccac ggtgacaggt ggaacatggt ggagaagagg gtggacctca agcgcagcgg   1440

ctggcatacc ttcccactca cggaggccat ccaggccttg tttgagcggg gcgagcggcg   1500

actcaaccta gacgtgcagt gtgacagctg ccaggagctg gccgtggtgc cggtgttcgt   1560

ggacccaggc gaagagtcgc accgaccctt tgtggtggtg caggctcggc tgggcgacag   1620

caggcaccgc attcgcaagc gaggcctgga gtgcgatggc cggaccaacc tctgttgcag   1680

gcaacagttc ttcattgact tccgcctcat cggctggaac gactggatca tagcacccac   1740

cggctactac ggcaactact gtgagggcag ctgcccagcc tacctggcag ggtccccgg   1800

ctctgcctcc tccttccaca cggctgtggt gaaccagtac cgcatgcggg gtctgaaccc   1860

cggcacggtg aactcctgct gcattcccac caagctgagc accatgtcca tgctgtactt   1920

cgatgatgag tacaacatcg tcaagcggga cgtgcccaac atgattgtgg aggagtgcgg   1980

ctgcgcctga cagtgcaagg caggggcacg gtggtggggc acggagggca gtcccgggtg   2040

ggcttcttcc agccccccgc gggaacgggg tacacggtgg gctgagtaca gtcattctgt   2100

tgggctgtgg agatagtgcc agggtgcggc ctgagatatt tttctacagc ttcatagagc   2160

aaccagtcaa aaccagagcg agaaccctca actgacatga aatactttaa aatgcacacg   2220

tagccacgca cagccagacg catcctgcca cccacacagc agcctccagg ataccagcaa   2280

atggatgcgg tgacaaatgg cagcttagct acaaatgcct gtcagtcgga gagaatgggg   2340

tgagcagcca ccattccacc agctggcccg gccacgtctc gaagttgcgc cttcccgagc   2400

acacataaaa gcacaaagac agagacgcag agagagagag agagccacgg agaggaaaag   2460

cagatgcagg ggtggggagc gcagctcggc ggaggctgcg tgtgccccgt ggcttttacc   2520
```

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```
aggcctgctc tgcctggctc gatgtctgct tcttcccagc ctgggatcct tcgtgcttca   2580

aggcctgggg agcctgtcct tccatgccct tgtcgaggga aagagaccca gaaaggacac   2640

aacccgtcag agacctggga gcaggggcaa tgaccgtttg actgtttgtg gcttgggcct   2700

ctgacatgac ttatgtgtgt gtgtgttttt ggggtgggga gggagggaga gaagaggggg   2760

ctaaatttga tgctttaact gatctccaac agttgacagg tcatccttgc cagttgtata   2820

actgaaaaag gacttttcta ccaggtatga ccttttaagt gaaaatctga attgttctaa   2880

atggaaagaa aaaaagttgc aatctgtgcc cttcattggg gacattcctc taggactggt   2940

ttggggacgg gtgggaatga cccctaggca aggggatgag accgcaggag gaaatggcgg   3000

ggaggtggca ttcttgaact gctgaggatg gggggtgtcc cctcagcgga ggccaaggga   3060

ggggagcagc ctagttggtc ttggagagat ggggaaggct ttcagctgat ttgcagaagt   3120

tgcccatgtg ggcccaacca tcagggctgg ccgtggacgt ggcccctgcc cactcacctg   3180

cccgcctgcc cgcccgcccg catagcactt gcagacctgc ctgaacgcac atgacatagc   3240

acttgccgat ctgcgtgtgc ccagaagtgg cccttggccg agcgccgaac tcgctcgccc   3300

tctagatgtc caagtgccac gtgaactatg caatttaaag ggttgaccca cactagacga   3360

aactggactc gtacgactct ttttatattt tttatacttg aaatgaaatc ctttgcttct   3420

tttttaagcg aatgattgct tttaatgttt gcactgattt agttgcatga ttagtcagaa   3480

actgccattt gaaaaaaaag ttatttttat agcagc                             3516
```

```
<210> SEQ ID NO 55
<211> LENGTH: 426
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

Met Pro Leu Leu Trp Leu Arg Gly Phe Leu Leu Ala Ser Cys Trp Ile
1               5                   10                  15

Ile Val Arg Ser Ser Pro Thr Pro Gly Ser Glu Gly His Ser Ala Ala
            20                  25                  30

Pro Asp Cys Pro Ser Cys Ala Leu Ala Ala Leu Pro Lys Asp Val Pro
        35                  40                  45

Asn Ser Gln Pro Glu Met Val Glu Ala Val Lys Lys His Ile Leu Asn
    50                  55                  60

Met Leu His Leu Lys Lys Arg Pro Asp Val Thr Gln Pro Val Pro Lys
65                  70                  75                  80

Ala Ala Leu Leu Asn Ala Ile Arg Lys Leu His Val Gly Lys Val Gly
                85                  90                  95

Glu Asn Gly Tyr Val Glu Ile Glu Asp Asp Ile Gly Arg Arg Ala Glu
            100                 105                 110

Met Asn Glu Leu Met Glu Gln Thr Ser Glu Ile Ile Thr Phe Ala Glu
        115                 120                 125

Ser Gly Thr Ala Arg Lys Thr Leu His Phe Glu Ile Ser Lys Glu Gly
    130                 135                 140

Ser Asp Leu Ser Val Val Glu Arg Ala Glu Val Trp Leu Phe Leu Lys
145                 150                 155                 160

Val Pro Lys Ala Asn Arg Thr Arg Thr Lys Val Thr Ile Arg Leu Phe
                165                 170                 175
```

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```
Gln Gln Gln Lys His Pro Gln Gly Ser Leu Asp Thr Gly Glu Glu Ala
            180                 185                 190

Glu Glu Val Gly Leu Lys Gly Glu Arg Ser Glu Leu Leu Leu Ser Glu
        195                 200                 205

Lys Val Val Asp Ala Arg Lys Ser Thr Trp His Val Phe Pro Val Ser
    210                 215                 220

Ser Ser Ile Gln Arg Leu Leu Asp Gln Gly Lys Ser Ser Leu Asp Val
225                 230                 235                 240

Arg Ile Ala Cys Glu Gln Cys Gln Glu Ser Gly Ala Ser Leu Val Leu
                245                 250                 255

Leu Gly Lys Lys Lys Lys Lys Glu Glu Glu Gly Glu Gly Lys Lys Lys
            260                 265                 270

Gly Gly Gly Glu Gly Gly Ala Gly Ala Asp Glu Glu Lys Glu Gln Ser
        275                 280                 285

His Arg Pro Phe Leu Met Leu Gln Ala Arg Gln Ser Glu Asp His Pro
    290                 295                 300

His Arg Arg Arg Arg Arg Gly Leu Glu Cys Asp Gly Lys Val Asn Ile
305                 310                 315                 320

Cys Cys Lys Lys Gln Phe Phe Val Ser Phe Lys Asp Ile Gly Trp Asn
                325                 330                 335

Asp Trp Ile Ile Ala Pro Ser Gly Tyr His Ala Asn Tyr Cys Glu Gly
            340                 345                 350

Glu Cys Pro Ser His Ile Ala Gly Thr Ser Gly Ser Ser Leu Ser Phe
        355                 360                 365

His Ser Thr Val Ile Asn His Tyr Arg Met Arg Gly His Ser Pro Phe
    370                 375                 380

Ala Asn Leu Lys Ser Cys Cys Val Pro Thr Lys Leu Arg Pro Met Ser
385                 390                 395                 400

Met Leu Tyr Tyr Asp Asp Gly Gln Asn Ile Ile Lys Lys Asp Ile Gln
                405                 410                 415

Asn Met Ile Val Glu Glu Cys Gly Cys Ser
            420                 425
```

<210> SEQ ID NO 56
<211> LENGTH: 2175
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

```
agtacagtat aaaacttcac agtgccaata ccatgaagag gagctcagac agctcttacc     60

acatgataca agagccggct ggtggaagag tggggaccag aaagagaatt tgctgaagag    120

gagaaggaaa aaaaaaacac caaaaaaaaa aataaaaaaa tccacacaca caaaaaaacc    180

tgcgcgtgag gggggaggaa aagcagggcc ttttaaaaag gcaatcacaa caacttttgc    240

tgccaggatg cccttgcttt ggctgagagg atttctgttg gcaagttgct ggattatagt    300

gaggagttcc cccaccccag gatccgaggg gcacagcgcg gcccccgact gtccgtcctg    360

tgcgctggcc gccctcccaa aggatgtacc caactctcag ccagagatgg tggaggccgt    420

caagaagcac attttaaaca tgctgcactt gaagaagaga cccgatgtca cccagccggt    480

acccaaggcg gcgcttctga acgcgatcag aaagcttcat gtgggcaaag tcggggagaa    540

cgggtatgtg gagatagagg atgacattgg aaggagggca gaaatgaatg aacttatgga    600
```

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```
gcagacctcg gagatcatca cgtttgccga gtcaggaaca gccaggaaga cgctgcactt    660

cgagatttcc aaggaaggca gtgacctgtc agtggtggag cgtgcagaag tctggctctt    720

cctaaaagtc cccaaggcca acaggaccag gaccaaagtc accatccgcc tcttccagca    780

gcagaagcac ccgcagggca gcttggacac aggggaagag gccgaggaag tgggcttaaa    840

gggggagagg agtgaactgt tgctctctga aaaagtagta gacgctcgga agagcacctg    900

gcatgtcttc cctgtctcca gcagcatcca gcggttgctg gaccagggca agagctccct    960

ggacgttcgg attgcctgtg agcagtgcca ggagagtggc gccagcttgg ttctcctggg   1020

caagaagaag aagaaagaag aggaggggga agggaaaaag aagggcggag gtgaaggtgg   1080

ggcaggagca gatgaggaaa aggagcagtc gcacagacct ttcctcatgc tgcaggcccg   1140

gcagtctgaa gaccaccctc atcgccggcg tcggcggggc ttggagtgtg atggcaaggt   1200

caacatctgc tgtaagaaac agttctttgt cagtttcaag gacatcggct ggaatgactg   1260

gatcattgct ccctctggct atcatgccaa ctactgcgag ggtgagtgcc cgagccatat   1320

agcaggcacg tccgggtcct cactgtcctt ccactcaaca gtcatcaacc actaccgcat   1380

gcggggccat agcccctttg ccaacctcaa atcgtgctgt gtgcccacca agctgagacc   1440

catgtccatg ttgtactatg atgatggtca aaacatcatc aaaaaggaca ttcagaacat   1500

gatcgtggag gagtgtgggt gctcatagag ttgcccagcc caggggggaaa gggagcaaga   1560

gttgtccaga gaagacagtg gcaaaatgaa gaaattttta aggtttctga gttaaccaga   1620

aaaatagaaa ttaaaaacaa aacaaaaaaa aaaacaaaaa aaaacaaaag taaattaaaa   1680

acaaaacctg atgaaacaga tgaaggaaga tgtggaaaaa atccttagcc agggctcaga   1740

gatgaagcag tgaaagagac aggaattggg agggaaaggg agaatggtgt accctttatt   1800

tcttctgaaa tcacactgat gacatcagtt gtttaaacgg ggtattgtcc tttcccccct   1860

tgaggttccc ttgtgagcct tgaatcaacc aatctagtct gcagtagtgt ggactagaac   1920

aacccaaata gcatctagaa agccatgagt ttgaaagggc ccatcacagg cactttccta   1980

cccaattacc caggtcataa ggtatgtctg tgtgacactt atctctgtgt atatcagcat   2040

acacacacac acacacacac acacacacac acacaggcat ttccacacat tacatatata   2100

cacatactgg taaaagaaca atcgtgtgca ggtggtcaca cttccttttt ctgtaccact   2160

tttgcaacaa aacaa                                                    2175


<210> SEQ ID NO 57
<211> LENGTH: 14507
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

Met Leu Lys Pro Ser Gly Leu Pro Gly Ser Ser Ser Pro Thr Arg Ser
1               5                   10                  15

Leu Met Thr Gly Ser Arg Ser Thr Lys Ala Thr Pro Glu Met Asp Ser
            20                  25                  30

Gly Leu Thr Gly Ala Thr Leu Ser Pro Lys Thr Ser Thr Gly Ala Ile
        35                  40                  45

Val Val Thr Glu His Thr Leu Pro Phe Thr Ser Pro Asp Lys Thr Leu
    50                  55                  60

Ala Ser Pro Thr Ser Ser Val Val Gly Arg Thr Thr Gln Ser Leu Gly
65                  70                  75                  80
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Val Met Ser Ser Ala Leu Pro Glu Ser Thr Ser Arg Gly Met Thr His
                85                  90                  95

Ser Glu Gln Arg Thr Ser Pro Ser Leu Ser Pro Gln Val Asn Gly Thr
            100                 105                 110

Pro Ser Arg Asn Tyr Pro Ala Thr Ser Met Val Ser Gly Leu Ser Ser
        115                 120                 125

Pro Arg Thr Arg Thr Ser Ser Thr Glu Gly Asn Phe Thr Lys Glu Ala
    130                 135                 140

Ser Thr Tyr Thr Leu Thr Val Glu Thr Thr Ser Gly Pro Val Thr Glu
145                 150                 155                 160

Lys Tyr Thr Val Pro Thr Glu Thr Ser Thr Thr Glu Gly Asp Ser Thr
                165                 170                 175

Glu Thr Pro Trp Asp Thr Arg Tyr Ile Pro Val Lys Ile Thr Ser Pro
            180                 185                 190

Met Lys Thr Phe Ala Asp Ser Thr Ala Ser Lys Glu Asn Ala Pro Val
        195                 200                 205

Ser Met Thr Pro Ala Glu Thr Thr Val Thr Asp Ser His Thr Pro Gly
    210                 215                 220

Arg Thr Asn Pro Ser Phe Gly Thr Leu Tyr Ser Ser Phe Leu Asp Leu
225                 230                 235                 240

Ser Pro Lys Gly Thr Pro Asn Ser Arg Gly Glu Thr Ser Leu Glu Leu
                245                 250                 255

Ile Leu Ser Thr Thr Gly Tyr Pro Phe Ser Ser Pro Glu Pro Gly Ser
            260                 265                 270

Ala Gly His Ser Arg Ile Ser Thr Ser Ala Pro Leu Ser Ser Ser Ala
        275                 280                 285

Ser Val Leu Asp Asn Lys Ile Ser Glu Thr Ser Ile Phe Ser Gly Gln
    290                 295                 300

Ser Leu Thr Ser Pro Leu Ser Pro Gly Val Pro Glu Ala Arg Ala Ser
305                 310                 315                 320

Thr Met Pro Asn Ser Ala Ile Pro Phe Ser Met Thr Leu Ser Asn Ala
                325                 330                 335

Glu Thr Ser Ala Glu Arg Val Arg Ser Thr Ile Ser Ser Leu Gly Thr
            340                 345                 350

Pro Ser Ile Ser Thr Lys Gln Thr Ala Glu Thr Ile Leu Thr Phe His
        355                 360                 365

Ala Phe Ala Glu Thr Met Asp Ile Pro Ser Thr His Ile Ala Lys Thr
    370                 375                 380

Leu Ala Ser Glu Trp Leu Gly Ser Pro Gly Thr Leu Gly Gly Thr Ser
385                 390                 395                 400

Thr Ser Ala Leu Thr Thr Thr Ser Pro Ser Thr Thr Leu Val Ser Glu
                405                 410                 415

Glu Thr Asn Thr His His Ser Thr Ser Gly Lys Glu Thr Glu Gly Thr
            420                 425                 430

Leu Asn Thr Ser Met Thr Pro Leu Glu Thr Ser Ala Pro Gly Glu Glu
        435                 440                 445

Ser Glu Met Thr Ala Thr Leu Val Pro Thr Leu Gly Phe Thr Thr Leu
    450                 455                 460

Asp Ser Lys Ile Arg Ser Pro Ser Gln Val Ser Ser Ser His Pro Thr
465                 470                 475                 480
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Arg Glu Leu Arg Thr Thr Gly Ser Thr Ser Gly Arg Gln Ser Ser Ser
                485                 490                 495

Thr Ala Ala His Gly Ser Ser Asp Ile Leu Arg Ala Thr Thr Ser Ser
            500                 505                 510

Thr Ser Lys Ala Ser Ser Trp Thr Ser Glu Ser Thr Ala Gln Gln Phe
        515                 520                 525

Ser Glu Pro Gln His Thr Gln Trp Val Glu Thr Ser Pro Ser Met Lys
    530                 535                 540

Thr Glu Arg Pro Pro Ala Ser Thr Ser Val Ala Ala Pro Ile Thr Thr
545                 550                 555                 560

Ser Val Pro Ser Val Val Ser Gly Phe Thr Thr Leu Lys Thr Ser Ser
                565                 570                 575

Thr Lys Gly Ile Trp Leu Glu Glu Thr Ser Ala Asp Thr Leu Ile Gly
            580                 585                 590

Glu Ser Thr Ala Gly Pro Thr Thr His Gln Phe Ala Val Pro Thr Gly
        595                 600                 605

Ile Ser Met Thr Gly Gly Ser Ser Thr Arg Gly Ser Gln Gly Thr Thr
    610                 615                 620

His Leu Leu Thr Arg Ala Thr Ala Ser Ser Glu Thr Ser Ala Asp Leu
625                 630                 635                 640

Thr Leu Ala Thr Asn Gly Val Pro Val Ser Val Ser Pro Ala Val Ser
                645                 650                 655

Lys Thr Ala Ala Gly Ser Ser Pro Pro Gly Gly Thr Lys Pro Ser Tyr
            660                 665                 670

Thr Met Val Ser Ser Val Ile Pro Glu Thr Ser Ser Leu Gln Ser Ser
        675                 680                 685

Ala Phe Arg Glu Gly Thr Ser Leu Gly Leu Thr Pro Leu Asn Thr Arg
    690                 695                 700

His Pro Phe Ser Ser Pro Glu Pro Asp Ser Ala Gly His Thr Lys Ile
705                 710                 715                 720

Ser Thr Ser Ile Pro Leu Leu Ser Ser Ala Ser Val Leu Glu Asp Lys
                725                 730                 735

Val Ser Ala Thr Ser Thr Phe Ser His His Lys Ala Thr Ser Ser Ile
            740                 745                 750

Thr Thr Gly Thr Pro Glu Ile Ser Thr Lys Thr Lys Pro Ser Ser Ala
        755                 760                 765

Val Leu Ser Ser Met Thr Leu Ser Asn Ala Ala Thr Ser Pro Glu Arg
    770                 775                 780

Val Arg Asn Ala Thr Ser Pro Leu Thr His Pro Ser Pro Ser Gly Glu
785                 790                 795                 800

Glu Thr Ala Gly Ser Val Leu Thr Leu Ser Thr Ser Ala Glu Thr Thr
                805                 810                 815

Asp Ser Pro Asn Ile His Pro Thr Gly Thr Leu Thr Ser Glu Ser Ser
            820                 825                 830

Glu Ser Pro Ser Thr Leu Ser Leu Pro Ser Val Ser Gly Val Lys Thr
        835                 840                 845

Thr Phe Ser Ser Ser Thr Pro Ser Thr His Leu Phe Thr Ser Gly Glu
    850                 855                 860

Glu Thr Glu Glu Thr Ser Asn Pro Ser Val Ser Gln Pro Glu Thr Ser
865                 870                 875                 880

Val Ser Arg Val Arg Thr Thr Leu Ala Ser Thr Ser Val Pro Thr Pro
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                885                 890                 895

Val Phe Pro Thr Met Asp Thr Trp Pro Thr Arg Ser Ala Gln Phe Ser
            900                 905                 910

Ser Ser His Leu Val Ser Glu Leu Arg Ala Thr Ser Ser Thr Ser Val
        915                 920                 925

Thr Asn Ser Thr Gly Ser Ala Leu Pro Lys Ile Ser His Leu Thr Gly
    930                 935                 940

Thr Ala Thr Met Ser Gln Thr Asn Arg Asp Thr Phe Asn Asp Ser Ala
945                 950                 955                 960

Ala Pro Gln Ser Thr Thr Trp Pro Glu Thr Ser Pro Arg Phe Lys Thr
                965                 970                 975

Gly Leu Pro Ser Ala Thr Thr Thr Val Ser Thr Ser Ala Thr Ser Leu
            980                 985                 990

Ser Ala Thr Val Met Val Ser Lys Phe Thr Ser Pro Ala Thr Ser Ser
        995                 1000                1005

Met Glu Ala Thr Ser Ile Arg Glu Pro Ser Thr Thr Ile Leu Thr Thr
    1010                1015                1020

Glu Thr Thr Asn Gly Pro Gly Ser Met Ala Val Ala Ser Thr Asn Ile
1025                1030                1035                1040

Pro Ile Gly Lys Gly Tyr Ile Thr Glu Gly Arg Leu Asp Thr Ser His
                1045                1050                1055

Leu Pro Ile Gly Thr Thr Ala Ser Ser Glu Thr Ser Met Asp Phe Thr
            1060                1065                1070

Met Ala Lys Glu Ser Val Ser Met Ser Val Ser Pro Ser Gln Ser Met
        1075                1080                1085

Asp Ala Ala Gly Ser Ser Thr Pro Gly Arg Thr Ser Gln Phe Val Asp
    1090                1095                1100

Thr Phe Ser Asp Asp Val Tyr His Leu Thr Ser Arg Glu Ile Thr Ile
1105                1110                1115                1120

Pro Arg Asp Gly Thr Ser Ser Ala Leu Thr Pro Gln Met Thr Ala Thr
                1125                1130                1135

His Pro Pro Ser Pro Asp Pro Gly Ser Ala Arg Ser Thr Trp Leu Gly
            1140                1145                1150

Ile Leu Ser Ser Ser Pro Ser Ser Pro Thr Pro Lys Val Thr Met Ser
        1155                1160                1165

Ser Thr Phe Ser Thr Gln Arg Val Thr Thr Ser Met Ile Met Asp Thr
    1170                1175                1180

Val Glu Thr Ser Arg Trp Asn Met Pro Asn Leu Pro Ser Thr Thr Ser
1185                1190                1195                1200

Leu Thr Pro Ser Asn Ile Pro Thr Ser Gly Ala Ile Gly Lys Ser Thr
                1205                1210                1215

Leu Val Pro Leu Asp Thr Pro Ser Pro Ala Thr Ser Leu Glu Ala Ser
            1220                1225                1230

Glu Gly Gly Leu Pro Thr Leu Ser Thr Tyr Pro Glu Ser Thr Asn Thr
        1235                1240                1245

Pro Ser Ile His Leu Gly Ala His Ala Ser Ser Glu Ser Pro Ser Thr
    1250                1255                1260

Ile Lys Leu Thr Met Ala Ser Val Val Lys Pro Gly Ser Tyr Thr Pro
1265                1270                1275                1280

Leu Thr Phe Pro Ser Ile Glu Thr His Ile His Val Ser Thr Ala Arg
                1285                1290                1295
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Met Ala Tyr Ser Ser Gly Ser Ser Pro Glu Met Thr Ala Pro Gly Glu
            1300                1305                1310

Thr Asn Thr Gly Ser Thr Trp Asp Pro Thr Thr Tyr Ile Thr Thr Thr
        1315                1320                1325

Asp Pro Lys Asp Thr Ser Ser Ala Gln Val Ser Thr Pro His Ser Val
    1330                1335                1340

Arg Thr Leu Arg Thr Thr Glu Asn His Pro Lys Thr Glu Ser Ala Thr
1345                1350                1355                1360

Pro Ala Ala Tyr Ser Gly Ser Pro Lys Ile Ser Ser Ser Pro Asn Leu
                1365                1370                1375

Thr Ser Pro Ala Thr Lys Ala Trp Thr Ile Thr Asp Thr Thr Glu His
            1380                1385                1390

Ser Thr Gln Leu His Tyr Thr Lys Leu Ala Glu Lys Ser Ser Gly Phe
        1395                1400                1405

Glu Thr Gln Ser Ala Pro Gly Pro Val Ser Val Val Ile Pro Thr Ser
    1410                1415                1420

Pro Thr Ile Gly Ser Ser Thr Leu Glu Leu Thr Ser Asp Val Pro Gly
1425                1430                1435                1440

Glu Pro Leu Val Leu Ala Pro Ser Glu Gln Thr Thr Ile Thr Leu Pro
                1445                1450                1455

Met Ala Thr Trp Leu Ser Thr Ser Leu Thr Glu Glu Met Ala Ser Thr
            1460                1465                1470

Asp Leu Asp Ile Ser Ser Pro Ser Ser Pro Met Ser Thr Phe Ala Ile
        1475                1480                1485

Phe Pro Pro Met Ser Thr Pro Ser His Glu Leu Ser Lys Ser Glu Ala
    1490                1495                1500

Asp Thr Ser Ala Ile Arg Asn Thr Asp Ser Thr Thr Leu Asp Gln His
1505                1510                1515                1520

Leu Gly Ile Arg Ser Leu Gly Arg Thr Gly Asp Leu Thr Thr Val Pro
                1525                1530                1535

Ile Thr Pro Leu Thr Thr Thr Trp Thr Ser Val Ile Glu His Ser Thr
            1540                1545                1550

Gln Ala Gln Asp Thr Leu Ser Ala Thr Met Ser Pro Thr His Val Thr
        1555                1560                1565

Gln Ser Leu Lys Asp Gln Thr Ser Ile Pro Ala Ser Ala Ser Pro Ser
    1570                1575                1580

His Leu Thr Glu Val Tyr Pro Glu Leu Gly Thr Gln Gly Arg Ser Ser
1585                1590                1595                1600

Ser Glu Ala Thr Thr Phe Trp Lys Pro Ser Thr Asp Thr Leu Ser Arg
                1605                1610                1615

Glu Ile Glu Thr Gly Pro Thr Asn Ile Gln Ser Thr Pro Pro Met Asp
            1620                1625                1630

Asn Thr Thr Thr Gly Ser Ser Ser Ser Gly Val Thr Leu Gly Ile Ala
        1635                1640                1645

His Leu Pro Ile Gly Thr Ser Ser Pro Ala Glu Thr Ser Thr Asn Met
    1650                1655                1660

Ala Leu Glu Arg Arg Ser Ser Thr Ala Thr Val Ser Met Ala Gly Thr
1665                1670                1675                1680

Met Gly Leu Leu Val Thr Ser Ala Pro Gly Arg Ser Ile Ser Gln Ser
                1685                1690                1695
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Leu Gly Arg Val Ser Ser Val Leu Ser Glu Ser Thr Thr Glu Gly Val
            1700                1705                1710

Thr Asp Ser Ser Lys Gly Ser Ser Pro Arg Leu Asn Thr Gln Gly Asn
        1715                1720                1725

Thr Ala Leu Ser Ser Ser Leu Glu Pro Ser Tyr Ala Glu Gly Ser Gln
    1730                1735                1740

Met Ser Thr Ser Ile Pro Leu Thr Ser Ser Pro Thr Thr Pro Asp Val
1745                1750                1755                1760

Glu Phe Ile Gly Gly Ser Thr Phe Trp Thr Lys Glu Val Thr Thr Val
                1765                1770                1775

Met Thr Ser Asp Ile Ser Lys Ser Ser Ala Arg Thr Glu Ser Ser Ser
            1780                1785                1790

Ala Thr Leu Met Ser Thr Ala Leu Gly Ser Thr Glu Asn Thr Gly Lys
        1795                1800                1805

Glu Lys Leu Arg Thr Ala Ser Met Asp Leu Pro Ser Pro Thr Pro Ser
    1810                1815                1820

Met Glu Val Thr Pro Trp Ile Ser Leu Thr Leu Ser Asn Ala Pro Asn
1825                1830                1835                1840

Thr Thr Asp Ser Leu Asp Leu Ser His Gly Val His Thr Ser Ser Ala
                1845                1850                1855

Gly Thr Leu Ala Thr Asp Arg Ser Leu Asn Thr Gly Val Thr Arg Ala
            1860                1865                1870

Ser Arg Leu Glu Asn Gly Ser Asp Thr Ser Ser Lys Ser Leu Ser Met
        1875                1880                1885

Gly Asn Ser Thr His Thr Ser Met Thr Tyr Thr Glu Lys Ser Glu Val
    1890                1895                1900

Ser Ser Ser Ile His Pro Arg Pro Glu Thr Ser Ala Pro Gly Ala Glu
1905                1910                1915                1920

Thr Thr Leu Thr Ser Thr Pro Gly Asn Arg Ala Ile Ser Leu Thr Leu
                1925                1930                1935

Pro Phe Ser Ser Ile Pro Val Glu Glu Val Ile Ser Thr Gly Ile Thr
            1940                1945                1950

Ser Gly Pro Asp Ile Asn Ser Ala Pro Met Thr His Ser Pro Ile Thr
        1955                1960                1965

Pro Pro Thr Ile Val Trp Thr Ser Thr Gly Thr Ile Glu Gln Ser Thr
    1970                1975                1980

Gln Pro Leu His Ala Val Ser Ser Glu Lys Val Ser Val Gln Thr Gln
1985                1990                1995                2000

Ser Thr Pro Tyr Val Asn Ser Val Ala Val Ser Ala Ser Pro Thr His
                2005                2010                2015

Glu Asn Ser Val Ser Ser Gly Ser Ser Thr Ser Ser Pro Tyr Ser Ser
            2020                2025                2030

Ala Ser Leu Glu Ser Leu Asp Ser Thr Ile Ser Arg Arg Asn Ala Ile
        2035                2040                2045

Thr Ser Trp Leu Trp Asp Leu Thr Thr Ser Leu Pro Thr Thr Thr Trp
    2050                2055                2060

Pro Ser Thr Ser Leu Ser Glu Ala Leu Ser Ser Gly His Ser Gly Val
2065                2070                2075                2080

Ser Asn Pro Ser Ser Thr Thr Thr Glu Phe Pro Leu Phe Ser Ala Ala
                2085                2090                2095

Ser Thr Ser Ala Ala Lys Gln Arg Asn Pro Glu Thr Glu Thr His Gly
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            2100                2105                2110

Pro Gln Asn Thr Ala Ala Ser Thr Leu Asn Thr Asp Ala Ser Ser Val
        2115                2120                2125

Thr Gly Leu Ser Glu Thr Pro Val Gly Ala Ser Ile Ser Ser Glu Val
    2130                2135                2140

Pro Leu Pro Met Ala Ile Thr Ser Arg Ser Asp Val Ser Gly Leu Thr
2145                2150                2155                2160

Ser Glu Ser Thr Ala Asn Pro Ser Leu Gly Thr Ala Ser Ser Ala Gly
                2165                2170                2175

Thr Lys Leu Thr Arg Thr Ile Ser Leu Pro Thr Ser Glu Ser Leu Val
            2180                2185                2190

Ser Phe Arg Met Asn Lys Asp Pro Trp Thr Val Ser Ile Pro Leu Gly
        2195                2200                2205

Ser His Pro Thr Thr Asn Thr Glu Thr Ser Ile Pro Val Asn Ser Ala
    2210                2215                2220

Gly Pro Pro Gly Leu Ser Thr Val Ala Ser Asp Val Ile Asp Thr Pro
2225                2230                2235                2240

Ser Asp Gly Ala Glu Ser Ile Pro Thr Val Ser Phe Ser Pro Ser Pro
                2245                2250                2255

Asp Thr Glu Val Thr Thr Ile Ser His Phe Pro Glu Lys Thr Thr His
            2260                2265                2270

Ser Phe Arg Thr Ile Ser Ser Leu Thr His Glu Leu Thr Ser Arg Val
        2275                2280                2285

Thr Pro Ile Pro Gly Asp Trp Met Ser Ser Ala Met Ser Thr Lys Pro
    2290                2295                2300

Thr Gly Ala Ser Pro Ser Ile Thr Leu Gly Glu Arg Arg Thr Ile Thr
2305                2310                2315                2320

Ser Ala Ala Pro Thr Thr Ser Pro Ile Val Leu Thr Ala Ser Phe Thr
                2325                2330                2335

Glu Thr Ser Thr Val Ser Leu Asp Asn Glu Thr Thr Val Lys Thr Ser
            2340                2345                2350

Asp Ile Leu Asp Ala Arg Lys Thr Asn Glu Leu Pro Ser Asp Ser Ser
        2355                2360                2365

Ser Ser Ser Asp Leu Ile Asn Thr Ser Ile Ala Ser Ser Thr Met Asp
    2370                2375                2380

Val Thr Lys Thr Ala Ser Ile Ser Pro Thr Ser Ile Ser Gly Met Thr
2385                2390                2395                2400

Ala Ser Ser Ser Pro Ser Leu Phe Ser Ser Asp Arg Pro Gln Val Pro
                2405                2410                2415

Thr Ser Thr Thr Glu Thr Asn Thr Ala Thr Ser Pro Ser Val Ser Ser
            2420                2425                2430

Asn Thr Tyr Ser Leu Asp Gly Gly Ser Asn Val Gly Gly Thr Pro Ser
        2435                2440                2445

Thr Leu Pro Pro Phe Thr Ile Thr His Pro Val Glu Thr Ser Ser Ala
    2450                2455                2460

Leu Leu Ala Trp Ser Arg Pro Val Arg Thr Phe Ser Thr Met Val Ser
2465                2470                2475                2480

Thr Asp Thr Ala Ser Gly Glu Asn Pro Thr Ser Ser Asn Ser Val Val
                2485                2490                2495

Thr Ser Val Pro Ala Pro Gly Thr Trp Thr Ser Val Gly Ser Thr Thr
            2500                2505                2510
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Asp Leu Pro Ala Met Gly Phe Leu Lys Thr Ser Pro Ala Gly Glu Ala
        2515                2520                2525

His Ser Leu Leu Ala Ser Thr Ile Glu Pro Ala Thr Ala Phe Thr Pro
    2530                2535                2540

His Leu Ser Ala Ala Val Val Thr Gly Ser Ser Ala Thr Ser Glu Ala
2545                2550                2555                2560

Ser Leu Leu Thr Thr Ser Glu Ser Lys Ala Ile His Ser Ser Pro Gln
                2565                2570                2575

Thr Pro Thr Thr Pro Thr Ser Gly Ala Asn Trp Glu Thr Ser Ala Thr
            2580                2585                2590

Pro Glu Ser Leu Leu Val Val Thr Glu Thr Ser Asp Thr Thr Leu Thr
        2595                2600                2605

Ser Lys Ile Leu Val Thr Asp Thr Ile Leu Phe Ser Thr Val Ser Thr
    2610                2615                2620

Pro Pro Ser Lys Phe Pro Ser Thr Gly Thr Leu Ser Gly Ala Ser Phe
2625                2630                2635                2640

Pro Thr Leu Leu Pro Asp Thr Pro Ala Ile Pro Leu Thr Ala Thr Glu
                2645                2650                2655

Pro Thr Ser Ser Leu Ala Thr Ser Phe Asp Ser Thr Pro Leu Val Thr
            2660                2665                2670

Ile Ala Ser Asp Ser Leu Gly Thr Val Pro Glu Thr Thr Leu Thr Met
        2675                2680                2685

Ser Glu Thr Ser Asn Gly Asp Ala Leu Val Leu Lys Thr Val Ser Asn
    2690                2695                2700

Pro Asp Arg Ser Ile Pro Gly Ile Thr Ile Gln Gly Val Thr Glu Ser
2705                2710                2715                2720

Pro Leu His Pro Ser Ser Thr Ser Pro Ser Lys Ile Val Ala Pro Arg
                2725                2730                2735

Asn Thr Thr Tyr Glu Gly Ser Ile Thr Val Ala Leu Ser Thr Leu Pro
            2740                2745                2750

Ala Gly Thr Thr Gly Ser Leu Val Phe Ser Gln Ser Ser Glu Asn Ser
        2755                2760                2765

Glu Thr Thr Ala Leu Val Asp Ser Ser Ala Gly Leu Glu Arg Ala Ser
    2770                2775                2780

Val Met Pro Leu Thr Thr Gly Ser Gln Gly Met Ala Ser Ser Gly Gly
2785                2790                2795                2800

Ile Arg Ser Gly Ser Thr His Ser Thr Gly Thr Lys Thr Phe Ser Ser
                2805                2810                2815

Leu Pro Leu Thr Met Asn Pro Gly Glu Val Thr Ala Met Ser Glu Ile
            2820                2825                2830

Thr Thr Asn Arg Leu Thr Ala Thr Gln Ser Thr Ala Pro Lys Gly Ile
        2835                2840                2845

Pro Val Lys Pro Thr Ser Ala Glu Ser Gly Leu Leu Thr Pro Val Ser
    2850                2855                2860

Ala Ser Ser Ser Pro Ser Lys Ala Phe Ala Ser Leu Thr Thr Ala Pro
2865                2870                2875                2880

Pro Thr Trp Gly Ile Pro Gln Ser Thr Leu Thr Phe Glu Phe Ser Glu
                2885                2890                2895

Val Pro Ser Leu Asp Thr Lys Ser Ala Ser Leu Pro Thr Pro Gly Gln
            2900                2905                2910
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Ser Leu Asn Thr Ile Pro Asp Ser Asp Ala Ser Thr Ala Ser Ser Ser
        2915                2920                2925

Leu Ser Lys Ser Pro Glu Lys Asn Pro Arg Ala Arg Met Met Thr Ser
    2930                2935                2940

Thr Lys Ala Ile Ser Ala Ser Ser Phe Gln Ser Thr Gly Phe Thr Glu
2945                2950                2955                2960

Thr Pro Glu Gly Ser Ala Ser Pro Ser Met Ala Gly His Glu Pro Arg
                2965                2970                2975

Val Pro Thr Ser Gly Thr Gly Asp Pro Arg Tyr Ala Ser Glu Ser Met
            2980                2985                2990

Ser Tyr Pro Asp Pro Ser Lys Ala Ser Ser Ala Met Thr Ser Thr Ser
        2995                3000                3005

Leu Ala Ser Lys Leu Thr Thr Leu Phe Ser Thr Gly Gln Ala Ala Arg
    3010                3015                3020

Ser Gly Ser Ser Ser Ser Pro Ile Ser Leu Ser Thr Glu Lys Glu Thr
3025                3030                3035                3040

Ser Phe Leu Ser Pro Thr Ala Ser Thr Ser Arg Lys Thr Ser Leu Phe
                3045                3050                3055

Leu Gly Pro Ser Met Ala Arg Gln Pro Asn Ile Leu Val His Leu Gln
            3060                3065                3070

Thr Ser Ala Leu Thr Leu Ser Pro Thr Ser Thr Leu Asn Met Ser Gln
        3075                3080                3085

Glu Glu Pro Pro Glu Leu Thr Ser Ser Gln Thr Ile Ala Glu Glu Glu
    3090                3095                3100

Gly Thr Thr Ala Glu Thr Gln Thr Leu Thr Phe Thr Pro Ser Glu Thr
3105                3110                3115                3120

Pro Thr Ser Leu Leu Pro Val Ser Ser Pro Thr Glu Pro Thr Ala Arg
                3125                3130                3135

Arg Lys Ser Ser Pro Glu Thr Trp Ala Ser Ser Ile Ser Val Pro Ala
            3140                3145                3150

Lys Thr Ser Leu Val Glu Thr Thr Asp Gly Thr Leu Val Thr Thr Ile
        3155                3160                3165

Lys Met Ser Ser Gln Ala Ala Gln Gly Asn Ser Thr Trp Pro Ala Pro
    3170                3175                3180

Ala Glu Glu Thr Gly Ser Ser Pro Ala Gly Thr Ser Pro Gly Ser Pro
3185                3190                3195                3200

Glu Met Ser Thr Thr Leu Lys Ile Met Ser Ser Lys Glu Pro Ser Ile
                3205                3210                3215

Ser Pro Glu Ile Arg Ser Thr Val Arg Asn Ser Pro Trp Lys Thr Pro
            3220                3225                3230

Glu Thr Thr Val Pro Met Glu Thr Thr Val Glu Pro Val Thr Leu Gln
        3235                3240                3245

Ser Thr Ala Leu Gly Ser Gly Ser Thr Ser Ile Ser His Leu Pro Thr
    3250                3255                3260

Gly Thr Thr Ser Pro Thr Lys Ser Pro Thr Glu Asn Met Leu Ala Thr
3265                3270                3275                3280

Glu Arg Val Ser Leu Ser Pro Ser Pro Pro Glu Ala Trp Thr Asn Leu
                3285                3290                3295

Tyr Ser Gly Thr Pro Gly Gly Thr Arg Gln Ser Leu Ala Thr Met Ser
            3300                3305                3310

Ser Val Ser Leu Glu Ser Pro Thr Ala Arg Ser Ile Thr Gly Thr Gly
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        3315                3320                3325

Gln Gln Ser Ser Pro Glu Leu Val Ser Lys Thr Thr Gly Met Glu Phe
    3330                3335                3340

Ser Met Trp His Gly Ser Thr Gly Gly Thr Thr Gly Asp Thr His Val
3345                3350                3355                3360

Ser Leu Ser Thr Ser Ser Asn Ile Leu Glu Asp Pro Val Thr Ser Pro
                3365                3370                3375

Asn Ser Val Ser Ser Leu Thr Asp Lys Ser Lys His Lys Thr Glu Thr
            3380                3385                3390

Trp Val Ser Thr Thr Ala Ile Pro Ser Thr Val Leu Asn Asn Lys Ile
        3395                3400                3405

Met Ala Ala Glu Gln Gln Thr Ser Arg Ser Val Asp Glu Ala Tyr Ser
    3410                3415                3420

Ser Thr Ser Ser Trp Ser Asp Gln Thr Ser Gly Ser Asp Ile Thr Leu
3425                3430                3435                3440

Gly Ala Ser Pro Asp Val Thr Asn Thr Leu Tyr Ile Thr Ser Thr Ala
                3445                3450                3455

Gln Thr Thr Ser Leu Val Ser Leu Pro Ser Gly Asp Gln Gly Ile Thr
            3460                3465                3470

Ser Leu Thr Asn Pro Ser Gly Gly Lys Thr Ser Ser Ala Ser Ser Val
        3475                3480                3485

Thr Ser Pro Ser Ile Gly Leu Glu Thr Leu Arg Ala Asn Val Ser Ala
    3490                3495                3500

Val Lys Ser Asp Ile Ala Pro Thr Ala Gly His Leu Ser Gln Thr Ser
3505                3510                3515                3520

Ser Pro Ala Glu Val Ser Ile Leu Asp Val Thr Thr Ala Pro Thr Pro
                3525                3530                3535

Gly Ile Ser Thr Thr Ile Thr Thr Met Gly Thr Asn Ser Ile Ser Thr
            3540                3545                3550

Thr Thr Pro Asn Pro Glu Val Gly Met Ser Thr Met Asp Ser Thr Pro
        3555                3560                3565

Ala Thr Glu Arg Arg Thr Thr Ser Thr Glu His Pro Ser Thr Trp Ser
    3570                3575                3580

Ser Thr Ala Ala Ser Asp Ser Trp Thr Val Thr Asp Met Thr Ser Asn
3585                3590                3595                3600

Leu Lys Val Ala Arg Ser Pro Gly Thr Ile Ser Thr Met His Thr Thr
                3605                3610                3615

Ser Phe Leu Ala Ser Ser Thr Glu Leu Asp Ser Met Ser Thr Pro His
            3620                3625                3630

Gly Arg Ile Thr Val Ile Gly Thr Ser Leu Val Thr Pro Ser Ser Asp
        3635                3640                3645

Ala Ser Ala Val Lys Thr Glu Thr Ser Thr Ser Glu Arg Thr Leu Ser
    3650                3655                3660

Pro Ser Asp Thr Thr Ala Ser Thr Pro Ile Ser Thr Phe Ser Arg Val
3665                3670                3675                3680

Gln Arg Met Ser Ile Ser Val Pro Asp Ile Leu Ser Thr Ser Trp Thr
                3685                3690                3695

Pro Ser Ser Thr Glu Ala Glu Asp Val Pro Val Ser Met Val Ser Thr
            3700                3705                3710

Asp His Ala Ser Thr Lys Thr Asp Pro Asn Thr Pro Leu Ser Thr Phe
        3715                3720                3725
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Leu Phe Asp Ser Leu Ser Thr Leu Asp Trp Asp Thr Gly Arg Ser Leu
    3730                3735                3740

Ser Ser Ala Thr Ala Thr Thr Ser Ala Pro Gln Gly Ala Thr Thr Pro
3745                3750                3755                3760

Gln Glu Leu Thr Leu Glu Thr Met Ile Ser Pro Ala Thr Ser Gln Leu
                3765                3770                3775

Pro Phe Ser Ile Gly His Ile Thr Ser Ala Val Thr Pro Ala Ala Met
            3780                3785                3790

Ala Arg Ser Ser Gly Val Thr Phe Ser Arg Pro Asp Pro Thr Ser Lys
        3795                3800                3805

Lys Ala Glu Gln Thr Ser Thr Gln Leu Pro Thr Thr Thr Ser Ala His
    3810                3815                3820

Pro Gly Gln Val Pro Arg Ser Ala Ala Thr Thr Leu Asp Val Ile Pro
3825                3830                3835                3840

His Thr Ala Lys Thr Pro Asp Ala Thr Phe Gln Arg Gln Gly Gln Thr
                3845                3850                3855

Ala Leu Thr Thr Glu Ala Arg Ala Thr Ser Asp Ser Trp Asn Glu Lys
            3860                3865                3870

Glu Lys Ser Thr Pro Ser Ala Pro Trp Ile Thr Glu Met Met Asn Ser
        3875                3880                3885

Val Ser Glu Asp Thr Ile Lys Glu Val Thr Ser Ser Ser Ser Val Leu
    3890                3895                3900

Arg Thr Leu Asn Thr Leu Asp Ile Asn Leu Glu Ser Gly Thr Thr Ser
3905                3910                3915                3920

Ser Pro Ser Trp Lys Ser Ser Pro Tyr Glu Arg Ile Ala Pro Ser Glu
                3925                3930                3935

Ser Thr Thr Asp Lys Glu Ala Ile His Pro Ser Thr Asn Thr Val Glu
            3940                3945                3950

Thr Thr Gly Trp Val Thr Ser Ser Glu His Ala Ser His Ser Thr Ile
        3955                3960                3965

Pro Ala His Ser Ala Ser Ser Lys Leu Thr Ser Pro Val Val Thr Thr
    3970                3975                3980

Ser Thr Arg Glu Gln Ala Ile Val Ser Met Ser Thr Thr Thr Trp Pro
3985                3990                3995                4000

Glu Ser Thr Arg Ala Arg Thr Glu Pro Asn Ser Phe Leu Thr Ile Glu
                4005                4010                4015

Leu Arg Asp Val Ser Pro Tyr Met Asp Thr Ser Ser Thr Thr Gln Thr
            4020                4025                4030

Ser Ile Ile Ser Ser Pro Gly Ser Thr Ala Ile Thr Lys Gly Pro Arg
        4035                4040                4045

Thr Glu Ile Thr Ser Ser Lys Arg Ile Ser Ser Ser Phe Leu Ala Gln
    4050                4055                4060

Ser Met Arg Ser Ser Asp Ser Pro Ser Glu Ala Ile Thr Arg Leu Ser
4065                4070                4075                4080

Asn Phe Pro Ala Met Thr Glu Ser Gly Gly Met Ile Leu Ala Met Gln
                4085                4090                4095

Thr Ser Pro Pro Gly Ala Thr Ser Leu Ser Ala Pro Thr Leu Asp Thr
            4100                4105                4110

Ser Ala Thr Ala Ser Trp Thr Gly Thr Pro Leu Ala Thr Thr Gln Arg
        4115                4120                4125
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Phe Thr Tyr Ser Glu Lys Thr Thr Leu Phe Ser Lys Gly Pro Glu Asp
    4130                4135                4140

Thr Ser Gln Pro Ser Pro Pro Ser Val Glu Glu Thr Ser Ser Ser Ser
4145                4150                4155                4160

Ser Leu Val Pro Ile His Ala Thr Thr Ser Pro Ser Asn Ile Leu Leu
                4165                4170                4175

Thr Ser Gln Gly His Ser Pro Ser Ser Thr Pro Pro Val Thr Ser Val
            4180                4185                4190

Phe Leu Ser Glu Thr Ser Gly Leu Gly Lys Thr Thr Asp Met Ser Arg
        4195                4200                4205

Ile Ser Leu Glu Pro Gly Thr Ser Leu Pro Pro Asn Leu Ser Ser Thr
    4210                4215                4220

Ala Gly Glu Ala Leu Ser Thr Tyr Glu Ala Ser Arg Asp Thr Lys Ala
4225                4230                4235                4240

Ile His His Ser Ala Asp Thr Ala Val Thr Asn Met Glu Ala Thr Ser
                4245                4250                4255

Ser Glu Tyr Ser Pro Ile Pro Gly His Thr Lys Pro Ser Lys Ala Thr
            4260                4265                4270

Ser Pro Leu Val Thr Ser His Ile Met Gly Asp Ile Thr Ser Ser Thr
        4275                4280                4285

Ser Val Phe Gly Ser Ser Glu Thr Thr Glu Ile Glu Thr Val Ser Ser
    4290                4295                4300

Val Asn Gln Gly Leu Gln Glu Arg Ser Thr Ser Gln Val Ala Ser Ser
4305                4310                4315                4320

Ala Thr Glu Thr Ser Thr Val Ile Thr His Val Ser Ser Gly Asp Ala
                4325                4330                4335

Thr Thr His Val Thr Lys Thr Gln Ala Thr Phe Ser Ser Gly Thr Ser
            4340                4345                4350

Ile Ser Ser Pro His Gln Phe Ile Thr Ser Thr Asn Thr Phe Thr Asp
        4355                4360                4365

Val Ser Thr Asn Pro Ser Thr Ser Leu Ile Met Thr Glu Ser Ser Gly
    4370                4375                4380

Val Thr Ile Thr Thr Gln Thr Gly Pro Thr Gly Ala Ala Thr Gln Gly
4385                4390                4395                4400

Pro Tyr Leu Leu Asp Thr Ser Thr Met Pro Tyr Leu Thr Glu Thr Pro
                4405                4410                4415

Leu Ala Val Thr Pro Asp Phe Met Gln Ser Glu Lys Thr Thr Leu Ile
            4420                4425                4430

Ser Lys Gly Pro Lys Asp Val Ser Trp Thr Ser Pro Pro Ser Val Ala
        4435                4440                4445

Glu Thr Ser Tyr Pro Ser Ser Leu Thr Pro Phe Leu Val Thr Thr Ile
    4450                4455                4460

Pro Pro Ala Thr Ser Thr Leu Gln Gly Gln His Thr Ser Ser Pro Val
4465                4470                4475                4480

Ser Ala Thr Ser Val Leu Thr Ser Gly Leu Val Lys Thr Thr Asp Met
                4485                4490                4495

Leu Asn Thr Ser Met Glu Pro Val Thr Asn Ser Pro Gln Asn Leu Asn
            4500                4505                4510

Asn Pro Ser Asn Glu Ile Leu Ala Thr Leu Ala Ala Thr Thr Asp Ile
        4515                4520                4525

Glu Thr Ile His Pro Ser Ile Asn Lys Ala Val Thr Asn Met Gly Thr
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    4530                4535                4540

Ala Ser Ser Ala His Val Leu His Ser Thr Leu Pro Val Ser Ser Glu
4545                4550                4555                4560

Pro Ser Thr Ala Thr Ser Pro Met Val Pro Ala Ser Ser Met Gly Asp
                4565                4570                4575

Ala Leu Ala Ser Ile Ser Ile Pro Gly Ser Glu Thr Thr Asp Ile Glu
            4580                4585                4590

Gly Glu Pro Thr Ser Ser Leu Thr Ala Gly Arg Lys Glu Asn Ser Thr
        4595                4600                4605

Leu Gln Glu Met Asn Ser Thr Thr Glu Ser Asn Ile Ile Leu Ser Asn
    4610                4615                4620

Val Ser Val Gly Ala Ile Thr Glu Ala Thr Lys Met Glu Val Pro Ser
4625                4630                4635                4640

Phe Asp Ala Thr Phe Ile Pro Thr Pro Ala Gln Ser Thr Lys Phe Pro
                4645                4650                4655

Asp Ile Phe Ser Val Ala Ser Ser Arg Leu Ser Asn Ser Pro Pro Met
            4660                4665                4670

Thr Ile Ser Thr His Met Thr Thr Thr Gln Thr Gly Ser Ser Gly Ala
        4675                4680                4685

Thr Ser Lys Ile Pro Leu Ala Leu Asp Thr Ser Thr Leu Glu Thr Ser
    4690                4695                4700

Ala Gly Thr Pro Ser Val Val Thr Glu Gly Phe Ala His Ser Lys Ile
4705                4710                4715                4720

Thr Thr Ala Met Asn Asn Asp Val Lys Asp Val Ser Gln Thr Asn Pro
                4725                4730                4735

Pro Phe Gln Asp Glu Ala Ser Ser Pro Ser Ser Gln Ala Pro Val Leu
            4740                4745                4750

Val Thr Thr Leu Pro Ser Ser Val Ala Phe Thr Pro Gln Trp His Ser
        4755                4760                4765

Thr Ser Ser Pro Val Ser Met Ser Ser Val Leu Thr Ser Ser Leu Val
    4770                4775                4780

Lys Thr Ala Gly Lys Val Asp Thr Ser Leu Glu Thr Val Thr Ser Ser
4785                4790                4795                4800

Pro Gln Ser Met Ser Asn Thr Leu Asp Asp Ile Ser Val Thr Ser Ala
                4805                4810                4815

Ala Thr Thr Asp Ile Glu Thr Thr His Pro Ser Ile Asn Thr Val Val
            4820                4825                4830

Thr Asn Val Gly Thr Thr Gly Ser Ala Phe Glu Ser His Ser Thr Val
        4835                4840                4845

Ser Ala Tyr Pro Glu Pro Ser Lys Val Thr Ser Pro Asn Val Thr Thr
    4850                4855                4860

Ser Thr Met Glu Asp Thr Thr Ile Ser Arg Ser Ile Pro Lys Ser Ser
4865                4870                4875                4880

Lys Thr Thr Arg Thr Glu Thr Glu Thr Thr Ser Ser Leu Thr Pro Lys
                4885                4890                4895

Leu Arg Glu Thr Ser Ile Ser Gln Glu Ile Thr Ser Ser Thr Glu Thr
            4900                4905                4910

Ser Thr Val Pro Tyr Lys Glu Leu Thr Gly Ala Thr Thr Glu Val Ser
        4915                4920                4925

Arg Thr Asp Val Thr Ser Ser Ser Ser Thr Ser Phe Pro Gly Pro Asp
    4930                4935                4940
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Gln Ser Thr Val Ser Leu Asp Ile Ser Thr Glu Thr Asn Thr Arg Leu
4945                4950                4955                4960

Ser Thr Ser Pro Ile Met Thr Glu Ser Ala Glu Ile Thr Ile Thr Thr
                4965                4970                4975

Gln Thr Gly Pro His Gly Ala Thr Ser Gln Asp Thr Phe Thr Met Asp
            4980                4985                4990

Pro Ser Asn Thr Thr Pro Gln Ala Gly Ile His Ser Ala Met Thr His
        4995                5000                5005

Gly Phe Ser Gln Leu Asp Val Thr Thr Leu Met Ser Arg Ile Pro Gln
    5010                5015                5020

Asp Val Ser Trp Thr Ser Pro Pro Ser Val Asp Lys Thr Ser Ser Pro
5025                5030                5035                5040

Ser Ser Phe Leu Ser Ser Pro Ala Met Thr Thr Pro Ser Leu Ile Ser
                5045                5050                5055

Ser Thr Leu Pro Glu Asp Lys Leu Ser Ser Pro Met Thr Ser Leu Leu
            5060                5065                5070

Thr Ser Gly Leu Val Lys Ile Thr Asp Ile Leu Arg Thr Arg Leu Glu
        5075                5080                5085

Pro Val Thr Ser Ser Leu Pro Asn Phe Ser Ser Thr Ser Asp Lys Ile
    5090                5095                5100

Leu Ala Thr Ser Lys Asp Ser Lys Asp Thr Lys Glu Ile Phe Pro Ser
5105                5110                5115                5120

Ile Asn Thr Glu Glu Thr Asn Val Lys Ala Asn Asn Ser Gly His Glu
                5125                5130                5135

Ser His Ser Pro Ala Leu Ala Asp Ser Glu Thr Pro Lys Ala Thr Thr
            5140                5145                5150

Gln Met Val Ile Thr Thr Thr Val Gly Asp Pro Ala Pro Ser Thr Ser
        5155                5160                5165

Met Pro Val His Gly Ser Ser Glu Thr Thr Asn Ile Lys Arg Glu Pro
    5170                5175                5180

Thr Tyr Phe Leu Thr Pro Arg Leu Arg Glu Thr Ser Thr Ser Gln Glu
5185                5190                5195                5200

Ser Ser Phe Pro Thr Asp Thr Ser Phe Leu Leu Ser Lys Val Pro Thr
                5205                5210                5215

Gly Thr Ile Thr Glu Val Ser Ser Thr Gly Val Asn Ser Ser Ser Lys
            5220                5225                5230

Ile Ser Thr Pro Asp His Asp Lys Ser Thr Val Pro Pro Asp Thr Phe
        5235                5240                5245

Thr Gly Glu Ile Pro Arg Val Phe Thr Ser Ser Ile Lys Thr Lys Ser
    5250                5255                5260

Ala Glu Met Thr Ile Thr Thr Gln Ala Ser Pro Pro Glu Ser Ala Ser
5265                5270                5275                5280

His Ser Thr Leu Pro Leu Asp Thr Ser Thr Thr Leu Ser Gln Gly Gly
                5285                5290                5295

Thr His Ser Thr Val Thr Gln Gly Phe Pro Tyr Ser Glu Val Thr Thr
            5300                5305                5310

Leu Met Gly Met Gly Pro Gly Asn Val Ser Trp Met Thr Thr Pro Pro
        5315                5320                5325

Val Glu Glu Thr Ser Ser Val Ser Ser Leu Met Ser Ser Pro Ala Met
    5330                5335                5340
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Thr Ser Pro Ser Pro Val Ser Ser Thr Ser Pro Gln Ser Ile Pro Ser
5345                5350                5355                5360

Ser Pro Leu Pro Val Thr Ala Leu Pro Thr Ser Val Leu Val Thr Thr
                5365                5370                5375

Thr Asp Val Leu Gly Thr Thr Ser Pro Glu Ser Val Thr Ser Ser Pro
            5380                5385                5390

Pro Asn Leu Ser Ser Ile Thr His Glu Arg Pro Ala Thr Tyr Lys Asp
        5395                5400                5405

Thr Ala His Thr Glu Ala Ala Met His His Ser Thr Asn Thr Ala Val
    5410                5415                5420

Thr Asn Val Gly Thr Ser Gly Ser Gly His Lys Ser Gln Ser Ser Val
5425                5430                5435                5440

Leu Ala Asp Ser Glu Thr Ser Lys Ala Thr Pro Leu Met Ser Thr Thr
                5445                5450                5455

Ser Thr Leu Gly Asp Thr Ser Val Ser Thr Ser Thr Pro Asn Ile Ser
            5460                5465                5470

Gln Thr Asn Gln Ile Gln Thr Glu Pro Thr Ala Ser Leu Ser Pro Arg
        5475                5480                5485

Leu Arg Glu Ser Ser Thr Ser Glu Lys Thr Ser Ser Thr Thr Glu Thr
    5490                5495                5500

Asn Thr Ala Phe Ser Tyr Val Pro Thr Gly Ala Ile Thr Gln Ala Ser
5505                5510                5515                5520

Arg Thr Glu Ile Ser Ser Ser Arg Thr Ser Ile Ser Asp Leu Asp Arg
                5525                5530                5535

Pro Thr Ile Ala Pro Asp Ile Ser Thr Gly Met Ile Thr Arg Leu Phe
            5540                5545                5550

Thr Ser Pro Ile Met Thr Lys Ser Ala Glu Met Thr Val Thr Thr Gln
        5555                5560                5565

Thr Thr Thr Pro Gly Ala Thr Ser Gln Gly Ile Leu Pro Trp Asp Thr
    5570                5575                5580

Ser Thr Thr Leu Phe Gln Gly Gly Thr His Ser Thr Val Ser Gln Gly
5585                5590                5595                5600

Phe Pro His Ser Glu Ile Thr Thr Leu Arg Ser Arg Thr Pro Gly Asp
                5605                5610                5615

Val Ser Trp Met Thr Thr Pro Pro Val Glu Glu Thr Ser Ser Gly Phe
            5620                5625                5630

Ser Leu Met Ser Pro Ser Met Thr Ser Pro Ser Pro Val Ser Ser Thr
        5635                5640                5645

Ser Pro Glu Ser Ile Pro Ser Ser Pro Leu Pro Val Thr Ala Leu Leu
    5650                5655                5660

Thr Ser Val Leu Val Thr Thr Thr Asn Val Leu Gly Thr Thr Ser Pro
5665                5670                5675                5680

Glu Pro Val Thr Ser Ser Pro Pro Asn Leu Ser Ser Pro Thr Gln Glu
                5685                5690                5695

Arg Leu Thr Thr Tyr Lys Asp Thr Ala His Thr Glu Ala Met His Ala
            5700                5705                5710

Ser Met His Thr Asn Thr Ala Val Ala Asn Val Gly Thr Ser Ile Ser
        5715                5720                5725

Gly His Glu Ser Gln Ser Ser Val Pro Ala Asp Ser His Thr Ser Lys
    5730                5735                5740

Ala Thr Ser Pro Met Gly Ile Thr Phe Ala Met Gly Asp Thr Ser Val
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5745                5750                5755                5760

Ser Thr Ser Thr Pro Ala Phe Phe Glu Thr Arg Ile Gln Thr Glu Ser
                5765                5770                5775

Thr Ser Ser Leu Ile Pro Gly Leu Arg Asp Thr Arg Thr Ser Glu Glu
            5780                5785                5790

Ile Asn Thr Val Thr Glu Thr Ser Thr Val Leu Ser Glu Val Pro Thr
        5795                5800                5805

Thr Thr Thr Thr Glu Val Ser Arg Thr Glu Val Ile Thr Ser Ser Arg
    5810                5815                5820

Thr Thr Ile Ser Gly Pro Asp His Ser Lys Met Ser Pro Tyr Ile Ser
5825                5830                5835                5840

Thr Glu Thr Ile Thr Arg Leu Ser Thr Phe Pro Phe Val Thr Gly Ser
                5845                5850                5855

Thr Glu Met Ala Ile Thr Asn Gln Thr Gly Pro Ile Gly Thr Ile Ser
            5860                5865                5870

Gln Ala Thr Leu Thr Leu Asp Thr Ser Ser Thr Ala Ser Trp Glu Gly
        5875                5880                5885

Thr His Ser Pro Val Thr Gln Arg Phe Pro His Ser Glu Glu Thr Thr
    5890                5895                5900

Thr Met Ser Arg Ser Thr Lys Gly Val Ser Trp Gln Ser Pro Pro Ser
5905                5910                5915                5920

Val Glu Glu Thr Ser Ser Pro Ser Ser Pro Val Pro Leu Pro Ala Ile
                5925                5930                5935

Thr Ser His Ser Ser Leu Tyr Ser Ala Val Ser Gly Ser Ser Pro Thr
            5940                5945                5950

Ser Ala Leu Pro Val Thr Ser Leu Leu Thr Ser Gly Arg Arg Lys Thr
        5955                5960                5965

Ile Asp Met Leu Asp Thr His Ser Glu Leu Val Thr Ser Ser Leu Pro
    5970                5975                5980

Ser Ala Ser Ser Phe Ser Gly Glu Ile Leu Thr Ser Glu Ala Ser Thr
5985                5990                5995                6000

Asn Thr Glu Thr Ile His Phe Ser Glu Asn Thr Ala Glu Thr Asn Met
                6005                6010                6015

Gly Thr Thr Asn Ser Met His Lys Leu His Ser Ser Val Ser Ile His
            6020                6025                6030

Ser Gln Pro Ser Gly His Thr Pro Pro Lys Val Thr Gly Ser Met Met
        6035                6040                6045

Glu Asp Ala Ile Val Ser Thr Ser Thr Pro Gly Ser Pro Glu Thr Lys
    6050                6055                6060

Asn Val Asp Arg Asp Ser Thr Ser Pro Leu Thr Pro Glu Leu Lys Glu
6065                6070                6075                6080

Asp Ser Thr Ala Leu Val Met Asn Ser Thr Thr Glu Ser Asn Thr Val
                6085                6090                6095

Phe Ser Ser Val Ser Leu Asp Ala Ala Thr Glu Val Ser Arg Ala Glu
            6100                6105                6110

Val Thr Tyr Tyr Asp Pro Thr Phe Met Pro Ala Ser Ala Gln Ser Thr
        6115                6120                6125

Lys Ser Pro Asp Ile Ser Pro Glu Ala Ser Ser Ser His Ser Asn Ser
    6130                6135                6140

Pro Pro Leu Thr Ile Ser Thr His Lys Thr Ile Ala Thr Gln Thr Gly
6145                6150                6155                6160
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Pro Ser Gly Val Thr Ser Leu Gly Gln Leu Thr Leu Asp Thr Ser Thr
                6165                6170                6175

Ile Ala Thr Ser Ala Gly Thr Pro Ser Ala Arg Thr Gln Asp Phe Val
            6180                6185                6190

Asp Ser Glu Thr Thr Ser Val Met Asn Asn Asp Leu Asn Asp Val Leu
        6195                6200                6205

Lys Thr Ser Pro Phe Ser Ala Glu Glu Ala Asn Ser Leu Ser Ser Gln
    6210                6215                6220

Ala Pro Leu Leu Val Thr Thr Ser Pro Ser Pro Val Thr Ser Thr Leu
6225                6230                6235                6240

Gln Glu His Ser Thr Ser Ser Leu Val Ser Val Thr Ser Val Pro Thr
                6245                6250                6255

Pro Thr Leu Ala Lys Ile Thr Asp Met Asp Thr Asn Leu Glu Pro Val
            6260                6265                6270

Thr Arg Ser Pro Gln Asn Leu Arg Asn Thr Leu Ala Thr Ser Glu Ala
        6275                6280                6285

Thr Thr Asp Thr His Thr Met His Pro Ser Ile Asn Thr Ala Val Ala
    6290                6295                6300

Asn Val Gly Thr Thr Ser Ser Pro Asn Glu Phe Tyr Phe Thr Val Ser
6305                6310                6315                6320

Pro Asp Ser Asp Pro Tyr Lys Ala Thr Ser Ala Val Val Ile Thr Ser
                6325                6330                6335

Thr Ser Gly Asp Ser Ile Val Ser Thr Ser Met Pro Arg Ser Ser Ala
            6340                6345                6350

Met Lys Lys Ile Glu Ser Glu Thr Thr Phe Ser Leu Ile Phe Arg Leu
        6355                6360                6365

Arg Glu Thr Ser Thr Ser Gln Lys Ile Gly Ser Ser Ser Asp Thr Ser
    6370                6375                6380

Thr Val Phe Asp Lys Ala Phe Thr Ala Ala Thr Thr Glu Val Ser Arg
6385                6390                6395                6400

Thr Glu Leu Thr Ser Ser Ser Arg Thr Ser Ile Gln Gly Thr Glu Lys
                6405                6410                6415

Pro Thr Met Ser Pro Asp Thr Ser Thr Arg Ser Val Thr Met Leu Ser
            6420                6425                6430

Thr Phe Ala Gly Leu Thr Lys Ser Glu Glu Arg Thr Ile Ala Thr Gln
        6435                6440                6445

Thr Gly Pro His Arg Ala Thr Ser Gln Gly Thr Leu Thr Trp Asp Thr
    6450                6455                6460

Ser Ile Thr Thr Ser Gln Ala Gly Thr His Ser Ala Met Thr His Gly
6465                6470                6475                6480

Phe Ser Gln Leu Asp Leu Ser Thr Leu Thr Ser Arg Val Pro Glu Tyr
                6485                6490                6495

Ile Ser Gly Thr Ser Pro Pro Ser Val Glu Lys Thr Ser Ser Ser Ser
            6500                6505                6510

Ser Leu Leu Ser Leu Pro Ala Ile Thr Ser Pro Ser Pro Val Pro Thr
        6515                6520                6525

Thr Leu Pro Glu Ser Arg Pro Ser Ser Pro Val His Leu Thr Ser Leu
    6530                6535                6540

Pro Thr Ser Gly Leu Val Lys Thr Thr Asp Met Leu Ala Ser Val Ala
6545                6550                6555                6560
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Ser Leu Pro Pro Asn Leu Gly Ser Thr Ser His Lys Ile Pro Thr Thr
                6565                6570                6575

Ser Glu Asp Ile Lys Asp Thr Glu Lys Met Tyr Pro Ser Thr Asn Ile
            6580                6585                6590

Ala Val Thr Asn Val Gly Thr Thr Thr Ser Glu Lys Glu Ser Tyr Ser
        6595                6600                6605

Ser Val Pro Ala Tyr Ser Glu Pro Pro Lys Val Thr Ser Pro Met Val
    6610                6615                6620

Thr Ser Phe Asn Ile Arg Asp Thr Ile Val Ser Thr Ser Met Pro Gly
6625                6630                6635                6640

Ser Ser Glu Ile Thr Arg Ile Glu Met Glu Ser Thr Phe Ser Leu Ala
                6645                6650                6655

His Gly Leu Lys Gly Thr Ser Thr Ser Gln Asp Pro Ile Val Ser Thr
            6660                6665                6670

Glu Lys Ser Ala Val Leu His Lys Leu Thr Thr Gly Ala Thr Glu Thr
        6675                6680                6685

Ser Arg Thr Glu Val Ala Ser Ser Arg Arg Thr Ser Ile Pro Gly Pro
    6690                6695                6700

Asp His Ser Thr Glu Ser Pro Asp Ile Ser Thr Glu Val Ile Pro Ser
6705                6710                6715                6720

Leu Pro Ile Ser Leu Gly Ile Thr Glu Ser Ser Asn Met Thr Ile Ile
                6725                6730                6735

Thr Arg Thr Gly Pro Pro Leu Gly Ser Thr Ser Gln Gly Thr Phe Thr
            6740                6745                6750

Leu Asp Thr Pro Thr Thr Ser Ser Arg Ala Gly Thr His Ser Met Ala
        6755                6760                6765

Thr Gln Glu Phe Pro His Ser Glu Met Thr Thr Val Met Asn Lys Asp
    6770                6775                6780

Pro Glu Ile Leu Ser Trp Thr Ile Pro Pro Ser Ile Glu Lys Thr Ser
6785                6790                6795                6800

Phe Ser Ser Ser Leu Met Pro Ser Pro Ala Met Thr Ser Pro Pro Val
                6805                6810                6815

Ser Ser Thr Leu Pro Lys Thr Ile His Thr Thr Pro Ser Pro Met Thr
            6820                6825                6830

Ser Leu Leu Thr Pro Ser Leu Val Met Thr Thr Asp Thr Leu Gly Thr
        6835                6840                6845

Ser Pro Glu Pro Thr Thr Ser Ser Pro Pro Asn Leu Ser Ser Thr Ser
    6850                6855                6860

His Glu Ile Leu Thr Thr Asp Glu Asp Thr Thr Ala Ile Glu Ala Met
6865                6870                6875                6880

His Pro Ser Thr Ser Thr Ala Ala Thr Asn Val Glu Thr Thr Ser Ser
                6885                6890                6895

Gly His Gly Ser Gln Ser Ser Val Leu Ala Asp Ser Glu Lys Thr Lys
            6900                6905                6910

Ala Thr Ala Pro Met Asp Thr Thr Ser Thr Met Gly His Thr Thr Val
        6915                6920                6925

Ser Thr Ser Met Ser Val Ser Ser Glu Thr Thr Lys Ile Lys Arg Glu
    6930                6935                6940

Ser Thr Tyr Ser Leu Thr Pro Gly Leu Arg Glu Thr Ser Ile Ser Gln
6945                6950                6955                6960

Asn Ala Ser Phe Ser Thr Asp Thr Ser Ile Val Leu Ser Glu Val Pro
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                6965                6970                6975

Thr Gly Thr Thr Ala Glu Val Ser Arg Thr Glu Val Thr Ser Ser Gly
            6980                6985                6990

Arg Thr Ser Ile Pro Gly Pro Ser Gln Ser Thr Val Leu Pro Glu Ile
        6995                7000                7005

Ser Thr Arg Thr Met Thr Arg Leu Phe Ala Ser Pro Thr Met Thr Glu
    7010                7015                7020

Ser Ala Glu Met Thr Ile Pro Thr Gln Thr Gly Pro Ser Gly Ser Thr
7025                7030                7035                7040

Ser Gln Asp Thr Leu Thr Leu Asp Thr Ser Thr Thr Lys Ser Gln Ala
                7045                7050                7055

Lys Thr His Ser Thr Leu Thr Gln Arg Phe Pro His Ser Glu Met Thr
            7060                7065                7070

Thr Leu Met Ser Arg Gly Pro Gly Asp Met Ser Trp Gln Ser Ser Pro
        7075                7080                7085

Ser Leu Glu Asn Pro Ser Ser Leu Pro Ser Leu Leu Ser Leu Pro Ala
    7090                7095                7100

Thr Thr Ser Pro Pro Pro Ile Ser Ser Thr Leu Pro Val Thr Ile Ser
7105                7110                7115                7120

Ser Ser Pro Leu Pro Val Thr Ser Leu Leu Thr Ser Ser Pro Val Thr
                7125                7130                7135

Thr Thr Asp Met Leu His Thr Ser Pro Glu Leu Val Thr Ser Ser Pro
            7140                7145                7150

Pro Lys Leu Ser His Thr Ser Asp Glu Arg Leu Thr Thr Gly Lys Asp
        7155                7160                7165

Thr Thr Asn Thr Glu Ala Val His Pro Ser Thr Asn Thr Ala Ala Ser
    7170                7175                7180

Asn Val Glu Ile Pro Ser Ser Gly His Glu Ser Pro Ser Ser Ala Leu
7185                7190                7195                7200

Ala Asp Ser Glu Thr Ser Lys Ala Thr Ser Pro Met Phe Ile Thr Ser
                7205                7210                7215

Thr Gln Glu Asp Thr Thr Val Ala Ile Ser Thr Pro His Phe Leu Glu
            7220                7225                7230

Thr Ser Arg Ile Gln Lys Glu Ser Ile Ser Ser Leu Ser Pro Lys Leu
        7235                7240                7245

Arg Glu Thr Gly Ser Ser Val Glu Thr Ser Ser Ala Ile Glu Thr Ser
    7250                7255                7260

Ala Val Leu Ser Glu Val Ser Ile Gly Ala Thr Thr Glu Ile Ser Arg
7265                7270                7275                7280

Thr Glu Val Thr Ser Ser Ser Arg Thr Ser Ile Ser Gly Ser Ala Glu
                7285                7290                7295

Ser Thr Met Leu Pro Glu Ile Ser Thr Thr Arg Lys Ile Ile Lys Phe
            7300                7305                7310

Pro Thr Ser Pro Ile Leu Ala Glu Ser Ser Glu Met Thr Ile Lys Thr
        7315                7320                7325

Gln Thr Ser Pro Pro Gly Ser Thr Ser Glu Ser Thr Phe Thr Leu Asp
    7330                7335                7340

Thr Ser Thr Thr Pro Ser Leu Val Ile Thr His Ser Thr Met Thr Gln
7345                7350                7355                7360

Arg Leu Pro His Ser Glu Ile Thr Thr Leu Val Ser Arg Gly Ala Gly
                7365                7370                7375
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Asp Val Pro Arg Pro Ser Ser Leu Pro Val Glu Glu Thr Ser Pro Pro
            7380                7385                7390

Ser Ser Gln Leu Ser Leu Ser Ala Met Ile Ser Pro Ser Pro Val Ser
        7395                7400                7405

Ser Thr Leu Pro Ala Ser Ser His Ser Ser Ser Ala Ser Val Thr Ser
    7410                7415                7420

Leu Leu Thr Pro Gly Gln Val Lys Thr Thr Glu Val Leu Asp Ala Ser
7425                7430                7435                7440

Ala Glu Pro Glu Thr Ser Ser Pro Pro Ser Leu Ser Ser Thr Ser Val
                7445                7450                7455

Glu Ile Leu Ala Thr Ser Glu Val Thr Thr Asp Thr Glu Lys Ile His
            7460                7465                7470

Pro Phe Ser Asn Thr Ala Val Thr Lys Val Gly Thr Ser Ser Ser Gly
        7475                7480                7485

His Glu Ser Pro Ser Ser Val Leu Pro Asp Ser Glu Thr Thr Lys Ala
    7490                7495                7500

Thr Ser Ala Met Gly Thr Ile Ser Ile Met Gly Asp Thr Ser Val Ser
7505                7510                7515                7520

Thr Leu Thr Pro Ala Leu Ser Asn Thr Arg Lys Ile Gln Ser Glu Pro
                7525                7530                7535

Ala Ser Ser Leu Thr Thr Arg Leu Arg Glu Thr Ser Thr Ser Glu Glu
            7540                7545                7550

Thr Ser Leu Ala Thr Glu Ala Asn Thr Val Leu Ser Lys Val Ser Thr
        7555                7560                7565

Gly Ala Thr Thr Glu Val Ser Arg Thr Glu Ala Ile Ser Phe Ser Arg
    7570                7575                7580

Thr Ser Met Ser Gly Pro Glu Gln Ser Thr Met Ser Gln Asp Ile Ser
7585                7590                7595                7600

Ile Gly Thr Ile Pro Arg Ile Ser Ala Ser Ser Val Leu Thr Glu Ser
                7605                7610                7615

Ala Lys Met Thr Ile Thr Thr Gln Thr Gly Pro Ser Glu Ser Thr Leu
            7620                7625                7630

Glu Ser Thr Leu Asn Leu Asn Thr Ala Thr Thr Pro Ser Trp Val Glu
        7635                7640                7645

Thr His Ser Ile Val Ile Gln Gly Phe Pro His Pro Glu Met Thr Thr
    7650                7655                7660

Ser Met Gly Arg Gly Pro Gly Gly Val Ser Trp Pro Ser Pro Pro Phe
7665                7670                7675                7680

Val Lys Glu Thr Ser Pro Pro Ser Ser Pro Leu Ser Leu Pro Ala Val
                7685                7690                7695

Thr Ser Pro His Pro Val Ser Thr Thr Phe Leu Ala His Ile Pro Pro
            7700                7705                7710

Ser Pro Leu Pro Val Thr Ser Leu Leu Thr Ser Gly Pro Ala Thr Thr
        7715                7720                7725

Thr Asp Ile Leu Gly Thr Ser Thr Glu Pro Gly Thr Ser Ser Ser Ser
    7730                7735                7740

Ser Leu Ser Thr Thr Ser His Glu Arg Leu Thr Thr Tyr Lys Asp Thr
7745                7750                7755                7760

Ala His Thr Glu Ala Val His Pro Ser Thr Asn Thr Gly Gly Thr Asn
                7765                7770                7775
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Val Ala Thr Thr Ser Ser Gly Tyr Lys Ser Gln Ser Ser Val Leu Ala
            7780                7785                7790

Asp Ser Ser Pro Met Cys Thr Thr Ser Thr Met Gly Asp Thr Ser Val
        7795                7800                7805

Leu Thr Ser Thr Pro Ala Phe Leu Glu Thr Arg Arg Ile Gln Thr Glu
    7810                7815                7820

Leu Ala Ser Ser Leu Thr Pro Gly Leu Arg Glu Ser Ser Gly Ser Glu
7825                7830                7835                7840

Gly Thr Ser Ser Gly Thr Lys Met Ser Thr Val Leu Ser Lys Val Pro
                7845                7850                7855

Thr Gly Ala Thr Thr Glu Ile Ser Lys Glu Asp Val Thr Ser Ile Pro
            7860                7865                7870

Gly Pro Ala Gln Ser Thr Ile Ser Pro Asp Ile Ser Thr Arg Thr Val
        7875                7880                7885

Ser Trp Phe Ser Thr Ser Pro Val Met Thr Glu Ser Ala Glu Ile Thr
    7890                7895                7900

Met Asn Thr His Thr Ser Pro Leu Gly Ala Thr Thr Gln Gly Thr Ser
7905                7910                7915                7920

Thr Leu Asp Thr Ser Ser Thr Thr Ser Leu Thr Met Thr His Ser Thr
                7925                7930                7935

Ile Ser Gln Gly Phe Ser His Ser Gln Met Ser Thr Leu Met Arg Arg
            7940                7945                7950

Gly Pro Glu Asp Val Ser Trp Met Ser Pro Pro Leu Leu Glu Lys Thr
        7955                7960                7965

Arg Pro Ser Phe Ser Leu Met Ser Ser Pro Ala Thr Thr Ser Pro Ser
    7970                7975                7980

Pro Val Ser Ser Thr Leu Pro Glu Ser Ile Ser Ser Ser Pro Leu Pro
7985                7990                7995                8000

Val Thr Ser Leu Leu Thr Ser Gly Leu Ala Lys Thr Thr Asp Met Leu
                8005                8010                8015

His Lys Ser Ser Glu Pro Val Thr Asn Ser Pro Ala Asn Leu Ser Ser
            8020                8025                8030

Thr Ser Val Glu Ile Leu Ala Thr Ser Glu Val Thr Thr Asp Thr Glu
        8035                8040                8045

Lys Thr His Pro Ser Ser Asn Arg Thr Val Thr Asp Val Gly Thr Ser
    8050                8055                8060

Ser Ser Gly His Glu Ser Thr Ser Phe Val Leu Ala Asp Ser Gln Thr
8065                8070                8075                8080

Ser Lys Val Thr Ser Pro Met Val Ile Thr Ser Thr Met Glu Asp Thr
                8085                8090                8095

Ser Val Ser Thr Ser Thr Pro Gly Phe Phe Glu Thr Ser Arg Ile Gln
            8100                8105                8110

Thr Glu Pro Thr Ser Ser Leu Thr Leu Gly Leu Arg Lys Thr Ser Ser
        8115                8120                8125

Ser Glu Gly Thr Ser Leu Ala Thr Glu Met Ser Thr Val Leu Ser Gly
    8130                8135                8140

Val Pro Thr Gly Ala Thr Ala Glu Val Ser Arg Thr Glu Val Thr Ser
8145                8150                8155                8160

Ser Ser Arg Thr Ser Ile Ser Gly Phe Ala Gln Leu Thr Val Ser Pro
                8165                8170                8175

Glu Thr Ser Thr Glu Thr Ile Thr Arg Leu Pro Thr Ser Ser Ile Met
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            8180                8185                8190

Thr Glu Ser Ala Glu Met Met Ile Lys Thr Gln Thr Asp Pro Pro Gly
        8195                8200                8205

Ser Thr Pro Glu Ser Thr His Thr Val Asp Ile Ser Thr Thr Pro Asn
    8210                8215                8220

Trp Val Glu Thr His Ser Thr Val Thr Gln Arg Phe Ser His Ser Glu
8225                8230                8235                8240

Met Thr Thr Leu Val Ser Arg Ser Pro Gly Asp Met Leu Trp Pro Ser
                8245                8250                8255

Gln Ser Ser Val Glu Glu Thr Ser Ser Ala Ser Ser Leu Leu Ser Leu
            8260                8265                8270

Pro Ala Thr Thr Ser Pro Ser Pro Val Ser Ser Thr Leu Val Glu Asp
        8275                8280                8285

Phe Pro Ser Ala Ser Leu Pro Val Thr Ser Leu Leu Asn Pro Gly Leu
    8290                8295                8300

Val Ile Thr Thr Asp Arg Met Gly Ile Ser Arg Glu Pro Gly Thr Ser
8305                8310                8315                8320

Ser Thr Ser Asn Leu Ser Ser Thr Ser His Glu Arg Leu Thr Thr Leu
                8325                8330                8335

Glu Asp Thr Val Asp Thr Glu Asp Met Gln Pro Ser Thr His Thr Ala
            8340                8345                8350

Val Thr Asn Val Arg Thr Ser Ile Ser Gly His Glu Ser Gln Ser Ser
        8355                8360                8365

Val Leu Ser Asp Ser Glu Thr Pro Lys Ala Thr Ser Pro Met Gly Thr
    8370                8375                8380

Thr Tyr Thr Met Gly Glu Thr Ser Val Ser Ile Ser Thr Ser Asp Phe
8385                8390                8395                8400

Phe Glu Thr Ser Arg Ile Gln Ile Glu Pro Thr Ser Ser Leu Thr Ser
                8405                8410                8415

Gly Leu Arg Glu Thr Ser Ser Ser Glu Arg Ile Ser Ser Ala Thr Glu
            8420                8425                8430

Gly Ser Thr Val Leu Ser Glu Val Pro Ser Gly Ala Thr Thr Glu Val
        8435                8440                8445

Ser Arg Thr Glu Val Ile Ser Ser Arg Gly Thr Ser Met Ser Gly Pro
    8450                8455                8460

Asp Gln Phe Thr Ile Ser Pro Asp Ile Ser Thr Glu Ala Ile Thr Arg
8465                8470                8475                8480

Leu Ser Thr Ser Pro Ile Met Thr Glu Ser Ala Glu Ser Ala Ile Thr
                8485                8490                8495

Ile Glu Thr Gly Ser Pro Gly Ala Thr Ser Glu Gly Thr Leu Thr Leu
            8500                8505                8510

Asp Thr Ser Thr Thr Thr Phe Trp Ser Gly Thr His Ser Thr Ala Ser
        8515                8520                8525

Pro Gly Phe Ser His Ser Glu Met Thr Thr Leu Met Ser Arg Thr Pro
    8530                8535                8540

Gly Asp Val Pro Trp Pro Ser Leu Pro Ser Val Glu Glu Ala Ser Ser
8545                8550                8555                8560

Val Ser Ser Ser Leu Ser Ser Pro Ala Met Thr Ser Thr Ser Phe Phe
                8565                8570                8575

Ser Thr Leu Pro Glu Ser Ile Ser Ser Ser Pro His Pro Val Thr Ala
            8580                8585                8590
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Leu Leu Thr Leu Gly Pro Val Lys Thr Thr Asp Met Leu Arg Thr Ser
        8595                8600                8605

Ser Glu Pro Glu Thr Ser Ser Pro Pro Asn Leu Ser Ser Thr Ser Ala
    8610                8615                8620

Glu Ile Leu Ala Thr Ser Glu Val Thr Lys Asp Arg Glu Lys Ile His
8625                8630                8635                8640

Pro Ser Ser Asn Thr Pro Val Val Asn Val Gly Thr Val Ile Tyr Lys
                8645                8650                8655

His Leu Ser Pro Ser Ser Val Leu Ala Asp Leu Val Thr Thr Lys Pro
            8660                8665                8670

Thr Ser Pro Met Ala Thr Thr Ser Thr Leu Gly Asn Thr Ser Val Ser
        8675                8680                8685

Thr Ser Thr Pro Ala Phe Pro Glu Thr Met Met Thr Gln Pro Thr Ser
    8690                8695                8700

Ser Leu Thr Ser Gly Leu Arg Glu Ile Ser Thr Ser Gln Glu Thr Ser
8705                8710                8715                8720

Ser Ala Thr Glu Arg Ser Ala Ser Leu Ser Gly Met Pro Thr Gly Ala
                8725                8730                8735

Thr Thr Lys Val Ser Arg Thr Glu Ala Leu Ser Leu Gly Arg Thr Ser
            8740                8745                8750

Thr Pro Gly Pro Ala Gln Ser Thr Ile Ser Pro Glu Ile Ser Thr Glu
        8755                8760                8765

Thr Ile Thr Arg Ile Ser Thr Pro Leu Thr Thr Thr Gly Ser Ala Glu
    8770                8775                8780

Met Thr Ile Thr Pro Lys Thr Gly His Ser Gly Ala Ser Ser Gln Gly
8785                8790                8795                8800

Thr Phe Thr Leu Asp Thr Ser Ser Arg Ala Ser Trp Pro Gly Thr His
                8805                8810                8815

Ser Ala Ala Thr His Arg Ser Pro His Ser Gly Met Thr Thr Pro Met
            8820                8825                8830

Ser Arg Gly Pro Glu Asp Val Ser Trp Pro Ser Arg Pro Ser Val Glu
        8835                8840                8845

Lys Thr Ser Pro Pro Ser Ser Leu Val Ser Leu Ser Ala Val Thr Ser
    8850                8855                8860

Pro Ser Pro Leu Tyr Ser Thr Pro Ser Glu Ser Ser His Ser Ser Pro
8865                8870                8875                8880

Leu Arg Val Thr Ser Leu Phe Thr Pro Val Met Met Lys Thr Thr Asp
                8885                8890                8895

Met Leu Asp Thr Ser Leu Glu Pro Val Thr Thr Ser Pro Pro Ser Met
            8900                8905                8910

Asn Ile Thr Ser Asp Glu Ser Leu Ala Thr Ser Lys Ala Thr Met Glu
        8915                8920                8925

Thr Glu Ala Ile Gln Leu Ser Glu Asn Thr Ala Val Thr Gln Met Gly
    8930                8935                8940

Thr Ile Ser Ala Arg Gln Glu Phe Tyr Ser Ser Tyr Pro Gly Leu Pro
8945                8950                8955                8960

Glu Pro Ser Lys Val Thr Ser Pro Val Val Thr Ser Ser Thr Ile Lys
                8965                8970                8975

Asp Ile Val Ser Thr Thr Ile Pro Ala Ser Ser Glu Ile Thr Arg Ile
            8980                8985                8990
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Glu Met Glu Ser Thr Ser Thr Leu Thr Pro Thr Pro Arg Glu Thr Ser
        8995                9000                9005

Thr Ser Gln Glu Ile His Ser Ala Thr Lys Pro Ser Thr Val Pro Tyr
    9010                9015                9020

Lys Ala Leu Thr Ser Ala Thr Ile Glu Asp Ser Met Thr Gln Val Met
9025                9030                9035                9040

Ser Ser Ser Arg Gly Pro Ser Pro Asp Gln Ser Thr Met Ser Gln Asp
                9045                9050                9055

Ile Ser Thr Glu Val Ile Thr Arg Leu Ser Thr Ser Pro Ile Lys Thr
            9060                9065                9070

Glu Ser Thr Glu Met Thr Ile Thr Thr Gln Thr Gly Ser Pro Gly Ala
        9075                9080                9085

Thr Ser Arg Gly Thr Leu Thr Leu Asp Thr Ser Thr Thr Phe Met Ser
    9090                9095                9100

Gly Thr His Ser Thr Ala Ser Gln Gly Phe Ser His Ser Gln Met Thr
9105                9110                9115                9120

Ala Leu Met Ser Arg Thr Pro Gly Asp Val Pro Trp Leu Ser His Pro
                9125                9130                9135

Ser Val Glu Glu Ala Ser Ser Ala Ser Phe Ser Leu Ser Ser Pro Val
            9140                9145                9150

Met Thr Ser Ser Ser Pro Val Ser Ser Thr Leu Pro Asp Ser Ile His
        9155                9160                9165

Ser Ser Ser Leu Pro Val Thr Ser Leu Leu Thr Ser Gly Leu Val Lys
    9170                9175                9180

Thr Thr Glu Leu Leu Gly Thr Ser Ser Glu Pro Glu Thr Ser Ser Pro
9185                9190                9195                9200

Pro Asn Leu Ser Ser Thr Ser Ala Glu Ile Leu Ala Ile Thr Glu Val
                9205                9210                9215

Thr Thr Asp Thr Glu Lys Leu Glu Met Thr Asn Val Val Thr Ser Gly
            9220                9225                9230

Tyr Thr His Glu Ser Pro Ser Ser Val Leu Ala Asp Ser Val Thr Thr
        9235                9240                9245

Lys Ala Thr Ser Ser Met Gly Ile Thr Tyr Pro Thr Gly Asp Thr Asn
    9250                9255                9260

Val Leu Thr Ser Thr Pro Ala Phe Ser Asp Thr Ser Arg Ile Gln Thr
9265                9270                9275                9280

Lys Ser Lys Leu Ser Leu Thr Pro Gly Leu Met Glu Thr Ser Ile Ser
                9285                9290                9295

Glu Glu Thr Ser Ser Ala Thr Glu Lys Ser Thr Val Leu Ser Ser Val
            9300                9305                9310

Pro Thr Gly Ala Thr Thr Glu Val Ser Arg Thr Glu Ala Ile Ser Ser
        9315                9320                9325

Ser Arg Thr Ser Ile Pro Gly Pro Ala Gln Ser Thr Met Ser Ser Asp
    9330                9335                9340

Thr Ser Met Glu Thr Ile Thr Arg Ile Ser Thr Pro Leu Thr Arg Lys
9345                9350                9355                9360

Glu Ser Thr Asp Met Ala Ile Thr Pro Lys Thr Gly Pro Ser Gly Ala
                9365                9370                9375

Thr Ser Gln Gly Thr Phe Thr Leu Asp Ser Ser Ser Thr Ala Ser Trp
            9380                9385                9390

Pro Gly Thr His Ser Ala Thr Thr Gln Arg Phe Pro Gln Ser Val Val
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        9395                9400                9405

Thr Thr Pro Met Ser Arg Gly Pro Glu Asp Val Ser Trp Pro Ser Pro
    9410                9415                9420

Leu Ser Val Glu Lys Asn Ser Pro Pro Ser Ser Leu Val Ser Ser Ser
9425                9430                9435                9440

Ser Val Thr Ser Pro Ser Pro Leu Tyr Ser Thr Pro Ser Gly Ser Ser
                9445                9450                9455

His Ser Ser Pro Val Pro Val Thr Ser Leu Phe Thr Ser Ile Met Met
            9460                9465                9470

Lys Ala Thr Asp Met Leu Asp Ala Ser Leu Glu Pro Glu Thr Thr Ser
        9475                9480                9485

Ala Pro Asn Met Asn Ile Thr Ser Asp Glu Ser Leu Ala Ala Ser Lys
    9490                9495                9500

Ala Thr Thr Glu Thr Glu Ala Ile His Val Phe Glu Asn Thr Ala Ala
9505                9510                9515                9520

Ser His Val Glu Thr Thr Ser Ala Thr Glu Glu Leu Tyr Ser Ser Ser
                9525                9530                9535

Pro Gly Phe Ser Glu Pro Thr Lys Val Ile Ser Pro Val Val Thr Ser
            9540                9545                9550

Ser Ser Ile Arg Asp Asn Met Val Ser Thr Thr Met Pro Gly Ser Ser
        9555                9560                9565

Gly Ile Thr Arg Ile Glu Ile Glu Ser Met Ser Ser Leu Thr Pro Gly
    9570                9575                9580

Leu Arg Glu Thr Arg Thr Ser Gln Asp Ile Thr Ser Ser Thr Glu Thr
9585                9590                9595                9600

Ser Thr Val Leu Tyr Lys Met Pro Ser Gly Ala Thr Pro Glu Val Ser
                9605                9610                9615

Arg Thr Glu Val Met Pro Ser Ser Arg Thr Ser Ile Pro Gly Pro Ala
            9620                9625                9630

Gln Ser Thr Met Ser Leu Asp Ile Ser Asp Glu Val Val Thr Arg Leu
        9635                9640                9645

Ser Thr Ser Pro Ile Met Thr Glu Ser Ala Glu Ile Thr Ile Thr Thr
    9650                9655                9660

Gln Thr Gly Tyr Ser Leu Ala Thr Ser Gln Val Thr Leu Pro Leu Gly
9665                9670                9675                9680

Thr Ser Met Thr Phe Leu Ser Gly Thr His Ser Thr Met Ser Gln Gly
                9685                9690                9695

Leu Ser His Ser Glu Met Thr Asn Leu Met Ser Arg Gly Pro Glu Ser
            9700                9705                9710

Leu Ser Trp Thr Ser Pro Arg Phe Val Glu Thr Thr Arg Ser Ser Ser
        9715                9720                9725

Ser Leu Thr Ser Leu Pro Leu Thr Thr Ser Leu Ser Pro Val Ser Ser
    9730                9735                9740

Thr Leu Leu Asp Ser Ser Pro Ser Ser Pro Leu Pro Val Thr Ser Leu
9745                9750                9755                9760

Ile Leu Pro Gly Leu Val Lys Thr Thr Glu Val Leu Asp Thr Ser Ser
                9765                9770                9775

Glu Pro Lys Thr Ser Ser Ser Pro Asn Leu Ser Ser Thr Ser Val Glu
            9780                9785                9790

Ile Pro Ala Thr Ser Glu Ile Met Thr Asp Thr Glu Lys Ile His Pro
        9795                9800                9805
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Ser Ser Asn Thr Ala Val Ala Lys Val Arg Thr Ser Ser Ser Val His
    9810                9815                9820

Glu Ser His Ser Ser Val Leu Ala Asp Ser Glu Thr Thr Ile Thr Ile
9825                9830                9835                9840

Pro Ser Met Gly Ile Thr Ser Ala Val Asp Asp Thr Thr Val Phe Thr
                9845                9850                9855

Ser Asn Pro Ala Phe Ser Glu Thr Arg Arg Ile Pro Thr Glu Pro Thr
            9860                9865                9870

Phe Ser Leu Thr Pro Gly Phe Arg Glu Thr Ser Thr Ser Glu Glu Thr
        9875                9880                9885

Thr Ser Ile Thr Glu Thr Ser Ala Val Leu Tyr Gly Val Pro Thr Ser
    9890                9895                9900

Ala Thr Thr Glu Val Ser Met Thr Glu Ile Met Ser Ser Asn Arg Ile
9905                9910                9915                9920

His Ile Pro Asp Ser Asp Gln Ser Thr Met Ser Pro Asp Ile Ile Thr
                9925                9930                9935

Glu Val Ile Thr Arg Leu Ser Ser Ser Ser Met Met Ser Glu Ser Thr
            9940                9945                9950

Gln Met Thr Ile Thr Thr Gln Lys Ser Ser Pro Gly Ala Thr Ala Gln
        9955                9960                9965

Ser Thr Leu Thr Leu Ala Thr Thr Thr Ala Pro Leu Ala Arg Thr His
    9970                9975                9980

Ser Thr Val Pro Pro Arg Phe Leu His Ser Glu Met Thr Thr Leu Met
9985                9990                9995                10000

Ser Arg Ser Pro Glu  Asn Pro Ser Trp Lys  Ser Ser Leu Phe Val  Glu
                10005                10010                10015

Lys Thr Ser Ser  Ser Ser Ser Leu Leu  Ser Leu Pro Val Thr  Thr Ser
            10020                10025                10030

Pro Ser Val  Ser Ser Thr Leu Pro  Gln Ser Ile Pro Ser  Ser Ser Phe
        10035                10040                10045

Ser Val  Thr Ser Leu Leu Thr  Pro Gly Met Val Lys  Thr Thr Asp Thr
    10050                10055                10060

Ser  Thr Glu Pro Gly Thr  Ser Leu Ser Pro Asn  Leu Ser Gly Thr Ser
10065                10070                10075                10080

Val Glu Ile Leu Ala  Ala Ser Glu Val Thr  Thr Asp Thr Glu Lys  Ile
                10085                10090                10095

His Pro Ser Ser  Ser Met Ala Val Thr  Asn Val Gly Thr Thr  Ser Ser
            10100                10105                10110

Gly His Glu  Leu Tyr Ser Ser Val  Ser Ile His Ser Glu  Pro Ser Lys
        10115                10120                10125

Ala Thr  Tyr Pro Val Gly Thr  Pro Ser Ser Met Ala  Glu Thr Ser Ile
    10130                10135                10140

Ser  Thr Ser Met Pro Ala  Asn Phe Glu Thr Thr  Gly Phe Glu Ala Glu
10145                10150                10155                10160

Pro Phe Ser His Leu  Thr Ser Gly Phe Arg  Lys Thr Asn Met Ser  Leu
                10165                10170                10175

Asp Thr Ser Ser  Val Thr Pro Thr Asn  Thr Pro Ser Ser Pro  Gly Ser
            10180                10185                10190

Thr His Leu  Leu Gln Ser Ser Lys  Thr Asp Phe Thr Ser  Ser Ala Lys
        10195                10200                10205
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Thr Ser Ser Pro Asp Trp Pro Pro Ala Ser Gln Tyr Thr Glu Ile Pro
10210 10215 10220

Val Asp Ile Ile Thr Pro Phe Asn Ala Ser Pro Ser Ile Thr Glu Ser
10225 10230 10235 10240

Thr Gly Ile Thr Ser Phe Pro Glu Ser Arg Phe Thr Met Ser Val Thr
10245 10250 10255

Glu Ser Thr His His Leu Ser Thr Asp Leu Leu Pro Ser Ala Glu Thr
10260 10265 10270

Ile Ser Thr Gly Thr Val Met Pro Ser Leu Ser Glu Ala Met Thr Ser
10275 10280 10285

Phe Ala Thr Thr Gly Val Pro Arg Ala Ile Ser Gly Ser Gly Ser Pro
10290 10295 10300

Phe Ser Arg Thr Glu Ser Gly Pro Gly Asp Ala Thr Leu Ser Thr Ile
10305 10310 10315 10320

Ala Glu Ser Leu Pro Ser Ser Thr Pro Val Pro Phe Ser Ser Ser Thr
10325 10330 10335

Phe Thr Thr Thr Asp Ser Ser Thr Ile Pro Ala Leu His Glu Ile Thr
10340 10345 10350

Ser Ser Ser Ala Thr Pro Tyr Arg Val Asp Thr Ser Leu Gly Thr Glu
10355 10360 10365

Ser Ser Thr Thr Glu Gly Arg Leu Val Met Val Ser Thr Leu Asp Thr
10370 10375 10380

Ser Ser Gln Pro Gly Arg Thr Ser Ser Ser Pro Ile Leu Asp Thr Arg
10385 10390 10395 10400

Met Thr Glu Ser Val Glu Leu Gly Thr Val Thr Ser Ala Tyr Gln Val
10405 10410 10415

Pro Ser Leu Ser Thr Arg Leu Thr Arg Thr Asp Gly Ile Met Glu His
10420 10425 10430

Ile Thr Lys Ile Pro Asn Glu Ala Ala His Arg Gly Thr Ile Arg Pro
10435 10440 10445

Val Lys Gly Pro Gln Thr Ser Thr Ser Pro Ala Ser Pro Lys Gly Leu
10450 10455 10460

His Thr Gly Gly Thr Lys Arg Met Glu Thr Thr Thr Thr Ala Leu Lys
10465 10470 10475 10480

Thr Thr Thr Thr Ala Leu Lys Thr Thr Ser Arg Ala Thr Leu Thr Thr
10485 10490 10495

Ser Val Tyr Thr Pro Thr Leu Gly Thr Leu Thr Pro Leu Asn Ala Ser
10500 10505 10510

Met Gln Met Ala Ser Thr Ile Pro Thr Glu Met Met Ile Thr Thr Pro
10515 10520 10525

Tyr Val Phe Pro Asp Val Pro Glu Thr Thr Ser Ser Leu Ala Thr Ser
10530 10535 10540

Leu Gly Ala Glu Thr Ser Thr Ala Leu Pro Arg Thr Thr Pro Ser Val
10545 10550 10555 10560

Phe Asn Arg Glu Ser Glu Thr Thr Ala Ser Leu Val Ser Arg Ser Gly
10565 10570 10575

Ala Glu Arg Ser Pro Val Ile Gln Thr Leu Asp Val Ser Ser Ser Glu
10580 10585 10590

Pro Asp Thr Thr Ala Ser Trp Val Ile His Pro Ala Glu Thr Ile Pro
10595 10600 10605

Thr Val Ser Lys Thr Thr Pro Asn Phe Phe His Ser Glu Leu Asp Thr

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    10610                10615                10620

Val  Ser Ser Thr Ala Thr  Ser His Gly Ala Asp  Val Ser Ser Ala Ile
10625                10630                10635                10640

Pro Thr Asn Ile Ser  Pro Ser Glu Leu Asp  Ala Leu Thr Pro Leu  Val
                10645                10650                10655

Thr Ile Ser Gly  Thr Asp Thr Ser Thr  Thr Phe Pro Thr Leu  Thr Lys
            10660                10665                10670

Ser Pro His  Glu Thr Glu Thr Arg  Thr Thr Trp Leu Thr  His Pro Ala
        10675                10680                10685

Glu Thr  Ser Ser Thr Ile Pro  Arg Thr Ile Pro Asn  Phe Ser His His
    10690                10695                10700

Glu  Ser Asp Ala Thr Pro  Ser Ile Ala Thr Ser  Pro Gly Ala Glu Thr
10705                10710                10715                10720

Ser Ser Ala Ile Pro  Ile Met Thr Val Ser  Pro Gly Ala Glu Asp  Leu
                10725                10730                10735

Val Thr Ser Gln  Val Thr Ser Ser Gly  Thr Asp Arg Asn Met  Thr Ile
            10740                10745                10750

Pro Thr Leu  Thr Leu Ser Pro Gly  Glu Pro Lys Thr Ile  Ala Ser Leu
        10755                10760                10765

Val Thr  His Pro Glu Ala Gln  Thr Ser Ser Ala Ile  Pro Thr Ser Thr
    10770                10775                10780

Ile  Ser Pro Ala Val Ser  Arg Leu Val Thr Ser  Met Val Thr Ser Leu
10785                10790                10795                10800

Ala Ala Lys Thr Ser  Thr Thr Asn Arg Ala  Leu Thr Asn Ser Pro  Gly
                10805                10810                10815

Glu Pro Ala Thr  Thr Val Ser Leu Val  Thr His Pro Ala Gln  Thr Ser
            10820                10825                10830

Pro Thr Val  Pro Trp Thr Thr Ser  Ile Phe Phe His Ser  Lys Ser Asp
        10835                10840                10845

Thr Thr  Pro Ser Met Thr Thr  Ser His Gly Ala Glu  Ser Ser Ser Ala
    10850                10855                10860

Val  Pro Thr Pro Thr Val  Ser Thr Glu Val Pro  Gly Val Val Thr Pro
10865                10870                10875                10880

Leu Val Thr Ser Ser  Arg Ala Val Ile Ser  Thr Thr Ile Pro Ile  Leu
                10885                10890                10895

Thr Leu Ser Pro  Gly Glu Pro Glu Thr  Thr Pro Ser Met Ala  Thr Ser
            10900                10905                10910

His Gly Glu  Glu Ala Ser Ser Ala  Ile Pro Thr Pro Thr  Val Ser Pro
        10915                10920                10925

Gly Val  Pro Gly Val Val Thr  Ser Leu Val Thr Ser  Ser Arg Ala Val
    10930                10935                10940

Thr  Ser Thr Thr Ile Pro  Ile Leu Thr Phe Ser  Leu Gly Glu Pro Glu
10945                10950                10955                10960

Thr Thr Pro Ser Met  Ala Thr Ser His Gly  Thr Glu Ala Gly Ser  Ala
                10965                10970                10975

Val Pro Thr Val  Leu Pro Glu Val Pro  Gly Met Val Thr Ser  Leu Val
            10980                10985                10990

Ala Ser Ser  Arg Ala Val Thr Ser  Thr Thr Leu Pro Thr  Leu Thr Leu
        10995                11000                11005

Ser Pro  Gly Glu Pro Glu Thr  Thr Pro Ser Met Ala  Thr Ser His Gly
    11010                11015                11020
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Ala Glu Ala Ser Ser Thr Val Pro Thr Val Ser Pro Glu Val Pro Gly
11025               11030               11035               11040

Val Val Thr Ser Leu Val Thr Ser Ser Ser Gly Val Asn Ser Thr Ser
                11045               11050               11055

Ile Pro Thr Leu Ile Leu Ser Pro Gly Glu Leu Glu Thr Thr Pro Ser
            11060               11065               11070

Met Ala Thr Ser His Gly Ala Glu Ala Ser Ser Ala Val Pro Thr Pro
        11075               11080               11085

Thr Val Ser Pro Gly Val Ser Gly Val Val Thr Pro Leu Val Thr Ser
    11090               11095               11100

Ser Arg Ala Val Thr Ser Thr Thr Ile Pro Ile Leu Thr Leu Ser Ser
11105               11110               11115               11120

Ser Glu Pro Glu Thr Thr Pro Ser Met Ala Thr Ser His Gly Val Glu
                11125               11130               11135

Ala Ser Ser Ala Val Leu Thr Val Ser Pro Glu Val Pro Gly Met Val
            11140               11145               11150

Thr Ser Leu Val Thr Ser Ser Arg Ala Val Thr Ser Thr Thr Ile Pro
        11155               11160               11165

Thr Leu Thr Ile Ser Ser Asp Glu Pro Glu Thr Thr Thr Ser Leu Val
    11170               11175               11180

Thr His Ser Glu Ala Lys Met Ile Ser Ala Ile Pro Thr Leu Ala Val
11185               11190               11195               11200

Ser Pro Thr Val Gln Gly Leu Val Thr Ser Leu Val Thr Ser Ser Gly
                11205               11210               11215

Ser Glu Thr Ser Ala Phe Ser Asn Leu Thr Val Ala Ser Ser Gln Pro
            11220               11225               11230

Glu Thr Ile Asp Ser Trp Val Ala His Pro Gly Thr Glu Ala Ser Ser
        11235               11240               11245

Val Val Pro Thr Leu Thr Val Ser Thr Gly Glu Pro Phe Thr Asn Ile
    11250               11255               11260

Ser Leu Val Thr His Pro Ala Glu Ser Ser Ser Thr Leu Pro Arg Thr
11265               11270               11275               11280

Thr Ser Arg Phe Ser His Ser Glu Leu Asp Thr Met Pro Ser Thr Val
                11285               11290               11295

Thr Ser Pro Glu Ala Glu Ser Ser Ser Ala Ile Ser Thr Thr Ile Ser
            11300               11305               11310

Pro Gly Ile Pro Gly Val Leu Thr Ser Leu Val Thr Ser Ser Gly Arg
        11315               11320               11325

Asp Ile Ser Ala Thr Phe Pro Thr Val Pro Glu Ser Pro His Glu Ser
    11330               11335               11340

Glu Ala Thr Ala Ser Trp Val Thr His Pro Ala Val Thr Ser Thr Thr
11345               11350               11355               11360

Val Pro Arg Thr Thr Pro Asn Tyr Ser His Ser Glu Pro Asp Thr Thr
                11365               11370               11375

Pro Ser Ile Ala Thr Ser Pro Gly Ala Glu Ala Thr Ser Asp Phe Pro
            11380               11385               11390

Thr Ile Thr Val Ser Pro Asp Val Pro Asp Met Val Thr Ser Gln Val
        11395               11400               11405

Thr Ser Ser Gly Thr Asp Thr Ser Ile Thr Ile Pro Thr Leu Thr Leu
    11410               11415               11420
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Ser Ser Gly Glu Pro Glu Thr Thr Thr Ser Phe Ile Thr Tyr Ser Glu
11425               11430               11435               11440

Thr His Thr Ser Ser Ala Ile Pro Thr Leu Pro Val Ser Pro Gly Ala
                11445               11450               11455

Ser Lys Met Leu Thr Ser Leu Val Ile Ser Ser Gly Thr Asp Ser Thr
            11460               11465               11470

Thr Thr Phe Pro Thr Leu Thr Glu Thr Pro Tyr Glu Pro Glu Thr Thr
        11475               11480               11485

Ala Ile Gln Leu Ile His Pro Ala Glu Thr Asn Thr Met Val Pro Arg
    11490               11495               11500

Thr Thr Pro Lys Phe Ser His Ser Lys Ser Asp Thr Thr Leu Pro Val
11505               11510               11515               11520

Ala Ile Thr Ser Pro Gly Pro Glu Ala Ser Ser Ala Val Ser Thr Thr
                11525               11530               11535

Thr Ile Ser Pro Asp Met Ser Asp Leu Val Thr Ser Leu Val Pro Ser
            11540               11545               11550

Ser Gly Thr Asp Thr Ser Thr Thr Phe Pro Thr Leu Ser Glu Thr Pro
        11555               11560               11565

Tyr Glu Pro Glu Thr Thr Ala Thr Trp Leu Thr His Pro Ala Glu Thr
    11570               11575               11580

Ser Thr Thr Val Ser Gly Thr Ile Pro Asn Phe Ser His Arg Gly Ser
11585               11590               11595               11600

Asp Thr Ala Pro Ser Met Val Thr Ser Pro Gly Val Asp Thr Arg Ser
                11605               11610               11615

Gly Val Pro Thr Thr Thr Ile Pro Pro Ser Ile Pro Gly Val Val Thr
            11620               11625               11630

Ser Gln Val Thr Ser Ser Ala Thr Asp Thr Ser Thr Ala Ile Pro Thr
        11635               11640               11645

Leu Thr Pro Ser Pro Gly Glu Pro Glu Thr Thr Ala Ser Ser Ala Thr
    11650               11655               11660

His Pro Gly Thr Gln Thr Gly Phe Thr Val Pro Ile Arg Thr Val Pro
11665               11670               11675               11680

Ser Ser Glu Pro Asp Thr Met Ala Ser Trp Val Thr His Pro Pro Gln
                11685               11690               11695

Thr Ser Thr Pro Val Ser Arg Thr Thr Ser Ser Phe Ser His Ser Ser
            11700               11705               11710

Pro Asp Ala Thr Pro Val Met Ala Thr Ser Pro Arg Thr Glu Ala Ser
        11715               11720               11725

Ser Ala Val Leu Thr Thr Ile Ser Pro Gly Ala Pro Glu Met Val Thr
    11730               11735               11740

Ser Gln Ile Thr Ser Ser Gly Ala Ala Thr Ser Thr Thr Val Pro Thr
11745               11750               11755               11760

Leu Thr His Ser Pro Gly Met Pro Glu Thr Thr Ala Leu Leu Ser Thr
                11765               11770               11775

His Pro Arg Thr Glu Thr Ser Lys Thr Phe Pro Ala Ser Thr Val Phe
            11780               11785               11790

Pro Gln Val Ser Glu Thr Thr Ala Ser Leu Thr Ile Arg Pro Gly Ala
        11795               11800               11805

Glu Thr Ser Thr Ala Leu Pro Thr Gln Thr Thr Ser Ser Leu Phe Thr
    11810               11815               11820

Leu Leu Val Thr Gly Thr Ser Arg Val Asp Leu Ser Pro Thr Ala Ser
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11825                11830                11835                11840

Pro Gly Val Ser Ala  Lys Thr Ala Pro Leu  Ser Thr His Pro Gly  Thr
                11845                11850                11855

Glu Thr Ser Thr  Met Ile Pro Thr Ser  Thr Leu Ser Leu Gly  Leu Leu
            11860                11865                11870

Glu Thr Thr  Gly Leu Leu Ala Thr  Ser Ser Ser Ala Glu  Thr Ser Thr
        11875                11880                11885

Ser Thr  Leu Thr Leu Thr Val  Ser Pro Ala Val Ser  Gly Leu Ser Ser
    11890                11895                11900

Ala  Ser Ile Thr Thr Asp  Lys Pro Gln Thr Val  Thr Ser Trp Asn Thr
11905                11910                11915                11920

Glu Thr Ser Pro Ser  Val Thr Ser Val Gly  Pro Pro Glu Phe Ser  Arg
                11925                11930                11935

Thr Val Thr Gly  Thr Thr Met Thr Leu  Ile Pro Ser Glu Met  Pro Thr
            11940                11945                11950

Pro Pro Lys  Thr Ser His Gly Glu  Gly Val Ser Pro Thr  Thr Ile Leu
        11955                11960                11965

Arg Thr  Thr Met Val Glu Ala  Thr Asn Leu Ala Thr  Thr Gly Ser Ser
    11970                11975                11980

Pro  Thr Val Ala Lys Thr  Thr Thr Thr Phe Asn  Thr Leu Ala Gly Ser
11985                11990                11995                12000

Leu Phe Thr Pro Leu  Thr Thr Pro Gly Met  Ser Thr Leu Ala Ser  Glu
                12005                12010                12015

Ser Val Thr Ser  Arg Thr Ser Tyr Asn  His Arg Ser Trp Ile  Ser Thr
            12020                12025                12030

Thr Ser Ser  Tyr Asn Arg Arg Tyr  Trp Thr Pro Ala Thr  Ser Thr Pro
        12035                12040                12045

Val Thr  Ser Thr Phe Ser Pro  Gly Ile Ser Thr Ser  Ser Ile Pro Ser
    12050                12055                12060

Ser  Thr Ala Ala Thr Val  Pro Phe Met Val Pro  Phe Thr Leu Asn Phe
12065                12070                12075                12080

Thr Ile Thr Asn Leu  Gln Tyr Glu Glu Asp  Met Arg His Pro Gly  Ser
                12085                12090                12095

Arg Lys Phe Asn  Ala Thr Glu Arg Glu  Leu Gln Gly Leu Leu  Lys Pro
            12100                12105                12110

Leu Phe Arg  Asn Ser Ser Leu Glu  Tyr Leu Tyr Ser Gly  Cys Arg Leu
        12115                12120                12125

Ala Ser  Leu Arg Pro Glu Lys  Asp Ser Ser Ala Thr  Ala Val Asp Ala
    12130                12135                12140

Ile  Cys Thr His Arg Pro  Asp Pro Glu Asp Leu  Gly Leu Asp Arg Glu
12145                12150                12155                12160

Arg Leu Tyr Trp Glu  Leu Ser Asn Leu Thr  Asn Gly Ile Gln Glu  Leu
                12165                12170                12175

Gly Pro Tyr Thr  Leu Asp Arg Asn Ser  Leu Tyr Val Asn Gly  Phe Thr
            12180                12185                12190

His Arg Ser  Ser Met Pro Thr Thr  Ser Thr Pro Gly Thr  Ser Thr Val
        12195                12200                12205

Asp Val  Gly Thr Ser Gly Thr  Pro Ser Ser Ser Pro  Ser Pro Thr Thr
    12210                12215                12220

Ala  Gly Pro Leu Leu Met  Pro Phe Thr Leu Asn  Phe Thr Ile Thr Asn
12225                12230                12235                12240
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Leu Gln Tyr Glu Glu  Asp Met Arg Arg Thr  Gly Ser Arg Lys Phe  Asn
                12245               12250               12255

Thr Met Glu Ser  Val Leu Gln Gly Leu  Leu Lys Pro Leu Phe  Lys Asn
            12260               12265               12270

Thr Ser Val  Gly Pro Leu Tyr Ser  Gly Cys Arg Leu Thr  Leu Leu Arg
        12275               12280               12285

Pro Glu  Lys Asp Gly Ala Ala  Thr Gly Val Asp Ala  Ile Cys Thr His
    12290               12295               12300

Arg  Leu Asp Pro Lys Ser  Pro Gly Leu Asn Arg  Glu Gln Leu Tyr Trp
12305               12310               12315               12320

Glu Leu Ser Lys Leu  Thr Asn Asp Ile Glu  Glu Leu Gly Pro Tyr  Thr
                12325               12330               12335

Leu Asp Arg Asn  Ser Leu Tyr Val Asn  Gly Phe Thr His Gln  Ser Ser
            12340               12345               12350

Val Ser Thr  Thr Ser Thr Pro Gly  Thr Ser Thr Val Asp  Leu Arg Thr
        12355               12360               12365

Ser Gly  Thr Pro Ser Ser Leu  Ser Ser Pro Thr Ile  Met Ala Ala Gly
    12370               12375               12380

Pro  Leu Leu Val Pro Phe  Thr Leu Asn Phe Thr  Ile Thr Asn Leu Gln
12385               12390               12395               12400

Tyr Gly Glu Asp Met  Gly His Pro Gly Ser  Arg Lys Phe Asn Thr  Thr
                12405               12410               12415

Glu Arg Val Leu  Gln Gly Leu Leu Gly  Pro Ile Phe Lys Asn  Thr Ser
            12420               12425               12430

Val Gly Pro  Leu Tyr Ser Gly Cys  Arg Leu Thr Ser Leu  Arg Ser Glu
        12435               12440               12445

Lys Asp  Gly Ala Ala Thr Gly  Val Asp Ala Ile Cys  Ile His His Leu
    12450               12455               12460

Asp  Pro Lys Ser Pro Gly  Leu Asn Arg Glu Arg  Leu Tyr Trp Glu Leu
12465               12470               12475               12480

Ser Gln Leu Thr Asn  Gly Ile Lys Glu Leu  Gly Pro Tyr Thr Leu  Asp
                12485               12490               12495

Arg Asn Ser Leu  Tyr Val Asn Gly Phe  Thr His Arg Thr Ser  Val Pro
            12500               12505               12510

Thr Ser Ser  Thr Pro Gly Thr Ser  Thr Val Asp Leu Gly  Thr Ser Gly
        12515               12520               12525

Thr Pro  Phe Ser Leu Pro Ser  Pro Ala Thr Ala Gly  Pro Leu Leu Val
    12530               12535               12540

Leu  Phe Thr Leu Asn Phe  Thr Ile Thr Asn Leu  Lys Tyr Glu Glu Asp
12545               12550               12555               12560

Met His Arg Pro Gly  Ser Arg Lys Phe Asn  Thr Thr Glu Arg Val  Leu
                12565               12570               12575

Gln Thr Leu Leu  Gly Pro Met Phe Lys  Asn Thr Ser Val Gly  Leu Leu
            12580               12585               12590

Tyr Ser Gly  Cys Arg Leu Thr Leu  Leu Arg Ser Glu Lys  Asp Gly Ala
        12595               12600               12605

Ala Thr  Gly Val Asp Ala Ile  Cys Thr His Arg Leu  Asp Pro Lys Ser
    12610               12615               12620

Pro  Gly Val Asp Arg Glu  Gln Leu Tyr Trp Glu  Leu Ser Gln Leu Thr
12625               12630               12635               12640
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Asn Gly Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu
                12645               12650               12655

Tyr Val Asn Gly Phe Thr His Trp Ile Pro Val Pro Thr Ser Ser Thr
            12660               12665               12670

Pro Gly Thr Ser Thr Val Asp Leu Gly Ser Gly Thr Pro Ser Ser Leu
        12675               12680               12685

Pro Ser Pro Thr Thr Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn
    12690               12695               12700

Phe Thr Ile Thr Asn Leu Lys Tyr Glu Glu Asp Met His Cys Pro Gly
12705               12710               12715               12720

Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Ser Leu Leu Gly
                12725               12730               12735

Pro Met Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg
            12740               12745               12750

Leu Thr Leu Leu Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp
        12755               12760               12765

Ala Ile Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg
    12770               12775               12780

Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Gly Ile Lys Glu
12785               12790               12795               12800

Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn Gly Phe
                12805               12810               12815

Thr His Gln Thr Ser Ala Pro Asn Thr Ser Thr Pro Gly Thr Ser Thr
            12820               12825               12830

Val Asp Leu Gly Thr Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro Thr
        12835               12840               12845

Ser Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile Thr
    12850               12855               12860

Asn Leu Gln Tyr Glu Glu Asp Met His His Pro Gly Ser Arg Lys Phe
12865               12870               12875               12880

Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Met Phe Lys
                12885               12890               12895

Asn Thr Ser Val Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu
            12900               12905               12910

Arg Pro Glu Lys Asn Gly Ala Ala Thr Gly Met Asp Ala Ile Cys Ser
        12915               12920               12925

His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg Glu Gln Leu Tyr
    12930               12935               12940

Trp Glu Leu Ser Gln Leu Thr His Gly Ile Lys Glu Leu Gly Pro Tyr
12945               12950               12955               12960

Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn Gly Phe Thr His Arg Ser
                12965               12970               12975

Ser Val Ala Pro Thr Ser Thr Pro Gly Thr Ser Thr Val Asp Leu Gly
            12980               12985               12990

Thr Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro Thr Thr Ala Val Pro
        12995               13000               13005

Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr
    13010               13015               13020

Gly Glu Asp Met Arg His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu
13025               13030               13035               13040

Arg Val Leu Gln Gly Leu Leu Gly Pro Leu Phe Lys Asn Ser Ser Val
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                13045                13050                13055

Gly Pro Leu Tyr  Ser Gly Cys Arg Leu  Ile Ser Leu Arg Ser  Glu Lys
            13060                13065                13070

Asp Gly Ala  Ala Thr Gly Val Asp  Ala Ile Cys Thr His  His Leu Asn
        13075                13080                13085

Pro Gln  Ser Pro Gly Leu Asp  Arg Glu Gln Leu Tyr  Trp Gln Leu Ser
    13090                13095                13100

Gln  Met Thr Asn Gly Ile  Lys Glu Leu Gly Pro  Tyr Thr Leu Asp Arg
13105                13110                13115                13120

Asn Ser Leu Tyr Val  Asn Gly Phe Thr His  Arg Ser Ser Gly Leu  Thr
                13125                13130                13135

Thr Ser Thr Pro  Trp Thr Ser Thr Val  Asp Leu Gly Thr Ser  Gly Thr
            13140                13145                13150

Pro Ser Pro  Val Pro Ser Pro Thr  Thr Thr Gly Pro Leu  Leu Val Pro
        13155                13160                13165

Phe Thr  Leu Asn Phe Thr Ile  Thr Asn Leu Gln Tyr  Glu Glu Asn Met
    13170                13175                13180

Gly  His Pro Gly Ser Arg  Lys Phe Asn Ile Thr  Glu Ser Val Leu Gln
13185                13190                13195                13200

Gly Leu Leu Lys Pro  Leu Phe Lys Ser Thr  Ser Val Gly Pro Leu  Tyr
                13205                13210                13215

Ser Gly Cys Arg  Leu Thr Leu Leu Arg  Pro Glu Lys Asp Gly  Val Ala
            13220                13225                13230

Thr Arg Val  Asp Ala Ile Cys Thr  His Arg Pro Asp Pro  Lys Ile Pro
        13235                13240                13245

Gly Leu  Asp Arg Gln Gln Leu  Tyr Trp Glu Leu Ser  Gln Leu Thr His
    13250                13255                13260

Ser  Ile Thr Glu Leu Gly  Pro Tyr Thr Leu Asp  Arg Asp Ser Leu Tyr
13265                13270                13275                13280

Val Asn Gly Phe Thr  Gln Arg Ser Ser Val  Pro Thr Thr Ser Thr  Pro
                13285                13290                13295

Gly Thr Phe Thr  Val Gln Pro Glu Thr  Ser Glu Thr Pro Ser  Ser Leu
            13300                13305                13310

Pro Gly Pro  Thr Ala Thr Gly Pro  Val Leu Leu Pro Phe  Thr Leu Asn
        13315                13320                13325

Phe Thr  Ile Thr Asn Leu Gln  Tyr Glu Glu Asp Met  Arg Arg Pro Gly
    13330                13335                13340

Ser  Arg Lys Phe Asn Thr  Thr Glu Arg Val Leu  Gln Gly Leu Leu Met
13345                13350                13355                13360

Pro Leu Phe Lys Asn  Thr Ser Val Ser Ser  Leu Tyr Ser Gly Cys  Arg
                13365                13370                13375

Leu Thr Leu Leu  Arg Pro Glu Lys Asp  Gly Ala Ala Thr Arg  Val Asp
            13380                13385                13390

Ala Val Cys  Thr His Arg Pro Asp  Pro Lys Ser Pro Gly  Leu Asp Arg
        13395                13400                13405

Glu Arg  Leu Tyr Trp Lys Leu  Ser Gln Leu Thr His  Gly Ile Thr Glu
    13410                13415                13420

Leu  Gly Pro Tyr Thr Leu  Asp Arg His Ser Leu  Tyr Val Asn Gly Phe
13425                13430                13435                13440

Thr His Gln Ser Ser  Met Thr Thr Thr Arg  Thr Pro Asp Thr Ser  Thr
                13445                13450                13455
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Met His Leu Ala  Thr Ser Arg Thr Pro  Ala Ser Leu Ser Gly  Pro Met
            13460                13465                13470

Thr Ala Ser  Pro Leu Leu Val Leu  Phe Thr Ile Asn Phe  Thr Ile Thr
        13475                13480                13485

Asn Leu  Arg Tyr Glu Glu Asn  Met His His Pro Gly  Ser Arg Lys Phe
    13490                13495                13500

Asn  Thr Thr Glu Arg Val  Leu Gln Gly Leu Leu  Arg Pro Val Phe Lys
13505                13510                13515                13520

Asn Thr Ser Val Gly  Pro Leu Tyr Ser Gly  Cys Arg Leu Thr Leu  Leu
                13525                13530                13535

Arg Pro Lys Lys  Asp Gly Ala Ala Thr  Lys Val Asp Ala Ile  Cys Thr
            13540                13545                13550

Tyr Arg Pro  Asp Pro Lys Ser Pro  Gly Leu Asp Arg Glu  Gln Leu Tyr
        13555                13560                13565

Trp Glu  Leu Ser Gln Leu Thr  His Ser Ile Thr Glu  Leu Gly Pro Tyr
    13570                13575                13580

Thr  Leu Asp Arg Asp Ser  Leu Tyr Val Asn Gly  Phe Thr Gln Arg Ser
13585                13590                13595                13600

Ser Val Pro Thr Thr  Ser Ile Pro Gly Thr  Pro Thr Val Asp Leu  Gly
                13605                13610                13615

Thr Ser Gly Thr  Pro Val Ser Lys Pro  Gly Pro Ser Ala Ala  Ser Pro
            13620                13625                13630

Leu Leu Val  Leu Phe Thr Leu Asn  Phe Thr Ile Thr Asn  Leu Arg Tyr
        13635                13640                13645

Glu Glu  Asn Met Gln His Pro  Gly Ser Arg Lys Phe  Asn Thr Thr Glu
    13650                13655                13660

Arg  Val Leu Gln Gly Leu  Leu Arg Ser Leu Phe  Lys Ser Thr Ser Val
13665                13670                13675                13680

Gly Pro Leu Tyr Ser  Gly Cys Arg Leu Thr  Leu Leu Arg Pro Glu  Lys
                13685                13690                13695

Asp Gly Thr Ala  Thr Gly Val Asp Ala  Ile Cys Thr His His  Pro Asp
            13700                13705                13710

Pro Lys Ser  Pro Arg Leu Asp Arg  Glu Gln Leu Tyr Trp  Glu Leu Ser
        13715                13720                13725

Gln Leu  Thr His Asn Ile Thr  Glu Leu Gly Pro Tyr  Ala Leu Asp Asn
    13730                13735                13740

Asp  Ser Leu Phe Val Asn  Gly Phe Thr His Arg  Ser Ser Val Ser Thr
13745                13750                13755                13760

Thr Ser Thr Pro Gly  Thr Pro Thr Val Tyr  Leu Gly Ala Ser Lys  Thr
                13765                13770                13775

Pro Ala Ser Ile  Phe Gly Pro Ser Ala  Ala Ser His Leu Leu  Ile Leu
            13780                13785                13790

Phe Thr Leu  Asn Phe Thr Ile Thr  Asn Leu Arg Tyr Glu  Glu Asn Met
        13795                13800                13805

Trp Pro  Gly Ser Arg Lys Phe  Asn Thr Thr Glu Arg  Val Leu Gln Gly
    13810                13815                13820

Leu  Leu Arg Pro Leu Phe  Lys Asn Thr Ser Val  Gly Pro Leu Tyr Ser
13825                13830                13835                13840

Gly Cys Arg Leu Thr  Leu Leu Arg Pro Glu  Lys Asp Gly Glu Ala  Thr
                13845                13850                13855
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Gly Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Thr Gly Pro Gly
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Leu Asp Arg Glu Gln Leu Tyr Leu Glu Leu Ser Gln Leu Thr His Ser
        13875               13880               13885

Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val
    13890               13895               13900

Asn Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Thr Gly Val
13905               13910               13915               13920

Val Ser Glu Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn Leu Arg
                13925               13930               13935

Tyr Met Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn Ile Thr
            13940               13945               13950

Asp Asn Val Met Gln His Leu Leu Ser Pro Leu Phe Gln Arg Ser Ser
        13955               13960               13965

Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg Ser Val
    13970               13975               13980

Lys Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr Leu Gln
13985               13990               13995               14000

Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe His Glu Leu
                14005               14010               14015

Ser Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro Tyr Ser Leu Asp
            14020               14025               14030

Lys Asp Ser Leu Tyr Leu Asn Gly Tyr Asn Glu Pro Gly Pro Asp Glu
        14035               14040               14045

Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Phe Leu Pro Pro Leu Ser
    14050               14055               14060

Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr Leu Asn
14065               14070               14075               14080

Phe Thr Ile Ser Asn Leu Gln Tyr Ser Pro Asp Met Gly Lys Gly Ser
                14085               14090               14095

Ala Thr Phe Asn Ser Thr Glu Gly Val Leu Gln His Leu Leu Arg Pro
            14100               14105               14110

Leu Phe Gln Lys Ser Ser Met Gly Pro Phe Tyr Leu Gly Cys Gln Leu
        14115               14120               14125

Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Thr
    14130               14135               14140

Thr Cys Thr Tyr His Pro Asp Pro Val Gly Pro Gly Leu Asp Ile Gln
14145               14150               14155               14160

Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Val Thr Gln Leu
                14165               14170               14175

Gly Phe Tyr Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr Ala
            14180               14185               14190

Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His Ile
        14195               14200               14205

Val Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr Ile
    14210               14215               14220

Thr Leu Leu Arg Asp Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys Gly
14225               14230               14235               14240

Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu Val Thr Asn Leu Thr
                14245               14250               14255

Met Asp Ser Val Leu Val Thr Val Lys Ala Leu Phe Ser Ser Asn Leu
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            14260               14265               14270

Asp Pro Ser  Leu Val Glu Gln Val  Phe Leu Asp Lys Thr  Leu Asn Ala
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Ser Phe  His Trp Leu Gly Ser  Thr Tyr Gln Leu Val  Asp Ile His Val
    14290               14295               14300

Thr  Glu Met Glu Ser Ser  Val Tyr Gln Pro Thr  Ser Ser Ser Ser Thr
14305               14310               14315               14320

Gln His Phe Tyr Leu  Asn Phe Thr Ile Thr  Asn Leu Pro Tyr Ser  Gln
                14325               14330               14335

Asp Lys Ala Gln  Pro Gly Thr Thr Asn  Tyr Gln Arg Asn Lys  Arg Asn
            14340               14345               14350

Ile Glu Asp  Ala Leu Asn Gln Leu  Phe Arg Asn Ser Ser  Ile Lys Ser
        14355               14360               14365

Tyr Phe  Ser Asp Cys Gln Val  Ser Thr Phe Arg Ser  Val Pro Asn Arg
    14370               14375               14380

His  His Thr Gly Val Asp  Ser Leu Cys Asn Phe  Ser Pro Leu Ala Arg
14385               14390               14395               14400

Arg Val Asp Arg Val  Ala Ile Tyr Glu Glu  Phe Leu Arg Met Thr  Arg
                14405               14410               14415

Asn Gly Thr Gln  Leu Gln Asn Phe Thr  Leu Asp Arg Ser Ser  Val Leu
            14420               14425               14430

Val Asp Gly  Tyr Ser Pro Asn Arg  Asn Glu Pro Leu Thr  Gly Asn Ser
        14435               14440               14445

Asp Leu  Pro Phe Trp Ala Val  Ile Leu Ile Gly Leu  Ala Gly Leu Leu
    14450               14455               14460

Gly  Val Ile Thr Cys Leu  Ile Cys Gly Val Leu  Val Thr Thr Arg Arg
14465               14470               14475               14480

Arg Lys Lys Glu Gly  Glu Tyr Asn Val Gln  Gln Gln Cys Pro Gly  Tyr
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Tyr Gln Ser His  Leu Asp Leu Glu Asp  Leu Gln
            14500               14505


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<212> TYPE: DNA
    <213> ORGANISM: Homo sapiens

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attgaggatg cgctcaacca actcttccga aacagcagca tcaagagtta tttttctgac 43320

tgtcaagttt caacattcag gtctgtcccc aacaggcacc acaccggggt ggactccctg 43380

tgtaacttct cgccactggc tcggagagta gacagagttg ccatctatga ggaatttctg 43440

cggatgaccc ggaatggtac ccagctgcag aacttcaccc tggacaggag cagtgtcctt 43500

gtggatgggt attctcccaa cagaaatgag cccttaactg ggaattctga ccttcccttc 43560

tgggctgtca tcctcatcgg cttggcagga ctcctgggag tcatcacatg cctgatctgc 43620

ggtgtcctgg tgaccacccg ccggcggaag aaggaaggag aatacaacgt ccagcaacag 43680

tgcccaggct actaccagtc acacctagac ctggaggatc tgcaatgact ggaacttgcc 43740

ggtgcctggg gtgcctttcc cccagccagg gtccaaagaa gcttggctgg ggcagaaata 43800

aaccatattg gtcgga 43816

<210> SEQ ID NO 59
<211> LENGTH: 267

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

Met Arg Leu Thr Val Leu Cys Ala Val Cys Leu Leu Pro Gly Ser Leu
1               5                   10                  15

Ala Leu Pro Leu Pro Gln Glu Ala Gly Gly Met Ser Glu Leu Gln Trp
            20                  25                  30

Glu Gln Ala Gln Asp Tyr Leu Lys Arg Phe Tyr Leu Tyr Asp Ser Glu
        35                  40                  45

Thr Lys Asn Ala Asn Ser Leu Glu Ala Lys Leu Lys Glu Met Gln Lys
    50                  55                  60

Phe Phe Gly Leu Pro Ile Thr Gly Met Leu Asn Ser Arg Val Ile Glu
65                  70                  75                  80

Ile Met Gln Lys Pro Arg Cys Gly Val Pro Asp Val Ala Glu Tyr Ser
                85                  90                  95

Leu Phe Pro Asn Ser Pro Lys Trp Thr Ser Lys Val Val Thr Tyr Arg
            100                 105                 110

Ile Val Ser Tyr Thr Arg Asp Leu Pro His Ile Thr Val Asp Arg Leu
        115                 120                 125

Val Ser Lys Ala Leu Asn Met Trp Gly Lys Glu Ile Pro Leu His Phe
    130                 135                 140

Arg Lys Val Val Trp Gly Thr Ala Asp Ile Met Ile Gly Phe Ala Arg
145                 150                 155                 160

Gly Ala His Gly Asp Ser Tyr Pro Phe Asp Gly Pro Gly Asn Thr Leu
                165                 170                 175

Ala His Ala Phe Ala Pro Gly Thr Gly Leu Gly Gly Asp Ala His Phe
            180                 185                 190

Asp Glu Asp Glu Arg Trp Thr Asp Gly Ser Ser Leu Gly Ile Asn Phe
        195                 200                 205

Leu Tyr Ala Ala Thr His Glu Leu Gly His Ser Leu Gly Met Gly His
    210                 215                 220

Ser Ser Asp Pro Asn Ala Val Met Tyr Pro Thr Tyr Gly Asn Gly Asp
225                 230                 235                 240

Pro Gln Asn Phe Lys Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Lys
                245                 250                 255

Leu Tyr Gly Lys Arg Ser Asn Ser Arg Lys Lys
            260                 265


<210> SEQ ID NO 60
<211> LENGTH: 1147
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

accaaatcaa ccataggtcc aagaacaatt gtctctggac ggcagctatg cgactcaccg      60

tgctgtgtgc tgtgtgcctg ctgcctggca gcctggccct gccgctgcct caggaggcgg     120

gaggcatgag tgagctacag tgggaacagg ctcaggacta tctcaagaga ttttatctct     180

atgactcaga aacaaaaaat gccaacagtt tagaagccaa actcaaggag atgcaaaaat     240

tctttggcct acctataact ggaatgttaa actcccgcgt catagaaata atgcagaagc     300

ccagatgtgg agtgccagat gttgcagaat actcactatt tccaaatagc ccaaaatgga     360
```

-continued

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cttccaaagt ggtcacctac aggatcgtat catatactcg agacttaccg catattacag    420

tggatcgatt agtgtcaaag gctttaaaca tgtggggcaa agagatcccc ctgcatttca    480

ggaaagttgt atggggaact gctgacatca tgattggctt tgcgcgagga gctcatgggg    540

actcctaccc atttgatggg ccaggaaaca cgctggctca tgcctttgcg cctgggacag    600

gtctcggagg agatgctcac ttcgatgagg atgaacgctg gacggatggt agcagtctag    660

ggattaactt cctgtatgct gcaactcatg aacttggcca ttctttgggt atgggacatt    720

cctctgatcc taatgcagtg atgtatccaa cctatggaaa tggagatccc caaaatttta    780

aactttccca ggatgatatt aaaggcattc agaaactata tggaaagaga agtaattcaa    840

gaaagaaata gaaacttcag gcagaacatc cattcattca ttcattggat tgtatatcat    900

tgttgcacaa tcagaattga taagcactgt tcctccactc catttagcaa ttatgtcacc    960

ctttttttatt gcagttggtt tttgaatgtc tttcactcct tttaaggata aactccttta   1020

tggtgtgact gtgtcttatt catctatact tgcagtgggt agatgtcaat aaatgttaca   1080

tacacaaata aataaaatgt ttattccatg gtaaatttaa aaaaaaaaaa aaaaaaaaaa   1140

aaaaaaa                                                             1147
```

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<210> SEQ ID NO 61
<211> LENGTH: 227
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

Met Asn Ile Lys Gly Ser Pro Trp Lys Gly Ser Leu Leu Leu Leu
1               5                   10                  15

Val Ser Asn Leu Leu Leu Cys Gln Ser Val Ala Pro Leu Pro Ile Cys
            20                  25                  30

Pro Gly Gly Ala Ala Arg Cys Gln Val Thr Leu Arg Asp Leu Phe Asp
        35                  40                  45

Arg Ala Val Val Leu Ser His Tyr Ile His Asn Leu Ser Ser Glu Met
    50                  55                  60

Phe Ser Glu Phe Asp Lys Arg Tyr Thr His Gly Arg Gly Phe Ile Thr
65                  70                  75                  80

Lys Ala Ile Asn Ser Cys His Thr Ser Ser Leu Ala Thr Pro Glu Asp
                85                  90                  95

Lys Glu Gln Ala Gln Gln Met Asn Gln Lys Asp Phe Leu Ser Leu Ile
            100                 105                 110

Val Ser Ile Leu Arg Ser Trp Asn Glu Pro Leu Tyr His Leu Val Thr
        115                 120                 125

Glu Val Arg Gly Met Gln Glu Ala Pro Glu Ala Ile Leu Ser Lys Ala
    130                 135                 140

Val Glu Ile Glu Glu Gln Thr Lys Arg Leu Leu Glu Gly Met Glu Leu
145                 150                 155                 160

Ile Val Ser Gln Val His Pro Glu Thr Lys Glu Asn Glu Ile Tyr Pro
                165                 170                 175

Val Trp Ser Gly Leu Pro Ser Leu Gln Met Ala Asp Glu Glu Ser Arg
            180                 185                 190

Leu Ser Ala Tyr Tyr Asn Leu Leu His Cys Leu Arg Arg Asp Ser His
        195                 200                 205

Lys Ile Asp Asn Tyr Leu Lys Leu Leu Lys Cys Arg Ile Ile His Asn
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-continued

210 215 220

Asn Asn Cys
225

<210> SEQ ID NO 62
<211> LENGTH: 1388
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

gggatcctta ttctatatct cttggtattt agtgtaaaaa ttttaaaatc tttacctagc 60

aatcttgagg aagaaacttg ataactgata atacatgaga ttgttaccta agtgaaatat 120

aatcctatat attcaacaaa ctttagagaa ataagataaa ttttaaagta aatgacttct 180

gtagttttat agatcctcca aaccaatcta gtctcagatc tcaccttcat catttctctc 240

atttcctttt ggcctaatta atcaaaatcc ttcctagaat gttcatttct ggccagtatg 300

tcttcctgaa tatgaataag aaataaaata ccatttgatg tttgaaatta tgggggtaat 360

ctcaatgacg gaaatagatg accaggaaaa gggaaacgaa tgcctgattc attatattca 420

tgaagatatc aaaggtttat aaagccaata tctgggaaag agaaaaccgt gagacttcca 480

gatcttctct ggtgaagtgt gtttcctgca acgatcacga acatgaacat caaaggatcg 540

ccatggaaag ggtccctcct gctgctgctg gtgtcaaacc tgctcctgtg ccagagcgtg 600

gccccottgc ccatctgtcc cggcggggct gcccgatgcc aggtgaccct tcgagacctg 660

tttgaccgcg ccgtcgtcct gtcccactac atccataacc tctcctcaga aatgttcagc 720

gaattcgata aacggtatac ccatggccgg gggttcatta ccaaggccat caacagctgc 780

cacacttctt cccttgccac ccccgaagac aaggagcaag cccaacagat gaatcaaaaa 840

gactttctga gcctgatagt cagcatattg cgatcctgga atgagcctct gtatcatctg 900

gtcacggaag tacgtggtat gcaagaagcc ccggaggcta tcctatccaa agctgtagag 960

attgaggagc aaaccaaacg gcttctagag ggcatggagc tgatagtcag ccaggttcat 1020

cctgaaacca aagaaaatga gatctaccct gtctggtcgg gacttccatc cctgcagatg 1080

gctgatgaag agtctcgcct ttctgcttat tataacctgc tccactgcct acgcagggat 1140

tcacataaaa tcgacaatta tctcaagctc ctgaagtgcc gaatcatcca caacaacaac 1200

tgctaagccc acatccattt catctatttc tgagaaggtc cttaatgatc cgttccattg 1260

caagcttctt ttagttgtat ctcttttgaa tccatgcttg ggtgtaacag gtctcctctt 1320

aaaaaataaa aactgactcc ttagagacat caaaatccaa aaaaaaaaaa aaaaaaaaaa 1380

aaaaaaaa 1388

<210> SEQ ID NO 63
<211> LENGTH: 132
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

Met Lys Ser Ser Gly Leu Phe Pro Phe Leu Val Leu Leu Ala Leu Gly
1 5 10 15

Thr Leu Ala Pro Trp Ala Val Glu Gly Ser Gly Lys Ser Phe Lys Ala
20 25 30

Gly Val Cys Pro Pro Lys Lys Ser Ala Gln Cys Leu Arg Tyr Lys Lys

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                                   -continued
        35                  40                  45

Pro Glu Cys Gln Ser Asp Trp Gln Cys Pro Gly Lys Lys Arg Cys Cys
    50                  55                  60

Pro Asp Thr Cys Gly Ile Lys Cys Leu Asp Pro Val Asp Thr Pro Asn
65                  70                  75                  80

Pro Thr Arg Arg Lys Pro Gly Lys Cys Pro Val Thr Tyr Gly Gln Cys
                85                  90                  95

Leu Met Leu Asn Pro Pro Asn Phe Cys Glu Met Asp Gly Gln Cys Lys
            100                 105                 110

Arg Asp Leu Lys Cys Cys Met Gly Met Cys Gly Lys Ser Cys Val Ser
        115                 120                 125

Pro Val Lys Ala
    130


<210> SEQ ID NO 64
<211> LENGTH: 598
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

cagagtcact cctgccttca ccatgaagtc cagcggcctc ttccccttcc tggtgctgct     60

tgccctggga actctggcac cttgggctgt ggaaggctct ggaaagtcct tcaaagctgg    120

agtctgtcct cctaagaaat ctgcccagtg ccttagatac aagaaacctg agtgccagag    180

tgactggcag tgtccaggga agaagagatg ttgtcctgac acttgtggca tcaaatgcct    240

ggatcctgtt gacaccccaa acccaacaag gaggaagcct gggaagtgcc cagtgactta    300

tggccaatgt ttgatgctta acccccccaa tttctgtgag atggatggcc agtgcaagcg    360

tgacttgaag tgttgcatgg gcatgtgtgg gaaatcctgc gtttcccctg tgaaagcttg    420

attcctgcca tatggaggag gctctggagt cctgctctgt gtggtccagg tcctttccac    480

cctgagactt ggctccacca ctgatatcct cctttgggga aaggcttggc acacagcagg    540

ctttcaagaa gtgccagttg atcaatgaat aaataaacga gcctatttct ctttgcac      598
```

That which is claimed:

1. A single-step screening method for identifying patients with an increased likelihood of having ovarian cancer, the method comprising detecting the expression level of three biomarker proteins in a body sample, wherein the biomarker proteins are HE4, CA125, and glycodelin, and wherein overexpression of at least one of the biomarker proteins is indicative of the patient having an increased likelihood of having ovarian cancer.

2. The method of claim **1**, wherein the body sample is a blood or serum sample.

3. The method of claim **1**, wherein the expression level of each of the three biomarker proteins is compared to the expression level of each of the three biomarker proteins in a normal patient population.

4. The method of claim **1**, wherein expression of the three biomarker proteins is detected using at least one antibody that specifically binds to HE4, at least one antibody that specifically binds to CA 125, and at least one antibody that specifically binds to glycodelin.

5. The method of claim **4**, wherein expression of the three biomarker proteins is detected using an ELISA format or a multiplex bead-based immunoassay.

6. The method of claim **1**, wherein the screening method is performed in an automated, semi-automated, or manual fashion.

7. The method of claim **1**, wherein the method is used to detect early-stage ovarian cancer.

8. The method of claim **1**, wherein the patients screened in accordance with the method of claim **1** are asymptomatic and have a family history of ovarian cancer or clinical risk factors indicating a high-risk for developing ovarian cancer.

9. The method of claim **1**, wherein the screening method is performed in a population of post-menopausal female patients.

10. The method of claim **1**, wherein patients identified as having an increased likelihood of having ovarian cancer are further subjected to additional diagnostic testing to determine if the patient has ovarian cancer, wherein the additional diagnostic testing is selected from the group consisting of pelvic examination, transvaginal ultrasound, CT scan, MRI, laparotomy, laparoscopy, and tissue sample biopsy.

11. The method of claim **10**, wherein patients identified as having an increased likelihood of having ovarian cancer that are determined not to currently have ovarian cancer are further monitored on a regular basis for the development of ovarian cancer.

12. The method of claim **1**, wherein the sensitivity of the screening method for identifying patients with an increased likelihood of having ovarian cancer is at least 80%.

13. The method of claim **1**, wherein the specificity of the screening method for identifying patients with an increased likelihood of having ovarian cancer is at least 75%.

* * * * *

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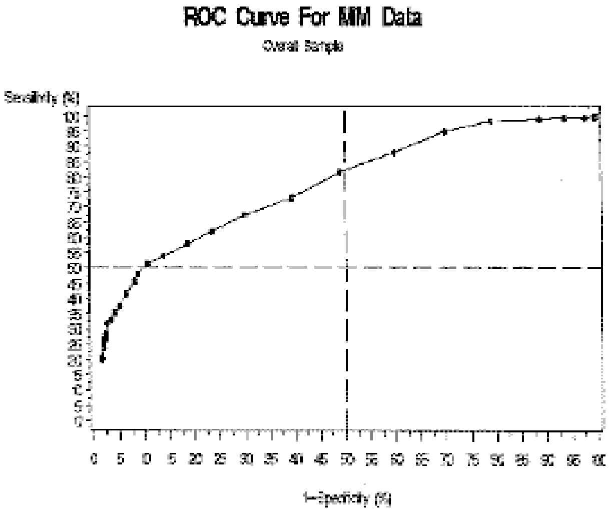
专利名称(译)	用于鉴定患有卵巢癌的可能性增加的患者的方法及其组合物		
公开(公告)号	US20090068690A1	公开(公告)日	2009-03-12
申请号	US12/261205	申请日	2008-10-30
申请(专利权)人(译)	TRIPATH IMAGING，INC.		
当前申请(专利权)人(译)	TRIPATH IMAGING，INC.		
[标]发明人	FISCHER TIMOTHY J MALINOWSKI DOUGLAS P HE QIN WHITEHEAD CLARK M CHEEK ROBERT L GROELKE JOHN W		
发明人	FISCHER, TIMOTHY J. MALINOWSKI, DOUGLAS P. HE, QIN WHITEHEAD, CLARK M. CHEEK, ROBERT L. GROELKE, JOHN W.		
IPC分类号	C12Q1/02 C12Q1/00 A61B5/00 A61B5/055 A61B10/00 G01N33/53		
CPC分类号	G01N33/57449		
优先权	60/762760 2006-01-27 US		
外部链接	Espacenet USPTO		

摘要(译)

提供了用于鉴定患有卵巢癌的可能性增加的患者的筛选方法。筛选方法涉及检测体样品中多种生物标志物的表达，其中生物标志物的过表达指示患卵巢癌的可能性增加。筛选方法可以进一步包括两步分析。感兴趣的生物标志物包括基因和蛋白质，其例如涉及DNA复制/细胞周期控制，细胞生长和增殖的缺陷，逃避细胞凋亡，血管生成或淋巴发生，或癌细胞运动和侵袭的机制。在本发明的一些方面，使用生物标志物特异性抗体在蛋白质水平检测生物标志物的表达，或使用核酸杂交技术在核酸水平检测生物标志物的表达。本文进一步公开了用于检测患者的卵巢癌的方法。进一步提供了用于实施本发明方法的试剂盒。