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Use of markers including filamin a in the diagnosis and treatment of prostate cancer

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(71) Applicant(s)
Berg LLC

(72) Inventor(s)
Narain, Niven Rajin; Vishnudas, Vivek K.; Sarangarajan, Rangaprasad; Akmaev, Viatcheslav R.

(74) Agent / Attorney
Spruson & Ferguson, GPO Box 3898, Sydney, NSW, 2001, AU

(56) Related Art
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- (71) **Applicant:** BERG LLC [US/US]; 1845 Elm Hill Pike,
Nashville, TN 37210 (US).
- (72) **Inventors:** NARAIN, Niven, Rajin; 73 Fresh Pond Park-
way, Cambridge, MA 02138 (US). VISHNUDAS, Vivek,
K.; 42 Kendall Court, Bedford, MA 01730 (US).
SARANGARAJAN, Rangaprasad; 454 Central Street,
Boylston, MA 01505 (US). AKMAEV, Viatcheslav, R.;
10 Mary Catherine Lane, Sudbury, MA 01776 (US).
- (74) **Agents:** MELLO, Jill Ann et al.; McCarter & English,
LLP, 265 Franklin Street, Boston, MA 02110 (US).
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(54) **Title:** USE OF MARKERS INCLUDING FILAMIN A IN THE DIAGNOSIS AND TREATMENT OF PROSTATE CANCER

(57) **Abstract:** Methods for diagnosing the presence of prostate cancer in a subject are provided, such methods including the detec-
tion of levels of variety of biomarkers diagnostic of prostate cancer, including filamin A alone, or in combination with one or more
additional biomarkers of prostate cancer, including, PSA, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tu-
bulin-beta 3, filamin B, and LY9. Additionally, age can be used as a predictor variable. The invention also provides methods of
treating prostate cancer which rely on diagnostic information obtained based on the detection of biomarkers of prostate cancer, in-
cluding filamin A alone, or in combination with one or more additional biomarkers of prostate cancer, including, PSA, keratin 4,
keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B, LY9, and/or age. Compositions in the form of kits
and panels of reagents for detecting the biomarkers of the invention are also provided.



USE OF MARKERS INCLUDING FILAMIN A IN THE DIAGNOSIS AND TREATMENT OF PROSTATE CANCER

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 62/088,931, filed on December 8, 2014; U.S. Provisional Application No. 62/134,956, filed on March 18, 2015; and U.S. Provisional Application No. 62/148,294, filed on April 16, 2015, the entire contents of each of which are expressly incorporated herein by reference.

INCORPORATION BY REFERENCE

All documents cited or referenced herein and all documents cited or referenced in the herein cited documents, together with any manufacturer's instructions, descriptions, product specifications, and product sheets for any products mentioned herein or in any document incorporated by reference herein, are hereby incorporated by reference, and may be employed in the practice of the invention.

BACKGROUND

A. FIELD OF THE INVENTION

The invention generally relates to novel biomarkers and combinations of biomarkers which can be used to detect and monitor prostate cancer. The invention also generally relates to methods for diagnosing, monitoring, and treating prostate cancer involving the detection of biomarkers of the invention.

B. BACKGROUND OF THE INVENTION

Prostate cancer is a leading cause of male cancer-related deaths—second only to lung cancer—and afflicts one out of nine men over the age of 65. According to the American Cancer Society, 241,000 new cases of prostate cancer were reported with about 30,000 prostate cancer-related deaths that same year. Although the disease is typically diagnosed in men over the age of 65, its impact is still significant in that the average life span of a man who dies from prostate cancer is reduced by nearly a decade on average. However, if prostate cancer is discovered early, 90% of the cases may be cured with surgery. Once the tumor spreads outside the area of the prostate gland and forms distant metastases, the disease is more difficult to treat. Therefore, early detection is of critical importance to the success of interventional therapies, and for reducing the mortality rate associated with prostate cancer.

Prostate cancer typically develops in the various tissues of the prostate, a gland in the male reproductive system. Most prostate cancers are slow growing. However, there are also a significant number of cases per year of aggressive prostate cancers, in which the cancer cells may metastasize from the prostate to other parts of the body, particularly to the bones and lymph nodes. Prostate

cancer may cause pain, difficulty in urinating, problems during sexual intercourse, or erectile dysfunction. Other symptoms can potentially develop during later stages of the disease.

Currently, prostate cancer is screened using only a limited number of detection means, including the digital rectal exam (DRE) and/or the measurement of the levels of prostate specific antigen (PSA). However, these approaches have an unacceptably high rate of false-positives. Indeed, most men (75%) with an elevated PSA level turn out not to have prostate cancer as determined by subsequent confirmatory prostate biopsies.

As such, the current screening tests are not specific enough to robustly screen for prostate cancer. Each year, based on the results of the DRE and PSA screens, about one million prostate biopsies are performed in the U.S. alone. Only 25% of these biopsies confirm the presence of cancer. PSA is secreted from epithelial cells of the prostate gland and is higher in blood due to increased number of prostate epithelial cells. When prostate cancers develop, PSA levels in the blood can start to climb. In the United States, the FDA has approved the PSA test for annual screening of prostate cancer in men of age 50 and older. PSA levels between 4 and 10 ng/mL are considered to be suspicious and consideration should be given to confirming the abnormal PSA with a repeat test. If indicated, a prostate biopsy is performed to obtain a tissue sample for histopathological analysis. Complications—such as infection, internal bleeding, allergic reactions, impotence, and urinary incontinence—induced by needless biopsies and treatments injure many more men than are potentially helped by early detection of cancers.

Indeed, the U.S. Preventative Services Task Force (USPSTF) estimates that about 90% of diagnosed men are treated and 2 in 1000 men will develop serious cardiovascular events, 1 in 1000 men will develop deep venous thrombosis, 29 in 1000 men will develop erectile dysfunction, 18 in 1000 men will develop urinary incontinence, and 1 in 1000 men will die due to treatment. A large majority of these men would have remained asymptomatic for life if left untreated. As such, most cancers found through PSA tests are not, in fact, dangerous. Nevertheless, given the lack of more effective predictors of prostate cancer, the field takes a more conservative approach in the use of biopsies and treatment, erring on the side of precaution but risking significant harm to otherwise healthy men.

Despite the current drawbacks in prostate cancer detection, the USPSTF estimates that one life will be saved for every 1,000 men screened every 1-4 years over a 10-year period. This overall outlook can be further improved by limiting unnecessary biopsies with the use of improved pre-biopsy screening methods that are associated with fewer false-positive results. With fewer unnecessary biopsies, fewer men will suffer the associated biopsy complications. In addition, fewer complications will also lead to an overall cost reduction to the healthcare system in the management of prostate cancer.

Accordingly, there is an unmet need for improved prostate cancer screening tools that may improve the accuracy of prostate cancer detection. Molecular-based biomarkers may address this need.

SUMMARY OF THE INVENTION

In view of the fact that prostate cancer remains a life threatening disease reaching a significant portion of the male population, there remains a need for efficient, *accurate*, and/or rapid molecular diagnosis means, optionally which do not suffer from a high proportion of false results. The development of molecular tests for the accurate detection of prostate cancer may also lead to improved management of appropriate therapies, and/or an overall improved survival rate. Thus, there remains a need to provide an improved diagnostic test for the detection of prostate cancer which may be more reliable and accurate than PSA and other current screening tests. Disclosed herein is a diagnostic test which addresses this need by providing the use of a new biomarker, filamin A, either used alone or in combination with other markers, for the accurate and/or reliable detection of prostate cancer.

The present invention is based, at least in part, on the discovery that filamin A is differentially regulated in prostate cancer cells. In particular, the invention is based on the surprising discovery that filamin A levels are significantly elevated in the serum of patients with prostate cancer. Accordingly, the invention provides methods for diagnosing and/or monitoring (*e.g.*, monitoring of disease progression or treatment) an oncological disease state, *e.g.*, prostate cancer, in a mammal. The invention also provides methods for treating or for adjusting treatment regimens based on diagnostic information relating to the levels of filamin A in the serum of a subject with an oncological disease state, *e.g.*, prostate cancer. The invention further provides panels and kits for practicing the methods of the invention.

In a first aspect of the invention, there is provided a method for diagnosing the presence of prostate cancer in a subject, wherein the subject has elevated prostate cancer antigen (PSA) level, comprising: (a) detecting the level of filamin A in a biological sample of the subject, and (b) comparing the level of filamin A in the biological sample with the level of filamin A in a normal control sample, wherein the level of filamin A above the level of filamin A in the control sample indicates the presence of prostate cancer in the subject.

In a second aspect of the invention there is provided a method for diagnosing the presence of prostate cancer in a subject, wherein the subject has elevated prostate cancer antigen (PSA) level, comprising: (a) contacting a biological sample with a reagent that selectively binds to filamin A; (b) allowing a complex to form between the reagent and filamin A; (c) detecting the level of the complex, and (d) comparing the level of the complex with a level of complex formed from a normal control sample, wherein the level of the complex formed from the biological sample above the level of the complex formed from the control sample indicates the presence of prostate cancer in the subject.

In a third aspect of the invention, there is provided a method of treating prostate cancer in a subject having elevated PSA level, comprising: (a) obtaining diagnostic information as to the level of filamin A in a biological sample from the subject, and (b) administering a therapeutically effective amount of an anti-cancer therapy to the subject if the level of filamin A in the biological sample is above the level of filamin A in a normal control sample.

In a fourth aspect of the invention, there is provide a kit for detecting filamin A in a biological sample from a subject having, suspected of having, or at risk for having prostate cancer when used in the method according to the first to third aspects of the invention, comprising at least one reagent for measuring the level of filamin A in the biological sample from the subject, and a set of instructions for measuring the level of filamin A in the biological sample from the subject.

In a fifth aspect of the invention, there is provided a panel when used in the method according to the first to third aspects of the invention, the panel comprising at least two detection reagents, wherein each detection reagent is specific for the detection of at least one prostate cancer marker of a set of markers, wherein the set of markers comprises filamin A and at least one other prostate cancer related marker selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3 and PSA.

In a sixth aspect of the invention there is provided a kit when used in the method of the first to third aspects of the invention, the kit comprising the panel according to the fifth aspect of the invention, and a set of instructions for obtaining diagnostic information based on a level of the one or more markers of prostate cancer.

Accordingly, in another aspect, the present invention provides a method for diagnosing the presence of prostate cancer in a subject, comprising: (a) detecting the level of filamin A in a biological sample of the subject, and (b) comparing the level of filamin A in the biological sample with a predetermined threshold value, wherein the level filamin A above the predetermined threshold value indicates the presence of prostate cancer in the subject.

In another aspect, the invention provides a method for diagnosing the presence of prostate cancer in a subject, comprising: (a) contacting a biological sample with a reagent that selectively binds to filamin A; (b) allowing a complex to form between the reagent and filamin A; (c) detecting the level of the complex, and (d) comparing the level of the complex with a predetermined threshold value, wherein the level of the complex above the predetermined threshold value indicates the presence of prostate cancer in the subject.

In certain embodiments, the diagnostic method further comprises detecting the level of one or more additional markers of prostate cancer.

The one or more additional markers of prostate cancer can include, but is not limited to, prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, kerton 18, keratin 19, and tubulin-beta 3. In another embodiment, the one or more additional markers of prostate cancer can include age. Age can be used as a continuous predictive biomarker. For example, increased age is associated with higher risk of having prostate cancer. Lower age is associated with decreased risk of having prostate cancer.

In certain other embodiments, the one or more additional markers can include genes that have been described in the literature as being specifically expressed in the prostate. These genes can include, for example, *prostate-specific membrane antigen* (PSM) (Fair et al., 1997, Prostate-specific membrane antigen. Prostate 32:140-148), *prostate stem cell antigen* (PSCA) (Reiter et al., 1998, Prostate stem cell antigen: a cell surface marker overexpressed in prostate cancer. Proc. Natl. Acad. Sci. USA 95:1735-1740), *TMPRSS2* (Lin et al., 1999. Prostate-localized and androgen-regulated expression of the membrane-bound serine protease TMPRSS2. Cancer Res. 59:4180-4184), *PDEF* (Oettgen et al., 2000, PDEF, a novel prostate epithelium-specific ETS transcription factor, interacts with the androgen receptor and activates prostate-specific antigen gene expression. J. Biol. Chem. 275:1216-1225), *prostate-specific gene-1* (Herness, 2003. A novel human prostate-specific gene-1 (HPG-1): molecular cloning, sequencing, and its potential involvement in prostate carcinogenesis. Cancer Res. 63:329-336), and even various *non-coding RNA's* (ncRNA's), like *PCA3* (Bussemakers et al., 1999. DD3: a new prostate-specific gene, highly overexpressed in prostate cancer, Cancer Res. 59:5975-5979), *PCGEM1* (Srikantan et al., 2000. PCGEM1, a prostate-specific gene, is overexpressed in prostate cancer. Proc. Natl. Acad. Sci. USA 97:12216-12221) and the gene cluster *P704P*, *P712P*, and *P775P* (Stolk et al., 2004. P704P, P712P, and P775P: A genomic cluster of prostate-specific genes. Prostate 60:214-226). Only a fraction of these markers have been associated with prostate cancer prognosis, progression and/or metastatic capacity and as such, their potential as valuable biomarkers and/or therapeutic targets is largely unknown.

In one embodiment, the prostate cancer is a prostate cancer characterized by overexpression of filamin A. In another embodiment, the prostate cancer is a prostate cancer characterized by overexpression of filamin A and overexpression of one or more additional markers selected from the group consisting of filamin B, LY9, keratin 5, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, or prostate specific antigen (PSA). In another embodiment, the prostate cancer is a prostate cancer characterized by overexpression of filamin A and overexpression of one or more additional markers selected from the group consisting of filamin B, LY9, keratin 5, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, or prostate specific antigen (PSA), and increased patient age. In another embodiment, the prostate cancer is a prostate cancer characterized by overexpression of filamin A and increased patient age. In another embodiment, the prostate cancer is a prostate cancer characterized by underexpression of filamin A and overexpression of one or more additional markers selected from the group consisting of filamin B, LY9, keratin 5, keratin 7, keratin

8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, or prostate specific antigen (PSA). In another embodiment, the prostate cancer is a prostate cancer characterized by underexpression of filamin A and overexpression of one or more additional markers selected from the group consisting of filamin B, LY9, keratin 5, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, or prostate specific antigen (PSA), and increased patient age. In another embodiment, the prostate cancer is a prostate cancer characterized by underexpression of filamin A and increased patient age.

In certain embodiments, the biological sample can be selected from the group consisting of blood, serum, urine, organ tissue, biopsy tissue, feces, skin, hair, and cheek tissue.

In various embodiments, the level of filamin A can be determined by an assay, such as an immunoassay or ELISA. Other suitable assays may be employed.

In certain embodiments, the step of determining the level of filamin A in the biological sample can comprise (i) contacting the biological sample with a reagent that selectively binds to the filamin A polypeptide to form a biomarker complex, and (ii) detecting the biomarker complex.

In some embodiments, the reagent can be an anti-filamin A antibody that selectively binds to at least one epitope of filamin A. In certain other embodiments, the anti-filamin A antibody may further comprise a detectable label. In other embodiments, the method may include a further step that contacts the anti-filamin A antibody / filamin A complex with a secondary antibody which selectively binds to the anti-filamin A antibody, and which itself carries a detectable tag or label.

In certain other embodiments, the step of determining the level of filamin A in the biological sample can be based on determining the amount of filamin A mRNA in the biological sample.

In some embodiments, an amplification reaction can be used for determining the amount of filamin A mRNA in the biological sample. The amplification reaction can include, but is not limited to, (a) a polymerase chain reaction (PCR); (b) a nucleic acid sequence-based amplification assay (NASBA); (c) a transcription mediated amplification (TMA); (d) a ligase chain reaction (LCR); or (e) a strand displacement amplification (SDA).

In still other embodiments, the step of determining the level of filamin A in the biological sample can be based on a hybridization assay, which can include using an oligonucleotide or probe that is complementary to a portion of a filamin A mRNA to hybridize thereto, wherein the oligonucleotide further comprises a detectable label or tag.

In certain embodiments, the prostate cancer is a prostatic intraepithelial neoplasia, adenocarcinoma, small cell carcinoma, or squamous cell carcinoma. In other embodiments, the prostate cancer can be an androgen-dependent prostate cancer. In still other embodiments, the prostate cancer can be an androgen-independent prostate cancer. In yet other embodiments, the prostate cancer can be an aggressive prostate cancer or a metastasized cancer. In still other embodiments, the prostate cancer can be a non-aggressive prostate cancer.

In embodiments where a diagnosis of prostate cancer is made, the invention also contemplates administering a therapeutic anti-cancer treatment, wherein the anti-cancer treatment is selected from

the group consisting of (a) radiation therapy, (b) chemotherapy, (c) surgery, (d) hormone therapy, (e) antibody therapy, (f) immunotherapy, (g) cytokine therapy, (h) growth factor therapy, and (d) any combination of (a)-(h).

In various embodiments, the methods of the invention can involve first selecting a subject suspected of having or being at risk of having prostate cancer and obtaining a biological sample from that subject suspected of having or being at risk of having prostate cancer.

In still other embodiments, the diagnostic methods of the invention may further comprise comparing the level of the one or more prostate cancer related markers in the biological sample, e.g., filamin A and one or more of PSA, filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, kartin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 with the level of the one or more prostate cancer related markers in a control sample selected from the group consisting of: a sample obtained from the same subject at an earlier time point than the biological sample, a sample from a subject with benign prostatic hyperplasia (BPH), a sample from a subject with non-metastatic prostate cancer, a sample from a subject with metastatic prostate cancer, a sample from a subject with androgen sensitive prostate cancer, a sample from a subject with androgen insensitive prostate cancer, a sample from a subject with aggressive prostate cancer, and a sample from a subject with non-aggressive prostate cancer.

In still other embodiments, the diagnostic methods of the invention can comprise differentiating between two prostate cancer states selected from the group consisting of: normal prostate and prostate cancer, benign prostate hyperplasia and prostate cancer, benign prostate hyperplasia and normal prostate, androgen dependent and androgen independent prostate cancer, aggressive prostate cancer and non-aggressive prostate cancer, and metastatic prostate cancer and non-metastatic prostate cancer.

In yet another aspect, the present invention provides a method for monitoring prostate cancer in a subject, the method comprising: (1) determining a level of filamin A in a first biological sample obtained at a first time from a subject having prostate cancer; (2) determining a level of filamin A in a second biological sample obtained from the subject at a second time, wherein the second time is later than the first time; and (3) comparing the level of filamin A in the second sample with the level of filamin A in the first sample, wherein a change in the level of filamin A is indicative of a change in prostate cancer status in the subject.

In certain embodiments, the determining steps (1) and (2) above further comprise determining the level of one or more additional prostate cancer related markers selected from the group consisting of PSA, filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1. In certain embodiments, the determining steps (1) and (2) above further comprise determining the level of the patient's age.

In certain embodiments, the subject is actively treated for prostate cancer prior to obtaining the second sample. In other embodiments, the subject is not actively treated for prostate cancer prior to obtaining the second sample.

In certain embodiments relating to monitoring prostate cancer, the increased level of filamin A and/or the one or more additional prostate cancer related markers in the second biological sample as compared to the first biological sample is indicative of progression of the prostate cancer in the subject.

In certain other embodiments relating to monitoring prostate cancer, a decreased or equivalent level of filamin A and/or the one or more additional prostate cancer related markers in the second biological sample as compared to the first biological sample is indicative of non-progression of the prostate cancer in the subject.

In other embodiments relating to monitoring prostate cancer, wherein the method further comprises comparing the level of the one or more prostate cancer related markers in the first biological sample or the second biological sample with the level of the one or more prostate cancer related markers in a control sample selected from the group consisting of: a normal control sample, a sample from a subject with benign prostatic hyperplasia (BPH), a sample from a subject with non-metastatic prostate cancer, a sample from a subject with metastatic prostate cancer, a sample from a subject with androgen sensitive prostate cancer, a sample from a subject with androgen insensitive prostate cancer, a sample from a subject with aggressive prostate cancer, and a sample from a subject with non-aggressive prostate cancer.

In still other embodiments, any of the methods of the invention can include detecting the size of the prostate tumor in the subject.

In still other embodiments, any of the methods further comprise obtaining a first sample and a second sample from the subject.

In still other embodiments, the diagnostic methods of the invention further comprise the step of selecting and/or administering a different treatment regimen for the subject based on progression of the prostate cancer in the subject.

In yet other embodiments, the diagnostic methods of the invention further comprise administering a therapeutic anti-cancer based on progression of the prostate cancer in the subject, wherein the anti-cancer treatment is selected from the group consisting of (a) radiation therapy, (b) chemotherapy, (c) surgery, (d) hormone therapy, (e) antibody therapy, (f) immunotherapy, (g) cytokine therapy, (h) growth factor therapy, and (d) any combination of (a)-(h).

In still other embodiments, the methods of the invention further comprise withholding an active treatment of the prostate cancer in the subject based on non-progression of the prostate cancer in the subject.

In another aspect, the present invention provides a method of treating prostate cancer in a subject, comprising: (a) obtaining a biological sample from a subject suspected of having prostate

cancer, (b) submitting the biological sample to obtain diagnostic information as to the level of filamin A, (c) administering a therapeutically effective amount of an anti-cancer therapy if the level of filamin A is above a threshold level.

In yet another aspect, the present invention provides a method of treating prostate cancer in a subject, comprising: (a) obtaining diagnostic information as to the level of filamin A in a biological sample, and (b) administering a therapeutically effective amount of an anti-cancer therapy if the level of filamin A is above a threshold level.

In still another aspect, the present invention provides a method of treating prostate cancer in a subject, comprising: (a) obtaining a biological sample from a subject suspected of having prostate cancer for use in identifying diagnostic information as to the level of filamin A, (b) measuring the level of filamin A in the biological sample, (c) recommending to a healthcare provider to administer an anti-cancer therapy if the level of filamin A is above a threshold level.

In certain embodiments, the method of the invention further comprises obtaining diagnostic information as to the level of one or more additional markers of prostate cancer.

In still other embodiments, the method of the invention further comprises obtaining diagnostic information as to the level of one or more additional markers of prostate cancer. The one or more additional markers of prostate cancer can include, but are not limited to, PSA, filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1. In another embodiment, the patient's age is determined. Age can be used as a continuous predictive variable. For example, increased age is associated with increased risk of prostate cancer. Conversely, decreased age is associated with decreased risk of prostate cancer.

In certain other embodiments, the method of the invention involves administering a therapeutically effective amount of an anti-cancer therapy if the level of filamin A and at least one of the additional markers of prostate cancer are above a threshold level.

In still other embodiments, the method of the invention involves recommending to a healthcare provider to administer an anti-cancer therapy if the level of filamin A and at least one of the additional markers of prostate cancer are above a threshold level.

The biological sample of any of the methods of the invention can be obtained from the blood, serum, urine, organ tissue, biopsy tissue, feces, skin, hair, or cheek tissue, or any other suitable tissue or bodily site.

In still further embodiments, the methods of treatment of the invention can measure the level of filamin A as determined by immunoassay or ELISA. In still other embodiments, the level of filamin A can be determined by (i) contacting the biological sample with a reagent that selectively binds to the filamin A to form a biomarker complex, and (ii) detecting the biomarker complex. The reagent can be an anti-filamin A antibody that selectively binds to at least one epitope of filamin A.

In certain other embodiments, the level of filamin A can be determined by measuring the amount of filamin A mRNA in the biological sample. The filamin A mRNA level can be determined by an amplification reaction, including (a) a polymerase chain reaction (PCR); (b) a nucleic acid sequence-based amplification assay (NASBA); (c) a transcription mediated amplification (TMA); (d) a ligase chain reaction (LCR); or (e) a strand displacement amplification (SDA). The level of filamin A mRNA can also be determined by a hybridization assay using an oligonucleotide that is complementary to a portion of a filamin A mRNA.

In still another aspect, the present invention relates to a kit for detecting filamin A in a biological sample comprising at least one reagent for measuring the level of filamin A in the biological sample, and a set of instructions for measuring the level of filamin A. The reagent can be an anti-filamin A antibody. The kit can also comprise a means to detect the anti-filamin A antibody, such as a detectable secondary antibody.

The kit of the invention may also include a reagent that is an oligonucleotide that is complementary to a filamin A mRNA.

The kit of the invention can also include a set of instructions which set forth an immunoassay or ELISA for detecting the filamin A level in the biological sample. The instruction may set forth an amplification or hybridization reaction for assaying the level of filamin A mRNA in the biological sample. The amplification reaction can be (a) a polymerase chain reaction (PCR); (b) a nucleic acid sequence-based amplification assay (NASBA); (c) a transcription mediated amplification (TMA); (d) a ligase chain reaction (LCR); or (e) a strand displacement amplification (SDA).

In still another aspect, the present invention provides a panel for use in a method of detecting at least two markers for prostate cancer, the panel comprising at least two detection reagents, wherein each detection reagent is specific for the detection of at least one prostate cancer marker of a set of markers, wherein the set of markers comprises filamin A and at least one other prostate cancer related marker selected from the group consisting of PSA, filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1. In another embodiment, the patient's age is also used as a continuous predictor variable.

In yet another aspect, the present invention provides a panel for use in a method of treating prostate cancer, the panel comprising at least two detection reagents, wherein each detection reagent is specific for the detection of at least one prostate cancer marker of a set of markers, wherein the set of markers comprises filamin A and at least one other prostate cancer related marker selected from the group consisting of PSA, filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1. In another embodiment, the patient's age is also used as a continuous predictor variable.

In still another aspect, the invention provides a panel for use in a method of monitoring the treatment of prostate cancer, the panel comprising at least two detection reagents, wherein each detection reagent is specific for the detection of at least one prostate cancer marker of a set of

markers, wherein the set of markers comprises filamin A and at least one other prostate cancer related marker selected from the group consisting of PSA, filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1. In another embodiment, the patient's age is also used as a continuous predictor variable.

In still another aspect, the present invention relates to the use of a panel comprising a plurality of detection reagents specific for detecting markers of prostate cancer in a method for diagnosing and/or treating prostate cancer, wherein at least one detection reagent of the panel is specific for detecting filamin A, and wherein the remaining one or more detection reagents are specific for detecting a prostate cancer marker selected from the group consisting of PSA, filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1. In another embodiment, the patient's age is also used as a continuous predictor variable.

In yet another aspect, the invention provides methods for diagnosing an abnormal prostate state in a subject comprising: (1) determining a level of filamin A in combination with one or more additional prostate cancer related markers selected from the group consisting of PSA, filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 in a biological sample from the subject; and (2) comparing the level of the filamin A and level of the one or more prostate cancer related markers in the biological sample with the corresponding levels in a normal control sample, wherein an altered level of the filamin A and the one or more prostate cancer related markers in the biological sample relative to the normal control sample is indicative of an abnormal prostate state in the subject. In another embodiment, the patient's age is also used as a continuous predictor variable.

In certain embodiments, the one or more prostate cancer related markers is selected from the group consisting of filamin B, LY9, and keratin 19. In certain embodiments, an increased level of filamin A and at least one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample relative to a normal control sample is indicative of an abnormal prostate state in the subject. In another embodiment, the patient's age is also used as a continuous predictor variable.

In certain embodiments, no increase in the detected level of expression of filamin A and at least one of the prostate-cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample relative to a normal control sample is indicative of a normal prostate state in the subject. In such embodiments, levels of one, two, or all three of filamin B, LY9, and keratin 19 can be detected. In certain embodiments, none of the markers have increased levels. In another embodiment, the patient's age is also used as a continuous predictor variable.

In certain embodiments, the method further comprises detecting the level of prostate specific antigen (PSA) in the biological sample and preferably further comprising comparing the level of PSA in the biological sample to the level of PSA in a normal control sample. In certain embodiments, an

increase in the level of filamin A and at least one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample relative to the normal control sample, in combination with an increase in the level of PSA in the biological sample as compared to a normal control sample has greater predictive value of the subject having an abnormal prostate state than the predictive value of a single marker alone. In certain embodiments, no increase in the detected level of expression of filamin A and in combination with the one or more prostate-cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample relative to the normal control sample, in further combination with a decreased or normal level of PSA in the biological sample as compared to the level of PSA in the normal control sample has a greater predictive value of the subject having a normal prostate state than any single marker alone. In another embodiment, the patient's age is also used as a continuous predictor variable.

Throughout the methods, kits, and panels of the invention, filamin A in combination with one or more of filamin B, LY9 and keratin 19 is understood filamin A in combination with any of filamin B; LY9; keratin 19; filamin B and LY9; filamin B and keratin 19; LY9 and keratin 19; or filamin B, LY9, and keratin 19. In one embodiment, the methods, kits and panels of the invention include filamin A in combination with filamin B, and Keratin 19 (KRT19). In one embodiment, the methods, kits and panels of the invention include filamin A in combination with filamin B, Keratin 19 (KRT19), and a determination of the patient's age.

Further, the invention contemplates that filamin A may be combined with any one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty or more other prostate cancer related markers in any combinations, including any of PSA, filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1. In one embodiment, the methods, kits and panels of the invention include filamin A in combination with filamin B, and Keratin 19 (KRT19).

In certain embodiments of the invention, the abnormal prostate state is prostate cancer.

In certain embodiments of the invention, the prostate cancer is androgen-dependent prostate cancer. In certain embodiments of the invention, the prostate cancer is androgen-independent prostate cancer. In certain embodiments of the invention, the prostate cancer is aggressive prostate cancer. In certain embodiments of the invention, the prostate cancer is non-aggressive prostate cancer.

In certain embodiments of the invention, the abnormal prostate state is benign prostate hyperplasia.

In another aspect, the invention provides a method for identifying a subject as being at increased risk for developing prostate cancer, the method comprising: (1) determining a level of filamin A in combination with one or more additional prostate cancer related markers selected from the group consisting of PSA, filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18,

keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 in a biological sample from the subject; and (2) comparing the level of filamin A and the one or more prostate cancer related markers in the biological sample with the level of the markers in a normal control sample, wherein an altered level of the markers in the biological sample relative to the control sample is indicative of an increased risk for developing prostate cancer in the subject. In another embodiment, the patient's age is also used as a continuous predictor variable.

In certain embodiments, filamin A detection is combined with detection of one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19. In certain embodiments, an increased level of filamin A and one or more prostate cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample relative to the normal control sample is indicative of an increased risk for developing prostate cancer in the subject. In certain embodiments, no increase in the detected level of expression of filamin A and of each of the one or more prostate-cancer related markers selected from the group consisting of filamin B, LY9, and keratin 19 in the biological sample relative to the normal control sample is indicative of no increased risk for developing prostate cancer in the subject. In another embodiment, the patient's age is also used as a continuous predictor variable.

In certain embodiments, the method further comprises detecting the level filamin A together with prostate specific antigen (PSA) in the biological sample. In this embodiment, the method involves comparing the levels of filamin A and PSA in the biological sample to the corresponding levels in a normal control sample. In certain embodiments, the method further comprises measuring the levels of one or more additional prostate cancer related markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 in the biological sample relative to the normal control sample, thereby increasing the predictive value of developing prostate cancer in the subject. In certain other embodiments, no increase in the detected level of expression of filamin A and PSA in the biological sample relative to the normal sample is indicative of having no increased risk for developing prostate cancer. In still further embodiments, no increase in the detected levels of one or more additional prostate cancer related markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 is indicative of no increased risk of prostate cancer, which has a greater predictive value of no increased risk of prostate cancer than evaluating filamin A and/or PSA alone. In another embodiment, the patient's age is also used as a continuous predictor variable.

In certain embodiments of the diagnostic or prognostic methods of the invention, the method of diagnosis of the invention is carried out on the basis of filamin A, optionally on the additional basis of PSA, and still optionally on the basis of one or more additional prostate cancer related markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15,

keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1. In certain embodiments, the one or more additional prostate cancer related markers is selected from the group consisting of keratin 7, keratin 8, and keratin 15. In certain other embodiments, the one or more additional prostate cancer related markers is selected from the group consisting of keratin 7 and keratin 15. In certain other embodiments, the one or more additional prostate cancer markers is selected from the group consisting of keratin 7, 15, and 19. In another embodiment, the patient's age is also used as a continuous predictor variable.

In certain embodiments, the control sample for filamin A and PSA is the same control sample as for the one or more additional prostate cancer related markers of the invention. In certain embodiments, the control sample for the filamin A and PSA is different from the control sample used for the one or more additional prostate cancer related markers of the invention. In still other embodiments, the control sample for the filamin A is different from the control sample used for PSA, which are each also different from the control sample used to measure the one or more additional prostate cancer markers.

In certain embodiments of the diagnostic methods of the invention, wherein one or more prostate cancer related markers that are combined with filamin A is selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, an increased level of one or more of the prostate cancer related markers in the biological sample relative to a normal control sample is indicative of an abnormal prostate state in the subject. In certain embodiments of the diagnostic methods of the invention, wherein one or more additional prostate cancer related markers is selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, a decreased or normal level of one or more of the additional prostate cancer related markers in the biological sample relative to a normal control sample is indicative of an abnormal prostate state in the subject. In certain embodiments of the diagnostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, an increased level of one or more of the additional prostate cancer related markers in the biological sample relative to a normal control sample is indicative of a normal prostate state in the subject. In certain embodiments of the diagnostic methods of the invention, wherein one or more prostate cancer related markers is selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, a decreased or normal level of one or more of the prostate cancer related markers in the biological sample relative to a normal control sample is indicative of a normal prostate state in the subject. In another embodiment, the patient's age is also used as a continuous predictor variable.

In certain embodiments of the prognostic methods of the invention, wherein the one or more additional prostate cancer related markers that are combined with filamin A is selected from the group consisting of PSA, filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, an increased level of one or more of the additional prostate cancer related markers in the biological sample relative to a normal control sample—in addition to increased filamin A—is indicative of an increased risk of developing prostate cancer in the subject. In certain embodiments of the prognostic methods of the invention, wherein one or more additional prostate cancer related markers is selected from the group consisting of PSA, filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, a decreased or normal level of one or more of the additional prostate cancer related markers in the biological sample relative to a normal control sample—in addition to decreased filamin A—is indicative of a decreased risk of developing prostate cancer in the subject. In certain embodiments of the prognostic methods of the invention, wherein one or more additional prostate cancer related markers is selected from the group consisting of PSA, filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, an increased level of one or more of the prostate cancer related markers in the biological sample relative to a normal control sample—in addition to increased filamin A—is indicative of increased risk of developing prostate cancer in the subject. In certain embodiments of the prognostic methods of the invention, wherein one or more additional prostate cancer related markers is selected from the group consisting of PSA, filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, a decreased or normal level of one or more of the additional prostate cancer related markers in the biological sample—in addition to decreased filamin A—relative to a normal control sample is indicative of no increased risk of developing prostate cancer in the subject. In another embodiment, the patient's age is also used as a continuous predictor variable.

In certain embodiments that involve the detection of both filamin A and PSA, the method of the invention can comprise detection of one or more additional prostate cancer related markers that are selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1. In certain embodiments, an increase in the level of both filamin A and PSA in combination with an increase in the level of at least one of the additional prostate cancer related markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 is indicative of an abnormal prostate state in the subject wherein the method has greater diagnostic or predictive value than the value of any of the individual markers alone. In certain other embodiments, a decrease in the level of both filamin A and PSA in combination with a decrease in the level of at least one of the

additional prostate cancer related markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 is indicative of a normal prostate state in the subject wherein the method has greater diagnostic or predictive value than the value of any of the individual markers alone. In another embodiment, the patient's age is also used as a continuous predictor variable.

In various embodiments of any of the diagnostic or prognostic methods of the invention, the method may further comprise comparing the level of the one or more prostate cancer related markers in the biological sample with the level of the one or more prostate cancer related markers in a control sample selected from the group consisting of: a sample obtained from the same subject at an earlier time point than the biological sample, a sample from a subject with benign prostatic hyperplasia (BPH), a sample from a subject with non-metastatic prostate cancer, a sample from a subject with metastatic prostate cancer, a sample from a subject with androgen sensitive prostate cancer, a sample from a subject with androgen insensitive prostate cancer, a sample from a subject with aggressive prostate cancer, and a sample from a subject with non-aggressive prostate cancer. In such embodiments, comparison with one or more additional control sample can facilitate differentiating between two prostate cancer states selected from the group consisting of: normal prostate and prostate cancer, benign prostate hyperplasia and prostate cancer, benign prostate hyperplasia and normal prostate, androgen dependent and androgen independent prostate cancer, aggressive prostate cancer and non-aggressive prostate cancer, and metastatic prostate cancer and non-metastatic prostate cancer; or differentiating between any two or more of normal prostate, prostate cancer, benign prostate hyperplasia, androgen dependent prostate cancer, androgen independent prostate cancer, aggressive prostate cancer, non-aggressive prostate cancer, metastatic prostate cancer, and non-metastatic prostate cancer.

In certain embodiments of the invention, when a tumor is present, the method further comprises detecting the size of the prostate tumor in the subject.

In certain embodiments of the diagnostic and prognostic methods the invention, the method further comprises obtaining a sample from a subject.

In certain embodiments of the diagnostic and prognostic methods the invention, the method further comprises selecting a subject who has or is suspected of having prostate cancer.

In certain embodiments of the invention, the method further comprises selecting a treatment regimen for the subject based on the level of the one or more prostate cancer markers. In certain embodiments of the invention, the method further comprises treating the subject with a treatment regimen based on the level of the one or more prostate cancer markers. In certain embodiments, a treatment regimen comprises one or more treatments selected from the group consisting of surgery, radiation, hormone therapy, antibody therapy, growth factor therapy, cytokine therapy, and chemotherapy.

Where applicable or not specifically disclaimed, any one of the embodiments described herein are contemplated to be able to combine with any other one or more embodiments, even though the embodiments are described under different aspects of the invention.

These and other embodiments are disclosed or are obvious from and encompassed by, the following Detailed Description.

BRIEF DESCRIPTION OF THE DRAWINGS

The following detailed description, given by way of example, but not intended to limit the invention solely to the specific embodiments described, may best be understood in conjunction with the accompanying drawings.

FIG. 1: Schematic representing the underlying principles of the Interrogative Platform Technology (a.k.a. Interrogative Biology™) provided in WO2012119129, the entire contents of which are incorporated herein by reference.

FIG. 2A, FIG. 2B, and FIG. 2C: Causal associations of keratins, including (FIG. 2A) KRT4, KRT8, KRT15 and (FIG. 2B) KRT18 and (FIG. 2C) KRT19 in human prostate cancer cells as inferred by the Interrogative Platform Technology.

FIG. 3A, FIG. 3B, FIG. 3C, and FIG. 3D: Mechanistic insight into regulation of keratins by mitochondrial function inferred by the Interrogative Platform Technology. (FIG. 3A) KRT8-KRT15 association is abolished upon ubidecaronone treatment. Note change of direction of arrow between and positions of KRT7 and KRT15 before treatment (FIG. 3A) and after treatment (FIG. 3B). (FIG. 3C) Tubulin-beta 3 interacts with a number of proteins. (FIG. 3D) Expression levels of keratin 19 in biological samples from subjects with prostate cancer or control samples.

FIG. 4: Inference of filamin B (FLNB) as a hub of activity in prostate cancer and as a biomarker using the Interrogative Platform Technology provided in WO2012119129.

FIG. 5: Portion of an inference map showing filamin B is connected directly to LY9, which is, in turn, connected to at least one other marker.

FIG. 6A and FIG. 6B: Validation of filamin B levels in human serum samples. Levels of filamin B (FIG. 6A) and PSA (FIG. 6B) were elevated in prostate cancer samples when compared to normal serum. Data represents percent average change, with normal donors set to 100% on a log scale.

FIG. 7: Validation of LY9 levels in human serum samples. Levels of LY9 were elevated in prostate cancer samples when compared to normal serum. Data represents percent average change, with normal donors set to 100% on a log scale.

FIG. 8A, FIG. 8B, and FIG. 8C: Validation of filamin B (FIG. 8A), LY9 (FIG. 8B), and PSA (FIG. 8C) levels in human serum samples. Data are shown as ng/ml of the marker in serum.

FIG. 9A and FIG 9B: (FIG. 9A) ROC curve analysis of sensitivity and false positive rate (FPR) of PSA, FLNB and the combination of PSA and FLNB and (FIG. 9B) area under the curve values (AUC) calculated based on the analysis. The combination of PSA and FLNB was more sensitive than either marker alone.

FIG. 10A and FIG. 10B: (FIG. 10A) ROC curve analysis of PSA, FLNB, LY9 and combinations of PSA, FLNB, and LY9 using linear and (FIG. 10B) non-linear scoring functions. The combination of PSA, LY9, and FLNB was more sensitive than any marker alone.

FIG. 11: Medical annotations for the serum samples used in connection with filamin A ELISA, as described in the Example 13.

FIG. 12: Medical annotations for the serum samples used in connection with keratin 19 ELISA, as described in the Example 13.

FIG. 13: Filamin A protein levels in serum from patients with and without prostate cancer as determined by ELISA.

FIG. 14: Keratin 19 protein levels in serum from patients with and without prostate cancer as determined by ELISA.

FIG. 15: ROC curve analysis for filamin A (FLNA) and filamin C (FLNC) and the combination (FLNA/C), as per Example 14.

FIG. 16: ROC curve analysis for keratin 18 (KRT18) and keratin 19 (KRT19) and the combination (KRT18/19), as per Example 14.

FIG. 17: AUC summary of AUC for PSA, Age, Filamin A (FLNA), Filamin B (FLNB), Keratin 19 (KRT19), and combinations thereof.

FIG. 18: PCA versus Else: Sensitivity match PSA.

FIG. 19: Predicted probability distribution for PCA versus Else.

FIG. 20: Accuracy analysis for PCA versus Else.

FIG. 21: Super High Gleason versus Else.

FIG. 22: Predicted probability distribution for Super High Gleason (8-10) versus Else.

FIG. 23: Accuracy Analysis for Super High Gleason (8-10) versus Else.

FIG. 24: High Gleason Versus Else.

FIG. 25: Predicted probability distribution for High Gleason (7 and above) versus Else.

FIG. 26: Accuracy Analysis for High Gleason (7 and above) versus Else.

FIG. 27: Prostate Cancer (PCA) versus Benign Prostatic Hyperplasia (BPH) Sensitivity.

FIG. 28: Predicted probability distribution for Prostate Cancer (PCA) versus Benign Prostatic Hyperplasia (BPH).

FIG. 29: Accuracy analysis for Prostate Cancer (PCA) versus Benign Prostatic Hyperplasia (BPH).

FIG. 30: FLNA, FLNB, and KRT19 expression in prostate cancer cells *in vitro*.

FIG. 31: FLNA, FLNB, and KRT19 expression in prostate cancer cells *in vitro*.

FIG. 32: Secretion of FLNA, FLNB, and KRT19 from prostate cancer cells *in vitro*.

FIG. 33: Transcriptional regulation of FLNA, FLNB, KRT19, and PSA expression by prostate-relevant stimuli of hypoxia (1% oxygen) *in vitro*.

FIG. 34: Transcriptional regulation of FLNA, FLNB, KRT19, and PSA expression by prostate-relevant stimuli of TNF α (10 ng/mL) *in vitro*.

FIG. 35: Transcriptional regulation of FLNA, FLNB, KRT19, and PSA expression by prostate-relevant stimuli of R1881 (1 nM) *in vitro*.

FIG. 36: Assessment of plasma FLNA and FLNB levels as biomarkers for prostate cancer.

DETAILED DESCRIPTION OF THE INVENTION

A. OVERVIEW

The identification of tumor markers or antigens associated with prostate cancer has stimulated considerable interest as promising tools for the screening, diagnosis, prognosis, clinical management and potential treatment of prostate cancer, and in particular, early detection of prostate cancer. Indeed, early detection mitigates the risk that the cancer will metastasize. Non-metastasized, local prostate tumors can often be cured by radical prostatectomy or radiation therapy, however for patients with distantly spread disease, no curative treatment is available. This emphasizes the need for new prostate (cancer) specific diagnostic tools that may improve the chances for accurate early detection.

While some prostate-specific markers are known, e.g., prostate-specific antigen and prostate stem cell antigen, very few biomarkers are in widespread or routine use as molecular diagnostics for prostate cancer. Accordingly, there remains a need for efficient, *accurate*, and rapid molecular diagnosis means, particularly which do not suffer from a high proportion of false results. The development of molecular tests for the accurate detection of prostate cancer will also lead to improved management of appropriate therapies, and an overall improved survival rate. Thus, there remains a need to provide an improved diagnostic test for the detection of prostate cancer which is more reliable and accurate than PSA and other current screening tests. The present invention addresses this need by providing the use of a new biomarker, filamin A, either used alone or in combination with other markers, for the accurate and reliable detection of prostate cancer.

As presently described herein, the invention at hand is based, at least in part, on the discovery that filamin A ("FLNA") is differentially regulated in prostate cancer cells and serves as a useful biomarker of prostate cancer. In one embodiment, filamin A can serve as a useful *diagnostic* biomarker to predict and/or detect the presence of prostate cancer in a subject. In another embodiment, filamin A can serve as a useful *prognostic* biomarker, serving to inform on the likely progression of prostate cancer in a subject with or without treatment. In still another embodiment, filamin A can serve as a useful *predictive* biomarker for helping to assess the likely response of prostate cancer to a particular treatment. Accordingly, the invention provides methods that use

biomarkers, e.g., filamin A, in the diagnosis of prostate cancer (e.g., prediction of the presence of prostate cancer in a subject), in the prognosis of prostate cancer (e.g., prediction of the course or outcome of prostate cancer with or without treatment), and in the assessment of therapies intended to treat prostate cancer (i.e., filamin A as a theragnostic or predictive marker). The invention further provides compositions of matter (e.g., oligonucleotide probes specific for filamin A mRNA, antibodies specific for filamin A, therapeutic agents that target filamin A), including panels comprising binding or detection reagents specific for filamin A and optionally other biomarkers for use in the methods of the invention, as well as kits for practicing the methods of the invention.

The following is a detailed description of the invention provided to aid those skilled in the art in practicing the present invention. Those of ordinary skill in the art may make modifications and variations in the embodiments described herein without departing from the spirit or scope of the present invention. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The terminology used in the description of the invention herein is for describing particular embodiments only and is not intended to be limiting of the invention. All publications, patent applications, patents, figures and other references mentioned herein are expressly incorporated by reference in their entirety.

Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and described the methods and/or materials in connection with which the publications are cited.

B. DEFINITIONS

Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this invention belongs. The following references, the entire disclosures of which are incorporated herein by reference, provide one of skill with a general definition of many of the terms (unless defined otherwise herein) used in this invention: Singleton et al., *Dictionary of Microbiology and Molecular Biology* (2nd ed. 1994); The Cambridge Dictionary of Science and Technology (Walker ed., 1988); The Glossary of Genetics, 5th Ed., R. Rieger et al. (eds.), Springer Verlag (1991); and Hale & Marham, the Harper Collins Dictionary of Biology (1991). Generally, the procedures of molecular biology methods described or inherent herein and the like are common methods used in the art. Such standard techniques can be found in reference manuals such as for example Sambrook et al., (2000, *Molecular Cloning--A Laboratory Manual*, Third Edition, Cold Spring Harbor Laboratories); and Ausubel et al., (1994, *Current Protocols in Molecular Biology*, John Wiley & Sons, New-York).

The following terms may have meanings ascribed to them below, unless specified otherwise. However, it should be understood that other meanings that are known or understood by those having

ordinary skill in the art are also possible, and within the scope of the present invention. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

As used herein, the singular forms "**a**", "**and**", and "**the**" include plural references unless the context clearly dictates otherwise. All technical and scientific terms used herein have the same meaning.

Unless specifically stated or obvious from context, as used herein, the term "**about**" is understood as within a range of normal tolerance in the art, for example within 2 standard deviations of the mean. About can be understood as within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1 %, 0.05%, or 0.01% of the stated value. Unless otherwise clear from context, all numerical values provided herein can be modified by the term about.

As used herein, the term "**age**" refers to the length of time that a subject has been alive. For example, the age of a subject is calculated from the date of birth of the subject to the current date. Age can be used as a continuous predictive variable for the presence of prostate cancer. For example, increased age is associated with increased risk of prostate cancer. Conversely, decreased age is associated with decreased risk of prostate cancer. Similarly, age can be used as a continuous predictive variable for the stage, or category, of the prostate cancer. For example, age can be used as a continuous predictive variable for the Gleason score of the prostate cancer.

As used herein, the term "**amplification**" refers to any known in vitro procedure for obtaining multiple copies ("amplicons") of a target nucleic acid sequence or its complement or fragments thereof. In vitro amplification refers to production of an amplified nucleic acid that may contain less than the complete target region sequence or its complement. Known in vitro amplification methods include, e.g., transcription-mediated amplification, replicase-mediated amplification, polymerase chain reaction (PCR) amplification, ligase chain reaction (LCR) amplification and strand-displacement amplification (SDA including multiple strand-displacement amplification method (MSDA)). Replicase-mediated amplification uses self-replicating RNA molecules, and a replicase such as Q- β -replicase (e.g., Kramer et al., U.S. Pat. No. 4,786,600). PCR amplification is well known and uses DNA polymerase, primers and thermal cycling to synthesize multiple copies of the two complementary strands of DNA or cDNA (e.g., Mullis et al., U.S. Pat. Nos. 4,683,195, 4,683,202, and 4,800,159). LCR amplification uses at least four separate oligonucleotides to amplify a target and its complementary strand by using multiple cycles of hybridization, ligation, and denaturation (e.g., EP Pat. App. Pub. No. 0 320 308). SDA is a method in which a primer contains a recognition site for a restriction endonuclease that permits the endonuclease to nick one strand of a hemimodified DNA duplex that includes the target sequence, followed by amplification in a series of primer extension and strand displacement steps (e.g., Walker et al., U.S. Pat. No. 5,422,252). Two other known strand-

displacement amplification methods do not require endonuclease nicking (Dattagupta et al., U.S. Pat. No. 6,087,133 and U.S. Pat. No. 6,124,120 (MSDA)). Those skilled in the art will understand that the oligonucleotide primer sequences of the present invention may be readily used in any in vitro amplification method based on primer extension by a polymerase. (see generally Kwoh et al., 1990, Am. Biotechnol. Lab. 8:14-25 and (Kwoh et al., 1989, Proc. Natl. Acad. Sci. USA 86, 1173-1177; Lizardi et al., 1988, BioTechnology 6:1197-1202; Malek et al., 1994, Methods Mol. Biol., 28:253-260; and Sambrook et al., 2000, Molecular Cloning--A Laboratory Manual, Third Edition, CSH Laboratories). As commonly known in the art, the oligos are designed to bind to a complementary sequence under selected conditions.

As used herein, the term “**antigen**” refers to a molecule, e.g., a peptide, polypeptide, protein, fragment, or other biological moiety, which elicits an antibody response in a subject, or is recognized and bound by an antibody.

As used herein, the term “**area under the curve**” or “AUC” refers to the area under the curve in a plot of sensitivity versus specificity. For example, see Figures 18, 21, 24, and 27. In one embodiment, the AUC for a biomarker, or combination of biomarkers, of the invention is 0.5. In another embodiment, the AUC for a biomarker, or combination of biomarkers, of the invention is 0.6. In another embodiment, the AUC for a biomarker, or combination of biomarkers, of the invention is 0.7. In another embodiment, the AUC for a biomarker, or combination of biomarkers, of the invention is 0.8. In another embodiment, the AUC for a biomarker, or combination of biomarkers, of the invention is 0.9. In another embodiment, the AUC for a biomarker, or combination of biomarkers, of the invention is 1.0. In specific embodiments, the AUC for a biomarker, or combination of biomarkers, of the invention is 0.5, 0.51, 0.52, 0.53, 0.54, 0.55, 0.56, 0.57, 0.58, 0.59, 0.6, 0.61, 0.62, 0.63, 0.64, 0.65, 0.66, 0.67, 0.68, 0.69, 0.7, 0.71, 0.72, 0.73, 0.74, 0.75, 0.76, 0.77, 0.78, 0.79, 0.8, 0.81, 0.82, 0.83, 0.84, 0.85, 0.86, 0.87, 0.88, 0.89, 0.9, 0.91, 0.92, 0.93, 0.94, 0.95, 0.96, 0.97, 0.98, 0.99 or 1.0. In one embodiment, the AUC for a biomarker, or combination of biomarkers, of the invention is at least 0.5. In another embodiment, the AUC for a biomarker, or combination of biomarkers, of the invention is at least 0.6. In another embodiment, the AUC for a biomarker, or combination of biomarkers, of the invention is at least 0.7. In another embodiment, the AUC for a biomarker, or combination of biomarkers, of the invention is at least 0.8. In another embodiment, the AUC for a biomarker, or combination of biomarkers, of the invention is at least 0.9. In another embodiment, the AUC for a biomarker, or combination of biomarkers, of the invention is at least 1.0. In specific embodiments, the AUC for a biomarker, or combination of biomarkers, of the invention is at least 0.5, 0.51, 0.52, 0.53, 0.54, 0.55, 0.56, 0.57, 0.58, 0.59, 0.6, 0.61, 0.62, 0.63, 0.64, 0.65, 0.66, 0.67, 0.68, 0.69, 0.7, 0.71, 0.72, 0.73, 0.74, 0.75, 0.76, 0.77, 0.78, 0.79, 0.8, 0.81, 0.82, 0.83, 0.84, 0.85, 0.86, 0.87, 0.88, 0.89, 0.9, 0.91, 0.92, 0.93, 0.94, 0.95, 0.96, 0.97, 0.98, 0.99 or 1.0

As used herein, the term “**biomarker**” is understood to mean a measurable characteristic that reflects in a quantitative or qualitative manner the physiological state of an organism. The

physiological state of an organism is inclusive of any disease or non-disease state, e.g., a subject having prostate cancer or a subject who is otherwise healthy. Said another way, biomarkers are characteristics that can be objectively measured and evaluated as indicators of normal processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarkers can be clinical parameters (e.g., age, performance status), laboratory measures (e.g., molecular biomarkers, such as prostate specific antigen), imaging-based measures, or genetic or other molecular determinants, such as phosphorylation or acetylation state of a protein marker, methylation state of nucleic acid, or any other detectable molecular modification to a biological molecule. Examples of biomarkers include, for example, polypeptides, peptides, polypeptide fragments, proteins, antibodies, hormones, polynucleotides, RNA or RNA fragments, microRNA (miRNAs), lipids, polysaccharides, and other bodily metabolites. Other examples of biomarkers include the age of the patient.

Preferably, a biomarker of the present invention is modulated (e.g., increased or decreased level) in a biological sample from a subject or a group of subjects having a first phenotype (e.g., having a disease) as compared to a biological sample from a subject or group of subjects having a second phenotype (e.g., not having the disease, e.g., a control). A biomarker may be differentially present at any level, but is generally present at a level that is increased relative to normal or control levels by at least 5%, by at least 10%, by at least 15%, by at least 20%, by at least 25%, by at least 30%, by at least 35%, by at least 40%, by at least 45%, by at least 50%, by at least 55%, by at least 60%, by at least 65%, by at least 70%, by at least 75%, by at least 80%, by at least 85%, by at least 90%, by at least 95%, by at least 100%, by at least 110%, by at least 120%, by at least 130%, by at least 140%, by at least 150%, or more; or is generally present at a level that is decreased relative to normal or control levels by at least 5%, by at least 10%, by at least 15%, by at least 20%, by at least 25%, by at least 30%, by at least 35%, by at least 40%, by at least 45%, by at least 50%, by at least 55%, by at least 60%, by at least 65%, by at least 70%, by at least 75%, by at least 80%, by at least 85%, by at least 90%, by at least 95%, or by 100% (i.e., absent). A biomarker is preferably differentially present at a level that is statistically significant (e.g., a p-value less than 0.05 and/or a q-value of less than 0.10 as determined using either Welch's T-test or Wilcoxon's rank-sum Test).

As used herein, the term "**biopsy**" or "biopsy tissue" refers to a sample of tissue (e.g., prostate tissue) that is removed from a subject for the purpose of determining if the sample contains cancerous tissue. The biopsy tissue is then examined (e.g., by microscopy) for the presence or absence of cancer.

As used herein, the term "**complementary**" refers to the broad concept of sequence complementarity between regions of two nucleic acid strands or between two regions of the same nucleic acid strand. It is known that an adenine residue of a first nucleic acid region is capable of forming specific hydrogen bonds ("base pairing") with a residue of a second nucleic acid region which is antiparallel to the first region if the residue is thymine or uracil. Similarly, it is known that a cytosine residue of a first nucleic acid strand is capable of base pairing with a residue of a second

nucleic acid strand which is antiparallel to the first strand if the residue is guanine. A first region of a nucleic acid is complementary to a second region of the same or a different nucleic acid if, when the two regions are arranged in an antiparallel fashion, at least one nucleotide residue of the first region is capable of base pairing with a residue of the second region. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, when the first and second portions are arranged in an antiparallel fashion, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion. More preferably, all nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion.

The term “**control sample**,” as used herein, refers to any clinically relevant comparative sample, including, for example, a sample from a healthy subject not afflicted with an oncological disorder, e.g., prostate cancer, or a sample from a subject from an earlier time point, e.g., prior to treatment, an earlier tumor assessment time point, at an earlier stage of treatment. A control sample can be a purified sample, protein, and/or nucleic acid provided with a kit. Such control samples can be diluted, for example, in a dilution series to allow for quantitative measurement of levels of analytes, e.g., markers, in test samples. A control sample may include a sample derived from one or more subjects. A control sample may also be a sample made at an earlier time point from the subject to be assessed. For example, the control sample could be a sample taken from the subject to be assessed before the onset of an oncological disorder, e.g., prostate cancer, at an earlier stage of disease, or before the administration of treatment or of a portion of treatment. The control sample may also be a sample from an animal model, or from a tissue or cell line derived from the animal model of oncological disorder, e.g., prostate cancer. The level of activity or expression of one or more markers (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9 or more markers) in a control sample consists of a group of measurements that may be determined, e.g., based on any appropriate statistical measurement, such as, for example, measures of central tendency including average, median, or modal values. Different from a control is preferably statistically significantly different from a control.

As used herein, “**changed as compared to a control**” sample or subject is understood as having a level of the analyte or diagnostic or therapeutic indicator (e.g., marker) to be detected at a level that is statistically different than a sample from a normal, untreated, or abnormal state control sample. Changed as compared to control can also include a difference in the rate of change of the level of one or more markers obtained in a series of at least two subject samples obtained over time. Determination of statistical significance is within the ability of those skilled in the art and can include any acceptable means for determining and/or measuring statistical significance, such as, for example, the number of standard deviations from the mean that constitute a positive or negative result, an increase in the detected level of a biomarker in a sample (e.g., prostate cancer sample) versus a control or healthy sample, wherein the increase is above some threshold value, or a decrease in the detected level of a biomarker in a sample (e.g., prostate cancer sample) versus a control or healthy sample,

wherein the decrease is below some threshold value. The threshold value can be determined by any suitable means by measuring the biomarker levels in a plurality of tissues or samples known to have a disease, e.g., prostate cancer, and comparing those levels to a normal sample and calculating a statistically significant threshold value.

The term “**control level**” refers to an accepted or pre-determined level of a marker in a subject sample. A control level can be a range of values. Marker levels can be compared to a single control value, to a range of control values, to the upper level of normal, or to the lower level of normal as appropriate for the assay.

In one embodiment, the control is a standardized control, such as, for example, a control which is predetermined using an average of the levels of expression of one or more markers from a population of subjects having no cancer, especially subjects having no prostate cancer. In still other embodiments of the invention, a control level of a marker is the level of the marker in a non-cancerous sample(s) derived from the subject having cancer. For example, when a biopsy or other medical procedure reveals the presence of cancer in one portion of the tissue, the control level of a marker may be determined using the non-affected portion of the tissue, and this control level may be compared with the level of the marker in an affected portion of the tissue.

In certain embodiments, the control can be from a subject, or a population of subject, having an abnormal prostate state. For example, the control can be from a subject suffering from benign prostate hyperplasia (BPH), androgen sensitive prostate cancer, androgen insensitive or resistant prostate cancer, aggressive prostate cancer, non-aggressive prostate cancer, metastatic prostate cancer, or non-metastatic prostate cancer. It is understood that not all markers will have different levels for each of the abnormal prostate states listed. It is understood that a combination of marker levels may be most useful to distinguish between abnormal prostate states, possibly in combination with other diagnostic methods. Further, marker levels in biological samples can be compared to more than one control sample (e.g., normal, abnormal, from the same subject, from a population control). Marker levels can be used in combination with other signs or symptoms of an abnormal prostate state to provide a diagnosis for the subject.

A control can also be a sample from a subject at an earlier time point, e.g., a baseline level prior to suspected presence of disease, before the diagnosis of a disease, at an earlier assessment time point during watchful waiting, before the treatment with a specific agent (e.g., chemotherapy, hormone therapy) or intervention (e.g., radiation, surgery). In certain embodiments, a change in the level of the marker in a subject can be more significant than the absolute level of a marker, e.g., as compared to control.

As used herein, “**detecting**”, “**detection**”, “**determining**”, and the like are understood to refer to an assay performed for identification of filamin A and/or an additional one or more specific markers in a sample, e.g., one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9 or more) markers selected from the group consisting of PSA, filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18,

keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 . The amount of marker expression or activity detected in the sample can be none or below the level of detection of the assay or method.

As used herein, the term "**DNA**" or "RNA" molecule or sequence (as well as sometimes the term "oligonucleotide") refers to a molecule comprised generally of the deoxyribonucleotides adenine (A), guanine (G), thymine (T) and/or cytosine (C). In "RNA", T is replaced by uracil (U).

The terms "**disorders**", "**diseases**", and "**abnormal state**" are used inclusively and refer to any deviation from the normal structure or function of any part, organ, or system of the body (or any combination thereof). A specific disease is manifested by characteristic symptoms and signs, including biological, chemical, and physical changes, and is often associated with a variety of other factors including, but not limited to, demographic, environmental, employment, genetic, and medically historical factors. Certain characteristic signs, symptoms, and related factors can be quantitated through a variety of methods to yield important diagnostic information. As used herein the disorder, disease, or abnormal state is an abnormal prostate state, including benign prostate hyperplasia and cancer, particularly prostate cancer. The abnormal prostate state of prostate cancer can be further subdivided into stages and grades of prostate cancer as provided, for example in Prostate. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 457-68 (incorporated herein by reference in its entirety). Further, abnormal prostate states can be classified as one or more of benign prostate hyperplasia (BPH), androgen sensitive prostate cancer, androgen insensitive or resistant prostate cancer, aggressive prostate cancer, non-aggressive prostate cancer, metastatic prostate cancer, and non-metastatic prostate cancer.

As used herein, a sample obtained at an "**earlier time point**" is a sample that was obtained at a sufficient time in the past such that clinically relevant information could be obtained in the sample from the earlier time point as compared to the later time point. In certain embodiments, an earlier time point is at least four weeks earlier. In certain embodiments, an earlier time point is at least six weeks earlier. In certain embodiments, an earlier time point is at least two months earlier. In certain embodiments, an earlier time point is at least three months earlier. In certain embodiments, an earlier time point is at least six months earlier. In certain embodiments, an earlier time point is at least nine months earlier. In certain embodiments, an earlier time point is at least one year earlier. Multiple subject samples (e.g., 3, 4, 5, 6, 7, or more) can be obtained at regular or irregular intervals over time and analyzed for trends in changes in marker levels. Appropriate intervals for testing for a particular subject can be determined by one of skill in the art based on ordinary considerations.

The term "**expression**" is used herein to mean the process by which a polypeptide is produced from DNA. The process involves the transcription of the gene into mRNA and the translation of this mRNA into a polypeptide. Depending on the context in which used, "expression" may refer to the production of RNA, or protein, or both.

As used herein, “**greater predictive value**” is understood as an assay that has significantly greater sensitivity and/or specificity, preferably greater sensitivity and specificity, than the test to which it is compared. The predictive value of a test can be determined using an ROC analysis. In an ROC analysis a test that provides perfect discrimination or accuracy between normal and disease states would have an area under the curve (AUC)=1, whereas a very poor test that provides no better discrimination than random chance would have AUC=0.5. As used herein, a test with a greater predictive value will have a statistically improved AUC as compared to another assay. The assays are preformed in an appropriate subject population.

A “**higher level of expression**”, “higher level”, and the like of a marker refers to an expression level in a test sample that is greater than the standard error of the assay employed to assess expression, and is preferably at least 25% more, at least 50% more, at least 75% more, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten times the expression level of the marker in a control sample (*e.g.*, sample from a healthy subject not having the marker associated disease, *i.e.*, an abnormal prostate state) and preferably, the average expression level of the marker or markers in several control samples.

As used herein, the term “**hybridization**,” as in “nucleic acid hybridization,” refers generally to the hybridization of two single-stranded nucleic acid molecules having complementary base sequences, which under appropriate conditions will form a thermodynamically favored double-stranded structure. Examples of hybridization conditions can be found in the two laboratory manuals referred above (Sambrook et al., 2000, *supra* and Ausubel et al., 1994, *supra*, or further in Higgins and Hames (Eds.) “Nucleic acid hybridization, a practical approach” IRL Press Oxford, Washington D.C., (1985)) and are commonly known in the art. In the case of a hybridization to a nitrocellulose filter (or other such support like nylon), as for example in the well-known Southern blotting procedure, a nitrocellulose filter can be incubated overnight at a temperature representative of the desired stringency condition (60-65°C for high stringency, 50-60°C for moderate stringency and 40-45°C for low stringency conditions) with a labeled probe in a solution containing high salt (6xSSC or 5xSSPE), 5xDenhardt's solution, 0.5% SDS, and 100 µg/ml denatured carrier DNA (*e.g.*, salmon sperm DNA). The non-specifically binding probe can then be washed off the filter by several washes in 0.2xSSC/0.1% SDS at a temperature which is selected in view of the desired stringency: room temperature (low stringency), 42°C (moderate stringency) or 65°C (high stringency). The salt and SDS concentration of the washing solutions may also be adjusted to accommodate for the desired stringency. The selected temperature and salt concentration is based on the melting temperature (T_m) of the DNA hybrid. Of course, RNA-DNA hybrids can also be formed and detected. In such cases, the conditions of hybridization and washing can be adapted according to well-known methods by the person of ordinary skill. Stringent conditions will be preferably used (Sambrook et al., 2000, *supra*). Other protocols or commercially available hybridization kits (*e.g.*, ExpressHyb® from BD Biosciences Clontech) using different annealing and washing solutions can also be used as well

known in the art. As is well known, the length of the probe and the composition of the nucleic acid to be determined constitute further parameters of the hybridization conditions. Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility. Hybridizing nucleic acid molecules also comprise fragments of the above described molecules. Furthermore, nucleic acid molecules which hybridize with any of the aforementioned nucleic acid molecules also include complementary fragments, derivatives and allelic variants of these molecules. Additionally, a hybridization complex refers to a complex between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary G and C bases and between complementary A and T bases; these hydrogen bonds may be further stabilized by base stacking interactions. The two complementary nucleic acid sequences hydrogen bond in an antiparallel configuration. A hybridization complex may be formed in solution (e.g., Cot or Rot analysis) or between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., membranes, filters, chips, pins or glass slides to which, e.g., cells have been fixed).

As used herein, the term "**identical**" or "percent identity" in the context of two or more nucleic acid or amino acid sequences, refers to two or more sequences or subsequences that are the same, or that have a specified percentage of amino acid residues or nucleotides that are the same (e.g., 60% or 65% identity, preferably, 70-95% identity, more preferably at least 95% identity), when compared and aligned for maximum correspondence over a window of comparison, or over a designated region as measured using a sequence comparison algorithm as known in the art, or by manual alignment and visual inspection. Sequences having, for example, 60% to 95% or greater sequence identity are considered to be substantially identical. Such a definition also applies to the complement of a test sequence. Preferably the described identity exists over a region that is at least about 15 to 25 amino acids or nucleotides in length, more preferably, over a region that is about 50 to 100 amino acids or nucleotides in length. Those having skill in the art will know how to determine percent identity between/among sequences using, for example, algorithms such as those based on CLUSTALW computer program (Thompson Nucl. Acids Res. 2 (1994), 4673-4680) or FASTDB (Brutlag Comp. App. Biosci. 6 (1990), 237-245), as known in the art. Although the FASTDB algorithm typically does not consider internal non-matching deletions or additions in sequences, i.e., gaps, in its calculation, this can be corrected manually to avoid an overestimation of the % identity. CLUSTALW, however, does take sequence gaps into account in its identity calculations. Also available to those having skill in this art are the BLAST and BLAST 2.0 algorithms (Altschul Nucl. Acids Res. 25 (1977), 3389-3402). The BLASTN program for nucleic acid sequences uses as defaults a word length (W) of 11, an expectation (E) of 10, M=5, N=4, and a comparison of both strands. For

amino acid sequences, the BLASTP program uses as defaults a wordlength (W) of 3, and an expectation (E) of 10. The BLOSUM62 scoring matrix (Henikoff Proc. Natl. Acad. Sci., USA, 89, (1989), 10915) uses alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of both strands. Moreover, the present invention also relates to nucleic acid molecules the sequence of which is degenerate in comparison with the sequence of an above-described hybridizing molecule. When used in accordance with the present invention the term "being degenerate as a result of the genetic code" means that due to the redundancy of the genetic code different nucleotide sequences code for the same amino acid. The present invention also relates to nucleic acid molecules which comprise one or more mutations or deletions, and to nucleic acid molecules which hybridize to one of the herein described nucleic acid molecules, which show (a) mutation(s) or (a) deletion(s).

The term "**including**" is used herein to mean, and is used interchangeably with, the phrase "including but not limited to."

A subject at "**increased risk for developing prostate cancer**" may or may not develop prostate cancer. Identification of a subject at increased risk for developing prostate cancer should be monitored for additional signs or symptoms of prostate cancer. The methods provided herein for identifying a subject with increased risk for developing prostate cancer can be used in combination with assessment of other known risk factors or signs of prostate cancer including, but not limited to decreased urinary stream, urgency, hesitancy, nocturia, incomplete bladder emptying, and age.

As used herein, the term "**in vitro**" refers to an artificial environment and to processes or reactions that occur within an artificial environment. In vitro environments can consist of, but are not limited to, test tubes and cell culture. The term "in vivo" refers to the natural environment (e.g., an animal or a cell) and to processes or reaction that occur within a natural environment.

As used herein, a "**label**" refers to a molecular moiety or compound that can be detected or can lead to a detectable signal. A label is joined, directly or indirectly, to a molecule, such as an antibody, a nucleic acid probe or the protein/antigen or nucleic acid to be detected (e.g., an amplified sequence). Direct labeling can occur through bonds or interactions that link the label to the nucleic acid (e.g., covalent bonds or non-covalent interactions), whereas indirect labeling can occur through the use of a "linker" or bridging moiety, such as oligonucleotide(s) or small molecule carbon chains, which is either directly or indirectly labeled. Bridging moieties may amplify a detectable signal. Labels can include any detectable moiety (e.g., a radionuclide, ligand such as biotin or avidin, enzyme or enzyme substrate, reactive group, chromophore such as a dye or colored particle, luminescent compound including a bioluminescent, phosphorescent or chemiluminescent compound, and fluorescent compound). Preferably, the label on a labeled probe is detectable in a homogeneous assay system, i.e., in a mixture, the bound label exhibits a detectable change compared to an unbound label.

The terms "**level of expression of a gene**", "gene expression level", "level of a marker", and the like refer to the level of mRNA, as well as pre-mRNA nascent transcript(s), transcript processing intermediates, mature mRNA(s) and degradation products, or the level of protein, encoded by the

gene in the cell. The “level” of one of more biomarkers means the absolute or relative amount or concentration of the biomarker in the sample.

A “**lower level of expression**” or “lower level” of a marker refers to an expression level in a test sample that is less than 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, or 10% of the expression level of the marker in a control sample (*e.g.*, sample from a healthy subjects not having the marker associated disease, *i.e.*, an abnormal prostate state) and preferably, the average expression level of the marker in several control samples.

The term “**modulation**” refers to upregulation (*i.e.*, activation or stimulation), down-regulation (*i.e.*, inhibition or suppression) of a response (*e.g.*, level of expression of a marker), or the two in combination or apart. A “modulator” is a compound or molecule that modulates, and may be, *e.g.*, an agonist, antagonist, activator, stimulator, suppressor, or inhibitor.

As used herein, “**negative fold change**” refers to “down-regulation” or “decrease (of expression)” of a gene that is listed herein.

As used herein, “**nucleic acid molecule**” or “polynucleotides”, refers to a polymer of nucleotides. Non-limiting examples thereof include DNA (*e.g.*, genomic DNA, cDNA), RNA molecules (*e.g.*, mRNA) and chimeras thereof. The nucleic acid molecule can be obtained by cloning techniques or synthesized. DNA can be double-stranded or single-stranded (coding strand or non-coding strand [antisense]). Conventional ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) are included in the term “nucleic acid” and polynucleotides as are analogs thereof. A nucleic acid backbone may comprise a variety of linkages known in the art, including one or more of sugar-phosphodiester linkages, peptide-nucleic acid bonds (referred to as “peptide nucleic acids” (PNA); Hydig-Hielsen et al., PCT Intl Pub. No. WO 95/32305), phosphorothioate linkages, methylphosphonate linkages or combinations thereof. Sugar moieties of the nucleic acid may be ribose or deoxyribose, or similar compounds having known substitutions, *e.g.*, 2' methoxy substitutions (containing a 2'-O-methylribofuranosyl moiety; see PCT No. WO 98/02582) and/or 2' halide substitutions. Nitrogenous bases may be conventional bases (A, G, C, T, U), known analogs thereof (*e.g.*, inosine or others; see *The Biochemistry of the Nucleic Acids* 5-36, Adams et al., ed., 11th ed., 1992), or known derivatives of purine or pyrimidine bases (see, Cook, PCT Int'l Pub. No. WO 93/13121) or “abasic” residues in which the backbone includes no nitrogenous base for one or more residues (Arnold et al., U.S. Pat. No. 5,585,481). A nucleic acid may comprise only conventional sugars, bases and linkages, as found in RNA and DNA, or may include both conventional components and substitutions (*e.g.*, conventional bases linked via a methoxy backbone, or a nucleic acid including conventional bases and one or more base analogs). An “isolated nucleic acid molecule”, as is generally understood and used herein, refers to a polymer of nucleotides, and includes, but should not be limited to DNA and RNA. The “isolated” nucleic acid molecule is purified from its natural *in vivo* state, obtained by cloning or chemically synthesized.

As used herein, the term “**obtaining**” is understood herein as manufacturing, purchasing, or otherwise coming into possession of.

As used herein, “**oligonucleotides**” or “oligos” define a molecule having two or more nucleotides (ribo or deoxyribonucleotides). The size of the oligo will be dictated by the particular situation and ultimately on the particular use thereof and adapted accordingly by the person of ordinary skill. An oligonucleotide can be synthesized chemically or derived by cloning according to well-known methods. While they are usually in a single-stranded form, they can be in a double-stranded form and even contain a “regulatory region”. They can contain natural rare or synthetic nucleotides. They can be designed to enhance a chosen criteria like stability for example. Chimeras of deoxyribonucleotides and ribonucleotides may also be within the scope of the present invention.

As used herein, “**one or more**” is understood as each value 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and any value greater than 10.

The term “**or**” is used inclusively herein to mean, and is used interchangeably with, the term “and/or,” unless context clearly indicates otherwise. For example, as used herein, filamin B or LY9 is understood to include filamin B alone, LY9 alone, and the combination of filamin B and LY9.

As used herein, “**patient**” or “subject” can mean either a human or non-human animal, preferably a mammal. By “subject” is meant any animal, including horses, dogs, cats, pigs, goats, rabbits, hamsters, monkeys, guinea pigs, rats, mice, lizards, snakes, sheep, cattle, fish, and birds. A human subject may be referred to as a patient. It should be noted that clinical observations described herein were made with human subjects and, in at least some embodiments, the subjects are human.

As used herein, “**positive fold change**” refers to “up-regulation” or “increase (of expression)” of a gene that is listed herein.

As used herein, “**preventing**” or “prevention” refers to a reduction in risk of acquiring a disease or disorder (*i.e.*, causing at least one of the clinical symptoms of the disease not to develop in a patient that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease). Prevention does not require that the disease or condition never occurs in the subject. Prevention includes delaying the onset or severity of the disease or condition.

As used herein, a “**predetermined threshold value**” or “threshold value” of a biomarker refers to the level of the biomarker (e.g., the expression level or quantity (e.g., ng/ml) in a biological sample) in a corresponding control/normal sample or group of control/normal samples obtained from normal or healthy subjects, e.g., those males that do not have prostate cancer. The predetermined threshold value may be determined prior to or concurrently with measurement of marker levels in a biological sample. The control sample may be from the same subject at a previous time or from different subjects.

As used herein, a “**probe**” is meant to include a nucleic acid oligomer or oligonucleotide that hybridizes specifically to a target sequence in a nucleic acid or its complement, under conditions that promote hybridization, thereby allowing detection of the target sequence or its amplified nucleic acid.

Detection may either be direct (i.e., resulting from a probe hybridizing directly to the target or amplified sequence) or indirect (i.e., resulting from a probe hybridizing to an intermediate molecular structure that links the probe to the target or amplified sequence). A probe's "target" generally refers to a sequence within an amplified nucleic acid sequence (i.e., a subset of the amplified sequence) that hybridizes specifically to at least a portion of the probe sequence by standard hydrogen bonding or "base pairing." Sequences that are "sufficiently complementary" allow stable hybridization of a probe sequence to a target sequence, even if the two sequences are not completely complementary. A probe may be labeled or unlabeled. A probe can be produced by molecular cloning of a specific DNA sequence or it can also be synthesized. Numerous primers and probes which can be designed and used in the context of the present invention can be readily determined by a person of ordinary skill in the art to which the present invention pertains.

As used herein, the terminology "**prognosis**", "staging" and "determination of aggressiveness" are defined herein as the prediction of the degree of severity of the prostate cancer and of its evolution as well as the prospect of recovery as anticipated from usual course of the disease. According to the present invention, once the aggressiveness of the prostate cancer has been determined appropriate methods of treatments can be chosen.

As used herein, "**prophylactic**" or "therapeutic" treatment refers to administration to the subject of one or more agents or interventions to provide the desired clinical effect. If it is administered prior to clinical manifestation of the unwanted condition (*e.g.*, disease or other unwanted state of the host animal) then the treatment is prophylactic, *i.e.*, it protects the host against developing at least one sign or symptom of the unwanted condition, whereas if administered after manifestation of the unwanted condition, the treatment is therapeutic (*i.e.*, it is intended to diminish, ameliorate, or maintain at least one sign or symptom of the existing unwanted condition or side effects therefrom).

As used herein, "**prostate cancer**," refers to any malignant or pre-malignant form of cancer of the prostate. The term includes prostate in situ carcinomas, invasive carcinomas, metastatic carcinomas and pre-malignant conditions. The term also encompasses any stage or grade of cancer in the prostate. Where the prostate cancer is "metastatic," the cancer has spread or metastasized beyond the prostate gland to a distant site, such as a lymph node or to the bone.

As used herein, a "**reference level**" of a biomarker means a level of the biomarker that is indicative of a particular disease state, phenotype, or lack thereof, as well as combinations of disease states, phenotypes, or lack thereof. A "positive" reference level of a biomarker means a level that is indicative of a particular disease state or phenotype. A "negative" reference level of a biomarker means a level that is indicative of a lack of a particular disease state or phenotype. For example, a "prostate cancer-positive reference level" of a biomarker means a level of a biomarker that is indicative of a positive diagnosis of prostate cancer in a subject, and a "prostate cancer-negative reference level" of a biomarker means a level of a biomarker that is indicative of a negative diagnosis of prostate cancer in a subject. A "reference level" of a biomarker may be an absolute or relative

amount or concentration of the biomarker, a presence or absence of the biomarker, a range of amount or concentration of the biomarker, a minimum and/or maximum amount or concentration of the biomarker, a mean amount or concentration of the biomarker, and/or a median amount or concentration of the biomarker; and, in addition, "reference levels" of combinations of biomarkers may also be ratios of absolute or relative amounts or concentrations of two or more biomarkers with respect to each other. Appropriate positive and negative reference levels of biomarkers for a particular disease state, phenotype, or lack thereof may be determined by measuring levels of desired biomarkers in one or more appropriate subjects, and such reference levels may be tailored to specific populations of subjects (e.g., a reference level may be age-matched so that comparisons may be made between biomarker levels in samples from subjects of a certain age and reference levels for a particular disease state, phenotype, or lack thereof in a certain age group). Such reference levels may also be tailored to specific techniques that are used to measure levels of biomarkers in biological samples (e.g., LC-MS, GC-MS, etc.), where the levels of biomarkers may differ based on the specific technique that is used.

As used herein, "**sample**" or "biological sample" includes a specimen or culture obtained from any source. Biological samples can be obtained from blood (including any blood product, such as whole blood, plasma, serum, or specific types of cells of the blood), urine, saliva, and the like. Biological samples also include tissue samples, such as biopsy tissues or pathological tissues that have previously been fixed (e.g., formaline snap frozen, cytological processing, etc.). In an embodiment, the biological sample is from blood. In another embodiment, the biological sample is a biopsy tissue from the prostate gland.

As use herein, the phrase "**specific binding**" or "specifically binding" when used in reference to the interaction of an antibody and a protein or peptide means that the interaction is dependent upon the presence of a particular structure (i.e., the antigenic determinant or epitope) on the protein; in other words the antibody is recognizing and binding to a specific protein structure rather than to proteins in general. For example, if an antibody is specific for epitope "A," the presence of a protein containing epitope A (or free, unlabeled A) in a reaction containing labeled "A" and the antibody will reduce the amount of labeled A bound to the antibody.

The phrase "**specific identification**" is understood as detection of a marker of interest with sufficiently low background of the assay and cross-reactivity of the reagents used such that the detection method is diagnostically useful. In certain embodiments, reagents for specific identification of a marker bind to only one isoform of the marker. In certain embodiments, reagents for specific identification of a marker bind to more than one isoform of the marker. In certain embodiments, reagents for specific identification of a marker bind to all known isoforms of the marker.

As used herein, the phrase "**subject suspected of having cancer**" refers to a subject that presents one or more symptoms indicative of a cancer or is being screened for a cancer (e.g., during a routine physical). A subject suspected of having cancer may also have one or more risk factors. A

subject suspected of having cancer has generally not been tested for cancer. However, a "subject suspected of having cancer" encompasses an individual who has received an initial diagnosis (e.g., a CT scan showing a mass or increased PSA level) but for whom the stage of cancer is not known. The term further includes people who once had cancer (e.g., an individual in remission).

The term "**such as**" is used herein to mean, and is used interchangeably, with the phrase "such as but not limited to."

As used herein, the term "**stage of cancer**" refers to a qualitative or quantitative assessment of the level of advancement of a cancer. Criteria used to determine the stage of a cancer include, but are not limited to, the size of the tumor, whether the tumor has spread to other parts of the body and where the cancer has spread (e.g., within the same organ or region of the body or to another organ).

As used herein, the term "**staging**" refers to commonly used systems for grading/stating cancer, e.g., prostate cancer. In one aspect, staging can take the form of the "Gleason Score", as well known in the art, is the most commonly used system for the grading/staging and prognosis of adenocarcinoma. The system describes a score between 2 and 10, with 2 being the least aggressive and 10 being the most aggressive. The score is the sum of the two most common patterns (grade 1-5) of tumor growth found. To be counted a pattern (grade) needs to occupy more than 5% of the biopsy specimen. The scoring system requires biopsy material (core biopsy or operative specimens) in order to be accurate; cytological preparations cannot be used. The "Gleason Grade" is the most commonly used prostate cancer grading system. It involves assigning numbers to cancerous prostate tissue, ranging from 1 through 5, based on how much the arrangement of the cancer cells mimics the way normal prostate cells form glands. Two grades are assigned to the most common patterns of cells that appear; these two grades (they can be the same or different) are then added together to determine the Gleason score (a number from 1 to 10). The Gleason system is based exclusively on the architectural pattern of the glands of the prostate tumor. It evaluates how effectively the cells of any particular cancer are able to structure themselves into glands resembling those of the normal prostate. The ability of a tumor to mimic normal gland architecture is called its differentiation, and experience has shown that a tumor whose structure is nearly normal (well differentiated) will probably have a biological behavior relatively close to normal, i.e., that is not very aggressively malignant.

A Gleason grading from very well differentiated (grade 1) to very poorly differentiated (grade 5) is usually done for the most part by viewing the low magnification microscopic image of the cancer. There are important additional details which require higher magnification, and an ability to accurately grade any tumor is achieved only through much training and experience in pathology. Gleason grades 1 and 2: These two grades closely resemble normal prostate. They are the least important grades because they seldom occur in the general population and because they confer a prognostic benefit which is only slightly better than grade 3. Both of these grades are composed by mass; in grade 2 they are more loosely aggregated, and some glands wander (invade) into the surrounding muscle (stroma). Gleason grade 3 is the most common grade and is also considered well

differentiated (like grades 1 and 2). This is because all three grades have a normal "gland unit" like that of a normal prostate; that is, every cell is part of a circular row which forms the lining of a central space (the lumen). The lumen contains prostatic secretion like normal prostate, and each gland unit is surrounded by prostate muscle which keeps the gland units apart. In contrast to grade 2, wandering of glands (invading) into the stroma (muscle) is very prominent and is the main defining feature. The cells are dark rather than pale and the glands often have more variable shapes.

Gleason Grade 4 is probably the most important grade because it is fairly common and because of the fact that if a lot of it is present, patient prognosis is usually (but not always) worsened by a considerable degree. Grade 4 also shows a considerable loss of architecture. For the first time, disruption and loss of the normal gland unit is observed. In fact, grade 4 is identified almost entirely by loss of the ability to form individual, separate gland units, each with its separate lumen (secretory space). This important distinction is simple in concept but complex in practice. The reason is that there are a variety of different-appearing ways in which the cancer's effort to form gland units can be distorted. Each cancer has its own partial set of tools with which it builds part of the normal structure. Grade 4 is like the branches of a large tree, reaching in a number of directions from the (well differentiated) trunk of grades 1, 2, and 3. Much experience is required for this diagnosis, and not all patterns are easily distinguished from grade 3. This is the main class of poorly differentiated prostate cancer, and its distinction from grade 3 is the most commonly important grading decision.

Gleason grade 5 is an important grade because it usually predicts another significant step towards poor prognosis. Its overall importance for the general population is reduced by the fact that it is less common than grade 4, and it is seldom seen in men whose prostate cancer is diagnosed early in its development. This grade too shows a variety of patterns, all of which demonstrate no evidence of any attempt to form gland units. This grade is often called undifferentiated, because its features are not significantly distinguishing to make it look any different from undifferentiated cancers which occur in other organs. When a pathologist looks at prostate cancer specimens under the microscope and gives them a Gleason grade, an attempt to identify two architectural patterns and assign a Gleason grade to each one is made. There may be a primary or most common pattern and then a secondary or second most common pattern which the pathologist will seek to describe for each specimen; alternatively, there may often be only a single pure grade. In developing his system, Dr. Gleason discovered that by giving a combination of the grades of the two most common patterns he could see in any particular patient's specimens, that he was better able to predict the likelihood that a particular patient would do well or badly. Therefore, although it may seem confusing, the Gleason score which a physician usually gives to a patient, is actually a combination or sum of two numbers which is accurate enough to be very widely used. These combined Gleason sums or scores may be determined as follows:

The lowest possible Gleason score is 2 (1+1), where both the primary and secondary patterns have a Gleason grade of 1 and therefore when added together their combined sum is 2.

Very typical Gleason scores might be 5 (2+3), where the primary pattern has a Gleason grade of 2 and the secondary pattern has a grade of 3, or 6 (3+3), a pure pattern..

Another typical Gleason score might be 7 (4+3), where the primary pattern has a Gleason grade of 4 and the secondary pattern has a grade of 3.

Finally, the highest possible Gleason score is 10 (5+5), when the primary and secondary patterns both have the most disordered Gleason grades of 5.

Another way of staging prostate cancer is by using the TNM System. It describes the extent of the primary tumor (T stage), the absence or presence of spread to nearby lymph nodes (N stage) and the absence or presence of distant spread, or metastasis (M stage). Each category of the TNM classification is divided into subcategories representative of its particular state. For example, primary tumors (T stage) may be classified into:

T1: The tumor cannot be felt during a digital rectal exam, or seen by imaging studies, but cancer cells are found in a biopsy specimen;

T2: The tumor can be felt during a DRE and the cancer is confined within the prostate gland;

T3: The tumor has extended through the prostatic capsule (a layer of fibrous tissue surrounding the prostate gland) and/or to the seminal vesicles (two small sacs next to the prostate that store semen), but no other organs are affected;

T4: The tumor has spread or attached to tissues next to the prostate (other than the seminal vesicles).

Lymph node involvement is divided into the following 4 categories:

N0: Cancer has not spread to any lymph nodes;

N1: Cancer has spread to a single regional lymph node (inside the pelvis) and is not larger than 2 centimeters;

N2: Cancer has spread to one or more regional lymph nodes and is larger than 2 centimeters, but not larger than 5 centimeters; and

N3: Cancer has spread to a lymph node and is larger than 5 centimeters (2 inches).

Metastasis is generally divided into the following two categories:

M0: The cancer has not metastasized (spread) beyond the regional lymph nodes; and

M1: The cancer has metastasized to distant lymph nodes (outside of the pelvis), bones, or other distant organs such as lungs, liver, or brain.

In addition, the Tstage is further divided into subcategories T1a-c T2a-c, T3a-c and T4a-b. The characteristics of each of these subcategories are well known in the art and can be found in a number of textbooks.

The terms "**test compound**" and "candidate compound" refer to any chemical entity, pharmaceutical, drug, and the like that is a candidate for use to treat or prevent a disease, illness, sickness, or disorder of bodily function (e.g., cancer). Test compounds comprise both known and potential therapeutic compounds. A test compound can be determined to be therapeutic by screening

using the screening methods of the present invention. In some embodiments of the present invention, test compounds include antisense compounds.

The term “**therapeutic effect**” refers to a local or systemic effect in animals, particularly mammals, and more particularly humans caused by a pharmacologically active substance. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or in the enhancement of desirable physical or mental development and conditions in an animal or human. A therapeutic effect can be understood as a decrease in tumor growth, decrease in tumor growth rate, stabilization or decrease in tumor burden, stabilization or reduction in tumor size, stabilization or decrease in tumor malignancy, increase in tumor apoptosis, and/or a decrease in tumor angiogenesis.

As used herein, “**therapeutically effective amount**” means the amount of a compound that, when administered to a patient for treating a disease, is sufficient to effect such treatment for the disease, *e.g.*, the amount of such a substance that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment, *e.g.*, is sufficient to ameliorate at least one sign or symptom of the disease, *e.g.*, to prevent progression of the disease or condition, *e.g.*, prevent tumor growth, decrease tumor size, induce tumor cell apoptosis, reduce tumor angiogenesis, prevent metastasis. When administered for preventing a disease, the amount is sufficient to avoid or delay onset of the disease. The “therapeutically effective amount” will vary depending on the compound, its therapeutic index, solubility, the disease and its severity and the age, weight, *etc.*, of the patient to be treated, and the like. For example, certain compounds discovered by the methods of the present invention may be administered in a sufficient amount to produce a reasonable benefit/risk ratio applicable to such treatment. Administration of a therapeutically effective amount of a compound may require the administration of more than one dose of the compound.

A “**transcribed polynucleotide**” or “nucleotide transcript” is a polynucleotide (*e.g.* an mRNA, hnRNA, a cDNA, or an analog of such RNA or cDNA) which is complementary to or having a high percentage of identity (*e.g.*, at least 80% identity) with all or a portion of a mature mRNA made by transcription of a marker of the invention and normal post-transcriptional processing (*e.g.* splicing), if any, of the RNA transcript, and reverse transcription of the RNA transcript.

As used herein, “**treatment**,” particularly “active treatment,” refers to performing an intervention to treat prostate cancer in a subject, *e.g.*, reduce at least one of the growth rate, reduction of tumor burden, reduce or maintain the tumor size, or the malignancy (*e.g.*, likelihood of metastasis) of the tumor; or to increase apoptosis in the tumor by one or more of administration of a therapeutic agent, *e.g.*, chemotherapy or hormone therapy; administration of radiation therapy (*e.g.*, pellet implantation, brachytherapy), or surgical resection of the tumor, or any combination thereof appropriate for treatment of the subject based on grade and stage of the tumor and other routine considerations. Active treatment is distinguished from “watchful waiting” (*i.e.*, not active treatment) in which the subject and tumor are monitored, but no interventions are performed to affect the tumor.

Watchful waiting can include administration of agents that alter effects caused by the tumor (e.g., incontinence, erectile dysfunction) that are not administered to alter the growth or pathology of the tumor itself.

The recitation of a listing of chemical group(s) in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable or aspect herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

Any compositions or methods provided herein can be combined with one or more of any of the other compositions and methods provided herein.

Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50.

Reference will now be made in detail to exemplary embodiments of the invention. While the invention will be described in conjunction with the exemplary embodiments, it will be understood that it is not intended to limit the invention to those embodiments. To the contrary, it is intended to cover alternatives, modifications, and equivalents as may be included within the spirit and scope of the invention as defined by the appended claims.

Exemplary compositions and methods of the present invention are described in more detail in the following sections: (C) Biomarkers of the invention; (D) Prostate tissue samples; (E) Detection and/or measurement of the biomarkers of the invention; (F) Isolated biomarkers; (G) Applications of biomarkers of the invention; (H) Therapeutics; (I) Drug screening; and (J) Kits/panels.

C. BIOMARKERS OF THE INVENTION

The present invention is based, at least in part, on the discovery that filamin A is differentially regulated in prostate cancer cells. In particular, the invention is based on the surprising discovery that filamin A levels are significantly elevated in the serum of patients with prostate cancer. Accordingly, the invention provides methods for diagnosing and/or monitoring (e.g., monitoring of disease progression or treatment) and/or prognosing an oncological disease state, e.g., prostate cancer, in a mammal. The invention also provides methods for treating or for adjusting treatment regimens based on diagnostic information relating to the levels of filamin A in the serum of a subject with an oncological disease state, e.g., prostate cancer. The invention further provides panels and kits for practicing the methods of the invention.

The present invention provides new biomarkers and combinations of biomarkers for use in diagnosing and/or prognosing an oncological disorder, and in particular, biomarkers for use in diagnosing and/or prognosing prostate cancer. The biomarkers of the invention are meant to

encompass any measurable characteristic that reflects in a quantitative or qualitative manner the physiological state of an organism, e.g., whether the organism has prostate cancer. The physiological state of an organism is inclusive of any disease or non-disease state, e.g., a subject having prostate cancer or a subject who is otherwise healthy. Said another way, the biomarkers of the invention include characteristics that can be objectively measured and evaluated as indicators of normal processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention, including, in particular, prostate cancer. Biomarkers can be clinical parameters (e.g., age, performance status), laboratory measures (e.g., molecular biomarkers, such as prostate specific antigen), imaging-based measures, or genetic or other molecular determinants, as well as combinations thereof. Examples of biomarkers include, for example, polypeptides, peptides, polypeptide fragments, proteins, antibodies, hormones, polynucleotides, RNA or RNA fragments, microRNA (miRNAs), lipids, polysaccharides, and other bodily metabolites that are diagnostic and/or indicative and/or predictive of an oncological disease, e.g., prostate cancer. Examples of biomarkers also include polypeptides, peptides, polypeptide fragments, proteins, antibodies, hormones, polynucleotides, RNA or RNA fragments, microRNA (miRNAs), lipids, polysaccharides, and other bodily metabolites which are diagnostic and/or indicative and/or predictive of any stage or clinical phase of an oncological disease, such as, prostate cancer. Clinical stage or phase can be represented by any means known in the art, for example, based on the Gleason Score system, e.g., Gleason grade 1, grade 2, grade 3, grade 4, or grade 5 prostate cancer.

In one aspect, the present invention relates to using, measuring, detecting, and the like of filamin A alone, or together with one or more additional biomarkers of prostate cancer, which can include, but are not limited to prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1. Other markers that may be used in combination with filamin A include any measurable characteristic described herein that reflects in a quantitative or qualitative manner the physiological state of an organism, e.g., whether the organism has prostate cancer. The physiological state of an organism is inclusive of any disease or non-disease state, e.g., a subject having prostate cancer or a subject who is otherwise healthy. The biomarkers of the invention that may be used in combination with filamin A include characteristics that can be objectively measured and evaluated as indicators of normal processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention, including, in particular, prostate cancer. Such combination biomarkers can be clinical parameters (e.g., age, performance status), laboratory measures (e.g., molecular biomarkers, such as prostate specific antigen), imaging-based measures, or genetic or other molecular determinants. Examples of biomarkers for use in combination with filamin A include, for example, polypeptides, peptides, polypeptide fragments, proteins, antibodies, hormones, polynucleotides, RNA or RNA fragments, microRNA (miRNAs), lipids, polysaccharides, and other bodily metabolites that are diagnostic and/or indicative and/or predictive of prostate cancer, or any particular stage or phase of

prostate cancer, e.g., Gleason grade 1, grade 2, grade 3, grade 4, or grade 5 prostate cancer or TNM classifications. In other embodiments, the present invention also involves the analysis and consideration of any clinical and/or patient-related health data, for example, data obtained from an Electronic Medical Record (e.g., collection of electronic health information about individual patients or populations relating to various types of data, such as, demographics, medical history, medication and allergies, immunization status, laboratory test results, radiology images, vital signs, personal statistics like age and weight, and billing information).

In certain embodiments, filamin A may be used in combination with at least one other biomarker, or more preferably, with at least two other biomarkers, or still more preferably, with at least three other biomarkers, or even more preferably with at least four other biomarkers. Still further, filamin A in certain embodiments, may be used in combination with at least five other markers, or at least six other biomarkers, or at least seven other biomarkers, or at least eight other biomarkers, or at least nine other biomarkers, or at least ten other biomarkers, or at least eleven other biomarkers, or at least twelve other biomarkers, or at least thirteen other biomarkers, or at least fourteen other biomarkers, or at least fifteen other biomarkers, or at least sixteen other biomarkers, or at least seventeen other biomarkers, or at least eighteen other biomarkers, or at least nineteen other biomarkers, or at least twenty other biomarkers. Further, filamin A may be used in combination with a multitude of other biomarkers, including, for example, with between about 20-50 other biomarkers, or between 50-100, or between 100-500, or between 500-1000, or between 1000-10,000 or biomarkers or more.

In certain embodiments, the present invention involves the detection and/or analysis filamin A I combination with at least one of the following set of biomarkers: prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1. The known function of these proteins is provided as follows, without wishing to be bound by theory:

Filamin A (FLN-A). Filamin A (also known as FLN-A, FLN1, ABP-280, OPD1, OPD2, Endothelial Actin-Binding Protein, CVD1, FMD, MNS, NHBP, XLVD, XMVD, Actin Binding Protein 280, Alpha-Filamin, Filamin-1, Filamin-A – each of which may appear herein and are considered equivalent terms as used herein) is a 280-kD protein that is thought to crosslink actin filaments into orthogonal networks in cortical cytoplasm. The large molecular-weight protein also participates in the anchoring of membrane proteins to the actin cytoskeleton. Remodeling of the cytoskeleton is central to the modulation of cell shape and migration cells. Filamin A, encoded by the *FLNA* gene, is a widely expressed protein that regulates reorganization of the actin cytoskeleton by interacting with integrins, transmembrane receptor complexes, and second messengers. At least two different isoforms are know, isoform 1 and isoform 2, all of which are contemplated by the invention and encompassed by the term “filamin A.” It will be appreciated that isoform 1 is the predominant transcript encoding filamin A. Isoform 2 includes an alternate in-frame exon and encodes a slightly

longer protein isoform. Interaction with FLNA may allow neuroblast migration from the ventricular zone into the cortical plate. FLNA tethers cell surface-localized furin, modulates its rate of internalization and directs its intracellular trafficking. Further reference to filamin A can be found in the scientific literature, for example, in Gorlin JB et al., (October 1993). "Actin-binding protein (ABP-280) filamin gene (FLN) maps telomeric to the color vision locus (R/GCP) and centromeric to G6PD in Xq28". *Genomics* 17 (2): 496–8, and Robertson SP et al. (March 2003). "Localized mutations in the gene encoding the cytoskeletal protein filamin A cause diverse malformations in humans". *Nat Genet* 33 (4): 487–91, each of which are incorporated herein by reference. The nucleotide and amino acid sequences of filamin A can be found as GenBank Accession No. NM_001456.3 (filamin A – isoform 1—mRNA transcript sequence—SEQ ID NO: 46) and the corresponding polypeptide sequence of NP_001447.2 (filamin A—isoform 1—polypeptide sequence—SEQ ID NO: 47) and as GenBank Accession No. NM_001110556.1 (filamin A—isoform 2—mRNA transcript sequence — SEQ ID NO: 48) and the corresponding polypeptide sequence of NP_001104026.1 (filamin A— isoform 2—polypeptide sequence—SEQ ID NO: 49). These GenBank numbers are incorporated herein by reference in the versions available on the earliest effective filing date of this application.

The present invention is based, at least in part, on the discovery that filamin A is differentially regulated in prostate cancer cells. In particular, the invention is based on the surprising discovery that filamin A levels are significantly elevated in the serum of patients with prostate cancer. Accordingly, the invention provides methods for diagnosing and/or monitoring (e.g., monitoring of disease progression or treatment) and/or prognosing an oncological disease state, e.g., prostate cancer, in a mammal. The invention also provides methods for treating or for adjusting treatment regimens based on diagnostic information relating to the levels of filamin A in the serum of a subject with an oncological disease state, e.g., prostate cancer. The invention further provides panels and kits for practicing the methods of the invention.

It is understood that the invention includes the use of any combination of one or more of the filamin A sequences provided in the sequence listing or any fragments thereof as long as the fragment can allow for the specific identification of filamin A. Methods of the invention and reagents can be used to detect single isoforms of filamin A, e.g., isoform 1 and isoform 2, combinations of filamin A isoforms, or all of the filamin A isoforms simultaneously. Unless specified, filamin A can be considered to refer to one or more isoforms of filamin A, including total filamin A. Moreover, it is understood that there are naturally occurring variants of filamin A, which may or may not be associated with a specific disease state, the use of which are also included in the instant application.

It is understood that the invention includes the use of any fragments of filamin A polypeptide as long as the fragment allows for the specific identification of filamin A by a detection method of the invention. For example, an ELISA antibody must be able to bind to the filamin A fragment so that detection is possible. Moreover, it is understood that there are naturally occurring variants of filamin A which may or may not be associated with a specific disease state, the use of which are also included

in this application. Accordingly, the present inventions also contemplates fragments and variants of filamin A which may be associated with a disease state, e.g., prostate cancer, and/or a particular stage or phase of a disease state, e.g., grades 1-5 of prostate cancer. It is also understood that the invention encompasses the use of nucleic acid molecules encoding filamin A, including for example, filamin A-encoding DNA, filamin A mRNA, and fragments and/or variants thereof. Reference to “filamin A” may refer to filamin A polypeptide or to the filamin A gene, unless otherwise indicated.

Keratin 4. Keratin 4, also known as K4; CK4; CK-4; CYK4, is a member of the keratin gene family. The type II cytokeratins consist of basic or neutral proteins which are arranged in pairs of heterotypic keratin chains coexpressed during differentiation of simple and stratified epithelial tissues. This type II cytokeratin is specifically expressed in differentiated layers of the mucosal and esophageal epithelia with family member KRT13. Mutations in these genes have been associated with White Sponge Nevus, characterized by oral, esophageal, and anal leukoplakia. The type II cytokeratins are clustered in a region of chromosome 12q12-q13.

As used herein, keratin 4 refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI Gene ID for human keratin 4 is 3851 and detailed information can be found at the NCBI website (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority). Homo sapiens keratin 4, GenBank Accession No. NM_002272 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 1 and 2. (The GenBank number is incorporated herein by reference in the version available on the filing date of the application to which this application claims priority.)

It is understood that the invention includes the use of any fragments of keratin 4 polypeptide as long as the fragment allow for the specific identification of keratin 4 by a detection method of the invention. For example, an ELISA antibody must be able to bind to the keratin 4 fragment so that detection is possible. Moreover, it is understood that there are naturally occurring variants of keratin 4 which may or may not be associated with a specific disease state, the use of which are also included in this application. Accordingly, the present inventions also contemplates fragments and variants of keratin 4 which may be associated with a disease state, e.g., prostate cancer, and/or a particular stage or phase of a disease state, e.g., grades 1-5 of prostate cancer. It is also understood that the invention encompasses the use of nucleic acid molecules encoding keratin 4, including for example, keratin 4-encoding DNA, keratin 4 mRNA, and fragments and/or variants thereof. Reference to “keratin 4” may refer to keratin 4 polypeptide or to the keratin 4 gene, unless otherwise indicated.

Keratin 7. Keratin 7, also known as CK7, K2C7, K7, SCL, CK-7; cytokeratin 7; cytokeratin-7; keratin, 55K type II cytoskeletal; keratin, simple epithelial type I, K7; keratin, type II cytoskeletal 7; keratin-7; sarcolectin; type II mesothelial keratin K7; and type-II keratin Kb7, is a member of the keratin gene family. The type II cytokeratins consist of basic or neutral proteins which are arranged in pairs of heterotypic keratin chains co-expressed during differentiation of simple and stratified epithelial tissues. This type II cytokeratin is specifically expressed in the simple epithelia

lining the cavities of the internal organs and in the gland ducts and blood vessels. The genes encoding the type II cytokeratins are clustered in a region of chromosome 12q12-q13. Alternative splicing may result in several transcript variants; however, not all variants have been fully described.

As used herein, keratin 7 refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI Gene ID for human keratin 7 is 3855 and detailed information can be found at the NCBI website (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority). Homo sapiens keratin 7, GenBank Accession No. NM_005556 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 3 and 4. (The GenBank number is incorporated herein by reference in the version available on the filing date of the application to which this application claims priority.)

It is understood that the invention includes the use of any fragments of keratin 7 polypeptide as long as the fragment allow for the specific identification of keratin 7 by a detection method of the invention. For example, an ELISA antibody must be able to bind to the keratin 7 fragment so that detection is possible. Moreover, it is understood that there are naturally occurring variants of keratin 7 which may or may not be associated with a specific disease state, the use of which are also included in this application. Accordingly, the present inventions also contemplates fragments and variants of keratin 7 which may be associated with a disease state, e.g., prostate cancer, and/or a particular stage or phase of a disease state, e.g., grades 1-5 of prostate cancer. It is also understood that the invention encompasses the use of nucleic acid molecules encoding keratin 7, including for example, keratin 7-encoding DNA, keratin 7 mRNA, and fragments and/or variants thereof. Reference to "keratin 7" may refer to keratin 7 polypeptide or to the keratin 7 gene, unless otherwise indicated.

Keratin 8. Keratin 8, also known as K8; KO; CK8; CK-8; CYK8; K2C8; CARD2 is a member of the type II keratin family clustered on the long arm of chromosome 12. Type I and type II keratins heteropolymerize to form intermediate-sized filaments in the cytoplasm of epithelial cells. The product of this gene typically dimerizes with keratin 18 to form an intermediate filament in simple single-layered epithelial cells. This protein plays a role in maintaining cellular structural integrity and also functions in signal transduction and cellular differentiation. Mutations in this gene cause cryptogenic cirrhosis. Alternatively spliced transcript variants have been found for this gene.

As used herein, keratin 8 refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI Gene ID for human keratin 8 is 3856 and detailed information can be found at the NCBI website (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority). Homo sapiens keratin 8, variant 1, GenBank Accession No. NM_001256282 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 5 and 6; and homo sapiens keratin 8, variant 3, GenBank Accession No. NM_001256293 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 7 and 8. (The GenBank numbers are incorporated herein by reference in the version available on the filing date of the application to which this application claims priority.)

It is understood that the invention includes the use of any fragments of keratin 8 polypeptide as long as the fragment allow for the specific identification of keratin 8 by a detection method of the invention. For example, an ELISA antibody must be able to bind to the keratin 8 fragment so that detection is possible. Moreover, it is understood that there are naturally occurring variants of keratin 8 which may or may not be associated with a specific disease state, the use of which are also included in this application. Accordingly, the present inventions also contemplates fragments and variants of keratin 8 which may be associated with a disease state, e.g., prostate cancer, and/or a particular stage or phase of a disease state, e.g., grades 1-5 of prostate cancer. It is also understood that the invention encompasses the use of nucleic acid molecules encoding keratin 8, including for example, keratin 8-encoding DNA, keratin 8 mRNA, and fragments and/or variants thereof. Reference to “keratin 8” may refer to keratin 8 polypeptide or to the keratin 8 gene, unless otherwise indicated.

Keratin 15. Keratin 15, also known as as K15; CK15; K1CO, is a member of the keratin gene family. The keratins are intermediate filament proteins responsible for the structural integrity of epithelial cells and are subdivided into cytokeratins and hair keratins. Most of the type I cytokeratins consist of acidic proteins which are arranged in pairs of heterotypic keratin chains and are clustered in a region on chromosome 17q21.2.

As used herein, keratin 15 refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI Gene ID for human keratin 15 is 3866 and detailed information can be found at the NCBI website (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority). Homo sapiens keratin 15, GenBank Accession No. NM_002275 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 9 and 10. (The GenBank number is incorporated herein by reference in the version available on the filing date of the application to which this application claims priority.)

It is understood that the invention includes the use of any fragments of keratin 15 polypeptide as long as the fragment allow for the specific identification of keratin 15 by a detection method of the invention. For example, an ELISA antibody must be able to bind to the keratin 15 fragment so that detection is possible. Moreover, it is understood that there are naturally occurring variants of keratin 15 which may or may not be associated with a specific disease state, the use of which are also included in this application. Accordingly, the present inventions also contemplates fragments and variants of keratin 15 which may be associated with a disease state, e.g., prostate cancer, and/or a particular stage or phase of a disease state, e.g., grades 1-5 of prostate cancer. It is also understood that the invention encompasses the use of nucleic acid molecules encoding keratin 15, including for example, keratin 15-encoding DNA, keratin 15 mRNA, and fragments and/or variants thereof. Reference to “keratin 15” may refer to keratin 15 polypeptide or to the keratin 15 gene, unless otherwise indicated.

Keratin 18. Keratin 18, also known as as K18; CYK18, encodes the type I intermediate filament chain keratin 18. Keratin 18, together with its filament partner keratin 8, are perhaps the most

commonly found members of the intermediate filament gene family. They are expressed in single layer epithelial tissues of the body. Mutations in this gene have been linked to cryptogenic cirrhosis. Two transcript variants encoding the same protein have been found for this gene.

As used herein, keratin 18 refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI Gene ID for human keratin 18 is 3875 and detailed information can be found at the NCBI website (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority). Homo sapiens keratin 18, variant 1, GenBank Accession No. NM_000224 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 11 and 12, and homo sapiens keratin 18, variant 2, GenBank Accession No. 199187 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 13 and 14. (The GenBank numbers are incorporated herein by reference in the version available on the filing date of the application to which this application claims priority.)

It is understood that the invention includes the use of any fragments of keratin 18 polypeptide as long as the fragment allow for the specific identification of keratin 18 by a detection method of the invention. For example, an ELISA antibody must be able to bind to the keratin 18 fragment so that detection is possible. Moreover, it is understood that there are naturally occurring variants of keratin 18 which may or may not be associated with a specific disease state, the use of which are also included in this application. Accordingly, the present inventions also contemplates fragments and variants of keratin 18 which may be associated with a disease state, e.g., prostate cancer, and/or a particular stage or phase of a disease state, e.g., grades 1-5 of prostate cancer. It is also understood that the invention encompasses the use of nucleic acid molecules encoding keratin 18, including for example, keratin 18-encoding DNA, keratin 18 mRNA, and fragments and/or variants thereof. Reference to “keratin 18” may refer to keratin 18 polypeptide or to the keratin 18 gene, unless otherwise indicated.

Keratin 19. Keratin 19, also known as K19; CK19; K1CS, is a member of the keratin gene family. The keratins are intermediate filament proteins responsible for the structural integrity of epithelial cells and are subdivided into cytokeratins and hair keratins. The type I cytokeratins consist of acidic proteins which are arranged in pairs of heterotypic keratin chains. Unlike its related family members, this smallest known acidic cytokeratin is not paired with a basic cytokeratin in epithelial cells. It is specifically expressed in the periderm, the transiently superficial layer that envelopes the developing epidermis. The type I cytokeratins are clustered in a region of chromosome 17q12-q21.

As used herein, keratin 19 refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI Gene ID for human keratin 19 is 3880 and detailed information can be found at the NCBI website (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority). Homo sapiens keratin 19, GenBank Accession No. NM_002276 amino acid and nucleotide sequences, respectively, are provided in SEQ

ID NOs: 15 and 16. (The GenBank number is incorporated herein by reference in the version available on the filing date of the application to which this application claims priority.)

It is understood that the invention includes the use of any fragments of keratin 19 polypeptide as long as the fragment allow for the specific identification of keratin 19 by a detection method of the invention. For example, an ELISA antibody must be able to bind to the keratin 19 fragment so that detection is possible. Moreover, it is understood that there are naturally occurring variants of keratin 19 which may or may not be associated with a specific disease state, the use of which are also included in this application. Accordingly, the present inventions also contemplates fragments and variants of keratin 19 which may be associated with a disease state, e.g., prostate cancer, and/or a particular stage or phase of a disease state, e.g., grades 1-5 of prostate cancer. It is also understood that the invention encompasses the use of nucleic acid molecules encoding keratin 19, including for example, keratin 19-encoding DNA, keratin 19 mRNA, and fragments and/or variants thereof. Reference to “keratin 19” may refer to keratin 19 polypeptide or to the keratin 8 gene, unless otherwise indicated.

Tubulin-beta 3. Tubulin-beta 3, also known as CDCBM; TUBB4; beta-4; CFEOM3A, is a class III member of the beta tubulin protein family. Beta tubulins are one of two core protein families (alpha and beta tubulins) that heterodimerize and assemble to form microtubules. This protein is primarily expressed in neurons and may be involved in neurogenesis and axon guidance and maintenance. Mutations in this gene are the cause of congenital fibrosis of the extraocular muscles type 3. Alternate splicing results in multiple transcript variants. A pseudogene of this gene is found on chromosome 6.

As used herein, Tubulin-beta 3 refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI Gene ID for human Tubulin-beta 3 is 10381 and detailed information can be found at the NCBI website (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority). Homo sapiens Tubulin-beta 3, variant 2, GenBank Accession No. NM_001197181 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 17 and 18. Homo sapiens Tubulin-beta 3, variant 1, GenBank Accession No. NM_006086 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 19 and 20. (The GenBank numbers are incorporated herein by reference in the versions available on the filing date of the application to which this application claims priority.)

It is understood that the invention includes the use of any fragments of Tubulin-beta 3 polypeptide as long as the fragment allow for the specific identification of Tubulin-beta 3 by a detection method of the invention. For example, an ELISA antibody must be able to bind to the Tubulin-beta 3 fragment so that detection is possible. Moreover, it is understood that there are naturally occurring variants of Tubulin-beta 3 which may or may not be associated with a specific disease state, the use of which are also included in this application. Accordingly, the present

inventions also contemplates fragments and variants of Tubulin-beta 3 which may be associated with a disease state, e.g., prostate cancer, and/or a particular stage or phase of a disease state, e.g., grades 1-5 of prostate cancer. It is also understood that the invention encompasses the use of nucleic acid molecules encoding Tubulin-beta 3, including for example, Tubulin-beta 3-encoding DNA, Tubulin-beta 3 mRNA, and fragments and/or variants thereof. Reference to "Tubulin-beta 3" may refer to Tubulin-beta 3 polypeptide or to the Tubulin-beta 3 gene, unless otherwise indicated.

Filamin B. Filamin B is also known as filamin-3, beta-filamin, ABP-280 homolog, filamin homolog 1, thyroid autoantigen, actin binding protein 278, actin-binding-like protein, Larsen syndrome 1 (autosomal dominant), AOI; FH1; SCT; TAP; LRS1; TAPP; FLN-B; FLN1L; ABP-278; and ABP-280. The gene encodes a member of the filamin family. The encoded protein interacts with glycoprotein Ib alpha as part of the process to repair vascular injuries. The platelet glycoprotein Ib complex includes glycoprotein Ib alpha, and it binds the actin cytoskeleton. Mutations in this gene have been found in several conditions: atelosteogenesis type 1 and type 3; boomerang dysplasia; autosomal dominant Larsen syndrome; and spondylocarpotarsal synostosis syndrome. Multiple alternatively spliced transcript variants that encode different protein isoforms have been described for this gene.

As used herein, filamin B refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI gene ID for filamin B is 2317 and detailed information can be found at the NCBI website (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority).

Homo sapiens filamin B, beta (FLNB), RefSeqGene on chromosome 3, locus NG_012801 is shown in SEQ ID NO: 21. Homo sapiens filamin B, beta (FLNB), transcript variant 1, GenBank Accession No. NM_001164317.1 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 22 and 23. Homo sapiens filamin B, beta (FLNB), transcript variant 3, GenBank Accession No. NM_001164318.1 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 24 and 25. Homo sapiens filamin B, beta (FLNB), transcript variant 4, GenBank Accession No. NM_001164319.1 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 26 and 27. Homo sapiens filamin B, beta (FLNB), transcript variant 2, GenBank Accession No. NM_001457.3 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 28 and 29. (Each GenBank number is incorporated herein by reference in the version available on the filing date of the application to which this application claims priority.)

It is understood that the invention includes the use of any combination of one or more of the filamin B sequences provided in the sequence listing or any fragments thereof as long as the fragment can allow for the specific identification of filamin B. Methods of the invention and reagents can be used to detect single isoforms of filamin B, combinations of filamin B isoforms, or all of the filamin B isoforms simultaneously. Unless specified, filamin B can be considered to refer to one or more isoforms of filamin B, including total filamin B. Moreover, it is understood that there are naturally

occurring variants of filamin B, which may or may not be associated with a specific disease state, the use of which are also included in the instant application.

In addition, it is understood that the invention includes the use of any fragments of filamin B polypeptide as long as the fragment allow for the specific identification of filamin B by a detection method of the invention. For example, an ELISA antibody must be able to bind to the filamin B fragment so that detection is possible. Moreover, it is understood that there are naturally occurring variants of filamin B which may or may not be associated with a specific disease state, the use of which are also included in this application. Accordingly, the present inventions also contemplates fragments and variants of filamin B which may be associated with a disease state, e.g., prostate cancer, and/or a particular stage or phase of a disease state, e.g., grades 1-5 of prostate cancer. It is also understood that the invention encompasses the use of nucleic acid molecules encoding filamin B, including for example, filamin B-encoding DNA, filamin B mRNA, and fragments and/or variants thereof. Reference to “filamin B” may refer to filamin B polypeptide or to the filamin B gene, unless otherwise indicated.

Lymphocyte Antigen 9. Lymphocyte antigen 9 (LY9) is also known as RP11-312J18.1, CD229, SLAMF3, hly9, mLY9, T-lymphocyte surface antigen Ly-9; and cell surface molecule Ly-9. LY9 belongs to the SLAM family of immunomodulatory receptors (see SLAMF1; MIM 603492) and interacts with the adaptor molecule SAP (SH2D1A; MIM 300490) (Graham et al., 2006).

As used herein, LY9 refers to both the gene and the protein unless clearly indicated otherwise by context. The NCBI gene ID for LY9 is 4063 and detailed information can be found at the NCBI website (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority).

Homo sapiens lymphocyte antigen 9 (LY9), transcript variant 2, GenBank Accession No. NM_001033667 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 30 and 31. Homo sapiens lymphocyte antigen 9 (LY9), transcript variant 3, GenBank Accession No. NM_001261456 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 32 and 33. Homo sapiens lymphocyte antigen 9 (LY9), transcript variant 4, GenBank Accession No. NM_001261457 amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 34 and 35. Homo sapiens lymphocyte antigen 9 (LY9), transcript variant 1, GenBank Accession No. NM_002348 is shown amino acid and nucleotide sequences, respectively, are provided in SEQ ID NOs: 36 and 37. (Each GenBank number is incorporated herein by reference in the version available on the filing date of the application to which this application claims priority.)

It is understood that the invention includes the use of any combination of one or more of the LY9 sequences provided in the sequence listing or any fragments thereof as long as the fragment can allow for the specific identification of LY9. Methods of the invention and reagents can be used to detect single isoforms of LY9, combinations of LY9 isoforms, or all of the LY9 isoforms simultaneously. Unless specified, LY9 can be considered to refer to one or more isoforms of LY9,

including total LY9. Moreover, it is understood that there are naturally occurring variants of LY9, which may or may not be associated with a specific disease state, the use of which are also included in the instant application.

In addition, it is understood that the invention includes the use of any fragments of LY9 polypeptide as long as the fragment allow for the specific identification of LY9 by a detection method of the invention. For example, an ELISA antibody must be able to bind to the LY9 fragment so that detection is possible. Moreover, it is understood that there are naturally occurring variants of LY9 which may or may not be associated with a specific disease state, the use of which are also included in this application. Accordingly, the present inventions also contemplates fragments and variants of LY9 which may be associated with a disease state, e.g., prostate cancer, and/or a particular stage or phase of a disease state, e.g., grades 1-5 of prostate cancer. It is also understood that the invention encompasses the use of nucleic acid molecules encoding LY9, including for example, LY9-encoding DNA, LY9 mRNA, and fragments and/or variants thereof. Reference to "LY9" may refer to LY9 polypeptide or to the LY9 gene, unless otherwise indicated.

Prostate Specific Antigen. Prostate-specific antigen (PSA) is also known as kallikrein-3, seminin, P-30 antigen, semenogelase, gamma-seminoprotein, APS, hK3, and KLK2A1. Kallikreins are a subgroup of serine proteases having diverse physiological functions. Growing evidence suggests that many kallikreins are implicated in carcinogenesis and some have potential as novel cancer and other disease biomarkers. This gene is one of the fifteen kallikrein subfamily members located in a cluster on chromosome 19. Its protein product is a protease present in seminal plasma. It is thought to function normally in the liquefaction of seminal coagulum, presumably by hydrolysis of the high molecular mass seminal vesicle protein. Serum level of this protein, called PSA in the clinical setting, is useful in the diagnosis and monitoring of prostatic carcinoma. Alternate splicing of this gene generates several transcript variants encoding different isoforms.

As used herein, PSA refers to both the gene and the protein, in both processed and unprocessed forms, unless clearly indicated otherwise by context. The NCBI gene ID for PSA is 354 and detailed information can be found at the NCBI website (incorporated herein by reference in the version available on the filing date of the application to which this application claims priority).

Homo sapiens PSA is located on chromosome 19 at 19q13.41 Sequence : NC_000019.9 (51358171..51364020). Four splice variants of human PSA are known. Prostate-specific antigen isoform 3 preproprotein, NM_001030047.1, is provided as SEQ ID NOs: 38 and 39. Prostate-specific antigen isoform 4 preproprotein, NM_001030048.1, is provided as SEQ ID NOs: 40 and 41. Prostate-specific antigen isoform 6 preproprotein, NM_001030050.1, is provided as SEQ ID NOs: 42 and 43. Prostate-specific antigen isoform 1 preproprotein, NM_001648.2, is provided in SEQ ID NOs: 44 and 45. (Each GenBank number is incorporated herein by reference in the version available on the filing date of the application to which this application claims priority).

It is understood that the invention includes the use of any combination of one or more of the PSA sequences provided in the sequence listing or any fragments thereof as long as the fragment can allow for the specific identification of PSA. Methods of the invention and reagents can be used to detect single isoforms of PSA, combinations of PSA isoforms, or all of the PSA isoforms simultaneously. Unless specified, PSA can be considered to refer to one or more isoforms of PSA, including total PSA. Moreover, it is understood that there are naturally occurring variants of PSA, which may or may not be associated with a specific disease state, the use of which are also included in the instant application.

In addition, it is understood that the invention includes the use of any fragments of PSA polypeptide as long as the fragment allow for the specific identification of PSA by a detection method of the invention. For example, an ELISA antibody must be able to bind to the PSA fragment so that detection is possible. Moreover, it is understood that there are naturally occurring variants of PSA which may or may not be associated with a specific disease state, the use of which are also included in this application. Accordingly, the present inventions also contemplates fragments and variants of PSA which may be associated with a disease state, e.g., prostate cancer, and/or a particular stage or phase of a disease state, e.g., grades 1-5 of prostate cancer. It is also understood that the invention encompasses the use of nucleic acid molecules encoding PSA, including for example, PSA-encoding DNA, PSA mRNA, and fragments and/or variants thereof. Reference to “PSA” may refer to PSA polypeptide or to the PSA gene, unless otherwise indicated.

Age. The age of a subject can be used as a continuous predictive variable for the presence of prostate cancer. For example, increased age is associated with increased risk of prostate cancer. Conversely, decreased age is associated with decreased risk of prostate cancer. Similarly, age can be used as a continuous predictive variable for the stage, or category, of the prostate cancer. For example, age can be used as a continuous predictive variable for the Gleason score of the prostate cancer.

The biomarkers of the invention, including in particular filamin A alone or in combination with any one or more of PSA, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9), may be detected as a polypeptide or a detectable fragment thereof. Alternatively, the biomarkers of the invention, including in particular filamin A alone or in combination with any one or more of PSA, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9), may be detected as nucleic acid molecules, such as DNA, RNA, mRNA, microRNA, and the like. In addition, combinations of biomarkers, including filamin A alone or in combination with any one or more of PSA, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9), may be detected as any combination of polypeptides and nucleic acid molecules. In certain embodiments, all of the biomarkers are in the form of polypeptides. In certain other embodiments, all of the biomarkers are in the form of

polynucleotides. In certain other embodiments, at least filamin A is in the form of a polypeptide, whereas any other markers tested can be a polypeptide or nucleic acid molecule. In still other embodiments, at least filamin A is in the form of a nucleic acid molecule, whereas any other markers tested can be a polypeptide or nucleic acid molecule.

In other embodiments, the biomarkers of the invention, including in particular filamin A alone or in combination with any one or more of PSA, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), lymphocyte antigen 9 (LY9), prostate-specific membrane antigen (PSM), prostate stem cell antigen (PSCA), TMPRSS2, PDEF, prostate-specific gene-1 (HPG-1), and non-coding RNAs (ncRNAs), including PCA3, PCGEM1, and the gene cluster P704P, P712P, and P775P, may be detected as a polypeptide or a detectable fragment thereof. Alternatively, the biomarkers of the invention, including in particular filamin A alone or in combination with any one or more of PSA, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), lymphocyte antigen 9 (LY9), prostate-specific membrane antigen (PSM), prostate stem cell antigen (PSCA), TMPRSS2, PDEF, prostate-specific gene-1 (HPG-1), and non-coding RNAs (ncRNAs), including PCA3, PCGEM1, and the gene cluster P704P, P712P, and P775P, may be detected as nucleic acid molecules, such as DNA, RNA, mRNA, microRNA, and the like. In addition, combinations of biomarkers, including filamin A alone or in combination with any one or more of PSA, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), lymphocyte antigen 9 (LY9), prostate-specific membrane antigen (PSM), prostate stem cell antigen (PSCA), TMPRSS2, PDEF, prostate-specific gene-1 (HPG-1), and non-coding RNAs (ncRNAs), including PCA3, PCGEM1, and the gene cluster P704P, P712P, and P775P, may be detected as any combination of polypeptides and nucleic acid molecules. In certain embodiments, all of the biomarkers are in the form of polypeptides. In certain other embodiments, all of the biomarkers are in the form of polynucleotides. In certain other embodiments, at least filamin A is in the form of a polypeptide, whereas any other markers tested can be a polypeptide or nucleic acid molecule. In still other embodiments, at least filamin A is in the form of a nucleic acid molecule, whereas any other markers tested can be a polypeptide or nucleic acid molecule.

The specific marker identified herein as prostate-specific membrane antigen (PSM) is further described in Sokoll et al., 1997, Prostate-specific antigen – Its discovery and biochemical characteristics, *Urol. Clin. North Am.*, 24:253-259, which is incorporated herein by reference.

The specific marker identified herein as prostate stem cell antigen (PSCA) is further described in Fair et al., 1997, Prostate-specific membrane antigen, *Prostate*, 32:140-148, which is incorporated herein by reference.

The specific marker identified herein as TMPRSS2 is further described in Lin et al., 1999, Prostate-localized and androgen-regulated expression of the membrane-bound serine protease TMPRSS2, *Cancer Res.*, 59:4180-4184, which is incorporated herein by reference.

The specific marker identified herein as PDEF is further described in Oettgen et al., PDEF, a novel prostate epithelium-specific ETS transcription factor interacts with the androgen receptor and activates prostate-specific antigen gene expression, *J. Biol. Chem.*, 275: 1216-1225, which is incorporated herein by reference.

The specific marker identified herein as prostate-specific gene-1 (HPG-1) is further described in Herness, A novel human prostate-specific gene-1 (HPG-1): molecular cloning, sequencing, and its potential involvement in prostate carcinogenesis, 2003, *Cancer Res.* 63:329-336, which is incorporated herein by reference.

The *non-coding RNA's* (ncRNA's) identified as *PCA3* is further described in Bussemakers et al., 1999, DD3: a new prostate-specific gene, highly overexpressed in prostate cancer, *Cancer Res.* 59:5975-5979, which is incorporated herein by reference.

The non-coding RNA identified as *PCGEM1* is further described in Srikantan et al., 2000. *PCGEM1*, a prostate-specific gene, is overexpressed in prostate cancer. *Proc. Natl. Acad. Sci. USA* 97:12216-12221, which is incorporated herein by reference.

The gene cluster *P704P*, *P712P*, and *P775P* is further described in Stolk et al., 2004. *P704P*, *P712P*, and *P775P*: A genomic cluster of prostate-specific genes. *Prostate* 60:214-226), which is incorporated herein by reference.

The present invention also contemplates the use of particular combinations of biomarkers.

In one embodiment, the invention contemplates marker sets with at least two (2) members, which may include, but are not limited to the following sets: filamin A together with PSA; filamin A together with PSA; filamin A together with LY9; filamin A together with keratin 4; filamin A together with keratin 7; filamin A together with keratin 8; filamin A together with keratin 15; filamin A together with keratin 18; filamin A together with keratin 19; filamin A together with tubulin-beta 3; filamin A together with prostate-specific membrane antigen (PSM); filamin A together with prostate stem cell antigen (PSCA); filamin A together with TMPRSS2; filamin A together with PDEF; filamin A together with prostate-specific gene-1 (HPG-1); filamin A together with PCA3; filamin A together with PCGEM1; and filamin A together with gene cluster *P704P*, *P712P*, and *P775P*; and filamin A together with patient age. Any marker set can additionally be used in combination with PSA.

In another embodiment, the invention contemplates marker sets with at least three (3) members, wherein one member is filamin A and the additional two members are selected from the following sets of two markers: filamin B, LY9; filamin B, keratin 4; filamin B, keratin 7; filamin B, keratin 8; filamin B, keratin 15; filamin B, keratin 18; filamin B, keratin 19; filamin B, tubulin-beta 3; filamin B, PSM; filamin B, PSCA; filamin B, TMPRSS2; filamin B, PDEF; filamin B, HPG-1; filamin B, PCA3; filamin B, PCGEM1; filamin B, *P704P/P712P/P775P*; LY9, keratin 4; LY9, keratin 7; LY9, keratin 8; LY9, keratin 15; LY9, keratin 18; LY9, keratin 19; LY9, tubulin-beta 3; LY9, PSM; LY9, PSCA; LY9, TMPRSS2; LY9, PDEF; LY9, HPG-1; LY9, PCA3; LY9, PCGEM1; LY9,

P704P/P712P/P775P; keratin 4, keratin 7; keratin 4, keratin 8; keratin 4, keratin 15; keratin 4, keratin 18; keratin 4, keratin 19; keratin 4, tubulin-beta 3; keratin 4, PSM; keratin 4, PSCA; keratin 4, TMPRSS2; keratin 4, PDEF; keratin 4, HPG-1; keratin 4, PCA3; keratin 4, PCGEM1; keratin 4, P704P/P712P/P775P; keratin 7, keratin 8; keratin 7, keratin 15; keratin 7, keratin 18; keratin 7, keratin 19; keratin 7, tubulin-beta 3; keratin 7, PSM; keratin 7, PSCA; keratin 7, TMPRSS2; keratin 7, PDEF; keratin 7, HPG-1; keratin 7, PCA3; keratin 7, PCGEM1; keratin 7, P704P/P712P/P775P; keratin 8, keratin 15; keratin 8, keratin 18; keratin 8, keratin 19; keratin 8, tubulin-beta 3; keratin 8, PSM; keratin 8, PSCA; keratin 8, TMPRSS2; keratin 8, PDEF; keratin 8, HPG-1; keratin 8, PCA3; keratin 8, PCGEM1; keratin 8, P704P/P712P/P775P; keratin 15, keratin 18; keratin 15, keratin 19; keratin 15, tubulin-beta 3; keratin 15, PSM; keratin 15, PSCA; keratin 15, TMPRSS2; keratin 15, PDEF; keratin 15, HPG-1; keratin 15, PCA3; keratin 15, PCGEM1; keratin 15, P704P/P712P/P775P; keratin 18, tubulin-beta 3; keratin 18, keratin 19; and keratin 19, tubulin-beta 3; keratin 18, PSM; keratin 18, PSCA; keratin 18, TMPRSS2; keratin 18, PDEF; keratin 18, HPG-1; keratin 18, PCA3; keratin 18, PCGEM1; keratin 18, P704P/P712P/P775P. Any marker set can be used in combination with patient age. Any marker set can additionally be used in combination with PSA.

In another embodiment, the invention contemplates marker sets with at least four (4) members, wherein one member is filamin A and the additional three members may include, but are not limited to the following sets: filamin B, LY9, keratin 4; filamin B, LY9, keratin 7; filamin B, LY9, keratin 8; filamin B, LY9, keratin 15; filamin B, LY9, keratin 18; filamin B, LY9, keratin 19; filamin B, LY9, tubulin-beta 3; filamin B, keratin 4, keratin 7; filamin B, keratin 4, keratin 8; filamin B, keratin 4, keratin 15; filamin B, keratin 4, keratin 18; filamin B, keratin 4, keratin 19; filamin B, keratin 4, tubulin-beta 3; filamin B, keratin 7, keratin 8; filamin B, keratin 7, keratin 15; filamin B, keratin 7, keratin 18; filamin B, keratin 7, keratin 19; filamin B, keratin 7, tubulin-beta 3; filamin B, keratin 8, keratin 15; filamin B, keratin 8, keratin 18; filamin B, keratin 8, keratin 19; filamin B, keratin 8, tubulin-beta 3; filamin B, keratin 15, keratin 18; filamin B, keratin 15, keratin 19; filamin B, keratin 15, tubulin-beta 3; filamin B, keratin 18, keratin 19; filamin B, keratin 18, tubulin-beta 3; filamin B, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 7; LY9, keratin 4, keratin 8; LY9, keratin 4, keratin 15; LY9, keratin 4, keratin 18; LY9, keratin 4, keratin 19; LY9, keratin 4, tubulin-beta 3; LY9, keratin 7, keratin 8; LY9, keratin 7, keratin 15; LY9, keratin 7, keratin 18; LY9, keratin 7, keratin 19; LY9, keratin 7, tubulin-beta 3; LY9, keratin 8, keratin 15; LY9, keratin 8, keratin 18; LY9, keratin 8, keratin 19; LY9, keratin 8, tubulin-beta 3; LY9, keratin 15, keratin 18; LY9, keratin 15, keratin 19; LY9, keratin 15, tubulin-beta 3; LY9, keratin 18, keratin 19; LY9, keratin 18, tubulin-beta 3; LY9, keratin 19, tubulin-beta 3; keratin 4, keratin 7, keratin 8; keratin 4, keratin 7, keratin 15; keratin 4, keratin 7, keratin 18; keratin 4, keratin 7, keratin 19; keratin 4, keratin 7, tubulin-beta 3; keratin 4, keratin 8, keratin 15; keratin 4, keratin 8, keratin 18; keratin 4, keratin 8, keratin 19; keratin 4, keratin 8, tubulin-beta 3; keratin 4, keratin 15, keratin 18; keratin 4, keratin 15, keratin 19; keratin 4, keratin 15, tubulin-beta 3; keratin 4, keratin 18, keratin 19; keratin 4,

keratin 19, tubulin-beta 3; keratin 7, keratin 8, keratin 15; keratin 7, keratin 8, keratin 18; keratin 7, keratin 8, keratin 19; keratin 7, keratin 8, tubulin-beta 3; keratin 7, keratin 8, tubulin-beta 3; keratin 7, keratin 15, keratin 18; keratin 7, keratin 15, keratin 19; keratin 7, keratin 15, tubulin-beta 3; keratin 7, keratin 18, keratin 19; keratin 7, keratin 18, tubulin-beta 3; keratin 15, keratin 18, keratin 19; keratin 15, keratin 18, tubulin-beta 3; and keratin 18, keratin 19, tubulin-beta 3. Any marker set can be used in combination with patient age. Any marker set can be used in combination with PSA. In addition, any of the above sets may be modified to replace one or more markers in the marker set with one or more of the following additional markers: prostate-specific membrane antigen (PSM), prostate stem cell antigen (PSCA), TMPRSS2, PDEF, prostate-specific gene-1 (HPG-1), PCA3, PCGEM1, and the gene cluster P704P, P712P, and P775P.

In another embodiment, the invention contemplates marker sets with at least five (5) members, wherein one member is filamin A and the additional four members may include, but are not limited to the following sets: filamin B, LY9, keratin 4, keratin 7; filamin B, LY9, keratin 4, keratin 8; filamin B, LY9, keratin 4, keratin 15; filamin B, LY9, keratin 4, keratin 18; filamin B, LY9, keratin 4, keratin 19; filamin B, LY9, keratin 4, tubulin-beta 3; filamin B, keratin 4, keratin 7, keratin 8; filamin B, keratin 4, keratin 7, keratin 15; filamin B, keratin 4, keratin 7, keratin 18; filamin B, keratin 4, keratin 7, tubulin-beta 3; filamin B, keratin 4, keratin 7, tubulin-beta 3; filamin B, keratin 7, keratin 8, keratin 15; filamin B, keratin 7, keratin 8, keratin 18; filamin B, keratin 7, keratin 8, keratin 19; filamin B, keratin 7, keratin 8, tubulin-beta 3; filamin B, keratin 8, keratin 15, keratin 18; filamin B, keratin 8, keratin 15, keratin 19; filamin B, keratin 8, keratin 15, tubulin-beta 3; filamin B, keratin 15, keratin 18, keratin 19; filamin B, keratin 15, keratin 18, tubulin-beta 3; filamin B, keratin 18, keratin 19, and tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 8; LY9, keratin 4, keratin 7, keratin 15; LY9, keratin 4, keratin 7, keratin 18; LY9, keratin 4, keratin 7, keratin 19; LY9, keratin 4, keratin 7, tubulin-beta 3; LY9, keratin 7, keratin 8, keratin 15; LY9, keratin 7, keratin 8, keratin 18; LY9, keratin 7, keratin 8, keratin 19; LY9, keratin 7, keratin 8, tubulin-beta 3; LY9, keratin 8, keratin 15, keratin 18; LY9, keratin 8, keratin 15, keratin 19; LY9, keratin 8, keratin 15, tubulin-beta 3; LY9, keratin 15, keratin 18, keratin 19; LY9, keratin 15, keratin 18, tubulin-beta 3; LY9, keratin 18, keratin 19, and tubulin-beta 3; keratin 4, keratin 7, keratin 8, keratin 15; keratin 4, keratin 7, keratin 8, keratin 18; keratin 4, keratin 7, keratin 8, keratin 19; keratin 4, keratin 7, keratin 8, tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 18; keratin 4, keratin 8, keratin 15, keratin 19; keratin 4, keratin 8, keratin 15, tubulin-beta 3; keratin 4, keratin 15, keratin 18, keratin 19; keratin 4, keratin 15, keratin 18, tubulin-beta 3; keratin 4, keratin 18, keratin 19, tubulin-beta 3; keratin 8, keratin 15, keratin 18, keratin 19; keratin 8, keratin 15, keratin 18, tubulin-beta 3; and keratin 15, keratin 18, keratin 19, tubulin-beta 3. Any marker set can be used in combination with PSA. In addition, any of the above sets may be modified to replace one or more markers in the marker set with one or more of the following additional markers: prostate-specific membrane antigen (PSM), prostate stem cell antigen (PSCA), TMPRSS2, PDEF, prostate-specific

gene-1 (HPG-1), PCA3, PCGEM1, and the gene cluster P704P, P712P, and P775P. Any marker set can be used in combination with patient age.

In another embodiment, the invention contemplates marker sets with at least six (6) members, wherein one member is filamin A and the additional five members may include, but are not limited to the following sets: keratin 8, keratin 15, keratin 18, keratin 19 tubulin-beta 3; keratin 7, keratin 15, keratin 18, keratin 19 tubulin-beta 3; keratin 7, keratin 8, keratin 18, keratin 19 tubulin-beta 3; keratin 7, keratin 8, keratin 15, keratin 19 tubulin-beta 3; keratin 7, keratin 8, keratin 15, keratin 18 tubulin-beta 3; keratin 7, keratin 8, keratin 15, keratin 18, keratin 19; keratin 4, keratin 15, keratin 18, keratin 19 tubulin-beta 3; keratin 4, keratin 8, keratin 18, keratin 19 tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 19 tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 18 tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 18, keratin 19; LY9, keratin 15, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 8, keratin 18, keratin 19 tubulin-beta 3; LY9, keratin 8, keratin 15, keratin 19 tubulin-beta 3; LY9, keratin 8, keratin 15, keratin 18, and tubulin-beta 3; LY9, keratin 8, keratin 15, keratin 18, keratin 19; filamin B, keratin 15, keratin 18, keratin 19 tubulin-beta 3; filamin B, keratin 8, keratin 18, keratin 19 tubulin-beta 3; filamin B, keratin 8, keratin 15, keratin 19 tubulin-beta 3; filamin B, keratin 8, keratin 15, keratin 18, and tubulin-beta 3; filamin B, keratin 8, keratin 15, keratin 18, keratin 19; filamen B, LY9, keratin 18, keratin 19 tubulin-beta 3; filamen B, LY9, keratin 15, keratin 19 tubulin-beta 3; filamen B, LY9, keratin 15, keratin 18, tubulin-beta 3; filamen B, LY9, keratin 15, keratin 18, keratin 19; filamen B, keratin 4, keratin 18, keratin 19 tubulin-beta 3; filamen B, keratin 4, keratin 15, keratin 19 tubulin-beta 3; filamen B, keratin 4, keratin 15, keratin 18, keratin 19; filamen B keratin 7, keratin 18, keratin 19 tubulin-beta 3; filamen B keratin 7, keratin 15, keratin 19, tubulin-beta 3; filamen B keratin 7, keratin 15, keratin 18, tubulin-beta 3; filamen B keratin 7, keratin 15, keratin 18, keratin 19; filamen B, keratin 8, keratin 18, keratin 19 tubulin-beta 3; filamen B, keratin 8, keratin 15, keratin 19 tubulin-beta 3; filamen B, keratin 8, keratin 15, keratin 18, keratin 19; LY9, keratin 4, keratin 18, keratin 19 and tubulin-beta 3; LY9, keratin 4, keratin 15, keratin 19 tubulin-beta 3; LY9, keratin 4, keratin 15, keratin 18, tubulin-beta 3; LY9, keratin 4, keratin 15, keratin 18, keratin 19; LY9, keratin 7, keratin 18, keratin 19 tubulin-beta 3; LY9, keratin 7, keratin 15, keratin 19 tubulin-beta 3; LY9, keratin 7, keratin 15, keratin 18, and tubulin-beta 3; LY9, keratin 7, keratin 15, keratin 18, keratin 19; LY9, keratin 8, keratin 18, keratin 19 tubulin-beta 3; LY9, keratin 8, keratin 15, keratin 19 tubulin-beta 3; LY9, keratin 8, keratin 15, keratin 18, and tubulin-beta 3; LY9, keratin 8, keratin 15, keratin 18, keratin 19; keratin 4, keratin 7, keratin 18, keratin 19 tubulin-beta 3; keratin 4, keratin 7, keratin 15, keratin 19 tubulin-beta 3; keratin 4, keratin 7, keratin 15, keratin 18, keratin 19; keratin 4, keratin 8, keratin 18, keratin 19 tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 19 tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 18, and tubulin-beta 3; keratin 4, keratin 8,

keratin 15, keratin 18, keratin 19; keratin 7, keratin 8, keratin 18, keratin 19 tubulin-beta 3; keratin 7, keratin 8, keratin 15, keratin 19 tubulin-beta 3; keratin 7, keratin 8, keratin 15, keratin 18, and tubulin-beta 3; keratin 7, keratin 8, keratin 15, keratin 18, keratin 19; filamen B, LY9, keratin 4, keratin 19, tubulin-beta 3; filamen B, LY9, keratin 4, keratin 18, tubulin-beta 3; filamen B, LY9, keratin 4, keratin 18, keratin 19; filamen B, LY9, keratin 7, keratin 19, tubulin-beta 3; filamen B, LY9, keratin 7, keratin 18, tubulin-beta 3; filamen B, LY9, keratin 7, keratin 18, keratin 19; filamen B, LY9, keratin 8, keratin 19, tubulin-beta 3; filamen B, LY9, keratin 8, keratin 18, tubulin-beta 3; filamen B, LY9, keratin 8, keratin 18, keratin 19; filamen B, LY9, keratin 15, keratin 19, tubulin-beta 3; filamen B, LY9, keratin 15, keratin 18, tubulin-beta 3; filamen B, LY9, keratin 15, keratin 18, keratin 19; filamen B, keratin 4, keratin 7, keratin 19, tubulin-beta 3; filamen B, keratin 4, keratin 7, keratin 18, keratin 19; filamen B, keratin 4, keratin 8, keratin 19, tubulin-beta 3; filamen B, keratin 4, keratin 8, keratin 18, keratin 19; filamen B, keratin 4, keratin 15, keratin 19, tubulin-beta 3; filamen B, keratin 4, keratin 15, keratin 18, tubulin-beta 3; filamen B, keratin 4, keratin 15, keratin 18, keratin 19; filamen B, keratin 7, keratin 8, keratin 19, tubulin-beta 3; filamen B, keratin 7, keratin 8, keratin 18, tubulin-beta 3; filamen B, keratin 7, keratin 8, keratin 18, keratin 19; filamen B, keratin 8, keratin 15, keratin 19, tubulin-beta 3; filamen B, keratin 8, keratin 15, keratin 18, tubulin-beta 3; filamen B, keratin 8, keratin 15, keratin 18, keratin 19; LY9, keratin 4, keratin 7, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 18, keratin 19; LY9, keratin 4, keratin 8, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 8, keratin 18, tubulin-beta 3; LY9, keratin 4, keratin 8, keratin 18, keratin 19; LY9, keratin 4, keratin 15, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 15, keratin 18, tubulin-beta 3; LY9, keratin 4, keratin 15, keratin 18, keratin 19; LY9, keratin 7, keratin 8, keratin 19, tubulin-beta 3; LY9, keratin 7, keratin 8, keratin 18, keratin 19; LY9, keratin 7, keratin 15, keratin 19, tubulin-beta 3; LY9, keratin 7, keratin 15, keratin 18, tubulin-beta 3; LY9, keratin 7, keratin 15, keratin 18, keratin 19; LY9, keratin 8, keratin 15, keratin 18, tubulin-beta 3; LY9, keratin 8, keratin 15, keratin 18, keratin 19; keratin 4, keratin 7, keratin 8, keratin 19, tubulin-beta 3; keratin 4, keratin 7, keratin 8, keratin 18, tubulin-beta 3; keratin 4, keratin 7, keratin 8, keratin 18, keratin 19; keratin 4, keratin 7, keratin 15, keratin 19, tubulin-beta 3; keratin 4, keratin 7, keratin 15, keratin 18, tubulin-beta 3; keratin 4, keratin 7, keratin 15, keratin 18, keratin 19; keratin 4, keratin 8, keratin 15, keratin 19, tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 18, tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 18, keratin 19; keratin 7, keratin 8, keratin 15, keratin 19, tubulin-beta 3; keratin 7, keratin 8, keratin 15, keratin 18, tubulin-beta 3; and keratin 7, keratin 8, keratin 15, keratin 18, keratin 19. Any marker set can be used in combination with PSA. In addition, any of the above sets may be modified to replace one or more markers in the marker set with one or more of the

following additional markers: prostate-specific membrane antigen (PSM), prostate stem cell antigen (PSCA), TMPRSS2, PDEF, prostate-specific gene-1 (HPG-1), PCA3, PCGEM1, and the gene cluster P704P, P712P, and P775P. Any marker set can be used in combination with patient age.

In another embodiment, the invention contemplates marker sets with at least seven (7) members, wherein one member is filamin A and the additional six members may include, but are not limited to the following sets: keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3; keratin 4, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3; keratin 4, keratin 7, keratin 15, keratin 18, keratin 19, tubulin-beta 3; keratin 4, keratin 7, keratin 8, keratin 18, keratin 19, tubulin-beta 3; keratin 4, keratin 7, keratin 8, keratin 15, keratin 19, tubulin-beta 3; keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19; LY9, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 7, keratin 15, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 7, keratin 8, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 7, keratin 8, keratin 15, keratin 19, tubulin-beta 3; LY9, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19; LY9, keratin 4, keratin 15, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 8, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 8, keratin 15, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 8, keratin 15, keratin 18, keratin 19; LY9, keratin 4, keratin 7, keratin 18, keratin 19, and tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 15, keratin 18, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 15, keratin 18, keratin 19; LY9, keratin 4, keratin 7, keratin 15, keratin 18, keratin 19; LY9, keratin 4, keratin 7, keratin 8, keratin 18, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 8, keratin 18, keratin 19; LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 19; and LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18. Any marker set can be used in combination with PSA. In addition, any of the above sets may be modified to replace one or more markers in the marker set with one or more of the following additional markers: prostate-specific membrane antigen (PSM), prostate stem cell antigen (PSCA), TMPRSS2, PDEF, prostate-specific gene-1 (HPG-1), PCA3, PCGEM1, and the gene cluster P704P, P712P, and P775P. Any marker set can be used in combination with patient age.

In another embodiment, the invention contemplates marker sets with at least eight (8) members, wherein one member is filamin A and the additional seven members may include, but are not limited to the following sets: keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 15, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 8, keratin 18, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 19, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, tubulin-beta 3; LY9, keratin 4, keratin 7, keratin 8,

keratin 15, keratin 18, keratin 19; filamin B, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, keratin 4, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, keratin 4, keratin 7, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, keratin 4, keratin 7, keratin 8, keratin 15, keratin 19, tubulin-beta 3; filamin B, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, tubulin-beta 3; filamin B, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19; filamin B, LY9, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 7, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 7, keratin 8, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 7, keratin 8, keratin 15, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 7, keratin 8, keratin 15, keratin 18, tubulin-beta 3; filamin B, LY9, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19; filamin B, LY9, keratin 4, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 8, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 8, keratin 15, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 8, keratin 15, keratin 18, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 8, keratin 15, keratin 18, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 8, keratin 15, keratin 18, keratin 19; filamin B, LY9, keratin 4, keratin 7, keratin 18, keratin 19, and tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 15, keratin 19, and tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 15, keratin 18, keratin 19; filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 18, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 18, keratin 19; filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 19; and filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18. Any marker set can be used in combination with PSA. In addition, any of the above sets may be modified to replace one or more markers in the marker set with one or more of the following additional markers: prostate-specific membrane antigen (PSM), prostate stem cell antigen (PSCA), TMPRSS2, PDEF, prostate-specific gene-1 (HPG-1), PCA3, PCGEM1, and the gene cluster P704P, P712P, and P775P. Any marker set can be used in combination with patient age.

In another embodiment, the invention contemplates marker sets with at least nine (9) members, wherein one member is filamin A and the additional eight members may include, but are not limited to the following sets: LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 15, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 18, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 19, tubulin-beta 3; filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, tubulin-beta 3; and filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin

18, keratin 19. Any marker set can be used in combination with PSA. In addition, any of the above sets may be modified to replace one or more markers in the marker set with one or more of the following additional markers: prostate-specific membrane antigen (PSM), prostate stem cell antigen (PSCA), TMPRSS2, PDEF, prostate-specific gene-1 (HPG-1), PCA3, PCGEM1, and the gene cluster P704P, P712P, and P775P. Any marker set can be used in combination with patient age.

In another embodiment, the invention contemplates marker sets with at least ten (10) members, wherein one member is filamin A and the additional nine members may include, but are not limited to the following sets: filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3. In addition, any of the above sets may be modified to replace one or more markers in the marker set with one or more of the following additional markers: prostate-specific membrane antigen (PSM), prostate stem cell antigen (PSCA), TMPRSS2, PDEF, prostate-specific gene-1 (HPG-1), PCA3, PCGEM1, and the gene cluster P704P, P712P, and P775P. Any marker set can be used in combination with patient age.

Any marker set can be used in combination with PSA.

The invention provides for the use of various combinations and sub-combinations of markers. It is understood that any single marker or combination of the markers provided herein can be used in the invention unless clearly indicated otherwise. Further, any single marker or combination of the markers of the invention can be used in conjunction with patient age. Alternatively, any single marker or combination of the markers of the invention can be used in conjunction with PSA. Alternatively, any single marker or combination of the markers of the invention can be used in conjunction with patient age and PSA.

Throughout the application, one or more of filamin B, LY9 and keratin 19 is understood as any of: filamin B; LY9; keratin 19; filamin B and LY9; filamin B and keratin 19; LY9 and keratin 19; or filamin B, LY9, and keratin 19. Further, any single marker or combination of the markers of the invention can be used in conjunction with PSA. Further, any single marker or combination of the markers of the invention can be used in conjunction with patient age. Preferably, each marker set includes, in addition if not already indicated, filamin A.

Throughout the application, combination of the filamin B and LY9 with PSA is understood as any of filamin B; LY9; filamin B and PSA; filamin B and LY9; LY9 and PSA; filamin B, LY9, and PSA. Preferably, each marker set includes, in addition if not already indicated, filamin A. Preferably, each marker set includes, in addition if not already indicated, patient age.

Throughout the application, one or more prostate cancer markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 is understood as any of keratin 4; keratin 7; keratin 8; keratin 15; keratin 18; tubulin beta-3; keratin 4 and keratin 7; keratin 4 and keratin 8; keratin 4 and keratin 15; keratin 4 and keratin 18; keratin 4 and tubulin beta-3; keratin 7 and keratin 8; keratin 7 and keratin 15; keratin 7 and keratin 18; keratin and tubulin beta-3; keratin 8 and keratin 15; keratin 8 and keratin 18; keratin 8 and tubulin beta-3; keratin 15 and keratin

18; keratin 15 and tubulin beta-3; keratin 18 and tubulin beta-3; keratin 4, keratin 7 and keratin 8; keratin 4, keratin 7 and keratin 15; keratin 4, keratin 7 and keratin 18; keratin 4, keratin 7 and tubulin beta-3; keratin 4, keratin 8 and keratin 15; keratin 4, keratin 8 and keratin 18; keratin 4, keratin 8 and tubulin beta-e; keratin 4, keratin 15 and keratin 18; keratin 4, keratin 15 and tubulin beta-e; keratin 4, keratin 18 and tubulin beta-3; kerton 4, keratin 7, keratin 8 and keratin 15; keratin 4, keratin 7, keratin 8 and keratin 18; keratin 4, keratin 7, keratin 8 and tubulin beta-3; keratin 4, keratin 8, keratin 15 and keratin 18; keratin 4, keratin 8, keratin 15 and tubulin beta-3; keratin 4, keratin 15, keratin 18 and tubulin beta-3; keratin 4, keratin 7, keratin 8, keratin 15 and keratin 18; keratin 4, keratin 7, keratin 8, keratin 15, and tubulin beta-3; keratin 4, keratin 7, keratin 8, keratin 18, and tubulin beta-3; keratin 4, keratin 7, keratin 15, keratin 18, and tubulin beta-3; keratin 4, keratin 8, keratin 15, keratin 18, and tubulin beta-3; or keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3. Further, any single marker or combination of the markers of the invention can be used in conjunction with PSA. Preferably, each marker set includes, in addition if not already indicated, filamin A. Preferably, each marker set includes, in addition if not already indicated, patient age.

Throughout the application, one or more prostate cancer markers selected from the group consisting of keratin 7, 15, and 19 is understood as any of keratin 7; keratin 15; keratin 19; keratin 7 and 15; keratin 7 and 19; keratin 15 and 19; and keratin 7, 15, and 19. Further, any single marker or combination of the markers of the invention can be used in conjunction with PSA. Preferably, each marker set includes, in addition if not already indicated, filamin A. Preferably, each marker set includes, in addition if not already indicated, patient age.

Throughout the application, one or more prostate cancer markers selected from the group consisting of keratin 7, 8, and 15 is understood as any of keratin 7; keratin 8; keratin 15; keratin 7 and 8; keratin 7 and 15; keratin 8 and 15; and keratin 7, 8, and 15. Further, any single marker or combination of the markers of the invention can be used in conjunction with PSA. Preferably, each marker set includes, in addition if not already indicated, filamin A. Preferably, each marker set includes, in addition if not already indicated, patient age.

Throughout the application, one or more prostate cancer markers selected from the group consisting of keratin 7 and 15 is understood as any of keratin 7; keratin 15; or keratin 7 and 15. Further, any single marker or combination of the markers of the invention can be used in conjunction with PSA. Preferably, each marker set includes, in addition if not already indicated, filamin A. Preferably, each marker set includes, in addition if not already indicated, patient age.

Throughout the application, one or more prostate cancer markers selected from the group consisting filamin B, LY9, or keratin 19 is understood as any of filamin B; LY9; keratin 19; filamin B and LY9; filamin B and keratin 19; LY9, and keratin 19; and filamin B, LY9, and keratin 19. Further, any single marker or combination of the markers of the invention can be used in conjunction with PSA. Preferably, each marker set includes, in addition if not already indicated, filamin A. Preferably, each marker set includes, in addition if not already indicated, patient age.

In another aspect, the present invention provides for the identification of a “diagnostic signature” or “disease profile” based on the levels of the biomarkers of the invention in a biological sample, including in a diseased tissue (e.g., prostate tumor) or directly from the serum or blood, that correlates with the presence and/or risk and/or prognosis of prostate cancer. The “levels of the biomarkers” can refer to the expression level of the biomarker genes, e.g., by measuring the expression levels of the biomarker mRNAs. The “levels of the biomarkers” can also refer to level of biomarker polypeptides in a biological sample, e.g., prostate tissue or serum. The collection or totality of expression levels of biomarker polypeptides and/or nucleic acid molecules provide a diagnostic signature that correlates with the presence and/or diagnosis and/or progression of prostate cancer. The biomarkers for obtaining a diagnostic signature or disease profile of the invention are meant to encompass any measurable characteristic that reflects in a quantitative or qualitative manner the physiological state of an organism, e.g, whether the organism has prostate cancer. The physiological state of an organism is inclusive of any disease or non-disease state, e.g., a subject having prostate cancer or a subject who is otherwise healthy. Said another way, the biomarkers used for identifying a diagnostic signature or disease profile of the invention include characteristics that can be objectively measured and evaluated as indicators of normal processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention, including, in particular, prostate cancer. Biomarkers can be clinical parameters (e.g., age, performance status), laboratory measures (e.g., molecular biomarkers, such as prostate specific antigen), imaging-based measures, or genetic or other molecular determinants. Examples of biomarkers include, for example, polypeptides, peptides, polypeptide fragments, proteins, antibodies, hormones, polynucleotides, RNA or RNA fragments, microRNA (miRNAs), lipids, polysaccharides, and other bodily metabolites that are diagnostic and/or indicative and/or predictive of an oncological disease, e.g., prostate cancer. Examples of biomarkers also include polypeptides, peptides, polypeptide fragments, proteins, antibodies, hormones, polynucleotides, RNA or RNA fragments, microRNA (miRNAs), lipids, polysaccharides, and other bodily metabolites which are diagnostic and/or indicative and/or predictive of any stage or clinical phase of an oncological disease, e.g., Gleason grade 1, grade 2, grade 3, grade 4, or grade 5 prostate cancer.

In a particular embodiment, a prostate cancer disease profile or diagnostic signature is determined on the basis of the combination of filamin A together with one or more additional biomarkers of prostate cancer, which can include, but are not limited to prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, as well as additional markers PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1. Other markers that may be used in combination with filamin A include any measurable characteristic that reflects in a quantitative or qualitative manner the physiological state of an organism, e.g, whether the organism has prostate cancer. Such characteristics may include patient age. The physiological state of an organism is inclusive of any disease or non-disease state, e.g., a subject

having prostate cancer or a subject who is otherwise healthy. Said another way, the biomarkers of the invention that may be used in combination with filamin A include characteristics that can be objectively measured and evaluated as indicators of normal processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention, including, in particular, prostate cancer. Such combination biomarkers can be clinical parameters (e.g., age, performance status), laboratory measures (e.g., molecular biomarkers, such as prostate specific antigen), imaging-based measures, or genetic or other molecular determinants. Example of biomarkers for use in combination with filamin A include, for example, polypeptides, peptides, polypeptide fragments, proteins, antibodies, hormones, polynucleotides, RNA or RNA fragments, microRNA (miRNAs), lipids, polysaccharides, and other bodily metabolites that are diagnostic and/or indicative and/or predictive of prostate cancer, or any particular stage or phase of prostate cancer, e.g., Gleason grade 1, grade 2, grade 3, grade 4, or grade 5 prostate cancer. In certain embodiments, biomarkers for use in combination with filamin A include polypeptides, peptides, polypeptide fragments, proteins, antibodies, hormones, polynucleotides, RNA or RNA fragments, microRNA (miRNAs), lipids, polysaccharides, and other bodily metabolites which are diagnostic and/or indicative and/or predictive of prostate cancer, or any stage or clinical phase thereof, e.g., Gleason grade 1, grade 2, grade 3, grade 4, or grade 5 prostate cancer or TNM classifications. In other embodiments, the present invention also involves the analysis and consideration of any clinical and/or patient-related health data, for example, data obtained from an Electronic Medical Record (e.g., collection of electronic health information about individual patients or populations relating to various types of data, such as, demographics, medical history, medication and allergies, immunization status, laboratory test results, radiology images, vital signs, personal statistics like age and weight, and billing information).

In certain embodiments, the diagnostic signature is obtained by (1) detecting the level of filamin A in a biological sample, (2) detecting the level(s) of one or more additional biomarkers that may include, but are not limited to prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, and (3) comparing the levels of filamin A and the one or more additional biomarkers to the levels of the same biomarkers from a control sample, (4) determining if the filamin A and the one or more additional biomarkers detected in the biological sample are above a certain threshold level. If filamin A and at least 1 additionally detected biomarker is above the threshold level, then the diagnostic signature is indicative of prostate cancer in the biological sample. In certain embodiments, the diagnostic signature can be determined based on an algorithm or computer program that predicts whether the biological sample is cancerous based on the levels of filamin A and the one or more additional biomarkers.

In certain other embodiments, the diagnostic signature is obtained by (1) detecting the level of filamin A in a biological sample, (2) detecting the level(s) of two or more additional biomarkers that may include, but are not limited to prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin

7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, and (3) comparing the levels of filamin A and the two or more additional biomarkers to the levels of the same biomarkers from a control sample, (4) determining if the filamin A and the two or more additional biomarkers detected in the biological sample are above a certain threshold level. If filamin A and at least 2 additionally detected biomarkers are above the threshold level, then the diagnostic signature is indicative of prostate cancer in the biological sample. In certain embodiments, the diagnostic signature can be determined based on an algorithm or computer program that predicts whether the biological sample is cancerous based on the levels of filamin A and the two or more additional biomarkers. In other embodiments, the diagnostic signature also takes into account the patient's age.

In certain other embodiments, the diagnostic signature is obtained by (1) detecting the level of filamin A in a biological sample, (2) detecting the level(s) of three or more additional biomarkers that may include, but are not limited to prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, and (3) comparing the levels of filamin A and the three or more additional biomarkers to the levels of the same biomarkers from a control sample, (4) determining if the filamin A and the three or more additional biomarkers detected in the biological sample are above a certain threshold level. If filamin A and at least 3 additionally detected biomarkers are above the threshold level, then the diagnostic signature is indicative of prostate cancer in the biological sample. In certain embodiments, the diagnostic signature can be determined based on an algorithm or computer program that predicts whether the biological sample is cancerous based on the levels of filamin A and the three or more additional biomarkers. In other embodiments, the diagnostic signature also takes into account the patient's age.

In other embodiments, the diagnostic signature is obtained by (1) detecting the level of filamin A in a biological sample, (2) detecting the level(s) of four or more additional biomarkers that may include, but are not limited to prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, and (3) comparing the levels of filamin A and the four or more additional biomarkers to the levels of the same biomarkers from a control sample, (4) determining if the filamin A and the four or more additional biomarkers detected in the biological sample are above a certain threshold level. If filamin A and at least 4 additionally detected biomarkers are above the threshold level, then the diagnostic signature is indicative of prostate cancer in the biological sample. In certain embodiments, the diagnostic signature can be determined based on an algorithm or computer program that predicts whether the biological sample is cancerous based on the levels of filamin A and the four or more additional biomarkers. In other embodiments, the diagnostic signature also takes into account the patient's age.

In other embodiments, the diagnostic signature is obtained by (1) detecting the level of filamin A in a biological sample, (2) detecting the level(s) of five or more additional biomarkers that may include, but are not limited to prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, and (3) comparing the levels of filamin A and the five or more additional biomarkers to the levels of the same biomarkers from a control sample, (4) determining if the filamin A and the five or more additional biomarkers detected in the biological sample are above a certain threshold level. If filamin A and at least 5 additionally detected biomarkers are above the threshold level, then the diagnostic signature is indicative of prostate cancer in the biological sample. In certain embodiments, the diagnostic signature can be determined based on an algorithm or computer program that predicts whether the biological sample is cancerous based on the levels of filamin A and the five or more additional biomarkers. In other embodiments, the diagnostic signature also takes into account the patient's age.

In other embodiments, the diagnostic signature is obtained by (1) detecting the level of filamin A in a biological sample, (2) detecting the level(s) of six or more additional biomarkers that may include, but are not limited to prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, and (3) comparing the levels of filamin A and the six or more additional biomarkers to the levels of the same biomarkers from a control sample, (4) determining if the filamin A and the six or more additional biomarkers detected in the biological sample are above a certain threshold level. If filamin A and at least 6 additionally detected biomarkers are above the threshold level, then the diagnostic signature is indicative of prostate cancer in the biological sample. In certain embodiments, the diagnostic signature can be determined based on an algorithm or computer program that predicts whether the biological sample is cancerous based on the levels of filamin A and the six or more additional biomarkers. In other embodiments, the diagnostic signature also takes into account the patient's age.

In other embodiments, the diagnostic signature is obtained by (1) detecting the level of filamin A in a biological sample, (2) detecting the level(s) of seven or more additional biomarkers that may include, but are not limited to prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, and (3) comparing the levels of filamin A and the seven or more additional biomarkers to the levels of the same biomarkers from a control sample, (4) determining if the filamin A and the seven or more additional biomarkers detected in the biological sample are above a certain threshold level. If filamin A and at least 7 additionally detected biomarkers are above the threshold level, then the diagnostic signature is indicative of prostate cancer in the biological sample. In certain embodiments, the diagnostic signature can be determined based on an algorithm or computer program that predicts whether the biological sample is cancerous based on the levels of filamin A and the

seven or more additional biomarkers. In other embodiments, the diagnostic signature also takes into account the patient's age.

In other embodiments, the diagnostic signature is obtained by (1) detecting the level of filamin A in a biological sample, (2) detecting the level(s) of eight or more additional biomarkers that may include, but are not limited to prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, and (3) comparing the levels of filamin A and the eight or more additional biomarkers to the levels of the same biomarkers from a control sample, (4) determining if the filamin A and the eight or more additional biomarkers detected in the biological sample are above a certain threshold level. If filamin A and at least 8 additionally detected biomarkers are above the threshold level, then the diagnostic signature is indicative of prostate cancer in the biological sample. In certain embodiments, the diagnostic signature can be determined based on an algorithm or computer program that predicts whether the biological sample is cancerous based on the levels of filamin A and the eight or more additional biomarkers. In other embodiments, the diagnostic signature also takes into account the patient's age.

In other embodiments, the diagnostic signature is obtained by (1) detecting the level of filamin A in a biological sample, (2) detecting the level(s) of nine or more additional biomarkers that may include, but are not limited to prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, and (3) comparing the levels of filamin A and the nine or more additional biomarkers to the levels of the same biomarkers from a control sample, (4) determining if the filamin A and the nine or more additional biomarkers detected in the biological sample are above a certain threshold level. If filamin A and at least 9 additionally detected biomarkers are above the threshold level, then the diagnostic signature is indicative of prostate cancer in the biological sample. In certain embodiments, the diagnostic signature can be determined based on an algorithm or computer program that predicts whether the biological sample is cancerous based on the levels of filamin A and the nine or more additional biomarkers. In other embodiments, the diagnostic signature also takes into account the patient's age.

In accordance with various embodiments, algorithms may be employed to predict whether or not a biological sample is likely to be diseased, e.g., have prostate cancer. The skilled artisan will appreciate that an algorithm can be any computation, formula, statistical survey, nomogram, look-up table, decision tree method, or computer program which processes a set of input variables (e.g., number of markers (n) which have been detected at a level exceeding some threshold level, or number of markers (n) which have been detected at a level below some threshold level) through a number of well-defined successive steps to eventually produce a score or "output," e.g., a diagnosis of prostate cancer. Any suitable algorithm—whether computer-based or manual-based (e.g., look-up table)—is contemplated herein.

In certain embodiments, an algorithm of the invention used to predict whether a biological sample has prostate cancer producing a score on the basis of the detected level of filamin A in the sample and the level(s) at least one, or two, or three, or four, or five, or six, or seven, or eight, or nine or more additional prostate cancer markers (e.g., selected from the group consisting of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1), wherein if the score is above a certain threshold score, then the biological sample has prostate cancer. In certain embodiments, the algorithm also produces a score using the patient's age as a continuous predictor variable. For example, increased age is associated with higher risk of prostate cancer.

In certain embodiments, an algorithm of the invention used to predict whether a biological sample has prostate cancer producing a score on the basis of the detected level of filamin A in the sample and the level(s) at least one, or two, or three, or four, or five, or six, or seven, or eight, or nine or more additional prostate cancer markers (e.g., selected from the group consisting of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1), wherein if the score is below a certain threshold score, then the biological sample has prostate cancer. In certain embodiments, the algorithm also produces a score using the patient's age as a continuous predictor variable.

In certain embodiments, an algorithm of the invention used to predict whether a biological sample has prostate cancer producing a score on the basis of the detected level of filamin A in the sample and the level(s) at least one, or two, or three, or four, or five, or six, or seven, or eight, or nine or more additional prostate cancer markers (e.g., selected from the group consisting of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1), wherein if the score is above a certain threshold score, then the biological sample does not have prostate cancer. In certain embodiments, the algorithm also produces a score using the patient's age as a continuous predictor variable.

In certain embodiments, an algorithm of the invention used to predict whether a biological sample has prostate cancer producing a score on the basis of the detected level of filamin A in the sample and the level(s) at least one, or two, or three, or four, or five, or six, or seven, or eight, or nine or more additional prostate cancer markers (e.g., selected from the group consisting of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1), wherein if the score is below a certain threshold score, then the biological sample does not have prostate cancer. In certain embodiments, the algorithm also produces a score using the patient's age as a continuous predictor variable.

Moreover, a prostate cancer disease profile or signature may be obtained by detecting filamin A in combination with at least one other biomarker, or more preferably, with at least two other biomarkers, or still more preferably, with at least three other biomarkers, or even more preferably with at least four other biomarkers. Still further, filamin A in certain embodiments, may be used in combination with at least five other markers, or at least six other biomarkers, or at least seven other biomarkers, or at least eight other biomarkers, or at least nine other biomarkers, or at least ten other biomarkers, or at least eleven other biomarkers, or at least twelve other biomarkers, or at least thirteen other biomarkers, or at least fourteen other biomarkers, or at least fifteen other biomarkers, or at least sixteen other biomarkers, or at least seventeen other biomarkers, or at least eighteen other biomarkers, or at least nineteen other biomarkers, or at least twenty other biomarkers. Further still, filamin A may be used in combination with a multitude of other biomarkers, including, for example, with between about 20-50 other biomarkers, or between 50-100, or between 100-500, or between 500-1000, or between 1000-10,000 or biomarkers or more. In certain embodiments, the patient's age is also used as a continuous predictor variable. For example, increased age is associated with increased risk of prostate cancer diagnosis.

In certain embodiments, the biomarkers of the invention can include variant sequences. More particularly, the binding agents/reagents used for detecting the biomarkers of the invention can bind and/or identify variants of the biomarkers of the invention. As used herein, the term "variant" comprehends nucleotide or amino acid sequences different from the specifically identified sequences, wherein one or more nucleotides or amino acid residues is deleted, substituted, or added. Variants may be naturally occurring allelic variants, or non-naturally occurring variants. Variant sequences (polynucleotide or polypeptide) preferably exhibit at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to a sequence disclosed herein. The percentage identity is determined by aligning the two sequences to be compared as described below, determining the number of identical residues in the aligned portion, dividing that number by the total number of residues in the inventive (queried) sequence, and multiplying the result by 100.

In addition to exhibiting the recited level of sequence identity, variants of the disclosed polypeptide biomarkers are preferably themselves expressed in subjects with prostate cancer at levels that are higher or lower than the levels of expression in normal, healthy individuals.

Variant sequences generally differ from the specifically identified sequence only by conservative substitutions, deletions or modifications. As used herein, a "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. In general, the following groups of amino acids represent conservative changes: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. Variants may also, or alternatively, contain other modifications, including the deletion or addition of amino acids that have

minimal influence on the antigenic properties, secondary structure and hydrophobic nature of the polypeptide. For example, a polypeptide may be conjugated to a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptide and polynucleotide sequences may be aligned, and percentages of identical amino acids or nucleotides in a specified region may be determined against another polypeptide or polynucleotide sequence, using computer algorithms that are publicly available. The percentage identity of a polynucleotide or polypeptide sequence is determined by aligning polynucleotide and polypeptide sequences using appropriate algorithms, such as BLASTN or BLASTP, respectively, set to default parameters; identifying the number of identical nucleic or amino acids over the aligned portions; dividing the number of identical nucleic or amino acids by the total number of nucleic or amino acids of the polynucleotide or polypeptide of the present invention; and then multiplying by 100 to determine the percentage identity.

Two exemplary algorithms for aligning and identifying the identity of polynucleotide sequences are the BLASTN and FASTA algorithms. The alignment and identity of polypeptide sequences may be examined using the BLASTP algorithm. BLASTX and FASTX algorithms compare nucleotide query sequences translated in all reading frames against polypeptide sequences. The FASTA and FASTX algorithms are described in Pearson and Lipman, Proc. Natl. Acad. Sci. USA 85:2444-2448, 1988; and in Pearson, Methods in Enzymol. 183:63-98, 1990. The FASTA software package is available from the University of Virginia, Charlottesville, Va. 22906-9025. The FASTA algorithm, set to the default parameters described in the documentation and distributed with the algorithm, may be used in the determination of polynucleotide variants. The readme files for FASTA and FASTX Version 2.0x that are distributed with the algorithms describe the use of the algorithms and describe the default parameters.

The BLASTN software is available on the NCBI anonymous FTP server and is available from the National Center for Biotechnology Information (NCBI), National Library of Medicine, Building 38A, Room 8N805, Bethesda, Md. 20894. The BLASTN algorithm Version 2.0.6 [Sep. 10, 1998] and Version 2.0.11 [Jan. 20, 2000] set to the default parameters described in the documentation and distributed with the algorithm, is preferred for use in the determination of variants according to the present invention. The use of the BLAST family of algorithms, including BLASTN, is described at NCBI's website and in the publication of Altschul, et al., "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs," Nucleic Acids Res. 25:3389-3402, 1997.

In an alternative embodiment, variant polypeptides are encoded by polynucleotide sequences that hybridize to a disclosed polynucleotide under stringent conditions. Stringent hybridization

conditions for determining complementarity include salt conditions of less than about 1 M, more usually less than about 500 mM, and preferably less than about 200 mM. Hybridization temperatures can be as low as 5°C, but are generally greater than about 22°C, more preferably greater than about 30°C, and most preferably greater than about 37°C. Longer DNA fragments may require higher hybridization temperatures for specific hybridization. Since the stringency of hybridization may be affected by other factors such as probe composition, presence of organic solvents and extent of base mismatching, the combination of parameters is more important than the absolute measure of any one alone. An example of "stringent conditions" is prewashing in a solution of 6XSSC, 0.2% SDS; hybridizing at 65°C, 6XSSC, 0.2% SDS overnight; followed by two washes of 30 minutes each in 1XSSC, 0.1% SDS at 65°C and two washes of 30 minutes each in 0.2XSSC, 0.1% SDS at 65°C.

D. TISSUE SAMPLES

The present invention may be practiced with any suitable biological sample that potentially contains, expresses, includes, a detectable disease biomarker, e.g., a polypeptide biomarker, a nucleic acid biomarkers, a mRNA biomarker, a microRNA biomarker. For example, the biological sample may be obtained from sources that include whole blood and serum to diseased and/or healthy tissue, for example, biopsy of prostate tumor. The methods of the invention may especially be applied to the study of any prostate tissue sample, i.e., a sample of prostate tissue or fluid, as well as cells (or their progeny) isolated from such tissue or fluid. In another embodiment, the present invention may be practiced with any suitable Prostate tissue samples which are freshly isolated or which have been frozen or stored after having been collected from a subject, or archival tissue samples, for example, with known diagnosis, treatment and/or outcome history. Prostate tissue may be collected by any non-invasive means, such as, for example, fine needle aspiration and needle biopsy, or alternatively, by an invasive method, including, for example, surgical biopsy.

The inventive methods may be performed at the single cell level (e.g., isolation and testing of cancerous cells from the prostate tissue sample). However, preferably, the inventive methods are performed using a sample comprising many cells, where the assay is "averaging" expression over the entire collection of cells and tissue present in the sample. Preferably, there is enough of the prostate tissue sample to accurately and reliably determine the expression levels of the set of genes of interest. In certain embodiments, multiple samples may be taken from the same prostate tissue in order to obtain a representative sampling of the tissue. In addition, sufficient biological material can be obtained in order to perform duplicate, triplicate or further rounds of testing.

Any commercial device or system for isolating and/or obtaining prostate tissue and/or blood or other biological products, and/or for processing said materials prior to conducting a detection reaction is contemplated.

In certain embodiments, the present invention relates to detecting biomarker nucleic acid molecules (e.g., mRNA encoding filamin A, antigen (PSA), filamin B, LY9, keratin 4, keratin 7,

keratin 8, keratin 15, kerton 18, keratin 19, and tubulin-beta 3). In such embodiments, RNA can be extracted from a biological sample, e.g., a prostate tissue sample, before analysis. Methods of RNA extraction are well known in the art (see, for example, J. Sambrook et al., "Molecular Cloning: A Laboratory Manual", 1989, 2nd Ed., Cold Spring Harbour Laboratory Press: New York). Most methods of RNA isolation from bodily fluids or tissues are based on the disruption of the tissue in the presence of protein denaturants to quickly and effectively inactivate RNases. Generally, RNA isolation reagents comprise, among other components, guanidinium thiocyanate and/or beta-mercaptoethanol, which are known to act as RNase inhibitors. Isolated total RNA is then further purified from the protein contaminants and concentrated by selective ethanol precipitations, phenol/chloroform extractions followed by isopropanol precipitation (see, for example, P. Chomczynski and N. Sacchi, *Anal. Biochem.*, 1987, 162: 156-159) or cesium chloride, lithium chloride or cesium trifluoroacetate gradient centrifugations.

Numerous different and versatile kits can be used to extract RNA (i.e., total RNA or mRNA) from bodily fluids or tissues (e.g., prostate tissue samples) and are commercially available from, for example, Ambion, Inc. (Austin, Tex.), Amersham Biosciences (Piscataway, N.J.), BD Biosciences Clontech (Palo Alto, Calif.), BioRad Laboratories (Hercules, Calif.), GIBCO BRL (Gaithersburg, Md.), and Qiagen, Inc. (Valencia, Calif.). User Guides that describe in great detail the protocol to be followed are usually included in all these kits. Sensitivity, processing time and cost may be different from one kit to another. One of ordinary skill in the art can easily select the kit(s) most appropriate for a particular situation.

In certain embodiments, after extraction, mRNA is amplified, and transcribed into cDNA, which can then serve as template for multiple rounds of transcription by the appropriate RNA polymerase. Amplification methods are well known in the art (see, for example, A. R. Kimmel and S. L. Berger, *Methods Enzymol.* 1987, 152: 307-316; J. Sambrook et al., "Molecular Cloning: A Laboratory Manual", 1989, 2^{sup.nd} Ed., Cold Spring Harbour Laboratory Press: New York; "Short Protocols in Molecular Biology", F. M. Ausubel (Ed.), 2002, 5^{sup.th} Ed., John Wiley & Sons; U.S. Pat. Nos. 4,683,195; 4,683,202 and 4,800,159). Reverse transcription reactions may be carried out using non-specific primers, such as an anchored oligo-dT primer, or random sequence primers, or using a target-specific primer complementary to the RNA for each genetic probe being monitored, or using thermostable DNA polymerases (such as avian myeloblastosis virus reverse transcriptase or Moloney murine leukemia virus reverse transcriptase).

In certain embodiments, the RNA isolated from the prostate tissue sample (for example, after amplification and/or conversion to cDNA or cRNA) is labeled with a detectable agent before being analyzed. The role of a detectable agent is to facilitate detection of RNA or to allow visualization of hybridized nucleic acid fragments (e.g., nucleic acid fragments hybridized to genetic probes in an array-based assay). Preferably, the detectable agent is selected such that it generates a signal which can be measured and whose intensity is related to the amount of labeled nucleic acids present in the

sample being analyzed. In array-based analysis methods, the detectable agent is also preferably selected such that it generates a localized signal, thereby allowing spatial resolution of the signal from each spot on the array.

Methods for labeling nucleic acid molecules are well-known in the art. For a review of labeling protocols, label detection techniques and recent developments in the field, see, for example, L. J. Kricka, *Ann. Clin. Biochem.* 2002, 39: 114-129; R. P. van Gijlswijk et al., *Expert Rev. Mol. Diagn.* 2001, 1: 81-91; and S. Joos et al., *J. Biotechnol.* 1994, 35: 135-153. Standard nucleic acid labeling methods include: incorporation of radioactive agents, direct attachment of fluorescent dyes (see, for example, L. M. Smith et al., *Nucl. Acids Res.* 1985, 13: 2399-2412) or of enzymes (see, for example, B. A. Connolly and P. Rider, *Nucl. Acids. Res.* 1985, 13: 4485-4502); chemical modifications of nucleic acid fragments making them detectable immunochemically or by other affinity reactions (see, for example, T. R. Broker et al., *Nucl. Acids Res.* 1978, 5: 363-384; E. A. Bayer et al., *Methods of Biochem. Analysis*, 1980, 26: 1-45; R. Langer et al., *Proc. Natl. Acad. Sci. USA*, 1981, 78: 6633-6637; R. W. Richardson et al., *Nucl. Acids Res.* 1983, 11: 6167-6184; D. J. Brigati et al., *Virol.* 1983, 126: 32-50; P. Tchen et al., *Proc. Natl Acad. Sci. USA*, 1984, 81: 3466-3470; J. E. Landegent et al., *Exp. Cell Res.* 1984, 15: 61-72; and A. H. Hopman et al., *Exp. Cell Res.* 1987, 169: 357-368); and enzyme-mediated labeling methods, such as random priming, nick translation, PCR and tailing with terminal transferase (for a review on enzymatic labeling, see, for example, J. Temsamani and S. Agrawal, *Mol. Biotechnol.* 1996, 5: 223-232).

Any of a wide variety of detectable agents can be used in the practice of the present invention. Suitable detectable agents include, but are not limited to: various ligands, radionuclides, fluorescent dyes, chemiluminescent agents, microparticles (such as, for example, quantum dots, nanocrystals, phosphors and the like), enzymes (such as, for example, those used in an ELISA, i.e., horseradish peroxidase, beta-galactosidase, luciferase, alkaline phosphatase), colorimetric labels, magnetic labels, and biotin, dioxigenin or other haptens and proteins for which antisera or monoclonal antibodies are available.

However, in some embodiments, the expression levels are determined by detecting the expression of a gene product (e.g., protein) thereby eliminating the need to obtain a genetic sample (e.g., RNA) from the prostate tissue sample.

In still other embodiments, the present invention relates to preparing a prediction model for prostate and/or the likelihood of relapse of prostate cancer by preparing a model for prostate cancer based on measuring the biomarkers of the invention in known control samples. More particularly, the present invention relates in some embodiments to preparing a predictive model by evaluating the biomarkers of the invention, e.g., filamin A in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1.

The skilled person will appreciate that patient tissue samples containing prostate cells or prostate cancer cells may be used in the methods of the present invention including, but not limited to those aimed at predicting relapse probability. In these embodiments, the level of expression of the signature gene can be assessed by assessing the amount, e.g. absolute amount or concentration, of a signature gene product, e.g., protein and RNA transcript encoded by the signature gene and fragments of the protein and RNA transcript) in a sample, e.g., stool and/or blood obtained from a patient. The sample can, of course, be subjected to a variety of well-known post-collection preparative and storage techniques (e.g. fixation, storage, freezing, lysis, homogenization, DNA or RNA extraction, ultrafiltration, concentration, evaporation, centrifugation, etc.) prior to assessing the amount of the signature gene product in the sample.

The invention further relates to the preparation of a model for prostate cancer or prostate cancer relapse by evaluating the biomarkers of the invention in known samples of prostate cancer. More particularly, the present invention relates to a prostate cancer model for diagnosing and/or monitoring and/or prognosing prostate cancer or prostate cancer relapse using the biomarkers of the invention, which can include filamin A and at least one other prostate cancer related marker selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSA, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1.

In the methods of the invention aimed at preparing a model for prostate cancer and/or prostate cancer relapse prediction, it is understood that the particular clinical outcome associated with each sample contributing to the model preferably should be known. Consequently, the model can be established using archived tissue samples. In the methods of the invention aimed at preparing a model for prostate cancer and/or prostate cancer relapse prediction, total RNA can be generally extracted from the source material of interest, generally an archived tissue such as a formalin-fixed, paraffin-embedded tissue, and subsequently purified. Methods for obtaining robust and reproducible gene expression patterns from archived tissues, including formalin-fixed, paraffin-embedded (FFPE) tissues are taught in U.S. Publ. No. 2004/0259105, which is incorporated herein by reference in its entirety. Commercial kits and protocols for RNA extraction from FFPE tissues are available including, for example, ROCHE High Pure RNA Paraffin Kit (Roche) MasterPure™ Complete DNA and RNA Purification Kit (EPICENTRE®Madison, Wis.); Paraffin Block RNA Isolation Kit (Ambion, Inc.) and RNeasy™ Mini kit (Qiagen, Chatsworth, Calif.).

The use of FFPE tissues as a source of RNA for RT-PCR has been described previously (Stanta et al., *Biotechniques* 11:304-308 (1991); Stanta et al., *Methods Mol. Biol.* 86:23-26 (1998); Jackson et al., *Lancet* 1:1391 (1989); Jackson et al., *J. Clin. Pathol.* 43:499-504 (1999); Finke et al., *Biotechniques* 14:448-453 (1993); Goldsworthy et al., *Mol. Carcinog.* 25:86-91 (1999); Stanta and Bonin, *Biotechniques* 24:271-276 (1998); Godfrey et al., *J. Mol. Diagnostics* 2:84 (2000); Specht et al., *J. Mol. Med.* 78:B27 (2000); Specht et al., *Am. J. Pathol.* 158:419-429 (2001)). For quick analysis of the RNA quality, RT-PCR can be performed utilizing a pair of primers targeting a short fragment

in a highly expressed gene, for example, actin, ubiquitin, gapdh or other well-described commonly used housekeeping gene. If the cDNA synthesized from the RNA sample can be amplified using this pair of primers, then the sample is suitable for the a quantitative measurements of RNA target sequences by any method preferred, for example, the DASL assay, which requires only a short cDNA fragment for the annealing of query oligonucleotides.

There are numerous tissue banks and collections including exhaustive samples from all stages of a wide variety of disease states, most notably cancer and in particular, prostate cancer. The ability to perform genotyping and/or gene expression analysis, including both qualitative and quantitative analysis on these samples enables the application of this methodology to the methods of the invention. In particular, the ability to establish a correlation of gene expression and a known predictor of disease extent and/or outcome by probing the genetic state of tissue samples for which clinical outcome is already known, allows for the establishment of a correlation between a particular molecular signature and the known predictor, such as a Gleason score, to derive a score that allows for a more sensitive prognosis than that based on the known predictor alone. The skilled person will appreciate that by building databases of molecular signatures from tissue samples of known outcomes, many such correlations can be established, thus allowing both diagnosis and prognosis of any condition. Thus, such approaches may be used to correlate the expression levels of the biomarkers of the invention, e.g., filamin A and at least one other prostate cancer related marker selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3 and PSA, to a particular stage of prostate cancer.

Tissue samples useful for preparing a model for prostate cancer prediction include, for example, paraffin and polymer embedded samples, ethanol embedded samples and/or formalin and formaldehyde embedded tissues, although any suitable sample may be used. In general, nucleic acids isolated from archived samples can be highly degraded and the quality of nucleic preparation can depend on several factors, including the sample shelf life, fixation technique and isolation method. However, using the methodologies taught in U.S. Publ. No. 2004/0259105, which have the significant advantage that short or degraded targets can be used for analysis as long as the sequence is long enough to hybridize with the oligonucleotide probes, highly reproducible results can be obtained that closely mimic results found in fresh samples.

Archived tissue samples, which can be used for all methods of the invention, typically have been obtained from a source and preserved. Preferred methods of preservation include, but are not limited to paraffin embedding, ethanol fixation and formalin, including formaldehyde and other derivatives, fixation as are known in the art. A tissue sample may be temporally "old", e.g. months or years old, or recently fixed. For example, post-surgical procedures generally include a fixation step on excised tissue for histological analysis. In a preferred embodiment, the tissue sample is a diseased tissue sample, particularly a prostate cancer tissue, including primary and secondary tumor tissues as well as lymph node tissue and metastatic tissue.

Thus, an archived sample can be heterogeneous and encompass more than one cell or tissue type, for example, tumor and non-tumor tissue. Preferred tissue samples include solid tumor samples including, but not limited to, tumors of the prostate. It is understood that in applications of the present invention to conditions other than prostate cancer, the tumor source can be brain, bone, heart, breast, ovaries, prostate, uterus, spleen, pancreas, liver, kidneys, bladder, stomach and muscle. Similarly, depending on the condition, suitable tissue samples include, but are not limited to, bodily fluids (including, but not limited to, blood, urine, serum, lymph, saliva, anal and vaginal secretions, perspiration and semen, of virtually any organism, with mammalian samples being preferred and human samples being particularly preferred). In embodiments directed to methods of establishing a model for prostate cancer relapse prediction, the tissue sample is one for which patient history and outcome is known. Generally, the invention methods can be practiced with the signature gene sequence contained in an archived sample or can be practiced with signature gene sequences that have been physically separated from the sample prior to performing a method of the invention.

E. DETECTION AND/OR MEASUREMENT OF BIOMARKERS

The present invention contemplates any suitable means, techniques, and/or procedures for detecting and/or measuring the biomarkers of the invention. The skilled artisan will appreciate that the methodologies employed to measure the biomarkers of the invention will depend at least on the type of biomarker being detected or measured (e.g., mRNA biomarker or polypeptide biomarker) and the source of the biological sample (e.g., whole blood versus prostate biopsy tissue). Certain biological sample may also require certain specialized treatments prior to measuring the biomarkers of the invention, e.g., the preparation of mRNA from a biopsy tissue in the case where mRNA biomarkers are being measured.

1. DETECTION OF NUCLEIC ACID BIOMARKERS

In certain embodiments, the invention involves the detection of nucleic acid biomarkers, e.g., mRNA biomarkers of filamin A alone or filamin A in combination with at least one other prostate cancer related marker selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSA, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1.

In various embodiments, the diagnostic/prognostic methods of the present invention generally involve the determination of expression levels of a set of genes in a prostate tissue sample. Determination of gene expression levels in the practice of the inventive methods may be performed by any suitable method. For example, determination of gene expression levels may be performed by detecting the expression of mRNA expressed from the genes of interest and/or by detecting the expression of a polypeptide encoded by the genes.

For detecting nucleic acids encoding biomarkers of the invention, any suitable method can be used, including, but not limited to, Southern blot analysis, Northern blot analysis, polymerase chain reaction (PCR) (see, for example, U.S. Pat. Nos. 4,683,195; 4,683,202, and 6,040,166; "PCR Protocols: A Guide to Methods and Applications", Innis et al. (Eds), 1990, Academic Press: New York), reverse transcriptase PCR (RT-PCT), anchored PCR, competitive PCR (see, for example, U.S. Pat. No. 5,747,251), rapid amplification of cDNA ends (RACE) (see, for example, "Gene Cloning and Analysis: Current Innovations, 1997, pp. 99-115); ligase chain reaction (LCR) (see, for example, EP 01 320 308), one-sided PCR (Ohara et al., Proc. Natl. Acad. Sci., 1989, 86: 5673-5677), in situ hybridization, Taqman-based assays (Holland et al., Proc. Natl. Acad. Sci., 1991, 88: 7276-7280), differential display (see, for example, Liang et al., Nucl. Acid. Res., 1993, 21: 3269-3275) and other RNA fingerprinting techniques, nucleic acid sequence based amplification (NASBA) and other transcription based amplification systems (see, for example, U.S. Pat. Nos. 5,409,818 and 5,554,527), Qbeta Replicase, Strand Displacement Amplification (SDA), Repair Chain Reaction (RCR), nuclease protection assays, subtraction-based methods, Rapid-Scan®, etc.

In other embodiments, gene expression levels of biomarkers of interest may be determined by amplifying complementary DNA (cDNA) or complementary RNA (cRNA) produced from mRNA and analyzing it using a microarray. A number of different array configurations and methods of their production are known to those skilled in the art (see, for example, U.S. Pat. Nos. 5,445,934; 5,532,128; 5,556,752; 5,242,974; 5,384,261; 5,405,783; 5,412,087; 5,424,186; 5,429,807; 5,436,327; 5,472,672; 5,527,681; 5,529,756; 5,545,531; 5,554,501; 5,561,071; 5,571,639; 5,593,839; 5,599,695; 5,624,711; 5,658,734; and 5,700,637). Microarray technology allows for the measurement of the steady-state mRNA level of a large number of genes simultaneously. Microarrays currently in wide use include cDNA arrays and oligonucleotide arrays. Analyses using microarrays are generally based on measurements of the intensity of the signal received from a labeled probe used to detect a cDNA sequence from the sample that hybridizes to a nucleic acid probe immobilized at a known location on the microarray (see, for example, U.S. Pat. Nos. 6,004,755; 6,218,114; 6,218,122; and 6,271,002). Array-based gene expression methods are known in the art and have been described in numerous scientific publications as well as in patents (see, for example, M. Schena et al., Science, 1995, 270: 467-470; M. Schena et al., Proc. Natl. Acad. Sci. USA 1996, 93: 10614-10619; J. J. Chen et al., Genomics, 1998, 51: 313-324; U.S. Pat. Nos. 5,143,854; 5,445,934; 5,807,522; 5,837,832; 6,040,138; 6,045,996; 6,284,460; and 6,607,885).

In one particular embodiment, the invention comprises a method for identification of prostate cancer cells in a biological sample by amplifying and detecting nucleic acids corresponding to the novel prostate cancer biomarkers, and or panels of biomarkers that include filamin A alone or filamin A in combination with one or more markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSA, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1. The biological sample may be any tissue or fluid in

which prostate cancer cells might be present. Various embodiments include radical prostatectomy specimens, pathological specimens, bone marrow aspirate, bone marrow biopsy, lymph node aspirate, lymph node biopsy, spleen tissue, fine needle aspirate, skin biopsy or organ tissue biopsy. Other embodiments include samples where the body fluid is peripheral blood, serum, plasma, lymph fluid, ascites, serous fluid, pleural effusion, sputum, cerebrospinal fluid, lacrimal fluid, stool, prostatic fluid or urine.

Nucleic acid used as a template for amplification can be isolated from cells contained in the biological sample, according to standard methodologies. (Sambrook et al., 1989) The nucleic acid may be genomic DNA or fractionated or whole cell RNA. Where RNA is used, it may be desired to convert the RNA to a complementary cDNA. In one embodiment, the RNA is whole cell RNA and is used directly as the template for amplification.

Pairs of primers that selectively hybridize to nucleic acids corresponding to any of the prostate cancer biomarker nucleotide sequences identified herein are contacted with the isolated nucleic acid under conditions that permit selective hybridization. Once hybridized, the nucleic acid:primer complex is contacted with one or more enzymes that facilitate template-dependent nucleic acid synthesis. Multiple rounds of amplification, also referred to as "cycles," are conducted until a sufficient amount of amplification product is produced. Next, the amplification product is detected. In certain applications, the detection may be performed by visual means. Alternatively, the detection may involve indirect identification of the product via chemiluminescence, radioactive scintigraphy of incorporated radiolabel or fluorescent label or even via a system using electrical or thermal impulse signals (Affymax technology; Bellus, 1994). Following detection, one may compare the results seen in a given patient with a statistically significant reference group of normal patients and prostate, cancer patients. In this way, it is possible to correlate the amount of nucleic acid detected with various clinical states.

The term primer, as defined herein, is meant to encompass any nucleic acid that is capable of priming the synthesis of a nascent nucleic acid in a template-dependent process. Typically, primers are oligonucleotides from ten to twenty base pairs in length, but longer sequences may be employed. Primers may be provided in double-stranded or single-stranded form, although the single-stranded form is preferred.

A number of template dependent processes are available to amplify the nucleic acid sequences present in a given template sample. One of the best known amplification methods is the polymerase chain reaction (referred to as PCR) which is described in detail in U.S. Pat. Nos. 4,683,195, 4,683,202 and 4,800,159, and in Innis et al., 1990, each of which is incorporated herein by reference in its entirety.

In PCR, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target nucleic acid sequence. An excess of deoxynucleoside triphosphates are added to a reaction mixture along with a DNA polymerase, e.g., Taq polymerase. If

the target nucleic acid sequence is present in a sample, the primers will bind to the target nucleic acid and the polymerase will cause the primers to be extended along the target nucleic acid sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target nucleic acid to form reaction products, excess primers will bind to the target nucleic acid and to the reaction products and the process is repeated.

A reverse transcriptase PCR amplification procedure may be performed in order to quantify the amount of mRNA amplified. Methods of reverse transcribing RNA into cDNA are well known and described in Sambrook et al., 1989. Alternative methods for reverse transcription utilize thermostable DNA polymerases. These methods are described in WO 90/07641 filed Dec. 21, 1990. Polymerase chain reaction methodologies are well known in the art.

Another method for amplification is the ligase chain reaction ("LCR"), disclosed in European Application No. 320 308, incorporated herein by reference in its entirety. In LCR, two complementary probe pairs are prepared, and in the presence of the target sequence, each pair will bind to opposite complementary strands of the target such that they abut. In the presence of a ligase, the two probe pairs will link to form a single unit. By temperature cycling, as in PCR, bound ligated units dissociate from the target and then serve as "target sequences" for ligation of excess probe pairs. U.S. Pat. No. 4,883,750 describes a method similar to LCR for binding probe pairs to a target sequence.

Qbeta Replicase, described in PCT Application No. PCT/US87/00880, also may be used as still another amplification method in the present invention. In this method, a replicative sequence of RNA which has a region complementary to that of a target is added to a sample in the presence of an RNA polymerase. The polymerase will copy the replicative sequence which may then be detected.

An isothermal amplification method, in which restriction endonucleases and ligases are used to achieve the amplification of target molecules that contain nucleotide 5'-[α -thio]-triphosphates in one strand of a restriction site also may be useful in the amplification of nucleic acids in the present invention. Walker et al. (1992), incorporated herein by reference in its entirety.

Strand Displacement Amplification (SDA) is another method of carrying out isothermal amplification of nucleic acids which involves multiple rounds of strand displacement and synthesis, i.e., nick translation. A similar method, called Repair Chain Reaction (RCR), involves annealing several probes throughout a region targeted for amplification, followed by a repair reaction in which only two of the four bases are present. The other two bases may be added as biotinylated derivatives for easy detection. A similar approach is used in SDA. Target specific sequences also may be detected using a cyclic probe reaction (CPR). In CPR, a probe having 3' and 5' sequences of non-specific DNA and a middle sequence of specific RNA is hybridized to DNA which is present in a sample. Upon hybridization, the reaction is treated with RNase H, and the products of the probe identified as distinctive products which are released after digestion. The original template is annealed to another cycling probe and the reaction is repeated.

Still other amplification methods described in GB Application No. 2 202 328, and in PCT Application No. PCT/US89/01025, each of which is incorporated herein by reference in its entirety, may be used in accordance with the present invention. In the former application, "modified" primers are used in a PCR like, template and enzyme dependent synthesis. The primers may be modified by labeling with a capture moiety (e.g., biotin) and/or a detector moiety (e.g., enzyme). In the latter application, an excess of labeled probes are added to a sample. In the presence of the target sequence, the probe binds and is cleaved catalytically. After cleavage, the target sequence is released intact to be bound by excess probe. Cleavage of the labeled probe signals the presence of the target sequence.

Other contemplated nucleic acid amplification procedures include transcription-based amplification systems (TAS), including nucleic acid sequence based amplification (NASBA) and 3SR. Kwoh et al. (1989); Gingeras et al., PCT Application WO 88/10315, incorporated herein by reference in their entirety. In NASBA, the nucleic acids may be prepared for amplification by standard phenol/chloroform extraction, heat denaturation of a clinical sample, treatment with lysis buffer and minispin columns for isolation of DNA and RNA or guanidinium chloride extraction of RNA. These amplification techniques involve annealing a primer which has target specific sequences. Following polymerization, DNA/RNA hybrids are digested with RNase H while double stranded DNA molecules are heat denatured again. In either case the single stranded DNA is made fully double stranded by addition of second target specific primer, followed by polymerization. The double-stranded DNA molecules are then multiply transcribed by a polymerase such as T7 or SP6. In an isothermal cyclic reaction, the RNA's are reverse transcribed into double stranded DNA, and transcribed once against with a polymerase such as T7 or SP6. The resulting products, whether truncated or complete, indicate target specific sequences.

Davey et al., European Application No. 329 822 (incorporated herein by reference in its entirety) disclose a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA), which may be used in accordance with the present invention. The ssRNA is a first template for a first primer oligonucleotide, which is elongated by reverse transcriptase (RNA-dependent DNA polymerase). The RNA is then removed from the resulting DNA:RNA duplex by the action of ribonuclease H (RNase H, an RNase specific for RNA in duplex with either DNA or RNA). The resultant ssDNA is a second template for a second primer, which also includes the sequences of an RNA polymerase promoter (exemplified by T7 RNA polymerase) 5' to its homology to the template. This primer is then extended by DNA polymerase (exemplified by the large "Klenow" fragment of E. coli DNA polymerase 1), resulting in a double-stranded DNA ("dsDNA") molecule, having a sequence identical to that of the original RNA between the primers and having additionally, at one end, a promoter sequence. This promoter sequence may be used by the appropriate RNA polymerase to make many RNA copies of the DNA. These copies may then re-enter the cycle leading to very swift amplification. With proper choice of enzymes, this amplification may be done isothermally without addition of enzymes at each

cycle. Because of the cyclical nature of this process, the starting sequence may be chosen to be in the form of either DNA or RNA.

Miller et al., PCT Application WO 89/06700 (incorporated herein by reference in its entirety) disclose a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. This scheme is not cyclic, i.e., new templates are not produced from the resultant RNA transcripts. Other amplification methods include "race" and "one-sided PCR.TM.." Frohman (1990) and Ohara et al. (1989), each herein incorporated by reference in their entirety.

Methods based on ligation of two (or more) oligonucleotides in the presence of nucleic acid having the sequence of the resulting "di-oligonucleotide", thereby amplifying the di-oligonucleotide, also may be used in the amplification step of the present invention. Wu et al. (1989), incorporated herein by reference in its entirety.

Oligonucleotide probes or primers of the present invention may be of any suitable length, depending on the particular assay format and the particular needs and targeted sequences employed. In a preferred embodiment, the oligonucleotide probes or primers are at least 10 nucleotides in length (preferably, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 . . .) and they may be adapted to be especially suited for a chosen nucleic acid amplification system and/or hybridization system used. Longer probes and primers are also within the scope of the present invention as well known in the art. Primers having more than 30, more than 40, more than 50 nucleotides and probes having more than 100, more than 200, more than 300, more than 500 more than 800 and more than 1000 nucleotides in length are also covered by the present invention. Of course, longer primers have the disadvantage of being more expensive and thus, primers having between 12 and 30 nucleotides in length are usually designed and used in the art. As well known in the art, probes ranging from 10 to more than 2000 nucleotides in length can be used in the methods of the present invention. As for the % of identity described above, non-specifically described sizes of probes and primers (e.g., 16, 17, 31, 24, 39, 350, 450, 550, 900, 1240 nucleotides, . . .) are also within the scope of the present invention. In one embodiment, the oligonucleotide probes or primers of the present invention specifically hybridize with a filamin A RNA (or its complementary sequence) or a filamin A mRNA. More preferably, the filamin A primers and probes will be chosen to detect a filamin A RNA which is associated with prostate cancer.

In other embodiments, the detection means can utilize a hybridization technique, e.g., where a specific primer or probe is selected to anneal to a target biomarker of interest, e.g., filamin A, and thereafter detection of selective hybridization is made. As commonly known in the art, the oligonucleotide probes and primers can be designed by taking into consideration the melting point of hybridization thereof with its targeted sequence (see below and in Sambrook et al., 1989, Molecular

Cloning--A Laboratory Manual, 2nd Edition, CSH Laboratories; Ausubel et al., 1994, in Current Protocols in Molecular Biology, John Wiley & Sons Inc., N.Y.).

To enable hybridization to occur under the assay conditions of the present invention, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least 70% (at least 71%, 72%, 73%, 74%), preferably at least 75% (75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%) and more preferably at least 90% (90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 100%) identity to a portion of a filamin A or polynucleotide of another biomarker of the invention. Probes and primers of the present invention are those that hybridize under stringent hybridization conditions and those that hybridize to biomarker homologs of the invention under at least moderately stringent conditions. In certain embodiments probes and primers of the present invention have complete sequence identity to the biomarkers of the invention (filamin A, gene sequences (e.g., cDNA or mRNA). It should be understood that other probes and primers could be easily designed and used in the present invention based on the biomarkers of the invention disclosed herein by using methods of computer alignment and sequence analysis known in the art (cf. Molecular Cloning: A Laboratory Manual, Third Edition, edited by Cold Spring Harbor Laboratory, 2000).

2. DETECTION OF POLYPEPTIDE BIOMARKERS

The present invention contemplates any suitable method for detecting polypeptide biomarkers of the invention. In certain embodiments, the detection method is an immunodetection method involving an antibody that specifically binds to one or more of the biomarkers of the invention, e.g., filamin A alone or filamin A in combination with at least one other prostate cancer related marker selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSA, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1. The steps of various useful immunodetection methods have been described in the scientific literature, such as, e.g., Nakamura et al. (1987), which is incorporated herein by reference.

In general, the immunobinding methods include obtaining a sample suspected of containing a biomarker protein, peptide or antibody, and contacting the sample with an antibody or protein or peptide in accordance with the present invention, as the case may be, under conditions effective to allow the formation of immunocomplexes.

The immunobinding methods include methods for detecting or quantifying the amount of a reactive component in a sample, which methods require the detection or quantitation of any immune complexes formed during the binding process. Here, one would obtain a sample suspected of containing a prostate specific protein, peptide or a corresponding antibody, and contact the sample with an antibody or encoded protein or peptide, as the case may be, and then detect or quantify the amount of immune complexes formed under the specific conditions.

In terms of biomarker detection, the biological sample analyzed may be any sample that is suspected of containing a prostate cancer-specific biomarker, such as, filamin A and at least one other prostate cancer related marker selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3 and PSA. The biological sample may be, for example, a prostate or lymph node tissue section or specimen, a homogenized tissue extract, an isolated cell, a cell membrane preparation, separated or purified forms of any of the above protein-containing compositions, or even any biological fluid that comes into contact with prostate tissues, including blood or lymphatic fluid.

Contacting the chosen biological sample with the protein (e.g., filamin A or antigen thereof to bind with a anti-filamin A antibody in the blood), peptide (e.g., filamin A fragment that binds with a anti-filamin A antibody in the blood), or antibody (e.g., as a detection reagent that binds filamin A in a biological sample) under conditions effective and for a period of time sufficient to allow the formation of immune complexes (primary immune complexes). Generally, complex formation is a matter of simply adding the composition to the biological sample and incubating the mixture for a period of time long enough for the antibodies to form immune complexes with, i.e., to bind to, any antigens present. After this time, the sample-antibody composition, such as a tissue section, ELISA plate, dot blot or Western blot, will generally be washed to remove any non-specifically bound antibody species, allowing only those antibodies specifically bound within the primary immune complexes to be detected.

In general, the detection of immunocomplex formation is well known in the art and may be achieved through the application of numerous approaches. These methods are generally based upon the detection of a label or marker, such as any radioactive, fluorescent, biological or enzymatic tags or labels of standard use in the art. U.S. patents concerning the use of such labels include U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149 and 4,366,241, each incorporated herein by reference. Of course, one may find additional advantages through the use of a secondary binding ligand such as a second antibody or a biotin/avidin ligand binding arrangement, as is known in the art.

The encoded protein (e.g., filamin A), peptide (e.g., filamin A peptide) or corresponding antibody (anti-filamin A antibody as detection reagent) employed in the detection may itself be linked to a detectable label, wherein one would then simply detect this label, thereby allowing the amount of the primary immune complexes in the composition to be determined.

Alternatively, the first added component that becomes bound within the primary immune complexes may be detected by means of a second binding ligand that has binding affinity for the encoded protein, peptide or corresponding antibody. In these cases, the second binding ligand may be linked to a detectable label. The second binding ligand is itself often an antibody, which may thus be termed a "secondary" antibody. The primary immune complexes are contacted with the labeled, secondary binding ligand, or antibody, under conditions effective and for a period of time sufficient to

allow the formation of secondary immune complexes. The secondary immune complexes are then generally washed to remove any non-specifically bound labeled secondary antibodies or ligands, and the remaining label in the secondary immune complexes is then detected.

Further methods include the detection of primary immune complexes by a two step approach. A second binding ligand, such as an antibody, that has binding affinity for the encoded protein, peptide or corresponding antibody is used to form secondary immune complexes, as described above. After washing, the secondary immune complexes are contacted with a third binding ligand or antibody that has binding affinity for the second antibody, again under conditions effective and for a period of time sufficient to allow the formation of immune complexes (tertiary immune complexes). The third ligand or antibody is linked to a detectable label, allowing detection of the tertiary immune complexes thus formed. This system may provide for signal amplification if this is desired.

The immunodetection methods of the present invention have evident utility in the diagnosis of conditions such as prostate cancer. Here, a biological or clinical sample suspected of containing either the encoded protein or peptide or corresponding antibody is used. However, these embodiments also have applications to non-clinical samples, such as in the titrating of antigen or antibody samples, in the selection of hybridomas, and the like.

The present invention, in particular, contemplates the use of ELISAs as a type of immunodetection assay. It is contemplated that the biomarker proteins or peptides of the invention will find utility as immunogens in ELISA assays in diagnosis and prognostic monitoring of prostate cancer. Immunoassays, in their most simple and direct sense, are binding assays. Certain preferred immunoassays are the various types of enzyme linked immunosorbent assays (ELISAs) and radioimmunoassays (RIA) known in the art. Immunohistochemical detection using tissue sections is also particularly useful. However, it will be readily appreciated that detection is not limited to such techniques, and Western blotting, dot blotting, FACS analyses, and the like also may be used.

In one exemplary ELISA, antibodies binding to the biomarkers of the invention are immobilized onto a selected surface exhibiting protein affinity, such as a well in a polystyrene microtiter plate. Then, a test composition suspected of containing the prostate cancer marker antigen, such as a clinical sample, is added to the wells. After binding and washing to remove non-specifically bound immune complexes, the bound antigen may be detected. Detection is generally achieved by the addition of a second antibody specific for the target protein, that is linked to a detectable label. This type of ELISA is a simple "sandwich ELISA." Detection also may be achieved by the addition of a second antibody, followed by the addition of a third antibody that has binding affinity for the second antibody, with the third antibody being linked to a detectable label.

In another exemplary ELISA, the samples suspected of containing the prostate cancer marker antigen are immobilized onto the well surface and then contacted with the anti-biomarker antibodies of the invention. After binding and washing to remove non-specifically bound immune complexes, the bound antigen is detected. Where the initial antibodies are linked to a detectable label, the

immune complexes may be detected directly. Again, the immune complexes may be detected using a second antibody that has binding affinity for the first antibody, with the second antibody being linked to a detectable label.

Irrespective of the format employed, ELISAs have certain features in common, such as coating, incubating or binding, washing to remove non-specifically bound species, and detecting the bound immune complexes. These are described as follows.

In coating a plate with either antigen or antibody, one will generally incubate the wells of the plate with a solution of the antigen or antibody, either overnight or for a specified period of hours. The wells of the plate will then be washed to remove incompletely adsorbed material. Any remaining available surfaces of the wells are then "coated" with a nonspecific protein that is antigenically neutral with regard to the test antisera. These include bovine serum albumin (BSA), casein and solutions of milk powder. The coating allows for blocking of nonspecific adsorption sites on the immobilizing surface and thus reduces the background caused by nonspecific binding of antisera onto the surface.

In ELISAs, it is probably more customary to use a secondary or tertiary detection means rather than a direct procedure. Thus, after binding of a protein or antibody to the well, coating with a non-reactive material to reduce background, and washing to remove unbound material, the immobilizing surface is contacted with the control human prostate, cancer and/or clinical or biological sample to be tested under conditions effective to allow immune complex (antigen/antibody) formation. Detection of the immune complex then requires a labeled secondary binding ligand or antibody, or a secondary binding ligand or antibody in conjunction with a labeled tertiary antibody or third binding ligand.

The phrase "under conditions effective to allow immune complex (antigen/antibody) formation" means that the conditions preferably include diluting the antigens and antibodies with solutions such as BSA, bovine gamma globulin (BGG) and phosphate buffered saline (PBS)/Tween. These added agents also tend to assist in the reduction of nonspecific background.

The "suitable" conditions also mean that the incubation is at a temperature and for a period of time sufficient to allow effective binding. Incubation steps are typically from about 1 to 2 to 4 h, at temperatures preferably on the order of 25 to 27°C, or may be overnight at about 4°C or so.

Following all incubation steps in an ELISA, the contacted surface is washed so as to remove non-complexed material. A preferred washing procedure includes washing with a solution such as PBS/Tween, or borate buffer. Following the formation of specific immune complexes between the test sample and the originally bound material, and subsequent washing, the occurrence of even minute amounts of immune complexes may be determined.

To provide a detecting means, the second or third antibody will have an associated label to allow detection. Preferably, this will be an enzyme that will generate color development upon incubating with an appropriate chromogenic substrate. Thus, for example, one will desire to contact and incubate the first or second immune complex with a urease, glucose oxidase, alkaline phosphatase

or hydrogen peroxidase-conjugated antibody for a period of time and under conditions that favor the development of further immune complex formation (e.g., incubation for 2 h at room temperature in a PBS-containing solution such as PBS-Tween).

After incubation with the labeled antibody, and subsequent to washing to remove unbound material, the amount of label is quantified, e.g., by incubation with a chromogenic substrate such as urea and bromocresol purple. Quantitation is then achieved by measuring the degree of color generation, e.g., using a visible spectra spectrophotometer.

The protein biomarkers of the invention (e.g., filamin A alone or in combination with any one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSA, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1) can also be measured, quantitated, detected, and otherwise analyzed using protein mass spectrometry methods and instrumentation. Protein mass spectrometry refers to the application of mass spectrometry to the study of proteins. Although not intending to be limiting, two approaches are typically used for characterizing proteins using mass spectrometry. In the first, intact proteins are ionized and then introduced to a mass analyzer. This approach is referred to as "top-down" strategy of protein analysis. The two primary methods for ionization of whole proteins are electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI). In the second approach, proteins are enzymatically digested into smaller peptides using a protease such as trypsin. Subsequently these peptides are introduced into the mass spectrometer and identified by peptide mass fingerprinting or tandem mass spectrometry. Hence, this latter approach (also called "bottom-up" proteomics) uses identification at the peptide level to infer the existence of proteins.

Whole protein mass analysis of the biomarkers of the invention can be conducted using time-of-flight (TOF) MS, or Fourier transform ion cyclotron resonance (FT-ICR). These two types of instruments are useful because of their wide mass range, and in the case of FT-ICR, its high mass accuracy. The most widely used instruments for peptide mass analysis are the MALDI time-of-flight instruments as they permit the acquisition of peptide mass fingerprints (PMFs) at high pace (1 PMF can be analyzed in approx. 10 sec). Multiple stage quadrupole-time-of-flight and the quadrupole ion trap also find use in this application.

The biomarkers of the invention can also be measured in complex mixtures of proteins and molecules that co-exist in a biological medium or sample, however, fractionation of the sample may be required and is contemplated herein. It will be appreciated that ionization of complex mixtures of proteins can result in situation where the more abundant proteins have a tendency to "drown" or suppress signals from less abundant proteins in the same sample. In addition, the mass spectrum from a complex mixture can be difficult to interpret because of the overwhelming number of mixture components. Fractionation can be used to first separate any complex mixture of proteins prior to mass spectrometry analysis. Two methods are widely used to fractionate proteins, or their peptide products from an enzymatic digestion. The first method fractionates whole proteins and is called two-

dimensional gel electrophoresis. The second method, high performance liquid chromatography (LC or HPLC) is used to fractionate peptides after enzymatic digestion. In some situations, it may be desirable to combine both of these techniques. Any other suitable methods known in the art for fractionating protein mixtures are also contemplated herein.

Gel spots identified on a 2D Gel are usually attributable to one protein. If the identity of the protein is desired, usually the method of in-gel digestion is applied, where the protein spot of interest is excised, and digested proteolytically. The peptide masses resulting from the digestion can be determined by mass spectrometry using peptide mass fingerprinting. If this information does not allow unequivocal identification of the protein, its peptides can be subject to tandem mass spectrometry for de novo sequencing.

Characterization of protein mixtures using HPLC/MS may also be referred to in the art as “shotgun proteomics” and MuDPIT (Multi-Dimensional Protein Identification Technology). A peptide mixture that results from digestion of a protein mixture is fractionated by one or two steps of liquid chromatography (LC). The eluent from the chromatography stage can be either directly introduced to the mass spectrometer through electrospray ionization, or laid down on a series of small spots for later mass analysis using MALDI.

The biomarkers of the present invention (e.g., filamin A alone or in combination with any one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSA, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1) can be identified using MS using a variety of techniques, all of which are contemplated herein. Peptide mass fingerprinting uses the masses of proteolytic peptides as input to a search of a database of predicted masses that would arise from digestion of a list of known proteins. If a protein sequence in the reference list gives rise to a significant number of predicted masses that match the experimental values, there is some evidence that this protein was present in the original sample. It will be further appreciated that the development of methods and instrumentation for automated, data-dependent electrospray ionization (ESI) tandem mass spectrometry (MS/MS) in conjunction with microcapillary liquid chromatography (LC) and database searching has significantly increased the sensitivity and speed of the identification of gel-separated proteins. Microcapillary LC-MS/MS has been used successfully for the large-scale identification of individual proteins directly from mixtures without gel electrophoretic separation (Link et al., 1999; Opitek et al., 1997).

Several recent methods allow for the quantitation of proteins by mass spectrometry. For example, stable (e.g., non-radioactive) heavier isotopes of carbon (^{13}C) or nitrogen (^{15}N) can be incorporated into one sample while the other one can be labeled with corresponding light isotopes (e.g. ^{12}C and ^{14}N). The two samples are mixed before the analysis. Peptides derived from the different samples can be distinguished due to their mass difference. The ratio of their peak intensities corresponds to the relative abundance ratio of the peptides (and proteins). The most popular methods for isotope labeling are SILAC (stable isotope labeling by amino acids in cell culture), trypsin-

catalyzed ^{18}O labeling, ICAT (isotope coded affinity tagging), iTRAQ (isobaric tags for relative and absolute quantitation). "Semi-quantitative" mass spectrometry can be performed without labeling of samples. Typically, this is done with MALDI analysis (in linear mode). The peak intensity, or the peak area, from individual molecules (typically proteins) is here correlated to the amount of protein in the sample. However, the individual signal depends on the primary structure of the protein, on the complexity of the sample, and on the settings of the instrument. Other types of "label-free" quantitative mass spectrometry, uses the spectral counts (or peptide counts) of digested proteins as a means for determining relative protein amounts.

In one embodiment, any one or more of the biomarkers of the invention (e.g., filamin A alone or in combination with any one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSA, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1) can be identified and quantified from a complex biological sample using mass spectroscopy in accordance with the following exemplary method, which is not intended to limit the invention or the use of other mass spectrometry-based methods.

In the first step of this embodiment, (A) a biological sample, e.g., a biological sample suspected of having prostate cancer, which comprises a complex mixture of protein (including at least one biomarker of interest) is fragmented and labeled with a stable isotope X. (B) Next, a known amount of an internal standard is added to the biological sample, wherein the internal standard is prepared by fragmenting a standard protein that is identical to the at least one target biomarker of interest, and labeled with a stable isotope Y. (C) This sample obtained is then introduced in an LC-MS/MS device, and multiple reaction monitoring (MRM) analysis is performed using MRM transitions selected for the internal standard to obtain an MRM chromatogram. (D) The MRM chromatogram is then viewed to identify a target peptide biomarker derived from the biological sample that shows the same retention time as a peptide derived from the internal standard (an internal standard peptide), and quantifying the target protein biomarker in the test sample by comparing the peak area of the internal standard peptide with the peak area of the target peptide biomarker.

Any suitable biological sample may be used as a starting point for LC-MS/MS/MRM analysis, including biological samples derived blood, urine, saliva, hair, cells, cell tissues, biopsy materials, and treated products thereof; and protein-containing samples prepared by gene recombination techniques.

Each of the above steps (A) to (D) is described further below.

Step (A) (Fragmentation and Labeling). In step (A), the target protein biomarker is fragmented to a collection of peptides, which is subsequently labeled with a stable isotope X. To fragment the target protein, for example, methods of digesting the target protein with a proteolytic enzyme (protease) such as trypsin, and chemical cleavage methods, such as a method using cyanogen bromide, can be used. Digestion by protease is preferable. It is known that a given mole quantity of

protein produces the same mole quantity for each tryptic peptide cleavage product if the proteolytic digest is allowed to proceed to completion. Thus, determining the mole quantity of tryptic peptide to a given protein allows determination of the mole quantity of the original protein in the sample. Absolute quantification of the target protein can be accomplished by determining the absolute amount of the target protein-derived peptides contained in the protease digestion (collection of peptides).

Accordingly, in order to allow the proteolytic digest to proceed to completion, reduction and alkylation treatments are preferably performed before protease digestion with trypsin to reduce and alkylate the disulfide bonds contained in the target protein.

Subsequently, the obtained digest (collection of peptides, comprising peptides of the target biomarker in the biological sample) is subjected to labeling with a stable isotope X. Examples of stable isotopes X include ^1H and ^2H for hydrogen atoms, ^{12}C and ^{13}C for carbon atoms, and ^{14}N and ^{15}N for nitrogen atoms. Any isotope can be suitably selected therefrom. Labeling by a stable isotope X can be performed by reacting the digest (collection of peptides) with a reagent containing the stable isotope. Preferable examples of such reagents that are commercially available include mTRAQ (registered trademark) (produced by Applied Biosystems), which is an amine-specific stable isotope reagent kit. mTRAQ is composed of 2 or 3 types of reagents (mTRAQ-light and mTRAQ-heavy; or mTRAQ-D0, mTRAQ-D4, and mTRAQ-D8) that have a constant mass difference therebetween as a result of isotope-labeling, and that are bound to the N-terminus of a peptide or the primary amine of a lysine residue.

Step (B) (Addition of the Internal Standard). In step (B), a known amount of an internal standard is added to the sample obtained in step (A). The internal standard used herein is a digest (collection of peptides) obtained by fragmenting a protein (standard protein) consisting of the same amino acid sequence as the target protein (target biomarker) to be measured, and labeling the obtained digest (collection of peptides) with a stable isotope Y. The fragmentation treatment can be performed in the same manner as above for the target protein. Labeling with a stable isotope Y can also be performed in the same manner as above for the target protein. However, the stable isotope Y used herein must be an isotope that has a mass different from that of the stable isotope X used for labeling the target protein digest. For example, in the case of using the aforementioned mTRAQ (registered trademark) (produced by Applied Biosystems), when mTRAQ-light is used to label a target protein digest, mTRAQ-heavy should be used to label a standard protein digest.

Step (C) (LC-MS/MS and MRM Analysis). In step (C), the sample obtained in step (B) is first placed in an LC-MS/MS device, and then multiple reaction monitoring (MRM) analysis is performed using MRM transitions selected for the internal standard. By LC (liquid chromatography) using the LC-MS/MS device, the sample (collection of peptides labeled with a stable isotope) obtained in step (B) is separated first by one-dimensional or multi-dimensional high-performance liquid chromatography. Specific examples of such liquid chromatography include cation exchange chromatography, in which separation is conducted by utilizing electric charge difference between

peptides; and reversed-phase chromatography, in which separation is conducted by utilizing hydrophobicity difference between peptides. Both of these methods may be used in combination.

Subsequently, each of the separated peptides is subjected to tandem mass spectrometry by using a tandem mass spectrometer (MS/MS spectrometer) comprising two mass spectrometers connected in series. The use of such a mass spectrometer enables the detection of several fmol levels of a target protein. Furthermore, MS/MS analysis enables the analysis of internal sequence information on peptides, thus enabling identification without false positives. Other types of MS analyzers may also be used, including magnetic sector mass spectrometers (Sector MS), quadrupole mass spectrometers (QMS), time-of-flight mass spectrometers (TOFMS), and Fourier transform ion cyclotron resonance mass spectrometers (FT-ICRMS), and combinations of these analyzers.

Subsequently, the obtained data are put through a search engine to perform a spectral assignment and to list the peptides experimentally detected for each protein. The detected peptides are preferably grouped for each protein, and preferably at least three fragments having an m/z value larger than that of the precursor ion and at least three fragments with an m/z value of, preferably, 500 or more are selected from each MS/MS spectrum in descending order of signal strength on the spectrum. From these, two or more fragments are selected in descending order of strength, and the average of the strength is defined as the expected sensitivity of the MRR transitions. When a plurality of peptides is detected from one protein, at least two peptides with the highest sensitivity are selected as standard peptides using the expected sensitivity as an index.

Step (D) (Quantification of the Target Protein in the Test Sample). Step (D) comprises identifying, in the MRM chromatogram detected in step (C), a peptide derived from the target protein (a target biomarker of interest) that shows the same retention time as a peptide derived from the internal standard (an internal standard peptide), and quantifying the target protein in the test sample by comparing the peak area of the internal standard peptide with the peak area of the target peptide. The target protein can be quantified by utilizing a calibration curve of the standard protein prepared beforehand.

The calibration curve can be prepared by the following method. First, a recombinant protein consisting of an amino acid sequence that is identical to that of the target biomarker protein is digested with a protease such as trypsin, as described above. Subsequently, precursor-fragment transition selection standards (PTFS) of a known concentration are individually labeled with two different types of stable isotopes (i.e., one is labeled with a stable isomer used to label an internal standard peptide (labeled with IS), whereas the other is labeled with a stable isomer used to label a target peptide (labeled with T). A plurality of samples are produced by blending a certain amount of the IS-labeled PTFS with various concentrations of the T-labeled PTFS. These samples are placed in the aforementioned LC-MS/MS device to perform MRM analysis. The area ratio of the T-labeled PTFS to the IS-labeled PTFS (T-labeled PTFS/IS-labeled PTFS) on the obtained MRM chromatogram is plotted against the amount of the T-labeled PTFS to prepare a calibration curve. The

absolute amount of the target protein contained in the test sample can be calculated by reference to the calibration curve.

3. ANTIBODIES AND LABELS (E.G., FLUORESCENT MOIETIES, DYES)

In some embodiments, the invention provides methods and compositions that include labels for the highly sensitive detection and quantitation of the biomolecules of the invention, e.g., filamin A alone or in combination with at least one other prostate cancer related marker selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSA, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1. One skilled in the art will recognize that many strategies can be used for labeling target molecules to enable their detection or discrimination in a mixture of particles (e.g., labeled anti-filamin A antibody or labeled secondary antibody, or labeled oligonucleotide probe that specifically hybridizes to filamin A mRNA). The labels may be attached by any known means, including methods that utilize non-specific or specific interactions of label and target. Labels may provide a detectable signal or affect the mobility of the particle in an electric field. In addition, labeling can be accomplished directly or through binding partners.

In some embodiments, the label comprises a binding partner that binds to the biomarker of interest, where the binding partner is attached to a fluorescent moiety. The compositions and methods of the invention may utilize highly fluorescent moieties, e.g., a moiety capable of emitting at least about 200 photons when simulated by a laser emitting light at the excitation wavelength of the moiety, wherein the laser is focused on a spot not less than about 5 microns in diameter that contains the moiety, and wherein the total energy directed at the spot by the laser is no more than about 3 microJoules. Moieties suitable for the compositions and methods of the invention are described in more detail below.

In some embodiments, the invention provides a label for detecting a biological molecule comprising a binding partner for the biological molecule that is attached to a fluorescent moiety, wherein the fluorescent moiety is capable of emitting at least about 200 photons when simulated by a laser emitting light at the excitation wavelength of the moiety, wherein the laser is focused on a spot not less than about 5 microns in diameter that contains the moiety, and wherein the total energy directed at the spot by the laser is no more than about 3 microJoules. In some embodiments, the moiety comprises a plurality of fluorescent entities, e.g., about 2 to 4, 2 to 5, 2 to 6, 2 to 7, 2 to 8, 2 to 9, 2 to 10, or about 3 to 5, 3 to 6, 3 to 7, 3 to 8, 3 to 9, or 3 to 10 fluorescent entities. In some embodiments, the moiety comprises about 2 to 4 fluorescent entities. In some embodiments, the biological molecule is a protein or a small molecule. In some embodiments, the biological molecule is a protein. The fluorescent entities can be fluorescent dye molecules. In some embodiments, the fluorescent dye molecules comprise at least one substituted indolium ring system in which the substituent on the 3-carbon of the indolium ring contains a chemically reactive group or a conjugated

substance. In some embodiments, the dye molecules are Alexa Fluor molecules selected from the group consisting of Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 647, Alexa Fluor 680 or Alexa Fluor 700. In some embodiments, the dye molecules are Alexa Fluor molecules selected from the group consisting of Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 680 or Alexa Fluor 700. In some embodiments, the dye molecules are Alexa Fluor 647 dye molecules. In some embodiments, the dye molecules comprise a first type and a second type of dye molecules, e.g., two different Alexa Fluor molecules, e.g., where the first type and second type of dye molecules have different emission spectra. The ratio of the number of first type to second type of dye molecule can be, e.g., 4 to 1, 3 to 1, 2 to 1, 1 to 1, 1 to 2, 1 to 3 or 1 to 4. The binding partner can be, e.g., an antibody.

In some embodiments, the invention provides a label for the detection of a biological marker of the invention, wherein the label comprises a binding partner for the marker and a fluorescent moiety, wherein the fluorescent moiety is capable of emitting at least about 200 photons when simulated by a laser emitting light at the excitation wavelength of the moiety, wherein the laser is focused on a spot not less than about 5 microns in diameter that contains the moiety, and wherein the total energy directed at the spot by the laser is no more than about 3 microJoules. In some embodiments, the fluorescent moiety comprises a fluorescent molecule. In some embodiments, the fluorescent moiety comprises a plurality of fluorescent molecules, e.g., about 2 to 10, 2 to 8, 2 to 6, 2 to 4, 3 to 10, 3 to 8, or 3 to 6 fluorescent molecules. In some embodiments, the label comprises about 2 to 4 fluorescent molecules. In some embodiments, the fluorescent dye molecules comprise at least one substituted indolium ring system in which the substituent on the 3-carbon of the indolium ring contains a chemically reactive group or a conjugated substance. In some embodiments, the fluorescent molecules are selected from the group consisting of Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 647, Alexa Fluor 680 or Alexa Fluor 700. In some embodiments, the fluorescent molecules are selected from the group consisting of Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 680 or Alexa Fluor 700. In some embodiments, the fluorescent molecules are Alexa Fluor 647 molecules. In some embodiments, the binding partner comprises an antibody. In some embodiments, the antibody is a monoclonal antibody. In other embodiments, the antibody is a polyclonal antibody.

In various embodiments, the binding partner for detecting a biomarker of interest, e.g., filamin A or filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3 and PSA, is an antibody or antigen-binding fragment thereof. The term "antibody," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, to refer to naturally occurring antibodies as well as non-naturally occurring antibodies, including, for example, single chain antibodies, chimeric, bifunctional and humanized antibodies, as well as antigen-binding fragments thereof. An "antigen-binding fragment" of an antibody refers to the part of the antibody that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. It will be appreciated that the choice of epitope or region of the molecule to which the antibody is raised will determine its

specificity, e.g., for various forms of the molecule, if present, or for total (e.g., all, or substantially all of the molecule).

Methods for producing antibodies are well-established. One skilled in the art will recognize that many procedures are available for the production of antibodies, for example, as described in *Antibodies, A Laboratory Manual*, Ed Harlow and David Lane, Cold Spring Harbor Laboratory (1988), Cold Spring Harbor, N.Y. One skilled in the art will also appreciate that binding fragments or Fab fragments which mimic antibodies can also be prepared from genetic information by various procedures (*Antibody Engineering: A Practical Approach* (Borrebaeck, C., ed.), 1995, Oxford University Press, Oxford; *J. Immunol.* 149, 3914-3920 (1992)). Monoclonal and polyclonal antibodies to molecules, e.g., proteins, and markers also commercially available (R and D Systems, Minneapolis, Minn.; HyTest, HyTest Ltd., Turku Finland; Abcam Inc., Cambridge, Mass., USA, Life Diagnostics, Inc., West Chester, Pa., USA; Fitzgerald Industries International, Inc., Concord, Mass. 01742-3049 USA; BiosPacific, Emeryville, Calif.).

In some embodiments, the antibody is a polyclonal antibody. In other embodiments, the antibody is a monoclonal antibody.

Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art (see, for example, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988). In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies.

Monoclonal antibodies may be prepared using hybridoma methods, such as the technique of Kohler and Milstein (*Eur. J. Immunol.* 6:511-519, 1976), and improvements thereto. These methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity. Monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Pat. No. 4,816,567. DNA encoding antibodies employed in the disclosed methods may be isolated and sequenced using conventional procedures. Recombinant antibodies, antibody fragments, and/or fusions thereof, can be expressed in vitro or in prokaryotic cells (e.g. bacteria) or eukaryotic cells (e.g. yeast, insect or mammalian cells) and further purified as necessary using well known methods.

More particularly, monoclonal antibodies (MAbs) may be readily prepared through use of well-known techniques, such as those exemplified in U.S. Pat. No. 4,196,265, incorporated herein by reference. Typically, this technique involves immunizing a suitable animal with a selected immunogen composition, e.g., a purified or partially purified expressed protein, polypeptide or peptide. The immunizing composition is administered in a manner effective to stimulate antibody producing cells. The methods for generating monoclonal antibodies (MAbs) generally begin along the same lines as those for preparing polyclonal antibodies. Rodents such as mice and rats are

preferred animals, however, the use of rabbit, sheep or frog cells is also possible. The use of rats may provide certain advantages (Goding, 1986, pp. 60-61), but mice are preferred, with the BALB/c mouse being most preferred as this is most routinely used and generally gives a higher percentage of stable fusions.

The animals are injected with antigen as described above. The antigen may be coupled to carrier molecules such as keyhole limpet hemocyanin if necessary. The antigen would typically be mixed with adjuvant, such as Freund's complete or incomplete adjuvant. Booster injections with the same antigen would occur at approximately two-week intervals. Following immunization, somatic cells with the potential for producing antibodies, specifically B lymphocytes (B cells), are selected for use in the MAb generating protocol. These cells may be obtained from biopsied spleens, tonsils or lymph nodes, or from a peripheral blood sample. Spleen cells and peripheral blood cells are preferred, the former because they are a rich source of antibody-producing cells that are in the dividing plasmablast stage, and the latter because peripheral blood is easily accessible. Often, a panel of animals will have been immunized and the spleen of the animal with the highest antibody titer will be removed and the spleen lymphocytes obtained by homogenizing the spleen with a syringe.

The antibody-producing B lymphocytes from the immunized animal are then fused with cells of an immortal myeloma cell, generally one of the same species as the animal that was immunized. Myeloma cell lines suited for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency, and enzyme deficiencies that render them incapable of growing in certain selective media which support the growth of only the desired fused cells (hybridomas).

The selected hybridomas would then be serially diluted and cloned into individual antibody-producing cell lines, which clones may then be propagated indefinitely to provide MAbs. The cell lines may be exploited for MAb production in two basic ways. A sample of the hybridoma may be injected (often into the peritoneal cavity) into a histocompatible animal of the type that was used to provide the somatic and myeloma cells for the original fusion. The injected animal develops tumors secreting the specific monoclonal antibody produced by the fused cell hybrid. The body fluids of the animal, such as serum or ascites fluid, may then be tapped to provide MAbs in high concentration. The individual cell lines also may be cultured *in vitro*, where the MAbs are naturally secreted into the culture medium from which they may be readily obtained in high concentrations. MAbs produced by either means may be further purified, if desired, using filtration, centrifugation and various chromatographic methods such as HPLC or affinity chromatography.

Large amounts of the monoclonal antibodies of the present invention also may be obtained by multiplying hybridoma cells *in vivo*. Cell clones are injected into mammals which are histocompatible with the parent cells, e.g., syngeneic mice, to cause growth of antibody-producing tumors. Optionally, the animals are primed with a hydrocarbon, especially oils such as pristane (tetramethylpentadecane) prior to injection.

In accordance with the present invention, fragments of the monoclonal antibody of the invention may be obtained from the monoclonal antibody produced as described above, by methods which include digestion with enzymes such as pepsin or papain and/or cleavage of disulfide bonds by chemical reduction. Alternatively, monoclonal antibody fragments encompassed by the present invention may be synthesized using an automated peptide synthesizer.

Antibodies may also be derived from a recombinant antibody library that is based on amino acid sequences that have been designed in silico and encoded by polynucleotides that are synthetically generated. Methods for designing and obtaining in silico-created sequences are known in the art (Knappik et al., J. Mol. Biol. 296:254:57-86, 2000; Krebs et al., J. Immunol. Methods 254:67-84, 2001; U.S. Pat. No. 6,300,064).

Digestion of antibodies to produce antigen-binding fragments thereof can be performed using techniques well known in the art. For example, the proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the "F(ab)" fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site. The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the "F(ab')₂" fragment, which comprises both antigen-binding sites. "Fv" fragments can be produced by preferential proteolytic cleavage of an IgM, IgG or IgA immunoglobulin molecule, but are more commonly derived using recombinant techniques known in the art. The Fv fragment includes a non-covalent V_H:V_L heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule (Inbar et al., Proc. Natl. Acad. Sci. USA 69:2659-2662 (1972); Hochman et al., Biochem. 15:2706-2710 (1976); and Ehrlich et al., Biochem. 19:4091-4096 (1980)).

Antibody fragments that specifically bind to the polypeptide biomarkers disclosed herein can also be isolated from a library of scFvs using known techniques, such as those described in U.S. Pat. No. 5,885,793.

A wide variety of expression systems are available in the art for the production of antibody fragments, including Fab fragments, scFv, VL and VHs. For example, expression systems of both prokaryotic and eukaryotic origin may be used for the large-scale production of antibody fragments. Particularly advantageous are expression systems that permit the secretion of large amounts of antibody fragments into the culture medium. Eukaryotic expression systems for large-scale production of antibody fragments and antibody fusion proteins have been described that are based on mammalian cells, insect cells, plants, transgenic animals, and lower eukaryotes. For example, the cost-effective, large-scale production of antibody fragments can be achieved in yeast fermentation systems. Large-scale fermentation of these organisms is well known in the art and is currently used for bulk production of several recombinant proteins.

Antibodies that bind to the polypeptide biomarkers employed in the present methods are well known to those of skill in the art and in some cases are available commercially or can be obtained without undue experimentation.

In still other embodiments, particularly where oligonucleotides are used as binding partners to detect and hybridize to mRNA biomarkers or other nucleic acid based biomarkers, the binding partners (e.g., oligonucleotides) can comprise a label, e.g., a fluorescent moiety or dye. In addition, any binding partner of the invention, e.g., an antibody, can also be labeled with a fluorescent moiety. The fluorescence of the moiety will be sufficient to allow detection in a single molecule detector, such as the single molecule detectors described herein. A "fluorescent moiety," as that term is used herein, includes one or more fluorescent entities whose total fluorescence is such that the moiety may be detected in the single molecule detectors described herein. Thus, a fluorescent moiety may comprise a single entity (e.g., a Quantum Dot or fluorescent molecule) or a plurality of entities (e.g., a plurality of fluorescent molecules). It will be appreciated that when "moiety," as that term is used herein, refers to a group of fluorescent entities, e.g., a plurality of fluorescent dye molecules, each individual entity may be attached to the binding partner separately or the entities may be attached together, as long as the entities as a group provide sufficient fluorescence to be detected.

Typically, the fluorescence of the moiety involves a combination of quantum efficiency and lack of photobleaching sufficient that the moiety is detectable above background levels in a single molecule detector, with the consistency necessary for the desired limit of detection, accuracy, and precision of the assay. For example, in some embodiments, the fluorescence of the fluorescent moiety is such that it allows detection and/or quantitation of a molecule, e.g., a marker, at a limit of detection of less than about 10, 5, 4, 3, 2, 1, 0.1, 0.01, 0.001, 0.00001, or 0.000001 pg/ml and with a coefficient of variation of less than about 20, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1% or less, e.g., about 10% or less, in the instruments described herein. In some embodiments, the fluorescence of the fluorescent moiety is such that it allows detection and/or quantitation of a molecule, e.g., a marker, at a limit of detection of less than about 5, 1, 0.5, 0.1, 0.05, 0.01, 0.005, 0.001 pg/ml and with a coefficient of variation of less than about 10%, in the instruments described herein. "Limit of detection," or LoD, as those terms are used herein, includes the lowest concentration at which one can identify a sample as containing a molecule of the substance of interest, e.g., the first non-zero value. It can be defined by the variability of zeros and the slope of the standard curve. For example, the limit of detection of an assay may be determined by running a standard curve, determining the standard curve zero value, and adding 2 standard deviations to that value. A concentration of the substance of interest that produces a signal equal to this value is the "lower limit of detection" concentration.

Furthermore, the moiety has properties that are consistent with its use in the assay of choice. In some embodiments, the assay is an immunoassay, where the fluorescent moiety is attached to an antibody; the moiety must have properties such that it does not aggregate with other antibodies or proteins, or experiences no more aggregation than is consistent with the required accuracy and

precision of the assay. In some embodiments, fluorescent moieties that are preferred are fluorescent moieties, e.g., dye molecules that have a combination of 1) high absorption coefficient; 2) high quantum yield; 3) high photostability (low photobleaching); and 4) compatibility with labeling the molecule of interest (e.g., protein) so that it may be analyzed using the analyzers and systems of the invention (e.g., does not cause precipitation of the protein of interest, or precipitation of a protein to which the moiety has been attached).

Any suitable fluorescent moiety may be used. Examples include, but are not limited to, Alexa Fluor dyes (Molecular Probes, Eugene, Oreg.). The Alexa Fluor dyes are disclosed in U.S. Pat. Nos. 6,977,305; 6,974,874; 6,130,101; and 6,974,305 which are herein incorporated by reference in their entirety. Some embodiments of the invention utilize a dye chosen from the group consisting of Alexa Fluor 647, Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 555, Alexa Fluor 610, Alexa Fluor 680, Alexa Fluor 700, and Alexa Fluor 750. Some embodiments of the invention utilize a dye chosen from the group consisting of Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 647, Alexa Fluor 700 and Alexa Fluor 750. Some embodiments of the invention utilize a dye chosen from the group consisting of Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 555, Alexa Fluor 610, Alexa Fluor 680, Alexa Fluor 700, and Alexa Fluor 750. Some embodiments of the invention utilize the Alexa Fluor 647 molecule, which has an absorption maximum between about 650 and 660 nm and an emission maximum between about 660 and 670 nm. The Alexa Fluor 647 dye is used alone or in combination with other Alexa Fluor dyes.

In some embodiments, the fluorescent label moiety that is used to detect a biomarker in a sample using the analyzer systems of the invention is a quantum dot. Quantum dots (QDs), also known as semiconductor nanocrystals or artificial atoms, are semiconductor crystals that contain anywhere between 100 to 1,000 electrons and range from 2-10 nm. Some QDs can be between 10-20 nm in diameter. QDs have high quantum yields, which makes them particularly useful for optical applications. QDs are fluorophores that fluoresce by forming excitons, which are similar to the excited state of traditional fluorophores, but have much longer lifetimes of up to 200 nanoseconds. This property provides QDs with low photobleaching. The energy level of QDs can be controlled by changing the size and shape of the QD, and the depth of the QDs' potential. One optical feature of small excitonic QDs is coloration, which is determined by the size of the dot. The larger the dot, the redder, or more towards the red end of the spectrum the fluorescence. The smaller the dot, the bluer or more towards the blue end it is. The bandgap energy that determines the energy and hence the color of the fluoresced light is inversely proportional to the square of the size of the QD. Larger QDs have more energy levels which are more closely spaced, thus allowing the QD to absorb photons containing less energy, i.e., those closer to the red end of the spectrum. Because the emission frequency of a dot is dependent on the bandgap, it is possible to control the output wavelength of a dot with extreme precision. In some embodiments the protein that is detected with the single molecule analyzer system is labeled with a QD. In some embodiments, the single molecule analyzer is used to

detect a protein labeled with one QD and using a filter to allow for the detection of different proteins at different wavelengths.

F. ISOLATED BIOMARKERS

1. ISOLATED POLYPEPTIDE BIOMARKERS

One aspect of the invention pertains to isolated marker proteins and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise antibodies directed against a marker protein or a fragment thereof. In one embodiment, the native marker protein can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, a protein or peptide comprising the whole or a segment of the marker protein is produced by recombinant DNA techniques. Alternative to recombinant expression, such protein or peptide can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, protein that is substantially free of cellular material includes preparations of protein having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When the protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, *i.e.*, it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such preparations of the protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the polypeptide of interest.

Biologically active portions of a marker protein include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the marker protein, which include fewer amino acids than the full length protein, and exhibit at least one activity of the corresponding full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the corresponding full-length protein. A biologically active portion of a marker protein of the invention can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length. Moreover, other biologically active portions, in which other regions of the

marker protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of the native form of the marker protein.

Preferred marker proteins are encoded by nucleotide sequences provided in the sequence listing. Other useful proteins are substantially identical (*e.g.*, at least about 40%, preferably 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%) to one of these sequences and retain the functional activity of the corresponding naturally-occurring marker protein yet differ in amino acid sequence due to natural allelic variation or mutagenesis.

To determine the percent identity of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. Preferably, the percent identity between the two sequences is calculated using a global alignment. Alternatively, the percent identity between the two sequences is calculated using a local alignment. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = # of identical positions/total # of positions (*e.g.*, overlapping positions) x100). In one embodiment the two sequences are the same length. In another embodiment, the two sequences are not the same length.

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an algorithm is incorporated into the BLASTN and BLASTX programs of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-410. BLAST nucleotide searches can be performed with the BLASTN program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTP program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, a newer version of the BLAST algorithm called Gapped BLAST can be utilized as described in Altschul *et al.* (1997) *Nucleic Acids Res.* 25:3389-3402, which is able to perform gapped local alignments for the programs BLASTN, BLASTP and BLASTX. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (*e.g.*, BLASTX and BLASTN) can be used. See the NCBI website. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) *CABIOS* 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is

part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85:2444-2448. When using the FASTA algorithm for comparing nucleotide or amino acid sequences, a PAM120 weight residue table can, for example, be used with a *k*-tuple value of 2.

The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted.

Another aspect of the invention pertains to antibodies directed against a protein of the invention. In preferred embodiments, the antibodies specifically bind a marker protein or a fragment thereof. The terms "antibody" and "antibodies" as used interchangeably herein refer to immunoglobulin molecules as well as fragments and derivatives thereof that comprise an immunologically active portion of an immunoglobulin molecule, (*i.e.*, such a portion contains an antigen binding site which specifically binds an antigen, such as a marker protein, *e.g.*, an epitope of a marker protein). An antibody which specifically binds to a protein of the invention is an antibody which binds the protein, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample, which naturally contains the protein. Examples of an immunologically active portion of an immunoglobulin molecule include, but are not limited to, single-chain antibodies (scAb), F(ab) and F(ab')₂ fragments.

An isolated protein of the invention or a fragment thereof can be used as an immunogen to generate antibodies. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments for use as immunogens. The antigenic peptide of a protein of the invention comprises at least 8 (preferably 10, 15, 20, or 30 or more) amino acid residues of the amino acid sequence of one of the proteins of the invention, and encompasses at least one epitope of the protein such that an antibody raised against the peptide forms a specific immune complex with the protein. Preferred epitopes encompassed by the antigenic peptide are regions that are located on the surface of the protein, *e.g.*, hydrophilic regions. Hydrophobicity sequence analysis, hydrophilicity sequence analysis, or similar analyses can be used to identify hydrophilic regions. In preferred embodiments, an isolated marker protein or fragment thereof is used as an immunogen.

The invention provides polyclonal and monoclonal antibodies. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope. Preferred polyclonal and monoclonal antibody compositions are ones that have been selected for antibodies directed against a protein of the invention. Particularly preferred polyclonal and monoclonal antibody preparations are ones that contain only antibodies directed

against a marker protein or fragment thereof. Methods of making polyclonal, monoclonal, and recombinant antibody and antibody fragments are well known in the art.

2. ISOLATED NUCLEIC ACID BIOMARKERS

One aspect of the invention pertains to isolated nucleic acid molecules, including nucleic acids which encode a marker protein or a portion thereof. Isolated nucleic acids of the invention also include nucleic acid molecules sufficient for use as hybridization probes to identify marker nucleic acid molecules, and fragments of marker nucleic acid molecules, *e.g.*, those suitable for use as PCR primers for the amplification of a specific product or mutation of marker nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA) and RNA molecules (*e.g.*, mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. In one embodiment, an "isolated" nucleic acid molecule (preferably a protein-encoding sequences) is free of sequences which naturally flank the nucleic acid (*i.e.*, sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecule can contain less than about 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. In another embodiment, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized. A nucleic acid molecule that is substantially free of cellular material includes preparations having less than about 30%, 20%, 10%, or 5% of heterologous nucleic acid (also referred to herein as a "contaminating nucleic acid").

A nucleic acid molecule of the present invention can be isolated using standard molecular biology techniques and the sequence information in the database records described herein. Using all or a portion of such nucleic acid sequences, nucleic acid molecules of the invention can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook *et al.*, ed., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

A nucleic acid molecule of the invention can be amplified using cDNA, mRNA, or genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, nucleotides corresponding to all or a portion of a nucleic

acid molecule of the invention can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which has a nucleotide sequence complementary to the nucleotide sequence of a marker nucleic acid or to the nucleotide sequence of a nucleic acid encoding a marker protein. A nucleic acid molecule which is complementary to a given nucleotide sequence is one which is sufficiently complementary to the given nucleotide sequence that it can hybridize to the given nucleotide sequence thereby forming a stable duplex.

Moreover, a nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence, wherein the full length nucleic acid sequence comprises a marker nucleic acid or which encodes a marker protein. Such nucleic acids can be used, for example, as a probe or primer. The probe/primer typically is used as one or more substantially purified oligonucleotides. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 15, more preferably at least about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 or more consecutive nucleotides of a nucleic acid of the invention.

Probes based on the sequence of a nucleic acid molecule of the invention can be used to detect transcripts or genomic sequences corresponding to one or more markers of the invention. In certain embodiments, the probes hybridize to nucleic acid sequences that traverse splice junctions. The probe comprises a label group attached thereto, *e.g.*, a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as part of a diagnostic test kit or panel for identifying cells or tissues which express or mis-express the protein, such as by measuring levels of a nucleic acid molecule encoding the protein in a sample of cells from a subject, *e.g.*, detecting mRNA levels or determining whether a gene encoding the protein or its translational control sequences have been mutated or deleted.

The invention further encompasses nucleic acid molecules that differ, due to degeneracy of the genetic code, from the nucleotide sequence of nucleic acids encoding a marker protein (*e.g.*, protein having the sequence provided in the sequence listing), and thus encode the same protein.

It will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequence can exist within a population (*e.g.*, the human population). Such genetic polymorphisms can exist among individuals within a population due to natural allelic variation and changes known to occur in cancer. An allele is one of a group of genes which occur alternatively at a given genetic locus. In addition, it will be appreciated that DNA polymorphisms that affect RNA expression levels can also exist that may affect the overall expression level of that gene (*e.g.*, by affecting regulation or degradation).

As used herein, the phrase "allelic variant" refers to a nucleotide sequence which occurs at a given locus or to a polypeptide encoded by the nucleotide sequence.

As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding a polypeptide corresponding to a marker of the invention. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of a given gene. Alternative alleles can be identified by sequencing the gene of interest in a number of different individuals. This can be readily carried out by using hybridization probes to identify the same genetic locus in a variety of individuals. Any and all such nucleotide variations and resulting amino acid polymorphisms or variations that are the result of natural allelic variation and that do not alter the functional activity are intended to be within the scope of the invention.

In another embodiment, an isolated nucleic acid molecule of the invention is at least 15, 20, 25, 30, 40, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 550, 650, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 2600, 2800, 3000, 3500, 4000, 4500, or more nucleotides in length and hybridizes under stringent conditions to a marker nucleic acid or to a nucleic acid encoding a marker protein. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% (65%, 70%, preferably 75%) identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in sections 6.3.1-6.3.6 of *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989). A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65°C.

G. BIOMARKER APPLICATIONS

The invention provides methods for diagnosing an abnormal prostate state, e.g., BPH or an oncological disease state, e.g., prostate cancer, in a subject. The invention further provides methods for prognosing or monitoring progression or monitoring response of an abnormal prostate state, e.g., BPH or prostate cancer, to a therapeutic treatment during active treatment or watchful waiting.

In one aspect, the present invention constitutes an application of diagnostic information obtainable by the methods of the invention in connection with analyzing, detecting, and/or measuring the prostate cancer biomarkers of the present invention, including filamin A alone or filamin A in combination with one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, which goes well beyond the discovered correlation between prostate cancer and the biomarkers of the invention.

For example, when executing the methods of the invention for detecting and/or measuring a polypeptide biomarkers of the present invention, as described herein, one contacts a biological sample with a detection reagent, e.g., a monoclonal antibody, which selectively binds to the biomarker of interest, forming a protein-protein complex, which is then further detected either directly (if the antibody comprises a label) or indirectly (if a secondary detection reagent is used, e.g., a secondary antibody, which in turn is labeled). Thus, the method of the invention transforms the polypeptide

markers of the invention to a protein-protein complex that comprises either a detectable primary antibody or a primary and further secondary antibody. Forming such protein-protein complexes is required in order to identify the presence of the biomarker of interest and necessarily changes the physical characteristics and properties of the biomarker of interest as a result of conducting the methods of the invention.

The same principal applies when conducting the methods of the invention for detecting nucleic acid biomarkers of the invention. In particular, when amplification methods are used to detect a biomarker of the invention (e.g., filamin A mRNA), the amplification process, in fact, results in the formation of a new population of amplicons – i.e., molecules that are newly synthesized and which were not present in the original biological sample, thereby physically transforming the biological sample. Similarly, when hybridization probes are used to detect a target biomarker, a physical new species of molecules is in effect created by the hybridization of the probes (optionally comprising a label) to the target biomarker mRNA (or other nucleic acid), which is then detected. Such polynucleotide products are effectively newly created or formed as a consequence of carrying out the method of the invention.

The invention provides, in one embodiment, methods for diagnosing an oncological disorder, e.g., prostate cancer. The methods of the present invention can be practiced in conjunction with any other method used by the skilled practitioner to prognose the occurrence or recurrence of an oncologic disorder and/or the survival of a subject being treated for an oncologic disorder. The diagnostic and prognostic methods provided herein can be used to determine if additional and/or more invasive tests or monitoring should be performed on a subject. It is understood that a disease as complex as an oncological disorder is rarely diagnosed using a single test. Therefore, it is understood that the diagnostic, prognostic, and monitoring methods provided herein are typically used in conjunction with other methods known in the art. For example, the methods of the invention may be performed in conjunction with a morphological or cytological analysis of the sample obtained from the subject, imaging analysis, and/or physical exam. Cytological methods would include immunohistochemical or immunofluorescence detection (and quantitation if appropriate) of any other molecular marker either by itself, in conjunction with other markers. Other methods would include detection of other markers by *in situ* PCR, or by extracting tissue and quantitating other markers by real time PCR. PCR is defined as polymerase chain reaction.

Methods for assessing tumor progression during watchful waiting or the efficacy of a treatment regimen, e.g., chemotherapy, radiation therapy, surgery, hormone therapy, or any other therapeutic approach useful for treating an oncologic disorder in a subject are also provided. In these methods the amount of marker in a pair of samples (a first sample obtained from the subject at an earlier time point or prior to the treatment regimen and a second sample obtained from the subject at a later time point, e.g., at a later time point when the subject has undergone at least a portion of the treatment regimen) is assessed. It is understood that the methods of the invention include obtaining

and analyzing more than two samples (e.g., 3, 4, 5, 6, 7, 8, 9, or more samples) at regular or irregular intervals for assessment of marker levels. Pairwise comparisons can be made between consecutive or non-consecutive subject samples. Trends of marker levels and rates of change of marker levels can be analyzed for any two or more consecutive or non-consecutive subject samples.

The invention also provides a method for determining whether an oncologic disorder, e.g., prostate cancer, is aggressive. The method comprises determining the amount of a marker present in a sample and comparing the amount to a control amount of the marker present in one or more control samples, as defined in Definitions, thereby determining whether an oncologic disorder is aggressive. Marker levels can be compared to marker levels in samples obtained at different times from the same subject or marker levels from normal or abnormal prostate state subjects. A rapid increase in the level of marker may be indicative of a more aggressive cancer than a slow increase or no increase or change in the marker level.

The methods of the invention may also be used to select a compound that is capable of modulating, *i.e.*, decreasing, the aggressiveness of an oncologic disorder, e.g., prostate cancer. In this method, a cancer cell is contacted with a test compound, and the ability of the test compound to modulate the expression and/or activity of a marker in the invention in the cancer cell is determined, thereby selecting a compound that is capable of modulating aggressiveness of an oncologic disorder.

Using the methods described herein, a variety of molecules, may be screened in order to identify molecules which modulate, e.g., increase or decrease the expression and/or activity of a marker of the invention, e.g., filamin A alone or filamin A in combination with one or more of PSA, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9), PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1. Compounds so identified can be provided to a subject in order to inhibit the aggressiveness of an oncologic disorder in the subject, to prevent the recurrence of an oncologic disorder in the subject, or to treat an oncologic disorder in the subject.

The present invention pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining the level of expression of one or more marker proteins or nucleic acids, in order to determine whether an individual is at risk of developing a disease or disorder, such as, without limitation, an oncological disorder, e.g., prostate cancer. Such assays can be used for prognostic or predictive purposes to thereby prophylactically treat an individual prior to the onset of the disorder.

Yet another aspect of the invention pertains to monitoring the influence of agents (*e.g.*, drugs or other therapeutic compounds) on the expression or activity of a biomarker of the invention in clinical trials. These and other applications are described in further detail in the following sections.

1. DIAGNOSTIC ASSAYS

An exemplary method for detecting the presence or absence or change of expression level of a marker protein or nucleic acid in a biological sample involves obtaining a biological sample (e.g. an oncological disorder-associated body fluid) from a test subject and contacting the biological sample with a compound or an agent capable of detecting the polypeptide or nucleic acid (e.g., mRNA, genomic DNA, or cDNA). The detection methods of the invention can thus be used to detect mRNA, protein, cDNA, or genomic DNA, for example, in a biological sample in vitro as well as in vivo.

Methods provided herein for detecting the presence, absence, change of expression level of a marker protein or nucleic acid in a biological sample include obtaining a biological sample from a subject that may or may not contain the marker protein or nucleic acid to be detected, contacting the sample with a marker-specific binding agent (i.e., one or more marker-specific binding agents) that is capable of forming a complex with the marker protein or nucleic acid to be detected, and contacting the sample with a detection reagent for detection of the marker—marker-specific binding agent complex, if formed. It is understood that the methods provided herein for detecting an expression level of a marker in a biological sample includes the steps to perform the assay. In certain embodiments of the detection methods, the level of the marker protein or nucleic acid in the sample is none or below the threshold for detection.

The methods include formation of either a transient or stable complex between the marker and the marker-specific binding agent. The methods require that the complex, if formed, be formed for sufficient time to allow a detection reagent to bind the complex and produce a detectable signal (e.g., fluorescent signal, a signal from a product of an enzymatic reaction, e.g., a peroxidase reaction, a phosphatase reaction, a beta-galactosidase reaction, or a polymerase reaction).

In certain embodiments, all markers are detected using the same method. In certain embodiments, all markers are detected using the same biological sample (e.g., same body fluid or tissue). In certain embodiments, different markers are detected using various methods. In certain embodiments, markers are detected in different biological samples.

2. PROTEIN DETECTION

In certain embodiments of the invention, the marker to be detected is a protein. Proteins are detected using a number of assays in which a complex between the marker protein to be detected and the marker specific binding agent would not occur naturally, for example, because one of the components is not a naturally occurring compound or the marker for detection and the marker specific binding agent are not from the same organism (e.g., human marker proteins detected using marker-specific binding antibodies from mouse, rat, or goat). In a preferred embodiment of the invention, the marker protein for detection is a human marker protein. In certain detection assays, the human markers for detection are bound by marker-specific, non-human antibodies, thus, the complex would not be formed in nature. The complex of the marker protein can be detected directly, e.g., by use of a

labeled marker-specific antibody that binds directly to the marker, or by binding a further component to the marker--marker-specific antibody complex. In certain embodiments, the further component is a second marker-specific antibody capable of binding the marker at the same time as the first marker-specific antibody. In certain embodiments, the further component is a secondary antibody that binds to a marker-specific antibody, wherein the secondary antibody preferably linked to a detectable label (e.g., fluorescent label, enzymatic label, biotin). When the secondary antibody is linked to an enzymatic detectable label (e.g., a peroxidase, a phosphatase, a beta-galactosidase), the secondary antibody is detected by contacting the enzymatic detectable label with an appropriate substrate to produce a colorimetric, fluorescent, or other detectable, preferably quantitatively detectable, product. Antibodies for use in the methods of the invention can be polyclonal, however, in a preferred embodiment monoclonal antibodies are used. An intact antibody, or a fragment or derivative thereof (e.g., Fab or F(ab')₂) can be used in the methods of the invention. Such strategies of marker protein detection are used, for example, in ELISA, RIA, western blot, and immunofluorescence assay methods.

In certain detection assays, the marker present in the biological sample for detection is an enzyme and the detection reagent is an enzyme substrate. For example, the enzyme can be a protease and the substrate can be any protein that includes an appropriate protease cleavage site. Alternatively, the enzyme can be a kinase and the substrate can be any substrate for the kinase. In preferred embodiments, the substrate which forms a complex with the marker enzyme to be detected is not the substrate for the enzyme in a human subject.

In certain embodiments, the marker--marker-specific binding agent complex is attached to a solid support for detection of the marker. The complex can be formed on the substrate or formed prior to capture on the substrate. For example, in an ELISA, RIA, immunoprecipitation assay, western blot, immunofluorescence assay, in gel enzymatic assay the marker for detection is attached to a solid support, either directly or indirectly. In an ELISA, RIA, or immunofluorescence assay, the marker is typically attached indirectly to a solid support through an antibody or binding protein. In a western blot or immunofluorescence assay, the marker is typically attached directly to the solid support. For in-gel enzyme assays, the marker is resolved in a gel, typically an acrylamide gel, in which a substrate for the enzyme is integrated.

3. NUCLEIC ACID DETECTION

In certain embodiments of the invention, the marker is a nucleic acid. Nucleic acids are detected using a number of assays in which a complex between the marker nucleic acid to be detected and a marker-specific probe would not occur naturally, for example, because one of the components is not a naturally occurring compound. In certain embodiments, the analyte comprises a nucleic acid and the probe comprises one or more synthetic single stranded nucleic acid molecules, e.g., a DNA molecule, a DNA-RNA hybrid, a PNA, or a modified nucleic acid molecule containing one or more

artificial bases, sugars, or backbone moieties. In certain embodiments, the synthetic nucleic acid is a single stranded DNA molecule that includes a fluorescent label. In certain embodiments, the synthetic nucleic acid is a single stranded oligonucleotide molecule of about 12 to about 50 nucleotides in length. In certain embodiments, the nucleic acid to be detected is an mRNA and the complex formed is an mRNA hybridized to a single stranded DNA molecule that is complementary to the mRNA. In certain embodiments, an RNA is detected by generation of a DNA molecule (i.e., a cDNA molecule) first from the RNA template using the single stranded DNA that hybridizes to the RNA as a primer, e.g., a general poly-T primer to transcribe poly-A RNA. The cDNA can then be used as a template for an amplification reaction, e.g., PCR, primer extension assay, using a marker-specific probe. In certain embodiments, a labeled single stranded DNA can be hybridized to the RNA present in the sample for detection of the RNA by fluorescence in situ hybridization (FISH) or for detection of the RNA by northern blot.

For example, in vitro techniques for detection of mRNA include northern hybridizations, in situ hybridizations, and rtPCR. In vitro techniques for detection of genomic DNA include Southern hybridizations. Techniques for detection of mRNA include PCR, northern hybridizations and in situ hybridizations. Methods include both qualitative and quantitative methods.

A general principle of such diagnostic, prognostic, and monitoring assays involves preparing a sample or reaction mixture that may contain a marker, and a probe, under appropriate conditions and for a time sufficient to allow the marker and probe to interact and bind, thus forming a complex that can be removed and/or detected in the reaction mixture. These assays can be conducted in a variety of ways known in the art, e.g., ELISA assay, PCR, FISH.

4. DETECTION OF EXPRESSION LEVELS

Marker levels can be detected based on the absolute expression level or a normalized or relative expression level. Detection of absolute marker levels may be preferable when monitoring the treatment of a subject or in determining if there is a change in the prostate cancer status of a subject. For example, the expression level of one or more markers can be monitored in a subject undergoing treatment for prostate cancer, e.g., at regular intervals, such as monthly intervals. A modulation in the level of one or more markers can be monitored over time to observe trends in changes in marker levels. Expression levels of the biomarkers of the invention, e.g., filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 in the subject may be higher than the expression level of those markers in a normal sample, but may be lower than the prior expression level, thus indicating a benefit of the treatment regimen for the subject. Similarly, rates of change of marker levels can be important in a subject who is not subject to active treatment for prostate cancer (e.g., watchful waiting). Changes, or not, in marker levels may be more relevant to treatment decisions for the subject than marker levels present in the

population. Rapid changes in marker levels in a subject who otherwise appears to have a normal prostate may be indicative of an abnormal prostate state, even if the markers are within normal ranges for the population.

As an alternative to making determinations based on the absolute expression level of the marker, determinations may be based on the normalized expression level of the marker. Expression levels are normalized by correcting the absolute expression level of a marker by comparing its expression to the expression of a gene that is not a marker, e.g., a housekeeping gene that is constitutively expressed. Suitable genes for normalization include housekeeping genes such as the actin gene, or epithelial cell-specific genes. This normalization allows the comparison of the expression level in one sample, e.g., a patient sample, to another sample, e.g., a non-cancer sample, or between samples from different sources.

Alternatively, the expression level can be provided as a relative expression level as compared to an appropriate control, e.g., population control, adjacent normal tissue control, earlier time point control, etc.. Preferably, the samples used in the baseline determination will be from non-cancer cells. The choice of the cell source is dependent on the use of the relative expression level. Using expression found in normal tissues as a mean expression score aids in validating whether the marker assayed is cancer specific (versus normal cells). In addition, as more data is accumulated, the mean expression value can be revised, providing improved relative expression values based on accumulated data. Expression data from cancer cells provides a means for grading the severity of the cancer state.

5. DIAGNOSTIC, PROGNOSTIC, AND TREATMENT METHODS

The invention provides methods for detecting an abnormal prostate state in a subject by

(1) contacting a biological sample from a subject with a panel of one or more detection reagents wherein each detection reagent is specific for one prostate-cancer related protein; wherein the prostate-cancer related proteins are selected from the prostate-cancer related protein set as follows: filamin A alone or filamin A in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 ;

(2) measuring the amount of each prostate-cancer related marker detected in the biological sample by each detection reagent; and

(3) comparing the level of expression of the one or more prostate-cancer related protein in the biological sample obtained from the subject with a level of expression of the one or more prostate-cancer related protein in a control sample, thereby detecting an abnormal prostate state.

In certain embodiments, detecting an abnormal prostate state comprises diagnosing prostate cancer status in a subject. In certain embodiments, an abnormal prostate state comprises identifying a predisposition to developing prostate cancer.

The invention provides methods for monitoring the treatment of prostate cancer in a subject by

(1) contacting a first biological sample obtained from the subject prior to administering at least a portion of a treatment regimen to the subject with a panel of one or more detection reagents wherein each detection reagent is specific for one prostate-cancer related protein; wherein the prostate-cancer related proteins are selected from the prostate protein set as follows: filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 ;

(2) contacting a second biological sample obtained from the subject after administering at least a portion of a treatment regimen to the subject with a panel of one or more detection reagents wherein each detection reagent is specific for one prostate-cancer related protein; wherein the prostate-cancer related proteins are selected from the prostate protein set as follows: filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 ;

(3) measuring the amount of prostate-cancer related marker detected in each the first biological sample and the second biological sample by each detection reagent; and

(4) comparing the level of expression of the one or more prostate-cancer related markers in the first sample with the expression level of the one or more prostate-cancer related markers in the second sample, thereby monitoring the treatment of prostate cancer in the subject.

The invention provides method of selecting for administration of active treatment or against administration of active treatment of prostate cancer in a subject by

(1) contacting a first biological sample obtained from the subject prior to administering a treatment regimen to the subject with a panel of one or more detection reagents wherein each detection reagent is specific for one prostate-cancer related protein; wherein the prostate-cancer related proteins are selected from the prostate protein set as follows: filamin A alone or in combination with prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 ;

(2) contacting a second biological sample obtained from the subject prior to administering a treatment regimen to the subject with a panel of one or more detection reagents wherein each detection reagent is specific for one prostate-cancer related protein; wherein the prostate-cancer related proteins are selected from the prostate protein set as follows: filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1;

(3) measuring the amount of prostate-cancer related marker detected in each the first biological sample and the second biological sample by each detection reagent; and

(4) comparing the level of expression of the one or more prostate-cancer related markers in the first sample with the expression level of the one or more prostate-cancer related markers in the second sample, wherein selecting for administration of active treatment or against administration of active treatment of prostate cancer is based on the presence or absence of changes in the level of expression of one or more markers between the first sample and the second sample.

In certain embodiments of the diagnostic and monitoring methods provided herein, one or more prostate-cancer related markers is two or more markers. In certain embodiments of the diagnostic and monitoring methods provided herein, one or more prostate-cancer related markers is three or more markers. In certain embodiments of the diagnostic and monitoring methods provided herein, one or more prostate-cancer related markers is four or more markers. In certain embodiments of the diagnostic and monitoring methods provided herein, one or more prostate-cancer related markers is five or more markers. In certain embodiments of the diagnostic and monitoring methods provided herein, one or more prostate-cancer related markers is six or more markers. In certain embodiments of the diagnostic and monitoring methods provided herein, one or more prostate-cancer related markers is seven or more markers. In certain embodiments of the diagnostic and monitoring methods provided herein, one or more prostate-cancer related markers is eight or more markers. In certain embodiments of the diagnostic and monitoring methods provided herein, one or more prostate-cancer related markers is nine or more markers.

In certain embodiments of the diagnostic methods provided herein, an increase in the level of expression of one or more prostate-cancer related markers selected from the group consisting of filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 in the biological sample as compared to the level of expression of the one or more prostate-cancer related markers in a normal control sample is an indication that the subject is afflicted with prostate cancer. In certain embodiments of the diagnostic methods provided herein, no increase in the detected expression level of filamin A or one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 in the biological sample as compared to the expression level in a normal control sample is an indication that the subject is not afflicted with prostate cancer or not predisposed to developing prostate cancer. In one embodiment, the age of the patient is also determined and used as a predictor variable. For example, increased patient age is an indication that the subject is afflicted with prostate cancer or is predisposed to developing prostate cancer.

In certain embodiments of the diagnostic methods provided herein, an increase in the level of expression of one or more prostate-cancer related markers selected from the group consisting of

filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 in the biological sample as compared to the level of expression of the one or more prostate-cancer related markers in a normal control sample is an indication that the subject is predisposed to developing prostate cancer. In one embodiment, the age of the patient is also determined and used as a predictor variable. For example, increased patient age is an indication that the subject is afflicted with prostate cancer or is predisposed to developing prostate cancer.

In certain embodiments of the monitoring methods provided herein, no increase in the detected level of expression of any of the one or more prostate-cancer related markers selected from the group consisting of filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 in the second sample as compared to the level of expression of the one or more prostate-cancer related markers in the first sample is an indication that the therapy is efficacious for treating prostate cancer in the subject. In certain embodiments the monitoring methods provided herein, further comprise comparing the level of expression of one or more prostate-cancer related markers selected from the group consisting of filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 in the first sample or the level of expression of one or more prostate-cancer related markers selected from the group consisting of filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 in the second sample with the expression of the one or more prostate-cancer related markers in a control sample.

In certain embodiments of the monitoring methods provided herein, an increase in the level of expression of the one or more prostate-cancer related markers selected from the group consisting of filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 in the second sample as compared to the level of expression of the one or more prostate-cancer related markers in the first sample is an indication for selection of active treatment of prostate cancer in the subject. In certain embodiments of the monitoring methods provided herein, no increase in the detected level of expression of any of the one or more prostate-cancer related markers selected from the group consisting of filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 in the second sample as compared to the level of expression of the one or more

prostate-cancer related markers in the first sample is an indication against selection of active treatment of prostate cancer in the subject. In certain embodiments of the monitoring methods provided herein, wherein an increased expression level of filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 in the second sample as compared to the expression level in the first sample is an indication that the therapy is not efficacious in the treatment of prostate cancer.

In certain embodiments of the diagnostic and monitoring methods provided herein, the one or more prostate-cancer related markers is selected from the group of filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1. In certain embodiments of the diagnostic and monitoring methods provided herein, the one or more prostate-cancer related markers comprise at least keratin 7, keratin 8, and keratin 15. In certain embodiments of the diagnostic and monitoring methods provided herein, the one or more prostate-cancer related markers is selected from the group of keratin 7, keratin 15, and keratin 19. In certain embodiments of the diagnostic and monitoring methods provided herein, the one or more prostate-cancer related markers comprise at least keratin 7 or keratin 15. In certain embodiments of the diagnostic and monitoring methods provided herein, the one or more prostate-cancer related markers comprise at least keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the biological sample is compared to the level of the one or more prostate-cancer related markers in a normal control sample is indicative of a modulation in prostate cancer status.

In certain embodiments of the monitoring methods provided herein, modulation of the level of expression of the one or more prostate-cancer related markers selected from the group consisting of filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 in the second sample as compared to the level of expression of the corresponding marker(s) in the first sample is indicative of a change in prostate cancer status in response to treatment of the prostate cancer in the subject. In certain embodiments of the monitoring methods provided herein, the methods further comprise comparing the level of expression of one or more prostate-cancer related markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the first sample; or the level of expression of one or more prostate-cancer related markers selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the second sample to the level of expression of one or more prostate-cancer related markers in a normal control sample.

In any of the aforementioned embodiments, the methods may also include a step of determining whether a subject having prostate cancer or who is being treated for prostate cancer is responsive to a particular treatment. Such a step can include, for example, measuring the level of

expression of one or more prostate-cancer related markers selected from the group consisting of filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 prior to administering an anti-prostate cancer treatment, and measuring the level of expression of one or more prostate-cancer related markers selected from the group consisting of filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 after administering the anti-prostate cancer treatment, and comparing the expression level before and after treatment. Determining that the prostate cancer is responsive to the treatment if the expression level of the one or more markers is lower than before treatment as compared to after treatment. The method may further include the step of adjusting the treatment to a higher dose in order to increase the responsiveness to the treatment, or adjusting the treatment to a lower dose in order to decrease the responsiveness to the treatment.

In any of the aforementioned embodiments, the methods may also include a step of determining whether a subject having prostate cancer or who is being treated for prostate cancer is responsive to a particular treatment. Such a step can include, for example, measuring the level of expression of one or more prostate-cancer related markers selected from the group consisting of filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 prior to administering an anti-prostate cancer treatment, and measuring the level of expression of one or more prostate-cancer related markers selected from the group consisting of filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 after administering the anti-prostate cancer treatment, and comparing the expression level before and after treatment. Determining that the prostate cancer is responsive to the treatment if the expression level of the one or more markers is higher than before treatment as compared to after treatment. The method may further include the step of adjusting the treatment to a higher dose in order to increase the responsiveness to the treatment, or adjusting the treatment to a lower dose in order to decrease the responsiveness to the treatment.

In any of the aforementioned embodiments, the methods may also include a step of determining whether a subject having prostate cancer or who is being treated for prostate cancer is not responsive to a particular treatment. Such a step can include, for example, measuring the level of expression of one or more prostate-cancer related markers selected from the group consisting of filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA,

TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 prior to administering an anti-prostate cancer treatment, and measuring the level of expression of one or more prostate-cancer related markers selected from the group consisting of filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 after administering the anti-prostate cancer treatment, and comparing the expression level before and after treatment. Determining that the prostate cancer is not responsive to the treatment if the expression level of the one or more markers is lower than before treatment as compared to after treatment. The method may further include the step of adjusting the treatment to a higher dose in order to increase the responsiveness to the treatment.

In any of the aforementioned embodiments, the methods may also include a step of determining whether a subject having prostate cancer or who is being treated for prostate cancer is not responsive to a particular treatment. Such a step can include, for example, measuring the level of expression of one or more prostate-cancer related markers selected from the group consisting of filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 prior to administering an anti-prostate cancer treatment, and measuring the level of expression of one or more prostate-cancer related markers selected from the group consisting of filamin A alone or in combination with one or more of prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1 after administering the anti-prostate cancer treatment, and comparing the expression level before and after treatment. Determining that the prostate cancer is not responsive to the treatment if the expression level of the one or more markers is higher than before treatment as compared to after treatment. The method may further include the step of adjusting the treatment to a higher dose in order to increase the responsiveness to the treatment.

In certain embodiments the diagnostic methods provided herein further comprise detecting the level of expression of prostate specific antigen (PSA) in the biological sample and preferably further comprise comparing the level of expression of PSA in the biological sample to a PSA expression level in a normal control sample. In certain embodiments, the combination of PSA level with one or more of the prostate-cancer maker levels increases the predictive value of the method.

In certain embodiments the monitoring methods provided herein further comprise detecting the level of expression of prostate specific antigen (PSA) in the first sample and the second sample, and preferably further comprising comparing the level of expression of PSA in the first sample with the level of expression of PSA in the second sample. In certain monitoring methods, the change in PSA level in combination with the change in prostate-cancer maker level increases the predictive value of the method.

In certain embodiments the diagnostic and monitoring methods provided herein further comprise comparing the detected level of the one or more prostate markers in the biological samples with one or more control samples wherein the control sample is one or more of a sample from the same subject at an earlier time point than the biological sample, a sample from a subject with benign prostatic hyperplasia (BPH), a sample from a subject with non-metastatic prostate cancer, a sample from a subject with metastatic prostate cancer, a sample from a subject with androgen sensitive prostate cancer, a sample from a subject with androgen insensitive prostate cancer, a sample from a subject with aggressive prostate cancer, and sample obtained from a subject with non-aggressive prostate cancer. Comparison of the marker levels in the biological samples with control samples from subjects with various normal and abnormal prostate states facilitates the differentiation between various prostate states including normal prostate and prostate cancer, benign prostate hyperplasia and prostate cancer, benign prostate hyperplasia and normal prostate, androgen dependent and androgen independent prostate cancer, aggressive prostate cancer and non-aggressive prostate cancer, aggressive prostate cancer and non-aggressive prostate cancer, or between any two or more prostate states including normal prostate, prostate cancer, benign prostate hyperplasia, androgen dependent prostate cancer, androgen independent prostate cancer, aggressive prostate cancer, non-aggressive prostate cancer, metastatic prostate cancer, and non-metastatic prostate cancer.

In certain embodiments the diagnostic and monitoring methods provided herein further comprising detecting the size of the prostate tumor in the subject. In certain embodiments the monitoring methods provided herein further comprise detecting a change in the size or relative aggressiveness of the tumor. In certain embodiments, the size of the prostate tumor in the subject is detected prior to administering the at least a portion of a treatment regimen to the subject. In certain embodiments, the size of the prostate tumor in the subject is detected after administering the at least a portion of a treatment regimen to the subject. Certain monitoring methods, further comprise comparing the size of the prostate tumor in the subject prior to administering the at least a portion of a treatment regimen to the subject to the size of the prostate tumor in the subject after administering the at least a portion of a treatment regimen to the subject. Certain other embodiments of the diagnostic and monitoring methods further comprise determining the particular stage or grade of prostate cancer, e.g., Gleason grade 1, grade 2, grade 3, grade 4, or grade 5 prostate cancer or TNM classifications. In other embodiments, the present invention also involves the analysis and consideration of any clinical and/or patient-related health data, for example, data obtained from an Electronic Medical Record (e.g., collection of electronic health information about individual patients or populations relating to various types of data, such as, demographics, medical history, medication and allergies, immunization status, laboratory test results, radiology images, vital signs, personal statistics like age and weight, and billing information).

In certain embodiments the diagnostic and monitoring methods provided herein further comprising obtaining a subject sample.

In certain embodiments the diagnostic and monitoring methods provided herein further comprising selecting a treatment regimen for the subject based on the level of expression of one or more of the prostate-cancer related markers selected from the group consisting of filamin A alone or filamin A in combination with one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1.

In certain embodiments the diagnostic and monitoring methods provided herein further comprise selecting a subject for having or being suspected of having prostate cancer.

In certain embodiments the diagnostic and monitoring methods provided herein further comprising treating the subject with a regimen including one or more treatments selected from the group consisting of surgery, radiation, hormone therapy, antibody therapy, therapy with growth factors, cytokines, and chemotherapy.

In certain embodiments the diagnostic and monitoring methods provided herein further comprise selecting the one or more specific treatment regimens for the subject based on the results of the diagnostic and monitoring methods provided herein. In one embodiment, a treatment regimen known to be effective against prostate cancer having the biomarker signature detected in the subject/sample is selected for the subject. In certain embodiments, the treatment method is started, change, revised, or maintained based on the results from the diagnostic or prognostic methods of the invention, e.g., when it is determined that the subject is responding to the treatment regimen, or when it is determined that the subject is not responding to the treatment regimen, or when it is determined that the subject is insufficiently responding to the treatment regimen. In certain embodiments, the treatment method is changed based on the results from the diagnostic or prognostic methods.

In certain other embodiments the diagnostic and monitoring methods provided herein further comprise introducing one or more specific treatment regimens for the subject based on the results of the diagnostic and monitoring methods provided herein. In one embodiment, a treatment regimen known to be effective against prostate cancer is selected for the subject. In certain embodiments, the treatment method is started, change, revised, or maintained based on the results from the diagnostic or prognostic methods of the invention, e.g., when it is determined that the subject is responding to the treatment regimen, or when it is determined that the subject is not responding to the treatment regimen, or when it is determined that the subject is insufficiently responding to the treatment regimen. In certain embodiments, the treatment method is changed based on the results from the diagnostic or prognostic methods.

In yet other embodiments the diagnostic and monitoring methods provided herein further comprise the step of administering a therapeutically effective amount of an anti-prostate cancer therapy based on the results of the diagnostic and monitoring methods provided herein. In one embodiment, a treatment regimen known to be effective against prostate cancer is selected for the subject. In certain embodiments, the treatment method is administered based on the results from the diagnostic or prognostic methods of the invention, e.g., when it is determined that the subject

expresses one or more biomarkers of the invention (e.g., filamin A alone or filamin A in combination with one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1) above some threshold level that is indicative of prostate cancer.

In yet other embodiments the diagnostic and monitoring methods provided herein further comprise the step of administering a therapeutically effective amount of an anti-prostate cancer therapy based on the results of the diagnostic and monitoring methods provided herein. In one embodiment, a treatment regimen known to be effective against prostate cancer is selected for the subject. In certain embodiments, the treatment method is administered based on the results from the diagnostic or prognostic methods of the invention, e.g., when it is determined that the subject expresses one or more biomarkers of the invention (e.g., filamin A alone or filamin A in combination with one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1) below some threshold level that is indicative of prostate cancer.

In yet other embodiments the diagnostic and monitoring methods provided herein further comprise the step of increasing, decreasing, or changing the dose of an anti-prostate cancer therapy based on the results of the diagnostic and monitoring methods provided herein. In one embodiment, a treatment regimen known to be effective against prostate cancer is selected for the subject. In certain embodiments, the treatment method is administered based on the results from the diagnostic or prognostic methods of the invention, e.g., when it is determined that the subject expresses one or more biomarkers of the invention (e.g., filamin A alone or filamin A in combination with one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1) above some threshold level that is indicative of prostate cancer.

In yet other embodiments the diagnostic and monitoring methods provided herein further comprise the step of increasing, decreasing, or changing the dose of an anti-prostate cancer therapy based on the results of the diagnostic and monitoring methods provided herein. In one embodiment, a treatment regimen known to be effective against prostate cancer is selected for the subject. In certain embodiments, the treatment method is administered based on the results from the diagnostic or prognostic methods of the invention, e.g., when it is determined that the subject expresses one or more biomarkers of the invention (e.g., filamin A alone or filamin A in combination with one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1) below some threshold level that is indicative of prostate cancer.

In certain embodiments, a change in the treatment regimen comprises changing a hormone based therapy treatment. In certain embodiments, treatments for prostate cancer include one or more of surgery, radiation, hormone therapy, antibody therapy, therapy with growth factors, cytokines, or

chemotherapy based on the results of a method of any one of claims 1-64 for an interval prior to performing a subsequent diagnostic, prognostic, or monitoring method provided herein.

In certain embodiments of the diagnostic and monitoring methods provided herein, the method further comprises isolating a component of the biological sample.

In certain embodiments of the diagnostic and monitoring methods provided herein, the method further comprises labeling a component of the biological sample.

In certain embodiments of the diagnostic and monitoring methods provided herein, the method further comprises amplifying a component of a biological sample.

In certain embodiments of the diagnostic and monitoring methods provided herein, the method comprises forming a complex with a probe and a component of a biological sample. In certain embodiments, forming a complex with a probe comprises forming a complex with at least one non-naturally occurring reagent. In certain embodiments of the diagnostic and monitoring methods provided herein, the method comprises processing the biological sample. In certain embodiments of the diagnostic and monitoring methods provided herein, the method of detecting a level of at least two markers comprises a panel of markers. In certain embodiments of the diagnostic and monitoring methods provided herein, the method of detecting a level comprises attaching the marker to be detected to a solid surface.

The invention provides methods of selecting for administration of active treatment or against administration of active treatment of prostate cancer in a subject comprising:

(1) detecting a level of one or more markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta in a first sample obtained from the subject having prostate cancer at a first time wherein the subject has not been actively treated for prostate cancer;

(2) detecting a level of one or more markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 in a second sample obtained from the subject at a second time, e.g., wherein the subject has not been actively treated;

(3) comparing the level of one or more markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 in the first sample with the level of one or more markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 in the second sample;

wherein selecting for administration of active treatment or against administration of active treatment of prostate cancer is based on the presence or absence of changes in the level of expression of one or more markers between the first sample and the second sample.

In certain embodiments, the method further comprising obtaining a third sample obtained from the subject at a third time (e.g., wherein the subject has not been actively treated), detecting a

level of one or more markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 in the third sample, and comparing the level of one or more markers selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 in the third sample with the level of the one or more markers in the first sample and/or the one or more markers in the second sample.

In certain embodiments, an increased level of filamin A alone or filamin A in combination with one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, in the second sample as compared to the level of the markers in the first sample is an indication that the therapy is not efficacious in the treatment of prostate cancer.

In certain embodiments, an increased level of filamin A alone or filamin A in combination with one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, in the second sample as compared to the level of the markers in the first sample is an indication for selecting active treatment for prostate cancer.

In certain embodiments, the method further comprises comparing the level of one or more markers selected from the group consisting of filamin A alone or filamin A in combination with one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, in the first sample or the level of one or more markers selected from the group consisting of filamin A alone or filamin A in combination with one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, in the second sample with the level of one or more of filamin A alone or filamin A in combination with one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, in a control sample. In certain embodiments, the method comprises detecting the level of filamin A in combination with one or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the first sample; detecting the level of filamin A in combination with one or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the second sample; and comparing the level of filamin A in combination with one or more of one or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the second sample with the one or more of the level of filamin A in combination with keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in the first sample. In certain embodiments, the method comprises detection of a subset of keratins such as keratin 7, keratin 8, and keratin 15; keratin 7, 15, and 19 in combination with filamin A; and keratin 7 or keratin 15. In certain embodiments, the method further comprises comparing the level of one or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in combination with

filamin A in the first sample; or the level of expression of one or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in combination with filamin A in the second sample to the level of one or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, and tubulin beta-3 in combination with filamin A in a control sample.

In certain embodiments, no change in the level of expression of one or more markers selected from the group consisting of filamin A alone or filamin A in combination with one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, between the first sample and the second sample is an indication for selecting against active treatment for prostate cancer.

In certain embodiments, the methods further comprise detecting the level of prostate specific antigen (PSA) in the first sample and the second sample, and then preferably further comprising comparing the level of PSA in the first sample with the level of PSA in the second sample.

In certain embodiments, a decrease in the level of one or more of filamin A alone or filamin A in combination with one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, in the second sample as compared to the level of one or more of filamin A alone or filamin A in combination with one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, in the first sample in combination with a decrease in the level of PSA in the second sample as compared to the level of PSA in the first sample has greater predictive value that the therapy is efficacious in treating prostate cancer in the subject than analysis of a single marker alone.

In certain embodiments, a decrease in the level of one or more of filamin A alone or filamin A in combination with one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, in the second sample as compared to the level of one or more of filamin A alone or filamin A in combination with one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1, in the first sample in combination with a decrease in the level of expression of PSA in the second sample as compared to the level of PSA in the first sample has greater predictive value for selecting against active treatment for prostate cancer than analysis of a single marker alone.

6. MONITORING CLINICAL TRIALS

Monitoring the influence of agents (*e.g.*, drug compounds) on the level of expression of a marker of the invention can be applied not only in basic drug screening or monitoring the treatment of a single subject, but also in clinical trials. For example, the effectiveness of an agent to affect marker expression can be monitored in clinical trials of subjects receiving treatment for an oncological disorder. In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (*e.g.*, an agonist, antagonist, peptidomimetic,

protein, peptide, nucleic acid, small molecule, or other drug candidate) comprising the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of one or more selected markers of the invention (e.g., filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, optionally in combination with PSA) in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression of the marker(s) in the post-administration samples; (v) comparing the level of expression of the marker(s) in the pre-administration sample with the level of expression of the marker(s) in the post-administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased expression of the marker gene(s) during the course of treatment may indicate ineffective dosage and the desirability of increasing the dosage. Conversely, decreased expression of the marker gene(s) may indicate efficacious treatment and no need to change dosage.

H.. TREATMENT/THERAPEUTICS

The present invention provides methods for use of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of filamin A, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9) to treat disease states in a subject, *e.g.*, a mammal, *e.g.*, a human.

The present invention also provides methods for treatment of a subject with prostate cancer with a therapeutic, *e.g.*, a nucleic acid based therapeutic, that modulates (*e.g.*, reduces, or increases, and preferably reduces) the expression or activity of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of filamin A alone or filamin A in combination with one or more of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, PSM, PSCA, TMPRSS2, PDEF, HPG-1, PCA3, and PCGEM1.

The invention also provides methods for selection and/or administration of known treatment agents, especially hormone based therapies vs. non-hormone based therapies, and aggressive or active treatment vs. “watchful waiting”, depending on the detection of a change in the level of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, or 9) markers selected from the group consisting of filamin A, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B (FLNB), and lymphocyte antigen 9 (LY9), as compared to a control. The selection of treatment regimens can further include the detection of PSA to assist in selection of the therapeutic methods. Selection of treatment methods can also include other diagnostic considerations and patient characteristics including results from imaging studies, tumor size or growth rates, risk of poor outcomes, disruption of daily activities, and age, Gleason scores (e.g., grade 1, grade 2, grade 3, grade 4, or grade 5 prostate cancer), TNM classifications, clinical and/or patient-related health data (e.g., data obtained from an Electronic Medical Record (e.g., collection of electronic health information about individual patients or populations relating to various types of data, such as, demographics, medical history, medication

and allergies, immunization status, laboratory test results, radiology images, vital signs, personal statistics like age and weight, and billing information).

As used herein, the term “aggressive oncological disorder”, such as aggressive prostate cancer, refers to an oncological disorder involving a fast-growing tumor. An aggressive oncological disorder typically does not respond, responds poorly, or loses response to therapeutic treatment. For example, an prostate cancer may be considered to become an aggressive prostate cancer upon loss of response to hormone therapy, necessitating treatment with chemotherapy, surgery, and/or radiation. As used herein, an aggressive prostate cancer, for example, is one that will likely or has metastasized. As used herein, an aggressive prostate cancer is one that will result in significant changes in quality of life as the tumor grows. Active treatment is therapeutically indicated for an aggressive oncological disorder, e.g., aggressive prostate cancer.

As used herein, the term “non-aggressive oncological disorder” such as a non-aggressive prostate cancer, refers to an oncological disorder involving a slow-growing tumor. A non-aggressive oncological disorder typically responds favorably or moderately to therapeutic treatment or grows so slowly that immediate treatment is not warranted. A non-aggressive prostate tumor is one that a person skilled in the art, e.g., an oncologist, may decide to not actively treat with routine interventions for the treatment of cancer, e.g., chemotherapy, radiation, surgery, as the active treatment may do more harm than the disease, particularly in an older subject. A non-aggressive prostate tumor is one that a person skilled in the art may decide to monitor with “watchful waiting” rather than subjecting the person to any active therapeutic interventions to alter the presence or growth of the tumor (e.g., radiation, surgery, chemotherapy, hormone therapy).

1. NUCLEIC ACID THERAPEUTICS

Nucleic acid therapeutics are well known in the art. Nucleic acid therapeutics include both single stranded and double stranded (i.e., nucleic acid therapeutics having a complementary region of at least 15 nucleotides in length that may be one or two nucleic acid strands) nucleic acids that are complementary to a target sequence in a cell. Nucleic acid therapeutics can be delivered to a cell in culture, e.g., by adding the nucleic acid to culture media either alone or with an agent to promote uptake of the nucleic acid into the cell. Nucleic acid therapeutics can be delivered to a cell in a subject, i.e., in vivo, by any route of administration. The specific formulation will depend on the route of administration.

As used herein, and unless otherwise indicated, the term “complementary,” when used to describe a first nucleotide sequence in relation to a second nucleotide sequence, refers to the ability of an oligonucleotide or polynucleotide comprising the first nucleotide sequence to hybridize and form a duplex structure under certain conditions with an oligonucleotide or polynucleotide comprising the second nucleotide sequence, as will be understood by the skilled person. Such conditions can, for example, be stringent conditions, where stringent conditions may include: 400 mM NaCl, 40 mM

PIPES pH 6.4, 1 mM EDTA, 50°C or 70°C for 12-16 hours followed by washing. Other conditions, such as physiologically relevant conditions as may be encountered inside an organism, can apply. The skilled person will be able to determine the set of conditions most appropriate for a test of complementarity of two sequences in accordance with the ultimate application of the hybridized nucleotides.

Sequences can be “fully complementary” with respect to each when there is base-pairing of the nucleotides of the first nucleotide sequence with the nucleotides of the second nucleotide sequence over the entire length of the first and second nucleotide sequences. However, where a first sequence is referred to as “substantially complementary” with respect to a second sequence herein, the two sequences can be fully complementary, or they may form one or more, but generally not more than 4, 3 or 2 mismatched base pairs upon hybridization, while retaining the ability to hybridize under the conditions most relevant to their ultimate application. However, where two oligonucleotides are designed to form, upon hybridization, one or more single stranded overhangs as is common in double stranded nucleic acid therapeutics, such overhangs shall not be regarded as mismatches with regard to the determination of complementarity. For example, a dsRNA comprising one oligonucleotide 21 nucleotides in length and another oligonucleotide 23 nucleotides in length, wherein the longer oligonucleotide comprises a sequence of 21 nucleotides that is fully complementary to the shorter oligonucleotide, may yet be referred to as “fully complementary” for the purposes described herein.

“Complementary” sequences, as used herein, may also include, or be formed entirely from, non-Watson-Crick base pairs and/or base pairs formed from non-natural and modified nucleotides, in as far as the above requirements with respect to their ability to hybridize are fulfilled. Such non-Watson-Crick base pairs includes, but not limited to, G:U Wobble or Hoogsteen base pairing.

The terms “complementary,” “fully complementary,” and “substantially complementary” herein may be used with respect to the base matching between the sense strand and the antisense strand of a dsRNA, or between an antisense nucleic acid or the antisense strand of dsRNA and a target sequence, as will be understood from the context of their use.

As used herein, a polynucleotide that is “substantially complementary to at least part of” a messenger RNA (mRNA) refers to a polynucleotide that is substantially complementary to a contiguous portion of the mRNA of interest (*e.g.*, an mRNA encoding filamin B, LY9, a keratin, tubulin-beta 3, or PSA) including a 5' UTR, an open reading frame (ORF), or a 3' UTR. For example, a polynucleotide is complementary to at least a part of filamin B, LY9, a keratin, tubulin-beta 3, or PSA mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding filamin B, LY9, a keratin, tubulin-beta 3, or PSA.

Nucleic acid therapeutics typically include chemical modifications to improve their stability and to modulate their pharmacokinetic and pharmacodynamic properties. For example, the modifications on the nucleotides can include, but are not limited to, LNA, HNA, CeNA, 2'-hydroxyl, and combinations thereof.

Nucleic acid therapeutics may further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage. The phosphorothioate or methylphosphonate internucleotide linkage modification may occur on any nucleotide of the sense strand or antisense strand or both (in nucleic acid therapeutics including a sense strand) in any position of the strand. For instance, the internucleotide linkage modification may occur on every nucleotide on the sense strand or antisense strand; each internucleotide linkage modification may occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand may contain both internucleotide linkage modifications in an alternating pattern. The alternating pattern of the internucleotide linkage modification on the sense strand may be the same or different from the antisense strand, and the alternating pattern of the internucleotide linkage modification on the sense strand may have a shift relative to the alternating pattern of the internucleotide linkage modification on the antisense strand.

A. SINGLE STRANDED THERAPEUTICS

Antisense nucleic acid therapeutic agent single stranded nucleic acid therapeutics, typically about 16 to 30 nucleotides in length and are complementary to a target nucleic acid sequence in the target cell, either in culture or in an organism.

Patents directed to antisense nucleic acids, chemical modifications, and therapeutic uses are provided, for example, in U.S. Patent No. 5,898,031 related to chemically modified RNA-containing therapeutic compounds, and U.S. Patent No. 6,107,094 related methods of using these compounds as therapeutic agent. U.S. Patent No. 7,432,250 related to methods of treating patients by administering single-stranded chemically modified RNA-like compounds; and U.S. Patent No. 7,432,249 related to pharmaceutical compositions containing single-stranded chemically modified RNA-like compounds. U.S. Patent No. 7,629,321 is related to methods of cleaving target mRNA using a single-stranded oligonucleotide having a plurality RNA nucleosides and at least one chemical modification. Each of the patents listed in the paragraph are incorporated herein by reference.

B. DOUBLE STRANDED THERAPEUTICS

In many embodiments, the duplex region is 15-30 nucleotide pairs in length. In some embodiments, the duplex region is 17-23 nucleotide pairs in length, 17-25 nucleotide pairs in length, 23-27 nucleotide pairs in length, 19-21 nucleotide pairs in length, or 21-23 nucleotide pairs in length.

In certain embodiments, each strand has 15-30 nucleotides.

The RNAi agents that are used in the methods of the invention include agents with chemical modifications as disclosed, for example, in Publications WO 2009/073809 and WO/2012/037254, the entire contents of each of which are incorporated herein by reference.

Nucleic acid therapeutic agents for use in the methods of the invention also include double stranded nucleic acid therapeutics. An "RNAi agent," "double stranded RNAi agent," double-

stranded RNA (dsRNA) molecule, also referred to as “dsRNA agent,” “dsRNA,” “siRNA,” “iRNA agent,” as used interchangeably herein, refers to a complex of ribonucleic acid molecules, having a duplex structure comprising two anti-parallel and substantially complementary, as defined below, nucleic acid strands. As used herein, an RNAi agent can also include dsRNA (see, e.g., US Patent publication 20070104688, incorporated herein by reference). In general, the majority of nucleotides of each strand are ribonucleotides, but as described herein, each or both strands can also include one or more non-ribonucleotides, e.g., a deoxyribonucleotide and/or a modified nucleotide. In addition, as used in this specification, an “RNAi agent” may include ribonucleotides with chemical modifications; an RNAi agent may include substantial modifications at multiple nucleotides. Such modifications may include all types of modifications disclosed herein or known in the art. Any such modifications, as used in a siRNA type molecule, are encompassed by “RNAi agent” for the purposes of this specification and claims. The RNAi agents that are used in the methods of the invention include agents with chemical modifications as disclosed, for example, in U.S. Provisional Application No. 61/561,710, filed on November 18, 2011, International Application No. PCT/US2011/051597, filed on September 15, 2010, and PCT Publication WO 2009/073809, the entire contents of each of which are incorporated herein by reference. The two strands forming the duplex structure may be different portions of one larger RNA molecule, or they may be separate RNA molecules. Where the two strands are part of one larger molecule, and therefore are connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting RNA chain is referred to as a “hairpin loop.” Where the two strands are connected covalently by means other than an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting structure is referred to as a “linker.” The RNA strands may have the same or a different number of nucleotides. The maximum number of base pairs is the number of nucleotides in the shortest strand of the dsRNA minus any overhangs that are present in the duplex. In addition to the duplex structure, an RNAi agent may comprise one or more nucleotide overhangs. The term “siRNA” is also used herein to refer to an RNAi agent as described above.

In another aspect, the agent is a single-stranded antisense RNA molecule. An antisense RNA molecule is complementary to a sequence within the target mRNA. Antisense RNA can inhibit translation in a stoichiometric manner by base pairing to the mRNA and physically obstructing the translation machinery, see Dias, N. *et al.*, (2002) *Mol Cancer Ther* 1:347-355. The antisense RNA molecule may have about 15-30 nucleotides that are complementary to the target mRNA. For example, the antisense RNA molecule may have a sequence of at least 15, 16, 17, 18, 19, 20 or more contiguous nucleotides complementary to the filamin B or LY9 sequences provided herein.

The term “antisense strand” refers to the strand of a double stranded RNAi agent which includes a region that is substantially complementary to a target sequence (e.g., a human TTR mRNA). As used herein, the term “region complementary to part of an mRNA encoding

transthyretin” refers to a region on the antisense strand that is substantially complementary to part of a TTR mRNA sequence. Where the region of complementarity is not fully complementary to the target sequence, the mismatches are most tolerated in the terminal regions and, if present, are generally in a terminal region or regions, *e.g.*, within 6, 5, 4, 3, or 2 nucleotides of the 5’ and/or 3’ terminus.

The term “sense strand,” as used herein, refers to the strand of a dsRNA that includes a region that is substantially complementary to a region of the antisense strand.

The invention also includes molecular beacon nucleic acids having at least one region which is complementary to a nucleic acid of the invention, such that the molecular beacon is useful for quantitating the presence of the nucleic acid of the invention in a sample. A “molecular beacon” nucleic acid is a nucleic acid comprising a pair of complementary regions and having a fluorophore and a fluorescent quencher associated therewith. The fluorophore and quencher are associated with different portions of the nucleic acid in such an orientation that when the complementary regions are annealed with one another, fluorescence of the fluorophore is quenched by the quencher. When the complementary regions of the nucleic acid are not annealed with one another, fluorescence of the fluorophore is quenched to a lesser degree. Molecular beacon nucleic acids are described, for example, in U.S. Patent 5,876,930.

I. DRUG SCREENING

As noted above, sets of biomarkers whose expression levels correlate with one or more selected prostate disease characteristics (*e.g.*, prostate cancer progression) are attractive targets for identification of new therapeutic agents via screens to detect compounds or entities that inhibit or enhance expression of these biomarker genes and/or their products. Accordingly, the present invention provides methods for the identification of compounds potentially useful for modulating prostate cancer progression. In particular, the present invention provides methods for the identification of compounds potentially useful for modulating prostate cancer progression wherein the compounds modulate (*e.g.*, increase or decrease, preferably decrease or inhibit) the expression of filamin A, and/or filamin A in combination with other biomarkers, including prostate specific antigen (PSA), filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, kerton 18, keratin 19, and tubulin-beta 3.

Such assays typically comprise a reaction between a marker of the invention and one or more assay components. The other components may be either the test compound itself, or a combination of test compounds and a natural binding partner of a marker of the invention. Compounds identified *via* assays such as those described herein may be useful, for example, for modulating, *e.g.*, inhibiting, ameliorating, treating, or preventing the disease. Compounds identified for modulating the expression level of one or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B, or LY9; optionally in combination with PSA, are preferably further tested for activity

useful in the treatment of cancer, preferably prostate cancer, e.g., inhibiting tumor cell growth, inhibiting tumor angiogenesis, inducing tumor cell apoptosis, etc.

The test compounds used in the screening assays of the present invention may be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. Test compounds may also be obtained by any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive; see, *e.g.*, Zuckermann *et al.*, 1994, *J. Med. Chem.* 37:2678-85); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library and peptoid library approaches are limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, 1997, *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994). *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carrell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

Libraries of compounds may be presented in solution (*e.g.*, Houghten, 1992, *Biotechniques* 13:412-421), or on beads (Lam, 1991, *Nature* 354:82-84), chips (Fodor, 1993, *Nature* 364:555-556), bacteria and/or spores, (Ladner, USP 5,223,409), plasmids (Cull *et al.*, 1992, *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith, 1990, *Science* 249:386-390; Devlin, 1990, *Science* 249:404-406; Cwirla *et al.*, 1990, *Proc. Natl. Acad. Sci.* 87:6378-6382; Felici, 1991, *J. Mol. Biol.* 222:301-310; Ladner, *supra.*).

The screening methods of the invention comprise contacting a cell, *e.g.*, a diseased cell, especially a prostate cancer cell, with a test compound and determining the ability of the test compound to modulate the expression and/or activity of filamin B, LY9, or keratin 19, optionally in combination with PSA, in the cell. The expression and/or activity of filamin B, LY9, or keratin 19; optionally in combination with PSA, can be determined using any methods known in the art, such as those described herein.

In another embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a marker of the invention or biologically active portions thereof. In yet another embodiment, the invention provides assays for screening candidate or test compounds which bind to a marker of the invention or biologically active portions thereof. Determining the ability of the test compound to directly bind to a marker can be accomplished, for example, by any method known in the art.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent capable of modulating the expression and/or activity of a marker of the invention identified as described herein can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment (e.g., of prostate cancer) with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatment as described above.

In certain embodiments, the screening methods are performed using cells contained in a plurality of wells of a multi-well assay plate. Such assay plates are commercially available, for example, from Stratagene Corp. (La Jolla, Calif.) and Corning Inc. (Acton, Mass.) and include, for example, 48-well, 96-well, 384-well and 1536-well plates.

Reproducibility of the results may be tested by performing the analysis more than once with the same concentration of the same candidate compound (for example, by incubating cells in more than one well of an assay plate). Additionally, since candidate compounds may be effective at varying concentrations depending on the nature of the compound and the nature of its mechanism(s) of action, varying concentrations of the candidate compound may be tested. Generally, candidate compound concentrations from 1 fM to about 10 mM are used for screening. Preferred screening concentrations are generally between about 10 pM and about 100 μ M.

The screening methods of the invention will provide "hits" or "leads," i.e., compounds that possess a desired but not optimized biological activity. Lead optimization performed on these compounds to fulfill all physicochemical, pharmacokinetic, and toxicologic factors required for clinical usefulness may provide improved drug candidates. The present invention also encompasses these improved drug candidates and their use as therapeutics for modulating prostate cancer progression.

J. KITS/PANELS

The invention also provides compositions and kits for diagnosing, prognosing, or monitoring a disease or disorder, recurrence of a disorder, or survival of a subject being treated for a disorder (e.g., an abnormal prostate state, BPH, an oncologic disorder, e.g., prostate cancer). These kits include one or more of the following: a detectable antibody that specifically binds to a marker of the invention, a detectable antibody that specifically binds to a marker of the invention, reagents for obtaining and/or preparing subject tissue samples for staining, and instructions for use.

The invention also encompasses kits for detecting the presence of a marker protein or nucleic acid in a biological sample. Such kits can be used to determine if a subject is suffering from or is at increased risk of developing an abnormal prostate state. For example, the kit can comprise a labeled

compound or agent capable of detecting a marker protein or nucleic acid in a biological sample and means for determining the amount of the protein or mRNA in the sample (*e.g.*, an antibody which binds the protein or a fragment thereof, or an oligonucleotide probe which binds to DNA or mRNA encoding the protein). Kits can also include instructions for use of the kit for practicing any of the methods provided herein or interpreting the results obtained using the kit based on the teachings provided herein. The kits can also include reagents for detection of a control protein in the sample not related to the abnormal prostate state, *e.g.*, actin for tissue samples, albumin in blood or blood derived samples for normalization of the amount of the marker present in the sample. The kit can also include the purified marker for detection for use as a control or for quantitation of the assay performed with the kit.

Kits include a panel of reagents for use in a method to diagnose prostate cancer in a subject (or to identify a subject predisposed to developing prostate cancer, *etc.*), the panel comprising at least two detection reagents, wherein each detection reagent is specific for one prostate cancer-specific protein, wherein said prostate cancer-specific proteins are selected from the prostate cancer-specific protein sets provided herein.

For antibody-based kits, the kit can comprise, for example: (1) a first antibody (*e.g.*, attached to a solid support) which binds to a first marker protein; and, optionally, (2) a second, different antibody which binds to either the first marker protein or the first antibody and is conjugated to a detectable label. In certain embodiments, the kit includes (1) a second antibody (*e.g.*, attached to a solid support) which binds to a second marker protein; and, optionally, (2) a second, different antibody which binds to either the second marker protein or the second antibody and is conjugated to a detectable label. The first and second marker proteins are different. In an embodiment, the first and second markers are markers of the invention, *e.g.*, filamin A, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B, LY9, and PSA. In certain embodiments, neither the first marker nor the second marker is PSA. In certain embodiments, the kit comprises a third antibody which binds to a third marker protein which is different from the first and second marker proteins, and a second different antibody that binds to either the third marker protein or the antibody that binds the third marker protein wherein the third marker protein is different from the first and second marker proteins.

For oligonucleotide-based kits, the kit can comprise, for example: (1) an oligonucleotide, *e.g.*, a detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a marker protein or (2) a pair of primers useful for amplifying a marker nucleic acid molecule. In certain embodiments, the kit can further include, for example: (1) an oligonucleotide, *e.g.*, a second detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a second marker protein or (2) a pair of primers useful for amplifying the second marker nucleic acid molecule. The first and second markers are different. In an embodiment, the first and second markers are markers of the invention, *e.g.*, filamin A, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin

19, tubulin-beta 3, filamin B, LY9, and PSA. In certain embodiments, neither the first marker nor the second marker is PSA. In certain embodiments, the kit can further include, for example: (1) an oligonucleotide, *e.g.*, a third detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a third marker protein or (2) a pair of primers useful for amplifying the third marker nucleic acid molecule wherein the third marker is different from the first and second markers. In certain embodiments, the kit includes a third primer specific for each nucleic acid marker to allow for detection using quantitative PCR methods.

For chromatography methods, the kit can include markers, including labeled markers, to permit detection and identification of one or more markers of the invention, *e.g.*, filamin A, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B, LY9, and optionally PSA, by chromatography. In certain embodiments, kits for chromatography methods include compounds for derivatization of one or more markers of the invention. In certain embodiments, kits for chromatography methods include columns for resolving the markers of the method.

Reagents specific for detection of a marker of the invention, *e.g.*, filamin A, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, filamin B, LY9, and PSA, allow for detection and quantitation of the marker in a complex mixture, *e.g.*, serum, tissue sample. In certain embodiments, the reagents are species specific. In certain embodiments, the reagents are not species specific. In certain embodiments, the reagents are isoform specific. In certain embodiments, the reagents are not isoform specific. In certain embodiments, the reagents detect total keratin 8, keratin 18, filamin B, PSA, or LY9.

In certain embodiments, the kits for the diagnosis, monitoring, or characterization of prostate cancer comprise at least one reagent specific for the detection of the level of expression of at least one marker selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, filamin B, and LY9. In certain embodiments, the kits further comprise instructions for the diagnosis, monitoring, or characterization of prostate cancer based on the level of expression of the at least one marker selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, filamin B, and LY9. In certain embodiments, the kits further comprise instructions to detect the level of PSA in a sample in which the at least one marker selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, filamin B, and LY9 is detected. In certain embodiments, the kits further comprise at least one reagent for the specific detection of PSA.

The invention provides kits comprising at least one reagent specific for the detection of a level of expression of at least one marker selected from the group consisting of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, filamin B, and LY9 and at least one reagent specific for the detection of a level of expression of PSA.

In certain embodiments, the kits can also comprise, *e.g.*, a buffering agents, a preservative, a protein stabilizing agent, reaction buffers. The kit can further comprise components necessary for

detecting the detectable label (*e.g.*, an enzyme or a substrate). The kit can also contain a control sample or a series of control samples which can be assayed and compared to the test sample. The controls can be control serum samples or control samples of purified proteins or nucleic acids, as appropriate, with known levels of target markers. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package, along with instructions for interpreting the results of the assays performed using the kit.

The kits of the invention may optionally comprise additional components useful for performing the methods of the invention.

The invention further provides panels of reagents for detection of one or more prostate-related marker in a subject sample and at least one control reagent. In certain embodiments, the control reagent is to detect the marker for detection in the biological sample wherein the panel is provided with a control sample containing the marker for use as a positive control and optionally to quantitate the amount of marker present in the biological sample. In certain embodiments, the panel includes a detection reagent for a marker not related to an abnormal prostate state that is known to be present or absent in the biological sample to provide a positive or negative control, respectively. The panel can be provided with reagents for detection of a control protein in the sample not related to the abnormal prostate state, *e.g.*, actin for tissue samples, albumin in blood or blood derived samples for normalization of the amount of the marker present in the sample. The panel can be provided with a purified marker for detection for use as a control or for quantitation of the assay performed with the panel.

In a preferred embodiment, the panel includes reagents for detection of two or more markers of the invention (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9), preferably in conjunction with a control reagent. In the panel, each marker is detected by a reagent specific for that marker. In certain embodiments, the panel further includes a reagent for the detection of PSA. In certain embodiments, the panel includes replicate wells, spots, or portions to allow for analysis of various dilutions (*e.g.*, serial dilutions) of biological samples and control samples. In a preferred embodiment, the panel allows for quantitative detection of one or more markers of the invention.

In certain embodiments, the panel is a protein chip for detection of one or more markers. In certain embodiments, the panel is an ELISA plate for detection of one or more markers. In certain embodiments, the panel is a plate for quantitative PCR for detection of one or more markers.

In certain embodiments, the panel of detection reagents is provided on a single device including a detection reagent for one or more markers of the invention and at least one control sample. In certain embodiments, the panel of detection reagents is provided on a single device including a detection reagent for two or more markers of the invention and at least one control sample. In certain embodiments, multiple panels for the detection of different markers of the invention are provided with at least one uniform control sample to facilitate comparison of results between panels.

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references and published patents and patent applications cited throughout the application are hereby incorporated by reference.

EXAMPLES

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, GenBank Accession and Gene numbers, and published patents and patent applications cited throughout the application are hereby incorporated by reference. Those skilled in the art will recognize that the invention may be practiced with variations on the disclosed structures, materials, compositions and methods, and such variations are regarded as within the ambit of the invention.

EXAMPLE 1: Identification of Keratins and Tubulin as Prostate Cancer Markers

Extracellular Keratins are known to influence the cell proliferation and metastasis of epithelial derived prostate cancers. Androgen refractory prostate cancers exhibit differential expression keratin 8 (K8) when compared to normal tissue. Modulation and degradation of keratins is in turn mediated by mitochondrial generation of Reactive Oxygen Species (ROS). Despite these advances a systematic approach to understanding of keratins and other EC proteins in prostate cancer metastasis and proliferation is lacking.

An interrogative systems biology based discovery platform (i.e., Interrogative Platform Technology or a.k.a. Interrogative Biology™) disclosed in WO2012119129 (incorporated herein by reference), and shown schematically in Figure 1, provides new mechanistic insights into understanding mitochondrial role in behavior of prostate cancer cells. The discovery platform involves discovery across a hierarchy of systems including in vitro human cell based models and human serum samples from prostate cancer patients and downstream data integration and mathematical modeling employing an Artificial Intelligence (AI) based informatic module. For cellular models, androgen sensitive LnCAP cell line and metastatic, androgen refractory PC3 cell line were treated with ubidecarenone (coenzyme Q10) in order to engage the mitochondrial machinery. Proteomic signatures were captured using a 2D LC-MS orbitrap technology. Total protein signatures were input to an AI based informatics module to generate causal protein networks (Figure 2). Wet lab assays that specifically measure mitochondrial ROS, ATP and caspase 3 activation confirmed changes in intracellular levels of these markers.

As shown in Figure 3, several novel protein causal interactions that govern induction of mitochondrial machinery by ubidecarenone in PC3 cells were observed. Causal protein maps revealed association of keratins 8 and 15 in PC3 models and not LnCAP. The keratin 8/15 association was lost upon treatment with ubidecarenone, and a direct association of keratins 7 and 15 was established (Figure 3).

These results suggest that a change in the interaction among keratins 7, 8, and 15 is particularly useful in demonstrating a response to treatment or a change in prostate cancer status in a subject. Further, keratins 8 and 15 were differentially associated in the androgen refractory, metastatic PC3 cell line and the androgen sensitive LnCAP cell line. This indicates that keratins 8 and 15 could be useful to differentiate between prostate cancer states, e.g., between androgen sensitive and metastatic, androgen refractory prostate cancer.

An increase in the expression of keratin 19 in relation to prostate cancer was confirmed using a panel of serum samples from subjects suffering from prostate cancer as compared to an appropriate matched control population. (See FIG. 2C and FIG. 3D).

Thus novel mechanistic insight into prostate cancer proliferation and mitochondrial role in modulating metastasis was gained with a novel chemical systems biology approach.

The results provided herein demonstrate that modulation of keratin and potential causal association in androgen refractory prostate cancer was inferred by the Platform technology. This provides a potential mechanism of keratin regulation in response to modulation of mitochondrial function was deciphered by the Platform technology. Thus, novel drivers of cancer pathophysiology were validated in patient serum samples.

EXAMPLE 2: Identification of Filamin B as a Prostate Cancer Marker

An interrogative systems biology based discovery platform (i.e., Interrogative Platform Technology or a.k.a. Interrogative Biology™) was used to obtain mechanistic insights into understanding the mitochondrial role in behavior of prostate cancer cells. The Platform technology, which is described in detail in WO2012119129, involves discovery across a hierarchy of systems including in vitro human cell based models and human serum samples from prostate cancer patients and downstream data integration and mathematical modeling employing an Artificial Intelligence (AI) based informatics module.

The results provided in this Example demonstrate the modulation of filamin B and LY9, and the potential causal association in androgen refractory prostate cancer that was inferred using the Platform technology. The Example provides potential mechanisms of filamin B and LY9 regulation in response to modulation of mitochondrial function that was deciphered by the Platform technology, and provides validation of the markers in patient serum samples.

Using the Platform methods, human prostate cancer cells PC3 (androgen insensitive, metastatic) and LnCap (androgen sensitive) were modeled in cancer microenvironments including hypoxia, reduced environments, and hyperglycemia and in presence of coenzyme Q10. Normal cells (human dermal fibroblasts (HDFa) and SV40 transformed human liver cells (THLE2)) were modeled under similar conditions mentioned above in Example 2. Proteomics of cellular proteins and proteins secreted in the supernatant were carried out by LCMS. Data were input into the Bayesian Network Inference (BNI) algorithms REFS™.

Causal associations between proteins were derived by the BNI. Differential network analysis was employed to tease out the hubs of activity in prostate cancer when compared to normal cells in normal microenvironments. Filamin B was identified as differential hub of activity in PC3 and not in LnCap and normal cells. That is, Filamin B was found to differ between androgen sensitive LnCAP cell line and metastatic, androgen refractory PC3 cell line. This indicates that Filamin B could be useful to differentiate between prostate cancer states, e.g., between androgen sensitive and metastatic, androgen refractory prostate cancer. The interaction matrix placing filamin B at the center of an interaction hub is shown in Figure 4. The interaction of LY9 with filamin B is shown in Figure 5.

EXAMPLE 3: Validation of Filamin B as a Prostate Cancer Marker in Human Samples

Having identified filamin B as a prostate cancer marker using the platform technology, human serum samples from normal subjects and subjects with prostate cancer were used to confirm filamin B as a prostate cancer marker.

Specifically, human serum samples were procured from a commercial vendor that sources human serum. Twenty samples were from normal donors and 20 samples were from patients diagnosed with prostate cancer. Prostate cancer samples were from patients with different prognosis and aggressiveness of cancers reported. Clinical characteristics of the subjects are provided in the table.

	Prostate Cancer	Control Group
Median Age	61 (47-86)	58 (45-72)
Ethnicity		
Caucasian	75%	85%
African American	15%	10%
Hispanic	10%	5%
Tumor Stage		
Stage I	20%	
Stage II	35%	
Stage III	5%	
Stage IV	40%	

Commercially available ELISA tests for filamin B and PSA were procured from commercial source. The assays were performed using the manufacturer's instructions. The results from the assay are shown in Figure 6. The results show the differential levels of FlnB and PSA in patients with a diagnosis for prostate cancer as compared to control subjects without prostate cancer.

As shown, both filamin B and PSA levels were elevated in serum samples from patients diagnosed with prostate cancer. The correlation between PSA and FlnB expression in serum samples is 0.20075, indicating a relatively low correlation between the variables. This demonstrates that filamin B and PSA are useful for the detection of prostate cancer in different subjects. These results

demonstrate that filamin B is useful for the diagnosis of prostate cancer, and that filamin B is useful for improving the detection of prostate cancer by PSA.

EXAMPLE 4: Validation of LY9 as a Prostate Cancer Marker in Human Samples

The same human serum samples used in Example 3 were further tested to detect the presence of LY9. A commercially available ELISA test for LY9 was procured from commercial source. The assay was performed using the manufactures' instructions. The results from the assay are shown in Figure 7. The results show the differential levels of LY9 in patients with a diagnosis for prostate cancer as compared to control subjects without prostate cancer. As shown, samples from subjects with prostate cancer were found to have higher levels of LY9 as compared to normal subjects. Results from assays of expression levels of both filamin B and LY9 in human serum with results expressed as ng/ml of protein are shown in Figure 8.

EXAMPLE 5: Analysis of Filamin B Levels Improves the Detection of Prostate Cancer as Compared to PSA Alone

Having demonstrated that the level of filamin B is increased in the serum of subjects with prostate cancer, the results were analyzed in conjunction with the study of PSA levels in the same samples to determine if the predictive value of filamin B and PSA together was better than either of the markers alone. Receiver operating characteristic (ROC) curve analysis of sensitivity and false positive rate (FPR) of PSA, filamin B, and the combination of PSA and filamin B was generated. The curves and the area under the curve (AUC) values are shown in Figures 9A and B. The goal of this analysis was to gauge the predictive power of the test independent of a specific cut-off. When using an ROC analysis, a test that provides perfect discrimination or accuracy between normal and disease states would have AUC=1, whereas a very poor test that provides no better discrimination than random chance would have AUC=0.5

As demonstrated by the analysis, filamin B alone performs very well and most importantly somewhat orthogonal to PSA. PSA is reported to have a very high false positive rate, e.g., about 75% (as reported in, Gilligan, "The new data on prostate cancer screening: What should we do now?," Cleveland Clin. J. Med. 76: 446-448, 2009, incorporated herein by reference). That is, it has a high sensitivity and low specificity. In the specific study presented, the AUC for FLNB is lower than that for PSA. However, the correlation level of 0.20075 determined in Example 3, indicates a relatively low correlation between the variables. That is, subjects identified as having an elevated filamin B level did not necessarily have a high PSA level, and the reverse was also true, suggesting that the markers in combination can provide a more predictive test than either marker alone.

This was confirmed in the ROC analysis. As shown, the combination of PSA and filamin B was found to have a higher AUC indicating better discrimination of the test than PSA alone, and to be more predictive than either of the markers alone. The combination of PSA and filamin B is a very

good predictor of prostate cancer and provides a drastic increase over the PSA test specificity, which is the primary problem with the test.

EXAMPLE 6: Analysis of Filamin B, LY9, and PSA Levels Together Improves the Detection of Prostate Cancer as Compared to any Marker Alone

Having demonstrated that each of filamin B, LY9, and PSA are all elevated in serum samples from subjects with prostate cancer, the ROC curve analysis was performed comparing each of the three markers individually to the combination of all three markers using a linear scoring function, and comparing the combination of filamin B and LY9, and the combination of filamin B and PSA, against the combination of all three markers using a non-linear scoring function to determine which combinations of the markers were more effective than each single marker for the detection of prostate cancer in a subject. As shown, the combination of all three markers was more predictive than any of the markers alone (Figure 10A). The combination of filamin B with PSA, either with or without LY9, was more predictive than the combination of filamin B with LY9 (Figure 10B). Additional samples can be analyzed to further refine the results. The AUC results are summarized in the table.

Marker	AUC
LY9	0.85
FLNB	0.78
PSA	0.87
LY9 + FLNB + PSA	0.98

EXAMPLE 7: Stratification of Subjects with Prostate Cancer using Keratin 4, Keratin 7, Keratin 8, Keratin 15, Keratin 18, Keratin 19, Tubulin-beta 3

As demonstrated in Examples 3 and 4 respectively, filamin B levels and LY9 levels can be used to distinguish subjects who are or are not suffering from prostate cancer. Further, as demonstrated in Examples 5 and 6, the analysis of both filamin B and PSA, optionally further in combination with LY9, is more sensitive than an analysis based on either marker alone. The markers keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3 are similarly analyzed, as described in Examples 3-6, in human samples.

A series of subject samples are obtained from an appropriate source, e.g., a commercial source, wherein the samples were obtained from subjects with different stages of prostate cancer, e.g., aggressive prostate cancer, androgen sensitive, androgen insensitive, metastatic; or from subjects not suffering from prostate cancer, e.g., subjects with normal prostate or subjects with BPH. The samples are analyzed for the expression level of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 15, and keratin 19;

and optionally further at least one of filamin B, LY9, and PSA. The level of the expression of the makers, alone and in various combinations, correlate with the presence or absence of disease, and with the severity of prostate cancer. For example, an increase in the expression level of one or more of keratin 19, filamin B, LY9, and PSA, as compared to a normal sample from a subject not suffering from prostate cancer, is indicative of prostate cancer in the subject. Expression levels of keratins 7, 8, and 15 may also be particularly useful in the stratification of subjects with prostate cancer.

EXAMPLE 8: Monitoring of Prostate Cancer Treatment using Keratin 4, Keratin 7, Keratin 8, Keratin 15, Keratin 18, Keratin 19, Tubulin-beta 3

At the time of diagnosis with prostate cancer, subjects are invited to participate in a trial. A subject sample, e.g., blood, is obtained. Periodically, throughout the monitoring, watchful waiting, or active treatment of the subject, e.g., chemotherapy, radiation therapy, surgery, hormone therapy, a new subject sample is obtained. At the end of the study, all subject samples are tested for the expression level of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 15, and keratin 19; and optionally further at least one of filamin B, LY9, and PSA. The subject samples are matched to the medical records of the subjects to correlate marker levels with prostate cancer status at the time of diagnosis, rate of progression of disease, response of subjects to one or more interventions, and transitions between androgen dependent and independent status. An increase in the expression level of one or more of keratin 19, filamin B, LY9, and PSA, as compared to a normal sample from a subject not suffering from prostate cancer, is indicative of prostate cancer in the subject. Expression levels of keratins 7, 8, and 15 may also be particularly useful in the diagnosis and monitoring of subjects with prostate cancer.

EXAMPLE 9 : Detection and Monitoring of Prostate Cancer using keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3

Despite its limitations, including a positive predictive value of only 25-40%, PSA remains the only generally accepted biomarker for prostate cancer. Moreover, as prostate cancer is most commonly a slow growing tumor in men of advanced age, treatment of the cancer may do more harm to the subject than the tumor itself would. Therefore, the tests together for the expression level of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 15, and keratin 19; and optionally further at least one of filamin B, LY9, and PSA are used for the detection and monitoring of prostate cancer. The level of the expression of the makers, alone and in various combinations are used in detection, including in routine, preventative, screening methods in men having an increased risk of prostate cancer (e.g., increased age, family history, race, etc.) or in monitoring of subjects diagnosed with prostate cancer prior to or during treatment may be useful to better identify subjects in need of further, potentially

more invasive, diagnostic tests, e.g., prostate exam or biopsy, digital rectal exam; or more aggressive treatment. Detection of levels of expression of the markers, or various combinations thereof, may also be indicative of a good or poor response to a specific treatment regimen prior to changes in other signs or symptoms, e.g., loss of tumor response to hormone therapy.

In routine screening methods for prostate cancer, a serum sample from a subject is tested for the level of expression of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 15, and keratin 19; and optionally further at least one of filamin B, LY9, and PSA. The levels are compared to one or more appropriate controls, e.g., other normal subjects, subjects with prostate cancer. Detection of an abnormal level of one or more of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 8, keratin 15, and keratin 19; indicates that the subject should be considered for further tests for the presence of prostate cancer. Changes in the level of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 8, keratin 15, and keratin 19, in the subject may be more indicative of a change in prostate cancer status than comparison to a population control.

In determining a therapeutic regimen for a subject with prostate cancer not yet being actively treated for prostate cancer (i.e., watchful waiting) can be tested at regular intervals to determine if there is a change in the level of expression of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 15, and keratin 19; and optionally further at least one of filamin B, LY9, and PSA. An modulation in the level of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 8, keratin 15, and keratin 19; and optionally further at least one of filamin B, LY9, and PSA indicates that the subject should be considered for further tests to monitor the prostate cancer and more active therapeutic interventions should be considered.

In a subject undergoing treatment for prostate cancer (e.g., hormone therapy, chemotherapy, radiation therapy, surgery) is tested prior to the initiation of the treatment and during and/ or after the treatment to determine if the treatment results in a decrease in the level of expression of at least one of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3, preferably at least one of keratin 7, keratin 15, and keratin 19; and optionally further at least one of filamin B, LY9, and PSA. A decrease in the level of keratin 19, filamin B, LY9, or PSA is indicative of response to treatment. Expression levels of keratins 7, 8, and 15 may also be particularly useful in the diagnosis and monitoring of subjects with prostate cancer.

EXAMPLE 10: Stratification of Subjects with Prostate Cancer using Filamin B, PSA, or LY9

As demonstrated in Examples 3 and 4 respectively, filamin B levels and LY9 levels can be used to distinguish subjects who are or are not suffering from prostate cancer. Further, as

demonstrated in Examples 5 and 6, the analysis of both filamin B and PSA, optionally further in combination with LY9, is more sensitive than an analysis based on either marker alone.

A series of subject samples are obtained from an appropriate source, e.g., a commercial source, wherein the samples were obtained from subjects with different stages of prostate cancer, e.g., aggressive prostate cancer, androgen sensitive, androgen insensitive, metastatic; or from subjects not suffering from prostate cancer, e.g., subjects with normal prostate or subjects with BPH. The samples are analyzed for the expression level of filamin B and PSA, and optionally the level of LY9, and further with one or more of keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, especially keratin 19. The level of filamin B, LY9, and PSA, alone and in various combinations, optionally with other markers, e.g., keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, especially keratin 19, correlate with the presence or absence of disease, and with the severity of prostate cancer.

EXAMPLE 11: Monitoring of Prostate Cancer Treatment using Filamin B, PSA, or LY9

At the time of diagnosis with prostate cancer, subjects are invited to participate in a trial. A subject sample, e.g., blood, is obtained. Periodically, throughout the monitoring, watchful waiting, or active treatment of the subject, e.g., chemotherapy, radiation therapy, surgery, hormone therapy, a new subject sample is obtained. At the end of the study, all subject samples are tested for the level of filamin B, PSA, and optionally in further combination with one or more of LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3. The subject samples are matched to the medical records of the subjects to correlate filamin B, PSA, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, or tubulin-beta 3 levels, as appropriate, with prostate cancer status at the time of diagnosis, rate of progression of disease, response of subjects to one or more interventions, and transitions between androgen dependent and independent status.

EXAMPLE 12: Detection and Monitoring of Prostate Cancer using Filamin B, PSA, or LY9

Despite its limitations, including a positive predictive value of only 25-40%, PSA remains the only generally accepted biomarker for prostate cancer. Moreover, as prostate cancer is most commonly a slow growing tumor in men of advanced age, treatment of the cancer may do more harm to the subject than the tumor itself would. As demonstrated herein, there is a low correlation between elevated levels of filamin B and PSA in subjects with prostate cancer. Further, elevated levels of LY9 have been demonstrated to be associated with prostate cancer. Therefore, the tests together, particularly filamin B and PSA, optionally in combination with one or more of LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, especially keratin 19, in detection, including in routine, preventative, screening methods in men having an increased risk of prostate cancer (e.g., increased age, family history, race, etc.) or in monitoring of subjects diagnosed with prostate cancer prior to or during treatment may be useful to better identify subjects in need of further,

potentially more invasive, diagnostic tests, e.g., prostate exam or biopsy, digital rectal exam; or more aggressive treatment. Detection of levels of expression of filamin B, PSA, LY9 keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, especially keratin 19, may also be indicative of a good or poor response to a specific treatment regimen prior to changes in other signs or symptoms, e.g., loss of tumor response to hormone therapy.

In routine screening methods for prostate cancer, a serum sample from a subject is tested for the level of expression of both filamin B and PSA, and optionally one or more of LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, especially keratin 19. The levels are compared to one or more appropriate controls, e.g., other normal subjects, subjects with prostate cancer. Detection of an abnormal level of one or more of filamin B, PSA, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3, especially keratin 19 indicates that the subject should be considered for further tests for the presence of prostate cancer. Changes in the level of filamin B, optionally in combination with one or more of PSA, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, or tubulin-beta 3, especially keratin 19 with PSA in the subject may be more indicative of a change in prostate cancer status than comparison to a population control.

In determining a therapeutic regimen for a subject with prostate cancer not yet being actively treated for prostate cancer (i.e., watchful waiting) can be tested at regular intervals to determine if there is a change in the level of expression of filamin B, PSA, LY9 keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3. An increase in the level of filamin B, PSA, keratin 19, or LY9 indicates that the subject should be considered for further tests to monitor the prostate cancer and more active therapeutic interventions should be considered.

In a subject undergoing treatment for prostate cancer (e.g., hormone therapy, chemotherapy, radiation therapy, surgery) is tested prior to the initiation of the treatment and during and/ or after the treatment to determine if the treatment results in a change in the level of expression of one or more of filamin B, PSA, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, and tubulin-beta 3. A decrease in the level of filamin B, PSA, keratin 19, or LY9 is indicative of response to treatment.

EXAMPLE 13: Detection of filamin A and keratin 19 by ELISA in human serum from patients with and without prostate cancer

ELISA assays were conducted on commercially available human serum samples to detect the levels of filamin A and keratin 19 in samples from patients with and without prostate cancer.

The commercial human serum samples used for the filamin A ELISA are shown in FIG. 11, the data/annotation of which is publicly available at the Asterand and Bioreclamation websites. The commercial human serum samples used for the keratin 19 ELISA are shown in FIG. 12, the data/annotation of which is publicly available at the Asterand and Bioreclamation websites.

For the filamin A test, the ELISA was conducted in accordance with the Human Filamin A (FLNa) ELISA kit, Catalog No. CSB-EL008724HU, which is commercially and publicly available from CEDARLANE (Cusabio), the contents of which are incorporated herein by reference.

For the keratin 19 test, the ELISA was conducted in accordance with the Human Keratin-19 (KRT19) ELISA Kit, Catalog No. E91239HU, which is commercially and publicly available from CEDARLANE (Cusabio), the contents of which are incorporated herein by reference.

FIG. 13 shows the filamin A protein levels in serum from patients with and without prostate cancer as determined by ELISA.

FIG. 14. shows the keratin 19 protein levels in serum from patients with and without prostate cancer as determined by ELISA.

EXAMPLE 14: Filamin A and Keratin 19 differentiate between patients with prostate cancer and normal individuals

The inventors have developed in-vitro models of prostate cancer based on a number of cancer and normal cell lines including the androgen independent PC3 and the androgen dependent LNCaP prostate cancer cell lines. Key regulatory nodes inferred by Berg Interrogative Biology™ were selected for a proof-of-concept validation in human serum as biomarkers of prostate cancer.

The initial two biomarkers FLNB and LY9 showed predictive power to differentiate between normal serum and serum from prostate cancer patients. This report reviews statistical characteristics of additional biomarkers, FLNA, FLNC, KRT18 and KRT19.

**STATISTICAL PERFORMANCE OF CANDIDATE MARKERS: BIORECLAMATION
SAMPLE SET #1:**

Human serum samples from normal individuals and individuals with prostate cancer were acquired from a commercial source, as per Example 13. The panel of biomarkers was measured by commercially available ELISA kits, as per Example 13.

FIG. 15 demonstrates the performance of the candidate markers in the set of 20 normal and 20 prostate cancer samples. FLN-A showed predictive power to differentiate between normal and cancer patients, whereas FLN-C did not show any positive trend. The combination panel of FLN-A and FLN-C did not improve on the performance of FLN-A alone.

**STATISTICAL PERFORMANCE OF CANDIDATE MARKERS: BIORECLAMATION
AND ASTERAND SAMPLE SET #2:**

Human serum samples from normal individuals and individuals with prostate cancer were acquired from two commercial sources, as per Example 13. The panel of biomarkers was measured by commercially available ELISA kits, as per Example 13.

FIG. 16 demonstrates the performance of the candidate markers in the set of 20 normal and 20 prostate cancer samples. KRT19 showed predictive power to differentiate between normal and cancer

patients. KRT18 did not show any differentiation between normal and cancer specimens. The combination panel of KRT18 and KRT19 did not improve on the performance of KRT19 alone.

CONCLUSION:

Based on the results of this proof-of-concept study, KRT19 and FLNA have the potential to differentiate between patients with prostate cancer and normal individuals. These two biomarkers may be evaluated in a larger clinical validation study by either a commercial or in-house developed ELISA assay. The results above demonstrate that FLNA and KRT19 are statistically significant biomarkers of prostate cancer and therefore may be a significant improvement over the current screening tools.

EXAMPLE 15: Filamin A, Filamin B, Keratin 19, and Age differentiate between patients with prostate cancer and normal individuals

To study whether the Prostate Cancer Panel test is equivalent, better, or weaker than PSA in screening for prostate cancer, we studied the above 4 comparisons with 4 different MVI (Multivariate Index) models to best study the utility of the panel.

Samples were divided as training/verification set and validation set. The verification set consisting of 332 samples was used to develop the models. The validation set of 171 samples were used to test the model.

The annotations of the validation samples were blinded. Probability unit linear regression models were estimated using the verification part of the sample set. Regression models were created to classify samples from the patients with diagnosed prostate cancer, with high Gleason Score (>6 and >7), and with benign prostate hyperplasia. Prostate cancer panel predictive algorithms were implemented based on the regression models and the probability cut-offs selected to achieve a certain level of test sensitivity or specificity. Each predictive algorithm was validated on the left-out validation sample set.

The biomarkers in the panel are:

- 1) Filamin - A
- 2) Filamin - B
- 3) Keratin -19
- 4) Age was used as a continuous predictor variable.

Using the panel in various combinations along with clinical information, the predictive power in screening for prostate cancer compared to PSA alone was tested. The specific study objectives were:

- 1) Determine the predictive power and the utility of the Biomarker panel to differentiate between samples from patients with and without prostate cancer.

- 2) Determine the predictive power of the Biomarker panel to differentiate between samples from patients with HIGH Gleason Score (8-10), INTERMEDIATE Gleason Score (7), and LOW Gleason Score (6) prostate cancer.
- 3) Determine the predictive power of the Biomarker panel to identify samples from patients with prostate cancer but low PSA (less than 4 ng/ml) concentration.
- 4) Determine the predictive power of the Biomarker panel to differentiate between samples from patients with prostate cancer and benign prostatic hyperplasia.

The terminology used for categories of cancer is:

Super High = Gleason Score 8 and above.

High = Gleason Score 7 and above

Low = Gleason score 6

Else = All other samples when a certain specified category is being compared with the rest of the samples.

Study Design

A retrospective and clinically annotated sample set from Mt.Sinai Hospital, Toronto, Canada was obtained. The sample matrix is serum and is frozen since its collection and processing.

This is a clinically annotated sample set with 662 samples from the patients at a Prostate Center. The patients were all comers for prostate gland biopsy. 120 samples from this set were used as a proof of concept set for the proposed Prostate Cancer Panel. The remaining samples were sorted as per the volume available. Anything short of 350ul was excluded and the samples were then segregated in 2: 1 ratio and identified as 'Verification' set and 'Validation' set.

All samples, irrespective of the verification or validation set, were analyzed using the prostate Cancer Panel in the CLIA certified laboratory. The laboratory was blinded to the sample's designation of 'verification' or 'validation' set.

The samples were randomized and separated as 'verification' and 'validation' set.

Participant recruitment and sampling

Serum samples were collected from 662 male patients. All patients were referred to a Prostate Center for a prostatic biopsy. These patients were suspicious for prostate cancer based on either clinical symptoms, digital-rectal examination, or, more frequently, due to a serum PSA elevation (beyond 3 ng/ml). The patients were consented to participate in this study by a personal interview and blood was drawn before any clinical manipulations or prostatic biopsy.

To establish the final diagnosis, the pathology report was examined by a clinical associate and patients were categorized as prostate cancer with Gleason score assigned (n=311), benign conditions

(n=122), atypical small acini proliferation (n=26), prostatic intraepithelial neoplasia (n=69), benign prostatic hyperplasia (n=60), inflammation (n=58), microfocus adenocarcinoma (n=16).

Sample Collection Protocol

- Venous blood was collected in SST tube, 5 mL from BD
- Tubes were kept vertically at room temperature for ½ - 1 hour, allowing the blood to clot.
- Samples were centrifuged at 2000 RCF for 10 minutes at 4°C.
- The supernatant serum was collected, aliquoted into 0.5 ml sterile screw-capped tubes, and labeled with the appropriate Identification Number.
- Samples were immediately stored at -80°C.

Data Collection

- There are 332 samples in the training and 171 samples in the validation dataset. Samples were randomized to make two groups.
- No. of total samples =332
- No. of Gleason above 8 =19
- No. of samples with Gleason 6=103
- No. of samples with No-Cancer=159
- No. of BPH samples=23

Study Population

The samples were transferred on dry ice and were stored at -80°C in the CLIA certified laboratory.

The samples are from a retrospective sample set with the following annotation:

- PSA test values
- Diagnosis
- Patient age
- Reason for biopsy
- Total biopsy cores, staging, and grading (Gleason score)
- Number of positive cores
- Tumor location

Reference standard and Rationale

- The PSA test is the reference standard against which the outcome of the Panel was compared.
- This retrospective sample set has documented PSA values which were used in data analysis.
- This set also had documented biopsy results with Gleason scores.

Validated Assays

All samples were tested using the assays described below:

- FLN – A ELISA: which measures FLN- A in serum and plasma by ELISA in the range of 3.125-200 ng/ml
- FLN – B ELISA which measures concentration of FLN-B in human serum and plasma by ELISA in the range of 0.156-10 pM
- Keratin -19 ELISA which measures soluble cytokeratin 19 fragments in human serum
- FLN –A IP MRM which measures the concentration of FLN A peptides from human serum using Immunoprecipitation and LC-MS/MS in the range of 125 pg/ml - 2000 pg/ml for P2, 250 pg/ml – 6000 pg/ml for P3 and 1125 pg/ml – 36000 pg/ml for P4.

Definition and Rationale of units

- PSA is reported in units of ng/ml. The values are taken from the annotations of the sample set.
- Filamin A ELISA : ng/ml
- Filamin A Peptide IP - MRM : pg/ml
- Keratin -19 fragment ELISA : ng/ml
- Filamin –B ELISA ; picomole , pM

Results

The models generated from the verification set samples generated the following AUC data in Table 1 and the predictive power data in Table 2.

Table 1*AUC summary for all dataset (Peptide in Log scale)*

	CA vs Others		CA vs BPH		High Gleason vs. Low		High Gleason vs. Others		Super High Gleason vs. Others	
	Biomarker	AUC	Biomarker	AUC	Biomarker	AUC	Biomarker	AUC	Biomarker	AUC
Individual	PSA	0.569	PSA	0.564	PSA	0.619	PSA	0.631	PSA	0.67
	Age	0.62	Age	0.621	Age	0.622	Age	0.662	Age	0.7
	FLNA	0.574	FLNA	0.696	FLNA	0.515	FLNA	0.56	FLNA	0.542
	FLNB	0.51	FLNB	0.516	FLNB	0.528	FLNB	0.515	FLNB	0.515
	Krt19	0.519	Krt19	0.618	Krt19	0.573	Krt19	0.567	Krt19	0.574
	P2-1	0.55	P2-1	0.636	P2-1	0.527	P2-1	0.551	P2-1	0.528
Two Combined (top)	P2-2	0.502	P2-2	0.582	P2-2	0.528	P2-2	0.552	P2-2	0.53
	P3-1	0.51	P3-1	0.524	P3-1	0.547	P3-1	0.529	P3-1	0.5
	P4-2	0.522	P4-2	0.595	P4-2	0.551	P4-2	0.555	P4-2	0.578
	Age & FLNB	0.63	FLNA & KRT19	0.717	Age & PSA	0.659	Age & PSA	0.696	Age & PSA	0.765
Three Combined (top)	Age & FLNB & PSA	0.635	FLNA & KRT19 & Age	0.735	PSA & Age & FLNB	0.685	PSA & Age & FLNB	0.717	PSA & Age & FLNB	0.804
Four Combined (top)	Age & FLNA & P2-1 & P2-2	0.637	FLNA & KRT19 & P2-1 & Age	0.746	PSA & Age & FLNB & P3-1	0.693	PSA & Age & FLNP & P3-1	0.723	PSA & Age & FLNB & P2-2	0.81
			FLAN & KRT19 & Age & P4-2	0.746					PSA & Age & FLNB & P2-2	0.81
Five Combined (top)	Age & FLNA & PSA & P2-2 & P2-1	0.644	FLNA & KRT19 & Age & P2-1 & P3-1	0.764	PSA & Age & FLNA & P3-1 & KRT19	0.694	No improvement		PSA & Age & FLNB & P2-2 & P2-1	0.811

Table 2

Summary of Predictive Power analysis of Verification Samples

Goal	Cut off	Sensitivity	Specificity	PPV	NPV
Differentiate between Cancer and Non Cancer samples					
Verification Set	0.4455	0.7712	0.3380	0.5566	0.5783
Gleason Score 8 and above Vs. Other samples					
Verification Set	0.01997	1.0000	0.2482	0.0752	1.0000
Gleason Score 7 and above Vs. Other samples					
Verification Set	0.1603	0.8136	0.4915	0.2857	0.9134
Prostate Cancer Vs. BPH samples					
Verification Set	0.8758	0.8035	0.6087	0.9392	0.2917

The predictive power and the utility of the Biomarker panel to differentiate between samples from patients with and without prostate cancer is shown below:

Goal	Cut off	Sensitivity	Specificity	PPV	NPV	Comments
Differentiate between Cancer and Non Cancer						
Verification Set	0.4455	0.7712	0.3380	0.5566	0.5783	
Validation Set	0.4455	0.8442	0.3580	0.5556	0.7073	p value significant for Odds Ratio

Verification Set

This model was trained to match the sensitivity of PSA = 4 cutoff and test the specificity of the above-identified biomarker panel compared to the PSA test. Figure 18 depicts PCA vs. Else: Sensitivity match PSA with a cutoff of 0.4455.

Validation Set

A boxplot of the predicted probability and the accuracy analysis are shown in Figures 19 and 20, respectively.

Next, the predictive power of the biomarker panel to differentiate between samples from patients with SUPER HIGH Gleason Score (8-10), HIGH Gleason Score (7 and above), and LOW Gleason Score (6) prostate cancer was determined.

Goal	Cut off	Sensitivity	Specificity	PPV	NPV	Comments
Gleason Score 8 and above Vs. Other samples						
Verification Set	0.01997	1.0000	0.2482	0.0752	1.0000	
Validation Set	0.01997	0.7500	0.2583	0.0509	0.9512	
Gleason Score 7 and above Vs. Other samples						
Verification Set	0.1603	0.8136	0.4915	0.2857	0.9134	
Validation Set	0.1603	0.7000	0.5116	0.2500	0.8800	p value significant for Odds Ratio

Verification Set

The model was trained to give a Sensitivity ≥ 0.95 . As per this model, the cut off generated was 0.01997. See Figure 21.

Validation Set

A boxplot of the predicted probability and the accuracy analysis are shown in Figure 22 and Figure 23, respectively.

Next, the predictive power of the biomarker panel to differentiate between samples from patients with a HIGH Gleason Score versus Everything Else was determined.

Verification Set

The model was trained to have sensitivity of greater than or equal to 0.8. The outcome was a cut off value for the Biomarker panel which was 0.1603. See Figure 24.

Validation Set

A boxplot of the predicted probability and the accuracy analysis are shown in Figure 25 and Figure 26, respectively.

Next, the predictive power of the biomarker panel to identify samples from patients with prostate cancer but low PSA (less than 4 ng/ml) concentration was determined. For this test, verification samples that had cancer were differentiated as low PSA (less than 4 ng/ml) and high PSA (greater than 4 ng/ml). Thus, the PSA AUC was equal to 1. Next, the low PSA and high PSA were predicted using the above-identified biomarker panel. The Table, below, depicts the AUC Summary for High PSA cancer versus Low PSA cancer.

AUC summary for High PSA cancer vs. Low PSA cancer

	High PSA CA versus LPSA CA	
	Biomarker	AUC
	Age	0.598
	FLNA	0.608
	FLNB	0.517
	KRT19	0.517
	P3-1	0.532
	P4-2	0.506
Two Combined (top)	FLNA & Age	0.664
Three Combined (top)	FLNA & Age & P4-2	0.669
Four Combined (top)	No improvement	
Five Combined (top)	No improvement	

Next, the predictive power of the biomarker panel to differentiate between samples from patients with prostate cancer and benign prostatic hyperplasia was determined. See Table, below.

Goal	Cut off	Sensitivity	Specificity	PPV	NPV	Comments
Prostate Cancer Vs. BPH						
Verification Set	0.8758	0.8035	0.6087	0.9392	0.2917	
Validation Set	0.8758	0.6790	0.3636	0.8871	0.1333	

Verification Set

The biomarker panel was set to get sensitivity greater than or equal to 0.8. The cut off generated by this model was 0.8758. See Figure 27.

Validation Set

A boxplot of the predicted probability and the accuracy analysis are shown in Figure 28 and Figure 29, respectively.

Conclusion

The verification and validation study indicates utility in four clinical applications of the PCA panel. The developed model significantly improved the ability to discriminate less aggressive forms from more aggressive forms. The AUC for discriminating samples taken from patients with Gleason Scores 8 and higher was 0.8 (versus 0.67 for PSA alone). The negative predictive value was very high for this model, if the patient value was below the model cutoff, the probability of the patient being disease free was 95%.

The model also performed well in discriminating patients with BPH versus prostate cancer. A patient value greater than the model cut-off was associated with an approximately 90% probability of the patient having prostate cancer instead of BPH. The AUC for this model was 0.75 (versus 0.56 for PSA alone).

The capabilities to discriminate samples from patients with prostate cancer from those without prostate cancer had predictive values in the 55-70 percentiles. However, AUC's were improved compared to the use of PSA alone.

Summary of Predictive Power analysis of Vervification/Validation Samples

Goal	Cut off	Sensitivity	Specificity	PPV	NPV	Comments
Differentiate between Cancer and Non Cancer						
Verification Set	0.4455	0.7712	0.3380	0.5566	0.5783	
Validation Set	0.4455	0.8442	0.3580	0.5556	0.7073	p value significant for Odds Ratio
Gleason Score 8 and above Vs. Other samples						
Verification Set	0.01997	1.0000	0.2482	0.0752	1.0000	
Validation Set	0.01997	0.7500	0.2583	0.0509	0.9512	
Gleason Score 7 and above Vs. Other samples						
Verification Set	0.1603	0.8136	0.4915	0.2857	0.9134	
Validation Set	0.1603	0.7000	0.5116	0.2500	0.8800	p value significant for Odds Ratio
Prostate Cancer Vs. BPH						
Verification Set	0.8758	0.8035	0.6087	0.9392	0.2917	
Validation Set	0.8758	0.6790	0.3636	0.8871	0.1333	

EXAMPLE 16: Identification and validatin of novel prostate cancer biomarkers

Prostate cancer is the most frequent cancer diagnosis among men and the second leading cause of cancer-related death. Despite the widespread use of digital rectal exam (DRE) and blood-based screening of prostate-specific antigen (PSA) for prostate cancer screening, there are significant limitations in their specificity and prognostic value. Biomarkers which distinguish i) PSA-low prostate cancer from benign prostatic hyperplasia (BPH) and (ii) indolent versus aggressive disease course represent unmet clinical needs. Experimentally, a panel of prostate cancer cell lines and non-tumorigenic, human primary cells were exposed to *in vitro* conditions designed to stimulate poor oxygenation, low pH, diminished nutrient microenvironments, and metabolic perturbations (24-48 h) followed by iTRAQ proteomic analysis of cell lysates. Using an Interrogative Biology platform, proteomic data were then subjected to Bayesian network learning to map molecular interactions, with cytoskeletal and scaffolding proteins Filamin A (FLNA), Filamin B (FLNB), and Keratin 19 (KRT19) identified as candidate prostate cancer biomarkers.

To validate biomarker expression, mRNA and protein was quantified in a panel of primary human prostate epithelial cells (HPrEC) and androgen-sensitive (LnCAP) or refractory (DU145, PC-3) prostate cancer cells, and each was differentially detected in one or more prostate cancer cell lines compared to HPrEC (Figures 30 and 31). Specifically, basal expression of FLNA, FLNB, and KRT19 in prostate cancer cells *in vitro* was assessed. mRNA and cell lysates were prepared from HPrEC,

LnCAP, DU145, and PC-3 cells. Expression of FLNA, FLNB, and KRT19 was assessed by quantitative RT-PCR and normalized to TBP. Cell lysates were resolved by SDS-PAGE and probed with antibodies specific for FLNA, FLNB, and KRT19. Representative images are shown in Figures 30 and 31. Densitometric analysis for FLNA, FLNB, and KRT19 are reported below each blot. Values represent means + SEM, N=3. * $p < 0.05$ compared to HPrEC.

Using proteomic analysis, peptides from FLNA, FLNB and KRT19 were also detected in cell culture media conditioned by prostate cancer cells (24 h), indicating that they can be secreted (Figure 32). Specifically, conditioned media from LnCAP, DU145, and PC-3 cells exposed to hypoxia (1% oxygen), TNF α (10 ng/mL), or R1881 (1 nM) for 24 hours was harvested, and proteomic analysis was performed. Values represent means + SEM, N=3. * $p < 0.05$ compared to normoxia control.

Importantly, unlike PSA expression, global regulation of FLNA, FLNB, and KRT19 expression remained unaltered after treatment with multiple prostate-cancer relevant stimuli (e.g., hypoxia, androgens, and inflammatory stimuli) (Figures 33-35). Specifically, mRNA was prepared from LnCAP, DU145, and PC-3 cells exposed to hypoxia (1% oxygen; A), TNF α (10 ng/mL; B), or R1881 (1 nM; C) for 24 h. Expression of FLNA, FLNB, and KRT19 was assessed by quantitative RT-PCR, normalized to TBP, and compared to PSA. Values represent means + SEM, N=3. * $p < 0.05$ compared to normoxia/control.

Assessment of plasma FLNA and FLNB levels as screening markers were assessed in a proof-of-concept sample cohort of 47 plasma samples (Figure 36). Residual lithium heparin plasma was collected from patient samples after the ordered tests were completed. The inclusion criteria were elevated PSA results (≥ 2.6 ng/mL), age of 45-70 years, and minimum volume of 700 μ L. Results demonstrate that FLNA and FLNB were detected in human plasma and have predictive power in identifying prostate cancer patients.

Finally, *in vivo* validation was next conducted in sera from men (N=447) with confirmed prostate cancer, benign prostate tumors, or BPH using LDT ELISA assays in a CLIA-certified laboratory. To assess the sensitivity and specificity of FLNA, FLNB, and KRT19 compared to PSA, ROC curve analysis was performed. The individual predictive power of each biomarker alone was comparable to that of PSA. However, the combination of age, levels of FLNA, FLNB, and KRT19 and PSA out-performed PSA alone in identification of patients with prostate cancer stratified compared to benign status, Gleason scores, and incidence of BPH. Together, these data indicate that FLNA, FLNB, and KRT19 can be used in conjunction with PSA and/or age for more sensitive and specific prostate cancer screening, a critical unmet need in the field.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments and methods described herein. Such equivalents are intended to be encompassed by the scope of the following claims.

It is understood that the detailed examples and embodiments described herein are given by way of example for illustrative purposes only, and are in no way considered to be limiting to the invention. Various modifications or changes in light thereof will be suggested to persons skilled in the art and are included within the spirit and purview of this application and are considered within the scope of the appended claims. For example, the relative quantities of the ingredients may be varied to optimize the desired effects, additional ingredients may be added, and/or similar ingredients may be substituted for one or more of the ingredients described. Additional advantageous features and functionalities associated with the systems, methods, and processes of the present invention will be apparent from the appended claims. Moreover, those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

1. A method for diagnosing the presence of prostate cancer in a subject, wherein the subject has elevated prostate cancer antigen (PSA) level, comprising: (a) detecting the level of filamin A in a biological sample of the subject, and (b) comparing the level of filamin A in the biological sample with the level of filamin A in a normal control sample, wherein the level of filamin A above the level of filamin A in the control sample indicates the presence of prostate cancer in the subject.
2. The method of claim 1, further comprising detecting the level of one or more additional markers of prostate cancer.
3. The method of claim 2, wherein the one or more additional markers of prostate cancer is selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, kartin 18, keratin 19, and tubulin-beta 3
4. The method of claim 3, wherein the level of filamin A protein is determined by mass spectrometry, immunoassay or ELISA.
5. A method for diagnosing the presence of prostate cancer in a subject, wherein the subject has elevated prostate cancer antigen (PSA) level, comprising: (a) contacting a biological sample with a reagent that selectively binds to filamin A; (b) allowing a complex to form between the reagent and filamin A; (c) detecting the level of the complex, and (d) comparing the level of the complex with a level of complex formed from a normal control sample, wherein the level of the complex formed from the biological sample above the level of the complex formed from the control sample indicates the presence of prostate cancer in the subject.
6. The method of claim 5, further comprising detecting the level of one or more additional markers of prostate cancer.
7. The method of claim 6, wherein the one or more additional markers of prostate cancer is selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, kartin 18, keratin 19, and tubulin-beta 3.
8. The method of claim 7, wherein the level of the one or more additional markers is increased as compared to a predetermined threshold value or wherein the level of the one or more additional markers is decreased as compared to a predetermined threshold value.
9. The method of any one of claims 1 to 8, wherein the biological sample is selected from the group consisting of blood, serum, urine, organ tissue, biopsy tissue, feces, skin, hair, and cheek tissue.
10. The method of any one of claims 1 to 9, wherein the prostate cancer is a prostatic intraepithelial neoplasia, adenocarcinoma, small cell carcinoma, squamous cell carcinoma, androgen-dependent prostate cancer, androgen-independent prostate cancer, aggressive prostate cancer, or non-aggressive prostate cancer.
11. The method of any one of claims 1 to 10, further comprising administering a therapeutic anti-cancer treatment where the diagnosis indicates the presence of prostate cancer in the subject, wherein the anti-cancer treatment is selected from the group consisting of (a) radiation therapy, (b)

chemotherapy, (c) surgery, (d) hormone therapy, (e) antibody therapy, (f) immunotherapy, (g) cytokine therapy, (h) growth factor therapy, and (d) any combination of (a)-(h).

12. The method of any one of the preceding claims further comprising selecting a subject suspected of having or being at risk of having prostate cancer.

13. The method of any one of the preceding claims, further comprising comparing the level of the one or more prostate cancer related markers in the biological sample with the level of the one or more prostate cancer related markers in a control sample selected from the group consisting of: a sample obtained from the same subject at an earlier time point than the biological sample, a sample from a subject with benign prostatic hyperplasia (BPH), a sample from a subject with non-metastatic prostate cancer, a sample from a subject with metastatic prostate cancer, a sample from a subject with androgen sensitive prostate cancer, a sample from a subject with androgen insensitive prostate cancer, a sample from a subject with aggressive prostate cancer, and a sample from a subject with non-aggressive prostate cancer.

14. The method of any one of the preceding claims, further comprising differentiating between two prostate cancer states selected from the group consisting of: normal prostate and prostate cancer, benign prostate hyperplasia and prostate cancer, benign prostate hyperplasia and normal prostate, androgen dependent and androgen independent prostate cancer, aggressive prostate cancer and non-aggressive prostate cancer, and metastatic prostate cancer and non-metastatic prostate cancer.

15. The method of any one of the preceding claims, further comprising determining the age of the subject.

16. The method of claim 15, wherein increased age of the subject as compared to a control further indicates the presence of prostate cancer in the subject.

17. A method of treating prostate cancer in a subject having elevated PSA level, comprising: (a) obtaining diagnostic information as to the level of filamin A in a biological sample from the subject, and (b) administering a therapeutically effective amount of an anti-cancer therapy to the subject if the level of filamin A in the biological sample is above the level of filamin A in a normal control sample.

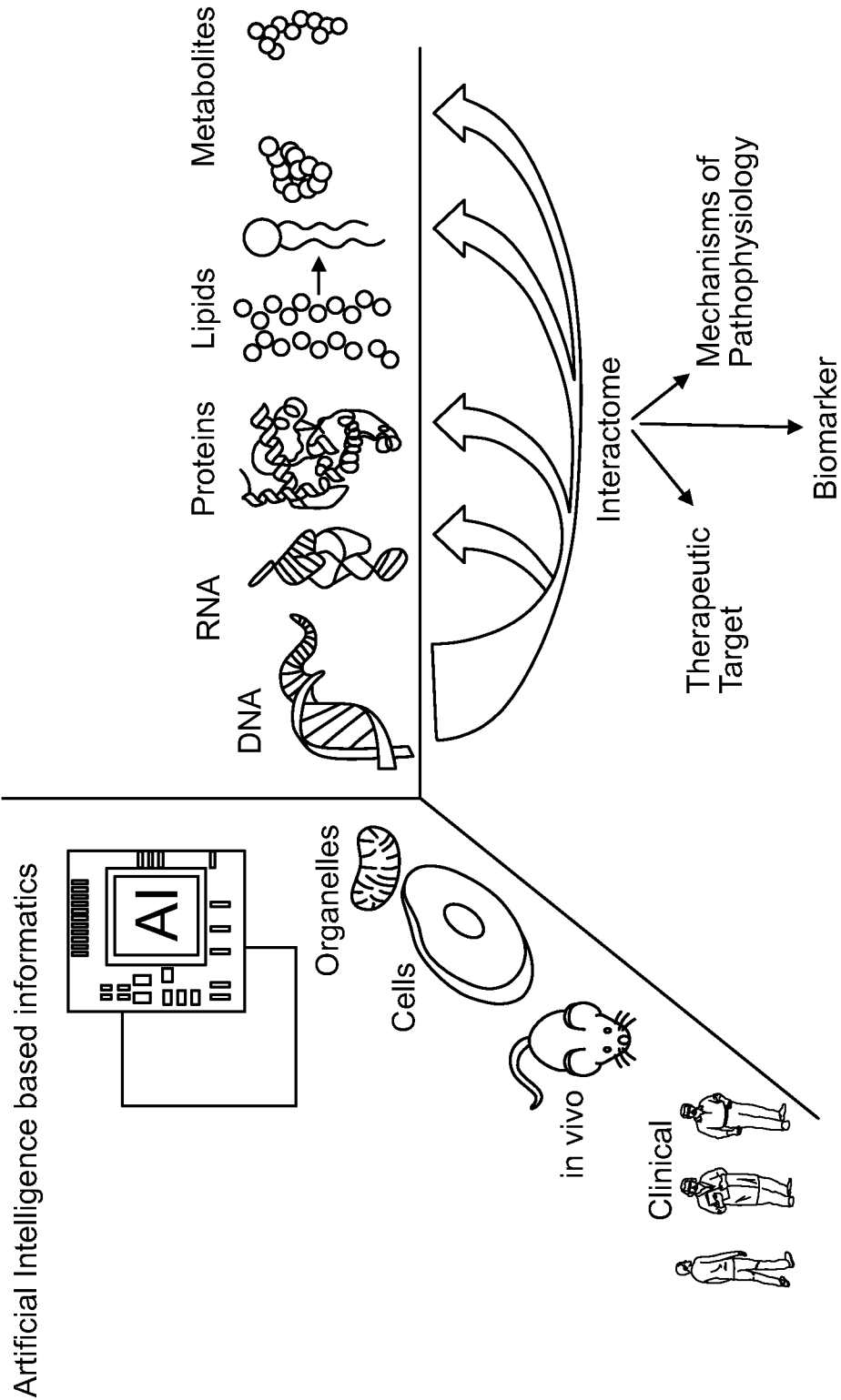
18. The method of claim 17, further comprising obtaining diagnostic information as to the level of one or more additional markers of prostate cancer.

19. The method of claim 17 or claim 18, wherein the one or more additional markers of prostate cancer is selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, kartin 18, keratin 19, and tubulin-beta 3.

20. A kit for detecting filamin A in a biological sample from a subject having, suspected of having, or at risk for having prostate cancer when used in the method of any one of claims 1-19, comprising at least one reagent for measuring the level of filamin A in the biological sample from the subject, and a set of instructions for measuring the level of filamin A in the biological sample from the subject.

21. The kit of claim 20, wherein the reagent is an anti-filamin A antibody or an oligonucleotide that is complementary to a filamin A mRNA.
22. A panel when used in the method of any one of claims 1 to 19, the panel comprising at least two detection reagents, wherein each detection reagent is specific for the detection of at least one prostate cancer marker of a set of markers, wherein the set of markers comprises filamin A and at least one other prostate cancer related marker selected from the group consisting of filamin B, LY9, keratin 4, keratin 7, keratin 8, keratin 15, keratin 18, keratin 19, tubulin-beta 3 and PSA.
23. A kit when used in the method of any one of claims 1 to 19, the kit comprising the panel of claim 22 and a set of instructions for obtaining diagnostic information based on a level of the one or more markers of prostate cancer.

FIG. 1



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FIG. 2A

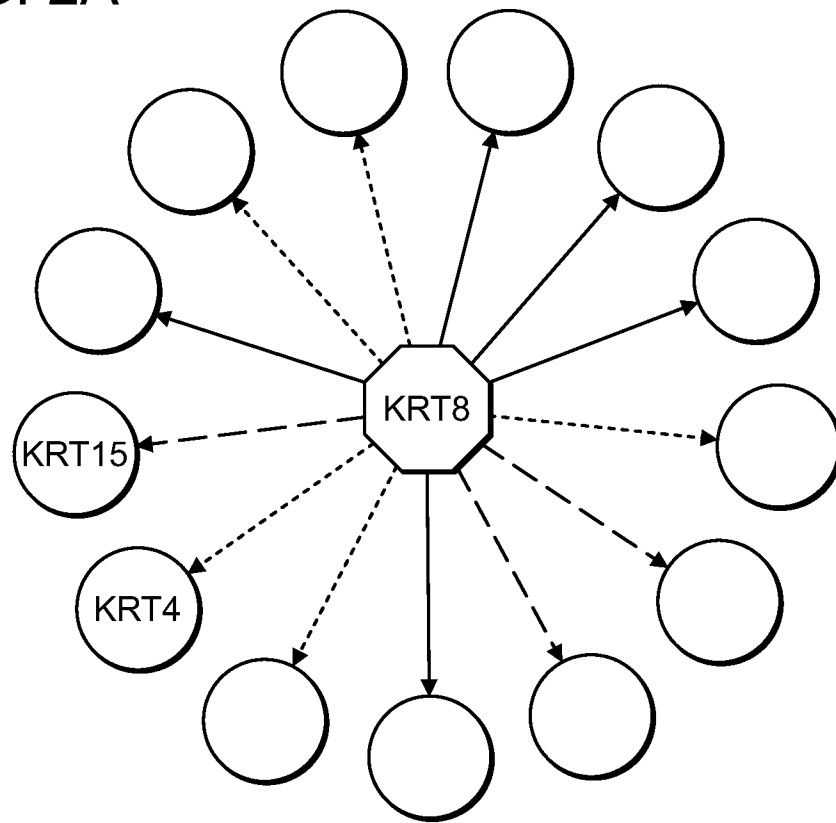
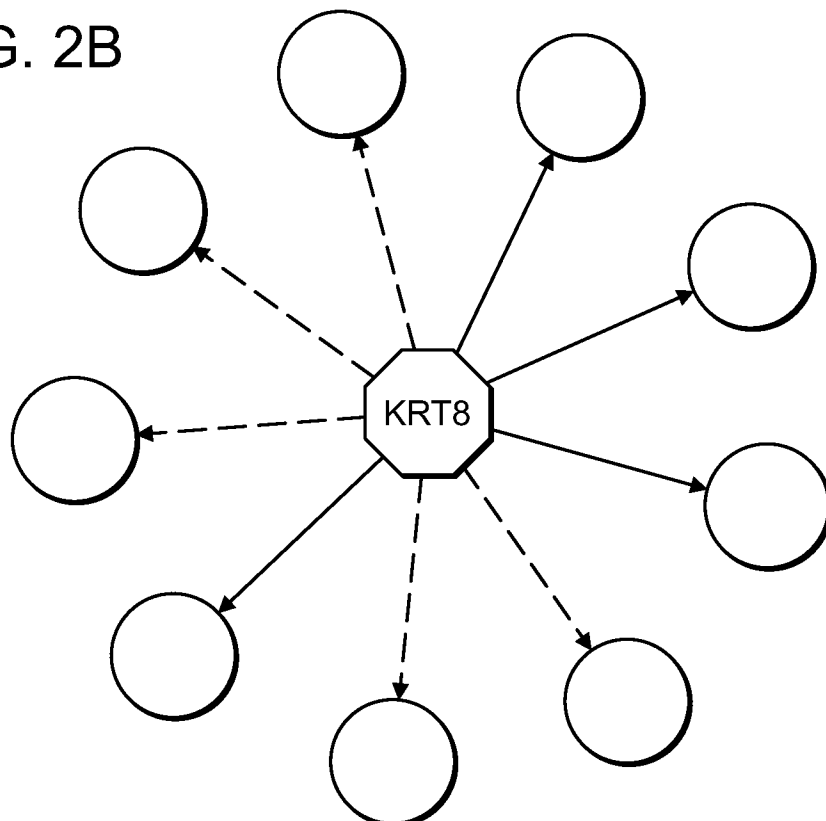


FIG. 2B



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FIG. 2C

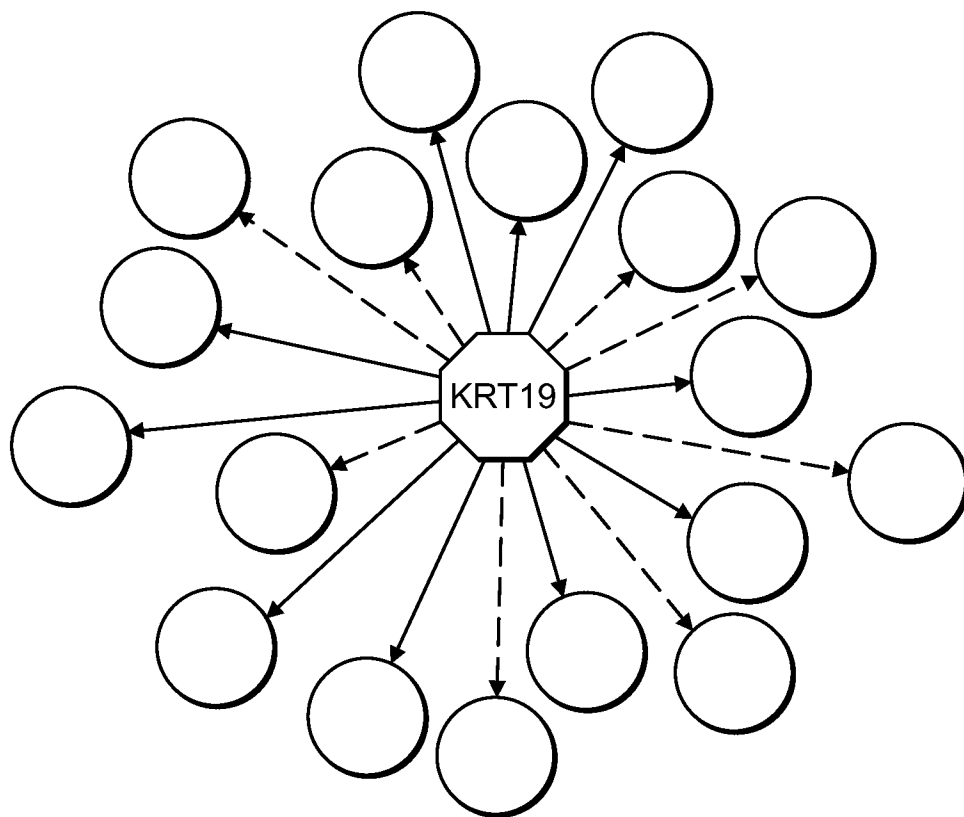


FIG. 3A

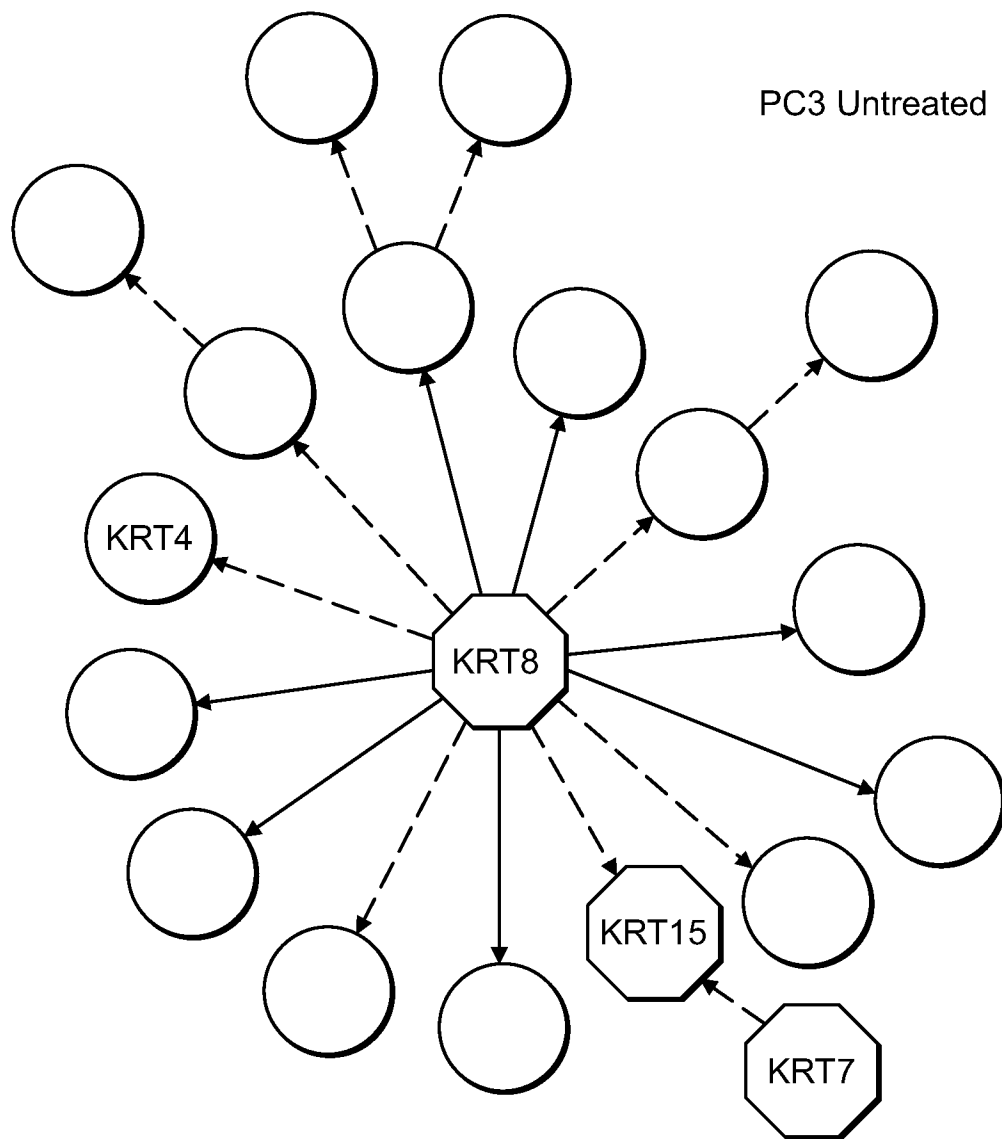
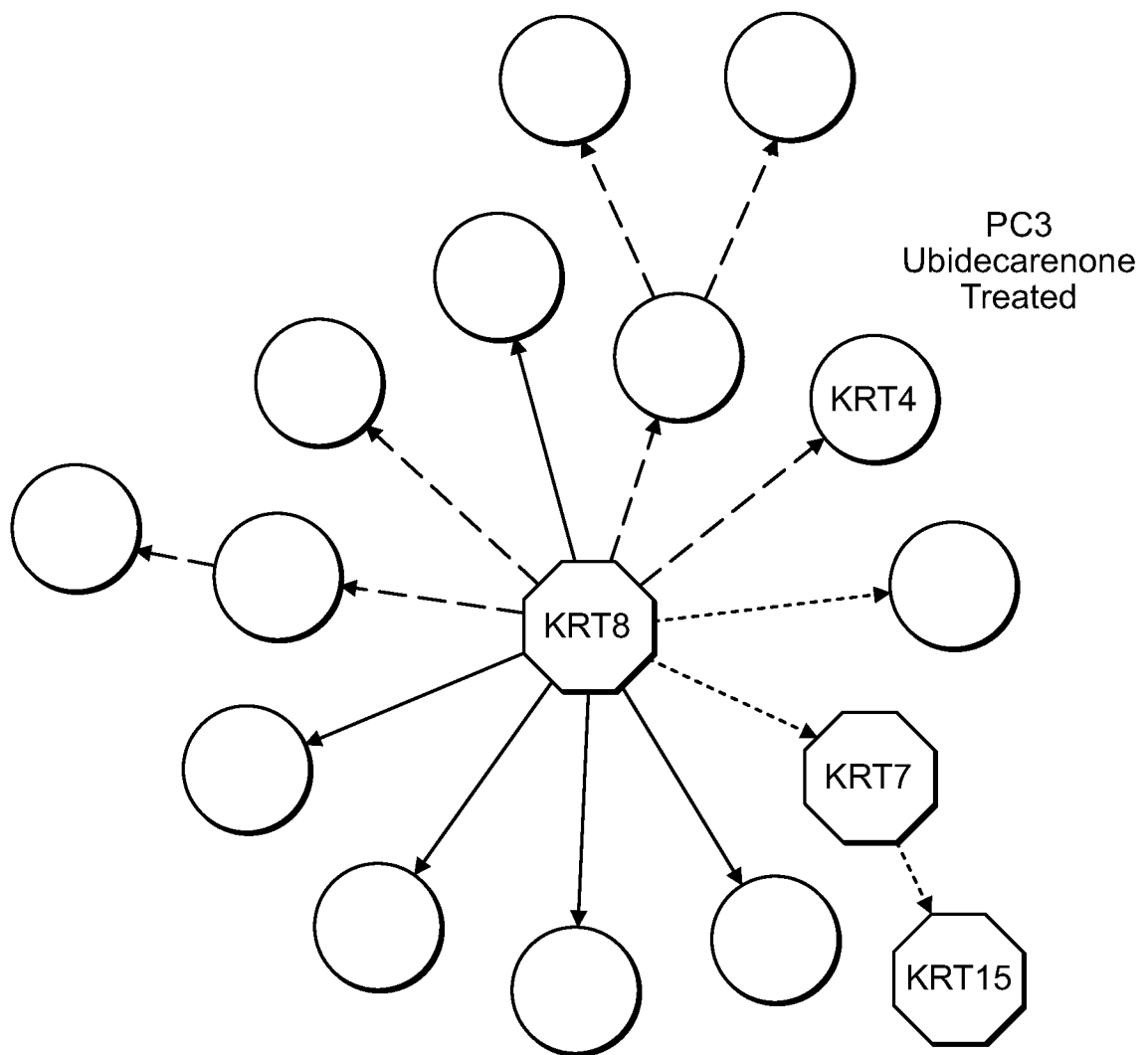
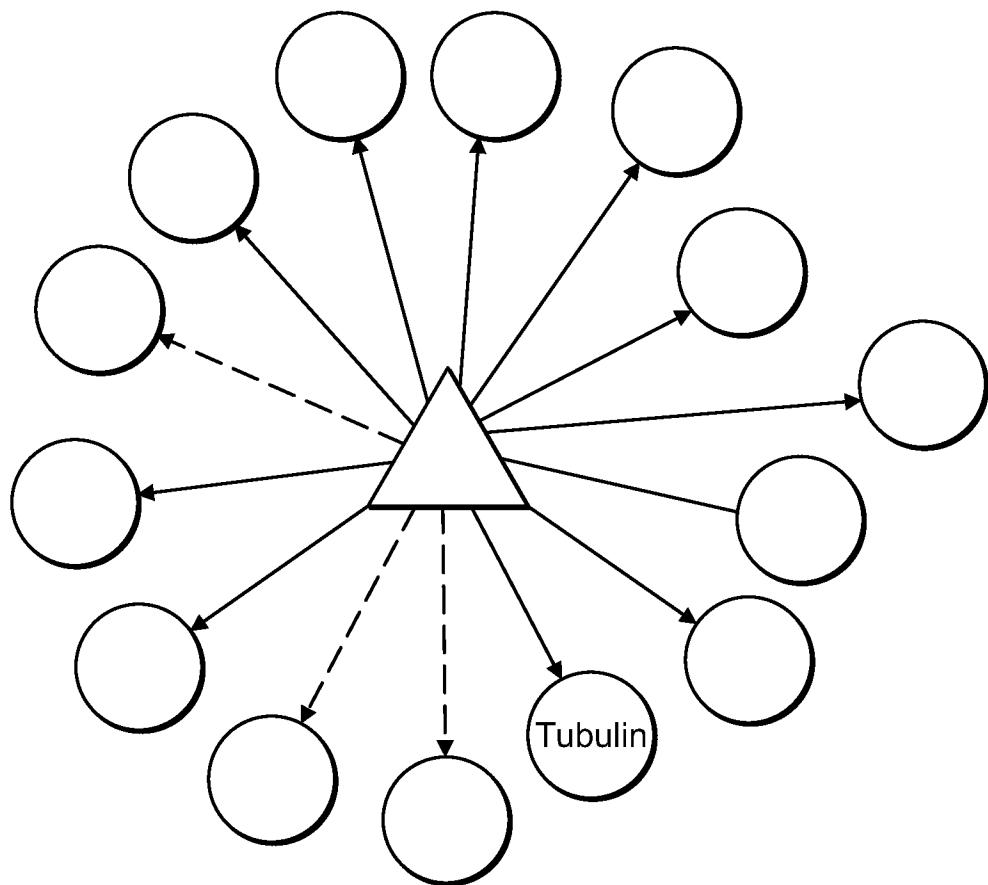


FIG. 3B



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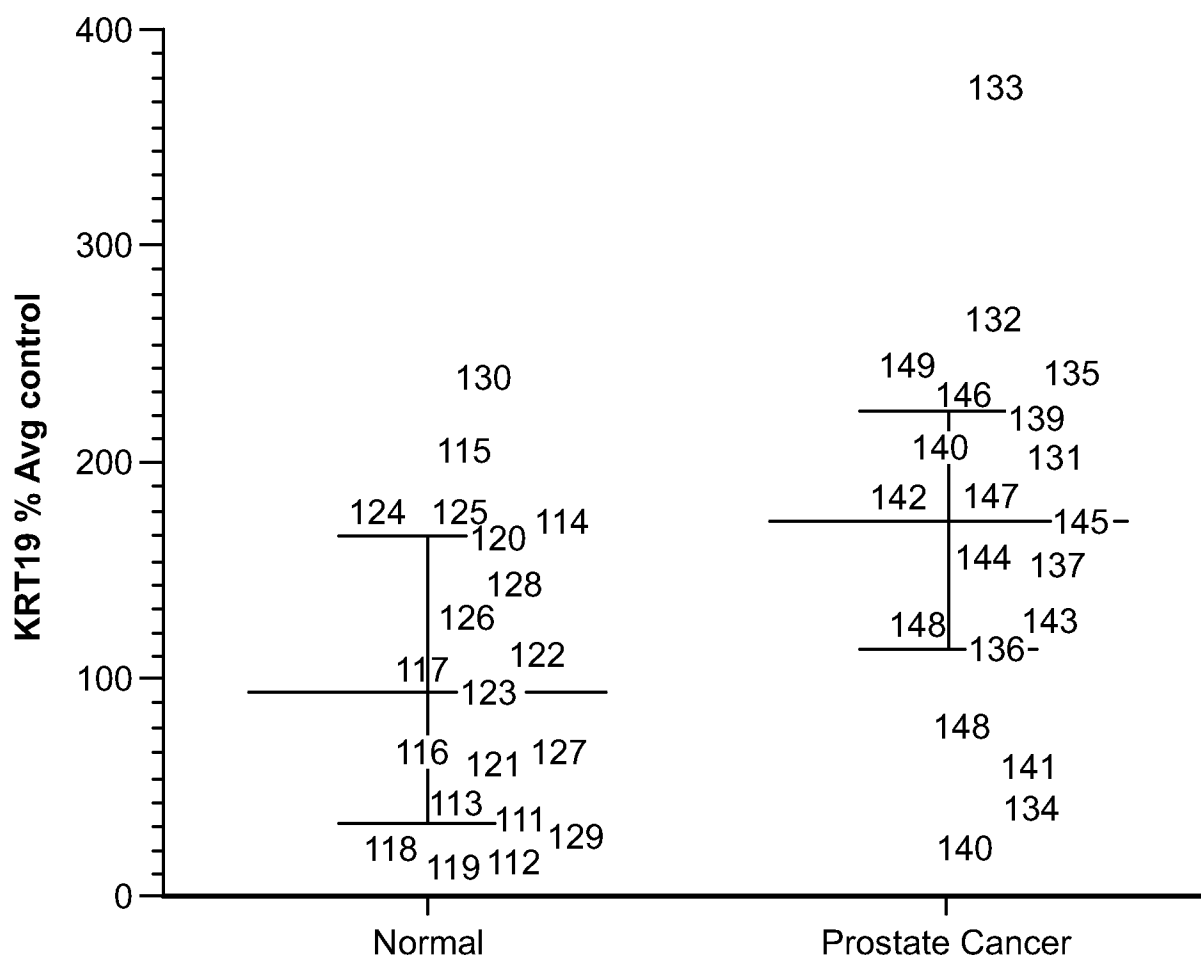
FIG. 3C



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FIG. 3D

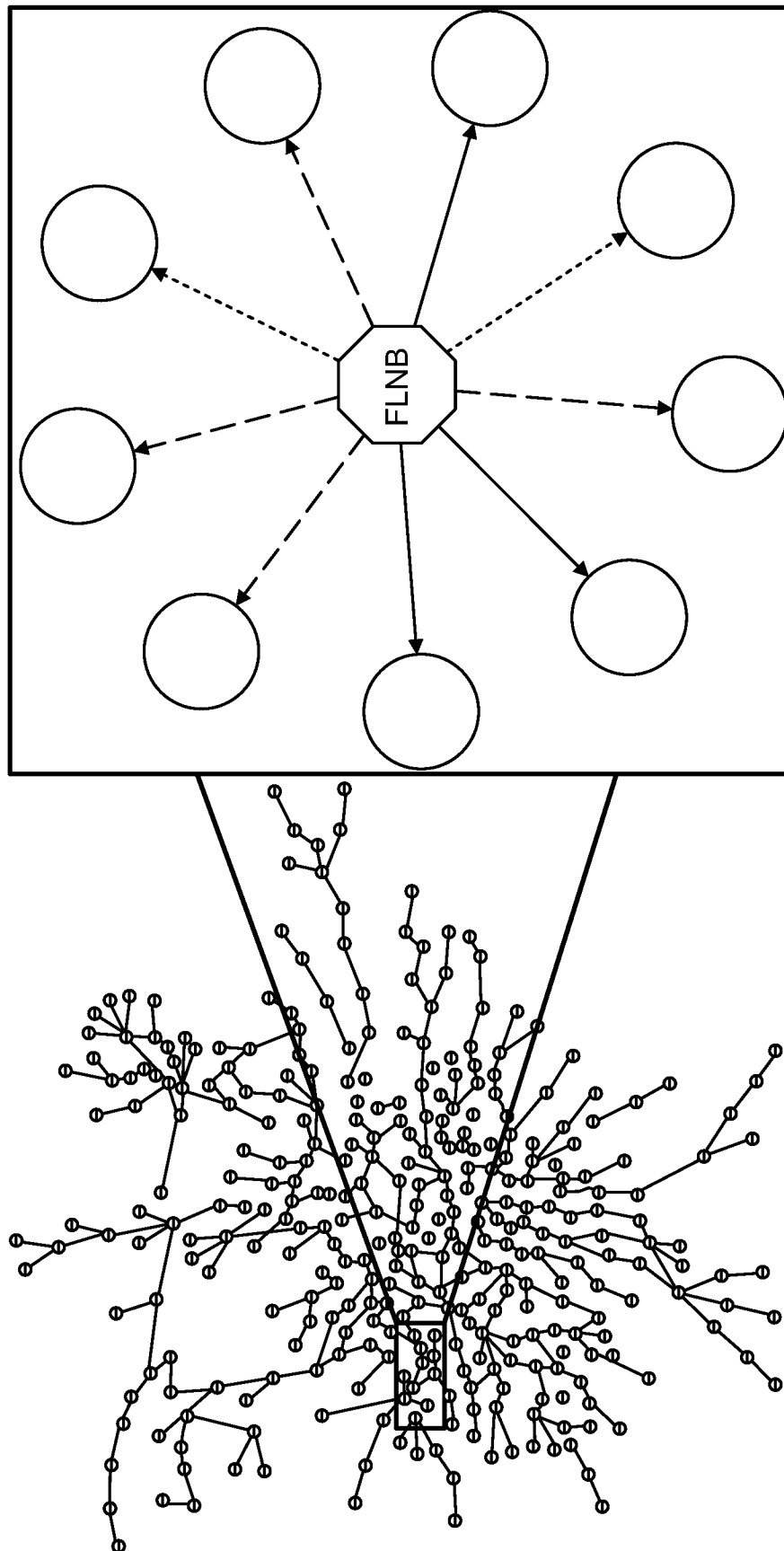
KRT19 Levels in Human Prostate Cancer Serum Set 2



Bars represent median with interquartile range

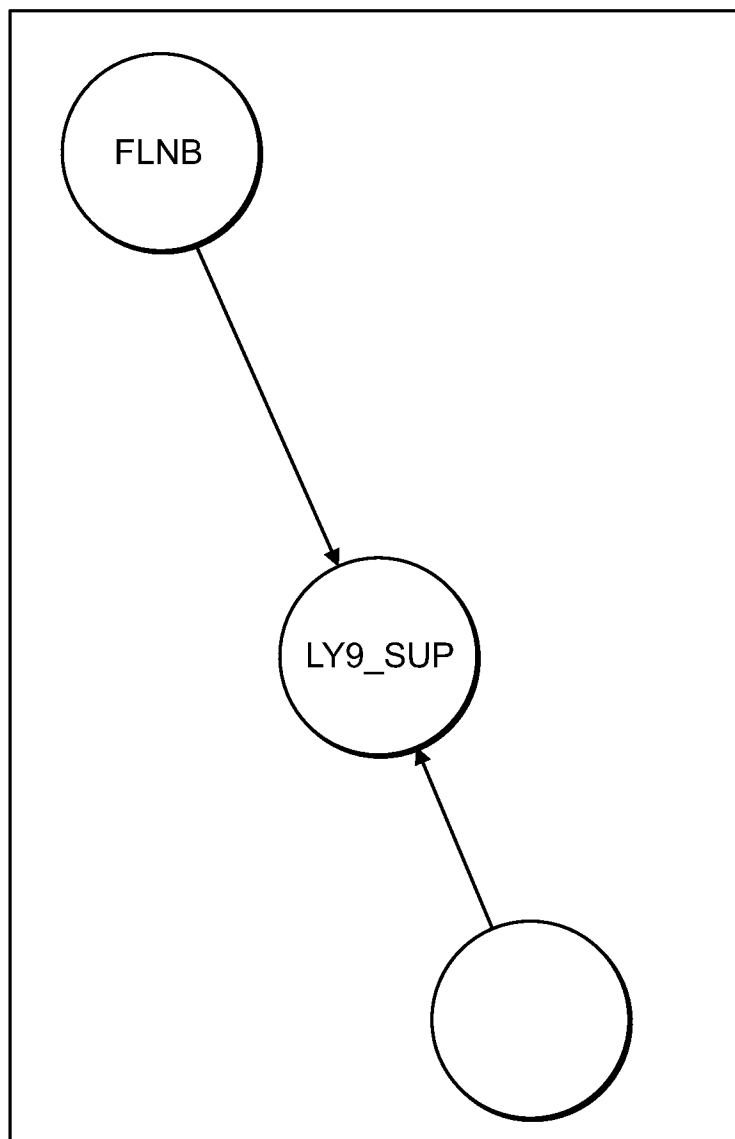
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FIG. 4



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FIG. 5



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FIG. 6A

Mean FLNB Levels in Human Serum n=2

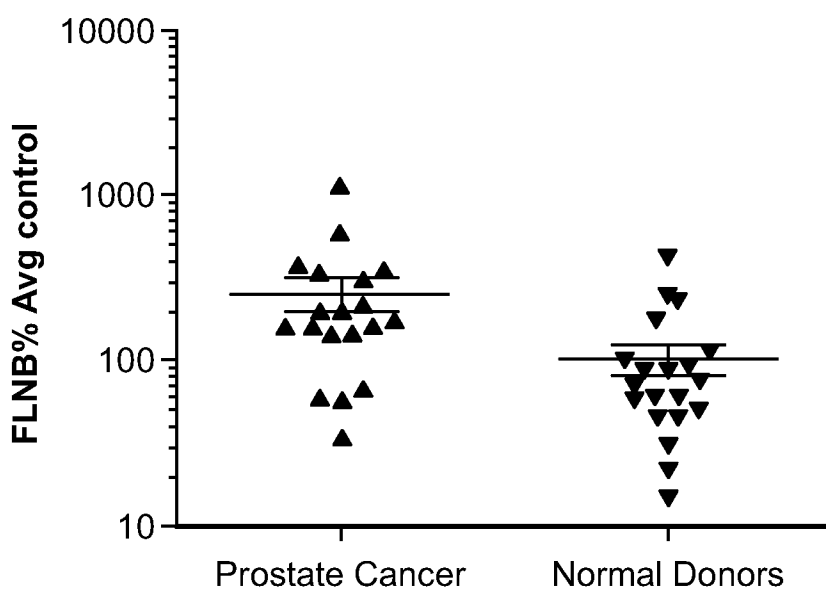
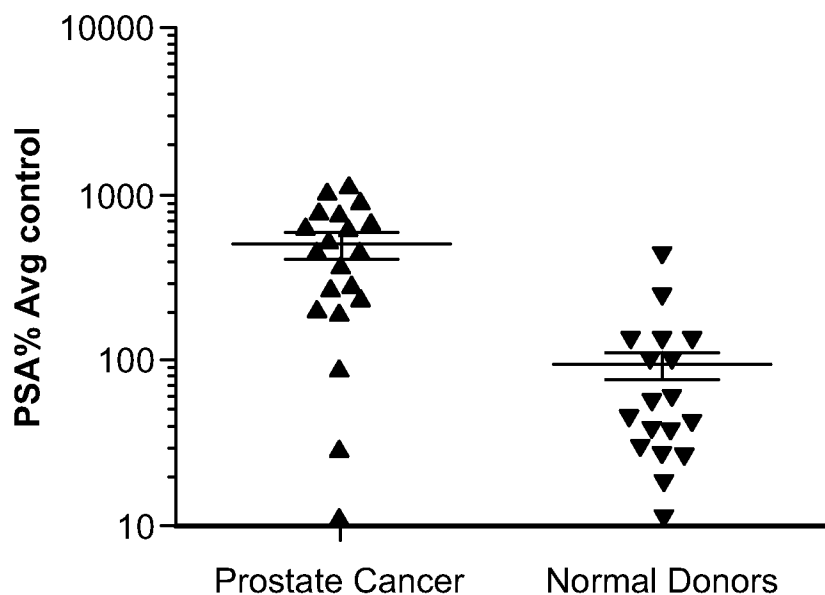


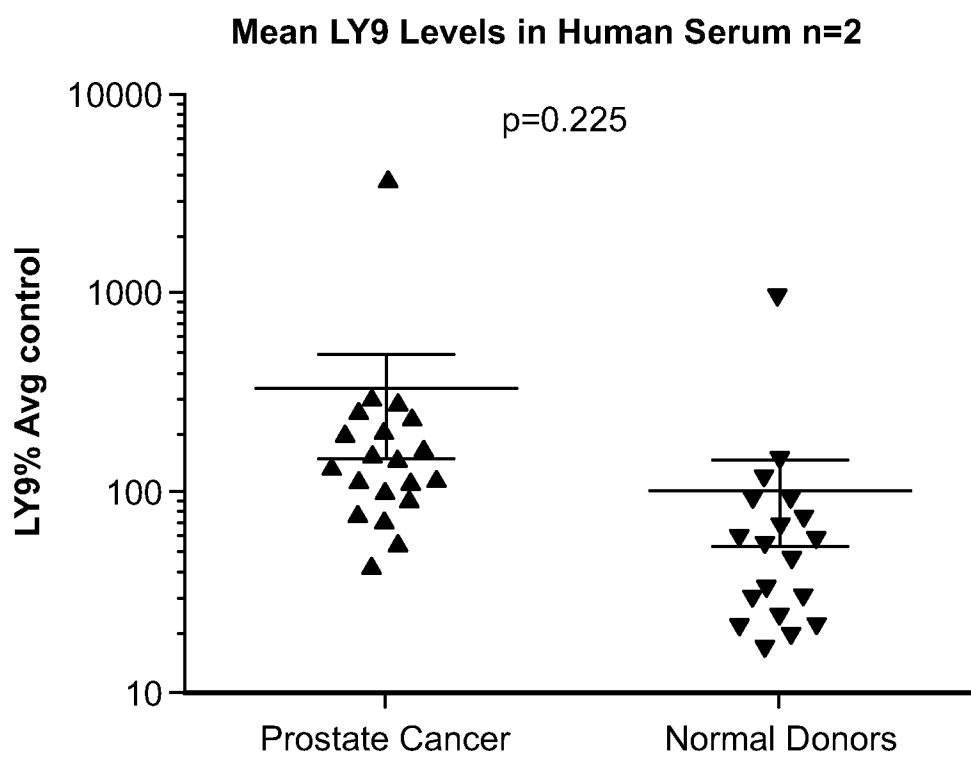
FIG. 6B

PSA Levels in Human Serum



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FIG. 7



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FIG. 8A

FLNB: p-value=0.001

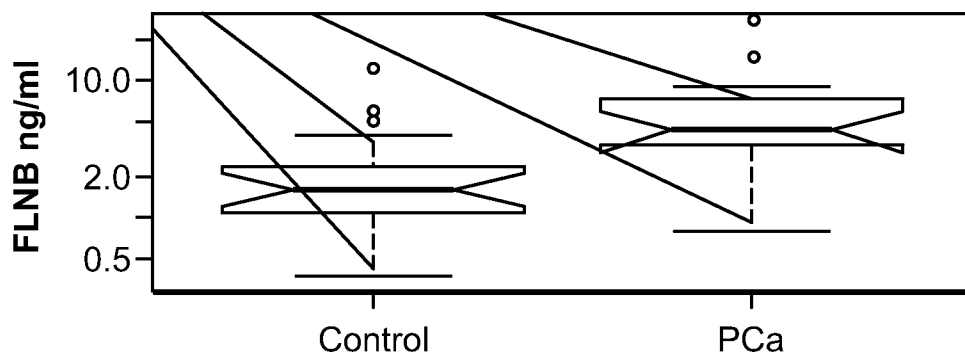


FIG. 8B

LY9: p-value=0.0014

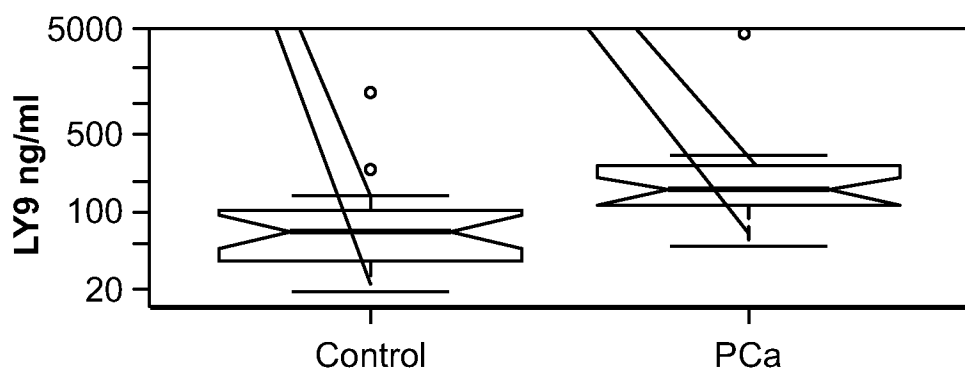
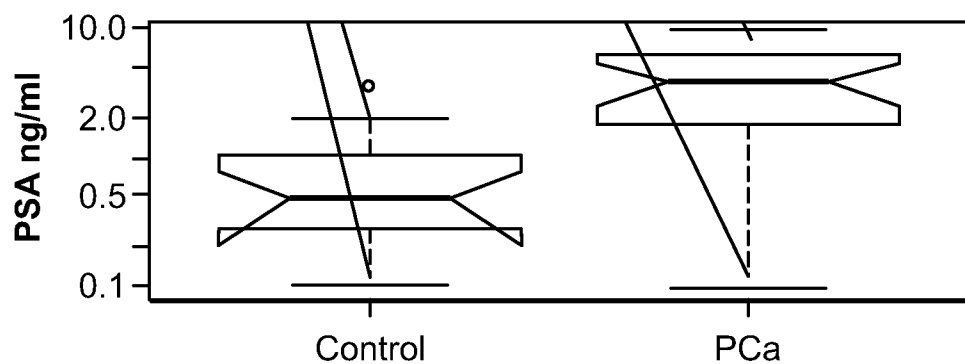


FIG. 8C

PSA: p-value=0.0002



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FIG. 9A

ROC curves for PSA, FLNB and combination

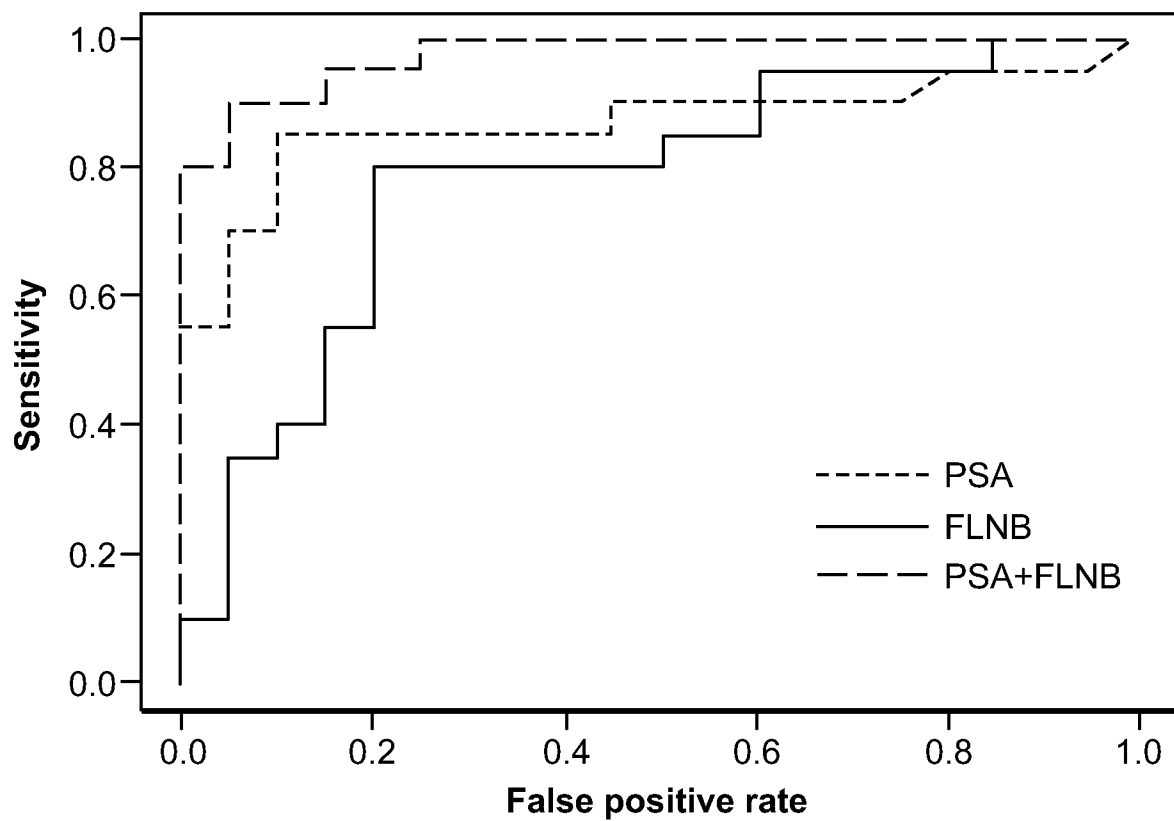


FIG. 9B

Marker	AUC
PSA	0.87
FLNB	0.78
PSA + FLNB	0.975

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FIG. 10A

Linear scoring function

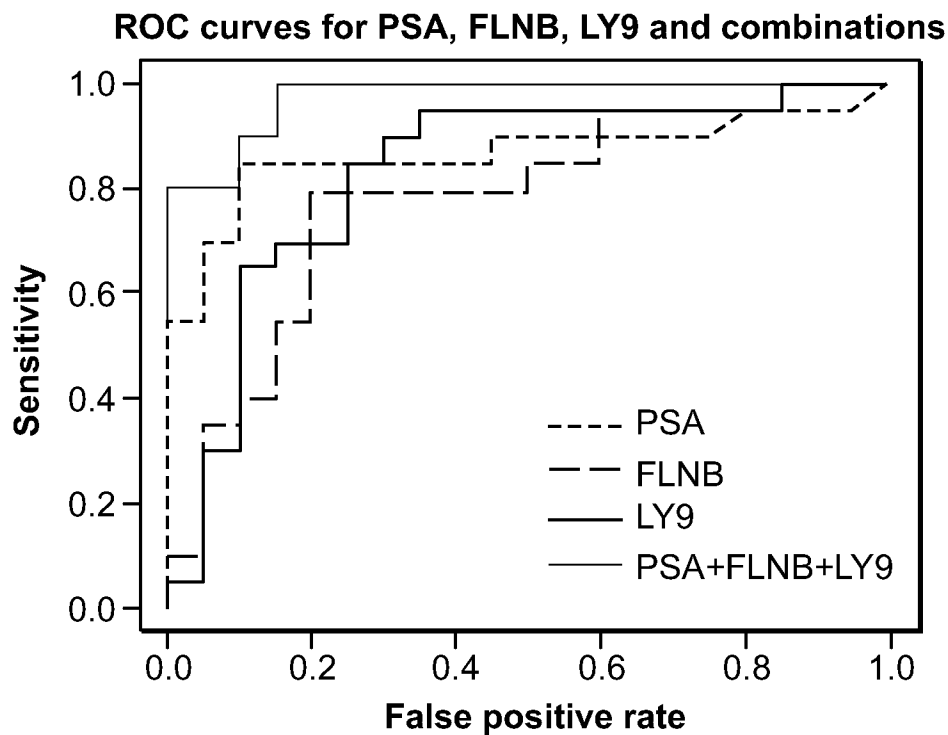
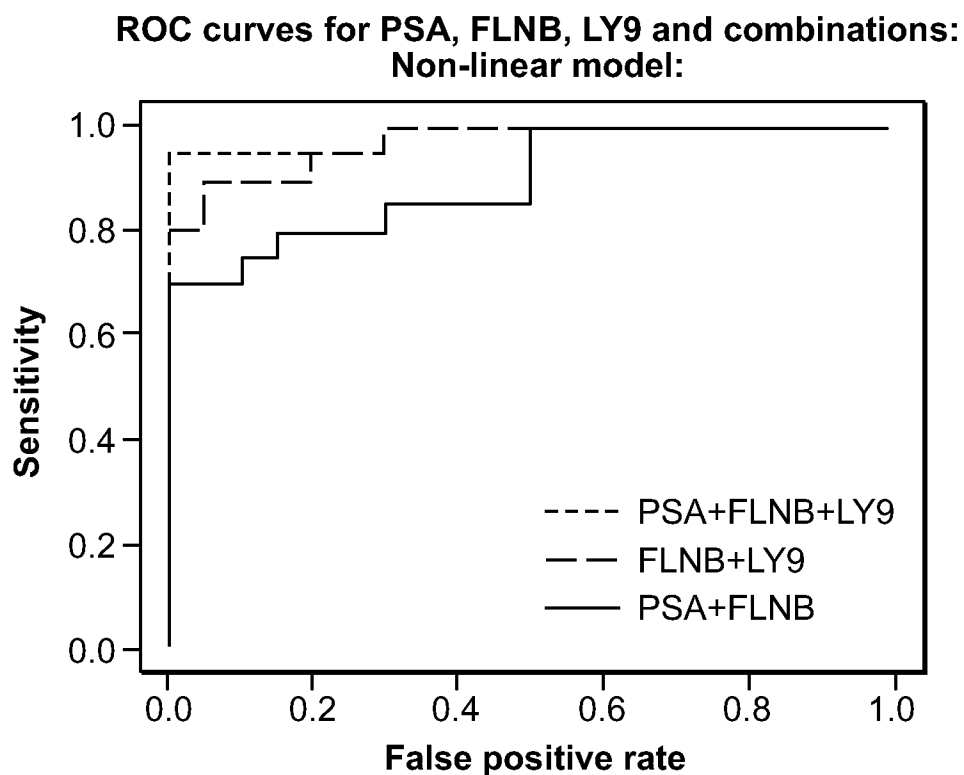


FIG. 10B

Non-Linear scoring function



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FIG. 11

Human Serum (Prostate Cancer)							
Label	Lot Number	UID	Gender	Medications	Race	Diagnosis	Age
1	BRH590798	71152	Male	Vitamin D, Citracal	Hispanic	Prostate cancer	59
2	BRH590799	70021	Male	Multivitamins	African American	Prostate Cancer	50
3	BRH590800	7074	Male	Multivitamin; Aspirin; Paxil; Albuterol; Levitra	Caucasian	Prostate Cancer	63
4	BRH590801	72295	Male	Aredia, Trelstar	Caucasian	Prostate cancer	76
5	BRH590802	72297	Male	Casodex, Metoprolol, Clonidine, Amlodipine, Zometa, Lupron	African American	Prostate cancer	59
6	BRH590803	23738	Male	Lexapro; Pravastatin	Caucasian	Prostate Cancer	49
7	BRH590804	23796	Male	Keppra; Aspirin; Calcium; Prilosec; Taxotere	Caucasian	Prostate Cancer	62
8	BRH590805	71712	Male	Aredia, Lupron, Casodex, Restoril, Hydroxycodone	Caucasian	Prostate cancer, 5'11 bone LN, Hypoproliferative anemia	75
9	BRH590806	71119	Male	Lipitor	Caucasian	Prostate cancer; Acid reflux, High Cholesterol	47
10	BRH590807	25716	Male	Prilosec; Lipitor	Caucasian	Prostate Cancer; High Cholesterol	54

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FIG. 11 (cont.)

Normal Serum					Other Comments	Surgery	Stage
Label	Lot Number	Gender	Race	Age			
21	BRH590923	Male	Caucasian	57	Date of diagnosis 4/29/11, Stage of prostate cancer TNM, T1C	Radiation for prostate cancer	TNM, T1C
22	BRH590924	Male	Caucasian	48	PSA Level: 4, grade = 3	Hernia	Pre-Treatment, 1C
23	BRH590925	Male	Caucasian	59		Double Hernia	Stage T1C; PSA Level:6; Gleason Score:7
24	BRH590926	Male	Caucasian	72	Patient undergoing chemotherapy		Stable disease state; 4
25	BRH590927	Male	African American	57			Stable disease state; 4
26	BRH590928	Male	Caucasian	48			Stage T1C
27	BRH590929	Male	Caucasian	59			Stage 4; Flare-Up
28	BRH590930	Male	Caucasian	68			Stable disease state; 4
29	BRH590931	Male	Caucasian	45	Prostate cancer stage T1C, Date of diagnosis 7/11, PSA level 2.6, Gleason score 6	Arthroscopic Knee Tonsillectomy, Appendectomy, Fissurectomy	T1C
30	BRH590932	Male	Caucasian	50			Stable; Stage T1C

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FIG. 11 (cont.)

11	BRH590808	30186	Male	Vytorin; Atenolol; Altace; Aspirin	Hispanic	Prostate Cancer; High Cholesterol	62
12	BRH590809	72135	Male	ASA; MVI; Vantin; Septra	African American	Prostate cancer	48
13	BRH590810	100989	Male	Casodex, Lupron	Caucasian	Prostate cancer	80
14	BRH590811	49545	Male	Tri-Cor; Prilosec; Klor-Con; Edecrin; Simvastatin; Vitamin D	Caucasian	Prostate Cancer; High Cholesterol	69
15	BRH590812	49568	Male	Lupron; Depot; synthroid	Caucasian	Prostate Cancer; High Cholesterol; HTN; Thyroid	54
16	BRH590813	49564	Male	Benicar; Atenolol; Neurotin; Plavix; Prednisone; Cymbalta; Zometa	Caucasian	Prostate Cancer	75
17	BRH590814	103500	Male	Prochlorperazine, maleate, Prednisone, Resveratrol, Synthroid, Lisinopril, Lasix	Caucasian	Prostate Cancer	86
18	BRH590815	45168	Male	None	Caucasian	Prostate Cancer	58
19	BRH590816	61323	Male	Aspirin; Benicar; Amlodipine; Triamterene; Multaq	Caucasian	Prostate Cancer; Atrial Fibrillation; High Cholesterol	60
20	BRH590817	61324	Male	Allopurinol; Aspirin; Vitamins	Caucasian	Prostate Cancer; Atrial Fibrillation	68

FIG. 11 (cont.)

Stage T1C	Robotic Prostatectomy (8/16/10) ; Heart Stents x4		31	BRH590933	Hispanic	58
T1C	Back surgery	Prostate cancer stage T1C; Date of diagnosis 9/16/11; PSA value 4.23; Gleason score 7	32	BRH590934	African American	46
Stable Disease State	Ulcers, Hernia	Date of diagnosis 4/17/01, Grade T1C, Gleason score 7; PSA=12.33	33	BRH590935	Caucasian	71
Stage 4; Stable	Appendectomy; Craniotomy; Thoracoscopy		34	BRH590936	Caucasian	66
Stage 4; Stable			35	BRH590937	Caucasian	52
Stage 4; Stable	Bariatric Surgery; Prostate Seed Implants		36	BRH590938	Caucasian	70
4	Partial Thyroidectomy 1958	Date of diagnosis 4/17/01, Grade T1C, Gleason score 7	37	BRH590939	Caucasian	71
PreTreatment		PSA= 4.4, Grade 7, Stage 3b	38	BRH590940	Caucasian	56
Stage T1C; PreTreatment	Cardiac Ablation	PSA Level= 2.6; Gleason Score=6	39	BRH590941	Caucasian	58
Stage T2b; PreTreatment	Valve Replacement Repair	PSA Level=9.3; Gleason Score=7, grade = 4	40	BRH590942	Caucasian	63

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FIG. 12

Label	Vendor	Prostate Cancer Stage	Case ID / Lot	Specimen ID	Age	Sex	Ethnicity	Clinical Test Results
111	Bioreclamation		BRH621393		67	Male	Hispanic	
112	Bioreclamation		BRH621389		49	Male	African American	
113	Bioreclamation		BRH621390		63	Male	African American	
114	Bioreclamation		BRH621391		54	Male	Hispanic	
115	Bioreclamation		BRH621392		66	Male	African American	

FIG. 12 (cont.)

Clinical Diagnosis (specimen)	Clinical Diagnoses (patient)	Medications
Normal control donor	Normal control donor (Status: Ongoing)	
Normal control donor	Normal control donor (Status: Ongoing)	
Normal control donor	Normal control donor (Status: Ongoing)	
Normal control donor	Normal control donor (Status: Ongoing)	
Normal control donor	Normal control donor (Status: Ongoing)	

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FIG. 12 (cont.)

116	Astrand		69871	248975A8	65	Male	Caucasian	
117	Astrand		66017	220676A8	56	Male	Caucasian	
118	Astrand		66010	220673A8	56	Male	Caucasian	
119	Astrand		65953	220643A8	59	Male	Caucasian	
120	Astrand		69874	248976A8	66	Male	Caucasian	
121	Astrand		67494	235614A8	55	Male	Caucasian	
122	Astrand		69865	248981A7	65	Male	Caucasian	
123	Astrand		67461	235607A6	56	Male	Caucasian	
124	Astrand		67502	235640A7	59	Male	Caucasian	
125	Astrand		69929	263798A7	62	Male	Caucasian	

FIG. 12 (cont.)

Normal control donor	Normal control donor (Status: Ongoing)	
Normal control donor	Normal control donor (Status: Ongoing)	
Normal control donor	Normal control donor (Status: Ongoing)	
Normal control donor	Normal control donor (Status: Ongoing)	
Normal control donor	Normal control donor (Status: Ongoing)	
Normal control donor	Normal control donor (Status: Ongoing)	
Normal control donor	Normal control donor (Status: Ongoing)	
Normal control donor	Normal control donor (Status: Ongoing)	
Normal control donor	Normal control donor (Status: Ongoing)	
Normal control donor	Normal control donor (Status: Ongoing)	

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FIG. 12 (cont.)

126	Astrand		69926	263785A8	65	Male	Caucasian	
127	Astrand		62916	196638A7	50	Male	Caucasian	
128	Astrand		69908	263789A8	66	Male	Caucasian	
129	Astrand		69892	263771A6	64	Male	Caucasian	
130	Astrand		69896	263762A8	69	Male	Caucasian	
131	Bioreclamation	Stage I	BRH621388	84101	85	Male		PSA: 0.1, Gleason score: 7 & 8
132	Bioreclamation	Stage I	BRH621384	71119	47	Male		PSA: 2.6, Gleason score: 6
133	Bioreclamation	Stage I	BRH621385	71299	66	Male		Gleason score: 7
134	Bioreclamation	Stage I	BRH621386	73599	57	Male		Gleason score: 7
135	Bioreclamation	Stage I	BRH621387	100989	80	Male		Gleason score: 7

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FIG. 12 (cont.)

Normal control donor	Normal control donor (Status: Ongoing)	
Normal control donor	Normal control donor (Status: Ongoing)	
Normal control donor	Normal control donor (Status: Ongoing)	
Normal control donor	Normal control donor (Status: Ongoing)	
Normal control donor	Normal control donor (Status: Ongoing)	
		Uroxatrol, Vesicare, Atenolol, Furosemide, KlorCon, ASA, Calcium chew
		Lipitor
		Levothyroxine, Metformin, Glimepiride, Avapro, Atenolol, Chlorothalidone, Proscar, Flomax
		Aspirin, Carvediol, Lipitor, Losartan, Januvia
		Casodex, Lupron

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FIG. 12 (cont.)

136	Astrand	Stage II	64938	220537A6	65	Male	Caucasian	PSA: 0.32(ng/ml)
137	Astrand	Stage II	64960	222331A8	55	Male	Caucasian	PSA: 4.5(ng/ml), Gleason score: 6(3+3=6)
138	Astrand	Stage II	67709	248842A6	56	Male	Caucasian	PSA: 5.34(ng/ml), Gleason score: 7(3+4=7)
139	Astrand	Stage II	65594	220578A8	59	Male	Caucasian	PSA: 7.5(ng/ml), Gleason score: 5(3+2=5)
140	Astrand	Stage II	65451	224670A8	73	Male	Caucasian	PSA: 15.7(ng/dl), Gleason score: 6(3+3=6)
141	Astrand	Stage III	64030	217315A8	56	Male	Caucasian	PSA: 2.8(ng/ml), Gleason score: 9(4+5=9)

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FIG. 12 (cont.)

Adenocarcinoma of the prostate gland	Hypertension (Status: Ongoing), Adenocarcinoma of the prostate gland (Status: New)	Enalapril
Adenocarcinoma of the prostate gland	Adenocarcinoma of the prostate gland (Status: New)	Multivitamin, Cod liver oil, Flonase
Adenocarcinoma of the prostate gland	Hypercholesterolemia (Status:), Depression (Status:), Anxiety (Status:), Gout (Status:), Borderline diabetes (Status:), Gastroesophageal reflux disease (Status:), Adenocarcinoma of the prostate gland (Status: New)	Crestor, Uloric, Tamsulosin, Amitiza, Nexium, Ambien, Xanax, Celexa
Adenocarcinoma of the prostate gland	Adenocarcinoma of the prostate gland (Status: New)	
Adenocarcinoma of the prostate gland	Hypertension (Status: Ongoing), Adenocarcinoma of the prostate gland (Status: New)	
Adenocarcinoma of the prostate gland	Pericarditis (Status: Past), Petit mal seizures (Status: Past), Increased cholesterol (Status: Ongoing), Adenocarcinoma of the prostate gland (Status: New)	Allegra-D, Zocor, Lexapro, Ambien, Viagra, Multivitamin, Tylenol pm

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FIG. 12 (cont.)

142	Astrand	Stage III	66588	238745A8	68	Male	Caucasian	PSA: 4.44(ng/ml), Gleason score: 8(4+4=8)
143	Astrand	Stage III	63718	217346A8	56	Male	Caucasian	PSA: 5.6(ng/ml), Gleason score: 6(3+3=6)
144	Astrand	Stage III	63191	190121A8	59	Male	Caucasian	PSA: 15.5(mmol/L), Gleason score: 7(3+4=7)
145	Astrand	Stage III	66517	238792A8	62	Male	Caucasian	PSA: 24.72(ng/ml), Gleason score: 9(4+5=9)
146	Astrand	Stage IV	66533	241880A8	76	Male	African American	PSA: 1.31(ng/ml)

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FIG. 12 (cont.)

Adenocarcinoma of the prostate gland	Sleep apnea (Status: Ongoing), Osteoarthritis (Status: Ongoing), Type 2 diabetes (Status: Ongoing), Gastroesophageal reflux disease (Status: Ongoing), Adenocarcinoma of the prostate gland (Status: New)	Alprazolam, Tramadol hcl, Loratadine, Lisinopril, Simvastatin, Metformin HCl, Ranitidine, Fenobirate, Glipizide, Actos
Adenocarcinoma of the prostate gland	Osteoarthritis of the neck (Status: Ongoing), Hypertension (Status: Ongoing), Adenocarcinoma of the prostate gland (Status: New)	Green vibrance, Diovan, Aspirin, Excedrin
Adenocarcinoma of the prostate gland	Hypertension (Status: Ongoing), Adenocarcinoma of the prostate gland (Status: New)	Gibomet, Enalapril
Acinar cell adenocarcinoma of the prost	Hypertension (Status: Ongoing), Hypercholesterolemia (Status: New), Glaucoma (Status: Ongoing), Acinar cell adenocarcinoma of the prostate Gland (Status: New)	Simvastatin, Amlodipine, Lisinopril, Latanoprost
	Cancer of the prostate - stage 4 (Status: Ongoing)	

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FIG. 12 (cont.)

147	Asterand	Stage IV	70060	262110A8	50	Male	Hispanic	PSA: 3.36(ng/mL), Gleason : 9(4+5=9)
148	Asterand	Stage IV	66534	241895A8	80	Male	Caucasian	PSA: 15.52(ng/ml)
149	Asterand	Stage IV	68411	196648A8	64	Male	Caucasian	PSA: 30(ng/dl), Gleason score:6(3+3=6)
150	Asterand	Stage IV	66950	245729A8	86	Male	Caucasian	PSA: 66.49(ng/ml)

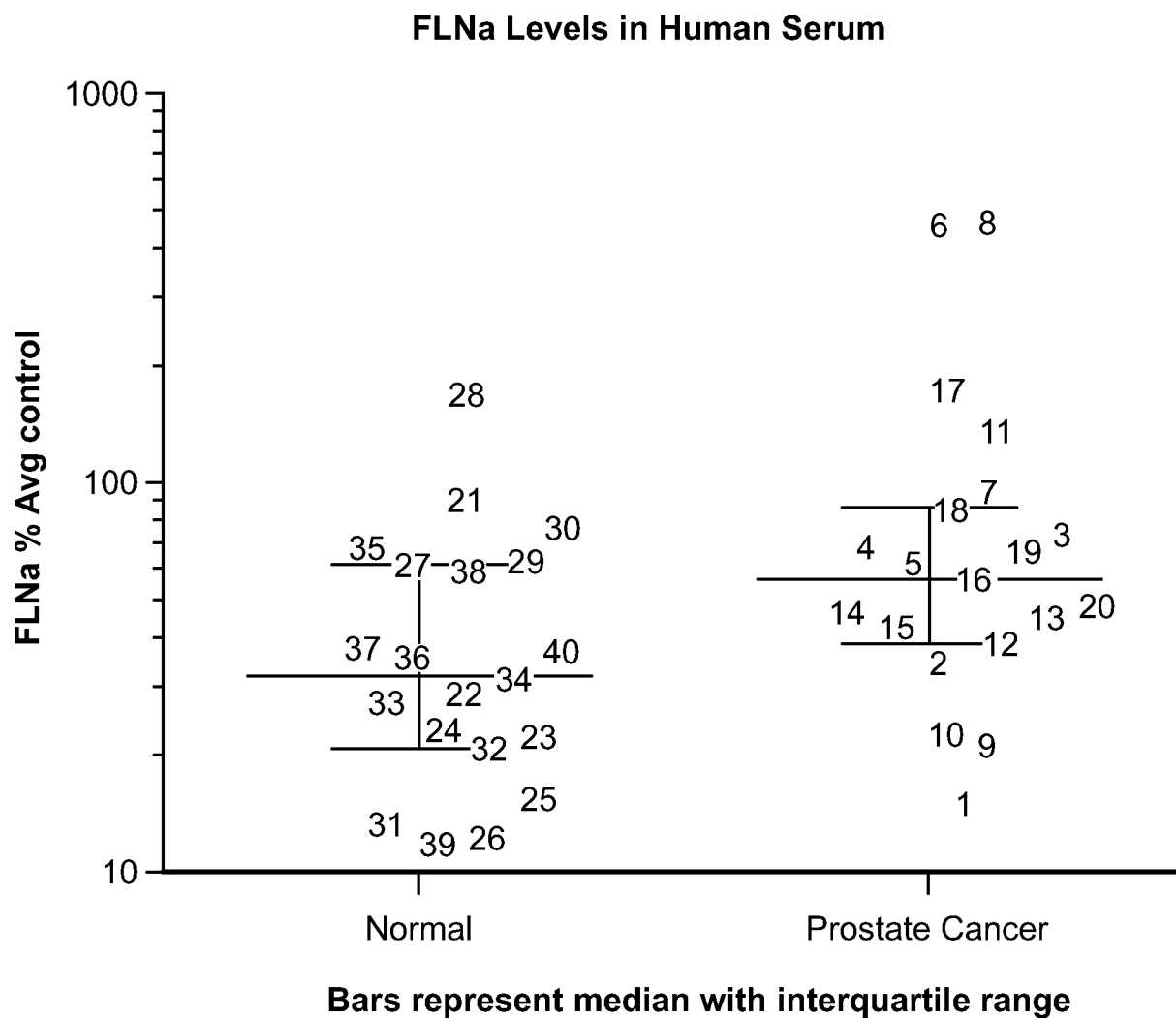
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FIG. 12 (cont.)

Adenocarcinoma of the prostate gland	Diverticulosis (Status: Ongoing), Bilateral inguinal hernia (Status: Ongoing), Depression (Status: Ongoing), Hematospermia (Status: Past), Gastroesophageal reflux disease (Status: Ongoing), Degenerative joint disease (Status: Ongoing), Adenocarcinoma of the prostate (Status: Ongoing), Metastatic neoplasm, adenocarcinoma of the bone marrow (Status: Ongoing)	Bicalutamide, Aredia, Lupron, Zometa, Paxil, Xqeva, Ketconazole, Hydrocortisone, Prednisone, Taxotere, Oxycodone, Fentanyl transdermal patch
	Cancer of the prostate - stage 4 (Status: Ongoing)	
Adenocarcinoma of the prostate gland	Adenocarcinoma of the prostate gland (Status: New)	Avodart
Prostate cancer Stage 4	Chronic obstructive pulmonary disease (Status: Ongoing), Cancer of the prostate - Stage 4 (Status: Ongoing), Degenerative disc disease (Status: Ongoing), Cataract (Status: Past), Cataract (Status: Past)	

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FIG. 13

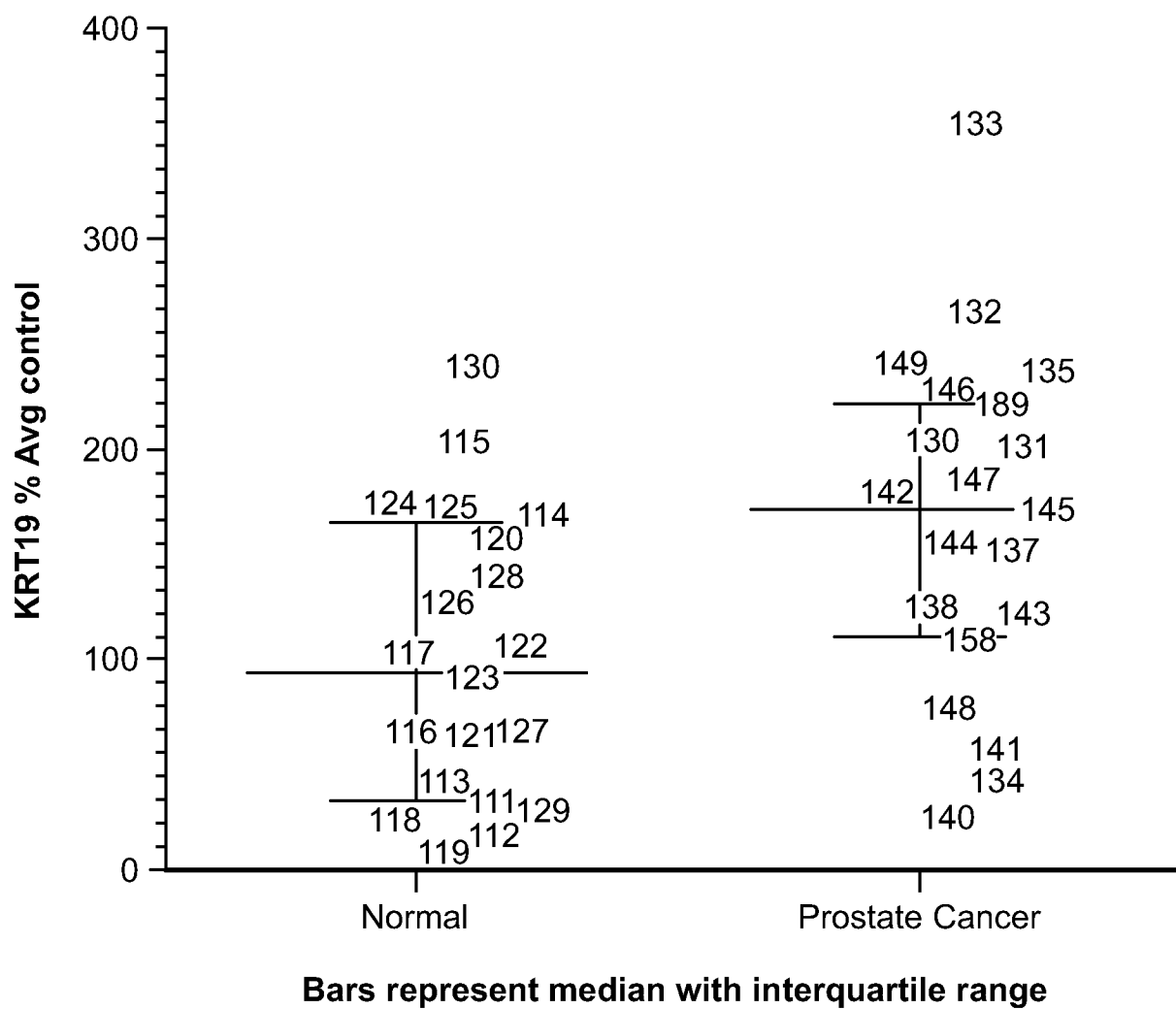
1. FLNa

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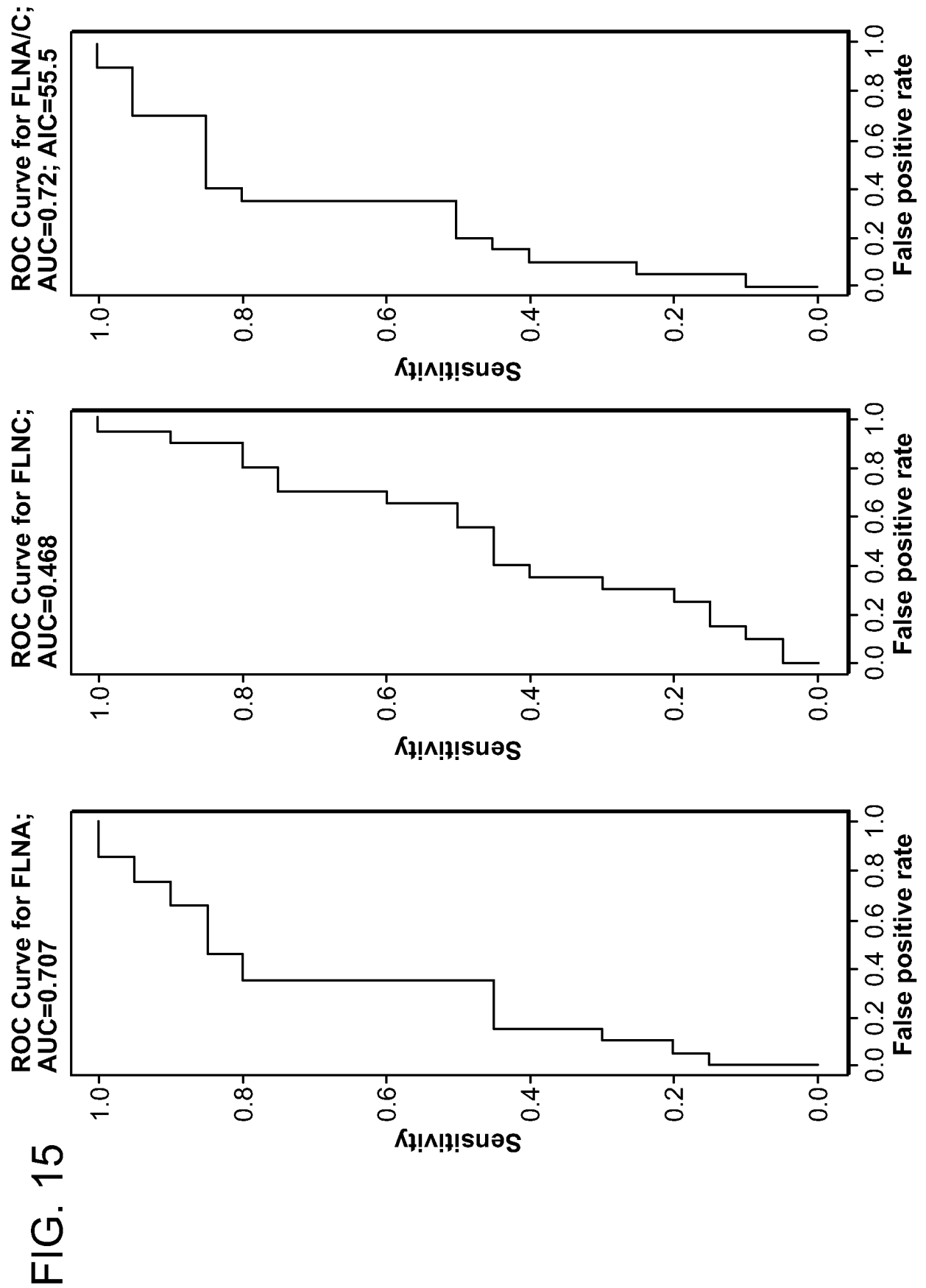
FIG. 14

2. KRT19

KRT19 Levels in Human Prostate Cancer Serum Set 2



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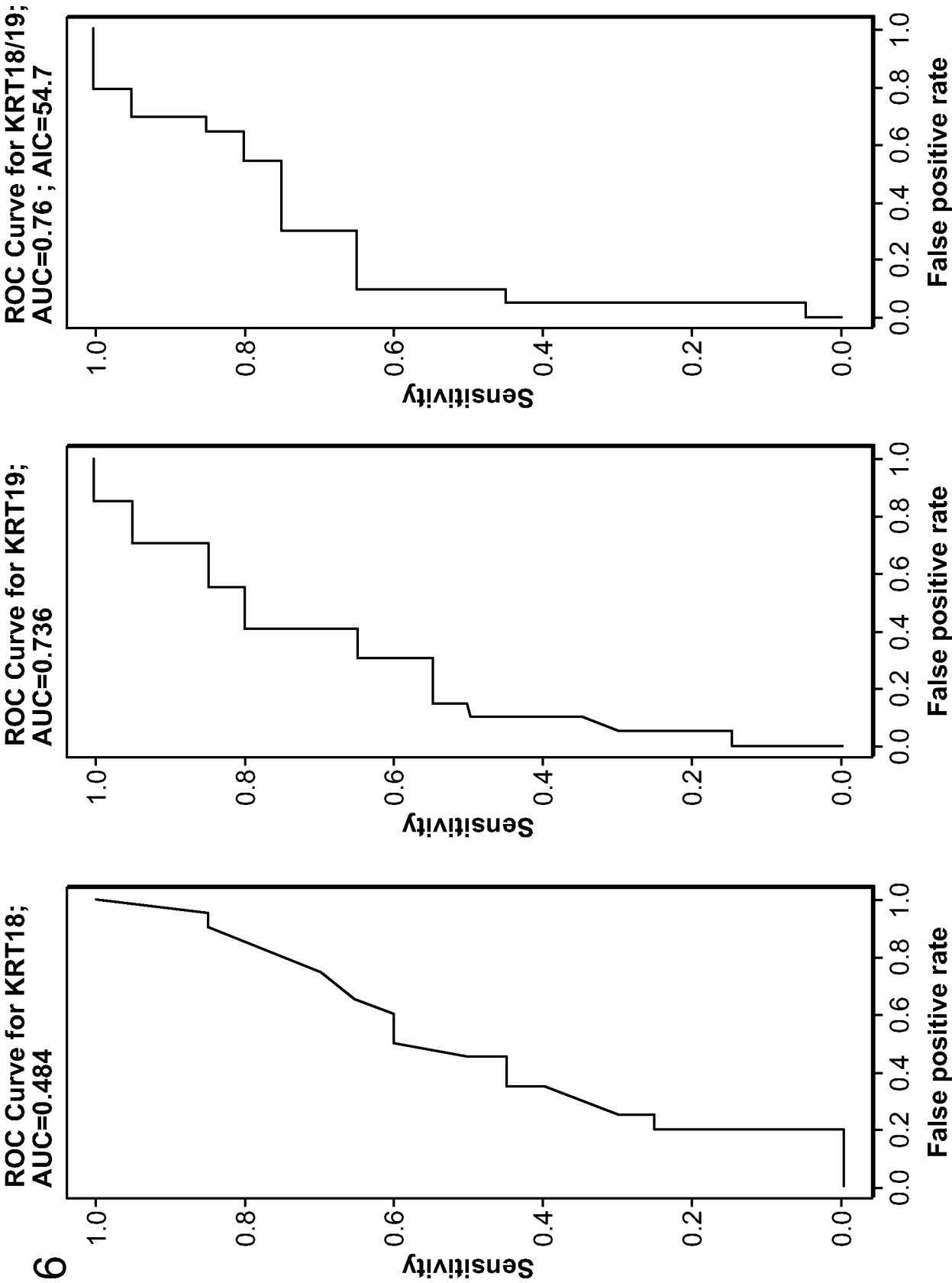


FIG. 16

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FIG. 17

	CA vs. Others		CA vs. BPH		High Gleason vs. Low		High Gleason vs. Others		Super High Gleason vs. Others	
	Biomarker	AUC	Biomarker	AUC	Biomarker	AUC	Biomarker	AUC	Biomarker	AUC
Individual	PSA	0.569	PSA	0.564	PSA	0.619	PSA	0.631	PSA	0.67
	Age	0.62	Age	0.621	Age	0.622	Age	0.662	Age	0.7
	FLNA	0.574	FLNA	0.696	FLNA	0.515	FLNA	0.56	FLNA	0.542
	FLNB	0.51	FLNB	0.516	FLNB	0.528	FLNB	0.515	FLNB	0.515
	Krt19	0.519	Krt19	0.618	Krt19	0.573	Krt19	0.567	Krt19	0.574
	P2-1	0.55	P2-1	0.636	P2-1	0.527	P2-1	0.551	P2-1	0.528
	P2-2	0.502	P2-2	0.582	P2-2	0.528	P2-2	0.552	P2-2	0.53
Two Combined (top)	P3-1	0.51	P3-1	0.524	P3-1	0.547	P3-1	0.529	P3-1	0.5
	P4-2	0.522	P4-2	0.595	P4-2	0.551	P4-2	0.555	P4-2	0.578
Three Combined (top)	Age & FLNB & PSA	0.63	FLNA & Krt19	0.717	Age & PSA	0.659	Age & PSA	0.696	Age & PSA	0.765
Four Combined (top)	Age & FLNA & P2-1 & P2-2	0.637	FLNA & Krt19 & P2-1 & Age	0.746	PSA & Age & FLNB	0.685	PSA & Age & FLNB	0.717	PSA & Age & FLNB	0.804
Five Combined (top)	Age & FLNA & PSA & P2-1 & P2-2	0.644	FLNA & Krt19 & P2-1 & P3-1	0.746	PSA & Age & FLNB & P3-1	0.693	PSA & Age & FLNB & P3-1	0.723	PSA & Age & FLNB & P2-2	0.81
			FLNA & Krt19 & P2-1 & P3-1	0.764	PSA & Age & FLNB & P3-1 & Krt19	0.694	No Improvement		PSA & Age & FLNB & P2-2 & P2-1	0.811

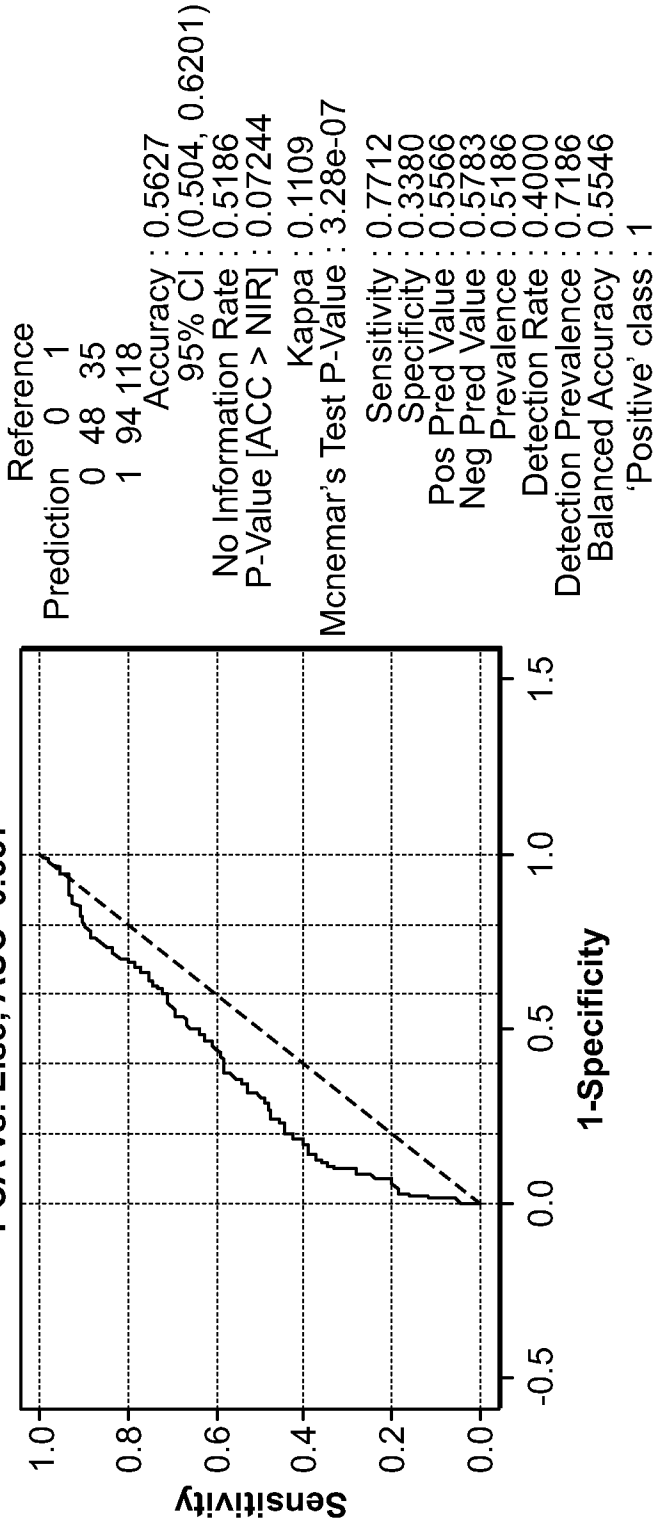
FIG. 18

PCA vs. Else: Sensitivity match PSA;
cutoff=0.4455

```
> title(main=list(paste("PSA&Age&FLNA&FLNB&P2-1&P4-2:PCA vs. Else;
AUC=",round(1r1$auc,3), sep=""), cex=1))
> mod1
call: glm(formula = as.factor(PCA) ~ PSA + Age + FLNA + FLNB + p21+
P42, family = binomial ("probit"), data = data)
Coefficients:
(Intercept)      PSA      Age      FLNA      FLNB      P21      P42
-1.875729  0.031445  0.024374 -0.001906  0.211370  0.144692 -0.067658
Degrees of Freedom: 294 Total (i.e. Null); 288 Residual
Null Deviance: 408.5
Residual Deviance: 389.9 AIC: 403.9
```

PSA&Age&FLNA& FLNB&P2-1&P4-2:
PCA vs. Else; AUC=0.637

> ConfusionMatrix(data\$prediction, data\$PCA, positive="1")
confusion Matrix and Statistics



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FIG. 19

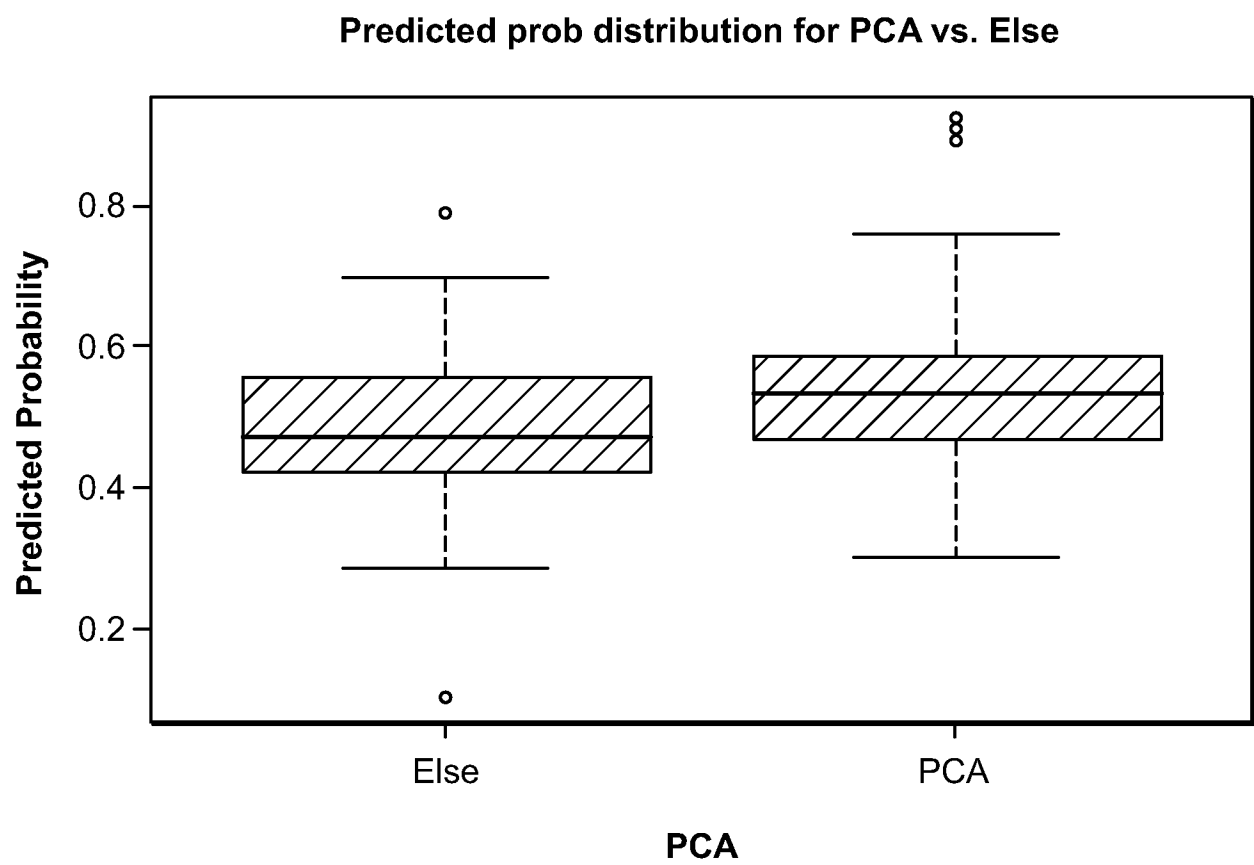


FIG. 20 Accuracy Analysis

Confusion Matrix and Statistics

Reference	
Prediction	0 1
0	29 12
1	52 65

Accuracy : 0.5949
95% CI : (0.514, 0.6722)

No Information Rate : 0.5127
P-Value [ACC > NIR] : 0.02304

Kappa : 0.1996
McNemar's Test P-Value : 1.088e-06

Sensitivity : 0.8442
Specificity : 0.3580
Pos Pred Value : 0.5556
Neg Pred Value : 0.7073
Prevalence : 0.4873
Detection Rate : 0.4114
Detection Prevalence : 0.7405
Balanced Accuracy : 0.6011

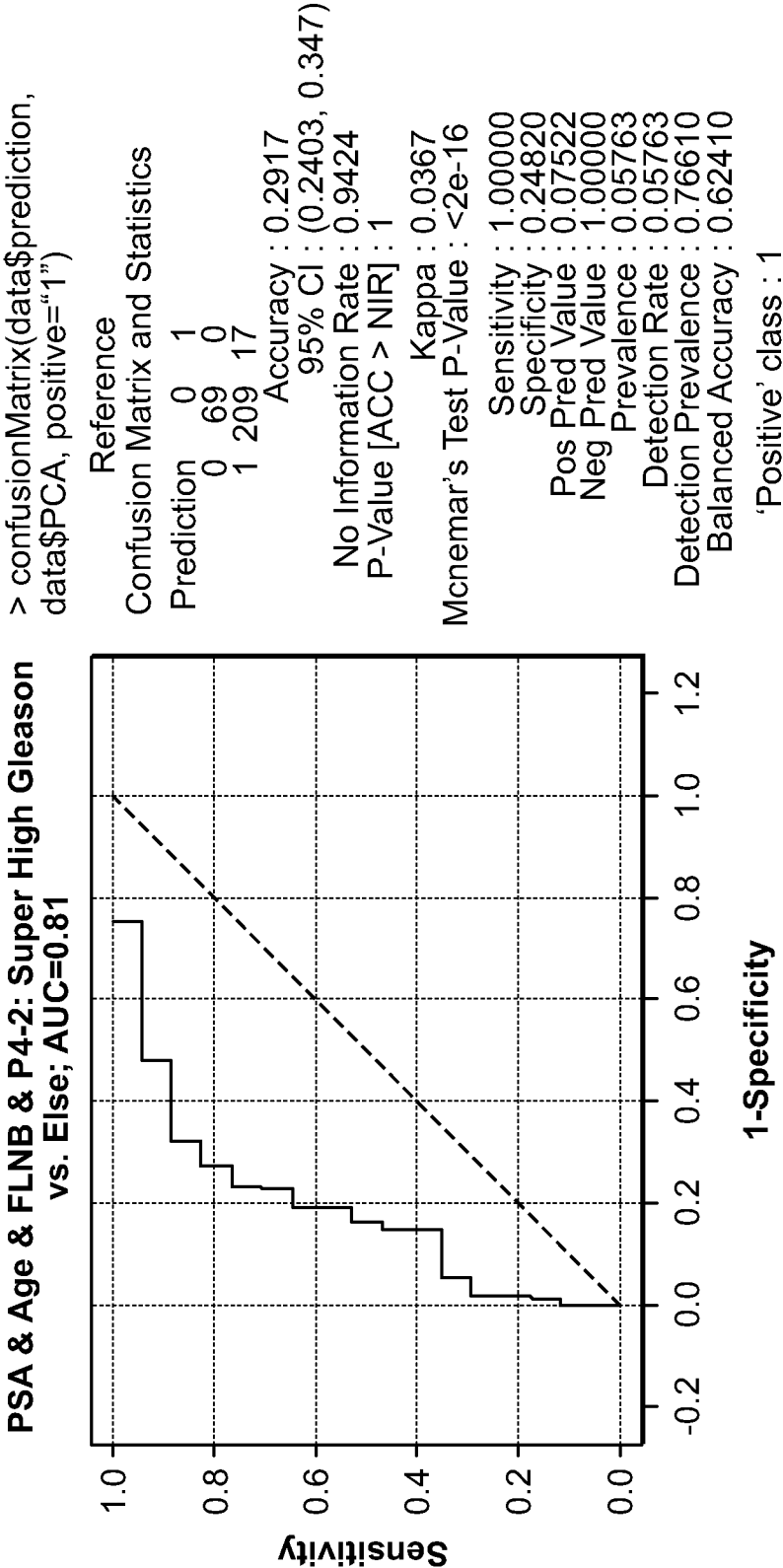
'Positive' class : 1

Relative risk	
Exposed group	
Number with positive (bad) outcome:	a= 65
Number with negative (good) outcome:	b= 52
Control group	
Number with positive (bad) outcome:	c= 12
Number with negative (good) outcome:	d= 29
Results	
Relative risk	1.8981
95 % CI	1.1482 to 3.1380
z statistic	2.499
	P = 0.0125

Odds ratio	
Cases with positive (bad) outcome	
Number in exposed group:	a= 65
Number in control group:	c= 12
Cases with negative (good) outcome	
Number in exposed group:	b= 52
Number in control group:	d= 29
Results	
Odds ratio	3.0208
95 % CI	1.4054 to 6.4933
z statistic	2.832
	P = 0.0046

FIG. 21 **Super High Gleason vs. Else: Sensitivity > =0.95; cutoff = 0.01997**

```
>mod1
call: glm(formula = as.factor(PCA) ~ PSA + Age + FLNB +P42, family = binominal ("probit"),
data = data)
Coefficients:
(Intercept)      PSA      Age      FLNB      P42
-3.21767      0.05097      0.03302     -0.31903     -0.10216
Degrees of Freedom: 294 Total (i.e. Null); 290 Residual
Null Deviance: 130
Residual Deviance: 107.9 AIC: 117.9
```



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FIG. 22

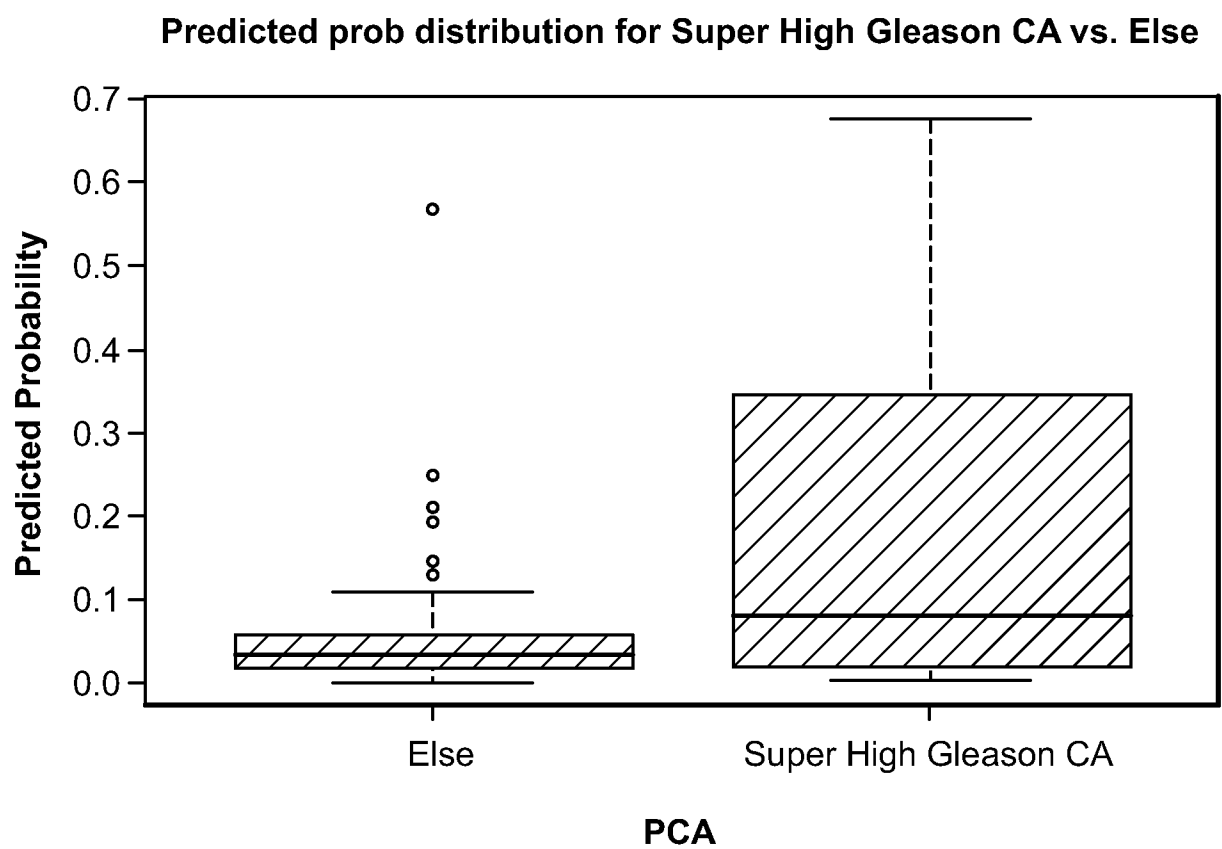


FIG. 23

Confusion Matrix and Statistics

Reference

Prediction

0

1

0

39

2

1

112

6

Accuracy : 0.283

95% CI : (0.2145, 0.3598)

No Information Rate : 0.9497

P-Value [ACC > NIR] : 1

Kappa : 0.0011

Mcnemar's Test P-Value : <2e-16

Sensitivity : 0.75000

Specificity : 0.25828

Pos Pred Value : 0.05085

Neg Pred Value : 0.95122

Prevalence : 0.05031

Detection Rate : 0.03774

Detection Prevalence : 0.74214

Balanced Accuracy : 0.50414

'Positive' class : 1

Relative risk

Exposed group	
Number with positive (bad) outcome:	a= 6
Number with negative (good) outcome:	b= 112
Control group	
Number with positive (bad) outcome:	c= 2
Number with negative (good) outcome:	d= 39
Test	
Results	
Relative risk	1.0424
95 % CI	0.2190 to 4.9624
z statistic	0.052
	P = 0.9584

Odds ratio

Cases with positive (bad) outcome	
Number in exposed group:	a= 6
Number in control group:	c= 2
Cases with negative (good) outcome	
Number in exposed group:	b= 112
Number in control group:	d= 39
Test	
Results	
Odds ratio	1.0446
95 % CI	0.2024 to 5.3923
z statistic	0.052
	P = 0.9584

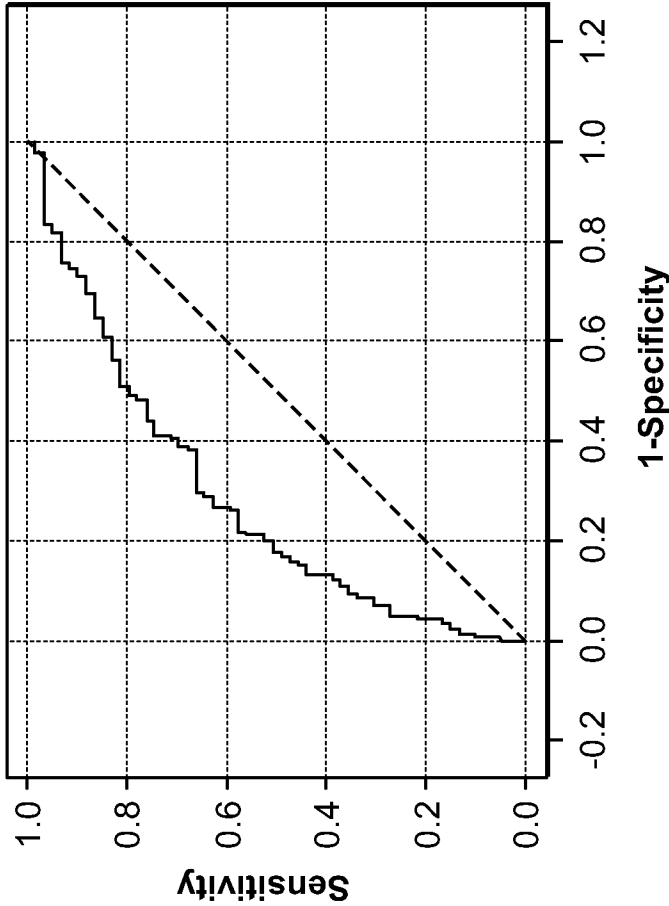
FIG. 24

High Gleason vs. Else: Sensitivity > =0.8;
cutoff = 0.1603

```
>mod1
call: glm(formula = as.factor(PCA) ~ PSA + Age + FLNB + P42, family = binominal ("probit"),
data = data)
Coefficients:
(Intercept)      PSA      Age      FLNB      P42
-2.05002      0.04659      0.02420      0.33548     -0.10820

Degrees of Freedom: 294 Total (i.e. Null); 290 Residual
Null Deviance: 295.2
Residual Deviance: 268 AIC: 278
```

PSA & Age & FLNB & P4-2: High Gleason
vs. Else; AUC=0.72



```
> confusionMatrix(data$prediction,
data$PCA, positive="1")
Confusion Matrix and Statistics

Prediction 0 1
0 116 11
1 120 48

Accuracy : 0.5559
95% CI : (0.4972, 0.6135)
No Information Rate : 0.8
P-Value [ACC > NIR] : 1

McNemar's Test P-Value : 0.1802
Sensitivity : 0.8136
Specificity : 0.4915
Pos Pred Value : 0.2857
Neg Pred Value : 0.9134
Prevalence : 0.2000
Detection Rate : 0.1627
Detection Prevalence : 0.5695
Balanced Accuracy : 0.6525
'Positive' class : 1
```

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FIG. 25

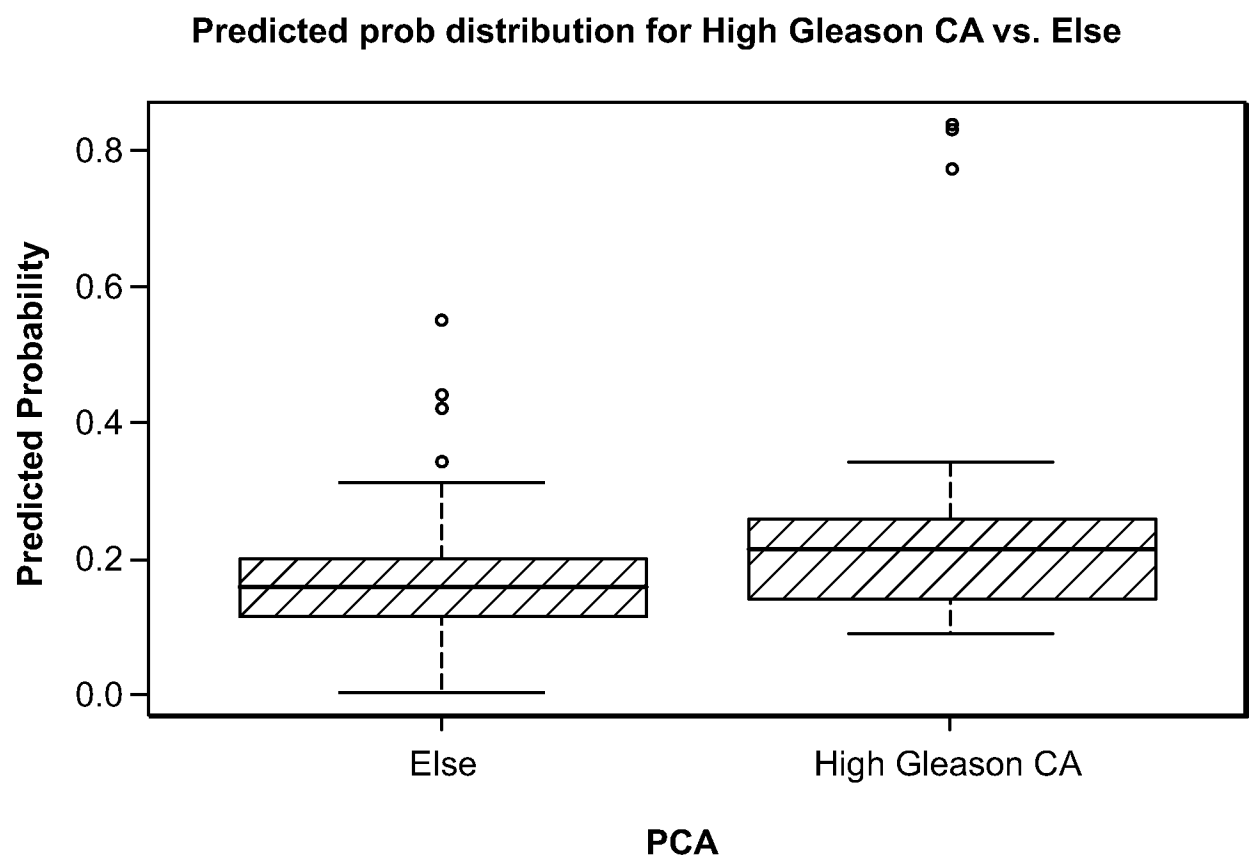


FIG. 26 Accuracy Analysis

Confusion Matrix and Statistics

Reference		
Prediction	0 1	
0	66 9	
1	63 21	
Accuracy : 0.5472		
95% CI : (0.4664, 0.6261)		
No Information Rate : 0.8113		
P-Value [ACC > NIR] : 1		
Kappa : 0.1252		
McNemar's Test P-Value : 4.208e-10		
Sensitivity : 0.7000		
Specificity : 0.5116		
Pos Pred Value : 0.2500		
Neg Pred Value : 0.8800		
Prevalence : 0.1887		
Detection Rate : 0.1321		
Detection Prevalence : 0.5283		
Balanced Accuracy : 0.6058		
'Positive' class : 1		

Relative risk

Exposed group	
Number with positive (bad) outcome:	a= 21
Number with negative (good) outcome:	b= 63
Control group	
Number with positive (bad) outcome:	c= 9
Number with negative (good) outcome:	d= 66
Results	
Relative risk	2.0833
95 % CI	1.0180 to 4.2635
z statistic	2.009
	P = 0.0446

Odds ratio

Cases with positive (bad) outcome	
Number in exposed group:	a= 21
Number in control group:	c= 9
Cases with negative (good) outcome	
Number in exposed group:	b= 63
Number in control group:	d= 66
Results	
Odds ratio	2.4444
95 % CI	1.0408 to 5.7409
z statistic	2.052
	P = 0.0402

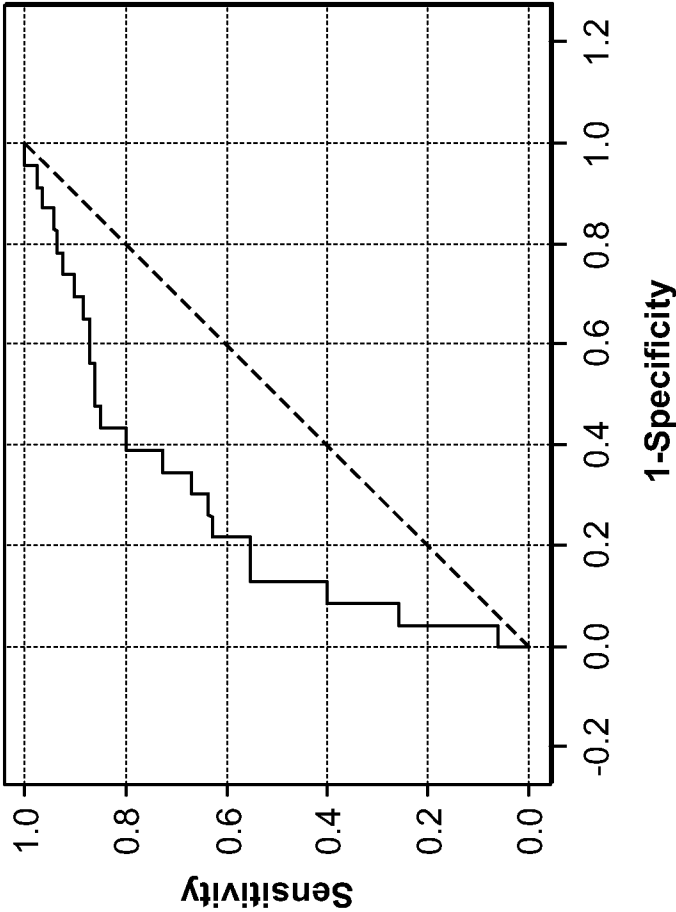
PCA vs. BPH: Sensitivity > =0.8; cutoff = 0.8758

FIG. 27

```
>mod1
call: glm(formula = as.factor(PCA) ~ Age + FLNA + KRT19 + P21, family = binomial ("probit"),
data = data)
Coefficients:
(Intercept)      Age      FLNA      KRT19      P21
 3.339085    0.017895 -0.003951 -0.076261 -0.566652

Degrees of Freedom: 195 Total (i.e. Null); 191 Residual
Null Deviance:      141.7
Residual Deviance:  127.6  AIC: 137.6
```

Age & FLNA & KRT-19 & P2-1 vs. BPH; AUC=0.746



```
> confusionMatrix(data$prediction,
data$PCA, positive="1")
Confusion Matrix and Statistics
Reference
Prediction 0 1
0 14 34
1 9 139
Accuracy : 0.7806
95% CI : (0.7161, 0.8364)
No Information Rate : 0.8827
P-Value [ACC > NIR] : 0.9999829
Kappa : 0.2802
McNemar's Test P-Value : 0.0002522
Sensitivity : 0.8035
Specificity : 0.6087
Pos Pred Value : 0.9392
Neg Pred Value : 0.2917
Prevalence : 0.8827
Detection Rate : 0.7092
Detection Prevalence : 0.7551
Balanced Accuracy : 0.7061
'Positive' class : 1
```

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FIG. 28

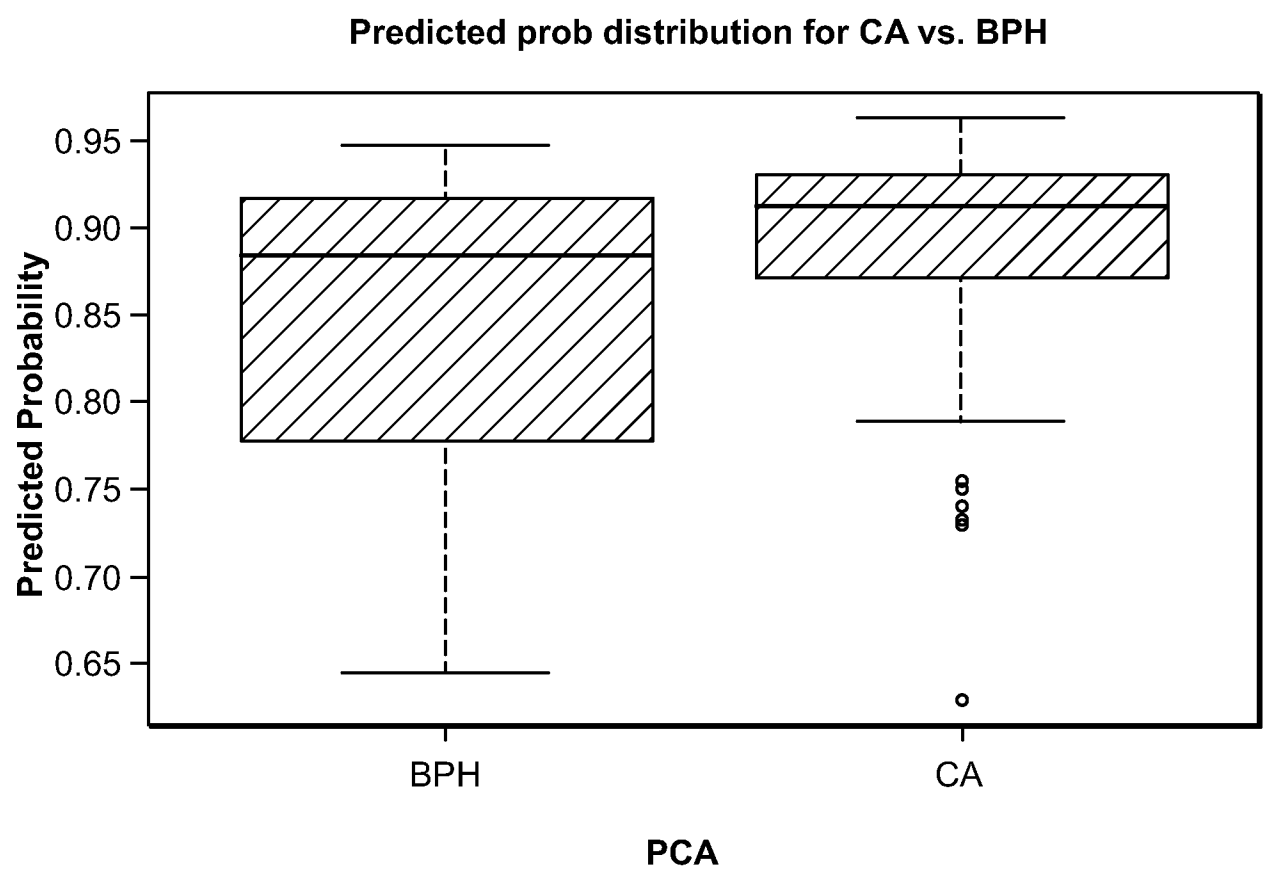


FIG. 29 Accuracy Analysis

Confusion Matrix and Statistics

Reference		
Prediction	0	1
	0	4
	1	7
		55
Accuracy : 0.6413		
95% CI : (0.5346, 0.7387)		
No Information Rate : 0.8804		
P-Value [ACC > NIR] : 1.000000		
Kappa : 0.0244		
McNemar's Test P-Value : 0.001728		
Sensitivity : 0.6790		
Specificity : 0.3636		
Pos Pred Value : 0.8871		
Neg Pred Value : 0.1333		
Prevalence : 0.8804		
Detection Rate : 0.5978		
Detection Prevalence : 0.6739		
Balanced Accuracy : 0.5213		
'Positive' class : 1		

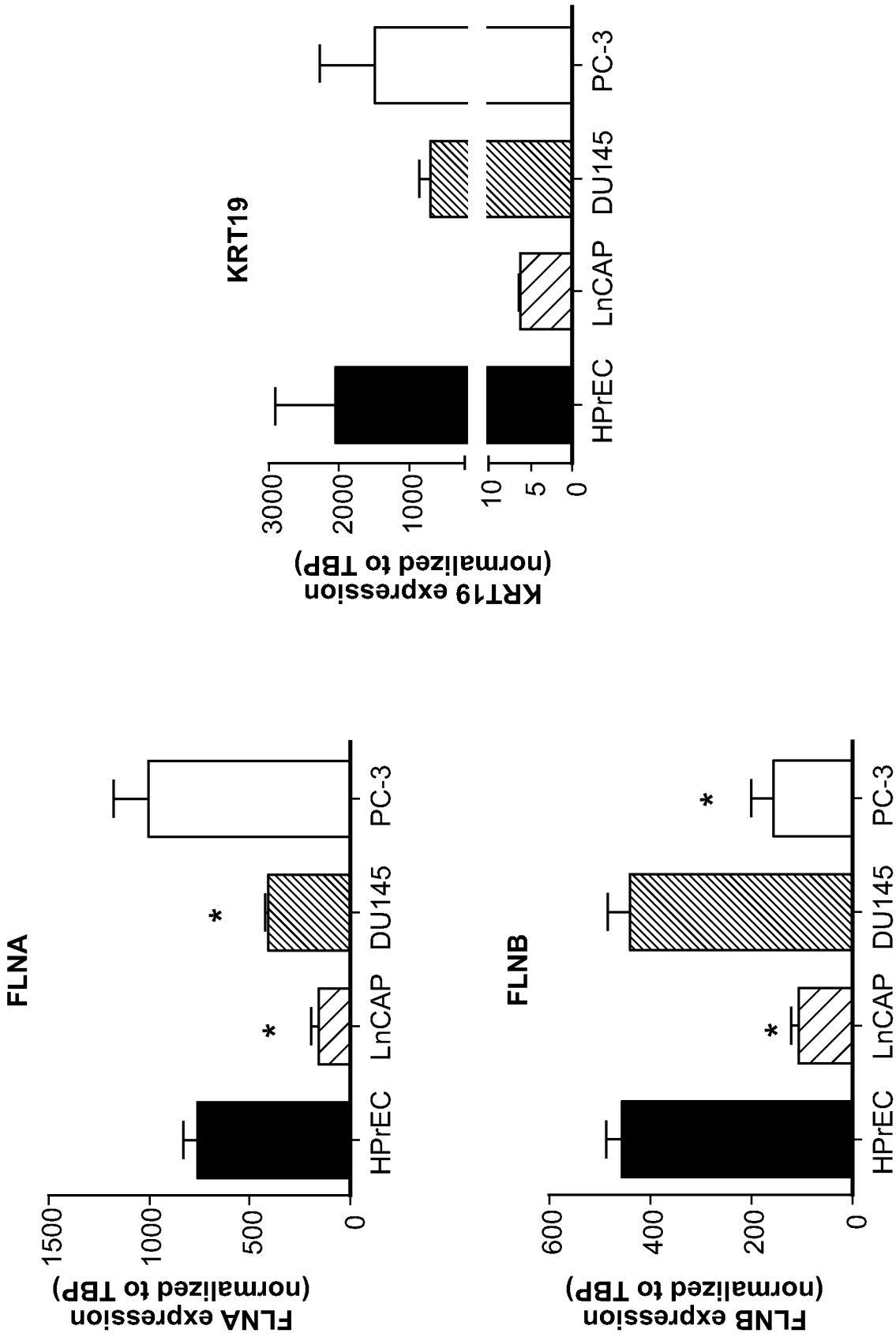
Relative risk

Exposed group	
Number with positive (bad) outcome: a=55	
Number with negative (good) outcome: b=7	
Control group	
Number with positive (bad) outcome: c=26	
Number with negative (good) outcome: d=4	
Test	
Results	
Relative risk	1.0236
95 % CI	0.8669 to 1.2085
z statistic	0.275
	P = 0.7834

Odds ratio

Cases with positive (bad) outcome	
Number in exposed group: a=55	
Number in control group: c=26	
Cases with negative (good) outcome	
Number in exposed group: b=7	
Number in control group: d=4	
Test	
Results	
Odds ratio	1.2088
95 % CI	0.3248 to 4.4983
z statistic	0.283
	P = 0.7773

FIG. 30 FLNA, FLNB, and KRT19 are expressed by prostate cancer cells



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FIG. 31

FLNA, FLNB, and KRT19 are expressed by prostate cancer cells

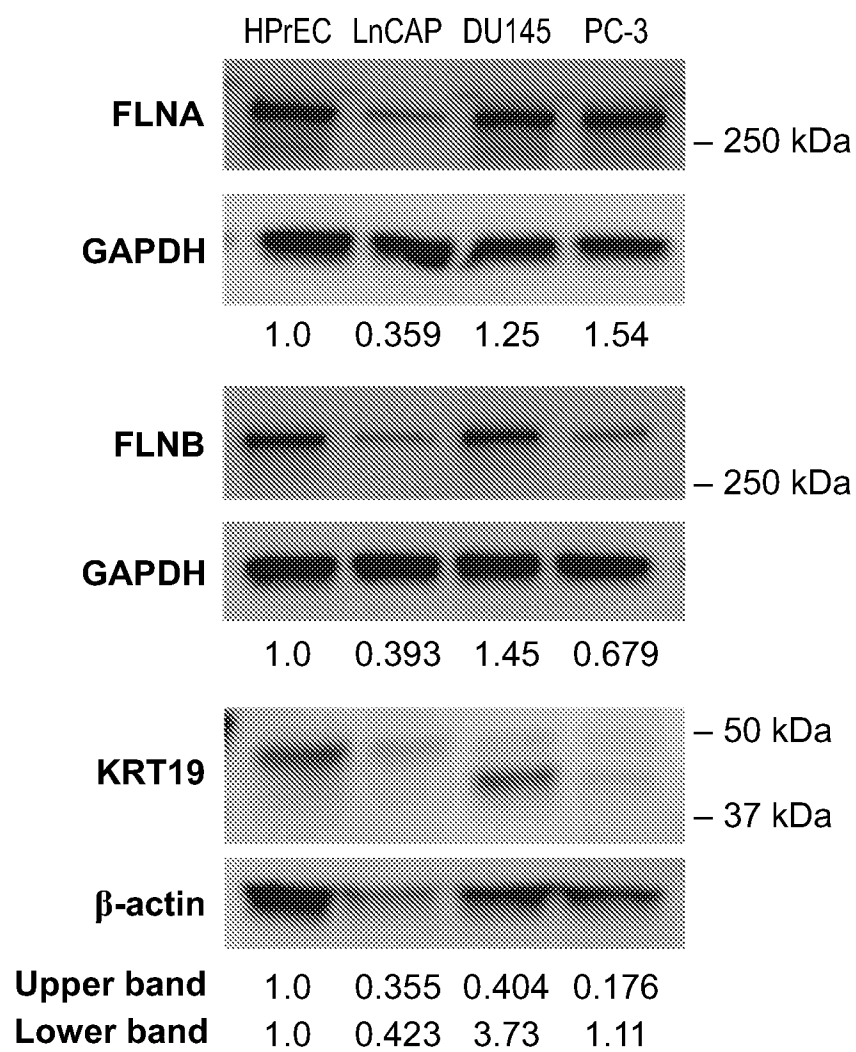


FIG. 32 FLNA, FLNB, and KRT19 are secreted from prostate cancer cells

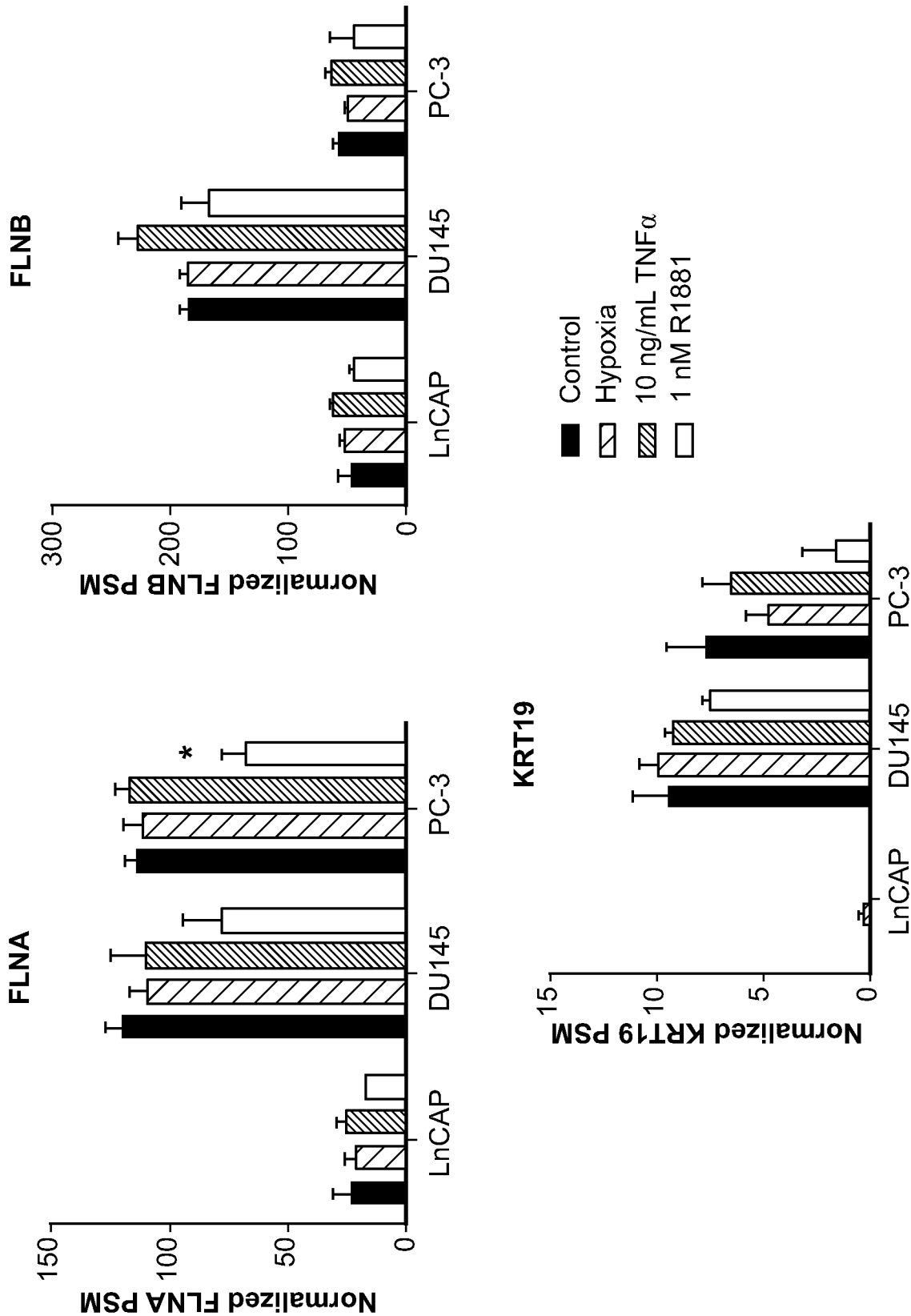


FIG. 33

Transcriptional regulation of FLNA, FLNB, and KRT19 expression differs from PSA: Hypoxia (1% oxygen).

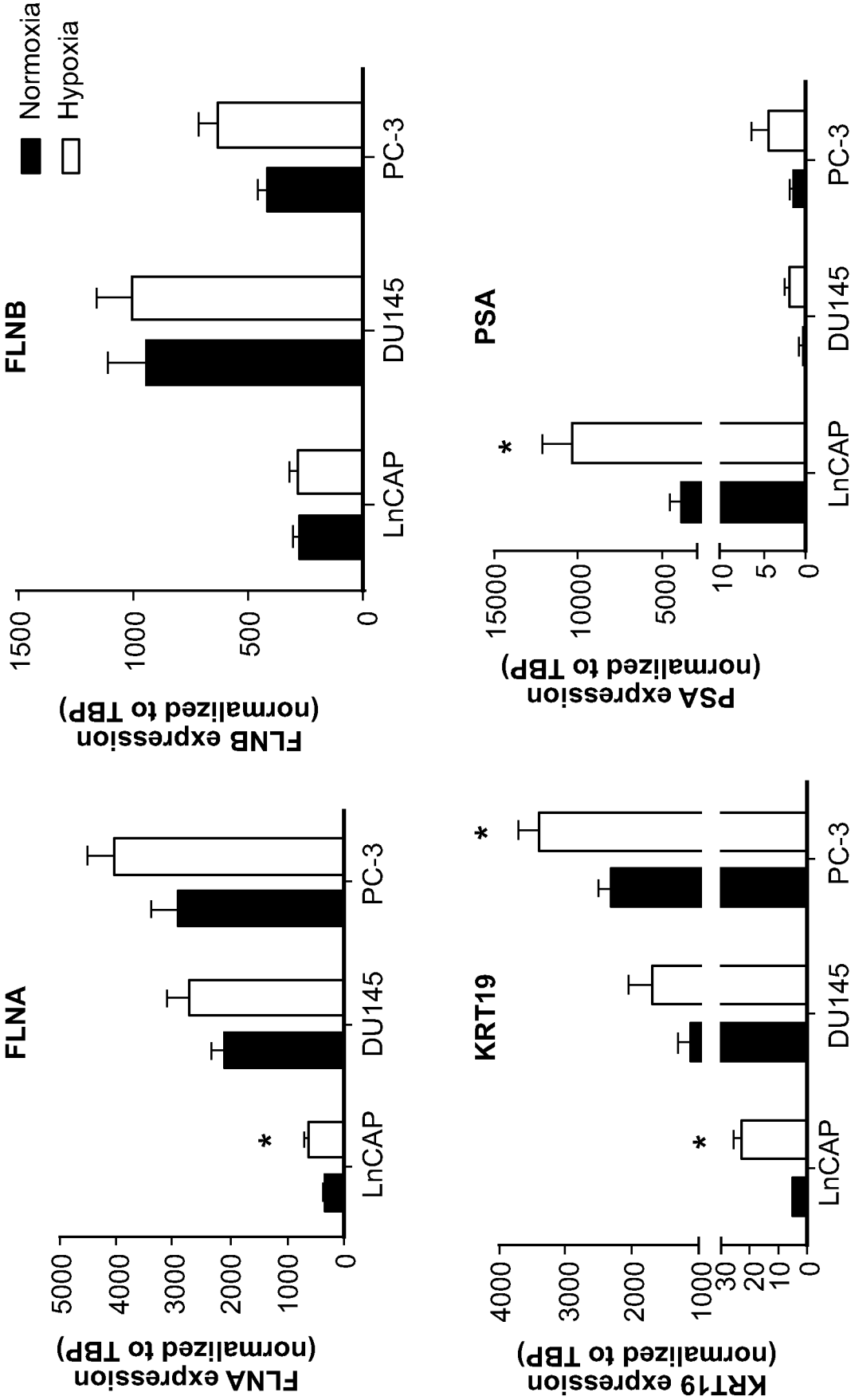


FIG. 34

Transcriptional regulation of FLNA, FLNB, and KRT19 expression differs from PSA: TNF α (10 ng/mL)

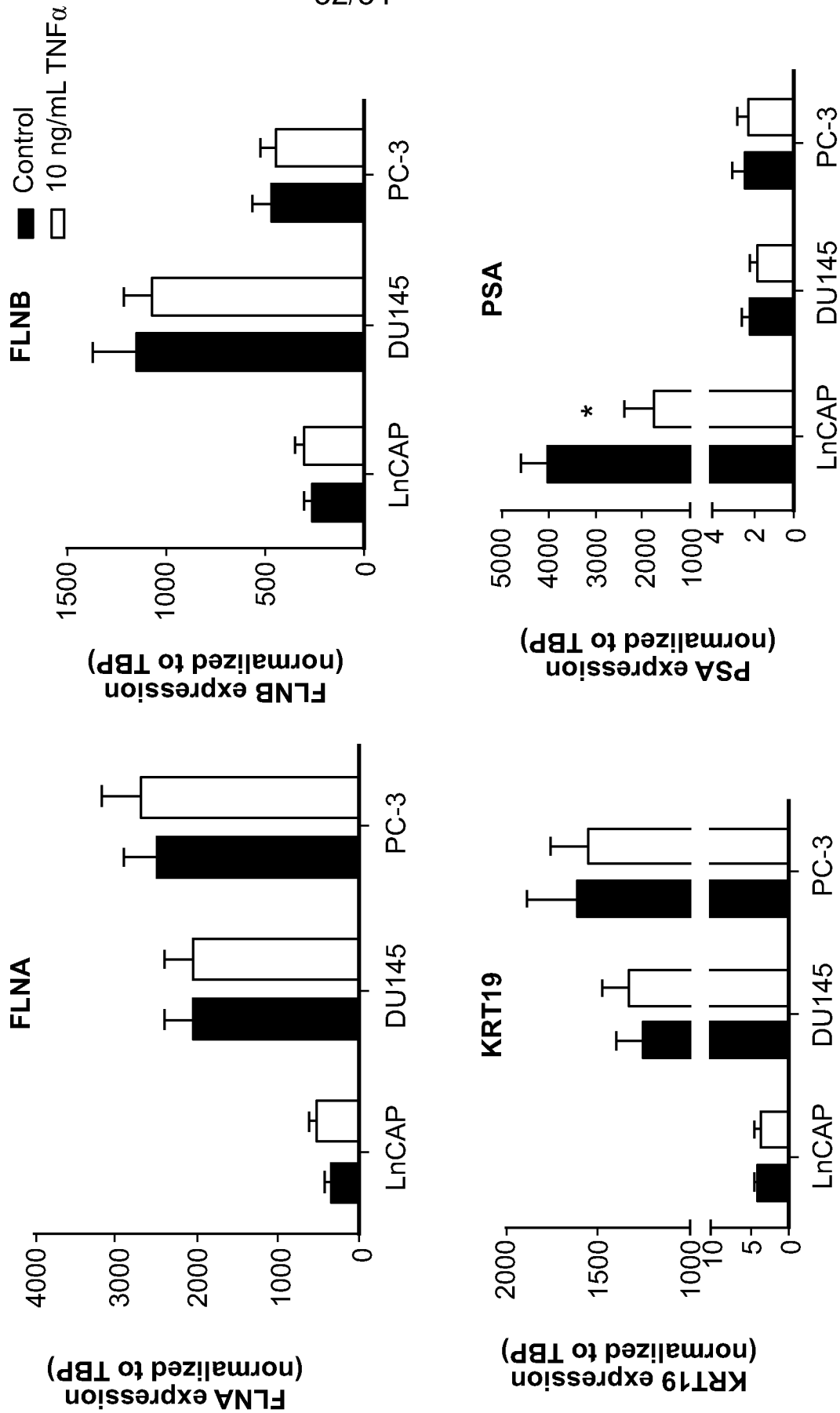


FIG. 35

Transcriptional regulation of FLNA, FLNB, and KRT19 expression differs from PSA: R1881 (1 nM)

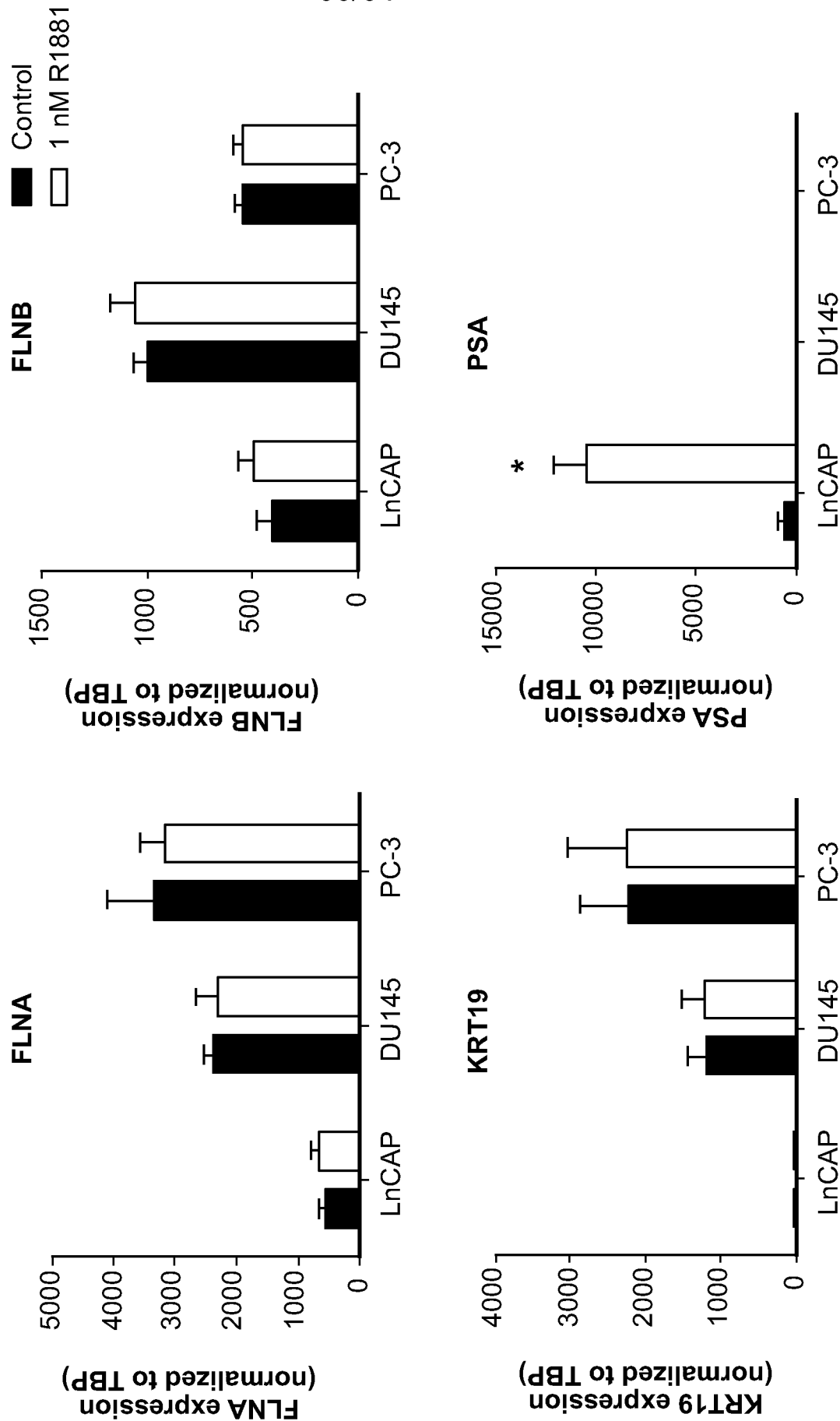
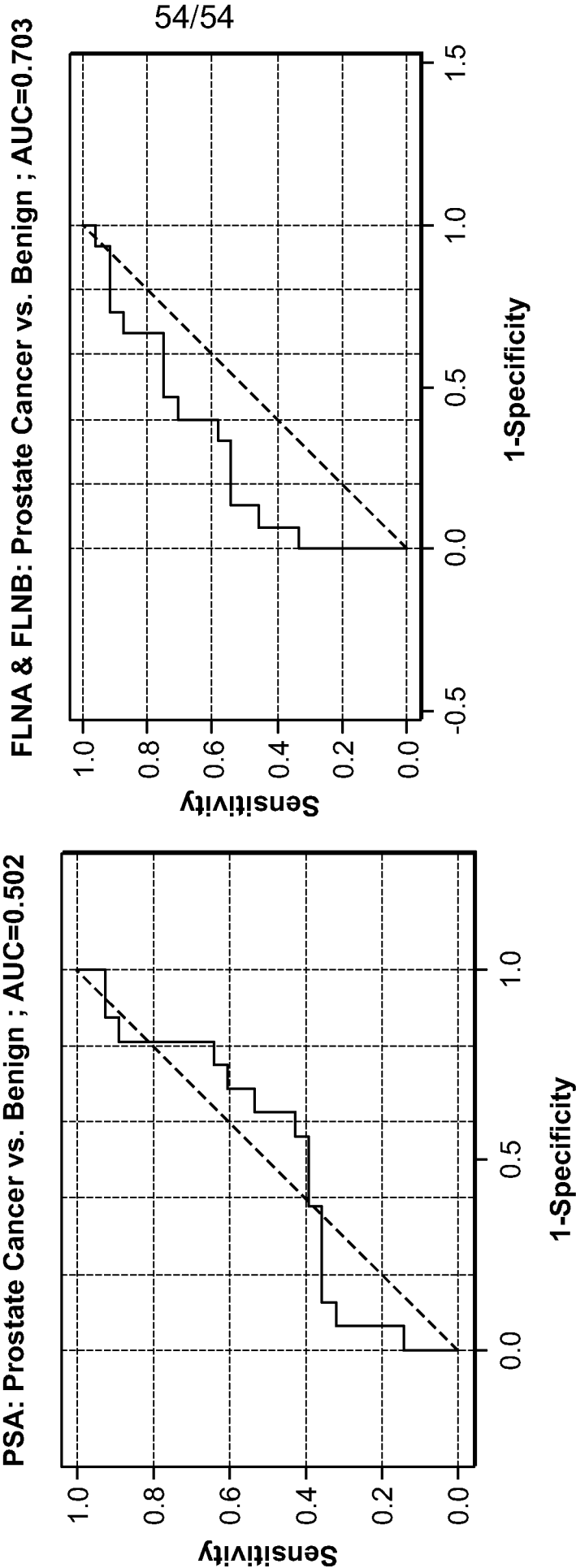


FIG. 36

FLNA and FLNB are detected in human plasma and have predictive power in identifying prostate cancer patients



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AKMAEV, VIATCHESLAV R.

<120> USE OF MARKERS INCLUDING FILAMIN A IN THE DIAGNOSIS AND
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85 90 95

11999210820_ST25

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 Leu Asp Gly Ile Ile Ala Glu Val Lys Ala Gln Tyr Glu Glu Met Ala
 260 265 270
 Lys Cys Ser Arg Ala Glu Ala Glu Ala Trp Tyr Gln Thr Lys Phe Glu
 275 280 285
 Thr Leu Gln Ala Gln Ala Gly Lys His Gly Asp Asp Leu Arg Asn Thr
 290 295 300
 Arg Asn Glu Ile Ser Glu Met Asn Arg Ala Ile Gln Arg Leu Gln Ala
 305 310 315 320
 Glu Ile Asp Asn Ile Lys Asn Gln Arg Ala Lys Leu Glu Ala Ala Ile
 325 330 335
 Ala Glu Ala Glu Glu Arg Gly Glu Leu Ala Leu Lys Asp Ala Arg Ala
 340 345 350
 Lys Gln Glu Glu Leu Glu Ala Ala Leu Gln Arg Gly Lys Gln Asp Met
 355 360 365

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Ala Arg Gln Leu Arg Glu Tyr Gln Glu Leu Met Ser Val Lys Leu Ala
370 375 380

Leu Asp Ile Glu Ile Ala Thr Tyr Arg Lys Leu Leu Glu Gly Glu Glu
385 390 395 400

Ser Arg Leu Ala Gly Asp Gly Val Gly Ala Val Asn Ile Ser Val Met
405 410 415

Asn Ser Thr Gly Gly Ser Ser Ser Gly Gly Gly Ile Gly Leu Thr Leu
420 425 430

Gly Gly Thr Met Gly Ser Asn Ala Leu Ser Phe Ser Ser Ser Ala Gly
435 440 445

Pro Gly Leu Leu Lys Ala Tyr Ser Ile Arg Thr Ala Ser Ala Ser Arg
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Arg Ser Ala Arg Asp
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<210> 4
<211> 1753
<212> DNA
<213> Homo sapiens

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 <213> Homo sapiens

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

Ser Ser Arg Ser Tyr Thr Ser Gly Pro Gly Ser Arg Ile Ser Ser Ser
50 55 60

Ser Phe Ser Arg Val Gly Ser Ser Asn Phe Arg Gly Gly Leu Gly Gly
65 70 75 80

Gly Tyr Gly Gly Ala Ser Gly Met Gly Gly Ile Thr Ala Val Thr Val
85 90 95

Asn Gln Ser Leu Leu Ser Pro Leu Val Leu Glu Val Asp Pro Asn Ile
100 105 110

Gln Ala Val Arg Thr Gln Glu Lys Glu Gln Ile Lys Thr Leu Asn Asn
115 120 125

Lys Phe Ala Ser Phe Ile Asp Lys Val Arg Phe Leu Glu Gln Gln Asn
130 135 140

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Lys Met Leu Glu Thr Lys Trp Ser Leu Leu Gln Gln Gln Lys Thr Ala
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 Arg Ser Asn Met Asp Asn Met Phe Glu Ser Tyr Ile Asn Asn Leu Arg
 165 170 175
 Arg Gln Leu Glu Thr Leu Gly Gln Glu Lys Leu Lys Leu Glu Ala Glu
 180 185 190
 Leu Gly Asn Met Gln Gly Leu Val Glu Asp Phe Lys Asn Lys Tyr Glu
 195 200 205
 Asp Glu Ile Asn Lys Arg Thr Glu Met Glu Asn Glu Phe Val Leu Ile
 210 215 220
 Lys Lys Asp Val Asp Glu Ala Tyr Met Asn Lys Val Glu Leu Glu Ser
 225 230 235 240
 Arg Leu Glu Gly Leu Thr Asp Glu Ile Asn Phe Leu Arg Gln Leu Tyr
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 Glu Glu Glu Ile Arg Glu Leu Gln Ser Gln Ile Ser Asp Thr Ser Val
 260 265 270
 Val Leu Ser Met Asp Asn Ser Arg Ser Leu Asp Met Asp Ser Ile Ile
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 Ala Glu Val Lys Ala Gln Tyr Glu Asp Ile Ala Asn Arg Ser Arg Ala
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 Glu Ala Glu Ser Met Tyr Gln Ile Lys Tyr Glu Glu Leu Gln Ser Leu
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 Ala Gly Lys His Gly Asp Asp Leu Arg Arg Thr Lys Thr Glu Ile Ser
 325 330 335
 Glu Met Asn Arg Asn Ile Ser Arg Leu Gln Ala Glu Ile Glu Gly Leu
 340 345 350
 Lys Gly Gln Arg Ala Ser Leu Glu Ala Ala Ile Ala Asp Ala Glu Gln
 355 360 365
 Arg Gly Glu Leu Ala Ile Lys Asp Ala Asn Ala Lys Leu Ser Glu Leu
 370 375 380
 Glu Ala Ala Leu Gln Arg Ala Lys Gln Asp Met Ala Arg Gln Leu Arg
 385 390 395 400
 Glu Tyr Gln Glu Leu Met Asn Val Lys Leu Ala Leu Asp Ile Glu Ile
 405 410 415

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Ala Thr Tyr Arg Lys Leu Leu Glu Gly Glu Glu Ser Arg Leu Glu Ser
420 425 430

Gly Met Gln Asn Met Ser Ile His Thr Lys Thr Thr Ser Gly Tyr Ala
435 440 445

Gly Gly Leu Ser Ser Ala Tyr Gly Gly Leu Thr Ser Pro Gly Leu Ser
450 455 460

Tyr Ser Leu Gly Ser Ser Phe Gly Ser Gly Ala Gly Ser Ser Ser Phe
465 470 475 480

Ser Arg Thr Ser Ser Ser Arg Ala Val Val Val Lys Lys Ile Glu Thr
485 490 495

Arg Asp Gly Lys Leu Val Ser Glu Ser Ser Asp Val Leu Pro Lys
500 505 510

<210> 6
<211> 1807
<212> DNA
<213> Homo sapiens

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 <211> 483
 <212> PRT
 <213> Homo sapiens

<400> 7

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Pro Arg Ala Phe Ser Ser Arg Ser Tyr Thr Ser Gly Pro Gly Ser Arg
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Ile Ser Ser Ser Ser Phe Ser Arg Val Gly Ser Ser Asn Phe Arg Gly
35 40 45

Gly Leu Gly Gly Gly Tyr Gly Gly Ala Ser Gly Met Gly Gly Ile Thr
50 55 60

Ala Val Thr Val Asn Gln Ser Leu Leu Ser Pro Leu Val Leu Glu Val
65 70 75 80

Asp Pro Asn Ile Gln Ala Val Arg Thr Gln Glu Lys Glu Gln Ile Lys
85 90 95

Thr Leu Asn Asn Lys Phe Ala Ser Phe Ile Asp Lys Val Arg Phe Leu
100 105 110

Glu Gln Gln Asn Lys Met Leu Glu Thr Lys Trp Ser Leu Leu Gln Gln
115 120 125

Gln Lys Thr Ala Arg Ser Asn Met Asp Asn Met Phe Glu Ser Tyr Ile
130 135 140

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				165					170					175	
Asn	Lys	Tyr	Glu	Asp	Glu	Ile	Asn	Lys	Arg	Thr	Glu	Met	Glu	Asn	Glu
			180					185					190		
Phe	Val	Leu	Ile	Lys	Lys	Asp	Val	Asp	Glu	Ala	Tyr	Met	Asn	Lys	Val
		195					200					205			
Glu	Leu	Glu	Ser	Arg	Leu	Glu	Gly	Leu	Thr	Asp	Glu	Ile	Asn	Phe	Leu
	210					215					220				
Arg	Gln	Leu	Tyr	Glu	Glu	Glu	Ile	Arg	Glu	Leu	Gln	Ser	Gln	Ile	Ser
225					230					235					240
Asp	Thr	Ser	Val	Val	Leu	Ser	Met	Asp	Asn	Ser	Arg	Ser	Leu	Asp	Met
				245					250					255	
Asp	Ser	Ile	Ile	Ala	Glu	Val	Lys	Ala	Gln	Tyr	Glu	Asp	Ile	Ala	Asn
			260					265					270		
Arg	Ser	Arg	Ala	Glu	Ala	Glu	Ser	Met	Tyr	Gln	Ile	Lys	Tyr	Glu	Glu
		275					280					285			
Leu	Gln	Ser	Leu	Ala	Gly	Lys	His	Gly	Asp	Asp	Leu	Arg	Arg	Thr	Lys
	290					295					300				
Thr	Glu	Ile	Ser	Glu	Met	Asn	Arg	Asn	Ile	Ser	Arg	Leu	Gln	Ala	Glu
305					310					315					320
Ile	Glu	Gly	Leu	Lys	Gly	Gln	Arg	Ala	Ser	Leu	Glu	Ala	Ala	Ile	Ala
				325					330					335	
Asp	Ala	Glu	Gln	Arg	Gly	Glu	Leu	Ala	Ile	Lys	Asp	Ala	Asn	Ala	Lys
			340					345					350		
Leu	Ser	Glu	Leu	Glu	Ala	Ala	Leu	Gln	Arg	Ala	Lys	Gln	Asp	Met	Ala
		355					360					365			
Arg	Gln	Leu	Arg	Glu	Tyr	Gln	Glu	Leu	Met	Asn	Val	Lys	Leu	Ala	Leu
	370					375					380				
Asp	Ile	Glu	Ile	Ala	Thr	Tyr	Arg	Lys	Leu	Leu	Glu	Gly	Glu	Glu	Ser
385					390					395					400
Arg	Leu	Glu	Ser	Gly	Met	Gln	Asn	Met	Ser	Ile	His	Thr	Lys	Thr	Thr
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Ser Gly Tyr Ala Gly Gly Leu Ser Ser Ala Tyr Gly Gly Leu Thr Ser
420 425 430

Pro Gly Leu Ser Tyr Ser Leu Gly Ser Ser Phe Gly Ser Gly Ala Gly
435 440 445

Ser Ser Ser Phe Ser Arg Thr Ser Ser Ser Arg Ala Val Val Val Lys
450 455 460

Lys Ile Glu Thr Arg Asp Gly Lys Leu Val Ser Glu Ser Ser Asp Val
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Leu Pro Lys

<210> 8
<211> 1901
<212> DNA
<213> Homo sapiens

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aaataaaacc tcagctagct ctgccaatgt caaaaaaaaa a 1901

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<210> 9
 <211> 456
 <212> PRT
 <213> Homo sapiens

<400> 9

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Gly Ser Leu Ser Gly Gly Gly Gly Ser Arg Ser Ile Ser Ala Ser Ser
35 40 45

Ala Arg Phe Val Ser Ser Gly Ser Gly Gly Gly Tyr Gly Gly Gly Met
50 55 60

Arg Val Cys Gly Phe Gly Gly Gly Ala Gly Ser Val Phe Gly Gly Gly
65 70 75 80

Phe Gly Gly Gly Val Gly Gly Gly Phe Gly Gly Gly Phe Gly Gly Gly
85 90 95

Asp Gly Gly Leu Leu Ser Gly Asn Glu Lys Ile Thr Met Gln Asn Leu
100 105 110

Asn Asp Arg Leu Ala Ser Tyr Leu Asp Lys Val Arg Ala Leu Glu Glu
115 120 125

Ala Asn Ala Asp Leu Glu Val Lys Ile His Asp Trp Tyr Gln Lys Gln
130 135 140

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Thr Pro Thr Ser Pro Glu Cys Asp Tyr Ser Gln Tyr Phe Lys Thr Ile
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 Glu Glu Leu Arg Asp Lys Ile Met Ala Thr Thr Ile Asp Asn Ser Arg
 165 170 175
 Val Ile Leu Glu Ile Asp Asn Ala Arg Leu Ala Ala Asp Asp Phe Arg
 180 185 190
 Leu Lys Tyr Glu Asn Glu Leu Ala Leu Arg Gln Gly Val Glu Ala Asp
 195 200 205
 Ile Asn Gly Leu Arg Arg Val Leu Asp Glu Leu Thr Leu Ala Arg Thr
 210 215 220
 Asp Leu Glu Met Gln Ile Glu Gly Leu Asn Glu Glu Leu Ala Tyr Leu
 225 230 235 240
 Lys Lys Asn His Glu Glu Glu Met Lys Glu Phe Ser Ser Gln Leu Ala
 245 250 255
 Gly Gln Val Asn Val Glu Met Asp Ala Ala Pro Gly Val Asp Leu Thr
 260 265 270
 Arg Val Leu Ala Glu Met Arg Glu Gln Tyr Glu Ala Met Ala Glu Lys
 275 280 285
 Asn Arg Arg Asp Val Glu Ala Trp Phe Phe Ser Lys Thr Glu Glu Leu
 290 295 300
 Asn Lys Glu Val Ala Ser Asn Thr Glu Met Ile Gln Thr Ser Lys Thr
 305 310 315 320
 Glu Ile Thr Asp Leu Arg Arg Thr Met Gln Glu Leu Glu Ile Glu Leu
 325 330 335
 Gln Ser Gln Leu Ser Met Lys Ala Gly Leu Glu Asn Ser Leu Ala Glu
 340 345 350
 Thr Glu Cys Arg Tyr Ala Thr Gln Leu Gln Gln Ile Gln Gly Leu Ile
 355 360 365
 Gly Gly Leu Glu Ala Gln Leu Ser Glu Leu Arg Cys Glu Met Glu Ala
 370 375 380
 Gln Asn Gln Glu Tyr Lys Met Leu Leu Asp Ile Lys Thr Arg Leu Glu
 385 390 395 400
 Gln Glu Ile Ala Thr Tyr Arg Ser Leu Leu Glu Gly Gln Asp Ala Lys
 405 410 415

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Met Ala Gly Ile Gly Ile Arg Glu Ala Ser Ser Gly Gly Gly Gly Ser
 420 425 430

Ser Ser Asn Phe His Ile Asn Val Glu Glu Ser Val Asp Gly Gln Val
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Val Ser Ser His Lys Arg Glu Ile
 450 455

<210> 10
 <211> 1861
 <212> DNA
 <213> Homo sapiens

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 a 1861

<210> 11
 <211> 430
 <212> PRT
 <213> Homo sapiens

<400> 11

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Gly Ser Val Gln Ala Pro Ser Tyr Gly Ala Arg Pro Val Ser Ser Ala
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Ala Ser Val Tyr Ala Gly Ala Gly Gly Ser Gly Ser Arg Ile Ser Val
35 40 45

Ser Arg Ser Thr Ser Phe Arg Gly Gly Met Gly Ser Gly Gly Leu Ala
50 55 60

Thr Gly Ile Ala Gly Gly Leu Ala Gly Met Gly Gly Ile Gln Asn Glu
65 70 75 80

Lys Glu Thr Met Gln Ser Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp
85 90 95

Arg Val Arg Ser Leu Glu Thr Glu Asn Arg Arg Leu Glu Ser Lys Ile
100 105 110

Arg Glu His Leu Glu Lys Lys Gly Pro Gln Val Arg Asp Trp Ser His
115 120 125

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

Val Asp Asn Ala Arg Ile Val Leu Gln Ile Asp Asn Ala Arg Leu Ala
145 150 155 160

Ala Asp Asp Phe Arg Val Lys Tyr Glu Thr Glu Leu Ala Met Arg Gln
165 170 175

Ser Val Glu Asn Asp Ile His Gly Leu Arg Lys Val Ile Asp Asp Thr
180 185 190

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Asn Ile Thr Arg Leu Gln Leu Glu Thr Glu Ile Glu Ala Leu Lys Glu
195 200 205

Glu Leu Leu Phe Met Lys Lys Asn His Glu Glu Glu Val Lys Gly Leu
210 215 220

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

Lys Ser Gln Asp Leu Ala Lys Ile Met Ala Asp Ile Arg Ala Gln Tyr
245 250 255

Asp Glu Leu Ala Arg Lys Asn Arg Glu Glu Leu Asp Lys Tyr Trp Ser
260 265 270

Gln Gln Ile Glu Glu Ser Thr Thr Val Val Thr Thr Gln Ser Ala Glu
275 280 285

Val Gly Ala Ala Glu Thr Thr Leu Thr Glu Leu Arg Arg Thr Val Gln
290 295 300

Ser Leu Glu Ile Asp Leu Asp Ser Met Arg Asn Leu Lys Ala Ser Leu
305 310 315 320

Glu Asn Ser Leu Arg Glu Val Glu Ala Arg Tyr Ala Leu Gln Met Glu
325 330 335

Gln Leu Asn Gly Ile Leu Leu His Leu Glu Ser Glu Leu Ala Gln Thr
340 345 350

Arg Ala Glu Gly Gln Arg Gln Ala Gln Glu Tyr Glu Ala Leu Leu Asn
355 360 365

Ile Lys Val Lys Leu Glu Ala Glu Ile Ala Thr Tyr Arg Arg Leu Leu
370 375 380

Glu Asp Gly Glu Asp Phe Asn Leu Gly Asp Ala Leu Asp Ser Ser Asn
385 390 395 400

Ser Met Gln Thr Ile Gln Lys Thr Thr Thr Arg Arg Ile Val Asp Gly
405 410 415

Lys Val Val Ser Glu Thr Asn Asp Thr Lys Val Leu Arg His
420 425 430

<210> 12
<211> 1485
<212> DNA
<213> Homo sapiens

<400> 12

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<210> 13
 <211> 430
 <212> PRT
 <213> Homo sapiens

<400> 13

Met Ser Phe Thr Thr Arg Ser Thr Phe Ser Thr Asn Tyr Arg Ser Leu
 1 5 10 15

Gly Ser Val Gln Ala Pro Ser Tyr Gly Ala Arg Pro Val Ser Ser Ala
 20 25 30

Ala Ser Val Tyr Ala Gly Ala Gly Gly Ser Gly Ser Arg Ile Ser Val
 35 40 45

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Ser Arg Ser Thr Ser Phe Arg Gly Gly Met Gly Ser Gly Gly Leu Ala
50 55 60

Thr Gly Ile Ala Gly Gly Leu Ala Gly Met Gly Gly Ile Gln Asn Glu
65 70 75 80

Lys Glu Thr Met Gln Ser Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp
85 90 95

Arg Val Arg Ser Leu Glu Thr Glu Asn Arg Arg Leu Glu Ser Lys Ile
100 105 110

Arg Glu His Leu Glu Lys Lys Gly Pro Gln Val Arg Asp Trp Ser His
115 120 125

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

Val Asp Asn Ala Arg Ile Val Leu Gln Ile Asp Asn Ala Arg Leu Ala
145 150 155 160

Ala Asp Asp Phe Arg Val Lys Tyr Glu Thr Glu Leu Ala Met Arg Gln
165 170 175

Ser Val Glu Asn Asp Ile His Gly Leu Arg Lys Val Ile Asp Asp Thr
180 185 190

Asn Ile Thr Arg Leu Gln Leu Glu Thr Glu Ile Glu Ala Leu Lys Glu
195 200 205

Glu Leu Leu Phe Met Lys Lys Asn His Glu Glu Glu Val Lys Gly Leu
210 215 220

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

Lys Ser Gln Asp Leu Ala Lys Ile Met Ala Asp Ile Arg Ala Gln Tyr
245 250 255

Asp Glu Leu Ala Arg Lys Asn Arg Glu Glu Leu Asp Lys Tyr Trp Ser
260 265 270

Gln Gln Ile Glu Glu Ser Thr Thr Val Val Thr Thr Gln Ser Ala Glu
275 280 285

Val Gly Ala Ala Glu Thr Thr Leu Thr Glu Leu Arg Arg Thr Val Gln
290 295 300

Ser Leu Glu Ile Asp Leu Asp Ser Met Arg Asn Leu Lys Ala Ser Leu
305 310 315 320

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Glu Asn Ser Leu Arg Glu Val Glu Ala Arg Tyr Ala Leu Gln Met Glu
325 330 335

Gln Leu Asn Gly Ile Leu Leu His Leu Glu Ser Glu Leu Ala Gln Thr
340 345 350

Arg Ala Glu Gly Gln Arg Gln Ala Gln Glu Tyr Glu Ala Leu Leu Asn
355 360 365

Ile Lys Val Lys Leu Glu Ala Glu Ile Ala Thr Tyr Arg Arg Leu Leu
370 375 380

Glu Asp Gly Glu Asp Phe Asn Leu Gly Asp Ala Leu Asp Ser Ser Asn
385 390 395 400

Ser Met Gln Thr Ile Gln Lys Thr Thr Thr Arg Arg Ile Val Asp Gly
405 410 415

Lys Val Val Ser Glu Thr Asn Asp Thr Lys Val Leu Arg His
420 425 430

<210> 14
<211> 1439
<212> DNA
<213> Homo sapiens

<400> 14
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ggcgctgggg gctctggttc ccgatctcc gtgtcccgtt ccaccagctt caggggcggc 240
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cagaacgaga aggagaccat gcaaagcctg aacgaccgcc tggcctctta cctggacaga 360
gtgaggagcc tggagaccga gaaccggagg ctggagagca aaatccggga gcacttggag 420
aagaagggac cccaggtcag agactggagc cattacttca agatcatcga ggacctgagg 480
gctcagatct tcgcaaatac tgtggacaat gcccgcatcg ttctgcagat tgacaatgcc 540
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cagctggaga cagagatcga ggctctcaag gaggagctgc tcttcatgaa gaagaaccac 720
gaagaggaag taaaaggcct acaagcccag attgccagct ctggggtgac cgtggaggta 780
gatgccccca aatctcagga cctcgccaag atcatggcag acatccgggc ccaatatgac 840
gagctggctc ggaagaaccg agaggagcta gacaagtact ggtctcagca gattgaggag 900
agcaccacag tggtcaccac acagtctgct gaggttggag ctgctgagac gacgctcaca 960

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ccctttgggg agcaggaggc caataaaaag ttcagagttc aaaaaaaaaa aaaaaaaaaa 1439

<210> 15
<211> 400
<212> PRT
<213> Homo sapiens

<400> 15

Met Thr Ser Tyr Ser Tyr Arg Gln Ser Ser Ala Thr Ser Ser Phe Gly
1 5 10 15

Gly Leu Gly Gly Gly Ser Val Arg Phe Gly Pro Gly Val Ala Phe Arg
20 25 30

Ala Pro Ser Ile His Gly Gly Ser Gly Gly Arg Gly Val Ser Val Ser
35 40 45

Ser Ala Arg Phe Val Ser Ser Ser Ser Gly Ala Tyr Gly Gly Gly
50 55 60

Tyr Gly Gly Val Leu Thr Ala Ser Asp Gly Leu Leu Ala Gly Asn Glu
65 70 75 80

Lys Leu Thr Met Gln Asn Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp
85 90 95

Lys Val Arg Ala Leu Glu Ala Ala Asn Gly Glu Leu Glu Val Lys Ile
100 105 110

Arg Asp Trp Tyr Gln Lys Gln Gly Pro Gly Pro Ser Arg Asp Tyr Ser
115 120 125

His Tyr Tyr Thr Thr Ile Gln Asp Leu Arg Asp Lys Ile Leu Gly Ala
130 135 140

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

Ala Ala Asp Asp Phe Arg Thr Lys Phe Glu Thr Glu Gln Ala Leu Arg
165 170 175

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Met Ser Val Glu Ala Asp Ile Asn Gly Leu Arg Arg Val Leu Asp Glu
180 185 190

Leu Thr Leu Ala Arg Thr Asp Leu Glu Met Gln Ile Glu Gly Leu Lys
195 200 205

Glu Glu Leu Ala Tyr Leu Lys Lys Asn His Glu Glu Glu Ile Ser Thr
210 215 220

Leu Arg Gly Gln Val Gly Gly Gln Val Ser Val Glu Val Asp Ser Ala
225 230 235 240

Pro Gly Thr Asp Leu Ala Lys Ile Leu Ser Asp Met Arg Ser Gln Tyr
245 250 255

Glu Val Met Ala Glu Gln Asn Arg Lys Asp Ala Glu Ala Trp Phe Thr
260 265 270

Ser Arg Thr Glu Glu Leu Asn Arg Glu Val Ala Gly His Thr Glu Gln
275 280 285

Leu Gln Met Ser Arg Ser Glu Val Thr Asp Leu Arg Arg Thr Leu Gln
290 295 300

Gly Leu Glu Ile Glu Leu Gln Ser Gln Leu Ser Met Lys Ala Ala Leu
305 310 315 320

Glu Asp Thr Leu Ala Glu Thr Glu Ala Arg Phe Gly Ala Gln Leu Ala
325 330 335

His Ile Gln Ala Leu Ile Ser Gly Ile Glu Ala Gln Leu Gly Asp Val
340 345 350

Arg Ala Asp Ser Glu Arg Gln Asn Gln Glu Tyr Gln Arg Leu Met Asp
355 360 365

Ile Lys Ser Arg Leu Glu Gln Glu Ile Ala Thr Tyr Arg Ser Leu Leu
370 375 380

Glu Gly Gln Glu Asp His Tyr Asn Asn Leu Ser Ala Ser Lys Val Leu
385 390 395 400

<210> 16
<211> 1490
<212> DNA
<213> Homo sapiens

<400> 16
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tccgtccgtg ctccgcctcg ccatgacttc ctacagctat cgccagtcgt cggccacgtc 180

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 gtcctcgtcc tcctcggggg cctacggcg cggctacggc ggcgtcctga ccgctccga 360
 cgggctgctg gcgggcaacg agaagctaac catgcagaac ctcaacgacc gcctggcctc 420
 ctacctggac aaggtgcgcg ccctggaggc ggccaacggc gagctagagg tgaagatccg 480
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<210> 17
 <211> 378
 <212> PRT
 <213> Homo sapiens

<400> 17

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

Asn Phe Ile Phe Gly Gln Ser Gly Ala Gly Asn Asn Trp Ala Lys Gly
 20 25 30

His Tyr Thr Glu Gly Ala Glu Leu Val Asp Ser Val Leu Asp Val Val
 35 40 45

Arg Lys Glu Cys Glu Asn Cys Asp Cys Leu Gln Gly Phe Gln Leu Thr
 50 55 60

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His Ser Leu Gly Gly Gly Thr Gly Ser Gly Met Gly Thr Leu Leu Ile
 65 70 75 80
 Ser Lys Val Arg Glu Glu Tyr Pro Asp Arg Ile Met Asn Thr Phe Ser
 85 90 95
 Val Val Pro Ser Pro Lys Val Ser Asp Thr Val Val Glu Pro Tyr Asn
 100 105 110
 Ala Thr Leu Ser Ile His Gln Leu Val Glu Asn Thr Asp Glu Thr Tyr
 115 120 125
 Cys Ile Asp Asn Glu Ala Leu Tyr Asp Ile Cys Phe Arg Thr Leu Lys
 130 135 140
 Leu Ala Thr Pro Thr Tyr Gly Asp Leu Asn His Leu Val Ser Ala Thr
 145 150 155 160
 Met Ser Gly Val Thr Thr Ser Leu Arg Phe Pro Gly Gln Leu Asn Ala
 165 170 175
 Asp Leu Arg Lys Leu Ala Val Asn Met Val Pro Phe Pro Arg Leu His
 180 185 190
 Phe Phe Met Pro Gly Phe Ala Pro Leu Thr Ala Arg Gly Ser Gln Gln
 195 200 205
 Tyr Arg Ala Leu Thr Val Pro Glu Leu Thr Gln Gln Met Phe Asp Ala
 210 215 220
 Lys Asn Met Met Ala Ala Cys Asp Pro Arg His Gly Arg Tyr Leu Thr
 225 230 235 240
 Val Ala Thr Val Phe Arg Gly Arg Met Ser Met Lys Glu Val Asp Glu
 245 250 255
 Gln Met Leu Ala Ile Gln Ser Lys Asn Ser Ser Tyr Phe Val Glu Trp
 260 265 270
 Ile Pro Asn Asn Val Lys Val Ala Val Cys Asp Ile Pro Pro Arg Gly
 275 280 285
 Leu Lys Met Ser Ser Thr Phe Ile Gly Asn Ser Thr Ala Ile Gln Glu
 290 295 300
 Leu Phe Lys Arg Ile Ser Glu Gln Phe Thr Ala Met Phe Arg Arg Lys
 305 310 315 320
 Ala Phe Leu His Trp Tyr Thr Gly Glu Gly Met Asp Glu Met Glu Phe
 325 330 335

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Thr Glu Ala Glu Ser Asn Met Asn Asp Leu Val Ser Glu Tyr Gln Gln
 340 345 350

Tyr Gln Asp Ala Thr Ala Glu Glu Glu Gly Glu Met Tyr Glu Asp Asp
 355 360 365

Glu Glu Glu Ser Glu Ala Gln Gly Pro Lys
 370 375

<210> 18
 <211> 1851
 <212> DNA
 <213> Homo sapiens

<400> 18
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 tccatttctc gactttccaa actggagagc ttcttgagag aaaagagaga gacaggtaca 180
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<210> 19
 <211> 450
 <212> PRT
 <213> Homo sapiens

<400> 19

Met Arg Glu Ile Val His Ile Gln Ala Gly Gln Cys Gly Asn Gln Ile
 1 5 10 15

Gly Ala Lys Phe Trp Glu Val Ile Ser Asp Glu His Gly Ile Asp Pro
 20 25 30

Ser Gly Asn Tyr Val Gly Asp Ser Asp Leu Gln Leu Glu Arg Ile Ser
 35 40 45

Val Tyr Tyr Asn Glu Ala Ser Ser His Lys Tyr Val Pro Arg Ala Ile
 50 55 60

Leu Val Asp Leu Glu Pro Gly Thr Met Asp Ser Val Arg Ser Gly Ala
 65 70 75 80

Phe Gly His Leu Phe Arg Pro Asp Asn Phe Ile Phe Gly Gln Ser Gly
 85 90 95

Ala Gly Asn Asn Trp Ala Lys Gly His Tyr Thr Glu Gly Ala Glu Leu
 100 105 110

Val Asp Ser Val Leu Asp Val Val Arg Lys Glu Cys Glu Asn Cys Asp
 115 120 125

Cys Leu Gln Gly Phe Gln Leu Thr His Ser Leu Gly Gly Gly Thr Gly
 130 135 140

Ser Gly Met Gly Thr Leu Leu Ile Ser Lys Val Arg Glu Glu Tyr Pro
 145 150 155 160

Asp Arg Ile Met Asn Thr Phe Ser Val Val Pro Ser Pro Lys Val Ser
 165 170 175

Asp Thr Val Val Glu Pro Tyr Asn Ala Thr Leu Ser Ile His Gln Leu
 180 185 190

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Val Glu Asn Thr Asp Glu Thr Tyr Cys Ile Asp Asn Glu Ala Leu Tyr
195 200 205

Asp Ile Cys Phe Arg Thr Leu Lys Leu Ala Thr Pro Thr Tyr Gly Asp
210 215 220

Leu Asn His Leu Val Ser Ala Thr Met Ser Gly Val Thr Thr Ser Leu
225 230 235 240

Arg Phe Pro Gly Gln Leu Asn Ala Asp Leu Arg Lys Leu Ala Val Asn
245 250 255

Met Val Pro Phe Pro Arg Leu His Phe Phe Met Pro Gly Phe Ala Pro
260 265 270

Leu Thr Ala Arg Gly Ser Gln Gln Tyr Arg Ala Leu Thr Val Pro Glu
275 280 285

Leu Thr Gln Gln Met Phe Asp Ala Lys Asn Met Met Ala Ala Cys Asp
290 295 300

Pro Arg His Gly Arg Tyr Leu Thr Val Ala Thr Val Phe Arg Gly Arg
305 310 315 320

Met Ser Met Lys Glu Val Asp Glu Gln Met Leu Ala Ile Gln Ser Lys
325 330 335

Asn Ser Ser Tyr Phe Val Glu Trp Ile Pro Asn Asn Val Lys Val Ala
340 345 350

Val Cys Asp Ile Pro Pro Arg Gly Leu Lys Met Ser Ser Thr Phe Ile
355 360 365

Gly Asn Ser Thr Ala Ile Gln Glu Leu Phe Lys Arg Ile Ser Glu Gln
370 375 380

Phe Thr Ala Met Phe Arg Arg Lys Ala Phe Leu His Trp Tyr Thr Gly
385 390 395 400

Glu Gly Met Asp Glu Met Glu Phe Thr Glu Ala Glu Ser Asn Met Asn
405 410 415

Asp Leu Val Ser Glu Tyr Gln Gln Tyr Gln Asp Ala Thr Ala Glu Glu
420 425 430

Glu Gly Glu Met Tyr Glu Asp Asp Glu Glu Glu Ser Glu Ala Gln Gly
435 440 445

Pro Lys
450

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<210> 20
 <211> 1794
 <212> DNA
 <213> Homo sapiens

<400> 20
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 agtatgaggg agatcgtgca catccaggcc ggccagtgcg gcaaccagat cggggccaag 180
 ttctgggaag tcatcagtga tgagcatggc atcgacccca gcggcaacta cgtgggcgac 240
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 gtgcctcgag ccattctggt ggacctgga cccggaacca tggacagtgt ccgctcaggg 360
 gcctttggac atctcttcag gcctgacaat ttcatctttg gtcagagtgg ggccggcaac 420
 aactgggcca agggtcacta cacggagggg gcggagctgg tggattcggg cctggatgtg 480
 gtgcggaagg agtgtgaaaa ctgcgactgc ctgcagggtt tccagctgac ccactcgctg 540
 gggggcggca cgggctccgg catgggcacg ttgctcatca gcaagggtgcg tgaggagtat 600
 cccgaccgca tcatgaacac cttcagcgtc gtgccctcac ccaagggtgc agacacgggtg 660
 gtggagccct acaacgccac gctgtccatc caccagctgg tggagaacac ggatgagacc 720
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 Lys Tyr His Gln Arg Pro Thr Phe Arg Gln Met Gln Leu Glu Asn Val
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 Ser Val Ala Leu Glu Phe Leu Asp Arg Glu Ser Ile Lys Leu Val Ser
 85 90 95
 Ile Asp Ser Lys Ala Ile Val Asp Gly Asn Leu Lys Leu Ile Leu Gly
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His Ile Ser Lys Ser Pro Phe Glu Val Ser Val Asp Lys Ala Gln Gly
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 <212> PRT
 <213> Homo sapiens

<400> 24

Met Pro Val Thr Glu Lys Asp Leu Ala Glu Asp Ala Pro Trp Lys Lys
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Val	Asn	Lys	Arg	Ile	Gly	Asn	Leu	Gln	Thr	Asp	Leu	Ser	Asp	Gly	Leu
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Arg	Leu	Ile	Ala	Leu	Leu	Glu	Val	Leu	Ser	Gln	Lys	Arg	Met	Tyr	Arg
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Lys	Tyr	His	Gln	Arg	Pro	Thr	Phe	Arg	Gln	Met	Gln	Leu	Glu	Asn	Val
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Glu	Asp	Glu	Gly	Asp	Asp	Asp	Ala	Lys	Lys	Gln	Thr	Pro	Lys	Gln	Arg
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Phe	Asn	Gln	Asn	Trp	Gln	Asp	Gly	Lys	Ala	Leu	Gly	Ala	Leu	Val	Asp
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Ser	Cys	Ala	Pro	Gly	Leu	Cys	Pro	Asp	Trp	Glu	Ser	Trp	Asp	Pro	Gln
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Lys	Leu	Lys	Pro	Gly	Ala	Pro	Leu	Lys	Pro	Lys	Leu	Asn	Pro	Lys	Lys
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Ala	Arg	Ala	Tyr	Gly	Arg	Gly	Ile	Glu	Pro	Thr	Gly	Asn	Met	Val	Lys
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Gln	Pro	Ala	Lys	Phe	Thr	Val	Asp	Thr	Ile	Ser	Ala	Gly	Gln	Gly	Asp

275

280

285

Val Met Val Phe Val Glu Asp Pro Glu Gly Asn Lys Glu Glu Ala Gln
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Val Thr Pro Asp Ser Asp Lys Asn Lys Thr Tyr Ser Val Glu Tyr Leu
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Pro Lys Val Thr Gly Leu His Lys Val Thr Val Leu Phe Ala Gly Gln
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His Ile Ser Lys Ser Pro Phe Glu Val Ser Val Asp Lys Ala Gln Gly
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Asp Ala Ser Lys Val Thr Ala Lys Gly Pro Gly Leu Glu Ala Val Gly
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Asn Ile Ala Asn Lys Pro Thr Tyr Phe Asp Ile Tyr Thr Ala Gly Ala
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Gly Val Gly Asp Ile Gly Val Glu Val Glu Asp Pro Gln Gly Lys Asn
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Thr Val Glu Leu Leu Val Glu Asp Lys Gly Asn Gln Val Tyr Arg Cys
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Val Tyr Lys Pro Met Gln Pro Gly Pro His Val Val Lys Ile Phe Phe
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Ala Gly Asp Thr Ile Pro Lys Ser Pro Phe Val Val Gln Val Gly Glu
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Ala Cys Asn Pro Asn Ala Cys Arg Ala Ser Gly Arg Gly Leu Gln Pro
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Lys Gly Val Arg Ile Arg Glu Thr Thr Asp Phe Lys Val Asp Thr Lys
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Ala Ala Gly Ser Gly Glu Leu Gly Val Thr Met Lys Gly Pro Lys Gly
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Leu Glu Glu Leu Val Lys Gln Lys Asp Phe Leu Asp Gly Val Tyr Ala
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Phe Glu Tyr Tyr Pro Ser Thr Pro Gly Arg Tyr Ser Ile Ala Ile Thr
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Trp Gly Gly His His Ile Pro Lys Ser Pro Phe Glu Val Gln Val Gly
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Pro Glu Ala Gly Met Gln Lys Val Arg Ala Trp Gly Pro Gly Leu His
 Page 129

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 565 570 575
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 580 585 590
 Lys Ile Glu Tyr Asn Asp Gln Asn Asp Gly Ser Cys Asp Val Lys Tyr
 595 600 605
 Trp Pro Lys Glu Pro Gly Glu Tyr Ala Val His Ile Met Cys Asp Asp
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 Glu Asp Ile Lys Asp Ser Pro Tyr Met Ala Phe Ile His Pro Ala Thr
 625 630 635 640
 Gly Gly Tyr Asn Pro Asp Leu Val Arg Ala Tyr Gly Pro Gly Leu Glu
 645 650 655
 Lys Ser Gly Cys Ile Val Asn Asn Leu Ala Glu Phe Thr Val Asp Pro
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 Lys Asp Ala Gly Lys Ala Pro Leu Lys Ile Phe Ala Gln Asp Gly Glu
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 Gly Gln Arg Ile Asp Ile Gln Met Lys Asn Arg Met Asp Gly Thr Tyr
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 Ala Cys Ser Tyr Thr Pro Val Lys Ala Ile Lys His Thr Ile Ala Val
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 Val Trp Gly Gly Val Asn Ile Pro His Ser Pro Tyr Arg Val Asn Ile
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 Gly Gln Gly Ser His Pro Gln Lys Val Lys Val Phe Gly Pro Gly Val
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 Glu Arg Ser Gly Leu Lys Ala Asn Glu Pro Thr His Phe Thr Val Asp
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 Cys Thr Glu Ala Gly Glu Gly Asp Val Ser Val Gly Ile Lys Cys Asp
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 Ala Arg Val Leu Ser Glu Asp Glu Glu Asp Val Asp Phe Asp Ile Ile
 785 790 795 800
 His Asn Ala Asn Asp Thr Phe Thr Val Lys Tyr Val Pro Pro Ala Ala
 805 810 815
 Gly Arg Tyr Thr Ile Lys Val Leu Phe Ala Ser Gln Glu Ile Pro Ala
 Page 130

820

825

830

Ser Pro Phe Arg Val Lys Val Asp Pro Ser His Asp Ala Ser Lys Val
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Lys Ala Glu Gly Pro Gly Leu Ser Lys Ala Gly Val Glu Asn Gly Lys
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Pro Thr His Phe Thr Val Tyr Thr Lys Gly Ala Gly Lys Ala Pro Leu
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Asn Val Gln Phe Asn Ser Pro Leu Pro Gly Asp Ala Val Lys Asp Leu
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Asp Ile Ile Asp Asn Tyr Asp Tyr Ser His Thr Val Lys Tyr Thr Pro
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Thr Gln Gln Gly Asn Met Gln Val Leu Val Thr Tyr Gly Gly Asp Pro
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Ile Pro Lys Ser Pro Phe Thr Val Gly Val Ala Ala Pro Leu Asp Leu
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Ser Lys Ile Lys Leu Asn Gly Leu Glu Asn Arg Val Glu Val Gly Lys
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Asp Gln Glu Phe Thr Val Asp Thr Arg Gly Ala Gly Gly Gln Gly Lys
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Leu Asp Val Thr Ile Leu Ser Pro Ser Arg Lys Val Val Pro Cys Leu
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Val Thr Pro Val Thr Gly Arg Glu Asn Ser Thr Ala Lys Phe Ile Pro
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Arg Glu Glu Gly Leu Tyr Ala Val Asp Val Thr Tyr Asp Gly His
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Pro Val Pro Gly Ser Pro Tyr Thr Val Glu Ala Ser Leu Pro Pro
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Asp Pro Ser Lys Val Lys Ala His Gly Pro Gly Leu Glu Gly Gly
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Gly Thr Gly Gly Leu Gly Leu Thr Val Glu Gly Pro Cys Glu Ala
 1070 1075 1080

Lys Ile Glu Cys Ser Asp Asn Gly Asp Gly Thr Cys Ser Val Ser
 Page 131

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Ile	Gln	Gln	Asn	Thr	Phe	Thr	Arg	Trp	Cys	Asn	Glu	His	Leu	Lys	Cys
			20					25					30		

Val	Asn	Lys	Arg	Ile	Gly	Asn	Leu	Gln	Thr	Asp	Leu	Ser	Asp	Gly	Leu
		35					40					45			

Arg	Leu	Ile	Ala	Leu	Leu	Glu	Val	Leu	Ser	Gln	Lys	Arg	Met	Tyr	Arg
	50					55					60				

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Lys Tyr His Gln Arg Pro Thr Phe Arg Gln Met Gln Leu Glu Asn Val
 65 70 75 80
 Ser Val Ala Leu Glu Phe Leu Asp Arg Glu Ser Ile Lys Leu Val Ser
 85 90 95
 Ile Asp Ser Lys Ala Ile Val Asp Gly Asn Leu Lys Leu Ile Leu Gly
 100 105 110
 Leu Val Trp Thr Leu Ile Leu His Tyr Ser Ile Ser Met Pro Val Trp
 115 120 125
 Glu Asp Glu Gly Asp Asp Asp Ala Lys Lys Gln Thr Pro Lys Gln Arg
 130 135 140
 Leu Leu Gly Trp Ile Gln Asn Lys Ile Pro Tyr Leu Pro Ile Thr Asn
 145 150 155 160
 Phe Asn Gln Asn Trp Gln Asp Gly Lys Ala Leu Gly Ala Leu Val Asp
 165 170 175
 Ser Cys Ala Pro Gly Leu Cys Pro Asp Trp Glu Ser Trp Asp Pro Gln
 180 185 190
 Lys Pro Val Asp Asn Ala Arg Glu Ala Met Gln Gln Ala Asp Asp Trp
 195 200 205
 Leu Gly Val Pro Gln Val Ile Thr Pro Glu Glu Ile Ile His Pro Asp
 210 215 220
 Val Asp Glu His Ser Val Met Thr Tyr Leu Ser Gln Phe Pro Lys Ala
 225 230 235 240
 Lys Leu Lys Pro Gly Ala Pro Leu Lys Pro Lys Leu Asn Pro Lys Lys
 245 250 255
 Ala Arg Ala Tyr Gly Arg Gly Ile Glu Pro Thr Gly Asn Met Val Lys
 260 265 270
 Gln Pro Ala Lys Phe Thr Val Asp Thr Ile Ser Ala Gly Gln Gly Asp
 275 280 285
 Val Met Val Phe Val Glu Asp Pro Glu Gly Asn Lys Glu Glu Ala Gln
 290 295 300
 Val Thr Pro Asp Ser Asp Lys Asn Lys Thr Tyr Ser Val Glu Tyr Leu
 305 310 315 320
 Pro Lys Val Thr Gly Leu His Lys Val Thr Val Leu Phe Ala Gly Gln
 325 330 335

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His Ile Ser Lys Ser Pro Phe Glu Val Ser Val Asp Lys Ala Gln Gly
340 345 350

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

Asn Ile Ala Asn Lys Pro Thr Tyr Phe Asp Ile Tyr Thr Ala Gly Ala
370 375 380

Gly Val Gly Asp Ile Gly Val Glu Val Glu Asp Pro Gln Gly Lys Asn
385 390 395 400

Thr Val Glu Leu Leu Val Glu Asp Lys Gly Asn Gln Val Tyr Arg Cys
405 410 415

Val Tyr Lys Pro Met Gln Pro Gly Pro His Val Val Lys Ile Phe Phe
420 425 430

Ala Gly Asp Thr Ile Pro Lys Ser Pro Phe Val Val Gln Val Gly Glu
435 440 445

Ala Cys Asn Pro Asn Ala Cys Arg Ala Ser Gly Arg Gly Leu Gln Pro
450 455 460

Lys Gly Val Arg Ile Arg Glu Thr Thr Asp Phe Lys Val Asp Thr Lys
465 470 475 480

Ala Ala Gly Ser Gly Glu Leu Gly Val Thr Met Lys Gly Pro Lys Gly
485 490 495

Leu Glu Glu Leu Val Lys Gln Lys Asp Phe Leu Asp Gly Val Tyr Ala
500 505 510

Phe Glu Tyr Tyr Pro Ser Thr Pro Gly Arg Tyr Ser Ile Ala Ile Thr
515 520 525

Trp Gly Gly His His Ile Pro Lys Ser Pro Phe Glu Val Gln Val Gly
530 535 540

Pro Glu Ala Gly Met Gln Lys Val Arg Ala Trp Gly Pro Gly Leu His
545 550 555 560

Gly Gly Ile Val Gly Arg Ser Ala Asp Phe Val Val Glu Ser Ile Gly
565 570 575

Ser Glu Val Gly Ser Leu Gly Phe Ala Ile Glu Gly Pro Ser Gln Ala
580 585 590

Lys Ile Glu Tyr Asn Asp Gln Asn Asp Gly Ser Cys Asp Val Lys Tyr
595 600 605

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Trp Pro Lys Glu Pro Gly Glu Tyr Ala Val His Ile Met Cys Asp Asp
 610 615 620
 Glu Asp Ile Lys Asp Ser Pro Tyr Met Ala Phe Ile His Pro Ala Thr
 625 630 635 640
 Gly Gly Tyr Asn Pro Asp Leu Val Arg Ala Tyr Gly Pro Gly Leu Glu
 645 650 655
 Lys Ser Gly Cys Ile Val Asn Asn Leu Ala Glu Phe Thr Val Asp Pro
 660 665 670
 Lys Asp Ala Gly Lys Ala Pro Leu Lys Ile Phe Ala Gln Asp Gly Glu
 675 680 685
 Gly Gln Arg Ile Asp Ile Gln Met Lys Asn Arg Met Asp Gly Thr Tyr
 690 695 700
 Ala Cys Ser Tyr Thr Pro Val Lys Ala Ile Lys His Thr Ile Ala Val
 705 710 715 720
 Val Trp Gly Gly Val Asn Ile Pro His Ser Pro Tyr Arg Val Asn Ile
 725 730 735
 Gly Gln Gly Ser His Pro Gln Lys Val Lys Val Phe Gly Pro Gly Val
 740 745 750
 Glu Arg Ser Gly Leu Lys Ala Asn Glu Pro Thr His Phe Thr Val Asp
 755 760 765
 Cys Thr Glu Ala Gly Glu Gly Asp Val Ser Val Gly Ile Lys Cys Asp
 770 775 780
 Ala Arg Val Leu Ser Glu Asp Glu Glu Asp Val Asp Phe Asp Ile Ile
 785 790 795 800
 His Asn Ala Asn Asp Thr Phe Thr Val Lys Tyr Val Pro Pro Ala Ala
 805 810 815
 Gly Arg Tyr Thr Ile Lys Val Leu Phe Ala Ser Gln Glu Ile Pro Ala
 820 825 830
 Ser Pro Phe Arg Val Lys Val Asp Pro Ser His Asp Ala Ser Lys Val
 835 840 845
 Lys Ala Glu Gly Pro Gly Leu Ser Lys Ala Gly Val Glu Asn Gly Lys
 850 855 860
 Pro Thr His Phe Thr Val Tyr Thr Lys Gly Ala Gly Lys Ala Pro Leu
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Asn Val Gln Phe Asn Ser Pro Leu Pro Gly Asp Ala Val Lys Asp Leu
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Asp Ile Ile Asp Asn Tyr Asp Tyr Ser His Thr Val Lys Tyr Thr Pro
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Thr Gln Gln Gly Asn Met Gln Val Leu Val Thr Tyr Gly Gly Asp Pro
 915 920 925

Ile Pro Lys Ser Pro Phe Thr Val Gly Val Ala Ala Pro Leu Asp Leu
 930 935 940

Ser Lys Ile Lys Leu Asn Gly Leu Glu Asn Arg Val Glu Val Gly Lys
 945 950 955 960

Asp Gln Glu Phe Thr Val Asp Thr Arg Gly Ala Gly Gly Gln Gly Lys
 965 970 975

Leu Asp Val Thr Ile Leu Ser Pro Ser Arg Lys Val Val Pro Cys Leu
 980 985 990

Val Thr Pro Val Thr Gly Arg Glu Asn Ser Thr Ala Lys Phe Ile Pro
 995 1000 1005

Arg Glu Glu Gly Leu Tyr Ala Val Asp Val Thr Tyr Asp Gly His
 1010 1015 1020

Pro Val Pro Gly Ser Pro Tyr Thr Val Glu Ala Ser Leu Pro Pro
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Asp Pro Ser Lys Val Lys Ala His Gly Pro Gly Leu Glu Gly Gly
 1040 1045 1050

Leu Val Gly Lys Pro Ala Glu Phe Thr Ile Asp Thr Lys Gly Ala
 1055 1060 1065

Gly Thr Gly Gly Leu Gly Leu Thr Val Glu Gly Pro Cys Glu Ala
 1070 1075 1080

Lys Ile Glu Cys Ser Asp Asn Gly Asp Gly Thr Cys Ser Val Ser
 1085 1090 1095

Tyr Leu Pro Thr Lys Pro Gly Glu Tyr Phe Val Asn Ile Leu Phe
 1100 1105 1110

Glu Glu Val His Ile Pro Gly Ser Pro Phe Lys Ala Asp Ile Glu
 1115 1120 1125

Met Pro Phe Asp Pro Ser Lys Val Val Ala Ser Gly Pro Gly Leu
 1130 1135 1140

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Glu	His	Gly	Lys	Val	Gly	Glu	Ala	Gly	Leu	Leu	Ser	Val	Asp	Cys
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Ser	Glu	Ala	Gly	Pro	Gly	Ala	Leu	Gly	Leu	Glu	Ala	Val	Ser	Asp
	1160					1165					1170			
Ser	Gly	Thr	Lys	Ala	Glu	Val	Ser	Ile	Gln	Asn	Asn	Lys	Asp	Gly
	1175					1180					1185			
Thr	Tyr	Ala	Val	Thr	Tyr	Val	Pro	Leu	Thr	Ala	Gly	Met	Tyr	Thr
	1190					1195					1200			
Leu	Thr	Met	Lys	Tyr	Gly	Gly	Glu	Leu	Val	Pro	His	Phe	Pro	Ala
	1205					1210					1215			
Arg	Val	Lys	Val	Glu	Pro	Ala	Val	Asp	Thr	Ser	Arg	Ile	Lys	Val
	1220					1225					1230			
Phe	Gly	Pro	Gly	Ile	Glu	Gly	Lys	Asp	Val	Phe	Arg	Glu	Ala	Thr
	1235					1240					1245			
Thr	Asp	Phe	Thr	Val	Asp	Ser	Arg	Pro	Leu	Thr	Gln	Val	Gly	Gly
	1250					1255					1260			
Asp	His	Ile	Lys	Ala	His	Ile	Ala	Asn	Pro	Ser	Gly	Ala	Ser	Thr
	1265					1270					1275			
Glu	Cys	Phe	Val	Thr	Asp	Asn	Ala	Asp	Gly	Thr	Tyr	Gln	Val	Glu
	1280					1285					1290			
Tyr	Thr	Pro	Phe	Glu	Lys	Gly	Leu	His	Val	Val	Glu	Val	Thr	Tyr
	1295					1300					1305			
Asp	Asp	Val	Pro	Ile	Pro	Asn	Ser	Pro	Phe	Lys	Val	Ala	Val	Thr
	1310					1315					1320			
Glu	Gly	Cys	Gln	Pro	Ser	Arg	Val	Gln	Ala	Gln	Gly	Pro	Gly	Leu
	1325					1330					1335			
Lys	Glu	Ala	Phe	Thr	Asn	Lys	Pro	Asn	Val	Phe	Thr	Val	Val	Thr
	1340					1345					1350			
Arg	Gly	Ala	Gly	Ile	Gly	Gly	Leu	Gly	Ile	Thr	Val	Glu	Gly	Pro
	1355					1360					1365			
Ser	Glu	Ser	Lys	Ile	Asn	Cys	Arg	Asp	Asn	Lys	Asp	Gly	Ser	Cys
	1370					1375					1380			
Ser	Ala	Glu	Tyr	Ile	Pro	Phe	Ala	Pro	Gly	Asp	Tyr	Asp	Val	Asn
	1385					1390					1395			

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Ile	Thr	Tyr	Gly	Gly	Ala	His	Ile	Pro	Gly	Ser	Pro	Phe	Arg	Val
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Pro	Val	Lys	Asp	Val	Val	Asp	Pro	Ser	Lys	Val	Lys	Ile	Ala	Gly
	1415					1420					1425			
Pro	Gly	Leu	Gly	Ser	Gly	Val	Arg	Ala	Arg	Val	Leu	Gln	Ser	Phe
	1430					1435					1440			
Thr	Val	Asp	Ser	Ser	Lys	Ala	Gly	Leu	Ala	Pro	Leu	Glu	Val	Arg
	1445					1450					1455			
Val	Leu	Gly	Pro	Arg	Gly	Leu	Val	Glu	Pro	Val	Asn	Val	Val	Asp
	1460					1465					1470			
Asn	Gly	Asp	Gly	Thr	His	Thr	Val	Thr	Tyr	Thr	Pro	Ser	Gln	Glu
	1475					1480					1485			
Gly	Pro	Tyr	Met	Val	Ser	Val	Lys	Tyr	Ala	Asp	Glu	Glu	Ile	Pro
	1490					1495					1500			
Arg	Ser	Pro	Phe	Lys	Val	Lys	Val	Leu	Pro	Thr	Tyr	Asp	Ala	Ser
	1505					1510					1515			
Lys	Val	Thr	Ala	Ser	Gly	Pro	Gly	Leu	Ser	Ser	Tyr	Gly	Val	Pro
	1520					1525					1530			
Ala	Ser	Leu	Pro	Val	Asp	Phe	Ala	Ile	Asp	Ala	Arg	Asp	Ala	Gly
	1535					1540					1545			
Glu	Gly	Leu	Leu	Ala	Val	Gln	Ile	Thr	Asp	Gln	Glu	Gly	Lys	Pro
	1550					1555					1560			
Lys	Arg	Ala	Ile	Val	His	Asp	Asn	Lys	Asp	Gly	Thr	Tyr	Ala	Val
	1565					1570					1575			
Thr	Tyr	Ile	Pro	Asp	Lys	Thr	Gly	Arg	Tyr	Met	Ile	Gly	Val	Thr
	1580					1585					1590			
Tyr	Gly	Gly	Asp	Asp	Ile	Pro	Leu	Ser	Pro	Tyr	Arg	Ile	Arg	Ala
	1595					1600					1605			
Thr	Gln	Thr	Gly	Asp	Ala	Ser	Lys	Cys	Leu	Ala	Thr	Gly	Pro	Gly
	1610					1615					1620			
Ile	Ala	Ser	Thr	Val	Lys	Thr	Gly	Glu	Glu	Val	Gly	Phe	Val	Val
	1625					1630					1635			
Asp	Ala	Lys	Thr	Ala	Gly	Lys	Gly	Lys	Val	Thr	Cys	Thr	Val	Leu
	1640					1645					1650			

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Thr	Pro	Asp	Gly	Thr	Glu	Ala	Glu	Ala	Asp	Val	Ile	Glu	Asn	Glu
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Asp	Gly	Thr	Tyr	Asp	Ile	Phe	Tyr	Thr	Ala	Ala	Lys	Pro	Gly	Thr
	1670					1675					1680			
Tyr	Val	Ile	Tyr	Val	Arg	Phe	Gly	Gly	Val	Asp	Ile	Pro	Asn	Ser
	1685					1690					1695			
Pro	Phe	Thr	Val	Met	Val	Thr	Glu	Glu	Ala	Tyr	Val	Pro	Val	Ser
	1700					1705					1710			
Asp	Met	Asn	Gly	Leu	Gly	Phe	Lys	Pro	Phe	Asp	Leu	Val	Ile	Pro
	1715					1720					1725			
Phe	Ala	Val	Arg	Lys	Gly	Glu	Ile	Thr	Gly	Glu	Val	His	Met	Pro
	1730					1735					1740			
Ser	Gly	Lys	Thr	Ala	Thr	Pro	Glu	Ile	Val	Asp	Asn	Lys	Asp	Gly
	1745					1750					1755			
Thr	Val	Thr	Val	Arg	Tyr	Ala	Pro	Thr	Glu	Val	Gly	Leu	His	Glu
	1760					1765					1770			
Met	His	Ile	Lys	Tyr	Met	Gly	Ser	His	Ile	Pro	Glu	Ser	Pro	Leu
	1775					1780					1785			
Gln	Phe	Tyr	Val	Asn	Tyr	Pro	Asn	Ser	Gly	Ser	Val	Ser	Ala	Tyr
	1790					1795					1800			
Gly	Pro	Gly	Leu	Val	Tyr	Gly	Val	Ala	Asn	Lys	Thr	Ala	Thr	Phe
	1805					1810					1815			
Thr	Ile	Val	Thr	Glu	Asp	Ala	Gly	Glu	Gly	Gly	Leu	Asp	Leu	Ala
	1820					1825					1830			
Ile	Glu	Gly	Pro	Ser	Lys	Ala	Glu	Ile	Ser	Cys	Ile	Asp	Asn	Lys
	1835					1840					1845			
Asp	Gly	Thr	Cys	Thr	Val	Thr	Tyr	Leu	Pro	Thr	Leu	Pro	Gly	Asp
	1850					1855					1860			
Tyr	Ser	Ile	Leu	Val	Lys	Tyr	Asn	Asp	Lys	His	Ile	Pro	Gly	Ser
	1865					1870					1875			
Pro	Phe	Thr	Ala	Lys	Ile	Thr	Asp	Asp	Ser	Arg	Arg	Cys	Ser	Gln
	1880					1885					1890			
Val	Lys	Leu	Gly	Ser	Ala	Ala	Asp	Phe	Leu	Leu	Asp	Ile	Ser	Glu
	1895					1900					1905			

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Thr	Asp 1910	Leu	Ser	Ser	Leu	Thr 1915	Ala	Ser	Ile	Lys	Ala 1920	Pro	Ser	Gly
Arg	Asp 1925	Glu	Pro	Cys	Leu	Leu 1930	Lys	Arg	Leu	Pro	Asn 1935	Asn	His	Ile
Gly	Ile 1940	Ser	Phe	Ile	Pro	Arg 1945	Glu	Val	Gly	Glu	His 1950	Leu	Val	Ser
Ile	Lys 1955	Lys	Asn	Gly	Asn	His 1960	Val	Ala	Asn	Ser	Pro 1965	Val	Ser	Ile
Met	Val 1970	Val	Gln	Ser	Glu	Ile 1975	Gly	Asp	Ala	Arg	Arg 1980	Ala	Lys	Val
Tyr	Gly 1985	Arg	Gly	Leu	Ser	Glu 1990	Gly	Arg	Thr	Phe	Glu 1995	Met	Ser	Asp
Phe	Ile 2000	Val	Asp	Thr	Arg	Asp 2005	Ala	Gly	Tyr	Gly	Gly 2010	Ile	Ser	Leu
Ala	Val 2015	Glu	Gly	Pro	Ser	Lys 2020	Val	Asp	Ile	Gln	Thr 2025	Glu	Asp	Leu
Glu	Asp 2030	Gly	Thr	Cys	Lys	Val 2035	Ser	Tyr	Phe	Pro	Thr 2040	Val	Pro	Gly
Val	Tyr 2045	Ile	Val	Ser	Thr	Lys 2050	Phe	Ala	Asp	Glu	His 2055	Val	Pro	Gly
Ser	Pro 2060	Phe	Thr	Val	Lys	Ile 2065	Ser	Gly	Glu	Gly	Arg 2070	Val	Lys	Glu
Ser	Ile 2075	Thr	Arg	Thr	Ser	Arg 2080	Ala	Pro	Ser	Val	Ala 2085	Thr	Val	Gly
Ser	Ile 2090	Cys	Asp	Leu	Asn	Leu 2095	Lys	Ile	Pro	Glu	Ile 2100	Asn	Ser	Ser
Asp	Met 2105	Ser	Ala	His	Val	Thr 2110	Ser	Pro	Ser	Gly	Arg 2115	Val	Thr	Glu
Ala	Glu 2120	Ile	Val	Pro	Met	Gly 2125	Lys	Asn	Ser	His	Cys 2130	Val	Arg	Phe
Val	Pro 2135	Gln	Glu	Met	Gly	Val 2140	His	Thr	Val	Ser	Val 2145	Lys	Tyr	Arg
Gly	Gln 2150	His	Val	Thr	Gly	Ser 2155	Pro	Phe	Gln	Phe	Thr 2160	Val	Gly	Pro

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Leu	Gly 2165	Glu	Gly	Gly	Ala	His 2170	Lys	Val	Arg	Ala	Gly 2175	Gly	Pro	Gly
Leu	Glu 2180	Arg	Gly	Glu	Ala	Gly 2185	Val	Pro	Ala	Glu	Phe 2190	Ser	Ile	Trp
Thr	Arg 2195	Glu	Ala	Gly	Ala	Gly 2200	Gly	Leu	Ser	Ile	Ala 2205	Val	Glu	Gly
Pro	Ser 2210	Lys	Ala	Glu	Ile	Thr 2215	Phe	Asp	Asp	His	Lys 2220	Asn	Gly	Ser
Cys	Gly 2225	Val	Ser	Tyr	Ile	Ala 2230	Gln	Glu	Pro	Gly	Asn 2235	Tyr	Glu	Val
Ser	Ile 2240	Lys	Phe	Asn	Asp	Glu 2245	His	Ile	Pro	Glu	Ser 2250	Pro	Tyr	Leu
Val	Pro 2255	Val	Ile	Ala	Pro	Ser 2260	Asp	Asp	Ala	Arg	Arg 2265	Leu	Thr	Val
Met	Ser 2270	Leu	Gln	Glu	Ser	Gly 2275	Leu	Lys	Val	Asn	Gln 2280	Pro	Ala	Ser
Phe	Ala 2285	Ile	Arg	Leu	Asn	Gly 2290	Ala	Lys	Gly	Lys	Ile 2295	Asp	Ala	Lys
Val	His 2300	Ser	Pro	Ser	Gly	Ala 2305	Val	Glu	Glu	Cys	His 2310	Val	Ser	Glu
Leu	Glu 2315	Pro	Asp	Lys	Tyr	Ala 2320	Val	Arg	Phe	Ile	Pro 2325	His	Glu	Asn
Gly	Val 2330	His	Thr	Ile	Asp	Val 2335	Lys	Phe	Asn	Gly	Ser 2340	His	Val	Val
Gly	Ser 2345	Pro	Phe	Lys	Val	Arg 2350	Val	Gly	Glu	Pro	Gly 2355	Gln	Ala	Gly
Asn	Pro 2360	Ala	Leu	Val	Ser	Ala 2365	Tyr	Gly	Thr	Gly	Leu 2370	Glu	Gly	Gly
Thr	Thr 2375	Gly	Ile	Gln	Ser	Glu 2380	Phe	Phe	Ile	Asn	Thr 2385	Thr	Arg	Ala
Gly	Pro 2390	Gly	Thr	Leu	Ser	Val 2395	Thr	Ile	Glu	Gly	Pro 2400	Ser	Lys	Val
Lys	Met 2405	Asp	Cys	Gln	Glu	Thr 2410	Pro	Glu	Gly	Tyr	Lys 2415	Val	Met	Tyr

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Thr	Pro	Met	Ala	Pro	Gly	Asn	Tyr	Leu	Ile	Ser	Val	Lys	Tyr	Gly
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Gly	Pro	Asn	His	Ile	Val	Gly	Ser	Pro	Phe	Lys	Ala	Lys	Val	Thr
	2435					2440					2445			
Gly	Gln	Arg	Leu	Val	Ser	Pro	Gly	Ser	Ala	Asn	Glu	Thr	Ser	Ser
	2450					2455					2460			
Ile	Leu	Val	Glu	Ser	Val	Thr	Arg	Ser	Ser	Thr	Glu	Thr	Cys	Tyr
	2465					2470					2475			
Ser	Ala	Ile	Pro	Lys	Ala	Ser	Ser	Asp	Ala	Ser	Lys	Val	Thr	Ser
	2480					2485					2490			
Lys	Gly	Ala	Gly	Leu	Ser	Lys	Ala	Phe	Val	Gly	Gln	Lys	Ser	Ser
	2495					2500					2505			
Phe	Leu	Val	Asp	Cys	Ser	Lys	Ala	Gly	Ser	Asn	Met	Leu	Leu	Ile
	2510					2515					2520			
Gly	Val	His	Gly	Pro	Thr	Thr	Pro	Cys	Glu	Glu	Val	Ser	Met	Lys
	2525					2530					2535			
His	Val	Gly	Asn	Gln	Gln	Tyr	Asn	Val	Thr	Tyr	Val	Val	Lys	Glu
	2540					2545					2550			
Arg	Gly	Asp	Tyr	Val	Leu	Ala	Val	Lys	Trp	Gly	Glu	Glu	His	Ile
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accctgaca	gtgacaagaa	caagacatac	tctgtggagt	atctgcccaa	ggtcaccggg	1140
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Lys Tyr His Gln Arg Pro Thr Phe Arg Gln Met Gln Leu Glu Asn Val
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Ser Val Ala Leu Glu Phe Leu Asp Arg Glu Ser Ile Lys Leu Val Ser
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Asp Ser Ala Pro Thr Val Val Ser Gly Ile Leu Gly Gly Ser Val Thr
 50 55 60

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

Ile Gly Pro Lys Asn Ala Leu Ala Phe Ala Arg Pro Lys Glu Asn Val
 85 90 95

Thr Ile Met Val Lys Ser Tyr Leu Gly Arg Leu Asp Ile Thr Lys Trp
 100 105 110

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

Tyr Lys Ala Gln Ile Asn Gln Arg Asn Phe Glu Val Thr Thr Glu Glu
 130 135 140

Glu Phe Thr Leu Phe Val Tyr Ala Pro Phe Ile Glu Lys Leu Ser Val
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Asp Ser Ala Pro Thr Val Val Ser Gly Ile Leu Gly Gly Ser Val Thr
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Leu Pro Leu Asn Ile Ser Val Asp Thr Glu Ile Glu Asn Val Ile Trp
 65 70 75 80

Ile Gly Pro Lys Asn Ala Leu Ala Phe Ala Arg Pro Lys Glu Asn Val
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Thr Ile Met Val Lys Ser Tyr Leu Gly Arg Leu Asp Ile Thr Lys Trp
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Ser Tyr Ser Leu Cys Ile Ser Asn Leu Thr Leu Asn Asp Ala Gly Ser
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Tyr Lys Ala Gln Ile Asn Gln Arg Asn Phe Glu Val Thr Thr Glu Glu
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Met Lys Ser Val Lys Val Ser Glu Asn Phe Ser Cys Asn Ile Thr Leu
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Met Cys Ser Val Lys Gly Ala Glu Lys Ser Val Leu Tyr Ser Trp Thr
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Pro Arg Glu Pro His Ala Ser Glu Ser Asn Gly Gly Ser Ile Leu Thr
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Val Ser Arg Thr Pro Cys Asp Pro Asp Leu Pro Tyr Ile Cys Thr Ala
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Gln Asn Pro Val Ser Gln Arg Ser Ser Leu Pro Val His Val Gly Gln
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Phe Cys Thr Asp Pro Gly Ala Ser Arg Gly Gly Thr Thr Gly Glu Thr
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Ala Cys Arg Asp Thr Glu Lys Val Val Trp Leu Phe Asn Thr Ser Ile
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Ser Arg Asp Pro Tyr Lys Asn Arg Val Trp Val Ser Ser Gln Asp Cys
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Gln Thr Ser₃₅ Leu Leu Phe Leu₄₀ Leu Met Gly Leu Arg Ala₄₅ Ser Gly Lys

Asp Ser₅₀ Ala Pro Thr Val Val₅₅ Ser Gly Ile Leu Gly₆₀ Gly Ser Val Thr

Leu Pro Leu Asn Ile Ser₇₀ Val Asp Thr Glu Ile₇₅ Glu Asn Val Ile Trp₈₀

Ile Gly Pro Lys Asn₈₅ Ala Leu Ala Phe Ala₉₀ Arg Pro Lys Glu Asn Val₉₅

Thr Ile Met Val₁₀₀ Lys Ser Tyr Leu Gly₁₀₅ Arg Leu Asp Ile Thr₁₁₀ Lys Trp

Ser Tyr Ser₁₁₅ Leu Cys Ile Ser Asn₁₂₀ Leu Thr Leu Asn Asp₁₂₅ Ala Gly Ser

Tyr Lys₁₃₀ Ala Gln Ile Asn Gln₁₃₅ Arg Asn Phe Glu Val₁₄₀ Thr Thr Glu Glu

Glu Phe Thr Leu Phe Val₁₅₀ Tyr Glu Gln Leu Gln₁₅₅ Glu Pro Gln Val Thr₁₆₀

Met Lys Ser Val₁₆₅ Lys Val Ser Glu Asn Phe₁₇₀ Ser Cys Asn Ile Thr₁₇₅ Leu

Met Cys Ser Val₁₈₀ Lys Gly Ala Glu Lys₁₈₅ Ser Val Leu Tyr Ser₁₉₀ Trp Thr

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Val Ser₂₁₀ Arg Thr Pro Cys Asp₂₁₅ Pro Asp Leu Pro Tyr₂₂₀ Ile Cys Thr Ala

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Phe Cys Thr Asp Pro₂₄₅ Gly Ala Ser Arg Gly₂₅₀ Gly Thr Thr Gly Glu Thr₂₅₅

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295

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Pro Ile Ser Gly Arg Tyr Glu Val Phe Asp Gln Val Thr Gln Glu Gly
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Asp Ser Ala Pro Thr Val Val Ser Gly Ile Leu Gly Gly Ser Val Thr
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Leu Pro Leu Asn Ile Ser Val Asp Thr Glu Ile Glu Asn Val Ile Trp
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Ile Gly Pro Lys Asn Ala Leu Ala Phe Ala Arg Pro Lys Glu Asn Val
 85 90 95

Thr Ile Met Val Lys Ser Tyr Leu Gly Arg Leu Asp Ile Thr Lys Trp
 100 105 110

Ser Tyr Ser Leu Cys Ile Ser Asn Leu Thr Leu Asn Asp Ala Gly Ser
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Tyr Lys Ala Gln Ile Asn Gln Arg Asn Phe Glu Val Thr Thr Glu Glu
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Glu Phe Thr Leu Phe Val Tyr Glu Gln Leu Gln Glu Pro Gln Val Thr
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Met Lys Ser Val Lys Val Ser Glu Asn Phe Ser Cys Asn Ile Thr Leu
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Met Cys Ser Val₁₈₀ Lys Gly Ala Glu₁₈₅ Lys Ser Val Leu Tyr Ser₁₉₀ Trp Thr
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 Val Ser₂₁₀ Arg Thr Pro Cys Asp₂₁₅ Pro Asp Leu Pro Tyr₂₂₀ Ile Cys Thr Ala
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 Phe Cys Thr Asp₂₄₅ Gly Ala Ser Arg Gly₂₅₀ Gly Thr Thr Gly Glu₂₅₅ Thr
 Val Val Gly Val₂₆₀ Leu Gly Glu Pro Val₂₆₅ Thr Leu Pro Leu Ala₂₇₀ Leu Pro
 Ala Cys Arg₂₇₅ Asp Thr Glu Lys Val₂₈₀ Val Trp Leu Phe Asn₂₈₅ Thr Ser Ile
 Ile Ser₂₉₀ Lys Glu Arg Glu Glu₂₉₅ Ala Ala Thr Ala Asp₃₀₀ Pro Leu Ile Lys
 Ser₃₀₅ Arg Asp Pro Tyr Lys₃₁₀ Asn Arg Val Trp Val₃₁₅ Ser Ser Gln Asp Cys₃₂₀
 Ser Leu Lys Ile Ser₃₂₅ Gln Leu Lys Ile Glu₃₃₀ Asp Ala Gly Pro Tyr₃₃₅ His
 Ala Tyr Val Cys₃₄₀ Ser Glu Ala Ser Ser₃₄₅ Val Thr Ser Met Thr₃₅₀ His Val
 Thr Leu Leu₃₅₅ Ile Tyr Arg Arg Leu₃₆₀ Arg Lys Pro Lys Ile₃₆₅ Thr Trp Ser
 Leu Arg₃₇₀ His Ser Glu Asp Gly₃₇₅ Ile Cys Arg Ile Ser₃₈₀ Leu Thr Cys Ser
 Val₃₈₅ Glu Asp Gly Gly Asn₃₉₀ Thr Val Met Tyr Thr₃₉₅ Trp Thr Pro Leu Gln₄₀₀
 Lys Glu Ala Val Val₄₀₅ Ser Gln Gly Glu Ser₄₁₀ His Leu Asn Val Ser₄₁₅ Trp
 Arg Ser Ser Glu₄₂₀ Asn His Pro Asn Leu₄₂₅ Thr Cys Thr Ala Ser₄₃₀ Asn Pro
 Val Ser Arg₄₃₅ Ser Ser His Gln Phe₄₄₀ Leu Ser Glu Asn Ile₄₄₅ Cys Ser Gly

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Pro Glu Arg Asn Thr Lys Leu Trp Ile Gly Leu Phe Leu Met Val Cys
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Leu Leu Cys Val Gly Ile Phe Ser Trp Cys Ile Trp Lys Arg Lys Gly
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Arg Cys Ser Val Pro Ala Phe Cys Ser Ser Gln Ala Glu Ala Pro Ala
485 490 495

Asp Thr Pro Glu Pro Thr Ala Gly His Thr Leu Tyr Ser Val Leu Ser
500 505 510

Gln Gly Tyr Glu Lys Leu Asp Thr Pro Leu Arg Pro Ala Arg Gln Gln
515 520 525

Pro Thr Pro Thr Ser Asp Ser Ser Ser Asp Ser Asn Leu Thr Thr Glu
530 535 540

Glu Asp Glu Asp Arg Pro Glu Val His Lys Pro Ile Ser Gly Arg Tyr
545 550 555 560

Glu Val Phe Asp Gln Val Thr Gln Glu Gly Ala Gly His Asp Pro Ala
565 570 575

Pro Glu Gly Gln Ala Asp Tyr Asp Pro Val Thr Pro Tyr Val Thr Glu
580 585 590

Val Glu Ser Val Val Gly Glu Asn Thr Met Tyr Ala Gln Val Phe Asn
595 600 605

Leu Gln Gly Lys Thr Pro Val Ser Gln Lys Glu Glu Ser Ser Ala Thr
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Ile Tyr Cys Ser Ile Arg Lys Pro Gln Val Val Pro Pro Pro Gln Gln
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Ala Ala Pro Leu Ile Leu Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
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Lys His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala
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Val Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
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His Cys Ile Arg Asn Lys Ser Val Ile Leu Leu Gly Arg His Ser Leu
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Phe His Pro Glu Asp Thr Gly Gln Val Phe Gln Val Ser His Ser Phe
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Pro His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg
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Pro Gly Asp Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu
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Pro Ala Glu Leu Thr Asp Ala Val Lys Val Met Asp Leu Pro Thr Gln
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Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile
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Glu Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu Gln Cys Val Asp Leu
          165        170        175

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His Val Ile Ser Asn Asp Val Cys Ala Gln Val His Pro Gln Lys Val
          180        185        190

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Thr Lys Phe Met Leu Cys Ala Gly Arg Trp Thr Gly Gly Lys Ser Thr
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Cys Ser Trp Val Ile Leu Ile Thr Glu Leu Thr Met Pro Ala Leu Pro
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Met Val Leu His Gly Ser Leu Val Pro Trp Arg Gly Gly Val
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35 40 45

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

His Cys Ile Arg Lys Pro Gly Asp Asp Ser Ser His Asp Leu Met Leu
65 70 75 80

Leu Arg Leu Ser Glu Pro Ala Glu Leu Thr Asp Ala Val Lys Val Met
85 90 95

Asp Leu Pro Thr Gln Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser
100 105 110

Gly Trp Gly Ser Ile Glu Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu
115 120 125

Gln Cys Val Asp Leu His Val Ile Ser Asn Asp Val Cys Ala Gln Val
130 135 140

His Pro Gln Lys Val Thr Lys Phe Met Leu Cys Ala Gly Arg Trp Thr
145 150 155 160

Gly Gly Lys Ser Thr Cys Ser Gly Asp Ser Gly Gly Pro Leu Val Cys
165 170 175

Asn Gly Val Leu Gln Gly Ile Thr Ser Trp Gly Ser Glu Pro Cys Ala
180 185 190

Leu Pro Glu Arg Pro Ser Leu Tyr Thr Lys Val Val His Tyr Arg Lys
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Trp Ile Lys Asp Thr Ile Val Ala Asn Pro
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 Lys His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala
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 Val Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
 50 55 60

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His Cys Ile Arg Asn Lys Ser Val Ile Leu Leu Gly Arg His Ser Leu
65 70 75 80

Phe His Pro Glu Asp Thr Gly Gln Val Phe Gln Val Ser His Ser Phe
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Pro His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg
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Pro Gly Asp Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu
115 120 125

Pro Ala Glu Leu Thr Asp Ala Val Lys Val Met Asp Leu Pro Thr Gln
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Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile
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Glu Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu Gln Cys Val Asp Leu
165 170 175

His Val Ile Ser Asn Asp Val Cys Ala Gln Val His Pro Gln Lys Val
180 185 190

Thr Lys Phe Met Leu Cys Ala Gly Arg Trp Thr Gly Gly Lys Ser Thr
195 200 205

Cys Ser Gly Asp Ser Gly Gly Pro Leu Val Cys Asn Gly Val Leu Gln
210 215 220

Gly Ile Thr Ser Trp Gly Ser Glu Pro Cys Ala Leu Pro Glu Arg Pro
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Ile Val Ala Asn Pro
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 Pro Asn Lys Val Lys Val Tyr Gly Pro Gly Val Ala Lys Thr Gly Leu
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 Lys Ala His Glu Pro Thr Tyr Phe Thr Val Asp Cys Ala Glu Ala Gly
 785 790 795 800
 Gln Gly Asp Val Ser Ile Gly Ile Lys Cys Ala Pro Gly Val Val Gly
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Pro Ala Glu Ala Asp Ile Asp Phe Asp Ile Ile Arg Asn Asp Asn Asp
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 Met Val Leu Phe Ala Asp Gln Ala Thr Pro Thr Ser Pro Ile Arg Val
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 Lys Val Glu Pro Ser His Asp Ala Ser Lys Val Lys Ala Glu Gly Pro
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 Gly Leu Ser Arg Thr Gly Val Glu Leu Gly Lys Pro Thr His Phe Thr
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 Val Asn Ala Lys Ala Ala Gly Lys Gly Lys Leu Asp Val Gln Phe Ser
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 Gly Leu Thr Lys Gly Asp Ala Val Arg Asp Val Asp Ile Ile Asp His
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 His Asp Asn Thr Tyr Thr Val Lys Tyr Thr Pro Val Gln Gln Gly Pro
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 Val Gly Val Asn Val Thr Tyr Gly Gly Asp Pro Ile Pro Lys Ser Pro
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 Phe Ser Val Ala Val Ser Pro Ser Leu Asp Leu Ser Lys Ile Lys Val
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 Ser Gly Leu Gly Glu Lys Val Asp Val Gly Lys Asp Gln Glu Phe Thr
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 Val Lys Ser Lys Gly Ala Gly Gly Gln Gly Lys Val Ala Ser Lys Ile
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 Val Gly Pro Ser Gly Ala Ala Val Pro Cys Lys Val Glu Pro Gly
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 Lys Val Lys Ala Phe Gly Pro Gly Leu Gln Gly Gly Ser Ala Gly
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	1130					1135					1140			
His	Ile	Pro	Gly	Ser	Pro	Phe	Lys	Ala	His	Val	Val	Pro	Cys	Phe
	1145					1150					1155			
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	1160					1165					1170			
Thr	Ala	Gly	Glu	Val	Gly	Gln	Phe	Gln	Val	Asp	Cys	Ser	Ser	Ala
	1175					1180					1185			
Gly	Ser	Ala	Glu	Leu	Thr	Ile	Glu	Ile	Cys	Ser	Glu	Ala	Gly	Leu
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Pro	Ala	Glu	Val	Tyr	Ile	Gln	Asp	His	Gly	Asp	Gly	Thr	His	Thr
	1205					1210					1215			
Ile	Thr	Tyr	Ile	Pro	Leu	Cys	Pro	Gly	Ala	Tyr	Thr	Val	Thr	Ile
	1220					1225					1230			
Lys	Tyr	Gly	Gly	Gln	Pro	Val	Pro	Asn	Phe	Pro	Ser	Lys	Leu	Gln
	1235					1240					1245			
Val	Glu	Pro	Ala	Val	Asp	Thr	Ser	Gly	Val	Gln	Cys	Tyr	Gly	Pro
	1250					1255					1260			
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	1265					1270					1275			
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	1460					1465					1470			
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	1475					1480					1485			
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Asp	Gly 1685	Ser	Glu	Val	Asp	Val 1690	Asp	Val	Val	Glu	Asn 1695	Glu	Asp	Gly
Thr	Phe 1700	Asp	Ile	Phe	Tyr	Thr 1705	Ala	Pro	Gln	Pro	Gly 1710	Lys	Tyr	Val
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2015						2020					2025			
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	2570					2575					2580			
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 <212> PRT
 <213> Homo sapiens

<400> 49

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			20					25					30		
Lys	Asp	Leu	Ala	Glu	Asp	Ala	Pro	Trp	Lys	Lys	Ile	Gln	Gln	Asn	Thr
		35					40					45			
Phe	Thr	Arg	Trp	Cys	Asn	Glu	His	Leu	Lys	Cys	Val	Ser	Lys	Arg	Ile
	50					55					60				
Ala	Asn	Leu	Gln	Thr	Asp	Leu	Ser	Asp	Gly	Leu	Arg	Leu	Ile	Ala	Leu
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Leu	Glu	Val	Leu	Ser	Gln	Lys	Lys	Met	His	Arg	Lys	His	Asn	Gln	Arg
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Pro	Thr	Phe	Arg	Gln	Met	Gln	Leu	Glu	Asn	Val	Ser	Val	Ala	Leu	Glu
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Phe	Leu	Asp	Arg	Glu	Ser	Ile	Lys	Leu	Val	Ser	Ile	Asp	Ser	Lys	Ala
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Ile Leu His Tyr Ser Ile Ser Met Pro Met Trp Asp Glu Glu Glu Asp
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Glu Glu Ala Lys Lys Gln Thr Pro Lys Gln Arg Leu Leu Gly Trp Ile
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Gln Asn Lys Leu Pro Gln Leu Pro Ile Thr Asn Phe Ser Arg Asp Trp
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Gln Ser Gly Arg Ala Leu Gly Ala Leu Val Asp Ser Cys Ala Pro Gly
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Leu Cys Pro Asp Trp Asp Ser Trp Asp Ala Ser Lys Pro Val Thr Asn
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Ala Arg Glu Ala Met Gln Gln Ala Asp Asp Trp Leu Gly Ile Pro Gln
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Val Ile Thr Pro Glu Glu Ile Val Asp Pro Asn Val Asp Glu His Ser
245 250 255

Val Met Thr Tyr Leu Ser Gln Phe Pro Lys Ala Lys Leu Lys Pro Gly
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Ala Pro Leu Arg Pro Lys Leu Asn Pro Lys Lys Ala Arg Ala Tyr Gly
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Pro Gly Ile Glu Pro Thr Gly Asn Met Val Lys Lys Arg Ala Glu Phe
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Thr Val Glu Thr Arg Ser Ala Gly Gln Gly Glu Val Leu Val Tyr Val
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Glu Asp Pro Ala Gly His Gln Glu Glu Ala Lys Val Thr Ala Asn Asn
325 330 335

Asp Lys Asn Arg Thr Phe Ser Val Trp Tyr Val Pro Glu Val Thr Gly
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Thr His Lys Val Thr Val Leu Phe Ala Gly Gln His Ile Ala Lys Ser
355 360 365

Pro Phe Glu Val Tyr Val Asp Lys Ser Gln Gly Asp Ala Ser Lys Val
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Thr Ala Gln Gly Pro Gly Leu Glu Pro Ser Gly Asn Ile Ala Asn Lys
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Thr Thr Tyr Phe Glu Ile Phe Thr Ala Gly Ala Gly Thr Gly Glu Val
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Glu Val Val Ile Gln Asp Pro Met Gly Gln Lys Gly Thr Val Glu Pro
420 425 430

Gln Leu Glu Ala Arg Gly Asp Ser Thr Tyr Arg Cys Ser Tyr Gln Pro
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Thr Met Glu Gly Val His Thr Val His Val Thr Phe Ala Gly Val Pro
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Ile Pro Arg Ser Pro Tyr Thr Val Thr Val Gly Gln Ala Cys Asn Pro
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Ser Ala Cys Arg Ala Val Gly Arg Gly Leu Gln Pro Lys Gly Val Arg
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Val Lys Glu Thr Ala Asp Phe Lys Val Tyr Thr Lys Gly Ala Gly Ser
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Gly Glu Leu Lys Val Thr Val Lys Gly Pro Lys Gly Glu Glu Arg Val
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Lys Gln Lys Asp Leu Gly Asp Gly Val Tyr Gly Phe Glu Tyr Tyr Pro
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Met Val Pro Gly Thr Tyr Ile Val Thr Ile Thr Trp Gly Gly Gln Asn
545 550 555 560

Ile Gly Arg Ser Pro Phe Glu Val Lys Val Gly Thr Glu Cys Gly Asn
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Gln Lys Val Arg Ala Trp Gly Pro Gly Leu Glu Gly Gly Val Val Gly
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Lys Ser Ala Asp Phe Val Val Glu Ala Ile Gly Asp Asp Val Gly Thr
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Leu Gly Phe Ser Val Glu Gly Pro Ser Gln Ala Lys Ile Glu Cys Asp
610 615 620

Asp Lys Gly Asp Gly Ser Cys Asp Val Arg Tyr Trp Pro Gln Glu Ala
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Gly Glu Tyr Ala Val His Val Leu Cys Asn Ser Glu Asp Ile Arg Leu
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Ser Pro Phe Met Ala Asp Ile Arg Asp Ala Pro Gln Asp Phe His Pro
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 690 695 700
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 Ala Leu Val Lys Asp Asn Gly Asn Gly Thr Tyr Ser Cys Ser Tyr Val
 725 730 735
 Pro Arg Lys Pro Val Lys His Thr Ala Met Val Ser Trp Gly Gly Val
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 Ser Ile Pro Asn Ser Pro Phe Arg Val Asn Val Gly Ala Gly Ser His
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 Pro Asn Lys Val Lys Val Tyr Gly Pro Gly Val Ala Lys Thr Gly Leu
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 Gln Gly Asp Val Ser Ile Gly Ile Lys Cys Ala Pro Gly Val Val Gly
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 Pro Ala Glu Ala Asp Ile Asp Phe Asp Ile Ile Arg Asn Asp Asn Asp
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 Thr Phe Thr Val Lys Tyr Thr Pro Arg Gly Ala Gly Ser Tyr Thr Ile
 835 840 845
 Met Val Leu Phe Ala Asp Gln Ala Thr Pro Thr Ser Pro Ile Arg Val
 850 855 860
 Lys Val Glu Pro Ser His Asp Ala Ser Lys Val Lys Ala Glu Gly Pro
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 Gly Leu Ser Arg Thr Gly Val Glu Leu Gly Lys Pro Thr His Phe Thr
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 Val Asn Ala Lys Ala Ala Gly Lys Gly Lys Leu Asp Val Gln Phe Ser
 900 905 910
 Gly Leu Thr Lys Gly Asp Ala Val Arg Asp Val Asp Ile Ile Asp His
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 His Asp Asn Thr Tyr Thr Val Lys Tyr Thr Pro Val Gln Gln Gly Pro
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Gly Pro Tyr Glu Val Glu Val Thr Tyr Asp Gly Val Pro Val Pro
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Gly Ser Pro Phe Pro Leu Glu Ala Val Ala Pro Thr Lys Pro Ser
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Lys Val Lys Ala Phe Gly Pro Gly Leu Gln Gly Gly Ser Ala Gly
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Ser Pro Ala Arg Phe Thr Ile Asp Thr Lys Gly Ala Gly Thr Gly
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Tyr	Leu	Pro	Val	Leu	Pro	Gly	Asp	Tyr	Ser	Ile	Leu	Val	Lys	Tyr
1925						1930					1935			
Asn	Glu	Gln	His	Val	Pro	Gly	Ser	Pro	Phe	Thr	Ala	Arg	Val	Thr
1940						1945					1950			
Gly	Asp	Asp	Ser	Met	Arg	Met	Ser	His	Leu	Lys	Val	Gly	Ser	Ala
1955						1960					1965			

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Ala	Asp 1970	Ile	Pro	Ile	Asn	Ile 1975	Ser	Glu	Thr	Asp	Leu 1980	Ser	Leu	Leu
Thr	Ala 1985	Thr	Val	Val	Pro	Pro 1990	Ser	Gly	Arg	Glu	Glu 1995	Pro	Cys	Leu
Leu	Lys 2000	Arg	Leu	Arg	Asn	Gly 2005	His	Val	Gly	Ile	Ser 2010	Phe	Val	Pro
Lys	Glu 2015	Thr	Gly	Glu	His	Leu 2020	Val	His	Val	Lys	Lys 2025	Asn	Gly	Gln
His	Val 2030	Ala	Ser	Ser	Pro	Ile 2035	Pro	Val	Val	Ile	Ser 2040	Gln	Ser	Glu
Ile	Gly 2045	Asp	Ala	Ser	Arg	Val 2050	Arg	Val	Ser	Gly	Gln 2055	Gly	Leu	His
Glu	Gly 2060	His	Thr	Phe	Glu	Pro 2065	Ala	Glu	Phe	Ile	Ile 2070	Asp	Thr	Arg
Asp	Ala 2075	Gly	Tyr	Gly	Gly	Leu 2080	Ser	Leu	Ser	Ile	Glu 2085	Gly	Pro	Ser
Lys	Val 2090	Asp	Ile	Asn	Thr	Glu 2095	Asp	Leu	Glu	Asp	Gly 2100	Thr	Cys	Arg
Val	Thr 2105	Tyr	Cys	Pro	Thr	Glu 2110	Pro	Gly	Asn	Tyr	Ile 2115	Ile	Asn	Ile
Lys	Phe 2120	Ala	Asp	Gln	His	Val 2125	Pro	Gly	Ser	Pro	Phe 2130	Ser	Val	Lys
Val	Thr 2135	Gly	Glu	Gly	Arg	Val 2140	Lys	Glu	Ser	Ile	Thr 2145	Arg	Arg	Arg
Arg	Ala 2150	Pro	Ser	Val	Ala	Asn 2155	Val	Gly	Ser	His	Cys 2160	Asp	Leu	Ser
Leu	Lys 2165	Ile	Pro	Glu	Ile	Ser 2170	Ile	Gln	Asp	Met	Thr 2175	Ala	Gln	Val
Thr	Ser 2180	Pro	Ser	Gly	Lys	Thr 2185	His	Glu	Ala	Glu	Ile 2190	Val	Glu	Gly
Glu	Asn 2195	His	Thr	Tyr	Cys	Ile 2200	Arg	Phe	Val	Pro	Ala 2205	Glu	Met	Gly
Thr	His 2210	Thr	Val	Ser	Val	Lys 2215	Tyr	Lys	Gly	Gln	His 2220	Val	Pro	Gly

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Ser	Pro	Phe	Gln	Phe	Thr	Val	Gly	Pro	Leu	Gly	Glu	Gly	Gly	Ala
	2225					2230					2235			
His	Lys	Val	Arg	Ala	Gly	Gly	Pro	Gly	Leu	Glu	Arg	Ala	Glu	Ala
	2240					2245					2250			
Gly	Val	Pro	Ala	Glu	Phe	Ser	Ile	Trp	Thr	Arg	Glu	Ala	Gly	Ala
	2255					2260					2265			
Gly	Gly	Leu	Ala	Ile	Ala	Val	Glu	Gly	Pro	Ser	Lys	Ala	Glu	Ile
	2270					2275					2280			
Ser	Phe	Glu	Asp	Arg	Lys	Asp	Gly	Ser	Cys	Gly	Val	Ala	Tyr	Val
	2285					2290					2295			
Val	Gln	Glu	Pro	Gly	Asp	Tyr	Glu	Val	Ser	Val	Lys	Phe	Asn	Glu
	2300					2305					2310			
Glu	His	Ile	Pro	Asp	Ser	Pro	Phe	Val	Val	Pro	Val	Ala	Ser	Pro
	2315					2320					2325			
Ser	Gly	Asp	Ala	Arg	Arg	Leu	Thr	Val	Ser	Ser	Leu	Gln	Glu	Ser
	2330					2335					2340			
Gly	Leu	Lys	Val	Asn	Gln	Pro	Ala	Ser	Phe	Ala	Val	Ser	Leu	Asn
	2345					2350					2355			
Gly	Ala	Lys	Gly	Ala	Ile	Asp	Ala	Lys	Val	His	Ser	Pro	Ser	Gly
	2360					2365					2370			
Ala	Leu	Glu	Glu	Cys	Tyr	Val	Thr	Glu	Ile	Asp	Gln	Asp	Lys	Tyr
	2375					2380					2385			
Ala	Val	Arg	Phe	Ile	Pro	Arg	Glu	Asn	Gly	Val	Tyr	Leu	Ile	Asp
	2390					2395					2400			
Val	Lys	Phe	Asn	Gly	Thr	His	Ile	Pro	Gly	Ser	Pro	Phe	Lys	Ile
	2405					2410					2415			
Arg	Val	Gly	Glu	Pro	Gly	His	Gly	Gly	Asp	Pro	Gly	Leu	Val	Ser
	2420					2425					2430			
Ala	Tyr	Gly	Ala	Gly	Leu	Glu	Gly	Gly	Val	Thr	Gly	Asn	Pro	Ala
	2435					2440					2445			
Glu	Phe	Val	Val	Asn	Thr	Ser	Asn	Ala	Gly	Ala	Gly	Ala	Leu	Ser
	2450					2455					2460			
Val	Thr	Ile	Asp	Gly	Pro	Ser	Lys	Val	Lys	Met	Asp	Cys	Gln	Glu
	2465					2470					2475			

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Cys	Pro	Glu	Gly	Tyr	Arg	Val	Thr	Tyr	Thr	Pro	Met	Ala	Pro	Gly
	2480					2485					2490			
Ser	Tyr	Leu	Ile	Ser	Ile	Lys	Tyr	Gly	Gly	Pro	Tyr	His	Ile	Gly
	2495					2500					2505			
Gly	Ser	Pro	Phe	Lys	Ala	Lys	Val	Thr	Gly	Pro	Arg	Leu	Val	Ser
	2510					2515					2520			
Asn	His	Ser	Leu	His	Glu	Thr	Ser	Ser	Val	Phe	Val	Asp	Ser	Leu
	2525					2530					2535			
Thr	Lys	Ala	Thr	Cys	Ala	Pro	Gln	His	Gly	Ala	Pro	Gly	Pro	Gly
	2540					2545					2550			
Pro	Ala	Asp	Ala	Ser	Lys	Val	Val	Ala	Lys	Gly	Leu	Gly	Leu	Ser
	2555					2560					2565			
Lys	Ala	Tyr	Val	Gly	Gln	Lys	Ser	Ser	Phe	Thr	Val	Asp	Cys	Ser
	2570					2575					2580			
Lys	Ala	Gly	Asn	Asn	Met	Leu	Leu	Val	Gly	Val	His	Gly	Pro	Arg
	2585					2590					2595			
Thr	Pro	Cys	Glu	Glu	Ile	Leu	Val	Lys	His	Val	Gly	Ser	Arg	Leu
	2600					2605					2610			
Tyr	Ser	Val	Ser	Tyr	Leu	Leu	Lys	Asp	Lys	Gly	Glu	Tyr	Thr	Leu
	2615					2620					2625			
Val	Val	Lys	Trp	Gly	Asp	Glu	His	Ile	Pro	Gly	Ser	Pro	Tyr	Arg
	2630					2635					2640			
Val	Val	Val	Pro											
	2645													