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(54) **Title**: MARKERS FOR ENDOMETRIAL CANCER

(57) **Abstract**: The invention relates to the surprising finding that biomarkers corresponding to ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1 R16A, RASSF7, RNF183, SIRT6, TJP3, EFEM-P2, S0CS2, and DCN are differentially expressed in control samples as compared to samples from patients having endometrial cancer and are therefore useful for detecting endometrial cancer. In particular these biomarkers having excellent sensitivity, specificity, and/or the ability to separate affected from non affected individuals. Furthermore, the inventors found that the differential expression of these biomarkers in primary endometrial cancer tumor tissue is correlated to their expression level in uterine fluid samples as compared to control values. Thus these biomarkers are robust in that they are found to be differentially expressed in several different types of samples from affected individuals.

MARKERS FOR ENDOMETRIAL CANCER

FIELD OF THE INVENTION

The invention relates to the detection diagnosis, and prognosis of uterine cancer. The invention relates to the surprising finding that biomarkers corresponding to ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN are differentially expressed in control samples as compared to samples from patients having endometrial cancer and are therefore useful for detecting endometrial cancer. In particular these biomarkers having excellent sensitivity, specificity, and/or the ability to separate affected from non affected individuals. Furthermore, the inventors found that the differential expression of these biomarkers in primary endometrial cancer tumor tissue is correlated to their expression level in uterine fluid samples as compared to control values. Thus these biomarkers are robust in that they are found to be differentially expressed in several different types of samples from affected and individuals.

BACKGROUND OF THE INVENTION

Each year in Europe there are about 150,000 new cases of endometrial cancer and about 46,000 women die from the disease (Ferlay *et al.* (2007) *Ann. Onc.* 18:581-592). In the United States, about 41,000 new case of endometrial carcinoma are diagnosed per year and 7,300 women die each year (see American Cancer Society statistics available on the internet). The incidence and death rate from endometrial cancer are increasing.

Endometrial cancer (EC) is the most frequent invasive tumors of the female genital tract and the fourth most common in women in western countries (Jemal *et al.* (2008) *CA Cancer J Clin* 58:71-96). New methods for the diagnosis, prognosis, and classification of endometrial cancer are needed to combat this deadly disease.

Often endometrial cancer is detected early, in its initial stages, by presentation of disease-related symptoms. Unfortunately, 20% of patients present with myometrial

invasion and/or lymph node affectation, which are main indicators related to poor prognosis, decrease in survival rate, and more advanced disease. The primary therapeutic modality for endometrial cancer is surgical treatment.

Common symptoms of uterine cancer (*e.g.*, endometrial cancer) include unusual vaginal bleeding or discharge, trouble urinating, pelvic pain, and pain during intercourse. Uterine cancer usually occurs after menopause. Other risk factors for endometrial cancer include being obese, taking estrogen-alone hormone replacement therapy, treatment with tamixofen and having a genetic predisposition to cancer (*e.g.*, Lynch Syndrome). The standard treatment for endometrial cancer varies depending on the stage of the disease. Treatment usually involves surgery to remove the uterus which is called a hysterectomy, although other options include hormone therapy and radiotherapy.

Methods routinely used in the clinic for diagnosing endometrial cancer include biopsy followed by cytological analysis and/or trans-vaginal ultrasound. The diagnosis of endometrial carcinoma is usually done by pathology examination of an endometrial aspirate (20-30%), and by biopsy-guided hysteroscopy (70-80%). The rate of success of diagnosis with hysteroscopy is over 90%, with false positives in the case of precursor lesions of the endometrial adenocarcinoma (hyperplasias); endometrial polyps, that present a non-negligible degree of malignancy (0-4.8%) and must be removed although asymptomatic or benign appearance; or in the case of diffuse forms of endometrial adenocarcinomas that are difficult to differentiate from an endometrial hyperplasia. Thus, there is a need for a less invasive diagnostic test based on molecular markers. Such a less invasive test based on molecular markers would allow for more routine screening of uterine cancer. A diagnostic test based of molecular markers obtained in a less invasive manner and that has sensitivity and specificity comparable to that of the endometrial biopsy can preclude unnecessary hysteroscopy.

Endometrial carcinomas can be classified into low grade (type I) and high-grade (type 2). Type I endometrioid endometrial cancer (sometimes called estrogen dependent), which represent approximately 80% of new cases, are low grade tumors associated with estrogen stimulation, usually developed in peri- or post-menopausal

women and are usually preceded by endometrial hyperplasia with or without atypia. Type II non-endometrioid endometrial cancer usually affects older women, are less differentiated and of worse prognosis, not associated with estrogen stimulation, and are related to atrophic endometrium or, occasionally, with endometrial polyps.

Type I cancers are typically known to have alterations in PTEN, KRAS2, DNA mismatch repair defects, CTNNB1, and have near diploid karyotype. Type II cancers typically have TP53 mutations and ErBB2 overexpression and are mostly non-diploid. Sugiyama *et al.* ((2003) *Clin. Can. Res.* 9:5589-5600) reported that certain genes are selectively up or down regulated in type I versus type II endometrial cancers. For example, they found that MLH1 was down-regulated in type I cancers as well as other genes related to DNA damage signaling and repair like O^6-methyl-guanine DNA methyltransferase, DNA polymerase α catalytic subunit, and Ku (p70/p80) antigen. VEGF-C was found to be upregulated in type I cancers at the protein and mRNA level as compared to type II cancers. KRAS was found to be upregulated in type II cancers. STAT1 was upregulated in type I cancers and STAT2 was upregulated in type II cancers. Konecny *et al.* ((2009) *British Journal of Cancer* 100, 89–95) report that the rate HER2 gene amplification as measured by fluorescence in situ hybridization was greater in type II cancers whereas EGFR expression as measured by IHC techniques was significantly lower in type II cancers. Deng *et al.* ((2005) *Clin. Can. Res.* vol. 11, no 23:8258-8264) report that EIG121 is a marker for type I estrogen associated cancers.

Uterine cancers are also classified histologically according to cell-type. The most common cell-type is referred to endometrioid and represents around 80% of the newly diagnosed cases. Other less common uterine cancers are referred to as serous and clear cell carcinomas. Most of the type I cancers are of the endometrioid cell-type whereas the type II cancers are more likely to be non-endometrioid uterine cancers. Type II cancers are more likely to metastasize and have a poorer prognosis than type I cancers. Type I cancers typically have a better prognosis and respond better to therapy.

A number of studies have examined gene-expression profiles for classifying uterine cancers. Sugiyama *et al.* ((2003) *Clin. Canc. Res.* 9:5589-5600) report that between

the type I and II cancers 45 gene were highly expressed in type I cancers and 24 highly expressed in type I cancers. Risinger *et al.* ((2003) *Canc. Res.* 63:6-11) report that microarray analysis of different histologic subtypes of endometrial cancer have distinct gene expression profiles. They found that 191 genes exhibited greater than 2-fold difference in expression between endometrioid and non-endometrioid endometrial cancers.

A number of endometrial cancer biomarkers for endometrial cancer have been identified. Elevated levels of CA 125, CA 15-3, and CA 19-9 are associated with shorter survival time. CA 125 correlates with tumor size and stage and is an independent predictor of the extrauterine spread.

Serum markers for the detection of uterine cancer have been reported in the literature. Yurkovetsky *et al.* ((2007) *Gyn. Onc.* 107:58-65) identified that prolactin is a serum biomarker with sensitivity and specificity for endometrial cancer. They found serum CA 125 CA 15-3 and CEA are higher in patients with Stage III disease as compared to stage I. A five-biomarker panel of prolactin, GH, eotaxin, E-selectin, and TSH discriminated endometrial cancer from ovarian and breast cancer.

Another important issue for clinicians for diagnosis of endometrial cancer relates to synchronous cancers. Guirguis *et al.* (*Gyn. Onc.* (2008) 108:370-376) have reported that 10% of ovarian cancer patients have a tumor in the endometrium and 5-25% of patients with endometrial cancer also have a tumor in the ovary. Determining the primary site of a cancer has important treatment implications. Stage III endometrial carcinoma is treated with surgery followed by chemotherapy and/or radiation; while dual primary stage I ovarian and endometrial cancers have a better prognosis and may not require adjuvant therapy.

Current methods of diagnosing endometrial cancer often create discomfort to the patient and sometimes rely on subjective interpretation of visual images. There is a need for less invasive methods of screening for endometrial cancer which are less subjective in interpretation. In addition there is a need for new markers that are useful for the early detection of endometrial cancer. Current methods for detecting endometrial cancer include the dilation and curettage method which is considered the

gold standard, but this method is invasive, can cause significant discomfort, and may require a trained pathologist for interpretation, and therefore is not suitable as a general screening tool. Another less invasive method for diagnosing endometrial cancer involves transvaginal ultrasound which measures the thickness of the endometrium. In a study of patients having post-menopausal bleeding, using a cutoff of 4 mm, it was found that transvaginal ultrasound had 100% sensitivity and 60% specificity (Gull *et al.* (2003) *Am. J. Obstet. Gynecol.* 188(2):401-408). In women without vaginal bleeding, the sensitivity of the endometrial thickness measurement was 17% for a threshold 6 mm and 33% for a threshold of 5 mm (Fleischer *et al.* (2001) *Am. J. Obstet. Gynecol.* 184:70-75). TVS has a high rate of false positives since other conditions besides endometrial cancer can produce a thicker endometrium. One potential problem with the use of TVS in pre- and peri-menopausal women is that the thickness of the endometrium varies as a function of the phase of the menstrual cycle. Furthermore, women taking tamoxifen also have thicker endometrium. Therefore there is a need for techniques and markers that can complement and/or improve the ability of TVS in the diagnosis of endometrial cancer.

Cleary there is room for improvement in the tools currently available for screening for endometrial cancer.

BRIEF SUMMARY OF THE INVENTION

The invention relates to the surprising finding that biomarkers corresponding to ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN are differentially expressed in control samples as compared to samples from patients having endometrial cancer and are therefore useful for detecting endometrial cancer. In particular these biomarkers having excellent sensitivity, specificity, and/or the ability to separate affected from non affected individuals. Furthermore, the inventors found that the differential expression of these biomarkers in primary endometrial cancer tumor tissue is correlated to their expression level in uterine fluid samples as compared to control values. Thus, these biomarkers are robust in that they are found to be differentially expressed in several different types of samples from affected individuals as compared to non-affected individuals.

Therefore, the present invention relates to an in vitro diagnostic method for the diagnosis of endometrial cancer or an increased likelihood of endometrial comprising detecting the level of

(1) from 1 to 17 biomarker(s) chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, and TJP3 in a sample from a patient wherein an increased level of said from 1 to 17 biomarkers compared to a control value indicates a diagnosis of endometrial cancer or increased likelihood of endometrial cancer and/or

(2) detecting the level of from 1 to 3 biomarkers chosen from EFEMP2, SOCS2, and DCN, wherein a decreased level of EFEMP2, SOCS2, and/or DCN compared to a control value indicates a diagnosis of endometrial cancer or increased likelihood of endometrial cancer.

Accordingly, the present invention relates to an in vitro diagnostic method for the diagnosis of endometrial cancer comprising

(1) detecting the level of from 1 to 17 biomarker(s) chosen from P4HB, GMIP, IKBKE, FASTKD1, DDR1, SIRT6, PHKG2, ACAA1, AP1M2, EPS8L2, P2RX4, PPFIBP2, PPP1R16A, CGN, RASSF7, RNF183, and TJP3 in a sample from a patient wherein an increased level of said from 1 to 17 biomarkers compared to a control value indicates the existence of endometrial cancer and/or

(2) detecting the level of from 1 to 3 biomarkers chosen from EFEMP2, SOCS2, and DCN, wherein a decreased level of EFEMP2, SOCS2, and/or DCN compared to a control value indicates the existence of endometrial cancer.

The biomarkers of Table 1 were found to be differential expressed between endometrial cancer samples and normal samples as determined by microarray studies (see Table 1 in the Detailed Description of the Invention). The inventors have found that individually each of the biomarkers of Table 1 have predictive value for the diagnosis of endometrial cancer. Furthermore, the levels of combinations of markers of Table 1 have additional predictive value for the diagnosis of endometrial cancer (See Example 5). For example, the inventors have surprisingly found that sub-groups of the biomarkers of Table 1 having from 2-20 biomarkers in various combinations to give fingerprint patterns have excellent predictive value for diagnosis or detection of endometrial cancer. Generally, if more than one of the

biomarkers of Table 1 are differentially expressed in a sample, this increases the likelihood that the individual has endometrial cancer. Moreover, the inventors have also found that addition of other biomarkers besides those listed in Table 1, to the fingerprint pattern also can increase predictive value, and can be useful for classifying endometrial cancers, for differential diagnosis of diseases other than endometrial cancer, and for endometrial cancer prognosis. Table 1 lists the ENSEMBL accession numbers for the genes, mRNA, and proteins corresponding to the biomarkers of the invention. Some of the biomarkers have alternative transcripts. The invention relates to determining the differential expression of any of these alternative transcripts (or protein isoforms) as long as it expression is correlated with the absence or presence of endometrial cancer. Preferred transcripts (or protein isoforms) for detecting endometrial cancer are those which were detected with the array probes as indicated in the Examples.

The inventors have also found that the markers of Table 1 can be detected in uterine fluid samples and that the level of expression of these markers are correlated in primary tumor and uterine fluid (*e.g.*, obtained by a uterine wash or aspiration).

The invention therefore provides methods for determining the level of from 1 to 20 of the biomarkers listed in Table 1 in a test sample. The method can comprise providing or obtaining a test sample from the patient; determining the level of from 1 to 20 of the biomarkers of Table 1 in the sample; and comparing the level of the biomarker(s) in the test sample(s) to a control value (*e.g.*, control sample, control value, or control score). A higher level of biomarker(s) which was found to be overexpressed in endometrial cancer as shown in Table 1 in the test sample obtained from the patient compared to the control value (*e.g.*, control sample, control value, and/or control score) indicates endometrial cancer, an increased likelihood of endometrial cancer, and/or a precancerous condition (*e.g.*, endometrial hyperplasia). A lower level of biomarker(s) which was found to be underexpressed in endometrial cancer as shown in Table 1 in the test sample obtained from the patient compared to level in the control value (*e.g.*, control sample, control value, and/or control score) indicates endometrial cancer, an increased likelihood of endometrial cancer, and/or a precancerous condition (*e.g.*, endometrial hyperlasia). The level of the biomarker(s) can be determined using appropriate assays, including RT-PCR, quantitative PCR,

multiplex PCR, Northern hybridization, microarray analysis, two-hybrid assays such as GAL4 DNA binding domain based assays, antibody based assays, EIA, blot assays, sandwich assays, and the like. The level of the biomarkers of Table 1 can be determined in body fluids and tissues for the diagnosis of endometrial cancer. The level of the biomarkers of Table 1 can be determined in tumor tissue obtained by biopsy for example. The level of the biomarkers of Table 1 can be determined in samples obtained from uterine aspirates and/or fluid. The level of the biomarkers of Table 1 can be determined in blood, serum, or plasma.

The biomarkers of Table 1 include ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, and TJP3, which were found to be upregulated in endometrial cancer and DCN, SOCS2, and EFEMP2 which were found to be down regulated in endometrial cancer in these studies. In one embodiment, the biomarkers for use in the method of the invention for detecting endometrial cancer or an increased likelihood of endometrial cancer include from 1 to 17 of the upregulated biomarkers listed in Table 1 and from 1 to 3 of the downregulated markers listed in Table 1.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising obtaining a sample from an individual and determining the level of one or more biomarkers chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

Accordingly, the present invention relates to an in vitro diagnostic method for the diagnosis of endometrial cancer comprising

(1) detecting the level of one or more biomarker(s) chosen from P4HB, GMIP, IKBKE, FASTKD1, DDR1, SIRT6, PHKG2, ACAA1, AP1M2, EPS8L2, P2RX4, PPFIBP2, PPP1R16A, CGN, RASSF7, RNF183, and TJP3 in a sample from a patient wherein an increased level of said one or more biomarkers compared to a control value indicates the existence of endometrial cancer and/or
(2) detecting the level of one or more biomarkers chosen from EFEMP2, SOCS2, and DCN, wherein a decreased level of EFEMP2, SOCS2, and/or DCN compared to a control value indicates the existence of endometrial cancer.

In a further embodiment, the present invention relates to an in vitro diagnostic method for the diagnosis of endometrial cancer comprising
(1) detecting the level of from 1 to 17 biomarker(s) chosen from P4HB, GMIP, IKBKE, FASTKD1, DDR1, SIRT6, PHKG2, ACAA1, AP1M2, EPS8L2, P2RX4, PPFIBP2, PPP1R16A, CGN, RASSF7, RNF183, and TJP3 in a sample from a patient wherein an increased level of said from 1 to 17 biomarkers compared to a control value indicates the existence of endometrial cancer and/or
(2) detecting the level of from 1 to 3 biomarkers chosen from EFEMP2, SOCS2, and DCN, wherein a decreased level of EFEMP2, SOCS2, and/or DCN compared to a control value indicates the existence of endometrial cancer.

In one embodiment, the in vitro diagnostic method comprises detecting the level of P4HB. In another embodiment, the in vitro diagnostic method comprises detecting the level of EFEMP2. In a further embodiment the in vitro method comprises detecting the level of IKBKE. In a further embodiment the in vitro diagnostic method comprises detecting the level of GMIP.

In accordance with the in vitro diagnostic method of the invention, the the level of one or more of GMIP, IKBKE, or EFEMP2 may be detected in addition to P4HB. The in vitro diagnostic method may further comprise detecting the level of one or more of P4HB, IKBKE, or GMIP in addition to EFEMP2. The in vitro diagnostic method may further comprise detecting the level of one or more of GMIP, EFEMP2, or P4HB in addition to IKBKE. It is also envisaged that the in vitro diagnostic method may further comprise detecting the level of FASTKD1, DDR1, SIRT6, and/or PHKG2. The in vitro diagnostic method may further comprise detecting the level of

from 1 to 12 biomarkers chosen from ACAA1, AP1M2, EPS8L2, P2RX4, PPFIBP2, PPP1R16A, CGN, RASSF7, RNF183, TJP3, SOCS2, and DCN.

In one embodiment, the patient has a risk factor for endometrial cancer or is being screened for endometrial cancer. Further, the sample from the patient may be (obtained) from a patient with abnormal uterine bleeding. In other words, the patient may suffer from abnormal uterine bleeding. The sample from said patient may also be (obtained) from a patient having an endometrium with increased thickness. The patient may, accordingly, have an endometrium with increased thickness.

The sample from the patient may be (obtained) from a pre-menopausal, peri-menopausal, or post-menopausal patient. Accordingly, the patient is a pre-menopausal, peri-menopausal, or post-menopausal patient. In one embodiment, the patient is pre-menopausal. In another embodiment, the patient is peri-menopausal. In a further embodiment, the patient is post-menopausal.

The sample may be a tissue sample, blood and/or serum, and/or uterine fluid.
In one embodiment, the sample is a uterine fluid sample. The uterine fluid sample may be obtained by aspiration.

In one embodiment, the level of the biomarkers is determined with an antibody in accordance with the present invention. The level of the biomarker(s) may also be determined by RT-PCR.

The following markers may be detected in accordance with the in vitro diagnostic method of the present invention: P4HB, IKBKE, EFEMP2, SOCS2, FASTKD1, GMIP, DDR1, SIRT6, PHKG2, EPS8L2, PPP1R16A, P2RX4, RASSF7, and/or TJP3. Also the following markers may be detected in accordance with the in vitro diagnostic method of the present invention: P4HB, IKBKE, SOCS2, GMIP, DDR1, SIRT6, PHKG2, EPS8L2, PPP1R16A, P2RX4, RASSF7, and/or TJP3.

The markers to be detected may be P2RX4, P4HB, PHKG2, PPFIBP2, and/or SOCS2. The markers to be detected may also be P4HB, RASSF7, RNF183 and/or IKBKE.

In one embodiment, the in vitro diagnostic method comprises the detection of from 2 to 20 markers.

Preferably, the combination of the following markers is detected: P4HB, EFEMP2, SIRT6, GMIP, FASTKD1 and DDR1. Also preferred is the detection of a combination of the following markers: P4HB, EFEMP2, SIRT6, GMIP, FASTKD1 and PHKG2. Also preferred is the detection of a combination of the following markers: P4HB, EFEMP2, SIRT6, ACAA1, AP1M2, EPS8L2, IKBKE, P2RX4, PPFIBP2 and PPP1R16A.

The following marker combinations are also preferably detected in accordance with the present invention:

GMIP, IKBKE, PFHB, EFEMP2;
DDR1, FASTKD1, GMIP, IKBKE, P4HB, PHKG2, SIRT6, EFEMP2;
P4HB, EFEMP2, IKBKE, GMIP, FASTKD1.

In context of the present invention combinations of markers which include a combination with P4HB (i.e. set of markers including P4HB) are particularly preferred.

Also envisaged herein is the detection of the following combination of markers:
DDR1, FASTKD1, GMIP, IKBKE, P4HB, PHKG2, SIRT6, EFEMP2; SOCS2;
P4HB, SOCS2;
GMIP, IKBKE, P4HB, SOCS2;
GMIP, IKBKE, P4HB, SOCS2, FASTKD1;
GMIP, IKBKE, P4HB, SOCS2, DDR1;
GMIP, IKBKE, P4HB, SOCS2, PHKG2;
GMIP, IKBKE, P4HB, SOCS2, SIRT6;
GMIP, IKBKE, P4HB, SOCS2, ACAA1;

GMIP, IKBKE, P4HB, SOCS2, AP1M2;
GMIP, IKBKE, P4HB, SOCS2, EFEMP2;
GMIP, IKBKE, P4HB, SOCS2, EPS8L2;
GMIP, IKBKE, P4HB, SOCS2, P2RX4;
GMIP, IKBKE, P4HB, SOCS2, PPFIB2;
GMIP, IKBKE, P4HB, SOCS2, PPP1R16A;
GMIP, IKBKE, P4HB, SOCS2, ACAA1, FASTKD1;
GMIP, IKBKE, P4HB, SOCS2, FASTKD1, PHKG2;
GMIP, IKBKE, P4HB, SOCS2, FASTKD1, SIRT6;
GMIP, IKBKE, P4HB, SOCS2;

One or more additional biomarkers may be detected in accordance with the herein disclosed in vitro diagnostic method. The one or more additional biomarkers may be chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one embodiment, the one or more additional biomarkers are chosen from differential diagnosis biomarkers.

The one or more auxiliary biomarkers may be chosen from prognostic markers. The one or more auxiliary biomarkers may be chosen from endometrial cancer classification markers.

In a further embodiment, the present invention relates to a nucleic acid chosen from
IKBKE mRNA, cDNA, or a complement thereof;
P4HB mRNA, cDNA, or a complement thereof;
SOCS2 mRNA, cDNA, or a complement thereo;f
GMIP mRNA, cDNA, or a complement thereof;
DDR1 mRNA, cDNA, or a complement thereof;
EPS8L2 mRNA, cDNA, or a complement thereof; and
PPP1R16A mRNA, cDNA, or a complement thereof,
for use in diagnosing endometrial cancer.

The invention also relates to a nucleic acid chosen from
Primers for IKBKE;

Primers for P4HB;
Primers for SOCS2;
Primers for GMIP;
Primers for DDR1;
Primers for EPS8L2; and
Primers for PPP1R16A;
for use in diagnosing endometrial cancer.

In one embodiment, the invention relates to a nucleic acid chosen from
probe for IKBKE;
probe for P4HB;
probe for SOCS2;
probe for GMIP;
probe for DDR1;
probe for EPS8L2; and
probe for PPP1R16A,
for use in diagnosing endometrial cancer.

Also a kit comprising two or more of the herein desribed probes for use in diagnosing endometrial cancer is envisaged in context of the present invention. Further, a kit comprising primers for two or more herein disclosed primers/primer pairs for use in diagnosing endometrial cancer is envisaged in context of the present invention.

In a further embodiment, the present invention relates to an antibody chosen from
an antibody to IKBKE;
an antibody to P4HB;
an antibody to SOCS2;
an antibody to GMIP;
an antibody to DDR1;
an antibody to EPS8L2; and
an antibody to PPP1R16A,
for use in diagnosing endometrial cancer.

Accordingly, a kit comprising antibodies to two or more herein disclosed antibodies for use in diagnosing endometrial cancer is envisaged. The invention further relates to a kit for obtaining uterine fluid for use in diagnosing endometrial cancer by assessing the levels of from 1-20 biomarkers as defined and described herein.

The in vitro diagnostic method of the present invention may comprise determining/detecting the level of 2 biomarkers, 3 biomarkers, 4 biomarkers, 5 biomarkers, 7 biomarkers, 10 biomarkers, 15 biomarkers or 20 biomarkers.

In one embodiment, the present invention relates to an in vitro diagnostic method for diagnosing endometrial cancer comprising obtaining a uterine fluid aspirate sample from a patient having a symptom or risk factor for endometrial cancer and determining the level of from 1 to 100 biomarkers markers that are differentially expressed in endometrial cancer as compared to control values representative of individuals not affected by endometrial cancer, wherein (1) if the levels of 1 to 100 biomarkers are upregulated in the endometrial aspirate sample in the patient and in the control value then the patient has an increased likelihood of having endometrial cancer and wherein (2) if the level of the 1 to 100 biomarkers are downregulated in the aspirate sample and then the patient has an increased likelihood of having endometrial cancer.

The present invention further relates to a nucleic acid chosen from
ACAA1 mRNA, cDNA, or a complement thereof;
AP1M2 mRNA, cDNA, or a complement thereof;
CGN mRNA, cDNA, or a complement thereo;f
FASTKD1 mRNA, cDNA, or a complement thereof;
P2RX4 mRNA, cDNA, or a complement thereof;
RASSF7 mRNA, cDNA, or a complement thereof;
RNF183 mRNA, cDNA, or a complement thereof;
PHKG2 mRNA, cDNA, or a complement thereof;
PPFIBP2 mRNA, cDNA, or a complement thereof,
SIRT6 mRNA, cDNA, or a complement thereof,
TJP3 mRNA, cDNA, or a complement thereof;
EFEMP2 mRNA, cDNA, or a complement thereof; and

DCN mRNA, cDNA, or a complement thereof,
for use in diagnosing endometrial cancer.

Also subject of the present invention is a nucleic acid chosen from
Primers for ACAA1;
Primers for AP1M2;
Primers for CGN;
Primers for FASTKD1;
Primers for P2RX4;
Primers for RASSSF7;
Primers for RNF183;
Primers for SIRT6;
Primers for PPFIBP2;
Primers for PHKG2;
Primers for TJP3;
Primers for EFEMP2;and
Primers for DCN;
for use in diagnosing endometrial cancer.

In a further embodiment, the present invention relates to a nucleic acid chosen from
probe for ACAA1;
probe for AP1M2;
probe for CGN;
probe for FASTKD1;
probe for P2RX4;
probe for RASSF7;
probe for RNF183;
probe for SIRT6;
probe for PPFIBP2;
probe for PKHG2;
probe for TJP3;
probe for EFEMP2; and
probe for DCN,
for use in diagnosing endometrial cancer.

In another embodiment, the invention relates to an antibody chosen from
an antibody to ACAA1;
an antibody to AP1M2;
an antibody to CGN;
an antibody to FASTKD1;
an antibody to P2RX4;
an antibody to RASSF7;
an antibody to RNF183;
an antibody to SIRT6;
an antibody to PPFIBP2;
an antibody to PKHG2;
an antibody to TJP3;
an antibody to EFEMP2; and
an antibody to DCN,
for use in diagnosing endometrial cancer.

The antibody/antibodies, nucleic acid(s), probes, primer(s)/primer pair(s), and/or kit(s) described and defined herein are useful in the in diagnosis of endometrial cancer in accordance with the present invention. Therefore the antibody/antibodies, nucleic acid(s), probes, primer(s)/primer pair(s), and/or kit(s) described and defined herein are for use in diagnosing endometrial cancer. Similarly, also the use of the antibody/antibodies, nucleic acid(s), probes, primer(s)/primer pair(s), and/or kit(s) for the preparation of a diagnostic composition for diagnosing endometrial cancer is envisaged. Also a diagnostic composition for use in diagnosing endometrial cancer and comprising the herein described and defined antibody/antibodies, nucleic acid(s), probes, primer(s)/primer pair(s), and/or kit(s) is envisaged in context of the present invention.

Diagnosing endometrial cancer may, in this context, comprise or relate to a diagnostic method practised on the human or animal body which comprises or includes the features relating to
(i) the diagnosis for curative purposes stricto sensu representing the deductive medical or veterinary decision phase as a purely intellectual exercise,

(ii) the preceding steps which are constitutive for making that diagnosis, and
(iii) the specific interactions with the human or animal body which occur when carrying those out among these preceding steps which are of a technical nature.

In a further embodiment, the present invention relates to an in vitro diagnostic method for diagnosing endometrial cancer comprising providing or obtaining a uterine fluid sample from a human patient having a symptom or risk factor for a gynecological cancer and determining the level of RNA expression of from 2 to 9 biomarkers chosen from P4HB, EFEMP2, GMIP, IKBKE, DDR1, FASTKD1, SIRT6, PKHG2, and SOCS2 by quantitative PCR wherein an increased level of from 1 to 7 biomarkers chosen from P4HB, GMIP, IKBKE, DDR1, FASTKD1, SIRT6, and PKHG2 and/or a decreased level of EFEMP2 or SOCS2 as compared to control indicates the existence of endometrial cancer. Preferably, the gynecological cancer is endometrial cancer.

In one embodiment, the expression level of 2 to 8 biomarkers chosen from P4HB, EFEMP2, GMIP, IKBKE, DDR1, FASTKD1, SIRT6, and PKHG2 may be determined. The 2 to 8 biomarkers may also be chosen from P4HB, GMIP, IKBKE, DDR1, FASTKD1, SIRT6, PKHG2, and SOCS2.

The detection of the level may comprise contacting said one or more biomarkers with primers and reagents capable of amplifying specifically said one or more biomarkers and detecting the level of said amplified one or more biomarkers with a probe or probes that hybridize to said amplified biomarker. The probe hybrids specifically to said amplified biomarker.

The following combinations of biomarkers may, in particular, be detected in accordance with the method of the present invention: P4HB and EFEMP2; P4HB and IKBKE; P4HB and GMIP; EFEMP2 and IKBKE; EFEMP2 and P4HB; P4HB, GMIP, and IKBKE; P4HB, GMIP, and IKBKE.

Also the following combination of markers may be detected in accordance with the present method, wherein said combination comprises IKBKE and P4HB; IKBKE and SOCS2; P4HB and SOCS2; GMIP and IKBKE; GMIP and P4HB; GMIP and SOCS2;

GMIP, SOCS2, and IKBKE; GMIP, SOCS2, and P4HB; GMIP, IKBKE, and P4HB; IKBKE,P4HB, and SOCS2; GMIP, IKBKE, P4HB, and SOCS2; GMIP, SOCS2, IKBKE, and EPS8L2; GMIP, SOCS2, P4HB, and EPS8L2; GMIP, IKBKE, P4HB, and EPS8L2; IKBKE, P4HB, SOCS2, and EPS8L2; GMIP, IKBKE, P4HB, SOCS2, and DDR1; GMIP, IKBKE, P4HB, SOCS2, EPS8L2, and PPP1R16A; GMIP, IKBKE, P4HB, SOCS2, PHKG2, and RASSF7; GMIP, IKBKE, P4HB, SOCS2, EPS8L2, and DDR1; GMIP, IKBKE, P4HB, SOCS2, EPS8L2, PPP1R16A, and DDR1; DDR1, EPS8L2, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPP1R16A, RASSF7, SIRT6, TJP3, and SOCS2; or DDR1, EPS8L2, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPP1R16A, RASSF7, SIRT6, TJP3, RNF183 and SOCS2.

Further, the following combination of markers may be detected in accordance with the present method, wherein said combination comprises GMIP, IKBKE, P4HB, SOCS2 and FASTKD1; GMIP, IKBKE, P4HB, SOCS2 and DDR1; GMIP, IKBKE, P4HB, SOCS2 and PHKG2; GMIP, IKBKE, P4HB, SOCS2 and SIRT6; GMIP, IKBKE, P4HB, SOCS2 and ACAA1; GMIP, IKBKE, P4HB, SOCS2 and EFEMP2; GMIP, IKBKE, P4HB, SOCS2 and EPS8L2; GMIP, IKBKE, P4HB, SOCS2 and P2RX4; GMIP, IKBKE, P4HB, SOCS2 and PPFIBP2; GMIP, IKBKE, P4HB, SOCS2 and PPP1R16A; GMIP, IKBKE, P4HB, SOCS2, ACAA1 and FASTKD1; GMIP, IKBKE, P4HB, SOCS2, PHKG2 and FASTKD1; GMIP, IKBKE, P4HB, SOCS2, SIRT6 and FASTKD1; ACAA1, AP1M2, EPS8L2, IKBKE, P2RX4, P4HB, PPFIBP2, PPP1R16A, SIRT6, and EFEMP2; GMIP, IKBKE, P4HB, and EFEMP2; DDR1, FASTKD1, PHKG2, SIRT6, SOCS2, GMIP, IKBKE, P4HB, and EFEMP2; DDR1, FASTKD1, PHKG2, SIRT6, GMIP, IKBKE, P4HB, and EFEMP2; or P4HB, EFEMP2, IKBKE, GMIP, and FASTKD1.

Further, the following combination of markers may be detected in accordance with the present method, wherein said combination comprises GMIP, IKBKE, P4HB, EFEMP2 and FASTKD1; GMIP, IKBKE, P4HB, EFEMP2and DDR1; GMIP, IKBKE, P4HB, EFEMP2 and PHKG2; GMIP, IKBKE, P4HB, EFEMP2 and SIRT6; GMIP, IKBKE, P4HB, EFEMP2 and ACAA1; GMIP, IKBKE, P4HB, SOCS2 and EFEMP2; GMIP, IKBKE, P4HB, EFEMP2 and EPS8L2; GMIP, IKBKE, P4HB, EFEMP2 and P2RX4; GMIP, IKBKE, P4HB, EFEMP2 and PPFIBP2; GMIP, IKBKE, P4HB,

EFEMP2and PPP1R16A; GMIP, IKBKE, P4HB, EFEMP2, ACAA1 and FASTKD1; GMIP, IKBKE, P4HB, EFEMP2, PHKG2 and FASTKD1; or GMIP, IKBKE, P4HB, EFEMP2, SIRT6 and FASTKD1.

The methods of the present invention may further comprise providing a uterine fluid sample obtained from a patient with a pipelle device or syringe wherein the patient has a risk factor or symptom of endometrial cancer; contacting said sample with an agent capable of preserving, preventing, or lessening the degradation of RNA in said uterine fluid sample; determining in said sample the expression level of mRNA corresponding to from 1 to 20 herein described markers (preferably 2 to 8 markers) and one or more endogenous genes using quantitative PCR; normalizing the expression level of from 1 to 20 (preferably 2 to 8 markers) herein described biomarkers with the one or more endogenous genes; comparing the normalized level of the from 1 to 20 (preferably 2 to 8 markers) biomarkers to a control value wherein differential expression of from1 to 20 (preferably 2 to 8 markers) of the biomarkers indicates endometrial cancer or an increased likelihood of endometrial cancer.

The present invention relates further to an in vitro diagnostic method comprising providing a uterine fluid sample obtained from a patient with a pipelle device or syringe wherein the patient has a risk factor or symptom of endometrial cancer; contacting said sample with an agent capable of preserving, preventing, or lessening the degradation of RNA in said uterine fluid sample; determining in said sample the expression level of mRNA corresponding to from 1 to 20 herein described markers (preferably 2 to 8 markers) and one or more endogenous genes using quantitative PCR; normalizing the expression level of from 1 to 20 (preferably 2 to 8 markers) herein described biomarkers with the one or more endogenous genes; comparing the normalized level of the from 1 to 20 (preferably 2 to 8 markers) biomarkers to a control value wherein differential expression of from1 to 20 (preferably 2 to 8 markers) of the biomarkers indicates endometrial cancer or an increased likelihood of endometrial cancer.

The one or more endogenous genes may be chosen from POLR2A, B2M, PFN1, HMBS, G6PD, and PABPN1.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising obtaining a sample from an individual and determining the level of from 1-17 biomarkers chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, and/or from 1 to 3 biomarkers chosen from EFEMP2, SOCS2, and DCN wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. In a specific aspect of this embodiment, when the level of from 1 to 17 biomarkers chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, are increased relative to a control value and/or the level from 1 to 3 biomarkers chosen from EFEMP2, SOCS2, and DCN are decreased relative to control value then this indicates endometrial cancer or an increased chance of having endometrial cancer. According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to another aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

Amongst the biomarkers of Table 1, the levels of CGN, P4HB, PPP1R16A, IKBKE, RASSF7, RNF183, and TJP3, were found to have the highest mean level of overexpression in the RT-PCR studies as compared to their expression in normal samples (*e.g.*, not having endometrial cancer). Thus, given that the RT-PCR experiments demonstrated a high level of overexpression in a statistically significant manner (all p-values are less than 0.0001 for the sample set studied) for these markers, they represent preferred markers for diagnosis of endometrial cancer and/or an increased likelihood of having endometrial cancer. Therefore, the levels of CGN, P4HB, PPP1R16A, IKBKE, RASSF7, RNF183, and TJP3 are excellent predictors of endometrial cancer and/or an increased likelihood of having endometrial cancer. The levels of these markers are less likely to give a false positive as compared to other markers whose expression levels are not as high and/or as significant. In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising obtaining a sample from an individual and determining the level of one

or more biomarkers chosen from CGN, P4HB, PPP1R16A, IKBKE, RASSF7, RNF183, and TJP3 wherein if one or more of said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of cancer. Fingerprint patterns/expression profiles having from 1-7 biomarkers chosen from CGN, P4HB, PPP1R16A, IKBKE, RASSF7, RNF183, and TJP3 and from 1-13 biomarkers chosen from ACAA1, AP1M2, DDR1, EPS8L2, FASTKD1, GMIP, P2RX4, PHKG2, PPFIBP2, SIRT6, EFEMP2, SOCS2, and DCN, are one example of a set preferred profiles for diagnosing and/or predicting an increased likelihood of endometrial cancer. Specific examples of such profiles are described below. According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

Amongst the biomarkers of Table 1, the level of some biomarkers were found to be able to differentiate samples from patients having cancer as compared to normal samples (or control) and samples from patients in the secretory phase of the menstrual cycle. Therefore, the levels of ACAA1, DDR1, EPS8L2, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, RASSF7, SIRT6, TJP3, SOCS2, and DCN are excellent predictors of endometrial cancer in pre- and post-menopausal women and in peri-menopausal women, the levels of these markers are less likely to give a false positive as compared to other markers who expression level varies as a function of cycle. In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising obtaining a sample from an individual and determining the level of one or more biomarkers chosen from ACAA1, DDR1, EPS8L2, GMIP, IKBKE, LSR, P2RX4, P4HB, PHKG2, PPFIBP2, RASSF7, SIRT6, TJP3, SOCS2, and DCN wherein if one or more of said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. Fingerprint patterns/expression profiles having from 1-15 markers chosen from ACAA1, DDR1, EPS8L2, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, SIRT6, TJP3, SOCS2, and DCN and from 1 to 5 markers chosen from AP1M2, CGN,

FASTKD1, RNF183, and EFEMP2 are one example of a set preferred profiles for diagnosing and/or predicting an increased likelihood of endometrial cancer since the expression level of at least one of the markers in the profile does not vary as a function of menstrual cycle phase. Specific examples of such profiles are described below. According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising obtaining a sample from an individual and determining the level of one or more biomarkers chosen from IKBKE, P4HB, SOCS2, GMIP, DDR1, EPS8L2, PPP1R16A, P2RX4, PHKG2, RASSF7, SIRT6, TJP3, AP1M2, RNF183, and DCN wherein if one or more of said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial and/or an increased likelihood of endometrial cancer. According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising obtaining a sample from an individual and determining the level of one or more biomarkers chosen from IKBKE, P4HB, SOCS2, GMIP, DDR1, EPS8L2, PPP1R16A, P2RX4, PHKG2, RASSF7, SIRT6, and TJP3, wherein if one or more of said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one

aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

In one embodiment of the invention, preferred biomarkers for diagnosing endometrial cancer and/or diagnosing an increased likelihood of endometrial cancer are IKBKE, P4HB, SOCS2, GMIP, DDR1, EPS8L2, and PPP1R16A. In one aspect, the level of the biomarker in primary tumor is determined. In one aspect, the level of the biomarker in blood, plasma, or serum is determined. In one aspect, the level of the biomarker uterine fluid is determined. Thus, the method according to this embodiment, comprise obtaining a sample and determining the level of from 1 to 7 biomarkers chosen from IKBKE, P4HB, SOCS2, GMIP, DDR1, EPS8L2, and PPP1R16A wherein differential expression of one or more of these biomarkers as compared to a control value indicates endometrial cancer and/or an increased risk of having endometrial cancer. In one aspect of this invention, the protein level of the biomarker is determined and/or estimated. In another aspect, the mRNA expression level is determined and/or estimated.

In one embodiment of the invention, preferred biomarkers for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer include GMIP, IKBKE, P4HB, RASSF7, DDR1, RNF183, EFEMP2 and SOCS2. GMIP, IKBKE, P4HB, RASSF7, DDR1, RNF183, EFEMP2 and SOCS2 were found to have excellent AUROC values and therefore are unexpectedly good classifiers in the sample set studied. In one aspect, the level of the biomarker in primary tumor is determined. In one aspect, the level of the biomarker in blood, plasma, or serum is determined. In one aspect, the level of the biomarker uterine fluid is determined. Thus, the method according to this embodiment, comprise obtaining a sample and determining the level of from 1 to 8 biomarkers chosen from GMIP, IKBKE, P4HB, RASSF7, DDR1, RNF183, EFEMP2 and SOCS2 wherein differential expression of one or more of these biomarkers as compared to a control value indicates endometrial cancer and/or an increased risk of having endometrial cancer. In one aspect of this invention, the protein level of the biomarker is determined and/or estimated. In another aspect, the mRNA expression level is determined and/or estimated.

In one embodiment of the invention, preferred biomarkers for diagnosing endometrial cancer and/or diagnosing an increased likelihood of endometrial cancer include P2RX4, P4HB, PHKG2, PPFIBP2 and SOCS2. As a result of these studies it was found that P2RX4, P4HB, PHKG2, PPFIBP2 and SOCS2 have excellent specificity for endometrial cancer diagnosis. In one aspect, the level of the biomarker in primary tumor is determined. In one aspect, the level of the biomarker in blood, plasma, or serum is determined. In one aspect, the level of the biomarker uterine fluid is determined. Thus, the method according to this embodiment, comprise obtaining a sample and determining the level of from 1 to 5 biomarkers chosen from P2RX4, P4HB, PHKG2, PPFIBP2 and SOCS2 wherein differential expression of one or more of these biomarkers as compared to a control value indicates endometrial cancer and/or an increased risk of having endometrial cancer. In one aspect of this invention, the protein level of the biomarker is determined and/or estimated. In another aspect, the mRNA expression level is determined and/or estimated.

In one embodiment of the invention, preferred biomarkers for diagnosing endometrial cancer and/or diagnosing an increased likelihood of endometrial cancer include IKBKE, P4HB, RASSF7, and RNF183. As a result of these studies it was found that IKBKE, P4HB, RASSF7, and RNF183 have excellent sensitivity for endometrial cancer diagnosis. In one aspect, the level of the biomarker in primary tumor is determined. In one aspect, the level of the biomarker in blood, plasma, or serum is determined. In one aspect, the level of the biomarker uterine fluid is determined. Thus, the method according to this embodiment, comprise obtaining a sample and determining the level of from 1 to 4 biomarkers chosen from IKBKE, P4HB, RASSF7, and RNF183 wherein differential expression of one or more of these biomarkers as compared to a control value indicates endometrial cancer and/or an increased risk of having endometrial cancer. In one aspect of this invention, the protein level of the biomarker is determined and/or estimated. In another aspect, the mRNA expression level is determined and/or estimated.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising obtaining a sample from an individual and determining the level of from 2 to 7 biomarkers chosen from GMIP, IKBKE, P4HB, SOCS2, EPS8L2,

PPP1R16A, and TJP3 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. As result of the studies disclosed herein, it was surprisingly found that combinations (*e.g.*, profiles and/or fingerprint patterns) of biomarkers chosen from GMIP, IKBKE, P4HB, SOCS2, EPS8L2, PPP1R16A, and TJP3 have excellent sensitivity and specificity for endometrial cancer and the AUROC values for various combinations of these markers are indicative of the ability of these markers to separate patients having endometrial cancer from those not having endometrial cancer.

According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising obtaining a sample from an individual and determining the level of from 2 to 9 biomarkers chosen from GMIP, IKBKE, P4HB, SOCS2, EFEMP2, PHKG2, SIRT6, DDR1, and FASTKD1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. As result of the studies disclosed herein, it was surprisingly found that combinations (*e.g.*, profiles and/or fingerprint patterns) of biomarkers chosen from GMIP, IKBKE, P4HB, SOCS2, EFEMP2, PHKG2, SIRT6, DDR1, and FASTKD1 have excellent sensitivity and specificity for endometrial cancer and the AUROC values for various combinations of these markers are indicative of the ability of these markers to separate patients having endometrial cancer from those not having endometrial cancer. According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined. In one specific aspect of this embodiment, the in vitro diagnostic method comprises

providing a uterine fluid sample obtained from a patient with a pipelle device or syringe wherein the patient has a risk factor or symptom of endometrial cancer; contacting said sample with an agent capable of preserving, preventing, or lessening the degradation of RNA in said uterine fluid sample; determining in said sample the expression level of mRNA corresponding to said from 2 to 9 markers and one or more endogenous genes using quantitative PCR; normalizing the expression level of said from 2 to 9 biomarkers with the one or more endogenous genes; comparing the normalized level of the from 2 to 9 biomarkers to a control value wherein differential expression of from 2 to 9 of the biomarkers indicates endometrial cancer or an increased likelihood of endometrial cancer. In one specifc aspect of this method, said one or more endogenous genes are chosen from POLR2A, B2M, PFN1, HMBS, G6PD, and PABPN1.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising obtaining a sample from an individual and determining the level of from 2 to 8 biomarkers chosen from GMIP, IKBKE, P4HB, EFEMP2, PHKG2, SIRT6, DDR1, and FASTKD1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. As result of the studies disclosed herein, it was surprisingly found that combinations (*e.g.*, profiles and/or fingerprint patterns) of biomarkers chosen from GMIP, IKBKE, P4HB, EFEMP2, PHKG2, SIRT6, DDR1, and FASTKD1 have excellent sensitivity and specificity for endometrial cancer and the AUROC values for various combinations of these markers are indicative of the ability of these markers to separate patients having endometrial cancer from those not having endometrial cancer. According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of 2 to 8 biomarkers are determined by quantitative PCR. In one specific aspect of this embodiment, the in vitro diagnostic method comprises providing a uterine fluid sample obtained from a patient with a pipelle device or syringe wherein the patient has a risk factor or symptom of endometrial cancer;

contacting said sample with an agent capable of preserving, preventing, or lessening the degradation of RNA in said uterine fluid sample; determining in said sample the expression level of mRNA corresponding to said from 2 to 9 markers and one or more endogenous genes using quantitative PCR; normalizing the expression level of said from 2 to 8 biomarkers with the one or more endogenous genes; comparing the normalized level of the from 2 to 8 biomarkers to a control value wherein differential expression of from 2 to 8 of the biomarkers indicates endometrial cancer or an increased likelihood of endometrial cancer. In one specifc aspect of this method, said one or more endogenous genes are chosen from POLR2A, B2M, PFN1, HMBS, G6PD, and PABPN1.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising obtaining a sample from an individual and determining the level of from 2 to 8 biomarkers chosen from GMIP, IKBKE, P4HB, SOCS2, PHKG2, SIRT6, DDR1, and FASTKD1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. As result of the studies disclosed herein, it was surprisingly found that combinations (*e.g.*, profiles and/or fingerprint patterns) of biomarkers chosen from GMIP, IKBKE, P4HB, SOCS2, PHKG2, SIRT6, DDR1, and FASTKD1 have excellent sensitivity and specificity for endometrial cancer and the AUROC values for various combinations of these markers are indicative of the ability of these markers to separate patients having endometrial cancer from those not having endometrial cancer. According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of 2 to 8 biomarkers are determined by quantitative PCR. In one specific aspect of this embodiment, the in vitro diagnostic method comprises providing a uterine fluid sample obtained from a patient with a pipelle device or syringe wherein the patient has a risk factor or symptom of endometrial cancer; contacting said sample with an agent capable of preserving, preventing, or lessening the degradation of RNA in said uterine fluid sample; determining in said sample the

expression level of mRNA corresponding to said from 2 to 8 markers and one or more endogenous genes using quantitative PCR; normalizing the expression level of said from 2 to 8 biomarkers with the one or more endogenous genes; comparing the normalized level of the from 2 to 8 biomarkers to a control value wherein differential expression of from 2 to 8 of the biomarkers indicates endometrial cancer or an increased likelihood of endometrial cancer. In one specifc aspect of this method, said one or more endogenous genes are chosen from POLR2A, B2M, PFN1, HMBS, G6PD, and PABPN1.

In one embodiment, the present invention provides a method for characterizing a sample obtained from a patient for prognostic, diagnostic and/or pharmacogenomic uses. Characterization of a sample obtained from a patient by determining the levels of one or more of the biomarkers of Table 1 can be used to provide information regarding diagnosis of endometrial cancer, disease progression, diagnosis of endometrial cancer type (and/or subtype), and selection of an appropriate therapeutic treatment. According to the method of the invention, a sample is obtained from an individual. The individual can be a healthy person, an individual diagnosed with cancer, an individual suspected of having cancer, an individual displaying one or more symptoms of cancer and/or an individual desiring screening for cancer. The method comprises the step of determining the level of the biomarker(s) of Table 1 in a sample obtained from a patient. Alternative methods for determining the biomarkers at the RNA and/or protein (IHC, mRNA expression analysis, etc) can be used in these methods. Detection of increased levels of from 1 to 17 the biomarkers of Table 1 that were found to be upregulated in endometrial cancer and/or detection of decreased levels of from 1 to 3 biomarkers that were found to be downregulated in endometrial cancer, compared to a control value, indicates that the patient has increased likelihood of having endometrial cancer.

In one embodiment, the invention provides a method for diagnosing a gynecological cancer comprising the use of diagnostic reagents for assaying for or detecting from 1 to 20 of the biomarkers listed in Table 1. In a more specific aspect of this embodiment, the diagnostic reagents are used for detecting the level of from 1 to 20 of the biomarkers listed in Table 1, for the diagnosis of endometrial cancer. In a more specific aspect of this embodiment, the diagnostic reagents are used for

detecting the level of from 1 to 20 of the biomarkers listed in Table 1, for the detection of endometrial cancer. In one aspect of this embodiment, the level of the mRNA corresponding to from 1 to 20 biomarkers is determined. In one aspect of this embodiment, the level of the mRNA corresponding to from 2 to 17 biomarkers is determined. In one aspect of this embodiment, the level of the mRNA corresponding to from 3 to 15 biomarkers is determined. In one aspect of this embodiment, the level of a protein or polypeptide corresponding to from 1 to 20 biomarkers is determined. In one aspect of this embodiment, the level of a protein or polypeptide corresponding to from 2 to 17 biomarkers is determined. In one aspect of this embodiment, the level of a protein or polypeptide corresponding to from 3 to 15 biomarkers is determined. In one aspect of this embodiment, the sample that is analyzed is a tumor sample. In one aspect of this embodiment, the sample is analyzed is a uterine fluid sample. In one aspect of this embodiment, the sample that is analyzed is a serum, blood, or plasma sample. In one aspect, the sample is that is used is obtained by using a soft, straw-like device (pipelle) that is used to suction off a small sample of lining from the uterus (*e.g.*, uterine fluid). In one aspect, the sample is obtained by using a sharp-edged tool called a curette by scraping a small sample and collecting it with a syringe or suction (*e.g.*, dilation and curettage). In one aspect, the sample is obtained by using an electronic suction device (*e.g.*, Vabra aspiration). In one aspect, the sample is obtained by using a spray of liquid (jet irrigation) to wash off some of the tissue that lines the uterus. In some aspects, a brush may be used to remove some of the lining before the washing is done. In one aspect, a blood, serum, or plasma sample is analyzed for from 1 to 20 of the biomarkers of the invention.

In microrarray studies, GMIP was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.0001 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of GMIP was also found to be correlated in primary tumor and uterine fluid. Thus, GMIP is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having GMIP are expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a

method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of GMIP and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. For example, GMIP alone has AUROC value in Table 6 of 0.88 IKBKE alone has an AUROC value of 0.90, when these two markers are combined together in a profile the AUROC value 0.92 with a substantial increase in specificity (increased AUROC value indicate increased ability to separate the population). According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

In microrarray studies, IKBKE was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.0001 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of IKBKE was also found to be correlated in primary tumor and uterine fluid. Thus, IKBKE is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having IKBKE are expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of IKBKE and from 2 to 19 biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. For example, IKBKE alone has AUROC value in Table 6 of 0.90, P4HB alone has an AUROC value of 0.97, when these two markers are combined together in a profile the AUROC value 0.98 with a substantial increase in specificity to 100% (increased AUROC value indicate increased ability to separate

the population). According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

In microrarray studies, P4HB was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.0001 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of P4HB was also found to be correlated in primary tumor and uterine fluid. Thus, P4HB is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having P4HB are expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of P4HB and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. For example, P4HB alone has AUROC value in Table 6 of 0.97, SOCS2 alone has an AUROC value of 0.93, when these two markers are combined together in a profile the AUROC value 1 with a substantial increase in specificity to 100% (increased AUROC value indicate increased ability to separate the population). According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

In microrarray studies, SOCS2 was found to be underexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.0001 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of SOCS2 was also found to be correlated in primary tumor and uterine fluid. Thus, SOCS2 is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having SOCS2 are expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of SOCS2 and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. For example, SOCS2 alone has AUROC value in Table 6 of 0.93, GMIP alone has an AUROC value of 0.88, when these two markers are combined together in a profile the AUROC value 0.999 with a substantial increase in sensitivity to 100% (increased AUROC value indicate increased ability to separate the population). According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

In microrarray studies, EPS8L2 was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.002 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of EPS8L2 was also found to be correlated in primary tumor and uterine fluid. Thus, EPS8L2 is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having EPS8L2 are

expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of EPS8L2 and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. For example, when EPS8L2 is combined with GMIP, IKBKE, P4HB, SOCS2, and DDR1 the AUROC value is 1 and the sensitivity is nearly 96% and the specificity is 100% (see Table 11). According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

In microrarray studies, RASSF7 was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.0005 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of RASSF7 was also found to be correlated in primary tumor and uterine fluid. Thus, RASSF7 is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having RASSF7 are expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of RASSF7 and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. For example, when RASSF7 is combined with DDR1, EPS8L2, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPP1R16A, SIRT6, TJP3 and SOCS2 the AUROC value is 1 and the sensitivity is 100% and the specificity is

100% (see Table 11). According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

In microrarray studies, DDR1 was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.02 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of DDR1 was also found to be correlated in primary tumor and uterine fluid. Thus, DDR1 is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having DDR1 are expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of DDR1 and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. For example, when DDR1 is combined with EPS8L2, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPP1R16A, SIRT6, TJP3, SOCS2, and RNF183 the AUROC value is 1 and the sensitivity is 100% and the specificity is 100% (see Table 11). According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

In microrarray studies, PPP1R16A was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In

RT-PCR studies this result was confirmed and a p-value of less than 0.0001 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of PPP1R16A was also found to be correlated in primary tumor and uterine fluid. Thus, PPP1R16A is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having PPP1R16A are expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of PPP1R16A and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. For example, when PPP1R16A is combined with GMIP, IKBKE, P4HB, SOCS2, and EPS8L2 the AUROC value is nearly 1 and the sensitivity is nearly 92% and the specificity is 100% (see Table 11). According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

In microrarray studies, PHKG2 was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.0001 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of PHKG2 was also found to be correlated in primary tumor and uterine fluid. Thus, PHKG2 is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having PHKG2 are expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and

determining the level of PHKG2 and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. For example, when PHKG2 is combined with DDR1, EPS8L2, GMIP, IKBKE, P2RX4, P4HB, PPP1R16A, SIRT6, TJP3, SOCS2, and RNF183 the AUROC value is 1 and the sensitivity is 100% and the specificity is 100% (see Table 11). According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

In microrarray studies, P2RX4 was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.0005 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of P2RX4 was also found to be correlated in primary tumor and uterine fluid. Thus, P2RX4 is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having P2RX4 are expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of P2RX4 and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. For example, when P2RX4 is combined with DDR1, EPS8L2, GMIP, IKBKE, P4HB, PHKG2, PPP1R16A, SIRT6, TJP3, SOCS2, and RNF183 the AUROC value is 1 and the sensitivity is 100% and the specificity is 100% (see Table 11). According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment,

the level of mRNA corresponding to the biomarker is determined. According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

In microrarray studies, ACAA1 was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.0001 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of ACAA1 was also found to be correlated in primary tumor and uterine fluid. Thus, ACAA1 is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having ACAA1 are expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of ACAA1 and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined.According to one aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

In microrarray studies, AP1M2 was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.0001 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of AP1M2 was also found to be correlated in primary tumor and uterine fluid. Thus, AP1M2 is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having AP1M2 are

expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of AP1M2 and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined.

In microrarray studies, CGN was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.0001 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of CGN was also found to be correlated in primary tumor and uterine fluid. Thus, CGN is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having CGN are expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of CGN and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined.

In microrarray studies, FASTKD1 was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In

RT-PCR studies this result was confirmed and a p-value of less than 0.0001 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of FASTKD1 was also found to be correlated in primary tumor and uterine fluid. Thus, FASTKD1 is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having FASTKD1 are expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of FASTKD1 and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined.

In microrarray studies, PPFIBP2 was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.02 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of PPFIBP2 was also found to be correlated in primary tumor and uterine fluid. Thus, PPFIBP2 is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having PPFIBP2 are expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of PPFIBP2 and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. According to one aspect of this embodiment, the

sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined.

In microrarray studies, RNF183 was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.0001 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of RNF183 was also found to be correlated in primary tumor and uterine fluid. Thus, RNF183 is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having RNF183 are expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of RNF183 and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. For example, when RNF183 is combined with DDR1, EPS8L2, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPP1R16A, SIRT6, TJP3, and SOCS2 the AUROC value is 1 and the sensitivity is 100% and the specificity is 100% (see Table 11). According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined.

In microrarray studies, SIRT6 was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.0001 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of SIRT6 was also found to be correlated in primary tumor and uterine fluid. Thus, SIRT6 is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood

of endometrial cancer. Furthermore, fingerprint patterns/profiles having SIRT6 are expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of SIRT6 and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. For example, when SIRT6 is combined with DDR1, EPS8L2, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPP1R16A, TJP3, SOCS2, and RNF183 the AUROC value is 1 and the sensitivity is 100% and the specificity is 100% (see Table 11). According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined.

In microrarray studies, TJP3 was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.0001 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of TJP3 was also found to be correlated in primary tumor and uterine fluid. Thus, TJP3 is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having TJP3 are expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of TJP3 and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. For example, when TJP3 is combined with DDR1, EPS8L2, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPP1R16A, SIRT6, SOCS2, and RNF183 the AUROC value is 1 and the sensitivity is 100% and the specificity is

100% (see Table 11). According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined.

In microrarray studies, EFEMP2 was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.0001 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of EFEMP2 was also found to be correlated in primary tumor and uterine fluid. Thus, EFEMP2 is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having EFEMP2 are expected to be useful for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of EFEMP2 and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined.

In microrarray studies, DCN was found to be overexpressed in samples from patients having endometrial cancer as compared to normal values (non-affected). In RT-PCR studies this result was confirmed and a p-value of less than 0.005 was obtained for aspirate samples from non-affected individuals versus aspirates from individuals having endometrial cancer comparisons. The expression of DCN was also found to be correlated in primary tumor and uterine fluid. Thus, DCN is an excellent biomarker for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer. Furthermore, fingerprint patterns/profiles having DCN are expected to be useful for diagnosing endometrial cancer and/or an increased

likelihood of endometrial cancer. In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer comprising obtaining a sample from an individual and determining the level of DCN, and from 2 to 19 other biomarkers chosen from Table 1 wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined.

In one embodiment, the invention provide an in vitro diagnostic method for the diagnosis of endometrial cancer or an increased likelihood of endometrial comprising detecting the level of (1) from 1 to 17 biomarker(s) chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, and TJP3 in a sample from a patient wherein an increased level of said from 1 to 17 biomarkers compared to a control value indicates a diagnosis of endometrial cancer or increased likelihood of endometrial cancer and/or (2) detecting the level of from 1 to 3 biomarkers chosen from EFEMP2, SOCS2, and DCN, wherein a decreased level of EFEMP2, SOCS2, and/or DCN compared to a control value indicates a diagnosis of endometrial cancer or increased likelihood of endometrial cancer. In one preferred aspect, the method of diagnosing endometrial cancer or an increased likelihood of endometrial cancer involves using one or more upregulated biomarkers and one or more downregulated biomarkers according to Table 1.

In one aspect of this embodiment, the patient has a risk factor for endometrial cancer or is being screened for endometrial cancer.

In one aspect of this embodiment, the sample from said patient is obtained from a patient with abnormal uterine bleeding.

In one aspect of this embodiment, the sample is from said patient is obtained from a patient having an endometrium with increased thickness.

In one aspect of this embodiment, the sample from said patient is obtained from a pre-menopausal, peri-menopausal, or post-menopausal patient.

In one aspect of this embodiment, the patient is pre-menopausal.

In one aspect of this embodiment, the patient is peri-menopausal.

In one aspect of this embodiment, the patient is post-menpausal.

In one aspect of this embodiment, the sample is chosen from a tissue sample, blood and/or serum, and uterine fluid.

In one aspect of this embodiment, the sample is a uterine fluid sample.

In one aspect of this embodiment, the uterine fluid sample is obtained by aspiration.

In one aspect of this embodiment, the level of the biomarker(s) is determined with an antibody.

In one aspect of this embodiment, the level of the biomarker(s) is determined by RT-PCR. In one specific aspect, the level of the biomarker is determined by quantitative RT-PCR.

In one aspect of this embodiment, the markers are chosen from IKBKE, P4HB, SOCS2, GMIP, DDR1, EPS8L2, PPP1R16A, P2RX4, PHKG2, RASSF7, SIRT6, and TJP3.

In one aspect of this embodiment, the marker(s) is chosen from P2RX4, P4HB, PHKG2, PPFIBP2, and SOCS2.

In one aspect of this embodiment, the markers are chosen from P4HB, RASSF7, RNF183, and IKBKE.

In one aspect of this embodiment, from 2 to 20 markers are detected.

In one aspect of this embodiment, one or more additional auxiliary biomarkers are detected.

In one aspect of this embodiment, the one or more auxiliary biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and additional biomarkers for detecting endometrial cancer.

In one aspect of this embodiment, the one or more auxiliary biomarkers are chosen from differential diagnosis biomarkers.

In one aspect of this embodiment, the one or more auxiliary biomarkers are chosen from prognostic markers.

In one aspect of this embodiment, the one or more auxiliary biomarkers are chosen from endometrial cancer classification markers.

In one aspect of this embodiment, the invention provides a nucleic acid chosen from IKBKE mRNA, cDNA, or a complement thereof; P4HB mRNA, cDNA, or a complement thereof; SOCS2 mRNA, cDNA, or a complement thereof; GMIP mRNA, cDNA, or a complement thereof; DDR1 mRNA, cDNA, or a complement thereof; EPS8L2 mRNA, cDNA, or a complement thereof; and PPP1R16A mRNA, cDNA, complement thereof, for use for diagnosing endometrial cancer or an increased likelihood of having endometrial cancer.

In one aspect of this embodiment, the invention provides a nucleic acid chosen from ACAA1 mRNA, cDNA, or a complement thereof; AP1M2 mRNA, cDNA, or a complement thereof; CGN mRNA, cDNA, or a complement thereof; P2RX4 mRNA, cDNA, or a complement thereof; PPFIBP2 mRNA, cDNA, or a complement thereof; RASSF7 mRNA, cDNA, or a complement thereof; TJP3 mRNA, cDNA, or a complement thereof; DCN mRNA, cDNA, or a complement thereof; and RNF183

mRNA, cDNA, or a complement thereof, for use for diagnosing endometrial cancer or an increased likelihood of having endometrial cancer.

In one aspect of this embodiment, the invention provides a nucleic acid chosen from EFEMP2 mRNA, cDNA, or a complement thereof; PHKG2 mRNA, cDNA, or a complement thereof; SIRT6 mRNA, cDNA, or a complement thereof; and FASTKD1 mRNA, cDNA, or a complement thereof, for use for diagnosing endometrial cancer or an increased likelihood of having endometrial cancer.

In one aspect of this embodiment, the invention provides primers chosen from primers for IKBKE; primers for P4HB; primers for SOCS2; primers for GMIP; primers for DDR1; primers for EPS8L2; and primers for PPP1R16A; for use for diagnosing endometrial cancer and/or an increased likelihood of having endometrial cancer.

In one aspect of this embodiment, the invention provides primers chosen from primers for ACAA1; primers for AP1M2; primers for CGN; primers for P2RX4; primers for PPFIBP2; primers for RASSF7; primers for RNF183; primers for TJP3; and primers for DCN; for use for diagnosing endometrial cancer and/or an increased likelihood of having endometrial cancer.
In one aspect of this embodiment, the invention provides primers chosen from primers for EFEMP2; primers for SIRT6; primers for PHKG2; and primers for FASTKD1; for use for diagnosing endometrial cancer and/or an increased likelihood of having endometrial cancer.

In one aspect of this embodiment, the invention provides a nucleic acid chosen from probe for IKBKE; probe for P4HB; probe for SOCS2; probe for GMIP; probe for DDR1; probe for EPS8L2; and probe for PPP1R16A,
for diagnosing endometrial cancer and/or an increased likelihood of having endometrial cancer.

In one aspect of this embodiment, the invention provides a nucleic acid chosen from probe for ACAA1; probe for AP1M2; probe for CGN; probe for P2RX4; probe for

PPFIBP2; probe for RASSF7; probe for RNF183; probe for TJP3; and probe for DCN,
for diagnosing endometrial cancer and/or an increased likelihood of having endometrial cancer.

In one aspect of this embodiment, the invention provides a nucleic acid chosen from probe for EFEMP2; probe for FASTKD1; probe for SIRT6; probe for GMIP; and probe for PHKG2, for diagnosing endometrial cancer and/or an increased likelihood of having endometrial cancer.

In one aspect of this embodiment, the invention provides a kit comprising two or more probes to the 1-20 biomarkers of the invention, for diagnosing endometrial cancer and/or an increased likelihood of cancer.

In one aspect of this embodiment, the invention provides a kit comprising primers for two or more of the 1-20 biomarkers of the invention for diagnosing endometrial cancer and/or an increased likelihood of cancer.

In one aspect of this embodiment, the invention provides an antibody chosen from an antibody to IKBKE; an antibody to P4HB; an antibody to SOCS2; an antibody to GMIP; an antibody to DDR1; an antibody to EPS8L2; and
an antibody to PPP1R16A, for diagnosing endometrial cancer and/or an increased likelihood of having endometrial cancer.

In one aspect of this embodiment, the invention provides an antibody chosen from an antibody to ACAA1; an antibody to AP1M2; an antibody to CGN; an antibody to P2RX4; an antibody to PPFIBP2; an antibody to RASSF7; an antibody to RNF183; an antibody to TJP3; and an antibody to DCN, for diagnosing endometrial cancer and/or an increased likelihood of having endometrial cancer.

In one aspect of this embodiment, the invention provides an antibody chosen from an antibody to EFEMP2; an antibody to FASTKD1; an antibody to SIRT6; an antibody to GMIP; and an antibody to PHKG2; for diagnosing endometrial cancer and/or an increased likelihood of having endometrial cancer.

In one aspect of this embodiment, the invention provides a kit comprising antibodies to two or more biomarkers of Table 1 for diagnosing endometrial cancer and/or an increased likelihood of cancer.

In aspect of this embodiment, the invention provides a kit for obtaining uterine fluid for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer by assessing the levels of from 1-20 biomarkers of Table 1.

In one aspect of this embodiment, the in vitro diagnostic method comprises determining the level of 2 biomarkers of the invention. In one aspect of this embodiment, the in vitro diagnostic method comprises determining the level of 3 biomarkers of the invention. In one aspect of this embodiment, the in vitro diagnostic method comprises determining the level of 4 biomarkers of the invention. In one aspect of this embodiment, the in vitro diagnostic method comprises determining the level of 5 biomarkers of the invention. In one aspect of this embodiment, the in vitro diagnostic method comprises determining the level of 5 biomarkers of the invention. In one aspect of this embodiment, the in vitro diagnostic method comprises determining the level of 7 biomarkers of the invention. In one aspect of this embodiment, the in vitro diagnostic method comprises determining the level of 10 biomarkers of the invention. In one aspect of this embodiment, the in vitro diagnostic method comprises determining the level of 15 biomarkers of the invention. In one aspect of this embodiment, the in vitro diagnostic method comprises determining the level of 20 biomarkers of the 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 pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In 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.

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows correlation of the expression level of biomarkers in primary tumor and in uterine fluid for the biomarkers including those of the invention. See Example 3 for details.

FIG. 2A and 2B is a box and whiskers plots represent the relative amount of RNA (RQ) present in the aspirate samples from patients having endometrial cancer as compared with the control samples for each gene as determined by RT-PCR. 30 tumor samples and 24 controls were considered in the plots. Boxes represent the interquartile range for each gene and the whiskers go from percentile 10 to 90 of the RQ values for each gene. The bar in the boxes represents the median RQ. The white boxes represent the values for the tumour samples of each gene and the shaded boxes the values for the control samples. See Example 4 for details.

FIG. 3 shows an example of the expression level of RNF183 as determined by RT-PCR in aspirates obtained from patients having endometrial cancer (RNF183_T), normals in secretory phase (RNF183_S), normals not having endometrial cancer (RNF183_N), and all normals together (RNF183_Nt).

FIG. 4 shows an example of the expression level of AP1M2 as determined by RT-PCR in aspirates obtained from patients having endometrial cancer (AP1M2_T), normals in secretory phase (AP1M2_S), normals not having endometrial cancer (AP1M2_N), and all normals together (AP1M2_Nt).

FIG. 5 shows an example of the expression level of CGN as determined by RT-PCR in aspirates obtained from patients having endometrial cancer (CGN_T), normals in secretory phase (CGN_S), normals not having endometrial cancer (CGN_N), and all normals together (CGN_Nt).

FIG. 6 shows an example of the expression level of FASTKD1 as determined by RT-PCR in aspirates obtained from patients having endometrial cancer (FASTKD1_T),

normals in secretory phase (FASTKD1_S), normals not having endometrial cancer (FASTKD1_N), and all normals together (FASTKD1_Nt).

FIG. 7 shows an example of the expression level of IKBKE as determined by RT-PCR in aspirates obtained from patients having endometrial cancer (IKBKE _T), normals in secretory phase (IKBKE_S), normals not having endometrial cancer (IKBKE_N), and all normals together (IKBKE_Nt).

FIG. 8 shows an example of the expression level of P4HB as determined by RT-PCR in aspirates obtained from patients having endometrial cancer (P4HB_T), normals in secretory phase (P4HB_S), normals not having endometrial cancer (P4HB_N), and all normals together (P4HB_Nt).

FIG. 9 shows an example of the expression level of SOCS2 as determined by RT-PCR in aspirates obtained from patients having endometrial cancer (SOCS2_T), normals in secretory phase (SOCS2_S), normals not having endometrial cancer (SOCS2_N), and all normals together (SOCS2_Nt).

FIG. 10 shows a western blot of endometrial cancer tissue with antibody against a Biomarker of the invention: P4HB. The samples tested include four normal tissues (N) and four tumor tissues (T). Normal and tumors tissues were obtained from the same patient. As a positive control: total protein extract from the endometrial tumour cell line Isikawa. See Example 6.

FIG. 11 shows a western blot of endometrial cancer tissue with antibody against a Biomarker of the invention: AP1M2. The samples tested include four normal tissues (N) and four tumor tissues (T) from 4 different patients. Matched normal and tumors tissues were obtained from the same patient. As a positive control: total protein extract from the endometrial tumor cell line Isikawa. See Example 6.

FIG. 12 shows a western blot of endometrial cancer tissue with antibody against a Biomarker of the invention: IKBKE. The samples tested include a normal tissue (N) and a tumor tissue (T). Matched normal and tumors tissue were obtained from the same patient. As a positive control: total protein extract from the endometrial tumor cell line Isikawa. See Example 6.

FIG. 13 shows a western blot of endometrial cancer tissue with antibody against a Biomarker of the invention: EPS8L2. The samples tested include 3 normal tissues (N) and 3 tumor tissues (T) from 3 different patients. As a positive control: total protein extract from the endometrial tumor cell line. Matched normal and tumors tissues were obtained from the same patient. See example 6.

FIG. 14 shows a western blot of endometrial cancer tissue with antibody against a Biomarker of the invention: DDR1. The samples tested include a normal tissue (N) and a tumor tissue (T). Matched normal and tumors tissue were obtained from the same patient. As a positive control: total protein extract from the endometrial tumor cell line Isikawa. See Example 6.

FIG. 15 shows a western blot of endometrial cancer tissue with antibody against a Biomarker of the invention: CGN. The samples tested include four normal tissues (N) and four tumor tissues (T) from four different patients. Matched normal and tumors tissues were obtained from the same patient. As a positive control: total protein extract from the endometrial tumor cell line Isikawa. See Example 6.

FIG. 16 shows a western blot of endometrial cancer tissue with antibody against a Biomarker of the invention: TJP3. The samples tested include a normal tissue (N) and a tumor tissue (T). Matched normal and tumors tissue were obtained from the same patient. As a positive control: total protein extract from the endometrial tumor cell line Isikawa. See Example 6.

FIG. 17 shows the calculated risk of cancer using 48 non-tumor samples and 33 tumor samples using the ACAA1, AP1M2, EPS8L2, IKBKE, P2RX4, P4HB, PPFIBP2, PPP1R16A, SIRT6, EFEMP2. See Example 5.

FIG. 18 shows the calculated risk of cancer using 48 non-tumor samples and 33 tumor samples using the FASTKD1, GMIP, P4HB, EFEMP2, SIRT6, and PHKG2. See Example 5.

FIG. 19 shows the calculated risk of cancer using 48 non-tumor samples and 33 tumor samples using the FASTKD1, GMIP, P4HB, EFEMP2, DDR1, and SIRT6. See Example 5.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the finding of the association of alterations in the mRNA expression levels of the biomarkers listed in Table 1 in samples from patients having endometrial cancer as compared to control values (*e.g.*, normal tissue (non-affected) or value). These biomarkers therefore represent endometrial cancer biomarkers. Additionally, the inventors surprisingly found that samples obtained from uterine fluid of endometrial cancer patients display expression profiles for the biomarkers listed in Table 1 that were generally correlated to the expression profiles from the primary tumor. Furthermore, a number of the markers found by the inventors are expected to be found on cell surfaces and/or in blood as blood based markers (or in other body fluids like uterine fluid). As shown in Example 6, the upregulated biomarkers of Table 1 were shown to be overexpressed at the protein level in primary tissue as compared to normal non-affected tissue. For example, the protein level of P4HB by western blot analysis, revealed that this biomarker is overexpressed at a protein level as well. FIG. 11 through FIG. 16 show overexpression, at the protein level, of AP1M2, IKBKE, EPS8L2, DDR1, CGN, and TJP3. Furthermore, P4HB, PPP1R16A and EPS8L2 presented a specific cytoplasmatic expression within the tumoral cells in all carcinoma histological types and grades, and an absence or faint cytoplasmatic staining within the normal epithelial glands as determined by tissue microarray (TMA) immunohistochemistry (IHC).

These studies provide endometrial cancer diagnostic biomarkers with excellent predictive value, alone or in combinations, that may be detected using methods which are less invasive as compared to the current standard of care. Furthermore, the inventors have identified specific subsets of biomarkers that are capable of distinguishing, in endometrial aspirates samples, endometrial cancer affected patients from different sub-groups of non-affected patients.

Several of the studies used to identify (expression microarray) and validate (RT-PCR) the biomarkers of the invention are described briefly below and in more detail in the Example section.

More specifically, the inventors performed gene expression analysis on expression microarrays to detect genes that are differentially expressed in endometrial cancer as compared to normal tissues. The gene expression microarray studies disclosed herein revealed that a number of genes in endometrial cancer samples were overexpressed as compared to normal endometrial tissue. It was found that ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, and TJP3, were overexpressed in endometrial cancer samples and EFEMP2, SOCS2, and DCN were underexpressed, as compared to their respective levels in normal endometrial tissue using a microarray experimental strategy. These results are summarized in Table 1 which has the common abbreviation for the gene, the ENSMBL accession numbers (corresponding to the gene, transcript(s), and protein related to the biomarkers of the invention), the fold change values and the p-values for statistical significance.

Table 1: Differential expression of endometrial cancer biomarkers in primary tumor as compared to control values (obtained from a pool of unaffected tissue, see Example 1).

				Array data	
Name	gene	Transcrip	Protein	Fold change	p-value
RASSF7	ENSG00000099849	ENST00000397583 ENST00000397582	ENSP00000380713 ENSP00000380712	1.94	0.07
CGN	ENSG00000143375	ENST00000271636	ENSP00000271636	1.79	0.22
AP1M2	ENSG00000129354	ENST00000250244	ENSP00000250244	1.71	0.11
PHKG2	ENSG00000156873	ENST00000328273	ENSP00000329968.	1.34	0.09
PPP1R16A	ENSG00000160972	ENST00000292539	ENSP00000292539	1.44	0.10
DDR1	ENSG00000137332	ENST00000259875 ENST00000400414 ENST00000400411 ENST00000383377 ENST00000400410	ENSP00000259875 ENSP00000383265 ENSP00000383262 ENSP00000372868 ENSP00000383261	1.93	0.13
P4HB	ENSG00000185624	ENST00000331483	ENSP00000327801	1.90	0.13
RNF183	ENSG00000165188	ENST00000297894	ENSP00000297894	1.73	0.19
IKBKE	ENSG00000143466	ENST00000367120	ENSP00000356087	1.37	0.17
EPS8L2	ENSG00000177106	ENST00000318562	ENSP00000320828	1.34	0.20
TJP3	ENSG00000105289	ENST00000262968 ENST00000382008	ENSP00000262968 ENSP00000371438	1.57	0.17
SIRT6	ENSG00000077463	ENST00000269860 ENST00000305232 ENST00000337491 ENST00000381935	ENSP00000269860 ENSP00000305310 ENSP00000337332 ENSP00000371360	1.27	0.15
GMIP	ENSG00000089639	ENST00000203556	ENSP00000203556	1.42	0.05
ACAA1	ENSG00000060971	ENST00000333167 ENST00000301810 ENST00000358122	ENSP00000333664 ENSP00000301810 ENSP00000350838	1.26	0.11
FASTKD1	ENSG00000138399	ENST00000260971 ENST00000361619 ENST00000361819	ENSP00000260971 ENSP00000354598 ENSP00000354821	1.71	0.06
DCN	ENSG00000011465	ENST00000052754 ENST00000228329 ENST00000303320 ENST00000350856	ENSP00000052754 ENSP00000228329 ENSP00000302031 ENSP00000308451	-2.55	0.06
SOCS2	ENSG00000120833	ENST00000340600 ENST00000393123	ENSP00000339428 ENSP00000376831	-1.69	0.06
EFEMP2	ENSG00000172638	ENST00000307998	ENSP00000309953	-1.22	0.08
P2RX4	ENSG00000135124	ENST00000337233 ENST00000359949	ENSP00000336607 ENSP00000353032	1.70	0.12
PPFIBP2	ENSG00000166387	ENST00000299492	ENSP00000299492	1.52	0.11

As shown in FIG. 1, it was found that the markers of Table 1 were also found to be differentially expressed in samples obtained from uterine fluid in patients having endometrial cancer. Markers which were not highly correlated fall off or further away from the correlation line in FIG. 1.

The overexpression of ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, and TJP3, and the underexpression of DCN, SOCS2, and EFEMP2 in endometrial cancer was validated by RT-PCR using an independent set of samples. The samples used in this study were obtained from uterine fluid of individuals having endometrial cancer and from patients not having endometrial cancer. These results are summarized in Table 2 and illustrated in FIG. 2A and FIG. 2B. These results demonstrate that these markers displayed statistically significant differential expression in endometrial cancer samples in samples from individuals having

endometrial cancer as compared to normal individuals and/or samples (*e.g.*, control value).

Table 2: Differential expression of biomarkers in aspirate samples from patients having endometrial cancer compared to aspirates from patients not having endometrial cancer.

	Mean RQ	SEM	p value
ACAA1	1.472	0.476	< 0.0001
AP1M2	1.688	0.422	< 0.0001
CGN	2.348	1.312	< 0.0001
DCN	0.246	0.196	0.002
DDR1	1.515	0.534	0.0167
EFEMP2	0.414	0.289	< 0.0001
EPS8L2	1.646	0.559	0.0016
FASTKD1	1.693	0.662	< 0.0001
GMIP	1.338	0.491	< 0.0001
IKBKE	2.877	1.617	< 0.0001
P2RX4	1.544	0.504	0.0002
P4HB	1.998	0.647	< 0.0001
PHKG2	1.557	0.378	< 0.0001
PPFIBP2	1.540	0.725	0.0094
PPP1R16A	1.915	0.789	< 0.0001
RASSF7	1.848	0.770	0.0001
RNF183	3.648	2.368	< 0.0001
SIRT6	1.611	0.550	< 0.0001
SOCS2	0.265	0.177	< 0.0001
TJP3	2.088	0.928	< 0.0001

The p-values were calculated using a non-parametic Mann-Whitney test. Mean RQ refers to relative quantity, and SEM refers to standard error of the mean.

The finding of the correlation of expression levels of these biomarkers in primary tissue and uterine fluid was surprising given the heterogeneity of uterine fluid and the findings in the initial microarrays studies. It is believed that this is the first time that that the levels of biomarkers in primary endometrial cancer were shown to be correlated in a statistically significant manner to those found in uterine fluid and therefore this provides a less invasive and more standardized method of screening for endometrial cancer and/or an increased risk of endometrial cancer. The invention

therefore provides a method for diagnosing endometrial cancer and/or an increased likelihood of endometrial cancer by obtaining a uterine fluid sample and determining the level of biomarkers differentially expressed in endometrial cancer as compared to control value. In one aspect, the uterine fluid sample is obtained by aspiration. In one aspect, the uterine fluid sample is obtained gently washing and/or rinse the uterine cavity. In one aspect, the level of mRNA is determined. In one aspect, the level of protein is determined. In one aspect, the biomarkers are chosen from the 20 listed in Table 1.

Surprisingly, the p-values for the individual biomarkers in Table 1 as determined in the microarray studies with one sample set were significantly improved upon when the same biomarkers were analyzed by a different technique (quantitative RT-PCR) using a different set of samples, obtained from the patient by a different method. In general the p-values were over 100 fold improved compared to the microarray studies.

The inventors have found that individually each of the biomarkers of Table 1 have predictive value for the diagnosis of endometrial cancer. Furthermore, combinations of these biomarkers have additional predictive value for the diagnosis of endometrial cancer. For example, the inventors have surprisingly found that numerous sub-groups of the biomarkers of Table 1 having from 2-20 biomarkers in various combinations give fingerprint patterns having excellent predictive value for diagnosis or detection of endometrial cancer. Additionally, the inventors have also contemplate that addition of other biomarkers besides those listed in Table 1, to the fingerprint pattern also can increase predictive value, and can be useful for classifying endometrial cancers, for differential diagnosis of diseases other than endometrial cancer, and for endometrial cancer prognosis.

In one embodiment, the present invention provides a method for characterizing a sample obtained from a patient for prognostic, diagnostic and/or pharmacogenomic uses. Characterization of the a sample obtained from a patient according to the levels one or more of the biomarkers of Table 1 can be used to provide information regarding disease progression, diagnosis of endometrial cancer type (and/or subtype), and selection of an appropriate therapeutic treatment. According to the method of

the invention, a sample is obtained from an individual. The individual can be a healthy person, an individual diagnosed with cancer, an individual suspected of having cancer, an individual displaying one or more symptoms of cancer and/or an individual desiring screening for cancer. The method comprises the step of determining the level of the biomarker(s) of Table 1 in a sample obtained for a patient. Alternative methods for determining the biomarkers (IHC, mRNA expression analysis, *etc*) can be used in these methods.

In one embodiment, the invention provides a method for diagnosing endometrial cancer and/or an increased likelihood of having endometrial cancer which comprises obtaining a sample from an individual and determining the level of from 1 to 20 biomarkers of Table 1 in the sample. If the level of from 1 to 17 of the upregulated biomarkers are increased relative to control value and/or the level of from 1 to 3 of the downregulated markers are decreased compared to control value, then the patient has an increased likelihood of having endometrial cancer.

In one embodiment, the invention provides a method for diagnosing endometrial cancer which comprises obtaining a sample from a patient having a symptom of endometrial cancer and determining the level of from 1 to 20 biomarkers of Table 1 in the sample. In one aspect of this embodiment, the symptom of endometrial cancer is chosen from vaginal bleeding and/or spotting in postmenopausal women, abnormal uterine bleeding, abnormal menstrual periods, bleeding between normal periods in premenopausal women in women older than 40, extremely long, heavy, or frequent episodes of bleeding, anemia caused by chronic loss of blood, lower abdominal pain or pelvic cramping, thin white or clear vaginal discharge in postmenopausal women, and suspect symptoms in peri-menopausal. Thus, in one aspect of this embodiment, the invention relates to a method for diagnosing endometrial cancer comprising obtaining or providing a sample from an individual having vaginal bleeding and/or spotting in postmenopausal women, abnormal uterine bleeding, abnormal menstrual periods, bleeding between normal periods in premenopausal women in women older than 40, extremely long, heavy, or frequent episodes of bleeding, anemia caused by chronic loss of blood, lower abdominal pain or pelvic cramping, thin white or clear vaginal discharge in postmenopausal women, or suspect symptoms in peri-menopausal and determining the level of from 1-17 biomarkers chosen from ACAA1,

AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, and/or from 1 to 3 biomarkers chosen from EFEMP2, SOCS2, and DCN wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. In a specific aspect of this embodiment, when the level of from 1 to 17 biomarkers chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, are increased relative to a control value and/or the level from 1 to 3 biomarkers chosen from EFEMP2, SOCS2, and DCN are decreased relative to control value then this indicates endometrial cancer or an increased chance of having endometrial cancer. According to one aspect of this embodiment, the levels of the one or more biomarkers for detecting endometrial cancer are normalized to one or more endogenous biomarkers or genes. According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to another aspect of this embodiment, the level of protein corresponding to the biomarker is determined.

In one embodiment, the invention provides a method for diagnosing endometrial cancer which comprises obtaining a sample from a patient having a risk factor for endometrial cancer and determining the level of from 1 to 20 biomarkers of Table 1 in the sample. In one aspect of this embodiment, the risk factor for endometrial cancer is chosen from high levels of estrogen, endometrial hyperplasia, obesity, hypertension, polycystic ovary syndrome, nulliparity, infertility, early menarche, late menopause, endometrial polyps or other benign growths of the uterine lining, diabetes, tamoxifen exposure, hyperplasia, high intake of animal fat, pelvic radiation therapy, breast cancer, ovarian cancer, heavy daily alcohol consumption, family history of cancer, family history of HNPCC, and being an HNPCC mutation carrier. In one aspect of this embodiment, the biomarkers are selected for distinguishing patients having tumor from those in secretory phase of the menstrual cycle. Thus, in one aspect of this embodiment, the invention relates to a method for diagnosing endometrial cancer comprising obtaining or providing a sample from an individual

having a risk factor for cancer which is high levels of estrogen, endometrial hyperplasia, obesity, hypertension, polycystic ovary syndrome, nulliparity, infertility, early menarche, late menopause, endometrial polyps or other benign growths of the uterine lining, diabetes, tamoxifen exposure, hyperplasia, high intake of animal fat, pelvic radiation therapy, breast cancer, ovarian cancer, heavy daily alcohol consumption, family history of cancer, family history of HNPCC, or being an HNPCC mutation carrier which is and determining the level of from 1-17 biomarkers chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, and/or from 1 to 3 biomarkers chosen from EFEMP2, SOCS2, and DCN wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. In a specific aspect of this embodiment, when the level of from 1 to 17 biomarkers chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, are increased relative to a control value and/or the level from 1 to 3 biomarkers chosen from EFEMP2, SOCS2, and DCN are decreased relative to control value then this indicates endometrial cancer or an increased chance of having endometrial cancer. According to one aspect of this embodiment, the levels of the one or more biomarkers for detecting endometrial cancer are normalized to one or more endogenous biomarkers or genes. According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to another aspect of this embodiment, the level of protein corresponding to the biomarker is determined. In a preferred aspect of this embodiment, the method involves determining the level of from 1-17 upregulated biomarkers of Table 1 and from 1-3 downregulated markers of Table 1 by quantitative PCR in a uterine fluid sample.

In one embodiment, the invention provides a method for diagnosing endometrial cancer which comprises obtaining a sample from a patient having an endometrium with an increased thickness. In one aspect of this embodiment, the thickness of the endometrium is measured by transvaginal ultrasound. "Increased thickness" refers a

thickness above a value common employed in the art to identify patients that warrant further work-up or investigation. The method of this embodiment involves determining the level determining the level of from 1 to 20 biomarkers of Table 1 in a sample obtained from a patient having an endometrium of increased thickness. According to an aspect of this embodiment, the sample is a uterine fluid sample. In another aspect of this embodiment, the level of from 1-20 mRNA biomarkers is determined. In another aspect of this embodiment, the level of from 1-20 protein biomarkers is determined. In one aspect of this embodiment, the biomarkers are chosen from those that are capable of distinguishing samples from endometrial cancer affected patients and from those patients having another condition that increases the thickness of the endometrium. Conditions that increases the thickness of the endometrium but are not necessarily present in endometrial cancer patients include, but are not limited to, tamoxifen exposure, exposure to hormones, phase of menstrual cycle (in general the endometrium thickness increase in going from proliferative to secretory phase). Some preferred biomarkers which performed well in separating samples from patients affected with endometrial cancer from non-endometrial cancer affected patients in the secretory phase are shown in Table 9 in the Examples. Thus, in one aspect of this embodiment, the invention relates to a method for diagnosing endometrial cancer comprising obtaining or providing a sample from an individual having increased endometrial thickness and determining the level of from 1-17 biomarkers chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, and/or from 1 to 3 biomarkers chosen from EFEMP2, SOCS2, and DCN wherein if said markers are differentially expressed compared to a control value, then the individual is diagnosed with endometrial cancer and/or an increased likelihood of endometrial cancer. In a specific aspect of this embodiment, when the level of from 1 to 17 biomarkers chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, are increased relative to a control value and/or the level from 1 to 3 biomarkers chosen from EFEMP2, SOCS2, and DCN are decreased relative to control value then this indicates endometrial cancer or an increased chance of having endometrial cancer. According to one aspect of this embodiment, the levels of the one or more biomarkers for detecting endometrial cancer are normalized to one or more endogenous biomarkers or genes.

According to one aspect of this embodiment, the sample is chosen from a tissue sample and a fluid sample. In one aspect, the fluid sample is a uterine fluid sample or uterine aspirate. According to one aspect of this embodiment, the level of mRNA corresponding to the biomarker is determined. According to another aspect of this embodiment, the level of protein corresponding to the biomarker is determined. In a preferred aspect of this embodiment, the method involves determining the level of from 1-17 upregulated biomarkers of Table 1 and from 1-3 downregulated markers of Table 1 by quantitative PCR in a uterine fluid sample.

Profiles, fingerprint patterns, and combinations

The initial microarray studies disclosed herein demonstrated that each of the biomarkers of Table 1, as independent biomarkers, have predictive value for diagnosing endometrial cancer. Furthermore, it was found that combinations of markers (e.g., profiles or fingerprint patterns) have increased predictive value for endometrial cancer. Thus, in addition to using these markers as individual markers, they can be used in combinations of 2 to 20 biomarkers for diagnosing endometrial cancer. In some embodiments additional markers can be included in the profile or fingerprint pattern for differential diagnostic purposes (exclude or confirm a disease or conditions other than endometrial cancer (*e.g.*, endometrial hyperplasia, endometrosis, ovarian cancer, fibroids, *etc.*)), classification of type of endometrial cancer (*e.g.*, type I versus type II), classification of cell type of endometrial cancer, and prognosis.

In one embodiment, the invention provides for profiles and/or fingerprint patterns having 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, of the biomarkers of Table 1. In one aspect of this embodiment, the level of mRNA corresponding to the biomarkers in the profile is determined for use in diagnosis endometrial cancer and/or an increased likelihood of endometrial cancer. In one aspect of this embodiment, the level of protein corresponding to the biomarkers in the profile is determined for use in diagnosis endometrial cancer and/or an increased likelihood of endometrial cancer. In one aspect of this embodiment, the level of the biomarkers is determined in a sample obtained from uterine fluid. In one aspect of

this embodiment, the level of the biomarkers is determined in a sample obtained from serum, blood, or plasma.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of an ACAA1 biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from AP1M2, CGN,
DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN. Combinations or subcombinations including ACAA1 are ACAA1 and AP1M2; ACAA1 and CGN; ACAA1 and DDR1; ACAA1 and EPS8L2; ACAA1 and FASTKD1; ACAA1and GMIP; ACAA1 and IKBKE; ACAA1 and P2RX4; ACAA1 and P4HB; ACAA1 and PHKG2; ACAA1 and PPFIBP2; ACAA1 and PPP1R16A; ACAA1 and RASSF7; ACAA1 and RNF183; ACAA1 and SIRT6; ACAA1 and TJP3; ACAA1 and EFEMP2; ACAA1 and SOCS2; or ACAA1 and DCN. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of an AP1M2 biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers,

prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN. Combinations or subcombinations including AP1M2 are AP1M2 and ACAA1; AP1M2 and CGN; AP1M2 and DDR1; AP1M2 and EPS8L2; AP1M2and FASTKD1; AP1M2and GMIP; AP1M2 and IKBKE; AP1M2 and P2RX4; AP1M2and P4HB; AP1M2 and PHKG2; AP1M2 and PPFIBP2; AP1M2 and PPP1R16A; AP1M2 and RASSF7; AP1M2 and RNF183; AP1M2 and SIRT6; AP1M2 and TJP3; AP1M2 and EFEMP2; AP1M2 and SOCS2; or AP1M2 and DCN. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of a CGN biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3,

EFEMP2, SOCS2, and DCN. Combinations or subcombinations including CGN are CGN and AP1M2; ACAA1 and CGN; CGN and DDR1; CGN and EPS8L2; CGN and FASTKD1; CGN and GMIP; CGN and IKBKE; CGN and P2RX4; CGN and P4HB; CGN and PHKG2; CGN and PPFIBP2; CGN and PPP1R16A; CGN and RASSF7; CGN and RNF183; CGN and SIRT6; CGN and TJP3; CGN and EFEMP2; CGN and SOCS2; or CGN and DCN. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of a DDR1 biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, CGN, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN. A preferred combination or subcombination useful for detecting endometrial cancer or an increased likelihood of endometrial cancer is DDR1 and P4HB; DDR1 and GMIP; DDR1 and IKBKE; DDR1 and EFEMP2; DDR1 and SOCS2; DDR1, P4HB, and GMIP; DDR1, P4HB, GMIP, and IKBKE; DDR1, P4HB, GMIP, IKBKE and EFEMP2; or DDR1, GMIP, IKBKE, P4HB, and SOCS2. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this

embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of an EPS8L2 biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, CGN, DDR1, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN. Combinations or subcombinations including EPS8L2 are EPS8L2 and AP1M2; EPS8L2 and CGN; EPS8L2 and DDR1; EPS8L2 and EPS8L2; EPS8L2 and FASTKD1; EPS8L2 and GMIP; EPS8L2 and IKBKE; EPS8L2 and P2RX4; EPS8L2 and P4HB; EPS8L2 and PHKG2; EPS8L2 and PPFIBP2; EPS8L2and PPP1R16A; EPS8L2 and RASSF7; EPS8L2 and RNF183; EPS8L2 and SIRT6; EPS8L2 and TJP3; EPS8L2 and EFEMP2; EPS8L2 and SOCS2; EPS8L2 and ACAA1; or EPS8L2 and DCN. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of a FASTKD1 biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment

the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN. A preferred combination or subcombination useful for detecting endometrial cancer or an increased likelihood of endometrial cancer is FASTD1 and P4HB; FASTKD1 and GMIP; FASTKD1 and IKBKE; FASTKD1 and EFEMP2; FASTKD1 and SOCS2; FASTD1 and DDR1; FASTKD1 and SIRT6; FASTKD1 and PHKG2; FASTKD1, P4HB, and GMIP; FASTKD1, P4HB and IKBKE; FASTKD1, P4HB, and EFEMP2; FASTKD1, P4HB, EFEMP2, IKBKE, and GMIP; FASTKD1, P4HB, EFEMP2, SIRT6, DDR1, and GMIP; or FASTKD1, P4HB, EFEMP2, SIRT6, PHKG2, and GMIP. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of a GMIP biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of

this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN. A preferred combination or subcombination useful for detecting endometrial cancer or an increased likelihood of endometrial cancer is GMIP and P4HB; FASTKD1 and GMIP; GMIP and IKBKE; GMIP and EFEMP2; GMIP and SOCS2; GMIP and DDR1; GMIP and SIRT6; GMIP and PHKG2; GMIP, P4HB, and IKBKE; GMIP, SOCS2, and IKBKE; GMIP, SOCS2, and P4HB; GMIP, IKBKE, P4HB, and EFEMP2; GMIP, IKBKE, P4HB, and SOCS2; GMIP, P4HB, EFEMP2, IKBKE, and FASTKD1; GMIP, P4HB, EFEMP2, SIRT6, DDR1, and FASTKD1; or GMIP, P4HB, EFEMP2, SIRT6, PHKG2, and FASTKD1. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of an IKBKE biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN. A preferred combination or subcombination useful for detecting endometrial cancer or an increased likelihood of endometrial cancer is IKBKE and P4HB; IKBKE and GMIP; IKBKE and FASTKD1; IKBKE and EFEMP2; IKBKE and

SOCS2; IKBKE and DDR1; IKBKE and SIRT6; IKBKE and PHKG2 ; IKBKE, P4HB, and GMIP; IKBKE, P4HB, and EFEMP2; IKBKE, GMIP, and EFEMP2; IKBKE, P4HB, and SOCS2; IKBKE, GMIP, P4HB, and SOCS2; IKBKE, GMIP, P4HB, and EFEMP2; IKBKE, P4HB, EFEMP2, GMIP, and FASTKD1; or IKBKE, DDR1, GMIP, P4HB, PHKG2, SIRT6, and EFEMP2. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of a P2RX4 biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN. Combinations or subcombinations including P2RX4 are P2RX4and AP1M2; P2RX4 and CGN; P2RX4 and DDR1; P2RX4 and EPS8L2; P2RX4and FASTKD1; P2RX4 and GMIP; P2RX4 and IKBKE; P2RX4 and P4HB; P2RX4 and PHKG2; P2RX4 and PPFIBP2; P2RX4 and PPP1R16A; P2RX4 and RASSF7; P2RX4 and RNF183; P2RX4 and SIRT6; P2RX4 and TJP3; P2RX4 and EFEMP2; P2RX4 and SOCS2; P2RX4 and ACAA1; or P2RX4 and DCN. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is

analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of a P4HB biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN. A preferred combination or subcombination useful for detecting endometrial cancer or an increased likelihood of endometrial cancer is FASTD1 and P4HB; P4HB and GMIP; P4HB and IKBKE; P4HB and EFEMP2; P4HB and SOCS2; P4HB and DDR1; P4HB and SIRT6; P4HB and PHKG2; P4HB, GMIP, and IKBKE; P4HB, GMIP, and SOCS2; P4HB, GMIP, and EFEMP2; P4HB, IKBKE, GMIP, and SOCS2; P4HB, IKBKE, GMIP, and EFEMP2; P4HB, EFEMP2, IKBKE, GMIP, and FASTKD1; P4HB, EFEMP2, SIRT6, GMIP, DDR1, and FASTKD1; P4HB, EFEMP2, SIRT6, GMIP, PHKG2, and FASTKD1; or DDR1, FASTKD1, GMIP, IKBKE, P4HB, PHKG2, SIRT6, and EFEMP2. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of a PHKG2 biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN. A preferred combination or subcombination useful for detecting endometrial cancer or an increased likelihood of endometrial cancer is PHKG2 and P4HB; PHKG2 and GMIP; PHKG2 and IKBKE; PHKG2 and EFEMP2; PHKG2 and SOCS2; PHKG2 and DDR1; PHKG2 and SIRT6; FASTKD1 and PHKG2; PHKG2, P4HB, and EFEMP2; PHKG2, P4HB, GMIP; PHKG2, P4HB, IKBKE, and EFEMP2; PHKG2, P4HB, IKBKE, and SOCS2; P4HB, EFEMP2, SIRT6, GMIP, PHKG2, and FASTKD1; or DDR1, FASTKD1, GMIP, IKBKE, P4HB, PHKG2, SIRT6, and EFEMP2 In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of a PPFIBP2 biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers

are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN. Combinations or subcombinations including PPFIBP2 are PPFIBP2 and AP1M2; PPFIBP2 and CGN; PPFIBP2 and DDR1; PPFIBP2 and EPS8L2; PPFIBP2 and FASTKD1; PPFIBP2 and GMIP; PPFIBP2 and IKBKE; PPFIBP2 and P2RX4; PPFIBP2and P4HB; PPFIBP2 and PHKG2; PPFIBP2and PPP1R16A; PPFIBP2 and RASSF7; PPFIBP2 and RNF183; PPFIBP2 and SIRT6; PPFIBP2 and TJP3; PPFIBP2 and EFEMP2; PPFIBP2 and SOCS2; PPFIBP2 and ACAA1; or PPFIBP2 and DCN. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of a PPP1R16A biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN. Combinations or subcombinations including PPP1R16A are PPP1R16A and AP1M2; PPP1R16A and CGN; PPP1R16A

and DDR1; PPP1R16A and EPS8L2; PPP1R16A and FASTKD1; PPP1R16A and GMIP; PPP1R16A and IKBKE; PPP1R16A and P2RX4; PPP1R16A and P4HB; PPP1R16A and PHKG2; PPFIBP2 and PPP1R16A; PPP1R16A and RASSF7; PPP1R16A and RNF183; PPP1R16A and SIRT6; PPP1R16A and TJP3; PPP1R16A and EFEMP2; PPP1R16A and SOCS2; PPP1R16A and ACAA1; or PPP1R16A and DCN. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of a RASSF7 biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN. Combinations or subcombinations including RASSF7 are RASSF7and AP1M2; RASSF7 and CGN; RASSF7 and DDR1; RASSF7and EPS8L2; RASSF7 and FASTKD1; RASSF7 and GMIP; RASSF7 and IKBKE; RASSF7 and P2RX4; RASSF7and P4HB; RASSF7 and PHKG2; RASSF7 and PPP1R16A; RASSF7 and RNF183; RASSF7 and SIRT6; RASSF7 and TJP3; RASSF7 and EFEMP2; RASSF7 and SOCS2; RASSF7 and ACAA1; or RASSF7 and DCN. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or

suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of a RNF183 biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, SIRT6, TJP3, EFEMP2, SOCS2, and DCN. Combinations or subcombinations including RNF183 are RNF183 and AP1M2; RNF183 and CGN; RNF183 and DDR1; RNF183 and EPS8L2; RNF183 and FASTKD1; RNF183 and GMIP; RNF183 and IKBKE; RNF183 and P2RX4; RNF183 and P4HB; RNF183 and PHKG2; RNF183 and PPP1R16A; RASSF7 and RNF183; RNF183 and SIRT6; RNF183 and TJP3; RNF183 and EFEMP2; RNF183 and SOCS2; RNF183 and ACAA1; or RNF183 and DCN. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of a SIRT6 biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one

or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN. A preferred combination or subcombination useful for detecting endometrial cancer or an increased likelihood of endometrial cancer is SIRT6 and P4HB; SIRT6 and GMIP; SIRT6 and IKBKE; SIRT6 and EFEMP2; SIRT6 and SOCS2; SIRT6 and DDR1; FASTKD1 and SIRT6; SIRT6 and PHKG2; SIRT6, P4HB, and EFEMP2; SIRT6, P4HB, and IKBKE; SIRT6, IKBKE, and EFEMP2; SIRT6, P4HB, and SOCS2; SIRT6, P4HB, IKBKE, and GMIP; SIRT6, P4HB, EFEMP2, GMIP, DDR1, and FASTKD1; SIRT6, P4HB, EFEMP2, GMIP, PHKG2, and FASTKD1; or SIRT6, P4HB, EFEMP2, GMIP, IKBKE, PHKG2, DDR1, and FASTKD1. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of a TJP3 biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of

this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, EFEMP2, SOCS2, and DCN. Combinations or subcombinations including TJP3 are TJP3 and AP1M2; TJP3 and CGN; TJP3 and DDR1; TJP3 and EPS8L2; TJP3 and FASTKD1; TJP3 and GMIP; TJP3 and IKBKE; TJP3 and P2RX4; TJP3 and P4HB; TJP3 and PHKG2; TJP3 and PPP1R16A; TJP3 and RNF183; TJP3 and SIRT6; TJP3 and RASSF7;TJP3 and EFEMP2; TJP3 and SOCS2; TJP3 and ACAA1; or TJP3 and DCN. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of an EFEMP2 biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, SOCS2, and DCN. A preferred combination or subcombination useful for detecting endometrial cancer or an increased likelihood of endometrial cancer is EFEMP2 and P4HB; EFEMP2 and GMIP; EFEMP2 and IKBKE; FASTKD1 and EFEMP2; EFEMP2 and SOCS2; EFEMP2 and DDR1; EFEMP2 and SIRT6; EFEMP2 and PHKG2; EFEMP2, P4HB, and IKBKE; EFEMP2, IKBKE, and GMIP; EFEMP2, IKBKE, and FASTKD1; EFEMP2, GMIP, and DDR1;

EFEMP2, SIRT6, and FASTKD1; EFEMP2, IKBKE, GMIP, and P4HB; EFEMP2, P4HB, IKBKE, GMIP, and FASTKD1; EFEMP2, P4HB, SIRT6, DDR1, GMIP, and FASTKD1; EFEMP2, P4HB, SIRT6, PHKG2, GMIP, and FASTKD1; or EFEMP2, P4HB, IKBKE, GMIP, DDR1, PHKG2, SIRT6, and FASTKD1; In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of a SOCS2 biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, and DCN. A preferred combination or subcombination useful for detecting endometrial cancer or an increased likelihood of endometrial cancer is SOCS2 and P4HB; SOCS2 and GMIP; SOCS2 and IKBKE; SOCS2 and EFEMP2; FASTKD1 and SOCS2; SOCS2 and DDR1; SOCS2 and SIRT6; SOCS21 and PHKG2; SOCS2, P4HB, and IKBKE; SOCS2, GMIP, and P4HB; SOCS2, P4HB, and IKBKE; GMIP, P4HB, IKBKE, and SOCS2; SOCS2, GMIP, IKBKE, P4HB, and DDR1; or SOCS2, DDR1, FASTKD1, GMIP, IKBKE, P4HB, PHKG2, SIRT6, and EFEMP2. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or

suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In one embodiment, the invention provides a method for diagnosing endometrial cancer comprising determining the level of a DCN biomarker in combination with the level of one or more biomarkers. In a specific aspect of this embodiment the one or more biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer. In one aspect of this embodiment, the one or more biomarkers are chosen from differential diagnosis biomarkers, biomarkers useful for detecting endometrial cancer, and biomarkers useful for classifying endometrial cancer. In one aspect of this embodiment, the one or more biomarkers useful for detecting endometrial cancer are chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, and SOCS2. Combinations or subcombinations including DCN are DCN and AP1M2; DCN and CGN; DCN and DDR1; DCN and EPS8L2; DCN and FASTKD1; DCN and GMIP; DCN and IKBKE; DCN and P2RX4; DCN and P4HB; DCN and PHKG2; DCN and PPP1R16A; DCN and RNF183; DCN and SIRT6; DCN and RASSF7; DCN and EFEMP2; DCN and SOCS2; or DCN and ACAA1. In one aspect of this embodiment, the level(s) of gene expression of the biomarker is determined. In another aspect of this embodiment, the level(s) of protein expression is determined. In one aspect of this embodiment, a tumor or suspected sample is analyzed. In another aspect a fluid sample is analyzed. In another aspect of this embodiment, a sample obtained from uterine fluid is analyzed. In yet another aspect of this embodiment, a serum or blood samples is analyzed. In one aspect, the sample that is analyzed is obtained from a cell.

In a preferred aspect of the in vitro diagnostic method of the invention the levels of a combination of markers is detected where said combination comprises IKBKE and P4HB; IKBKE and SOCS2; P4HB and SOCS2; GMIP and IKBKE; GMIP and P4HB; GMIP and SOCS2; GMIP, SOCS2, and IKBKE; GMIP, SOCS2, and P4HB; GMIP,

IKBKE, and P4HB; IKBKE,P4HB, and SOCS2; GMIP, IKBKE, P4HB, and SOCS2; GMIP, SOCS2, IKBKE, and EPS8L2; GMIP, SOCS2, P4HB, and EPS8L2; GMIP, IKBKE, P4HB, and EPS8L2; IKBKE, P4HB, SOCS2, and EPS8L2; GMIP, IKBKE, P4HB, SOCS2, and DDR1; GMIP, IKBKE, P4HB, SOCS2, EPS8L2, and PPP1R16A; GMIP, IKBKE, P4HB, SOCS2, PHKG2, and RASSF7; GMIP, IKBKE, P4HB, SOCS2, EPS8L2, and DDR1; GMIP, IKBKE, P4HB, SOCS2, EPS8L2, PPP1R16A, and DDR1; DDR1, EPS8L2, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPP1R16A, RASSF7, SIRT6, TJP3, and SOCS2; or DDR1, EPS8L2, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPP1R16A, RASSF7, SIRT6, TJP3, RNF183 and SOCS2.

In another preferred aspect of the in vitro diagnostic method of the invention a the levels of a combination of markers is detected where said combination comprises GMIP, IKBKE, P4HB, SOCS2 and FASTKD1; GMIP, IKBKE, P4HB, SOCS2 and DDR1; GMIP, IKBKE, P4HB, SOCS2 and PHKG2; GMIP, IKBKE, P4HB, SOCS2 and SIRT6; GMIP, IKBKE, P4HB, SOCS2 and ACAA1; GMIP, IKBKE, P4HB, SOCS2 and EFEMP2; GMIP, IKBKE, P4HB, SOCS2 and EPS8L2; GMIP, IKBKE, P4HB, SOCS2 and P2RX4; GMIP, IKBKE, P4HB, SOCS2 and PPFIBP2; GMIP, IKBKE, P4HB, SOCS2 and PPP1R16A; GMIP, IKBKE, P4HB, SOCS2, ACAA1 and FASTKD1; GMIP, IKBKE, P4HB, SOCS2, PHKG2 and FASTKD1; GMIP, IKBKE, P4HB, SOCS2, SIRT6 and FASTKD1; ACAA1, AP1M2, EPS8L2, IKBKE, P2RX4, P4HB, PPFIBP2, PPP1R16A, SIRT6, and EFEMP2; GMIP, IKBKE, P4HB, and EFEMP2; DDR1, FASTKD1, PHKG2, SIRT6, SOCS2, GMIP, IKBKE, P4HB, and EFEMP2; DDR1, FASTKD1, PHKG2, SIRT6, GMIP, IKBKE, P4HB, and EFEMP2; or P4HB, EFEMP2, IKBKE, GMIP, and FASTKD1.

In yet another preferred aspect of the in vitro diagnostic method of the invention the levels of a combination of markers is detected where said combination comprises GMIP, IKBKE, P4HB, EFEMP2 and FASTKD1; GMIP, IKBKE, P4HB, EFEMP2and DDR1; GMIP, IKBKE, P4HB, EFEMP2 and PHKG2; GMIP, IKBKE, P4HB, EFEMP2 and SIRT6; GMIP, IKBKE, P4HB, EFEMP2 and ACAA1; GMIP, IKBKE, P4HB, SOCS2 and EFEMP2; GMIP, IKBKE, P4HB, EFEMP2 and EPS8L2; GMIP, IKBKE, P4HB, EFEMP2 and P2RX4; GMIP, IKBKE, P4HB, EFEMP2 and PPFIBP2; GMIP, IKBKE, P4HB, EFEMP2and PPP1R16A; GMIP, IKBKE, P4HB, EFEMP2,

ACAA1 and FASTKD1; GMIP, IKBKE, P4HB, EFEMP2, PHKG2 and FASTKD1; or GMIP, IKBKE, P4HB, EFEMP2, SIRT6 and FASTKD1.

Auxiliary Biomarkers

"Auxiliary biomarkers" refer to biomarkers that can be used in conjunction with the one or more biomarkers of Table 1. The auxiliary biomarkers can be used in the methods of the invention to provide further characterization of a disease or condition a patient may have.

Differential diagnosis biomarkers are useful for distinguishing between diseases that may present with similar clinical symptoms. For example, a patient may have symptoms of endometrial cancer (*e.g.*, vaginal bleeding and/or pelvic pain) but these symptoms can also be caused by different diseases (*e.g.*, ovarian cancer). Therefore, the differential diagnosis biomarkers provide information for characterization a disease. Examples of diseases that may present similar symptoms as endometrial cancer include uterine fibroids, endometriosis, endometrial hyperplasia, uterine sarcoma - another type of uterus cancer, uterine leiomyomas, endometrial polyp (type of polyp), cervical cancer, atrophic endometrium, adenomyosis, atrophic vaginitis, ovarian tumour, leiomyosarcoma, and endometrial proliferation.

According to the inventors' finding that the level of biomarkers in primary endometrial cancer tissue can be correlated to their levels in uterine fluid, it is contemplated that uterine fluid samples can be used for differential diagnosis of conditions other than endometrial cancer. Thus, in one aspect, the invention provides a method for the differential diagnosis of endometrial cancer by obtaining a uterine fluid sample from a patient and determining the level of one or more biomarkers that are capable of distinguishing endometrial cancer from non-endometrial cancer. Differential diagnosis biomarkers for endometriosis are useful for distinguishing endometriosis from endometrial cancer. Differential diagnosis biomarkers for ovarian cancer are useful for distinguishing ovarian cancer from endometrial cancer. Examples of biomarkers useful for distinguishing endometrial cancer from ovarian cancer include, but are not limited to, those described in Yurkovetsky *et al.* (*Gyn. Onc.* (2007) 107:58-65) where they reported a five-

biomarker panel of prolactin, GH, eotaxin, E-selectin, and TSH for discriminating endometrial cancer from ovarian and breast cancer.

A number of endometrial cancer biomarkers have been identified. CA 125 correlates with tumor size and stage and is an independent predictor of the extrauterine spread. Serum markers for the detection of uterine cancer have been reported in the literature.

Prognosis biomarkers: Elevated levels of CA 125, CA 15-3, and CA 19-9 are associated with shorter survival time. They found serum CA 125 CA 15-3 and CEA are higher in patients with Stage III disease as compared to stage I. Another group of prognostic markers include estrogen receptor, progesterone receptor, and HER2.

Biomarkers for classifying endometrial cancer include those for estimating stage of the cancer, cell-type, and/or type of endometrial cancer (*e.g.*, type I verus type II). Examples of biomarkers for classifying endometrial cancer include, but are not limited to, those described in Sugiyama *et al.* (2003) *Clin. Can. Res.* 9:5589-5600. Genes showing higher expression in type I as compared to type II include MMP11, RHOG, and platelet-derived growth factor B subunit precursor, STAT2, octamer-binding transcription factor 1, and GATA-6, growth factor VEGF-C precursor, caspase (caspase 1/IL-1 β converting enzyme). Genes showing higher expression in type II as compared to type I included PIRIN, EGR1, STAT1, IFN regulatory factor 1, and KRAS. Konecny *et al.* ((2009) *British Journal of Cancer* 100, 89–95) report that the rate HER2 gene amplification as measured by fluorescence in situ hybridization was greater in type II cancers whereas EGFR expression as measured by IHC techniques was significantly lower in type II cancers. Deng *et al.* ((2005) *Clin. Can. Res.* vol. 11, no 23:8258-8264) report that EIG121 is a marker for type I estrogen associated cancers. Markers for classifying endometrial cancer can also be used to distinguish different histological types of endometrial cancer like serous and endometrioid cancers. Risinger *et al.* ((2003) *Canc. Res.* 63:6-11) identified biomarkers that could distinguish papillary serous cancers from endometrioid cancers. For example AGR2, TFF3, DUSP6, IGF2, FOLR1, and UCHL1 were found to be differentially expressed between papillary serous and endometrioid cancers as found by microarray and validated by RT-PCR. AGR2, TFF3, DUSP6 were found to

be upregulated in endometrioid type cancers whereas IGF2, FOLR1 and UCHL1 were found to be upregulated in papillary serous cancers.

According to the inventor's finding that the level of biomarkers in primary endometrial cancer tissue can be correlated to their levels in uterine fluid, it is contemplated that uterine fluid samples can be used to classify the type of endometrial cancer. Classifying the type of endometrial cancer can refer to distinguishing type I and type II cancers. Classifying the type of endometrial cancer can also refer to determining the histological type and/or sub-type of endometrial cancer. Thus, in one aspect, the invention provides a method for classifying an endometrial cancer by obtaining a uterine fluid sample from a patient and determining the level of one or more biomarkers that are capable of classifying an endometrial cancer.

"Auxiliary biomarkers for detecting endometrial cancer" refer to biomarkers that can be used in addition to the biomarkers of Table 1 for the diagnosis of endometrial cancer and/or an increased risk of having endometrial cancer: Yurkovetsky *et al.* (*Gyn. Onc.* (2007) 107:58-65) identified that prolactin is a serum biomarker with sensitivity and specificity for endometrial cancer. Yurkovetsky *et al.* found that prolactin, GH, eotaxin, E-selectin, and TSH were useful markers for diagnosising endometrial cancer.

In some aspects of these embodiments, one or more auxiliary biomarkers are examined for alterations in a sample from a patient suspected of having endometrial cancer. In a specific aspect, the auxiliary biomarkers are chosen from serum biomarkers. In a more specific aspect the serum biomarkers are one or more proteins chosen from CA 125, CA 15-3, CA 19-9, CEA, AFP, CA 72-4, VEGF, bFGF, IGFBPI, HGF, ErbB2, EGFR, TGF α, Fas, FasL, Cyfra 21-1, MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12, MMP-13, tPAI, sICAM, sVCAM, sE-selectin, adiponectin, resistin, IL-6, IL-8, TNF α, TNFR I, G-CSF, CD40L, IL-2R, IP-10, MCP-1, MIP-1α, MIP-1β, MIF, eotaxin, RANTES, FSH, LH, TSH, ACTH, Prolactin, GH, βHCG, hK8, hK10, active PAI-1, ULBP-1, ULBP-2, ULBP-3, MICA, angiostatin, SCC, serum amyloid A, TTR, S100, mesothelin, and myeloperoxidase (MPO). In a more specific aspect, the serum biomarkers are chosen from prolactin, GH, eotaxin, e-selectin and FSH. In an even more specific aspect, the serum

biomarker is prolactin. In some aspects, the auxiliary biomarker(s) can be examined in uterine aspirates (e.g., mRNA level and/or protein levels).

Samples

The invention, in some embodiments, relates to characterizing one or more biomarkers of Table 1, from a sample from a patient suspected of having endometrial cancer or desiring screening for cancer. Examples of such samples that can be used in the invention are fluid, tissue samples, and/or cells. Depending on the specific marker, the methods used for characterizing the biomarkers of the invention can include *e.g.*, examining the DNA copy number of the gene corresponding to the biomarker, detecting the protein related to the biomarker, determining the mRNA expression levels of the biomarker, *etc.* The invention is useful for a number of applications including diagnosis, prognosis, staging, predicting response to therapy. The inventors have found evidence of differential expression of the biomarkers of Table 1 in a number of different samples including mRNA in primary tumor, protein in primary tumor, and mRNA in aspirates, and protein in aspirates. The biomarkers of Table 1 include those that are overexpressed in samples from endometrial cancer patients as compared to normal levels. Additionally some of the biomarkers of Table 1 are underexpressed in samples from endometrial cancer patients as compared to normal levels

The invention, in some embodiments, relates to characterizing one or more of the biomarkers of Table 1, from a patient sample (*e.g.*, tumor, cancer cell, sample suspected of being cancer, body fluid (*e.g.*, uterine fluid), blood, serum, plasma, and vaginal blood/discharge) and/or from a "normal" cell, from an individual (or alternatively a control value can be used in lieu of the normal value from the cell).

In one aspect, the sample to be analyzed is obtained from a patient that has risk factors for endometrial cancer. Risk factors for endometrial cancer include, but are not limited to, having Lynch Syndrome, being genetically related to a person having Lynch Syndrome, obese, taking estrogen-alone hormone replacement therapy, and prior treatment with tamixofen.

In one aspect of this embodiment, the sample is analyzed is a uterine fluid sample. In one aspect, the sample is that is used is obtained by using a soft, straw-like device (pipelle) to suction off a small sample of lining from the uterus. In one aspect, the sample is obtained by using a sharp-edged tool called a curette by scraping a small sample and collect it with a syringe or suction (*e.g.*, dilation and curettage). In one aspect, the sample is obtained by using an electronic suction device (*e.g.*, Vabra aspiration). In one aspect, the sample is obtained by using a spray of liquid (jet irrigation) to wash off some of the tissue that lines the uterus. In some aspects, a brush may be used to remove some of the lining before the washing is done.

In one embodiment, the sample for analyzing the biomarkers is obtained using a syringe or pipelle type device. In one embodiment, the device for collection of the uterine fluid sample from an internal cavity (*e.g.*, uterus) of a patient, comprises a barrel having an opening at one end thereof, a plunger operable axially within the barrel, the barrel and the plunger defining a fluid chamber having a volume which varies on axial movement of the plunger within the barrel, and a hollow, elongate tube extending from the fluid chamber through the opening in the barrel, the tube being in operative engagement with the plunger for axial movement to extend and retract the tube within respect to the barrel on axial movement of the plunger, and the tube being in fluid communication with the fluid chamber to provide a fluid flow path to and from the fluid chamber through the hollow tube. In one aspect of this embodiment, after the sample is obtained using the device, it is stored in an agent that preserves the integrity of the biomarkers of interest. For example, when the biomarker being analyzed is a nucleic acid like RNA, the sample can be stored in an agent that prevents degradation of RNA molecules in the sample, or if the biomarker is a protein the sample can be stored e.g., in an agent that preserves protein. Example of agents that prevent degradation of RNA molecules in a sample are RNase inhibitors (*e.g.*, RNeasy from Qiagen, SUPERase•In™ from Ambion or ScriptGuard™ RNase Inhibitor from epicenter biotechnologies) or molecules that precipitate RNA out of biological solutions (*e.g.*, triphenylmethane dyes (*e.g.*, methyl green, crystal violet, and pararosaniline), cresyl violet, polyamines, and cobalt ions). Example of agents that prevent the degradation of protein is protease inhibitors (*e.g.*, PMSF (phenylmethanesulfonyl fluoride, Complete protease inhibitor cocktail from Roche, or Pepstatin) or agents that fix tissues (formalin).

Thus the invention provides in one embodiment, an in vitro diagnostic method for endometrial cancer comprising obtaining a uterine fluid aspirate sample from a patient having a symptom or risk factor for endometrial cancer and determining the level of from 1 to 100 biomarkers markers that are differentially expressed in endometrial cancer as compared to control values representative of individuals not affected by endometrial cancer, wherein (1) if the levels of 1-100 biomarkers are upregulated in the endometrial aspirate sample in the patient and in the control value then the patient has an increased likelihood of having endometrial cancer and wherein (2) if the level of the 1-100 biomarkers are downregulated in the aspirate sample and then the patient has an increased likelihood of having endometrial cancer. The biomarkers of this aspect can be any biomarkers that are differentially represented in endometrial cancer patient samples compared to samples from patients not affected with endometrial cancer and are useful for diagnosis of endometrial cancer or an increased likelihood of endometrial cancer. Preferred biomarkers are the 1-20 described herein in Table 1.

Methods of Detecting Biomarkers

The invention relates to the identification of biomarkers that are useful for diagnosing endometrial cancer. The invention provides methods for detecting one or more of the biomarkers of Table 1 for diagnosing endometrial cancer. The method of the invention can be used to detect one or more proteins corresponding to the biomarkers of Table 1 for diagnosing endometrial cancer. The method of the invention can be used to detect one or more mRNA corresponding to the biomarkers of Table 1 for diagnosing endometrial cancer. The biomarkers can be detected in a sample obtained from a patient *e.g.*, a sample obtained from uterine tissue, uterine fluid, or blood.

In some embodiments, the method of the invention involves obtaining a sample and determining the level of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, of the biomarkers of Table 1 in the sample. In a specific aspect, the method involves determining the level of 2 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of 3 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of 4

or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of 5 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of 6 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of 7 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of 8 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of 9 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of 10 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of 11 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of 12 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of 13 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of 14 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of 15 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of 20 of the biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of from 2 to 20 of the biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of from 3 to 20 of the biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of from 3 to 17 of the biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of from 4 to 17 of the biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of from 5 to 17 of the biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of from 10 to 17 of the biomarkers listed in Table 1. In one aspect of this embodiment, the method involves determining the level of less than 500 different biomarkers. In one aspect of this embodiment, the method involves determining the level of less than 250 different biomarkers. In one aspect of this embodiment, the method involves determining the level of less than 100 different biomarkers. In one aspect of this embodiment, the method involves determining the level of less than 50 different biomarkers. Increased levels of one or more biomarkers of Table 1 that are overexpressed and/or decreased eels of one or more biomarkers of Table 1 that are underexpressed indicate that there is an increased likelihood of endometrial cancer.

It is understood that in some aspects of this embodiment, the biomarkers analyzed include more than those listed in Table 1.

In some aspects of these embodiments, the method involves obtaining a sample and determining the level of mRNA of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, of the biomarkers of Table 1 in the sample. In a specific aspect, the method involves determining the level of mRNA of 2 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of 3 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of 4 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of 5 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of 6 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of 7 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of 8 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of 9 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of 10 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of 11 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of 12 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of 13 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of 14 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of 15 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of 20 of the biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of from 2 to 20 of the biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of from 3 to 20 of the biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of from 3 to 17 of the biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of from 4 to 17 of the biomarkers listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of from 5 to 17 of the biomarkers

listed in Table 1. In a specific aspect, the method involves determining the level of mRNA of from 10 to 20 of the biomarkers listed in Table 1. In one aspect of this embodiment, the method involves determining the level of mRNA of less than 500 different biomarkers. In one aspect of this embodiment, the method involves determining the level of mRNA of less than 250 different biomarkers. In one aspect of this embodiment, the method involves determining the level of mRNA of less than 100 different biomarkers. In one aspect of this embodiment, the method involves determining the level of mRNA of less than 50 different biomarkers. Increased levels of one or more mRNAs corresponding to the biomarkers of Table 1 that are overexpressed and/or decreased levels of one or more biomarkers of Table 1 that are underexpressed indicate that there is an increased likelihood of endometrial cancer. It is understood that in some aspects of this embodiment, the biomarkers analyzed include more than those listed in Table 1.

In some aspects of these embodiments, the method involves obtaining a sample and determining the protein level of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, of the biomarkers of Table 1 in the sample. In a specific aspect, the method involves determining the protein level of 2 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of 3 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of 4 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of 5 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of 6 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of 7 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of 8 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of 9 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of 10 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of 11 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of 12 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of 13 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining

the protein level of 14 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of 15 or more biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of 20 of the biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of from 2 to 20 of the biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of from 3 to 20 of the biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of from 3 to 17 of the biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of from 4 to 17 of the biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of from 5 to 17 of the biomarkers listed in Table 1. In a specific aspect, the method involves determining the protein level of from 10 to 17 of the biomarkers listed in Table 1. In one aspect of this embodiment, the method involves determining the protein level of less than 500 different biomarkers. In one aspect of this embodiment, the method involves determining the protein level of less than 250 different biomarkers. In one aspect of this embodiment, the method involves determining the protein level of less than 100 different biomarkers. In one aspect of this embodiment, the method involves determining the protein level of less than 50 different biomarkers. In one aspect of this embodiment, the method involves determining the protein level of from 1 to 10 different biomarkers. Increased levels of one or more proteins corresponding to the biomarkers of Table 1 indicate that there is an increased likelihood of endometrial cancer. It is understood that in some aspects of this embodiment, the biomarkers analyzed include more than those listed in Table 1.

In one embodiment, the invention provides a method for detecting one or more protein biomarkers in serum, blood, and/or plasma. In a specific aspect of this embodiment, the one or more biomarkers are chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN. In a more specific aspect, the one or more biomarkers are chosen from IKBKE, P4HB, SOCS2, GMIP, DDR1, EPS8L2, PPP1R16A, P2RX4, PHKG2, RASSF7, SIRT6, TJP3, AP1M2, RNF183, and DCN. In another specific aspect of this embodiment, the method comprises detecting the level of IKBKE. In another specific aspect of

this embodiment, the method comprises detecting the level of P4HB. In another specific aspect of this embodiment, the method comprises detecting the level of SOCS2. In another specific aspect of this embodiment, the method comprises detecting the level of GMIP. In another specific aspect of this embodiment, the method comprises detecting the level of AP1M2. In another specific aspect of this embodiment, the method comprises detecting the level of EPS8L2. In another specific aspect of this embodiment, the method comprises detecting the level of DDR1. In another specific aspect of this embodiment, the method comprises detecting the level of CGN. In another specific aspect of this embodiment, the method comprises detecting the level of TJP3.

In some aspects of these embodiments, the method involves determining the level of 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, 30, 35, 40, or 50 or more of biomarkers in addition to one or more of those listed in Table 1. These markers can be those whose expression levels are known to be altered in patients having endometrial cancer. Alternatively, the additional biomarkers can be used for differential diagnosis of other diseases (*e.g.*, endometriosis, ovarian cancer, and fibroids), for classifying the type of cancer, prognostic information and/or for providing information for selecting a therapy. In a specific aspect of this embodiment, the additional biomarkers are analyzed in uterine fluid samples.

In a specific aspect of the invention, the one or more biomarkers listed in Table 1 are detected on an array having different probes on the array which are oligonucleotides having from about 5 to 200 bases in length. In another specific aspect, each of the different probes on the array is an oligonucleotide having from about 15 to 200, 15 to 150, 15 to 100, 15 to 75, 15 to 60, or 20 to 55 bases in length. In one aspect, the array has probes to 2 or more biomarkers listed in Table 1. In one aspect, the array has probes to 3 or more biomarkers listed in Table 1. In one aspect, the array has probes to 4 or more biomarkers listed in Table 1. In one aspect, the array has probes to 5 or more biomarkers listed in Table 1. In one aspect, the array has probes to 6 or more biomarkers listed in Table 1. In one aspect, the array has probes to 7 or more biomarkers listed in Table 1. In one aspect, the array has probes to less than 1000

different genes. In one aspect, the array has probes to less than 500 different genes. In one aspect, the array has probes to less than 100 different genes.

In some aspects of these embodiments, the copy number of the one or more biomarkers listed in Table 1 is determined. In another aspect of this embodiment, the copy number profile of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 of the biomarkers of Table 1 (or loci corresponding to the biomarker) are determined for detecting endometrial cancer.

In one aspect, the invention provides primers that can hybridize to a nucleic acid corresponding to a biomarker listed in Table 1 and be used to amplify a nucleic acid or fragment thereof corresponding to said biomarker for diagnosing endometrial cancer according to the methods of the invention. In a more specific aspect, the primers are designed to amplify one or more exons of the biomarker. In another aspect, the primers are designed to amplify a fragment of one or more exons of the biomarker. In one aspect, the primers are suitable for RT-PCR analysis. In one aspect, the method of the invention involves the use of primers to amplify a nucleic acid corresponding to a biomarker of Table 1, and detecting the amplification product with a probe to the amplification product. In another aspect, the method of the invention involves the use of primers to amplify a nucleic acid corresponding to a biomarker of Table 1, and detecting the amplification product with a dye that allows for quantification of the amplification product.

In one aspect, the invention provides probes to the biomarkers of Table 1 for detecting a nucleic acid or fragment thereof corresponding to the biomarker. The probes can be used in the methods of the invention *e.g.*, for diagnosing endometrial cancer. In a specific aspect, the probe is for the biomarker mRNA or a nucleic acid, is obtained from the mRNA corresponding to the biomarker. In a specific aspect, the probe corresponds to two contiguous exons of the biomarker of Table 1, (or fragments of two or more contiguous exons). In a specific aspect, the probe corresponds to an exon of the biomarker or a fragment thereof. In a specific aspect, the probe corresponds to at least a portion of the promoter region of the biomarker and at least a portion of exon 1 of the biomarker.

In one aspect of the invention, a multiplex PCR assay is used to assess the levels of from 2 to 20 of the biomarkers of Table 1 to detect the presence or absence of endometrial cancer. In a more specific aspect, the levels of from 3 to 20 biomarkers of Table 1 are assessed by multiplex PCR. In a more specific aspect, the levels of from 4 to 20 biomarkers of Table 1 are assessed by multiplex PCR. In a more specific aspect, the levels of from 5 to 20 biomarkers of Table 1 are assessed by multiplex PCR. In a more specific aspect, the levels of from 6 to 20 biomarkers of Table 1 are assessed by multiplex PCR. In a more specific aspect, the levels of from 7 to 20 biomarkers of Table 1 are assessed by multiplex PCR. In a more specific aspect, the levels of from 8 to 20 or more biomarkers of Table 1 are assessed by multiplex PCR. In a more specific aspect, the levels of from 9 to 20 biomarkers of Table 1 are assessed by multiplex PCR. In a more specific aspect, the levels of from 10 to 20 or more biomarkers of Table 1 are assessed by multiplex PCR. In a more specific aspect, the levels of from 15 to 20 biomarkers of Table 1 are assessed by multiplex PCR. In a more specific aspect, the levels of from 20 of the biomarkers of Table 1 are assessed by multiplex PCR.

Quantitative PCR

In some embodiments, the invention relies on quantitative PCR to determine the level of one or more biomarkers of Table 1. In a specific aspect the quantitative PCR method is quantitative RT-PCR. The methods can be semi-quantitative or fully quantitative.

The methods of the invention for detecting the biomarkers of the invention can comprise competitive quantitative PCR or real-time quantitative PCR which both estimate target gene concentration in a sample by comparison with standard curves constructed from amplifications of serial dilutions of standard DNA. Quantitative PCR or real-time quantitative PCR differ substantially in how the standard curves are generated. In competitive QPCR, an internal competitor DNA is added at a known concentration to both serially diluted standard samples and unknown (*e.g.*, obtained from a patient) samples. After coamplification, ratios of the internal competitor and target PCR products are calculated for both standard dilutions and unknown samples, and a standard curve is constructed that plots competitor-target PCR product ratios against the initial target DNA concentration of the standard dilutions. Given equal

amplification efficiency of competitor and target DNA, the concentration of the latter in patient samples can be extrapolated from this standard curve.

In real-time QPCR, the accumulation of amplification product is measured continuously in both standard dilutions of target DNA and samples containing unknown amounts of target DNA. A standard curve is constructed by correlating initial template concentration in the standard samples with the number of PCR cycles (C_t) necessary to produce a specific threshold concentration of product. In the test samples, target PCR product accumulation is measured after the same C_t, which allows interpolation of target DNA concentration from the standard curve. Although real-time QPCR permits more rapid and facile measurement of target DNA during routine analyses, competitive QPCR remains an important alternative for target quantification in environmental samples. The coamplification of a known amount of competitor DNA with target DNA is an intuitive way to correct for sample-to-sample variation of amplification efficiency due to the presence of inhibitory substrates and large amounts of background DNA that are obviously absent from the standard dilutions.

Another type of QPCR is applied quantitatively PCR. Often termed "relative quantitative PCR," this method determines the relative concentrations of specific nucleic acids. In the context of the present invention, RT-PCR is performed on mRNA species isolated from patients. By determining that the concentration of a specific mRNA species, it can be determined if the gene encoding the specific mRNA species is differentially expressed.

In one embodiment, the invention provides a method comprising, obtaining a test sample from cells, tissue, or fluid of a patient; detecting the level of one or more of the biomarkers of Table 1 and comparing the level of the biomarker(s) in the sample to the level expected for a normal sample (or control value).

In one embodiment, the invention provides a method comprising, obtaining a suspected tumor sample from a patient; detecting the level of one or more biomarkers listed in Table 1 and comparing the level of biomarker(s) in the sample to the level expected for a normal unaffected sample (or control value).

In one embodiment, the invention provides a method comprising, obtaining a sample from a patient comprising a cell; detecting the level of one or more of the biomarkers of Table 1 in said cell and comparing the level of the biomarker(s) in the cell to the level expected for a normal unaffected cell (or control value).

In one embodiment, the invention provides a method comprising, obtaining a test sample from a fluid of a patient; detecting the level of one or more of the biomarkers of Table 1 and comparing the level of the biomarker(s) in the sample to the level expected for a normal unaffected sample. In one aspect of this embodiment, the fluid is uterine fluid obtained by aspiration. In one aspect of this embodiment, the fluid is uterine fluid obtained by aspiration with a cornier pipelle. In one aspect of this embodiment, the fluid is uterine fluid. In another aspect of this embodiment, the fluid is vaginal discharge. In one embodiment, the invention provides a method comprising, obtaining a test sample from a blood or serum sample from a patient; and detecting the level of one or more of the biomarkers of Table 1 and comparing the level of the biomarker(s) in the sample to the level expected for a normal unaffected sample.

In one embodiment, the invention provides a method comprising, obtaining a test sample from the urine of a patient; detecting the level of one or more of the biomarkers of Table 1 and comparing the level of the biomarkers in the urine to the level expected for a control value.

In one embodiment, the invention provides a method comprising, obtaining a test sample from the uterus of a patient using a brush; and detecting the level of one or more of the biomarkers of Table 1 and comparing the level of the biomarkers in the sample to the level expected for a normal sample.

The presence of increased levels of one or more of the biomarkers of Table 1 can indicate endometrial cancer or a precancerous condition in the tissue *e.g.*, endometrial hyperplasia. In one aspect of this embodiment, the method involves identifying a patient in need of analysis of one or more biomarkers of Table 1.

In another aspect of this embodiment, the present invention provides methods for diagnosing or predicting a endometrial cancer. The method of this aspect can comprise (1) obtaining a test sample from cells, tissue, and/or fluid (2) obtaining a control sample from cells, tissue, or fluid that is normal, or obtaining a normal control value, and (3) detecting or measuring in both the test sample and the control sample the level of one or more mRNA transcripts corresponding to one or more of the biomarkers of Table 1. If the level of the one or more transcripts is higher in the test sample than that in the control sample, this indicates endometrial cancer (and/or and increased risk of having endometrial cancer) or a precancerous condition in the test sample cells or tissue. In another aspect the control sample may be obtained from a different individual or be a normalized value based on baseline data obtained from a population. In one aspect of this embodiment, the method involves identifying a patient in need of analysis of one or more of the biomarkers of Table 1. In one aspect, the patient in need of analysis of one or more of the biomarkers of Table 1 is one that is at risk of having endometrial cancer, is suspected of having endometrial cancer, or and/or is undergoing screening.

In yet another aspect of this embodiment, the method comprises, obtaining a test sample from cells, tissue, or fluid; detecting the number of DNA copies of one or more of the biomarkers of Table 1 ((*e.g.*, per cell) in the sample; and comparing the number of DNA copies detected (for example, quantitatively and/or qualitatively) in the sample to a control sample or a known value (or a control value), thereby determining whether the copy number of the biomarker(s) is amplified in the test sample. In one aspect of this embodiment, the method involves identifying a patient in need of analysis of one or more of the biomarkers of Table 1. In one aspect, the patient in need of analysis of one or more of the biomarkers of Table 1 is one that is at risk of having endometrial cancer, is suspected of having endometrial cancer, or and/or is undergoing screening.

In yet another aspect of this embodiment, the method comprises (1) obtaining a test sample from cells, tissue, or fluid; contacting the sample with an antibody to a protein or fragment thereof corresponding to one or more of the biomarkers of Table 1, and detecting in the test sample, the level of the biomarker(s), wherein an increased level the biomarker(s), as compared to a control value indicates the patient

may have a precancerous or a cancerous condition. In another aspect, the control value may be obtained from a different individual or be a normalized value based on baseline data obtained from a population. Alternatively, a given level of a biomarker, representative of the endometrial cancer-free population, that has been previously established based on measurements from normal, endometrial cancer-free patients, can be used as a control value. A control data point from a reference database, based on data obtained from control samples representative of an endometrial cancer-free population, also can be used as a control value. In one aspect of this embodiment, the method involves identifying a patient in need of analysis of one or more of the biomarkers of Table 1. In one aspect, the patient in need of analysis of the biomarker(s) is one that is at risk of having endometrial cancer, is suspected of having endometrial cancer, or and/or is undergoing screening.

In some embodiments, the method of the invention involves comparing the expression of a biomarker of the invention to an endogenous biomarker. For example, the expression level of one or more of the biomarkers listed in Table 1 are normalized to the level of expression of an endogenous biomarker. Thus, in one specific aspect, the endogenous biomarker is chosen from POLR2A, B2M, PFN1, HMBS, G6PD, and PABPN1. The ENSMBL reference numbers are given below for these endogenous biomarkers.

Name	Gene	Transcript	Protein
POLR2A	ENSG00000181222	ENST00000322644	ENSP00000314949
B2M	ENSG00000166710	ENST00000349264	ENSP00000340858
PFN1	ENSG00000108518	ENST00000225655	ENSP00000225655
HMBS	ENSG00000149397	ENST00000278715	ENSP00000278715
G6PD	ENSG00000160211	ENST00000393562	ENSP00000377192
PABPN1	ENSG00000100836	ENST00000216727	ENSP00000216727

Diagnostic and Prognostic Reagents

The invention provides reagents for detecting the biomarkers of the invention (*e.g.*, those in Table 1). The reagents are useful for detecting protein and nucleic acid levels of the biomarkers of Table 1 for detecting and/or diagnosing endometrial cancer. The reagents below can be used for detecting combinations of the biomarkers to diagnose endometrial cancer. Specific examples of nucleic acids,

probes, primers, etc. related to each of the individual biomarkers are given in the Examples.

In one embodiment, the invention provides an ACAA1 nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying an ACAA1 nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to an ACAA1 nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to an ACAA1 protein for detecting endometrial cancer. In a related aspect the invention provides an ACAA1 polypeptide for generating an antibody. In yet another related aspect, the invention provides an ACAA1 polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides an AP1M2 nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying an AP1M2 nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to an AP1M2 nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to an AP1M2 protein for detecting endometrial cancer. In a related aspect the invention provides an AP1M2 polypeptide for generating an antibody. In yet another related aspect, the invention provides an AP1M2 polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides a CGN nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying a CGN nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to a CGN nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to a CGN protein for detecting endometrial cancer. In a related aspect the invention provides a CGN polypeptide for generating an antibody. In yet another related aspect, the invention provides a CGN polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides a DDR1 nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying a DDR1 nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to a DDR1 nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to a DDR1 protein for detecting endometrial cancer. In a related aspect the invention provides a DDR1 polypeptide for generating an antibody. In yet another related aspect, the invention provides a DDR1 polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides an EPS8L2 nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying an EPS8L2 nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to an EPS8L2 nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to an EPS8L2 protein for detecting endometrial cancer. In a related aspect the invention provides an EPS8L2 polypeptide for generating an antibody. In yet another related aspect, the invention provides an EPS8L2 polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides a FASTKD1 nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying a FASTKD1 nucleic acid for detecting endometrial cancer. In another

related aspect the invention provides a probe that can hybridize to a FASTKD1 nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to a FASTKD1 protein for detecting endometrial cancer. In a related aspect the invention provides a FASTKD1 polypeptide for generating an antibody. In yet another related aspect, the invention provides a FASTKD1 polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides a GMIP nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying a GMIP nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to a GMIP nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to a GMIP protein for detecting endometrial cancer. In a related aspect the invention provides a GMIP polypeptide for generating an antibody. In yet another related aspect, the invention provides a GMIP polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides an IKBKE nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying an IKBKE nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to an IKBKE nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to an IKBKE protein for detecting endometrial cancer. In a related aspect the invention provides an IKBKE polypeptide for generating an antibody. In yet another related aspect, the invention provides an IKBKE polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides a P2RX4 nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying a P2RX4 nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to a P2RX4 nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to a P2RX4 protein for detecting endometrial cancer. In a related aspect the invention provides a P2RX4 polypeptide for generating an antibody. In yet another related aspect, the invention provides a P2RX4 polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides a P4HB nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying a P4HB nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to a P4HB nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to a P4HB protein for detecting endometrial cancer. In a related aspect the invention provides a P4HB polypeptide for generating an antibody. In yet another related aspect, the invention provides a P4HB polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides a PHKG2 nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying a PHKG2 nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to a PHKG2 nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to a PHKG2 protein for detecting endometrial cancer. In a related aspect the invention provides a PHKG2 polypeptide for generating an antibody. In

yet another related aspect, the invention provides a PHKG2 polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides a PPFIBP2 nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying a PPFIBP2 nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to a PPFIBP2 nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to a PPFIBP2 protein for detecting endometrial cancer. In a related aspect the invention provides a PPFIBP2 polypeptide for generating an antibody. In yet another related aspect, the invention provides a PPFIBP2 polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides a PPP1R16A nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying a PPP1R16A nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to a PPP1R16A nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to a PPP1R16A protein for detecting endometrial cancer. In a related aspect the invention provides a PPP1R16A polypeptide for generating an antibody. In yet another related aspect, the invention provides a PPP1R16A polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides a RASSF7 nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying a RASSF7 nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to a RASSF7 nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to a RASSF7 protein for detecting endometrial cancer. In a related aspect the invention provides a RASSF7 polypeptide for generating an antibody. In yet another related aspect, the invention provides a RASSF7 polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides a RNF183 nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying a RNF183 nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to a RNF183 nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to a RNF183 protein for detecting endometrial cancer. In a related aspect the invention provides a RNF183 polypeptide for generating an antibody. In yet another related aspect, the invention provides a RNF183 polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides a SIRT6 nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying a SIRT6 nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to a SIRT6 nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to a SIRT6 protein for detecting endometrial cancer. In a related aspect the invention provides a SIRT6 polypeptide for generating an antibody. In yet another related aspect, the invention provides a SIRT6 polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides a TJP3 nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying a TJP3 nucleic acid for detecting endometrial cancer. In another related

aspect the invention provides a probe that can hybridize to a TJP3 nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to a TJP3 protein for detecting endometrial cancer. In a related aspect the invention provides a TJP3 polypeptide for generating an antibody. In yet another related aspect, the invention provides a TJP3 polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides an EFEMP2 nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying an EFEMP2 nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to an EFEMP2 nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to an EFEMP2 protein for detecting endometrial cancer. In a related aspect the invention provides an EFEMP2 polypeptide for generating an antibody. In yet another related aspect, the invention provides an EFEMP2 polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides a SOCS2 nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying a SOCS2 nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to a SOCS2 nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to a SOCS2 protein for detecting endometrial cancer. In a related aspect the invention provides a SOCS2 polypeptide for generating an antibody. In yet another related aspect, the invention provides a SOCS2 polypeptide for generating an immune response against the marker.

In one embodiment, the invention provides a DCN nucleic acid for detecting endometrial cancer. In a related aspect, the invention provides primers for amplifying a DCN nucleic acid for detecting endometrial cancer. In another related aspect the invention provides a probe that can hybridize to a DCN nucleic acid for detecting endometrial cancer.

In another related aspect, the invention provides an antibody that binds immunologically to a DCN protein for detecting endometrial cancer. In a related aspect the invention provides a DCN polypeptide for generating an antibody. In yet another related aspect, the invention provides a DCN polypeptide for generating an immune response against the marker.

Kits

The invention also provides kits for detecting one or more of the biomarkers of Table 1. In one embodiment, the kit is useful for detecting and/or diagnosing a gynecological cancer. In another embodiment, the kit is useful for detecting and/or diagnosing endometrial cancer. In one aspect, the kit contains reagents for detecting CGN. In one aspect, the kit contains means for detecting CGN. In one aspect, the kit contains reagents for detecting AP1M2. In one aspect, the kit contains means for detecting AP1M2. In one aspect, the kit contains reagents for detecting EPS8L2. In one aspect, the kit contains means for detecting EPS8L2. In one aspect, the kit contains reagents for detecting IKBKE. In one aspect, the kit contains means for detecting IKBKE. In one aspect, the kit contains reagents for detecting PPP1R16A. In one aspect, the kit contains means for detecting PPP1R16A. In one aspect, the kit contains reagents for detecting RASSF7. In one aspect, the kit contains means for detecting RASSF7. In one aspect, the kit contains reagents for detecting TJP3. In one aspect, the kit contains means for detecting TJP3. In one aspect, the kit contains reagents for detecting P2RX4. In one aspect, the kit contains means for detecting P2RX4. In one aspect, the kit contains reagents for detecting RNF183. In one aspect, the kit contains means for detecting RNF183. In one aspect, the kit contains reagents for detecting GMIP. In one aspect, the kit contains means for detecting GMIP. In one aspect, the kit contains reagents for detecting PHKG2. In one aspect, the kit contains means for detecting PHKG2. In one aspect, the kit contains reagents for detecting P4HB. In one aspect, the kit contains means for detecting P4HB. In

one aspect, the kit contains reagents for detecting PPFIBP2. In one aspect, the kit contains means for detecting PPFIBP2. In one aspect, the kit contains reagents for detecting FASTKD1. In one aspect, the kit contains means for detecting FASTKD1. In one aspect, the kit contains reagents for detecting DDR1. In one aspect, the kit contains means for detecting DDR1. In one aspect, the kit contains reagents for detecting SIRT6. In one aspect, the kit contains means for detecting SIRT6. In one aspect, the kit contains reagents for detecting ACAA1. In one aspect, the kit contains means for detecting ACAA1. In one aspect, the kit contains reagents for detecting DCN. In one aspect, the kit contains means for detecting DCN. In one aspect, the kit contains reagents for detecting SOCS2. In one aspect, the kit contains means for detecting SOCS2. In one aspect, the kit contains reagents for detecting EFEMP2. In one aspect, the kit contains means for detecting EFEMP2.

In one aspect, the kit contains reagents for detecting from 2 to 20 of the biomarkers of Table 1. In one aspect, the kit contains means for detecting from 2 to 20 of the biomarkers of Table 1. In one aspect, the kit contains reagents for detecting from 3 to 20 of the biomarkers of Table 1. In one aspect, the kit contains means for detecting from 3 to 20 of the biomarkers of Table 1. In one aspect, the kit contains reagents for detecting from 4 to 20 of the biomarkers of Table 1. In one aspect, the kit contains means for detecting from 4 to 20 of the biomarkers of Table 1. In one aspect, the kit contains reagents for detecting from 5 to 20 of the biomarkers of Table 1. In one aspect, the kit contains means for detecting from 5 to 20 of the biomarkers of Table 1. In one aspect, the kit contains reagents for detecting from 6 to 20 of the biomarkers of Table 1. In one aspect, the kit contains means for detecting from 6 to 20 of the biomarkers of Table 1. In one aspect, the kit contains reagents for detecting from 7 to 20 of the biomarkers of Table 1. In one aspect, the kit contains means for detecting from 7 to 20 of the biomarkers of Table 1. In one aspect, the kit contains reagents for detecting from 8 to 20 of the biomarkers of Table 1. In one aspect, the kit contains means for detecting from 8 to 20 of the biomarkers of Table 1. In one aspect, the kit contains reagents for detecting from 9 to 20 of the biomarkers of Table 1. In one aspect, the kit contains means for detecting from 9 to 20 of the biomarkers of Table 1. In one aspect, the kit contains means for detecting from 10 to 20 of the biomarkers of Table 1. In one aspect, the kit contains means for detecting from 10 to 20 of the biomarkers of Table 1. In one aspect, the kit contains

means for detecting from 15 to 20 of the biomarkers of Table 1. In one aspect, the kit comprises reagents for the RT-PCR evaluation of from 1 to 20 of the biomarkers of Table 1. In one aspect, the kit comprises means for the RT-PCR evaluation of from 1 to 20 of the biomarkers of Table 1. In one aspect, the kit comprises reagents for microarray evaluation of from 1 to 20 of the biomarkers of Table 1. In one aspect, the kit comprises means for microarray evaluation of from 1 to 20 of the biomarkers of Table 1. In one aspect, the kit comprises reagents for antibody-based evaluation of from 1 to 20 of the biomarkers of Table 1. In one aspect, the kit comprises means for antibody-based evaluation of from 1 to 20 of the biomarkers of Table 1. In one aspect, the kit has reagents for detecting different biomarkers in addition to one or more of those listed in Table 1. In one aspect, the kit has means for detecting different biomarkers in addition to the 1 to 20 of those listed in Table 1. In one aspect, the kit has reagents for multiplex PCR of from 2 to 20 markers of Table 1. In one aspect, the kit has means for multiplex PCR of from 2 to 20 markers of Table 1.

In some aspects, the kit has a device for obtaining a sample for analysis. In one aspect the device is a pipelle. In another aspect, the device is as described in US patent no. 7,207,951, Issued Apr 24, 2007, which is incorporated by herein reference in its entirety. In another aspect, the device is curettage. In another aspect, the device is a brush. One example of a brush device is the tao brush

In some aspects, the kit has an agent to stabilizing the samples obtained from the patient. For example, in a specific aspect, the agent is a buffer for stabilizing the sample obtained from the patient comprises an RNA preserving solution. In another aspect, the agent is useful for stabilizing blood or serum samples.

Diagnostic Antibodies to the Biomarkers of Table 1

Diagnostic antibodies to one or more of the biomarkers of Table 1 (also referred to as a target protein) for diagnostic uses can be obtained in any number of ways. Furthermore, antibodies to some of the biomarkers of Table 1 are commercially available or described in the literature. These known antibodies can be used in the methods of the invention and/or as the basis of engineering new antibodies. Phage display techniques can be used to generate antibodies to one or more of the

biomarkers of Table 1. Standard hybridoma technologies can be used to generate antibodies to one or more of the biomarkers of Table 1. Antibodies to some of the biomarkers of Table 1 are known in the art see the examples. In some aspects, the antibody to one or more of the biomarkers of Table 1 is derived from an animal source (*e.g.*, mouse, rat, or rabbit).

Polyclonal Antibodies

The target protein antibodies may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant t will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent may include the target protein polypeptide (or fragment thereof) or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Freund's complete adjuvant and M PL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization protocol may be selected by one skilled in the art without undue experimentation.

Monoclonal Antibodies

The target protein antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler and Milstein (1975) *Nature* 256:495. In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

The immunizing agent will typically include the target protein polypeptide (or fragment thereof) or a fusion protein thereof. Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or spleen cells or

lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103). Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, Calif. and the American Type Culture Collection, Manassas, Va. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor (1984) *J. Immunol.* 133:3001; Brodeur *et al.*, Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63).

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against target protein. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard (1980) Anal. Biochem. 107:220.

After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods [Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103]. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be grown in vivo as ascites in a mammal.

The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Pat. No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences [U.S. Pat. No. 4,816,567; Morrison *et al.*, supra] or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy

chain is truncated generally at any point in the Fc region so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

In vitro methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art.

Phage Display

Antibodies to the biomarkers of the invention can also be made by using combinatorial libraries to screen for synthetic antibody clones with the desired activity or activities. In principle, synthetic antibody clones are selected by screening phage libraries containing phage that display various fragments of antibody variable region (Fv) fused to phage coat protein. Such phage libraries are panned by affinity chromatography against the desired antigen. Clones expressing Fv fragments capable of binding to the desired antigen are adsorbed to the antigen and thus separated from the non-binding clones in the library. The binding clones are then eluted from the antigen, and can be further enriched by additional cycles of antigen adsorption/elution. Antibodies to the biomarkers of the invention can be obtained by designing a suitable antigen screening procedure to select for the phage clone of interest followed by construction of a full length antibody clone using the Fv sequences from the phage clone of interest and suitable constant region (Fc) sequences described in Kabat *et al.*, Sequences of Proteins of Immunological Interest, Fifth Edition, NIH Publication 91-3242, Bethesda MD (1991), vols. 1-3.

Antibody Conjugates

The antibodies (and fragments thereof) of the invention can be conjugated to molecules for diagnostic purposes. For example, an antibody to a biomarker of Table 1 can be conjugated to a detectable label (*e.g.*, for imaging purposes) for diagnosing or detecting endometrial cancer. Suitable detectable markers include, but are not limited to, a radioisotope, a nanoparticle, a fluorescent compound, a bioluminescent compound, chemiluminescent compound, a metal chelator or an enzyme. Techniques for conjugating diagnostic agents to antibodies are well known (Holmes *et al.* (2001) Curr Protoc Cytom. May; Chapter 4:Unit 4.2; Kumar *et al*

(2008) ACS Nano. Mar;2(3):449-56; Rosenthal *et al.* (2006) *Laryngoscope* Sep;116(9):1636-41). Additionally kits for conjugating agents to diagnostic antibodies are commercially available.

Data and Information

In one aspect of the invention, the present invention relates to methods for comparing and compiling data wherein the data is stored in electronic or paper format. Electronic format can be selected from the group consisting of electronic mail, disk, compact disk (CD), digital versatile disk (DVD), memory card, memory chip, ROM or RAM, magnetic optical disk, tape, video, video clip, microfilm, internet, shared network, shared server and the like; wherein data is displayed, transmitted or analyzed via electronic transmission, video display, telecommunication, or by using any of the above stored formats; wherein data is compared and compiled at the site of sampling specimens or at a location where the data is transported following a process as described above. The data of this embodiment is information regarding the results of the analysis of the biomarkers of Table 1.

The biomarkers, reagents, targets, assays, tests, inquiries and methodologies described herein can be employed in a variety of contexts, including diagnostic discovery, diagnostic development, safety and efficacy monitoring, comparative studies, marketing and the like. The information provided by the invention can be communicated to regulators, physicians and other healthcare providers, manufacturers, owners, investors, patients, and/or the general public. This information and the like can be used in exploratory research, pre-clinical and clinical settings, labeling, production, advertising, and sales, for example.

Definitions

As used herein an "ACAA1 biomarker" refers to an "ACAA1 nucleic acid" or an "ACAA1 protein" that can be specifically detected. An ACAA1 nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human ACAA1 gene or a fragment thereof. For example, an ACAA1 nucleic acid can be a cDNA, or fragment thereof, corresponding to an ACAA1 mRNA molecule. An ACAA1 protein refers to a protein (or fragment thereof) encoded or expressed by the

ACAA1 gene. Examples of ACAA1 biomarkers are given in the examples as well as some reagents useful for detecting ACAA1 biomarkers, nucleic acids, and proteins.

As used herein an "AP1M2 biomarker" refers to an "AP1M2 nucleic acid" or an "AP1M2 protein" that can be specifically detected. An AP1M2 nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human AP1M2 gene or a fragment thereof. For example, an AP1M2 nucleic acid can be a cDNA, or fragment thereof, corresponding to an AP1M2 mRNA molecule. An AP1M2 protein refers to a protein (or fragment thereof) encoded or expressed by the AP1M2 gene. Examples of AP1M2 biomarkers are given in the examples as well as some reagents useful for detecting AP1M2 biomarkers, nucleic acids, and proteins.

As used herein a "CGN biomarker" refers to a "CGN nucleic acid" or a "CGN protein" that can be specifically detected. A CGN nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human CGN gene or a fragment thereof. For example, a CGN nucleic acid can be a cDNA, or fragment thereof, corresponding to a CGN mRNA molecule. A CGN protein refers to a protein (or fragment thereof) encoded or expressed by the CGN gene. Examples of CGN biomarkers are given in the examples as well as some reagents useful for detecting CGN biomarkers, nucleic acids, and proteins.

As used herein a "DDR1 biomarker" refers to a "DDR1 nucleic acid" or a "DDR1 protein" that can be specifically detected. A DDR1 nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human DDR1 gene or a fragment thereof. For example, a DDR1 nucleic acid can be a cDNA, or fragment thereof, corresponding to a DDR1 mRNA molecule. A DDR1 protein refers to a protein (or fragment thereof) encoded or expressed by the DDR1 gene. Examples of DDR1 biomarkers are given in the examples as well as some reagents useful for detecting DDR1 biomarkers, nucleic acids, and proteins.

As used herein an "EPS8L2 biomarker" refers to an "EPS8L2 nucleic acid" or an "EPS8L2 protein" that can be specifically detected. An EPS8L2 nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human EPS8L2 gene or a fragment thereof. For example, an EPS8L2nucleic acid can be a

cDNA, or fragment thereof, corresponding to an EPS8L2 mRNA molecule. An EPS8L2 protein refers to a protein (or fragment thereof) encoded or expressed by the EPS8L2 gene. Examples of EPS8L2 biomarkers are given in the examples as well as some reagents useful for detecting EPS8L2 biomarkers, nucleic acids, and proteins.

As used herein a "FASTKD1 biomarker" refers to a "FASTKD1 nucleic acid" or an "FASTKD1 protein" that can be specifically detected. A FASTKD1 nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human FASTKD1 gene or a fragment thereof. For example, a FASTKD1 nucleic acid can be a cDNA, or fragment thereof, corresponding to an FASTKD1 mRNA molecule. A FASTKD1 protein refers to a protein (or fragment thereof) encoded or expressed by the FASTKD1 gene. Examples of FASTKD1 biomarkers are given in the examples as well as some reagents useful for detecting FASTKD1 biomarkers, nucleic acids, and proteins.

As used herein a "GMIP biomarker" refers to an "GMIP nucleic acid" or an "GMIP protein" that can be specifically detected. An GMIP nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human GMIP gene or a fragment thereof. For example, a GMIP nucleic acid can be a cDNA, or fragment thereof, corresponding to a GMIP mRNA molecule. A GMIP protein refers to a protein (or fragment thereof) encoded or expressed by the GMIP gene. Examples of GMIP biomarkers are given in the examples as well as some reagents useful for detecting GMIP biomarkers, nucleic acids, and proteins.

As used herein an "IKBKE biomarker" refers to an "IKBKE nucleic acid" or an "IKBKE protein" that can be specifically detected. An IKBKE nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human IKBKE gene or a fragment thereof. For example, an IKBKE nucleic acid can be a cDNA, or fragment thereof, corresponding to an IKBKE mRNA molecule. An IKBKE protein refers to a protein (or fragment thereof) encoded or expressed by the IKBKE gene. Examples of IKBKE biomarkers are given in the examples as well as some reagents useful for detecting IKBKE biomarkers, nucleic acids, and proteins.

As used herein a "P2RX4 biomarker" refers to a "P2RX4 nucleic acid" or an "P2RX4 protein" that can be specifically detected. A P2RX4 nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human P2RX4 gene or a fragment thereof. For example, a P2RX4 nucleic acid can be a cDNA, or fragment thereof, corresponding to a P2RX4 mRNA molecule. A P2RX4 protein refers to a protein (or fragment thereof) encoded or expressed by the P2RX4 gene. Examples of P2RX4 biomarkers are given in the examples as well as some reagents useful for detecting P2RX4 biomarkers, nucleic acids, and proteins.

As used herein a "P4HB biomarker" refers to a "P4HB nucleic acid" or a "P4HB protein" that can be specifically detected. A P4HB nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human P4HB gene or a fragment thereof. For example, a P4HB nucleic acid can be a cDNA, or fragment thereof, corresponding to a P4HB mRNA molecule. A P4HB protein refers to a protein (or fragment thereof) encoded or expressed by the P4HB gene. Examples of P4HB biomarkers are given in the examples as well as some reagents useful for detecting P4HB biomarkers, nucleic acids, and proteins.

As used herein a "PHKG2 biomarker" refers to a "PHKG2 nucleic acid" or an "PHKG2 protein" that can be specifically detected. A PHKG2 nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human AP1M2 gene or a fragment thereof. For example, a PHKG2 nucleic acid can be a cDNA, or fragment thereof, corresponding to a PHKG2 mRNA molecule. A PHKG2 protein refers to a protein (or fragment thereof) encoded or expressed by the PHKG2 gene. Examples of PHKG2 biomarkers are given in the examples as well as some reagents useful for detecting PHKG2 biomarkers, nucleic acids, and proteins.

As used herein a "PPFIBP2 biomarker" refers to a "PPFIBP2 biomarker nucleic acid" or a "PPFIBP2 biomarker protein" that can be specifically detected. A PPFIBP2 biomarker nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human PPFIBP2 biomarker gene or a fragment thereof. For example, a PPFIBP2 biomarker nucleic acid can be a cDNA, or fragment thereof, corresponding to an PPFIBP2 biomarker mRNA molecule. A PPFIBP2 biomarker protein refers to a protein (or fragment thereof) encoded or expressed by the

PPFIBP2 biomarker gene. Examples of PPFIBP2 biomarker biomarkers are given in the examples as well as some reagents useful for detecting PPFIBP2 biomarker biomarkers, nucleic acids, and proteins.

As used herein a "PPP1R16A biomarker" refers to a "PPP1R16A nucleic acid" or a "PPP1R16A protein" that can be specifically detected. A PPP1R16A nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human PPP1R16A gene or a fragment thereof. For example, a PPP1R16A nucleic acid can be a cDNA, or fragment thereof, corresponding to a PPP1R16A mRNA molecule. A PPP1R16A protein refers to a protein (or fragment thereof) encoded or expressed by the PPP1R16A gene. Examples of PPP1R16A biomarkers are given in the examples as well as some reagents useful for detecting PPP1R16A biomarkers, nucleic acids, and proteins.

As used herein a "TJP3 biomarker" refers to a "TJP3 nucleic acid" or a "TJP3 protein" that can be specifically detected. A TJP3 nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human TJP3 gene or a fragment thereof. For example, a TJP3 nucleic acid can be a cDNA, or fragment thereof, corresponding to a TJP3 mRNA molecule. A TJP3 protein refers to a protein (or fragment thereof) encoded or expressed by the TJP3 gene. Examples of TJP3 biomarkers are given in the examples as well as some reagents useful for detecting TJP3 biomarkers, nucleic acids, and proteins.

As used herein an "RASSF7 biomarker" refers to an "RASSF7 nucleic acid" or an "RASSF7 protein" that can be specifically detected. An RASSF7 nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human RASSF7 gene or a fragment thereof. For example, an RASSF7 nucleic acid can be a cDNA, or fragment thereof, corresponding to an RASSF7 mRNA molecule. An RASSF7 protein refers to a protein (or fragment thereof) encoded or expressed by the RASSF7 gene. Examples of RASSF7 biomarkers are given in the examples as well as some reagents useful for detecting RASSF7 biomarkers, nucleic acids, and proteins.

As used herein a "RNF183 biomarker" refers to a "RNF183 nucleic acid" or a "RNF183 protein" that can be specifically detected. A RNF183 nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human RNF183 gene or a fragment thereof. For example, a RNF183 nucleic acid can be a cDNA, or fragment thereof, corresponding to a RNF183 mRNA molecule. A RNF183 protein refers to a protein (or fragment thereof) encoded or expressed by the RNF183 gene. Examples of RNF183 biomarkers are given in the examples as well as some reagents useful for detecting RNF183 biomarkers, nucleic acids, and proteins.

As used herein a "SIRT6 biomarker" refers to a "SIRT6 nucleic acid" or a "SIRT6 protein" that can be specifically detected. A SIRT6 nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human SIRT6 gene or a fragment thereof. For example, a SIRT6 nucleic acid can be a cDNA, or fragment thereof, corresponding to a SIRT6 mRNA molecule. A SIRT6 protein refers to a protein (or fragment thereof) encoded or expressed by the SIRT6 gene. Examples of SIRT6 biomarkers are given in the examples as well as some reagents useful for detecting SIRT6 biomarkers, nucleic acids, and proteins.

As used herein a "DCN biomarker" refers to a "DCN nucleic acid" or a "DCN protein" that can be specifically detected. A DCN nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human DCN gene or a fragment thereof. For example, a DCN nucleic acid can be a cDNA, or fragment thereof, corresponding to a DCN mRNA molecule. A DCN protein refers to a protein (or fragment thereof) encoded or expressed by the DCN gene. Examples of LSR biomarkers are given in the examples as well as some reagents useful for detecting DCN biomarkers, nucleic acids, and proteins.

As used herein a "SOCS2 biomarker" refers to a "SOCS2 nucleic acid" or a "SOCS2 protein" that can be specifically detected. A SOCS2 nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human SOCS2 gene or a fragment thereof. For example, a SOCS2 nucleic acid can be a cDNA, or fragment thereof, corresponding to a SOCS2 mRNA molecule. A SOCS2 protein refers to a protein (or fragment thereof) encoded or expressed by the SOCS2

gene. Examples of SOCS2 biomarkers are given in the examples as well as some reagents useful for detecting SOCS2 biomarkers, nucleic acids, and proteins.

As used herein an "EFEMP2 biomarker" refers to an "EFEMP2 nucleic acid" or an "EFEMP2 protein" that can be specifically detected. An EFEMP2 nucleic acid can be a RNA molecule, DNA molecule, or other nucleic acid that corresponds to the human EFEMP2 gene or a fragment thereof. For example, an EFEMP2 nucleic acid can be a cDNA, or fragment thereof, corresponding to an EFEMP2 mRNA molecule. An EFEMP2 protein refers to a protein (or fragment thereof) encoded or expressed by the EFEMP2 gene. Examples of EFEMP2 biomarkers are given in the examples as well as some reagents useful for detecting EFEMP2 biomarkers, nucleic acids, and proteins.

As used herein, the term "sensitivity" refers to the proportion of reference test positive (diseased) subjects who test positive with the screening test.

As used herein, the term "specificity" refers to the proportion of reference test negative (healthy) subjects who test negative with the screening test.

As used herein, the term "secretory phase" refers to a phase of the menstrual cycle that is distinguishable from the other phases of the menstrual cycle using standard procedures in the art, *e.g.*, pathological examination of tissue obtained from endometrium or uterus. Secretory phase is associated with bleeding (menstruation).

As used herein, the term "ROC" or "receiver operator characteristic" refers to a graphical plot of sensitivity vs. (1-specificity) or in other words a plot of true positive rate versus fraction of false positives. The area under the ROC, or AUROC, curve can range from 0 to 1. An area under the ROC curve of 1 is a perfect test or separation of groups while an area under the ROC of 0.5 indicates that the classifier is essentially unable to separate the groups and is therefore not useful.

A "cancer" in an animal refers to the presence of cells possessing characteristics typical of cancer-causing cells, for example, uncontrolled proliferation, loss of specialized functions, immortality, significant metastatic potential, significant

increase in anti-apoptotic activity, rapid growth and proliferation rate, and certain characteristic morphology and cellular markers.

The phrase "detecting a cancer" or "diagnosing a cancer" refers to determining the presence or absence of cancer or a precancerous condition in an animal. "Detecting a cancer" also can refer to obtaining evidence regarding the likelihood of the presence of precancerous or cancerous cells in the animal or assessing the predisposition of a patient to the development of a cancer. Detecting a cancer can be accomplished using the methods of this invention alone, in combination with other methods, or in light of other information regarding the state of health of the animal.

A "tumor," as used herein, refers to all neoplastic cell growth and proliferation, whether malignant or benign, and all precancerous and cancerous cells and tissues.

The term "precancerous" refers to cells or tissues having characteristics relating to changes that may lead to malignancy or cancer.

In general, a "gene" is a region on the genome that is capable of being transcribed to an RNA that either has a regulatory function, a catalytic function, and/or encodes a protein. An eukaryotic gene typically has introns and exons, which may organize to produce different RNA splice variants that encode alternative versions of a mature protein. The skilled artisan will appreciate that the present invention encompasses all encoding transcripts that may be found, including splice variants, allelic variants and transcripts that occur because of alternative promoter sites or alternative poly-adenylation sites of the biomarkers as listed in Table 1. A "full-length" gene or RNA therefore encompasses any naturally occurring splice variants, allelic variants, other alternative transcripts, splice variants generated by recombinant technologies which bear the same function as the naturally occurring variants, and the resulting RNA molecules. A "fragment" of a gene, including an oncogene, can be any portion from the gene, which may or may not represent a functional domain, for example, a catalytic domain, a DNA binding domain, *etc.* A fragment may preferably include nucleotide sequences that encode for at least 25 contiguous amino acids, and preferably at least about 30, 40, 50, 60, 65, 70, 75 or more contiguous amino acids or any integer thereabout or therebetween. In some aspects of the invention, the skilled

artisan recognizes that the term gene is used interchangeably with the term “locus”, which refers more generically to a region of genomic DNA regardless if it codes for RNA, protein, or a regulatory element.

A "differentially expressed gene transcript", as used herein, refers to a gene, transcript that is found at a different level in different cell or tissue types of an organism having a tumor or cancer, compared to the level or state of the gene transcript found in the cells of the same tissue in a healthy organism, or in the cells of the same tissue in the same organism. Multiple copies of gene transcripts may be found in an organism having the tumor or cancer, while fewer copies of the same gene transcript are found in a healthy organism or healthy cells of the same tissue in the same organism, or vice-versa for underexpressed genes. In general, differentially expressed transcripts are those which when measured in an affected sample or sample from an affected patient have a detectably different level of expression as compared to a control value which is representative of a non-affected sample or sample from a non-affected patient. Examples of differential expression include a change of 10% or more, 20% or more 30% or more, 40% or more, or 50% or more in affected as compared to non-affected.

As used herein the term "polypeptide" means a sequence of amino acids joined together by peptide bonds. The amino acid sequence of the polypeptide can determined by the sequence of the DNA bases which encode the amino acids of the polypeptide chain. The polypeptides described herein include, but are not limited to, complete proteins, fragments of complete proteins, epitopes of proteins etc. As used herein the term polypeptide, peptide, and protein refer to molecule having two or more amino acid residues (natural or unnatural) joined together by one or more peptide bonds.

A "differentially expressed gene," can be a target, fingerprint, or pathway gene. For example, a "fingerprint gene", as used herein, refers to a differentially expressed gene whose expression pattern can be used as a prognostic or diagnostic marker for the evaluation of tumors and cancers, or which can be used to identify compounds useful for the treatment of tumors and cancers, for example, endometrial cancer.

Fingerprint genes can be one or more genes (or corresponding biomarkers *e.g.*, protein) corresponding to the biomarkers of Table 1.

A "fingerprint pattern", as used herein, refers to a pattern generated when the expression pattern of a series (which can range from two up to all the fingerprint genes that exist for a given state) of fingerprint genes is determined. A fingerprint pattern also may be referred to as n "profile". A fingerprint pattern or expression profile having from 1 to 20 of the biomarkers of Table 1 can be used in the same diagnostic, prognostic, and methods of the invention.

"Pathway genes", as used herein, are genes that encode proteins or polypeptides that interact with other gene products involved in tumors and cancers. Pathway genes also can exhibit target gene and/or fingerprint gene characteristics.

A "detectable" RNA expression level, as used herein, means a level that is detectable by standard techniques currently known in the art or those that become standard at some future time, and include for example, differential display, RT (reverse transcriptase)-coupled polymerase chain reaction (PCR), Northern Blot, and/or RNase protection analyses.

The nucleic acid molecules of the invention, for example, those corresponding to one or more biomarkers of Table 1, and its subsequences/alternative transcripts, can be inserted into a vector, as described below, which will facilitate expression of the insert. The nucleic acid molecules and the polypeptides they encode can be used directly as diagnostic agents, or can be used (directly in the case of the polypeptide or indirectly in the case of a nucleic acid molecule) to generate antibodies that, in turn, are clinically useful as a diagnostic agent. Accordingly, vectors containing the nucleic acids of the invention, cells transfected with these vectors, the polypeptides expressed, and antibodies generated against either the entire polypeptide or an antigenic fragment thereof, are among the aspects of the invention.

An "isolated DNA molecule" is a fragment of DNA that has been separated from the chromosomal or genomic DNA of an organism. Isolation also is defined to connote a degree of separation from original source or surroundings.

"Complementary DNA" (cDNA), often referred to as "copy DNA", is a single-stranded DNA molecule that is formed from an mRNA template by the enzyme reverse transcriptase. Those skilled in the art also use the term "cDNA" to refer to a double-stranded DNA molecule that comprises such a single-stranded DNA molecule and its complement DNA strand.

The term "expression" refers to the biosynthesis of a gene product.

A "cloning vector" is a nucleic acid molecule, for example, a plasmid, cosmid or bacteriophage that has the capability of replicating autonomously in a host cell. Cloning vectors typically contain (i) one or a small number of restriction endonuclease recognition sites at which foreign DNA sequences can be inserted in a determinable fashion without loss of an essential biological function of the vector, and (ii) a marker gene that is suitable for use in the identification and selection of cells transformed or transfected with the cloning vector. Marker genes include, but are not limited to, genes that provide tetracycline resistance or ampicillin resistance..

An "expression vector" is a nucleic acid construct, generated recombinantly or synthetically, bearing a series of specified nucleic acid elements that enable transcription of a particular gene in a host cell. Typically, gene expression is placed under the control of certain regulatory elements, including constitutive or inducible promoters, tissue-preferred regulatory elements, and enhancers.

A "recombinant host" may be any prokaryotic or eukaryotic cell that contains either a cloning vector or expression vector. This term also includes those prokaryotic or eukaryotic cells that have been genetically engineered to contain the cloned gene(s) in the chromosome or genome of the host cell.

The term "operably linked" is used to describe the connection between regulatory elements and a gene or its coding region. That is, gene expression is typically placed under the control of certain regulatory elements, including constitutive or inducible promoters, tissue-specific regulatory elements, and enhancers. Such a gene or coding region is said to be "operably linked to" or "operatively linked to" or

"operably associated with" the regulatory elements, meaning that the gene or coding region is controlled or influenced by the regulatory element.

"Sequence homology" is used to describe the sequence relationships between two or more nucleic acids, polynucleotides, proteins, or polypeptides, and is understood in the context of and in conjunction with the terms including: (a) reference sequence, (b) comparison window, (c) sequence identity, (d) percentage of sequence identity, and (e) substantial identity or "homologous."

A "reference sequence" is a defined sequence used as a basis for sequence comparison. A reference sequence may be a subset of or the entirety of a specified sequence; for example, a segment of a full-length cDNA or gene sequence, or the complete cDNA or gene sequence. For polypeptides, the length of the reference polypeptide sequence can be chosen from at least about 16 amino acids, at least about 20 amino acids, at least about 25 amino acids, and about 35 amino acids, about 50 amino acids, or about 100 amino acids. For nucleic acids, the length of the reference nucleic acid sequence can be chosen from at least about 50 nucleotides, at least about 60 nucleotides, at least about 75 nucleotides, and about 100 nucleotides or about 300 nucleotides or any integer thereabout or there between.

A "comparison window" includes reference to a contiguous and specified segment of a polynucleotide sequence, wherein the polynucleotide sequence may be compared to a reference sequence and wherein the portion of the polynucleotide sequence in the comparison window may comprise additions, substitutions, or deletions (*i.e.*, gaps) compared to the reference sequence (which does not comprise additions, substitutions, or deletions) for optimal alignment of the two sequences. Generally, the comparison window is at least 20 contiguous nucleotides in length, and optionally can be 30, 40, 50, 100, or longer. Those of skill in the art understand that to avoid a misleadingly high similarity to a reference sequence due to inclusion of gaps in the polynucleotide sequence a gap penalty is typically introduced and is subtracted from the number of matches.

Methods of alignment of sequences for comparison are well-known in the art. Optimal alignment of sequences for comparison may be conducted by the local

homology algorithm of Smith and Waterman (1981) *Adv. Appl. Math.*, 2: 482,; by the homology alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.*, 48: 443 ; by the search for similarity method of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA*, 8: 2444; by computerized implementations of these algorithms, including, but not limited to: CLUSTAL in the PC/Gene program by Intelligenetics, Mountain View, Calif., GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 7 Science Dr., Madison, Wisc., USA; the CLUSTAL program is well described by Higgins and Sharp (1988) *Gene* 73: 237-244; Corpet *et al.* (1988) *Nucleic Acids Research*, 16:881-90; Huang, *et al.*, Computer Applications in the Biosciences, 8:1-6, 1992; and Pearson, *et al.* (1994) Methods in Molecular Biology, 24:7-331. The BLAST family of programs which can be used for database similarity searches includes: BLASTN for nucleotide query sequences against nucleotide database sequences; BLASTX for nucleotide query sequences against protein database sequences; BLASTP for protein query sequences against protein database sequences; TBLASTN for protein query sequences against nucleotide database sequences; and TBLASTX for nucleotide query sequences against nucleotide database sequences. See, Current Protocols in Molecular Biology, Chapter 19, Ausubel, *et al.*, Eds., Greene Publishing and Wiley-Interscience, New York, 1995. New versions of the above programs or new programs altogether will undoubtedly become available in the future, and can be used with the present invention.

Unless otherwise stated, sequence identity/similarity values provided herein refer to the value obtained using the BLAST 2.0 suite of programs, or their successors, using default parameters. Altschul *et al.* (1997) *Nucleic Acids Res*, 2:3389-3402. It is to be understood that default settings of these parameters can be readily changed as needed in the future.

As those ordinary skilled in the art will understand, BLAST searches assume that proteins can be modeled as random sequences. However, many real proteins comprise regions of nonrandom sequences which may be homopolymeric tracts, short-period repeats, or regions enriched in one or more amino acids. Such low-complexity regions may be aligned between unrelated proteins even though other regions of the protein are entirely dissimilar. A number of low-complexity filter

programs can be employed to reduce such low-complexity alignments. For example, the SEG (Wooten and Federhen, (1993) *Comput. Chem.* 17:149-163) and XNU (Claverie and States (1993) *Comput. Chem.*, 17:191-1) low-complexity filters can be employed alone or in combination.

"Sequence identity" or "identity" in the context of two nucleic acid or polypeptide sequences includes reference to the residues in the two sequences which are the same when aligned for maximum correspondence over a specified comparison window, and can take into consideration additions, deletions and substitutions. When percentage of sequence identity is used in reference to proteins it is recognized that residue positions which are not identical often differ by conservative amino acid substitutions, where amino acid residues are substituted for other amino acid residues with similar chemical properties (for example, charge or hydrophobicity) and therefore do not deleteriously change the functional properties of the molecule. Where sequences differ in conservative substitutions, the percent sequence identity may be adjusted upwards to correct for the conservative nature of the substitution. Sequences which differ by such conservative substitutions are said to have sequence similarity. Approaches for making this adjustment are well-known to those of skill in the art. Typically this involves scoring a conservative substitution as a partial rather than a full mismatch, thereby increasing the percentage sequence identity. Thus, for example, where an identical amino acid is given a score of 1 and a non-conservative substitution is given a score of zero, a conservative substitution is given a score between zero and 1. The scoring of conservative substitutions is calculated, for example, according to the algorithm of Meyers and Miller (1988) *Computer Applic. Biol. Sci.*, 4: 11-17 for example, as implemented in the program PC/GENE (Intelligenetics, Mountain View, Calif., USA).

"Percentage of sequence identity" means the value determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions, substitutions, or deletions (*i.e.*, gaps) as compared to the reference sequence (which does not comprise additions, substitutions, or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both

sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity.

The term "substantial identity" or "homologous" in their various grammatical forms in the context of polynucleotides means that a polynucleotide comprises a sequence that has a desired identity, for example, at least 60% identity, preferably at least 70% sequence identity, more preferably at least 80%, still more preferably at least 90% and even more preferably at least 95%, compared to a reference sequence using one of the alignment programs described using standard parameters. One of skill will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like. Substantial identity of amino acid sequences for these purposes n normally means sequence identity of at least 60%, more preferably at least 70%, 80%, 90%, and even more preferably at least 95%.

Another indication that nucleotide sequences are substantially identical is if two molecules hybridize to each other under stringent conditions. However, nucleic acids which do not hybridize to each other under stringent conditions are still substantially identical if the polypeptides which they encode are substantially identical. This may occur, for example, when a copy of a nucleic acid is created using the maximum codon degeneracy permitted by the genetic code. One indication that two nucleic acid sequences are substantially identical is that the polypeptide which the first nucleic acid encodes is immunologically cross reactive with the polypeptide encoded by the second nucleic acid, although such cross-reactivity is not required for two polypeptides to be deemed substantially identical.

The term "substantial identity" or "homologous" in their various grammatical forms in the context of peptides indicates that a peptide comprises a sequence that has a desired identity, for example, at least 60% identity, preferably at least 70% sequence identity to a reference sequence, more preferably 80%, still more preferably 85%, even more preferably at least 90% or 95% sequence identity to the reference sequence over a specified comparison window. Preferably, optimal alignment is

conducted using the homology alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.*, 48:443. An indication that two peptide sequences are substantially identical is that one peptide is immunologically reactive with antibodies raised against the second peptide, although such cross-reactivity is not required for two polypeptides to be deemed substantially identical. Thus, a peptide is substantially identical to a second peptide, for example, where the two peptides differ only by a conservative substitution. Peptides which are "substantially similar" share sequences as noted above except that residue positions which are not identical may differ by conservative amino acid changes. Conservative substitutions typically include, but are not limited to, substitutions within the following groups: glycine and alanine; valine, isoleucine, and leucine; aspartic acid and glutamic acid; asparagine and glutamine; serine and threonine; lysine and arginine; and phenylalanine and tyrosine, and others as known to the skilled person.

"Biological subject" as used herein refers to a target biological object obtained, reached, or collected *in vivo*, *ex-vivo*, or *in situ*, that contains or is suspected of containing nucleic acids or polypeptides corresponding to a biomarker of Table 1.

"Biological sample" as used herein refers to a sample obtained from a biological subject, including sample of biological tissue or fluid origin, obtained, reached, or collected *in vivo*, *ex-vivo*, or *in situ*, that contains or is suspected of containing nucleic acids or polypeptides corresponding to a biomarker of Table 1. A biological sample also includes samples from a region of a biological subject containing precancerous or cancer cells or tissues. Such samples can be, but are not limited to, organs, tissues, fractions and cells isolated from mammals including, humans such as a patient. Biological samples also may include sections of the biological sample including tissues, for example, frozen sections taken for histologic purposes. A biological sample, as described herein, can be: a "control" or a "control sample" or a "test sample". A biological sample can be obtained from the uterus using commonly employed clinical practices (*e.g.*, aspiration, brush, curettage, or hysteroscopy).

A "control" or "control value" refers to a representative of healthy, endometrial cancer-free biological subject or information obtained from a different individual or a normalized value, which can be based on baseline data obtained from a population

or other acceptable sources. A control also can refer to a given level of a biomarker of Table 1, representative of the endometrial cancer-free population, that has been previously established based on measurements from normal, endometrial cancer-free individuals. A control also can be a reference data point in a database based on data obtained from control samples representative of a cancer-free population. Further, a control can be established by a specific age, sex, ethnicity or other demographic parameters. In some contexts, the control is implicit in the particular measurement. A control value or control can also refer to a "control score". Control scores can be values obtained from the determination of the expression level of one or more biomarkers of the invention. For example, different programs and algorithms are commercially available for generating formulas that yield a score value based on the measurement of the levels of one or more biomarkers, that can indicate whether an individual is likely to have a condition or not. In another example, a score over or below a certain threshold that may indicate an increased (or decreased) likelihood of having the disease. A control score value can be based on a single marker or a combination of markers.

A "control sample" refers to a sample of biological material representative of healthy, cancer-free animals or a normal biological subject obtained from a cancer-free population. The level of a biomarker of Table 1, in a control sample is desirably typical of the general population of normal, cancer-free animals of the same species. This sample either can be collected from an animal for the purpose of being used in the methods described in the present invention or it can be any biological material representative of normal, cancer-free animals suitable for use in the methods of this invention. A control sample also can be obtained from normal tissue from the animal that has cancer or is suspected of having cancer.

A "test sample" as used herein refers to a biological sample, including sample of biological tissue or fluid origin, obtained, reached, or collected *in vivo*, *ex-vivo*, or *in situ*, that contains or is suspected of containing nucleic acids or polypeptides corresponding to a biomarker of Table 1. A test sample also includes biological samples containing precancerous or cancer cells or tissues. A test sample also may include sections of the biological sample including tissues, for example, frozen sections taken for histologic purposes.

"Providing a biological subject, a biological sample, or a test sample" means to obtain a biological subject *in vivo*, *ex-vivo*, or *in situ*, including tissue or cell sample for use in the methods described in the present invention. Most often, this will be done by removing a sample of cells from an animal, but also can be accomplished *in vivo*, *ex-vivo*, or *in situ*, or by using previously isolated cells (for example, isolated from another person, at another time, and/or for another purpose). The sample can also be obtained from sources such as blood, serum, and uterine fluid.

"Data" includes, but is not limited to, information obtained that relates to "biological sample", "test sample", "control sample", and/or "control", as described above, wherein the information is applied in generating a test level for diagnostics, prevention, monitoring or therapeutic use. The present invention relates to methods for comparing and compiling data wherein the data is stored in electronic or paper formats. Electronic format can be selected from the group consisting of electronic mail, disk, compact disk (CD), digital versatile disk (DVD), memory card, memory chip, ROM or RAM, magnetic optical disk; tape, video, video clip, microfilm, internet, shared network, shared server and the like; wherein data is displayed, transmitted or analyzed via electronic transmission, video display, telecommunication, or by using any of the above stored formats; wherein data is compared and compiled at the site of sampling specimens or at a location where the data is transported following a process as: described above.

"Overexpression" of a gene or an "increased," or "elevated," level of a ribonucleotide or protein refers to a level of the gene, ribonucleotide or polypeptide that, in comparison with a control level/value of gene, ribonucleotides or polypeptide, is detectably higher. Comparison may be carried out by statistical analyses on numeric measurements of the expression; or, it may be done through visual examination of experimental results by qualified researchers. Examples of overexpression include a change of 10% or more, 20% or more 30% or more, 40% or more, or 50% or more in affected as compared to non-affected.

"Underexpression" of a gene or a "decreased," or "lower," level of a ribonucleotide or protein refers to a level of the gene, ribonucleotide or polypeptide that, in comparison with a control level of gene, ribonucleotides or polypeptide, is detectably lower. Comparison may be carried out by statistical analyses on numeric measurements of the expression; or, it may be done through visual examination of experimental results by qualified researchers. Examples of underexpression include a change of 10% or more, 20% or more 30% or more, 40% or more, or 50% or more in affected as compared to non-affected.

A level of ribonucleotide or polypeptide, that is "expected" in a control sample refers to a level that represents a typical, cancer-free sample, and from which an elevated, or diagnostic, presence of the polypeptide or polynucleotide, can be distinguished. Preferably, an "expected" level will be controlled for such factors as the age, sex, medical history, *etc.* of the mammal, as well as for the particular biological subject being tested.

The terms "isolated," "purified," or "biologically pure" refer to material that is free to varying degrees from components which normally accompany it as found in its native state. "Isolate" denotes a degree of separation from original source or surroundings. "Purify" denotes a degree of separation that is higher than isolation. A "purified" or "biologically pure" protein is sufficiently free of other materials such that any impurities do not materially affect the biological properties of the protein or cause other adverse consequences. That is, a nucleic acid or peptide of this invention is purified if it is substantially free of cellular material, viral material, or culture medium when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. Purity and homogeneity are typically determined using analytical chemistry techniques, for example, polyacrylamide gel electrophoresis or high performance liquid chromatography. The term "purified" can denote that a nucleic acid or protein gives rise to essentially one band in an electrophoretic gel. For a protein that can be subjected to modifications, for example, phosphorylation or glycosylation, different modifications may give rise to different isolated proteins, which can be separately purified. Various levels of purity may be applied as needed according to this invention in the different methodologies

set forth herein; the customary purity standards known in the art may be used if no standard is otherwise specified.

An "isolated nucleic acid molecule" can refer to a nucleic acid molecule, depending upon the circumstance, that is separated from the 5' and 3' coding sequences of genes or gene fragments contiguous in the naturally occurring genome of an organism. The term "isolated nucleic acid molecule" also includes nucleic acid molecules which are not naturally occurring, for example, nucleic acid molecules created-by recombinant DNA techniques.

"Nucleic acid" refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form. The term encompasses nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral methyl phosphonates, 2-O-methyl ribonucleotides, and peptide-nucleic acids (PNAs).

Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively, modified variants thereof (for example, degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with suitable mixed base and/or deoxyinosine residues (Batzer *et al.* (1991) *Nucleic Acid Res*, 19:081; Ohtsuka *et al.* (1985) *J. Biol. Chem.*, 260:2600-2608; Rossolini *et al.* (1994) *Mol. Cell Probes*, 8:91-98). The term nucleic acid can be used interchangeably with gene, cDNA, mRNA, oligonucleotide, and polynucleotide.

A "label" or a "detectable moiety" is a composition that when linked with the nucleic acid or protein molecule of interest renders the latter detectable, via spectroscopic, photochemical, biochemical, immunochemical, or chemical means. For example,

useful labels include radioactive isotopes, magnetic beads, metallic beads, colloidal particles, fluorescent dyes, electron-dense reagents, enzymes (for example, as commonly used in an ELISA), biotin, digoxigenin, or haptens. A "labeled nucleic acid or oligonucleotide probe" is one that is bound, either covalently, through a linker or a chemical bond, or noncovalently, through ionic bonds, van der Waals forces, electrostatic attractions, hydrophobic interactions, or hydrogen bonds, to a label such that the presence of the nucleic acid or probe may be detected by detecting the presence of the label bound to the nucleic acid or probe.

As used herein a "nucleic acid or oligonucleotide probe" is defined as a nucleic acid capable of binding to a target nucleic acid of complementary sequence through one or more types of chemical bonds, usually through complementary base pairing, usually through hydrogen bond formation. As used herein, a probe may include natural (*i.e.*, A, G, C, or T) or modified bases (7-deazaguanosine, inosine, *etc.*). In addition, the bases in a probe may be joined by a linkage other than a phosphodiester bond, so long as it does not unduly interfere with hybridization. It will be understood by one of skill in the art that probes may bind target sequences lacking complete complementarity with the probe sequence depending upon the stringency of the hybridization conditions. The probes are preferably directly labeled with isotopes, for example, chromophores, lumiphores, chromogens, or indirectly labeled with biotin to which a streptavidin complex may later bind. By assaying for the presence or absence of the probe, one can detect the presence or absence of a target gene of interest.

The phrase "selectively (or specifically) hybridizes to" refers to the binding, duplexing, or hybridizing of a molecule only to a particular nucleotide sequence under stringent hybridization conditions when that sequence is present in a complex mixture (for example, total cellular or library DNA or RNA).

The phrase "stringent hybridization conditions" refers to conditions under which a probe will hybridize to its target complementary sequence, typically in a complex mixture of nucleic acids, but to no other sequences. Stringent conditions are sequence-dependent and circumstance-dependent; for example, longer sequences can hybridize with specificity at higher temperatures. An extensive guide to the

hybridization of nucleic acids is found in Tijssen (1993) Techniques in Biochemistry and Molecular Biology-Hybridization with Nucleic Probes, "Overview of principles of hybridization and the strategy of nucleic acid assays". In the context of the present invention, 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% homologous to each other typically remain hybridized to each other. Preferably, the conditions are such that sequences at least about 65%, more preferably at least about 70%, and even more preferably at least about 75% or more homologous to each other typically remain hybridized to each other.

Generally, stringent conditions are selected to be about 5 to 10 C lower than the thermal melting point (Tm) for the specific sequence at a defined ionic strength pH. The Tm is the temperature (under defined ionic strength, pH, and nucleic concentration) at which 50% of the probes complementary to the target hybridize to the target sequence at equilibrium (as the target sequences are present in excess, at Tm, 50% of the probes are occupied at equilibrium). Stringent conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30 C for short probes (for example, 10 to 50 nucleotides) and at least about 60 C for long probes (for example, greater than 50 nucleotides). Stringent conditions also may be achieved with the addition of destabilizing agents, for example, formamide. For selective or specific hybridization, a positive signal is at least two times background, preferably 10 times background hybridization.

Exemplary stringent hybridization conditions can be as following, for example: 50% formamide, 5xSSC and 1% SDS, incubating at 42 C, or 5xSSC and 1% SDS, incubating at 65 C., with wash in 0.2xSSC and 0.1% SDS at 65 C. Alternative conditions include, for example, conditions at least as stringent as hybridization at 68 C for 20 hours, followed by washing in 2xSSC, 0.1% SDS, twice for 30 minutes at 55 C and three times for 15 minutes at 60 C. Another alternative set of conditions is hybridization in 6xSSC at about 45 C, followed by one or more washes in 0.2xSSC, 0.1% SDS at 50-65 C. For PCR, a temperature of about 36 C is typical for low

stringency amplification, although annealing temperatures may vary between about 32 C and 48 C depending on primer length. For high stringency PCR amplification, a temperature of about 62 C is typical, although high stringency annealing temperatures can range from about 50 C to about 65 C, depending on the primer length and specificity. Typical cycle conditions for both high and low stringency amplifications include a denaturation phase of 90 C to 95 C for 30 sec. to 2 min., an annealing phase lasting 30 sec. to 2 min., and an extension phase of about 72 C for 1 to 2 min.

Nucleic acids that do not hybridize to each other under stringent conditions can still be substantially identical if the polypeptides which they encode are substantially identical. This occurs, for example, when a copy of a nucleic acid is created using the maximum codon degeneracy permitted by the genetic code. In such cases, the nucleic acids typically hybridize under moderately stringent hybridization conditions. Exemplary "moderately stringent hybridization conditions" include a hybridization in a buffer of 40% formamide, 1 M NaCl, 1% SDS at 37 C, and a wash in 1xSSC at 45 C. A positive hybridization is at least twice background. Those of ordinary skill will readily recognize that alternative hybridization and wash conditions can be utilized to provide conditions of similar stringency.

The term "target gene" or “target biomarker” or “target nucleic acid” or “target protein” can refer to a target nucleic acid (DNA and RNA) or protein (or polypeptide), (*e.g.*, corresponding to the biomarkers in Table 1) and can include their polymorphic variants, alleles, mutants, and interspecies homologs that have (i) substantial nucleotide sequence homology (for example, at least 60% identity, preferably at least 70% sequence identity, more preferably at least 80%, still more preferably at least 90% and even more preferably at least 95%) with the nucleotide sequence indicated in Ensembl database for the indicated ID number; or (ii) at least 65% sequence homology with the amino acid sequence as indicated in the Ensembl record; or (iii) substantial nucleotide sequence homology (for example, at least 60% identity, preferably at least 70% sequence identity, more preferably at least 80%, still more preferably at least 90% and even more preferably at least 95%) with the nucleotide sequence as set forth in the Ensembl record with substantial sequence homology with the encoded amino acid sequence. As used in herein, and unless

otherwise specified, these terms refer the entire gene sequence, mRNA sequence, and/or protein sequence as well as fragments of these sequences. In a more specific definition, these terms refer to the minimal amount of nucleic acid or amino acid sequence that can be used to identify biomarker in a specific manner. The skilled artisan recognizes that the target genes/biomarker can have numerous splice forms and variants. When referring to a specific target gene or locus by a reference number (*e.g.*, Entrez gene ID or Ensembl), all splices forms and variant which are included in the various embodiments of the invention. The target gene/biomarker can also comprise a regulatory element. These sequences are representative of one particular individual in the population of humans. Humans vary from one to another in their gene sequences. These variations are very minimal, sometimes occurring at a frequency of about 1 to 10 nucleotides per gene. Different forms of any particular gene exist within the human population. These different forms are called allelic variants. Allelic variants often do not change the amino acid sequence of the encoded protein; such variants are termed synonymous. Even if they do change the encoded amino acid (non-synonymous), the function of the protein is not typically affected. Such changes are evolutionarily or functionally neutral. When a gene ID (*e.g.*, genbank or Ensembl) is referred to in the present application all allelic variants are intended to be encompassed by the term. The gene ID sequences given for a biomarker are provided merely as representative examples of a wild-type human sequence. The invention is not limited to a single allelic form of the amplified genes or regions (and proteins they encode).

Examples

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques used by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1: Identification of Endometrial Cancer Biomarkers

In order to identify biomarkers for predicting and/or diagnosing endometrial cancer, gene expression levels from fifty-six endometrial primary tumors in several differentiation stages were compared with 10 normal (*i.e.*, not having endometrial cancer) endometrial tissues by DNA microarray technique. This technique allows us to check the expression of the whole genome in a particular type of cell, tissue, organ, or in this case, check the differential gene expression between endometrial cancer and healthy endometrial tissue. A microarray chip contains small DNA sequences arranged in a regular pattern with specific addresses for probes for typically thousands of genes.

The amount of specific mRNAs in a sample can be estimated by it hybridization signal on the array.

Sample Description

Tumor samples were obtained from patients who underwent surgery and control tissue was obtained from non affected regions of endometrial tissue from the same patients. During preparation of the specimens, care was taken to macroscopically dissect the cancer away from any adjacent myometrium.

Ten control samples (nine of them were paired with their corresponding tumor samples and the tenth was an atrophic endometrium) were used and the basic characteristics of the other test samples are summarized in Table 3 below.

Table 3. Affected Samples used in Microarray studies

Samples	Sample Diagnosis	Tumor Grade	FIGO stage
1	Endometroid carcinoma	G1	Ia
2	Endometroid carcinoma	G1	Ib
3	Endometroid carcinoma	G1	Ib
4	Endometroid carcinoma	G1	Ib
5	Endometroid carcinoma	G1	Ia
6	Endometroid carcinoma	G1	Ia
7	Endometroid carcinoma	G1	Ia
8	Endometroid carcinoma	G2	Ib
9	Endometroid carcinoma	G2	IIb
10	Endometroid carcinoma	G2	IIIa
11	Endometroid carcinoma	G2	Ib
12	Endometroid carcinoma	G2	Ic
13	Endometroid carcinoma	G2	Ia
14	Endometroid carcinoma	G2	Ic
15	Endometroid carcinoma	G2	Ic
16	Endometroid carcinoma	G2	Ib
17	Endometroid carcinoma	G2	IIb
18	Endometroid carcinoma	G2	IIb
19	Endometroid carcinoma	G2	Ib
20	Endometroid carcinoma	G2	Ic
21	Endometroid carcinoma	G2	IVb
22	Endometroid carcinoma	G2	IIb
23	Endometroid carcinoma	G2	Ic
24	Endometroid carcinoma	G2	IIb
25	Endometroid carcinoma	G2	Ib
26	Endometroid carcinoma	G2	Ic
27	Endometroid carcinoma	G2	Ib
28	Endometroid carcinoma	G2	Ib
29	Endometroid carcinoma	G2	IIb
30	Endometroid carcinoma	G2	Ib
31	Endometroid carcinoma	G3	Ic
32	Endometroid carcinoma	G3	IIIa
33	Endometroid carcinoma	G3	IIb
34	Endometroid carcinoma	G3	IIb
35	Endometroid carcinoma	G3	Ib
36	Endometroid carcinoma	G3	IIa
37	Endometroid carcinoma	G3	IIa
38	Endometroid carcinoma	G3	Ic
40	ATIPIC HIPERPLASIA		
41	ATIPIC HIPERPLASIA		
42	ATIPIC HIPERPLASIA		
43	Serous carcinoma	G3	IIIc
44	Serous carcinoma	G3	IIIc
45	Serous carcinoma	G3	Ib
46	Serous carcinoma	G3	Ib
47	Serous carcinoma	G3	IIIa
48	Clara cell type	G3	IIIc
49	Undifferenciated	G3	IIb
50	Undifferenciated	G3	IIIa
51	Villoglandular	G3	Ib
52	Villoglandular	G2	Ib
53	Adeno-squamous	G2	Ib
54	Adeno-squamous	G2	IIb
55	Adeno-squamous	G3	Ic
56	Mucinous type	G3	IIIa

Total RNA was extracted with the RNeasy mini kit (Qiagen, Hilden, Germany), following the instructions provided by the manufacturer. Quantity and quality of the obtained RNA was measured with a Nanodrop (Nandrop ND-1000, Agilent 2100

Bioanalyzer) and low quality RNA was discarded from the array hybridization process.

Microarray Design

Microarrays for Gene Expression were designed by the Tethys algorithm using the ENSEMBL database. For sequences where we did not find high quality probes, we complemented the design with Oryzon Optimized Agilent probes. DNA microarray synthesis was outsourced to Agilent.

The Whole Genome Gene Expression Array contains:

- 20148 Oryzon High Quality probes from ENSEMBL Database.
- 5698 Oryzon Tm optimized Agilent probes.

The total number of probes was 25846.

aRNA labeling

Cy3 and Cy5 labeled aRNA was produced using the MessageAmplification kit by Ambion (Ref: 1819 for 96x kit or Ref: 1751 for 20x kit). These kits are used with some modifications introduced by Oryzon genomics. RNA labeling was performed essentially using the Eberwine protocol (Van Gelder, 1992) commercialized by Ambion with the MessageAmplification Kit (Ambion/Applied Biosystems) with minor modifications. 500 ng of total RNA was reverse transcribed in presence of oligo$(dT)_{24}$, second-strand synthesis was generated and transcription of this dsDNA was prepared using CTP_Cy3 or CTP_Cy5 (PerkinElmer). Amplified cRNA was quantified by Nanodrop ND-1000 and cRNA quality was controlled with the Agilent RNA Bionalyzer 2100.

Microarray hybridization

Microarray hybridization was performed at 60°C and 17 hours hybridization time according to Agilent indications, using Agilent gaskets (G2534-60002), Agilent hybridization chambers (G2534A) and in an Agilent DNA Hybridization Oven (G2545A). Oryzon hybridization controls are also used in hybridization process. Controls for the hybridization process corresponding to 3 cDNA clones of maize (Xet, Zm42,Exp) were included in all analysis. Exp is used as the negative spike control and was not amplified nor labeled. For Xet and Zm42 PCR fragments were

generated by PCR amplification from the vector with universal primers and cRNA was generated using in vitro transcription systems (T7 or T3 Megascript kit; Ambion) with CTP_Cy3 or CTP_Cy5 (PerkinElmer). Both of the positive spike controls Xet and Zm42 were with both the Cy5 and Cy3 fluorofor.

Data Acquisition

Initial Raw Data were obtained using an Agilent DNA Microarray Scanner (G2505B) and Agilent acquisition software (Feature Extraction Software). The extraction protocol performed does not use background subtraction, computation of dye biases and ratio correction.

Data analysis

A large number of controls were included in the microarray designs to monitor scanner and array performance and to control spatial homogeneity and correct deviations. This way, the overall error on the microarray data measurements can be estimated by the spreading analysis of the data from the controls.

The mean fold change or M values can be ranked based on their probability of being different from 0, according to the absolute value of the regularized t-statistic (Baldi and Long, 2001) which uses a Bayesian framework to derive a modified and improved t-student statistics. To make Fold Change based selection, the mean M distribution was used. This distribution is adjusted to a normal distribution and an iterative process is used to define the mean M numbers that are outside the distribution. The cut-off is chosen as n times the Standard deviations (σ) from the mean. This method generates a robust mean and standard deviation and allows to dynamically adjusting the cut-off value to the noise distribution of the data. Typically, values with mean FC>3σ or mean FC<-3σ of the sample data distribution were selected.

An indirect analysis comparison where the expression levels of particular biomarkers in tumor samples were compared to a reference RNA pool obtained from a group of over 20 cell lines (melanoma, lung cancer, ovarian cancer, colon cancer, and several non-cancer cell lines). The expression level of particular genes in the normal samples (controls) were compared to the same reference pool and final expression

fold changes between tumor and normal endometrial tissue were generated *in silico* eliminating the reference pool.

Candidate genes were selected as biomarkers for endometrial cancer based on fold overexpression, p-value, and other factors. Table 1 in the Detailed Description of the Invention shows 17 overexpressed genes and 3 genes underexpresssed identified using these procedures. The overexpression of these genes was validated by RT-PCR as described in the next examples.

The results from the microarray studies are summarized in Table 1 in the Detailed Description of the Invention, which shows the common abbreviation used for the gene, the ENSMBL gene, transcript and protein accession numbers along with the fold overexpression and calculated p-values.

Example 2: Uterine Fluid Sample Preparation

Endometrial aspirates were collected with the help of a Cornier pipelle, after complete informed consent was obtained from all patients. The aspirate (uterine fluid) was immediately transferred to an eppendorf tube containing 500 microliters of a RNA preserving solution (RNA later, Ambion). The sample was centrifuged and the pellet containing a representative population of cells from the uterine cavity was further processed for RNA extraction (Qiagen). Quality tests (Bioanalyzer) were performed before the analysis of gene expression by Taqman technology for the selected markers of endometrial carcinoma.

Example 3: Correlation of Biomarkers in Primary Tumor and in Uterine Fluid

The levels of biomarkers from primary tumor sample and uterine fluid sample obtained by the procedure of Example 2 were compared as by RT-PCR following the general RT-PCR protocol as described in Example 4. The biomarkers in this study included ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN whose expression level was found to be surprisingly correlated between the primary tumor and endometrial aspirates (uterine fluid). See Figure 1. As can be seen in Figure 1, the expression level of a number of biomarkers of endometrial cancer are correlated in uterine fluid and primary tumor. In

particular, it was found that there was a high level of correlation of expression of biomarkers corresponding to ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN in tumor sample and in samples obtained from uterine fluid. Thus, the inventors have surprisingly finding of a group of genes that can be used to diagnosis or predict an increased likelihood of endometrial cancer based on their expression levels in samples obtained from uterine fluid. Furthermore, the inventors have shown that uterine fluid can be used to assess biomarkers for endometrial cancer. For example, prognostic biomarkers for endometrial cancer, biomarkers for staging endometrial cancer, biomarkers for determining the type of endometrial cancer (*e.g.*, Type 1 vs. Type II) or type (endometrioid, clear cell, serrous, *etc.*), auxiliary diagnostic biomarkers, differential diagnosis biomarkers, can be assayed in uterine fluid to characterize the cancer.

Example 4: Confirmation of Overexpression of Biomarkers byquantitative RT-PCR

Once array data were obtained, a group of upregulated and downregulated genes in tumor samples compared with normal tissue were selected in-part based on their p-values and standard deviations. These candidates were selected to determine their expression levels by an independent technique using a different set of tumor samples.

Microfluidic Cards (MFC) from Applied Biosystems were used to perform RT-PCR with RNA isolated from tumor and normal endometrial tissue samples. In this case both types of tissues, healthy and carcinogenic were obtained from the same patient by microdissection procedures. These studies confirmed the microarray results for most of the markers of Table 1. Another set of RT-PCT studies were performed using aspirates obtained from endometrial cancer patients (confirmed) and aspirates from non-affected individuals. These studies using aspirates samples are described in more detail below.

Aspirate samples were obtained following a procedure similar to that described in Example 2. The description of patient characteristics for the affected and non-affected samples are given in Table 4 and Table 5 below.

Briefly, wells of the Microfluidic Card contain Applied Biosystems fluorogenic 5′ nuclease assays that detect the real-time amplification of the array selected targets. Relative levels of gene expression are determined from the fluorescence data generated during PCR using the ABI PRISM® 7900HT Sequence Detection System (7900HT SDS) Relative Quantification software.

Data analysis was made using the comparative ΔΔCt method of relative quantification. Differentially expressed genes were confirmed by thorough statistical analysis using a modified T- test.

The samples used for the study described in this Example included:
Samples from 30 patients having endometrial cancer: 25 endometroid adenocarcinomas with 9 in G3, 9 in G2 and 7 in G1. And 5 tumor samples from different type II carcinomas (4 in G3 and 1 in G2)

Samples from 24 patients not having endometrial cancer ("controls" or "normals"). These were a heterogeneous mix of samples some of them from patients with other non-tumoral pathologies liked polyps: 4 samples from patients with atrophic endometriod, 4 normal samples, two from patients having polyps from post-menopausical women and 11 samples from pre-menopausical women (7 of them in secretory phase and 4 in proliferative phase of the cycle). See Tables below for a summary of samples.

Table 4: Affected Samples for RT-PCR Studies

Aspirates from women with a tumor	Sample Diagnosis	Tumor Grade	FIGO stage
1	Endometroid carcinoma	G1	IIb
2	Endometroid carcinoma	G1	Ia
3	Endometroid carcinoma	G1	Ib
4	Endometroid carcinoma	G1	Ib
5	Endometroid carcinoma	G1	Ia
6	Endometroid carcinoma	G1	Ia
7	Endometroid carcinoma	G1	Ib
8	Endometroid carcinoma	G2	IIb
9	Endometroid carcinoma	G2	Ib
10	Endometroid carcinoma	G2	Ib
11	Endometroid carcinoma	G2	Ib
12	Endometroid carcinoma	G2	Ib
13	Endometroid carcinoma	G2	Ia
14	Endometroid carcinoma	G2	Ia
15	Endometroid carcinoma	G2	Ib
16	Endometroid carcinoma	G2	Ib
17	Endometroid carcinoma	G3	IIb
18	Endometroid carcinoma	G3	Ic
19	Endometroid carcinoma	G3	Ic
20	Endometroid carcinoma	G3	Ib
21	Endometroid carcinoma	G3	Ic
22	Endometroid carcinoma	G3	Ib
23	Endometroid carcinoma	G3	Ib
24	Endometroid carcinoma	G3	Ib
25	Endometroid carcinoma	G3	Ic
26	Clara Cell type	G3	IIb
27	Clara Cell type	G3	IIIc
28	Adeno-squamous	G3	IIIa
29	Undifferenciated	G3	IIIc
30	squamo-transitional	G2	Ib

Table 5: Non-Affected Samples for RT-PCR Studies

Control aspirates
7 pre-menopausic in secretory phase
6 pre-menopausic in proliferative phase
11 aspirates from postmenopausical women

Experimental procedures

RNA samples were isolated from aspirate samples following the procedure above described and a quality control was performed previously to final sample selection. Aspirate samples were collected as described in Example 2.

RT-PCR was performed following Applied Biosystem standard protocol for the 7900HT system. The protocol consisted in a two-step method where the first step is

the generation of cDNA from the RNA samples using a High Capacity cDNA Kit and the second step is the amplification of cDNA, once loaded in the MFC, by the ABI PRISM® 7900 HT system.

RT-PCR data were collected for a set of 20 genes identified in Example 1 and quantified relative to POLR2A levels. The RQ values for the aspirates corresponding to the 30 tumor samples and the 24 samples that were not endometrial cancer (normals) are illustrated in a box and whiskers plot, see Figure 2A and 2B. Table 2 in the Detailed Description of the Invention gives a summary of the mean RQ values, standard error of the mean and p-values calculated for these markers in this sample set. As can be seen, the p-values obtained using the control sample set in the microarray studies (Table 1) were significantly improved in a different sample set using different techniques (microarray versus RT-PCR) and different sources of sample (aspirates versus primary tumor). In most cases the p-value improved over 100-fold for the biomarkers. This is related in part to the robust nature of the microarray experimental design and robust selection of markers based on the Inventors' criteria.

The next table shows the sensitivity and specificity for each individual gene on the patent application and the area under de ROC (AUROC) curve for each gene when comparing the RQ values from the 30 tumour samples and the 24 control samples. A support vector machine (SVM) program was used to calculate the data. As can be seen in the table below, the markers identified in these studies have excellent sensitivity and/or specificity for predicting an increased likelihood and/or diagnosis of endometrial cancer. Furthermore, the AUROC values for these biomarkers indicate that these markers are very useful for diagnosis of endometrial cancer.

Table 6: Sensitivity, Specificity and AUROC values for the biomarkers of the invention determined from aspirates samples in affected (endometrial cancer) and non-affected individuals.

GENE	sensitivity	specificity	AUROC
ACAA1	66.67%	90.00%	0.81
AP1M2	58.33%	86.67%	0.83
CGN	79.17%	76.67%	0.81
DDR1	79.17%	90.00%	0.89
EPS8L2	70.83%	86.67%	0.81
FASTKD1	70.83%	76.67%	0.84
GMIP	75.00%	83.33%	0.88
IKBKE	83.33%	73.33%	0.90
P2RX4	62.50%	96.67%	0.82
P4HB	91.67%	96.67%	0.97
PHKG2	70.83%	93.33%	0.84
PPFIBP2	58.33%	96.67%	0.78
PPP1R16A	75.00%	80.00%	0.85
RASSF7	100.00%	60.00%	0.89
RNF183	95.83%	73.33%	0.88
SIRT6	79.17%	73.33%	0.84
TJP3	79.17%	76.67%	0.82
EFEMP2	66.67%	83.33%	0.88
SOCS2	79.17%	93.33%	0.93
DCN	66.67%	90.00%	0.85

Control samples were a heterogeneous group with pre and post-menopausical women. At the same time, aspirates from pre-menopausical women could be divided in two categories depending of the uterine endometrial cycle phase they were when the sample was taken: proliferative or secretory. The characterization of secretory versus proliferative phase patients was accomplished by a pathologist using standard techniques.

Some of the genes tested could give a false positive result for endometrial cancer if the aspirate was taken from pre-menopausical women in secretory phase. In order to check which genes could give false positives depending of the cycle phase or which others could distinguish between tumour samples and secretory phase, we performed a statistical analysis comparing tumours with different control groups.

- tumors versus control samples (all the control samples: 24 samples)
- tumors versus control samples minus the ones in secretory phase: 17 samples
- tumors samples versus control samples in secretory phase: 7 samples

- tumors samples versus control samples from postmenopausical women: 11 samples

The area ROC for each comparison was calculated using the GraphPad Prism program and anova test was applied to see if the differences among these groups were significant.

In the Tables below the following abbreviations are used for p-values:
*** $p<0.0001$
** $p<0.001$
*$p<0.01$
ns (not significant).

As it is shown on the tables there are genes, like P4HB or SOCS2, which separate the tumour samples from the control independently of the nature of the control samples (post-menopausical, pre-menopausical in secretory or in proliferative). Other genes like P2RX4 or PPFIBP2, could distinguish between a tumour sample (affected) and a sample in secretory phase better as compared to controls from postmenopausical women.

This observation opens the possibility of using different algorithms and/or different set of genes depending if the test is interrogating pre-menopausical or post-menopausical women. Furthermore, a primary modality for screening for endometrial problems is the trans-vaginal ultrasound which is used to estimate endometrial thickness where patients having a thicker endometrium (over a certain threshold) are likely to have endometrial cancer or another disease or condition. Endometrium thickness also varies as a function of the phase of the menstrual with individuals in secretory phase having a thicker endometrium as compared to individuals in proliferative phase. Thus, these finding indicate that the methods and biomarkers of the invention can be used to aid and improve the ability of transvaginal ultrasound to identify endometrial cancer.

Table 7: Summary of Data for RT-PCR Studies comparing the expression levels of biomarkers in aspirates (30) from patients affected with endometrial cancer and aspirates obtained from individuals all patients non affected with endometrial cancer (24).

Comparison por 30T/ 24Crtl	ROC 30Tvs24Ctrl	Anova
P4HB	0.974	***
SOCS2	0.955	***
IKBKE	0.897	***
RNF183	0.883	***
EFEMP2	0.881	***
PHKG2	0.875	***
DCN	0.854	***
PPP1R16A	0.846	***
AP1M2	0.843	***
FASTKD1	0.838	***
SIRT6	0.836	***
CGN	0.829	***
GMIP	0.824	***
TJP3	0.824	***
RASSF7	0.817	***
ACAA1	0.817	***
EPS8L2	0.813	***
P2RX4	0.807	***
DDR1	0.769	**
PPFIBP2	0.745	*

Table 7 shows that the 20 biomarkers capable of distinguishing aspirates from endometrial cancer affected patients from aspirate from all control non-affected patients with high ROC values and/or excellent statistical significance.

Table 8: Summary of Data for RT-PCR Studies comparing the expression levels of biomarkers in aspirates (30) from patients affected with endometrial cancer and aspirates obtained from individuals patients non-affected with endometrial cancer and that were not in secretory phase (17)

comparison 30T/ 17 Ctrl	ROC 30T vs 17Ctrl	Anova
P4HB	0.963	***
SOCS2	0.936	***
RNF183	0.904	***
EFEMP2	0.900	***
FASTKD1	0.863	***
AP1M2	0.859	***
IKBKE	0.858	***
PHKG2	0.845	***
CGN	0.832	***
SIRT6	0.828	**
PPP1R16A	0.817	**
DCN	0.801	**
TJP3	0.8	**
GMIP	0.798	***
RASSF7	0.798	**
ACAA1	0.784	**
EPS8L2	0.767	**
P2RX4	0.728	*
DDR1	0.680	ns
PPFIBP2	0.644	ns

Table 8 shows the rankings of 20 biomarkers of the invention capable of distinguishing aspirates from endometrial cancer affected patients from aspirates from all control non-affected patients excluding patients in the secretory phase. Table 7 shows the biomarkers of the invention have high ROC values and/or excellent statistical significance for separating these populations.

Table 9: Summary of Data for RT-PCR studies comparing the expression levels of biomarkers in aspirates (30) from patients affected with endometrial cancer and aspirates obtained from individuals patients non affected with endometrial cancer and that were in secretory phase (7)

comparison 30T/ 7 Sec	ROC 30T vs 7 Sec	Anova
P4HB	1	**
SOCS2	1.000	***
P2RX4	1	***
IKBKE	0.991	***
PPFIBP2	0.991	**
DDR1	0.986	**
DCN	0.981	**
PHKG2	0.948	**
EPS8L2	0.924	*
PPP1R16A	0.917	**
GMIP	0.9	*
ACAA1	0.895	*
TJP3	0.881	*
RASSF7	0.864	*
SIRT6	0.857	*
EFEMP2	0.833	ns
RNF183	0.831	ns
CGN	0.82	ns
AP1M2	0.805	ns
FASTKD1	0.779	ns

As can be seen in the Table 9 preferred markers capable of distinguishing aspirates from endometrial cancer affected patients from aspirates from non-endometrial cancer affected patients in secretory phase include P4HB, SOCS2 P2RX4, IKBKE, PPFIB2, DDR1 and DCN which have high ROC values and/or excellent statistical significance.

As seen from the data in Tables 7 & 9 above examples of genes capable of differentiating between aspirates from patients having tumor and aspirates from all non-affected patients (including secretory phase) and/or between aspirates from patients having tumor and aspirates from non-affected patients in secretory phase include P4HB, SOCS2, and IKBKE which have high statistical significance and ROC values.

Table 10: Summary of Data for RT-PCR Studies comparing the expression levels of biomarkers in aspirates (30) from patients affected with endometrial cancer and aspirates obtained from post-menopausal patients non affected with endometrial cancer (11).

Ranking por 30T/ 11N	ROC 30Tvs11crtl postm	Anova
PHKG2	0.9476	*
P4HB	0.9424	***
EFEMP2	0.903	***
RNF183	0.8909	***
SOCS2	0.8667	*
FASTKD1	0.8439	**
GMIP	0.8394	**
SIRT6	0.8364	**
AP1M2	0.8182	*
IKBKE	0.7955	ns
CGN	0.7864	*
PPP1R16A	0.7652	ns
TJP3	0.7515	ns
RASSF7	0.7515	ns
ACAA1	0.7242	ns
DCN	0.7167	ns
EPS8L2	0.697	ns
P2RX4	0.6303	ns
DDR1	0.5879	ns
PPFIBP2	0.5318	ns

As can be seen in the Table 10 preferred markers capable of distinguishing aspirates from endometrial cancer affected patients from aspirate from post menopausal non endometrial cancer affected patients include PHKG2, P4HB, EFEMP2, RNF183, and SOCS2 which have high ROC values and/or excellent statistical significance.

In reference to Figure 2A and 2B (box and whisker plot), RQ: relative quantity, it is the relative amount of RNA for a specific gene present on the tumours samples referred to the amount present on the control sample for the same gene.

To calculate the RQ the Ct values of each gene were normalise respect to the Ct of the endogenous gene to get the delta Ct. The formula $2^{-(deltaCt)}$ was used to calculate de RQ.

A number of endogenous genes can be used as a control for normalization as well as other controls for normalization. In one example a preferred endogenous gene has the following characteristics: it is a gene constitutively expressed in the same tissue under different circumstances like for example cancer development. So it could be used to normalize differences in the amount of cDNA when loading the samples or variations due to experimental reasons for the qRT-PCR.

We have tested four different housekeeping genes as possible endogenous genes for normalization purposes: 18S, B2M, PFN-1 and POLR2A. Finally, POLR2A was the most stable gene from all of them and all the calculations and statistics were done using it as endogenous. Its expression level is similar to the genes questioned in our test and different as compared to 18 S whose expression is quiet high compared to the genes selected for the test. It is contemplated that endogenous biomarkers such as POLR2A, B2M, PFN1, HMBS, G6PD, or PABPN1 or another stable gene can be used for normalization purposes in the methods of the inventionif they so require.

Example 5: Profiles for Diagnosing Endometrial Cancer

A support vector machine based algorithm was used to identify combinations of markers of Table 1 that are useful for predicting endometrial cancer and/or an increased likelihood of having endometrial cancer. In particular, the publically available program DTREG program was used to analyze the data (see the www at DTREG.COM).

Support vector machine algorithm can be used for many applications including identifying gene expression profiles for separating populations having different phenotypic characteristics. The idea behind the algorithm is a multidimensional representation of the data, *e.g.*, each marker is plotted on a different dimension and a plane is sought though this multidimensional representation of the data that can separate the phenotypes. The plan through the "middle" is referred to as the separating hyperplane and represents a solution: answers (*e.g.*, expression level over a given threshold value) that fall on one side of the line fall into one category (*e.g.*, cancer) and answers (*e.g.*, expression level over a given threshold value) that follow on the other side of the line correspond to the other category (*e.g.*, no cancer). A

number of separating hyper plane can be possible for each dataset. The question becomes which is the best separating hyperplane. In support vector machine theory, the best solution is referred to as the maximum margin hyperplane. This maximum margin hyperplane is the one that separates the two groups and adopts the maximal distance from any one of the given expression profiles.

Although individual genes show a high sensitivity and specificity, these parameters are even higher when combined several genes. Some examples of the sensitivity , specificity and AUROC genes combined two to two, three to three, four to four, five to five, six to six, seven to seven and all of them together. See the Table below for a summary of the data.

Table 11: Data Summarizing Predictive Values for Combinations

combinations	sensitivity	specificity	AUROC
IKBKE+P4HB	91.67%	100.00%	0.978
IKBKE+SOCS2	79.17%	96.67%	0.951
P4HB+SOCS2	91.67%	100.00%	1
GMIP+IKBKE	79.17%	90.00%	0.915
GMIP+P4HB	95.83%	96.67%	0.982
GMIP+SOCS2	100.00%	86.67%	0.999
GMIP+SOCS2+IKBKE	95.83%	100.00%	1
GMIP+SOCS2+P4HB	91.67%	100.00%	0.983
GMIP+IKBKE+P4HB	91.67%	100.00%	0.978
IKBKE+P4HB+SOCS2	91.67%	100.00%	0.981
GMIP+IKBKE+P4HB+SOCS2	100.00%	100.00%	1
GMIP+SOCS2+IKBKE+EPS8L2	91.67%	100.00%	0.993
GMIP+SOCS2+P4HB+EPS8L2	91.67%	100.00%	0.976
GMIP+IKBKE+P4HB+EPS8L2	91.67%	100.00%	0.976
IKBKE+P4HB+SOCS2+EPS8L2	87.50%	100.00%	0.981
GMIP+IKBKE+P4HB+SOCS2+DDR1	91.67%	100.00%	1
GMIP+IKBKE+P4HB+SOCS2+EPS8L2+PPP1R16A	91.67%	100.00%	0.999
GMIP+IKBKE+P4HB+SOCS2+PHKG2+RASSF7	95.83%	100.00%	1
GMIP+IKBKE+P4HB+SOCS2+DDR1+EPS8L2	95.83%	100.00%	1
GMIP+IKBKE+P4HB+SOCS2+EPS8L2+PPP1R16A+DDR1	95.83%	100.00%	1
DDR1+EPS8L2+GMIP+IKBKE+P2RX4+P4HB+PHKG2+PPP1R16A+RASSF7+SIRT6+TJP3+SOCS2	100.00%	100.00%	1
DDR1+EPS8L2+GMIP+IKBKE+P2RX4+P4HB+PHKG2+PPP1R16A+RASSF7+SIRT6+TJP3+SOCS2+RNF183	100.00%	100.00%	1
ALL TOGETHER: 20 GENES	100.00%	100.00%	1

As can be seen in the Table above very high sensitivity and specificities were obtained for combinations of the biomarkers of the invention and the AUROC values are very high. Thus, these results show that combinations of 2 or more markers chosen from ACAA1, AP1M2, CGN, DDR1, EPS8L2, FASTKD1, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPFIBP2, PPP1R16A, RASSF7, RNF183, SIRT6, TJP3, EFEMP2, SOCS2, and DCN give unexpectedly good sensitivity and specificity for predicting an increased likelihood and/or diagnosing endometrial cancer. These results were obtained from samples from uterine fluid and indicate that combinations of biomarkers detected in uterine fluid can be useful for diagnosing and/or characterizing endometrial cancer. Furthermore, these results were obtained in samples from pre and post menopausal women and therefore represents a set of

markers that can be examined across these types of patients. It is noted that different programs and algorithms can be used to generate profiles or fingerprint patterns. The invention is intended to encompass profiles and/or fingerprint patterns using programs and algorithms other than DTREG as used herein. The profiles identified in Table 11 are non-limiting examples used to illustrate that combinations of the biomarkers of Table 1 have excellent sensitivity and specificity for endometrial cancer.

Additional combinations

The values of sensitivity and specificity although fully define the validity of a diagnostic test have the disadvantage of not providing relevant information when making a clinical decision to a particular test result. However, they have the advantage of been intrinsic properties to the test and define its validity irrespective of the prevalence of the disease in the population to which it applies.

Sensitivity

It is the probability of classifying correctly an individual patient or the probability that a individual with cancer obtains a positive result when applying the diagnostic test

Specificity

It is the probability of classifying correctly a healthy individual or the probability that a healthy individual obtaining a negative result when applying the diagnostic test Sensitivity and specificity can, therefore, to assess the validity of a diagnostic test. However, these concepts are not much help in clinical practice. When a patient undergoes a diagnostic test, the doctor has no a priori information about their diagnosis so the question arises to the next one: given a positive (or negative) on the test? What is the probability that the individual tested has the disease (or not)? These probabilities are known as positive predictive value and negative predictive value of a particular test. Positive predictive value is the probability of having the disease if the individual has a positive result when applying the diagnostic test. Negative predictive value is the probability that an individual who has obtained a negative result on the test, is actually healthy.

Clinicians prefer diagnostic tests with high negative predictive value as they can not allow people with cancer get a wrong diagnosis. For this reason we have prioritized these combinations which give us the highest negative predictive values.

The follow values in Table 12 were calculated using the indicated markers as determined by RT-PCR in uterine fluid samples.

Table 12

	DTREG-SVM				
combinations	sensitivity	specificity	AUROC	NPV	PPV
P4HB+SOCS2	91,67%	100,00%	1	93,75%	100,00%
GMIP+IKBKE+P4HB+SOCS2	100,00%	100,00%	1	100,00%	100,00%
GMIP+IKBKE+P4HB+SOCS2+FASTKD1	100,00%	100,00%	1	100,00%	100,00%
GMIP+IKBKE+P4HB+SOCS2+DDR1	95,83%	100,00%	1	96,77%	100,00%
GMIP+IKBKE+P4HB+SOCS2+PHKG2	91,67%	100,00%	1	93,75%	100,00%
GMIP+IKBKE+P4HB+SOCS2+SIRT6	91,67%	100,00%	1	93,75%	100,00%
GMIP+IKBKE+P4HB+SOCS2+ACAA1	100,00%	100,00%	1	100,00%	100,00%
GMIP+IKBKE+P4HB+SOCS2+AP1M2	91,67%	96,67%	0,979	93,55%	95,65%
GMIP+IKBKE+P4HB+SOCS2+EFEMP2	91,67%	100,00%	1	93,75%	100,00%
GMIP+IKBKE+P4HB+SOCS2+EPS8L2	91,67%	100,00%	1	93,75%	100,00%
GMIP+IKBKE+P4HB+SOCS2+P2RX4	83,33%	96,67%	0,964	87,88%	95,24%
GMIP+IKBKE+P4HB+SOCS2+PPFIBP2	91,67%	96,67%	0,979	93,55%	95,65%
GMIP+IKBKE+P4HB+SOCS2+PPP1R16A	95,83%	100,00%	1	96,77%	100,00%
GMIP+IKBKE+P4HB+SOCS2+ACAA1+FASTKD1	100,00%	100,00%	1	100,00%	100,00%
GMIP+IKBKE+P4HB+SOCS2+FASTKD1+PHKG2	100,00%	100,00%	1	100,00%	100,00%
GMIP+IKBKE+P4HB+SOCS2+FASTKD1+SIRT6	100,00%	100,00%	1	100,00%	100,00%
ACAA1+AP1M2+EPS8L2+IKBKE+P2RX4+P4HB+PPFIBP2+PPP1R16A+SIRT6+EFEMP2	100,00%	100,00%	1	100,00%	100,00%
GMIP+IKBKE+P4HB+EFEMP2	100,00%	93,33%	0,999	100,00%	92,31%
DDR1+FASTKD1+GMIP+IKBKE+P4HB+PHKG2+SIRT6+EFEMP2+SOCS2	100,00%	100,00%	1	100,00%	100,00%
DDR1+FASTKD1+GMIP+IKBKE+P4HB+PHKG2+SIRT6+EFEMP2	100,00%	100,00%	1	100,00%	100,00%
P4HB+EFEMP2+IKBKE+GMIP+FASTKD1	100,00%	100,00%	1	100,00%	100,00%

The combinations shown in FIG. 18 (P4HB, EFEMP2, SIRT6, DDR1, GMIP, and FASTKD1) and FIG. 19 (P4HB, EFEMP2, SIRT6, PHKG2, GMIP, and FASTKD1) , and the combination of all 20 markers have sensitivities, specificities, NPVs, and PPVs of 100% and AUROCs of 1.

Maximizing Negative Predictive Value: New samples: three new cancer samples and 24 no tumor samples giving a total amount of samples in the following analysis (33T and 48 non tumor) with the additional sample having the following characteristics:

Aspirates from women with a tumor	Sample Diagnosis	Tumor Grade	FIGO stage
31	Endometroid carcinoma	G1	IA
32	Endometroid carcinoma	G2	IB
33	Endometroid/squamo-transitional	G3	IA

Control aspirates
4 pre-menopausic in secretory phase
5 pre-menopausic in proliferative phase
4 pre-menopausic (unknown cycle phase)
11 aspirates from postmenopausical women

The calculated the risk of cancer for 48 non tumor and 33 tumor samples using the following combination of genes ACAA1, AP1M2, EPS8L2, IKBKE, P2RX4, P4HB, PPFIBP2, PPP1R16A, SIRT6, and EFEMP2 the result is shown in FIG. 17.

FIG. 18 shows the calculated risk of cancer for the 48 non-tumor and 33 tumor samples using FASTKD1, GMIP, P4HB, EFEMP2, DDR1, and SIRT6.

FIG. 19 shows the calculated risk of cancer for the 48 non-tumor and 33 tumor samples using FASTKD1, GMIP, P4HB, EFEMP2, PHKG2, and SIRT6.

As shown on FIG. 17, the first combination is able to classify all the samples correctly but the percentage of some healthy samples of having cancer are very close to 50%: some cancer samples are too close to be misclassified when using this combination. In summary, the risk of misclassifying cancer patients with a false diagnosis. Although the combinations in FIG. 18 and FIG. 19 misclassify one and two healthy patients samples respectively, both of them classify correctly all the cancer patients and they do it with a higher percentage of risk of cancer than the previous combination. For that reason these combinations are valuable from a clinical point of view. Example 6: Detection of Protein Corresponding to the Biomarkers of Table 1

Detection of protein corresponding to the Biomarkers of Table 1 can be accomplished by any number of means available to the skill artisan. According to this method samples from controls (or a control value is established) and affected individuals are obtained (*e.g.*, serum, tissue, and uterine fluid) and probe for with antibodies selective or specific to the particular biomarker. One method for detecting the proteins is by western blot analysis and is exemplified as in the case of P4HB.

Western blot analysis from human samples from normal endometrial yissue and tumour endometrial cancer tissues in order to test the protein level of P4HB (aprox. 60 kDa) in these samples.

Gels were loaded with 40 ug of total protein extracts from each sample. As can be seen in Figure 10, tumor samples stained much more strongly for P4HB as compared to normal tissue.

The samples tested include four normal tissues (N) and four tumour tissues (T). Normal and tumours tissues were obtained from the same patient. As a positive control: total protein extract from the endometrial tumour cell line Isikawa. The Antibody used: LS-C38385 from LifeSpan.

The results confirm to protein level the results obtained in the array and the TaqMan experiments.

Western blot analysis was performed for AP1M2, IKBKE, EPS8L2, DDR1, CGN, and TJP3. See FIG.X through FIG.X. These results confirm at the protein level the results obtained in the array and the TaqMan experiments for these biomarkers.

For immunohistochemistry validation, tissue microarrays were constructed. In order to cover the complete range from normal tissue to different types and grades of endometrial carcinomas, representative areas from 70 paraffin-embedded carcinomas (56 endometrioid, 6 serous papillary, 1 mucinous, 4 clear cell carcinomas, 3 carcinosarcomas), and 11 non-neoplastic endometria (4 atrophic, 3 proliferative, 1 secretory endometrial and 3 hyperplasias), were carefully selected and marked on individual paraffin blocks. Two tissue cores of 1mm in diameter were obtained from each paraffin block and were precisely arrayed in a new paraffin block. Sections of 5μm were obtained from all tissue microarray paraffin blocks. The protocol was approved by the Institutional Review Board at Hospital Vall D'Hebron, and informed consent was obtained from all of the patients. P4HB, PPP1R16A and EPS8L2 were detected by the indirect immunoperoxidase assay with citrate buffer pH 7,3 for antigen retrieval. Sections were incubated with a primary antibodies against P4HB (LS-C38385) and PPP1R16A (H00084988-M06) for 1 h at room temperature using a

dilution 1:500 and 1:100, respectively, and EPS8L2 (H00064787-B01) overnight at 1:100 dilution. Thereafter sections were incubated with peroxidase conjugated goat anti-mouse immunoglobulin (EnVision Dual System, DAKO, Glostrup, Denmark). Endogenous peroxidase activity was quenched with 3% H2O2. Sections were washed, and reactions were developed with diaminobenzidine, followed by counterstaining with haematoxylin. Semiquantitative evaluation of the proteins was performed by three independent investigators, scoring the intensity of the stained and the percentage of positive cells.

TMA immunohistochemistry confirmed the differential expression of the three proteins at the tumoral glands when compared to the normal endometrial glands. P4HB, PPP1R16A and EPS8L2 presented a specific cytoplasmatic expression within the tumoral cells in all carcinoma histological types and grades, and an absence or faint cytoplasmatic stain within the normal epithelial glands. These results confirm at the protein level the results obtained for these proteins in the microarray and quantitative PCR experiments described herein.Example 7: ACAA1

ACAA1 was found to be overexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that ACAA1 was overexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue and it was surprisingly found that ACAA1 was overexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the methods described in Examples 2-4. Example 5 shows that ACAA1 can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

The sequence of an mRNA corresponding to ACAA1 is given in ENSEMBL accession no. ENST00000333167 and has a sequence as in SEQ ID NO:1

1 ATGTGGTTCTGCGCGTGTGCGGACGGCTGTCTGTTAACTCCGCGGTCAGTTCCCGGACTG
61 GTGGCTGGTCTGCAGGGTTGACCTGCGCA**ATG**CAGAGGCTGCAGGTAGTGCTGGGCCACC
121 TGAGGGGTCCGGCCGATTCCGGCTGGATGCCGCAGGCCGCGCCTTGCCTGAGCGGTGCCC
181 CGCAGGCCTCGGCCGCGGACGTGGTGGTGGTGCACGGGCGGCGCACGGCCATCTGCCGGG
241 CGGGCCGCGGCGGCTTCAAGGACACCACCCCCGACGAGCTTCTCTCGGCAGTCATGACCG
301 CGGTTCTCAAGGACGTGAATCTGAGGCCGGAACAGCTGGGGGACATCTGTGTCGGAAATG
361 TGCTGCAGCCTGGGGCCGGGGCAATCATGGCCCGAATCGCCCAGTTTCTGAGTGACATCC
421 CGGAGACTGTGCCTTTGTCCACTGTCAATAGACAGTGTTCGTCGGGGCTACAGGCAGTGG

481 CCAGCATAGCAGGTGGCATCAGAAATGGGTCTTATGACATTGGCATGGCCTGTGGGGTGG
541 AGTCCATGTCCCTGGCTGACAGAGGGAACCCTGGAAATATTACTTCGCGCTTGATGGAGA
601 AGGAGAAGGCCAGAGATTGCCTGATTCCTATGGGGATAACCTCTGAGAATGTGGCTGAGC
661 GGTTTGGCATTTCACGGGAGAAGCAGGATACCTTTGCCCTGGCTTCCCAGCAGAAGGCAG
721 CAAGAGCCCAGAGCAAGGGCTGTTTCCAAGCTGAGATTGTGCCTGTGACCACCACGGTCC
781 ATGATGACAAGGGCACCAAGAGGAGCATCACTGTGACCCAGGATGAGGGTATCCGCCCCA
841 GCACCACCATGGAGGGCCTGGCCAAACTGAAGCCTGCCTTCAAGAAAGATGGTTCTACCA
901 CAGCTGGAAACTCTAGCCAGGTGAGTGATGGGGCAGCTGCCATCCTGCTGGCCCGGAGGT
961 CCAAGGCAGAAGAGTTGGGCCTTCCCATCCTTGGGGTCCTGAGGTCTTATGCAGTGGTTG
1021 GGGTCCCACCTGACATCATGGGCATTGGACCTGCCTATGCCATCCCAGTAGCTTTGCAAA
1081 AAGCAGGGCTGACAGTGAGTGACGTGGACATCTTCGAGATCAATGAGGCCTTTGCAAGCC
1141 AGGCTGCCTACTGTGTGGAGAAGCTACGACTCCCCCCTGAGAAGGTGAACCCCCTGGGGG
1201 GTGCAGTGGCCTTAGGGCACCCACTGGGCTGCACTGGGGCACGACAGGTCATCACGCTGC
1261 TCAATGAGCTGAAGCGCCGTGGGAAGAGGGCATACGGAGTGGTGTCCATGTGCATCGGGA
1321 CTGGAATGGGAGCCGCTGCCGTCTTTGAATACCCTGGGAAC**TGA**GTGAGGTCCCAGGCTG
1381 GAGGC**GCTACGCAGACAGTCCTGCTGCTCTAGCAGCAAGGCAGTAACACCACAAAAGCAA**
1441 **AACCA**CATGGGAAAACTCAGCACTGGTGGTGGTGGCAGTGGACAGATCAAGGCACTTCAA
1501 CTCATTTGGAAAATGTGAACACTGATGACATGGTATAGGAGTGGGTGGGGTGTTGAGCCA
1561 CCCATCAGACCCTCTTTAGCTGTGCAAGATAAAAGCAGCCTGGGTCACCCAGGCCACAAG
1621 GCCATGGTTAATTCTTAAGGCAAGGCAAATCCATGGATGAGAAGTGCAATGGGCATAGTA
1681 AAAGTGCATGAATTT

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000333664 and has a sequence as in SEQ ID NO:2

1 MQRLQVVLGHLRGPADSGWMPQAAPCLSGAPQASAADVVVVHGRRTAICRAGRGGFKDTT
61 PDELLSAVMTAVLKDVNLRPEQLGDICVGNVLQPGAGAIMARIAQFLSDIPETVPLSTVN
121 RQCSSGLQAVASIAGGIRNGSYDIGMACGVESMSLADRGNPGNITSRLMEKEKARDCLIP
181 MGITSENVAERFGISREKQDTFALASQQKAARAQSKGCFQAEIVPVTTTVHDDKGTKRSI
241 TVTQDEGIRPSTTMEGLAKLKPAFKKDGSTTAGNSSQVSDGAAAILLARRSKAEELGLPI
301 LGVLRSYAVVGVPPDIMGIGPAYAIPVALQKAGLTVSDVDIFEINEAFASQAAYCVEKLR
361 LPPEKVNPLGGAVALGHPLGCTGARQVITLLNELKRRGKRAYGVVSMCIGTGMGAAAVFE
421 YPGN

Primers for amplifying the sequence ACAA1 can be designed using primer design software such as Oligo Calc and/or Primer 3.

Examples of primer pairs for amplifying ACAA1 include those in

Forward SEQ ID NO:3 GAGCTTCTCTCGGCAGTCAT
Reverse SEQ ID NO:4 CTCAGAAACTGGGCGATTC

Forward SEQ ID NO:5 GCAATCATGGCCCGAATC
Reverse SEQ ID NO:6 CCCCGACGAACACTGTCTAT

Forward SEQ ID NO:7 GTGCCTTTGTCCACTGTCAA
Reverse SEQ ID NO:8 ACAGGCCATGCCAATGTC

Forward SEQ ID NO:9 TCACGGGAGAAGCAGGATAC
Reverse SEQ ID NO:10 CTCTTGGTGCCCTTGTCATC

Forward SEQ ID NO:11 GGCTGACAGTGAGTGACGTG

Reverse SEQ ID NO:12 AGGGGGTTCACCTTCTCAG

Forward SEQ ID NO:13 GTGGCATCAGAAATGGGTCT
Reverse SEQ ID NO:14 CTCTGGCCTTCTCCTTCTCC

Forward SEQ ID NO:15 ATTACTTCGCGCTTGATGGA
Reverse SEQ ID NO:16 AGGGCAAAGGTATCCTGCTT

Forward SEQ ID NO:17 GCCTGCCTTCAAGAAAGATG
Reverse SEQ ID NO:18 TAAGACCTCAGGACCCCAAG

Forward SEQ ID NO:19 TGGGGTCCTGAGGTCTTATG
Reverse SEQ ID NO:20 TCTCGAAGATGTCCACGTCA

Forward SEQ ID NO:21 GTGGCATCAGAAATGGGTCT
Reverse SEQ ID NO:22 AGGGCAAAGGTATCCTGCTT

Forward SEQ ID NO:23 TGACCCAGGATGAGGGTATC
Reverse SEQ ID NO:24 TCTCGAAGATGTCCACGTCA

Forward SEQ ID NO:25 GGAGACTGTGCCTTTGTCCA
Reverse SEQ ID NO:26 CTCTGTCAGCCAGGGACAT

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting ACAA1 can be derived from any number of sources depending on the desired use (e.g., using the above described primers and appropriate reagents). Other examples of probes include

SEQID NO:27 CGGTTCTCAAGGACGTGAAT
SEQ ID NO:28 AGTGACATCCCGGAGACTGT
SEQ ID NO:29 GTGGCATCAGAAATGGGTCT
SEQ ID NO:30 AGCTGAGATTGTGCCTGTGA
SEQ ID NO:31 ATCAATGAGGCCTTTGCAAG
SEQ ID NO:32 ACAGAGGGAACCCTGGAAAT
SEQ ID NO:33 GATTGCCTGATTCCTATGGG
SEQ ID NO:34 GTCCAAGGCAGAAGAGTTGG
SEQ ID NO:35 ATGCCATCCCAGTAGCTTTG
SEQ ID NO:36 GCCTGTGGGATAACCTCTGA
SEQ ID NO:37 AAACTGAAGCCTGCCTTCAA
SEQ ID NO:38 ATAGACAGTGTTCGTCGGGG

A probe for detecting a ACAA1 nucleic acid that was used on the microarray has a sequence as in SEQ ID NO:39

GCTACGCAGACAGTCCTGCTGCTCTAGCAGCAAGGCAGTAACACCACAAAA GCAAAACCA

Other probes to ACAA1 are known in the art and/or can be readily designed by the skilled artisan.

Antibodies against ACAA1 include, but are not limited to, Rabbit polyclonal anti-ACAA1 Cat# HPA006764 from atlas antibodies (just recognizes the first transcript); and Mouse polyclonal antibody raised against a full-length human ACAA1 protein. Catalog # : H00000030-B01 from abnova (MaxPab).

Example 8: AP1M2

AP1M2 (adaptor-related protein complex 1, mu 2 subunit) also known as D9Ertd818e, HSMU1B, MU-1B, MU1B) was found to be overexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that AP1M2 was overexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue and it was surprisingly found that AP1M2 was overexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the method described in Examples 2-4. Example 5 shows that AP1M2 can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

AP1M2 is a subunit of the heterotetrameric clathrin adaptor-related protein complex 1 (AP-1), that play pivotal roles in many vesicle trafficking pathways within the cell. This protein is capable of interacting with tyrosine-based sorting signals. AP1 is expressed exclusively in epithelial cells. All AP complexes comprise two large subunits of 100–130 kDa (α and β1 in AP1), a medium subunit of 50 kDa (μ1 in AP1), and a small subunit of 17–20 kDa (σ1 in AP1). PMID: 10338135

In clathrin-coated vesicles, AP-2 is located between the lipid bilayer and clathrin lattice, and presumably is anchoring clathrin to membrane. AP1M2 is member of the adaptor medium chain family termed Mu1B, which is specifically expressed in polarized epithelial cells and some exocrine cells. Mu1B is most closely related to

the ubiquitously-expressed Mu1A subunit of AP-1 (79% identity at the amino acid level).

The sequence of an mRNA corresponding to AP1M2 is given in ENSEMBL accession number ENST00000250244 and has a sequence as in SEQ ID NO:40

GGCGCTTCCGCAGGAAGAAGGAAGCGGCGCCGCCATCGCCTCCCGGCGCTCCCTCCCCGACTCCTAAGTC
CTTCGGCCGCCACCATGTCCGCCTCGGCTGTCTTCATTCTGGACGTTAAGGGCAAGCCATTGATCAGCCG
CAACTACAAGGGCGATGTGGCCATGAGCAAGATTGAGCACTTCATGCCTTTGCTGGTACAGCGGGAGGAG
GAAGGCGCCCTGGCCCCGCTGCTGAGCCACGGCCAGGTCCACTTCCTATGGATCAAACACAGCAACCTCT
ACTTGGTGGCCACCACATCGAAGAATGCCAATGCCTCCCTGGTGTACTCCTTCCTGTATAAGACAATAGA
GGTATTCTGCGAATACTTCAAGGAGCTGGAGGAGGAGAGCATCCGGGACAACTTTGTCATCGTCTACGAG
TTGCTGGACGAGCTCATGGACTTTGGCTTCCCGCAGACCACCGACAGCAAGATCCTGCAGGAGTACATCA
CTCAGCAGAGCAACAAGCTGGAGACGGGCAAGTCACGGGTGCCACCCACTGTCACCAACGCTGTGTCCTG
GCGCTCCGAGGGTATCAAGTATAAGAAGAACGAGGTCTTCATTGATGTCATAGAGTCTGTCAACCTGCTG
GTCAATGCCAACGGCAGCGTCCTTCTGAGCGAAATCGTCGGTACCATCAAGCTCAAGGTGTTTCTGTCAG
GAATGCCAGAGCTGCGGCTGGGCCTCAATGACCGCGTGCTCTTCGAGCTCACTGGCCGCAGCAAGAACAA
ATCAGTAGAGCTGGAGGATGTAAAATTCCACCAGTGCGTGCGGCTCTCTCGCTTTGACAACGACCGCACC
ATCTCCTTCATCCCGCCTGATGGTGACTTTGAGCTCATGTCATACCGCCTCAGCACCCAGGTCAAGCCAC
TGATCTGGATTGAGTCTGTCATTGAGAAGTTCTCCCACAGCCGCGTGGAGATCATGGTCAAGGCCAAGGG
GCAGTTTAAGAAACAGTCAGTGGCCAACGGTGTGGAGATATCTGTGCCTGTACCCAGCGATGCCGACTCC
CCCAGATTCAAGACCAGTGTGGGCAGCGCCAAGTATGTGCCGGAGAGAAACGTCGTGATTTGGAGTATTA
AGTCTTTCCCGGGGGGCAAGGAGTACTTGATGCGAGCCCACTTTGGCCTCCCCAGTGTGGAAAAGGAAGA
GGTGGAGGGCCGGCCCCCCATCGGGGTCAAGTTTGAGATCCCCTACTTCACCGTCTCTGGGATCCAGGTC
CGATACATGAAGATCATTGAGAAAAGTGGTTACCAGGCCCTGCCCTGGGTTCGCTACATCACCCAGAGTG
GCGATTACCAACTTCGTACCAGCTAGAAGGGAGAAGAGATGGGGGCTTGAACACGGGGCTTCCTTACAGC
CCCGGATGCAGATTTTAGAGGGAGGGCAGGTGCGGGCTGTGTGTGTCTGTGTGAGGGCAGGTCCTGGACT
TGGCAGTTTCTTGCTCCCAGCACCCGCCCCTTCCTCACCTCTTCCTTATTCCATAGGCTGGGAGAGAAAC
TCTCTGCTTCCCTCGCCCTTGGAGCTTTCCCCATCCCCCTGATTTTATATGAAGAAATAGAAGAGGGGCT
TGAAGTCCCCCTCGCGAGTGCCTTCTTGCAATTACCTGCCTTAGCGGGTGTTGCGGGTCCCTCCTTCACA
GCCGCTGAGCCCAGAGGTCCCGCTGGCCCCTCCTCTGAATTTTAGGATGTCATTAAAAAGATGAATCTA

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000250244 and has a sequence as in SEQ ID NO:41

MSASAVFILDVKGKPLISRNYKGDVAMSKIEHFMPLLVQREEEGALAPLLSHGQVHFLWIKHSNLYLVATTSKNA
NASLVYSFLYKTIEVFCEYFKELEEES
IRDNFVIVYELLDELMDFGFPQTTDSKILQEYITQQSNKLETGKSRVPPTVTNAVSWR
SEGIKYKKNEVFIDVIESVNLLVNANGSVLLSEIVGTIKLKVFLSGMPELRLGLNDRV
LFELTGRSKNKSVELEDVKFHQCVRLSRFDNDRTISFIPPDGDFELMSYRLSTQVKPL
IWIESVIEKFSHSRVEIMVKAKGQFKKQSVANGVEISVPVPSDADSPRFKTSVGSAKY
VPERNVVIWSIKSFPGGKEYLMRAHFGLPSVEKEEVEGRPPIGVKFEIPYFTVSGIQV
RYMKIIEKSGYQALPWVRYITQSGDYQLRTS

Primers for amplifying the sequence ENST00000250244 can be designed using primer design software such as Oligo Calc.

Examples of primer pairs for amplifying AP1M2 include:

Forward SEQ ID NO:42 CGCCACCATGTCCGCCTCGGCTG
Reverse SEQ ID NO:43 GCTCAATCTTGCTCATGGCCAC (Ex2)

Forward SEQ ID NO:44 CAGGTCCACTTCCTATGGATC (ex 2)
Reverse SEQ ID NO:45 CAAAGTTGTCCCGGATGCTC (Ex4)

Forward SEQ ID NO:46 CGCTCCGAGGGTATCAAG (EX5)
Reverse SEQ ID NO:47 CTTGCTGCGGCCAGTGAGC (ex6-7)

Forward SEQ ID NO:48 GACTTTGAGCTCATGTCATACC (Ex7)
Reverse SEQ ID NO:49 CTTAATACTCCAAATCACGACG (Ex9)

Forward SEQ ID NO:50 GTTTGAGATCCCCTACTTC (Ex10)
Reverse SEQ ID NO:51 GCCTGGTAACCACTTTTCTCAATG (Ex11)

Forward SEQ ID NO:52 CTGGGTTCGCTACATCACC (Ex11)
Reverse SEQ ID NO:53 GCCCCGTGTTCAAGC (Ex12)

Forward SEQ ID NO:54 CATGCCTTTGCTGGTACAG (Ex2)
Reverse SEQ ID NO:55 GAGTACACCAGGGAGGCATTG (Ex3)

Forward SEQ ID NO:56 CTCCCTGGTGTACTCCTTC (Ex3)
Reverse SEQ ID NO:57 GCTGTCGGTGGTCTGCGGGAA G (Ex4)

Forward SEQ ID NO:58 CAGCAAGATCCTGCAGGAG (Ex4-5)
Reverse SEQ ID NO:59 CAGGTTGACAGACTCTATG (Ex5)

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting AP1M2 can be derived from any number of sources depending on the desired use (e.g., using the above described primers and appropriate reagents). Examples of probes include:

SEQ ID NO:60
ATGAAGAAATAGAAGAGGGGCTTGAAGTCCTCCTCGCGAGTGCCTTCTTGCA
ATTACCTG

SEQ ID NO:61
CCAGGTCCACTTCCTATGGATCAAACACAGCAACCTCTACTTGGTGGCCACC
ACATCG

SEQ ID NO:62
GACAATAGAGGTATTCTGCGAATACTTCAAGGAGCTGGAGGAG

SEQ ID NO:63
CAATGACCGCGTGCTCTTCGAGCTCACTGGCCGCAGCAAGAACAAATCAGT
AGA

SEQ ID NO:64
TTTCCCGGGGGGCAAGGAGTACTTGATGCGAGCCCACTTTGGCCTCCCCAGT
GTGG

Other probes to AP1M2 are known in the art and/or can be readily designed by the skilled artisan.

Antibodies against AP1M2 include, but are not limited to, Proteintech Group, Inc. Cat# 10618-1-AP which is an affinity purified rabbit polyclonal antibody with an antigen which was a recombinant AP1M2 protein that included the amino acids 1-320 of the protein and from Abnova Cat# H00010053-B01, which is a mouse polyclonal antibody against the full length protein.

Example 9: CGN

CGN (also known as DKFZp779N1112, FLJ39281, and KIAA1319) was found to be overexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that CGN was overexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue and it was surprisingly found that CGN was overexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the method described in Examples 2-4. Example 5 shows that CGN can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

The sequence of an mRNA corresponding to CGN is given in ENSEMBL accession number ENST00000271636 and has a sequence as in SEQ ID NO:65

ENSG00000143375: gene, just one transcript
ENST00000271636
GAGGGAGCTCCGAGGACGAGGGGGAGGGCCGGAGCTGCGCGTGCTGCTTTGCCCGAGCCCGAGCCCGAGC
CCGAGCCCGAGCCCGAGCCCGAGCCCGAACGCAAGCCTGGGAGCGCGGAGCCCGGCTAGGGACTCCTCCT
ATTT**ATG**GAGCAGGCACCCAACATGGCTGAGCCCCGGGGCCCCGTAGACCATGGAGTCCAGATTCGCTTC
ATCACAGAGCCAGTGAGTGGTGCAGAGATGGGCACTCTACGTCGAGGTGGACGACGCCCAGCTAAGGATG
CAAGAGCCAGTACCTACGGGGTTGCTGTGCGTGTGCAGGGAATCGCTGGGCAGCCCTTTGTGGTGCTCAA
CAGTGGGGAGAAAGGCGGTGACTCCTTTGGGGTCCAAATCAAGGGGGCCAATGACCAAGGGGCCTCAGGA
GCTCTGAGCTCAGATTTGGAACTCCCTGAGAACCCCTACTCTCAGGTCAAGGGATTTCCTGCCCCCTCGC
AGAGCAGCACATCTGATGAGGAGCCTGGGGCCTACTGGAATGGAAAGCTACTCCGTTCCCACTCCCAGGC
CTCACTGGCAGGCCCTGGCCCAGTGGATCCTAGTAACAGAAGCAACAGCATGCTGGAGCTAGCCCCGAAA
GTGGCTTCCCCAGGTAGCACCATTGACACTGCTCCCCTGTCTTCAGTGGACTCACTCATCAACAAGTTTG
ACAGTCAACTTGGAGGCCAGGCCCGGGGTCGGACTGGCCGCCGAACACGGATGCTACCCCCTGAACAGCG
CAAACGGAGCAAGAGCCTGGACAGCCGCCTCCCACGGGACACCTTTGAGGAACGGGAGCGCCAGTCCACC
AACCACTGGACCTCTAGCACAAAATATGACAACCATGTGGGCACTTCGAAGCAGCCAGCCCAGAGCCAGA

ACCTGAGTCCTCTCAGTGGCTTTAGCCGTTCTCGTCAGACTCAGGACTGGGTCCTTCAGAGTTTTGAGGA
GCCGCGGAGGAGTGCACAGGACCCCACCATGCTGCAGTTCAAATCAACTCCAGACCTCCTTCGAGACCAG
CAGGAGGCAGCCCCACCAGGCAGTGTGGACCATATGAAGGCCACCATCTATGGCATCCTGAGGGAGGGAA
GCTCAGAAAGTGAAACCTCTGTGAGGAGGAAGGTTAGTTTGGTGCTGGAGAAGATGCAGCCTCTAGTGAT
GGTTTCTTCTGGTTCTACTAAGGCCGTGGCAGGGCAGGGTGAGCTTACCCGAAAAGTGGAGGAGCTACAG
CGAAAGCTGGATGAAGAGGTGAAGAAGCGGCAGAAGCTAGAGCCATCCCAAGTTGGGCTGGAGCGGCAGC
TGGAGGAGAAAACAGAAGAGTGCAGCCGACTGCAGGAGCTGCTGGAGAGGAGGAAGGGGGAGGCCCAGCA
GAGCAACAAGGAGCTCCAGAACATGAAGCGCCTCTTGGACCAGGGTGAAGATTTACGACATGGGCTGGAG
ACCCAGGTGATGGAGCTGCAGAACAAGCTGAAACATGTCCAGGGTCCTGAGCCTGCTAAGGAGGTGTTAC
TGAAGGACCTGTTAGAGACCCGGGAACTTCTGGAAGAGGTCTTGGAGGGGAAACAGCGAGTAGAGGAGCA
GCTGAGGCTGCGGGAGCGGGAGTTGACAGCCCTGAAGGGGGCCCTGAAAGAGGAGGTAGCCTCCCGTGAC
CAGGAGGTGGAACATGTCCGGCAGCAGTACCAGCGAGACACAGAGCAGCTCCGCAGGAGCATGCAAGATG
CAACCCAGGACCATGCAGTGCTGGAGGCCGAGAGGCAGAAGATGTCAGCCCTTGTGCGAGGGCTGCAGAG
GGAGCTGGAGGAGACTTCAGAGGAGACAGGGCATTGGCAGAGTATGTTCCAGAAGAACAAGGAGGATCTT
AGAGCCACCAAGCAGGAACTCCTGCAGCTGCGAATGGAGAAGGAGGAGATGGAAGAGGAGCTTGGAGAGA
AGATAGAGGTCTTGCAGAGGGAATTAGAGCAGGCCCGAGCTAGTGCTGGAGATACTCGCCAGGTTGAGGT
GCTCAAGAAGGAGCTGCTCCGGACACAGGAGGAGCTTAAGGAACTGCAGGCAGAACGGCAGAGCCAGGAG
GTGGCTGGGCGACACCGGGACCGGGAGTTGGAGAAGCAGCTGGCGGTCCTGAGGGTCGAGGCTGATCGAG
GTCGGGAGCTGGAAGAACAGAACCTCCAGCTACAAAAGACCCTCCAGCAACTGCGACAGGACTGTGAAGA
GGCTTCCAAGGCTAAGATGGTGGCCGAGGCAGAGGCAACAGTGCTGGGGCAGCGGCGGGCCGCAGTGGAG
ACGACGCTTCGGGAGACCCAGGAGGAAAATGACGAATTCCGCCGGCGCATCCTGGGTTTGGAGCAGCAGC
TGAAGGAGACTCGAGGTCTGGTGGATGGTGGGGAAGCGGTGGAGGCACGACTACGGGACAAGCTGCAGCG
GCTGGAGGCAGAGAAACAGCAGCTGGAGGAGGCCCTGAATGCGTCCCAGGAAGAGGAGGGGAGTCTGGCA
GCAGCCAAGCGGGCACTGGAGGCACGCCTAGAGGAGGCTCAGCGGGGGCTGGCCCGCCTGGGGCAGGAGC
AGCAGACACTGAACCGGGCCCTGGAGGAGGAAGGGAAGCAGCGGGAGGTGCTCCGGCGAGGCAAGGCTGA
GCTGGAGGAGCAGAAGCGTTTGCTGGACAGGACTGTGGACCGACTGAACAAGGAGTTGGAGAAGATCGGG
GAGGACTCTAAGCAAGCCCTGCAGCAGCTCCAGGCCCAGCTGGAGGATTATAAGGAAAAGGCCCGGCGGG
AGGTGGCAGATGCCCAGCGCCAGGCCAAGGATTGGGCCAGTGAGGCTGAGAAGACCTCTGGAGGACTGAG
CCGACTTCAGGATGAGATCCAGAGGCTGCGGCAGGCCCTGCAGGCATCCCAGGCTGAGCGGGACACAGCC
CGGCTGGACAAAGAGCTACTGGCCCAGCGACTGCAGGGGCTGGAGCAAGAGGCAGAGAACAAGAAGCGTT
CCCAGGACGACAGGGCCCGGCAGCTGAAGGGTCTCGAGGAAAAAGTCTCACGGCTGGAAACAGAGTTAGA
TGAGGAGAAGAACACCGTGGAGCTGCTAACAGATCGGGTGAATCGTGGCCGGGACCAGGTGGATCAGCTG
AGGACAGAGCTCATGCAGGAAAGGTCTGCTCGGCAGGACCTGGAGTGTGACAAAATCTCCTTGGAGAGAC
AGAACAAGGACCTGAAGACCCGGTTGGCCAGCTCAGAAGGCTTCCAGAAGCCTAGTGCCAGCCTCTCTCA
GCTTGAGTCCCAGAATCAGTTGTTGCAGGAGCGGCTACAGGCTGAAGAGAGGGAGAAGACAGTTCTGCAG
TCTACCAATCGAAAACTGGAGCGGAAAGTTAAAGAACTATCCATCCAGATTGAAGACGAGCGGCAGCATG
TCAATGACCAGAAAGACCAGCTAAGCCTGAGGGTGAAGGCTTTGAAGCGTCAGGTGGATGAAGCAGAAGA
GGAAATTGAGCGACTGGACGGCCTGAGGAAGAAGGCCCAGCGTGAGGTGGAGGAGCAGCATGAGGTCAAT
GAACAGCTCCAGGCCCGGATCAAGTCTCTGGAGAAGGACTCCTGGCGCAAAGCTTCCCGCTCAGCTGCTG
AGTCAGCTCTCAAAAACGAAGGGCTGAGCTCAGATGAGGAATTCGACAGTGTCTACGATCCCTCGTCCAT
TGCATCACTGCTTACGGAGAGCAACCTACAGACCAGCTCCTGT**TAG***CTCGTGGTCCTCAAGGACTCAGAA*
ACCAGGCTCGAGGCCTATCCCAGCAAGTGCTGCTCTGCTCTGCCCACCCTGGGTTCTGCATTCCTATGGG
TGACCCAATTATTCAGACCTAAGACAGGGAGGGGTCAGAGTGATGGTGATAAAAAAAAAAAAATCATCAGC
AATAAGCTGATAGATGGACTTTCCACTGTAGGAGTGGACATTTCAAGCCAACTGAGCCTTTTCCTCAAGT
GCCGACACCTCCCTCATCTCTCTTATAGTGGAAGGATGGTCAGCATTAGGCTGATGGGGACTGAGAAGGA
TAGGAAGGGATAGAAATTGCCATGTGTATAAAGCTTTATTCTTTAGCCCTTAACCCTAAGGCTCAGGGAA
ATACCCTATGTTATTGTGCTCCCTGGATTCCTGCAACTCATTTTCCTTCCACTCTGGAGCAGGGTGAGGG
GAATGTTATGGGTAACAGACATGCAGGCATGGCTCTACCCATTTCTTTGCACAAGTATGGGGCCCATGTG
GTAGTCCCCATACCCCTCCAGTTCCTATATTTTTGTCTTCTTCCTTTCCCCTCTTTGCCATTCCTACCTT
GCATTTTTCCTGTCAGTGCCTTAGCCAAGGCAAGGAGATAAGGATGCTCTTCTTGCTTTTTATATCTGCA
CATTCATACCTCTCCAAAGACCAGCTTTTCCCCAGCCAGGGCCCTCAGCCTTCCCTGCTGCCCCAGTGAT
TGATTGAGAGAGCTGTTGGGGTTTCTCTGCCAATGACCCCTGGGAGAGGGACTTTGGTAGGGTCATGATA
AAGTGGCGGGGGTCTGGTCCTGCTCAGGGTTTTCATCCTTCCTCCTCTCCCTCCTCTGTGACTGTGGATA
TGGTTATAAGGTGGTTGCACCTGGGAGCCCTGACAACTGGCTGCACAAATTCCAAAAGTAAAGGTGTCAG
TCCCTGTGGCCTTCCTTGGGGCTTCTCTGACCACATGTGCCCAACTTCAATAAGAGAACCAAGGGACCCT
CATTTTCTGAGGTGCTTGGCTCTGATTCAGGGCTTTGCAAGGGGTTAGAAGCTGACTGTAAAAATGGGAA
GAGGCAACGGAAGACATTTATTTCTCCTTTGGATTTTGGGGAGAACCAAGCCCTGGTAGGGAAGAGGTAA
GGGGGATGATTCACCTCCATATTTCCTAAGCAGGTTGTATAGGGAGCCGGTGGCAGGAGGAAGGCTGTTT
TCACAAATGACTTGTAATGTCGTGATTAAAAAAATTCCTATATTCTTCTGCAAATCAAACGTTCTTTCCC
AATCCAATCCAGCCTTGGTTTTATTTTAAATTAAATATTAAAATTACACATTTATATTGAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAA

The start and stop codons are indicated in bold.

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000271636 and has a sequence as in SEQ ID NO:66

MEQAPNMAEPRGPVDHGVQIRFITEPVSGAEMGTLRRGGRRPAK
DARASTYGVAVRVQGIAGQPFVVLNSGEKGGDSFGVQIKGANDQGASGALSSDLELPE
NPYSQVKGFPAPSQSSTSDEEPGAYWNGKLLRSHSQASLAGPGPVDPSNRSNSMLELA
PKVASPGSTIDTAPLSSVDSLINKFDSQLGGQARGRTGRRTRMLPPEQRKRSKSLDSR
LPRDTFEERERQSTNHWTSSTKYDNHVGTSKQPAQSQNLSPLSGFSRSRQTQDWVLQS
FEEPRRSAQDPTMLQFKSTPDLLRDQQEAAPPGSVDHMKATIYGILREGSSESETSVR
RKVSLVLEKMQPLVMVSSGSTKAVAGQGELTRKVEELQRKLDEEVKKRQKLEPSQVGL
ERQLEEKTEECSRLQELLERRKGEAQQSNKELQNMKRLLDQGEDLRHGLETQVMELQN
KLKHVQGPEPAKEVLLKDLLETRELLEEVLEGKQRVEEQLRLRERELTALKGALKEEV
ASRDQEVEHVRQQYQRDTEQLRRSMQDATQDHAVLEAERQKMSALVRGLQRELEETSE
ETGHWQSMFQKNKEDLRATKQELLQLRMEKEEMEEELGEKIEVLQRELEQARASAGDT
RQVEVLKKELLRTQEELKELQAERQSQEVAGRHRDRELEKQLAVLRVEADRGRELEEQ
NLQLQKTLQQLRQDCEEASKAKMVAEAEATVLGQRRAAVETTLRETQEENDEFRRRIL
GLEQQLKETRGLVDGGEAVEARLRDKLQRLEAEKQQLEEALNASQEEEGSLAAAKRAL
EARLEEAQRGLARLGQEQQTLNRALEEEGKQREVLRRGKAELEEQKRLLDRTVDRLNK
ELEKIGEDSKQALQQLQAQLEDYKEKARREVADAQRQAKDWASEAEKTSGGLSRLQDE
IQRLRQALQASQAERDTARLDKELLAQRLQGLEQEAENKKRSQDDRARQLKGLEEKVS
RLETELDEEKNTVELLTDRVNRGRDQVDQLRTELMQERSARQDLECDKISLERQNKDL
KTRLASSEGFQKPSASLSQLESQNQLLQERLQAEEREKTVLQSTNRKLERKVKELSIQ
IEDERQHVNDQKDQLSLRVKALKRQVDEAEEEIERLDGLRKKAQREVEEQHEVNEQLQ
ARIKSLEKDSWRKASRSAAESALKNEGLSSDEEFDSVYDPSSIASLLTESNLQTSSC

Primers for amplifying the sequence CGN can be designed using primer design software such as Oligo Calc. Examples of primer pairs for amplifying CGN include those in

Forward SEQ ID NO:67 GCTTTAGCCGTTCTCGTCA
Reverse SEQ ID NO:68 CTGGTCTCGAAGGAGGTCTG

Forward SEQ ID NO:69 CAGACCTCCTTCGAGACCAG
Reverse SEQ ID NO:70 TTCCTCCTCACAGAGGTTTCA

Forward SEQ ID NO:71 TACAGCGAAAGCTGGATGAA
Reverse SEQ ID NO:72 AGTCGGCTGCACTCTTCTGT

Forward SEQ ID NO:73 TGCAGAACAAGCTGAAACAT
Reverse SEQ ID NO:74 GCTGCTCCTCTACTCGCTGT

Forward SEQ ID NO:75 GGGCATTGGCAGAGTATGTT
Reverse SEQ ID NO:76 TTCCATCTCCTCCTTCTCCA

Forward SEQ ID NO:77 CAGCAACTGCGACAGGACT
Reverse SEQ ID NO:78 CATTTTCCTCCTGGGTCTCC

Forward SEQ ID NO:79: CTGAGCTGGAGGAGCAGAAG
Reverse SEQ ID NO:80 TGCAGGGCTTGCTTAGAGTC

Forward SEQ ID NO:81 TGGAGCAAGAGGCAGAGAAC
Reverse SEQ ID NO:82 ACTCTGTTTCCAGCCGTGAG

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting CGN can be derived from any number of sources depending on the desired use (e.g., using the above described primers and appropriate reagents). Other examples of probes include

SEQ ID NO:83 CAGGACTGGGTCCTTCAGAG
SEQ ID NO:84 CAGGCAGTGTGGACCATATG
SEQ ID NO:85 GCTAGAGCCATCCCAAGTTG
SEQ ID NO:86 TGAGCCTGCTAAGGAGGTGT
SEQ ID NO:87 TAGAGCCACCAAGCAGGAAC
SEQ ID NO:88 TTCCAAGGCTAAGATGGTGG
SEQ ID NO:89 GACAGGACTGTGGACCGACT
SEQ ID NO:90 TGAAGGGTCTCGAGGAAAAA
Probe from the array SEQ ID NO:91
GGGAAGAGGTAAGGGGGATGATTCACCTCCATATTTCCTAAGCAGGTTGTAT AGGGAGCC

Antibodies to CGN include, but are not limited to Rabbit Anti-Human Cingulin (CGN) Polyclonal, Unconjugated Cat# LS-C22229-100, from lifespan bioscience (C-terminal region); and Mouse Anti-Human Cingulin (CGN) Monoclonal, Unconjugated, Clone 6a40 Cat# LS-C22230-100, from Lifespan Bioscience (C-terminal region).

Example 10: DDR1

DDR1 was found to be overexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that DDR1 was overexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue and it was surprisingly found that DDR1 was overexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the method described in Examples 2-4. Example 5 shows that DDR1 can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

The sequence of an mRNA corresponding to DDR1 is given in ENSEMBL accession no. ENST00000376570 and has a sequence as in SEQ ID NO:92

```
   1 GTCTTCCCCTCGTGGGCCCTGAGCGGGACTGCAGCCAGCCCCCTGGGGCGCCAGCTTTG
  61 AGGCCCCCGACAGCTGCTCTCGGGAGCCGCCTCCCGACACCCGAGCCCCGCCGGCGCCTC
 121 CCGCTCCCGGCTCCCGGCTCCTGGCTCCCTCCGCCTCCCCCGCCCCTCGCCCCGCCGCC
 181 AAGAGGCCCCGCTCCCGGGTCGGACGCCTGGGTCTGCCGGGAAGAGCGATGAGAGGTGTC
 241 TGAAGGTGGCTATTCACTGAGCGATGGGGTTGGACTTGAAGGAATGCCAAGAGATGCTGC
 301 CCCCACCCCCTTAGGCCCGAGGGATCAGGAGCTATGGGACCAGAGGCCCTGTCATCTTTA
 361 CTGCTGCTGCTCTTGGTGGCAAGTGGAGATGCTGACATGAAGGGACATTTTGATCCTGCC
 421 AAGTGCCGCTATGCCCTGGGCATGCAGGACCGGACCATCCCAGACAGTGACATCTCTGCT
 481 TCCAGCTCCTGGTCAGATTCCACTGCCGCCCGCCACAGCAGGTTGGAGAGCAGTGACGGG
 541 GATGGGGCCTGGTGCCCCGCAGGGTCGGTGTTTCCCAAGGAGGAGGAGTACTTGCAGGTG
 601 GATCTACAACGACTGCACCTGGTGGCTCTGGTGGGCACCCAGGGACGGCATGCCGGGGGC
 661 CTGGGCAAGGAGTTCTCCCGGAGCTACCGGCTGCGTTACTCCCGGGATGGTCGCCGCTGG
 721 ATGGGCTGGAAGGACCGCTGGGGTCAGGAGGTGATCTCAGGCAATGAGGACCCTGAGGGA
 781 GTGGTGCTGAAGGACCTTGGGCCCCCCATGGTTGCCCGACTGGTTCGCTTCTACCCCCGG
 841 GCTGACCGGGTCATGAGCGTCTGTCTGCGGGTAGAGCTCTATGGCTGCCTCTGGAGGGAT
 901 GGACTCCTGTCTTACACCGCCCCTGTGGGGCAGACAATGTATTTATCTGAGGCCGTGTAC
 961 CTCAACGACTCCACCTATGACGGACATACCGTGGGCGGACTGCAGTATGGGGGTCTGGGC
1021 CAGCTGGCAGATGGTGTGGTGGGGCTGGATGACTTTAGGAAGAGTCAGGAGCTGCGGGTC
1081 TGGCCAGGCTATGACTATGTGGGATGGAGCAACCACAGCTTCTCCAGTGGCTATGTGGAG
1141 ATGGAGTTTGAGTTTGACCGGCTGAGGGCCTTCCAGGCTATGCAGGTCCACTGTAACAAC
1201 ATGCACACGCTGGGAGCCCGTCTGCCTGGCGGGGTGGAATGTCGCTTCCGGCGTGGCCCT
1261 GCCATGGCCTGGGAGGGGGAGCCCATGCGCCACAACCTAGGGGGCAACCTGGGGGACCCC
1321 AGAGCCCGGGCTGTCTCAGTGCCCCTTGGCGGCCGTGTGGCTCGCTTTCTGCAGTGCCGC
1381 TTCCTCTTTGCGGGGCCCTGGTTACTCTTCAGCGAAATCTCCTTCATCTCTGATGTGGTG
1441 AACAATTCCTCTCCGGCACTGGGAGGCACCTTCCCGCCAGCCCCCTGGTGGCCGCCTGGC
1501 CCACCTCCCACCAACTTCAGCAGCTTGGAGCTGGAGCCCAGAGGCCAGCAGCCCGTGGCC
1561 AAGGCCGAGGGGAGCCCGACCGCCATCCTCATCGGCTGCCTGGTGGCCATCATCCTGCTC
1621 CTGCTGCTCATCATTGCCCTCATGCTCTGGCGGCTGCACTGGCGCAGGCTCCTCAGCAAG
1681 GCTGAACGGAGGGTGTTGGAAGAGGAGCTGACGGTTCACCTCTCTGTCCCTGGGGACACT
1741 ATCCTCATCAACAACCGCCCAGGTCCTAGAGAGCCACCCCCGTACCAGGAGCCCCGGCCT
1801 CGTGGGAATCCGCCCCACTCCGCTCCCTGTGTCCCCAATGGCTCTGCCTACAGTGGGGAC
1861 TATATGGAGCCTGAGAAGCCAGGCGCCCCGCTTCTGCCCCCACCTCCCCAGAACAGCGTC
1921 CCCCATTATGCCGAGGCTGACATTGTTACCCTGCAGGGCGTCACCGGGGGCAACACCTAT
1588 CCCCATTATGCCGAGGCTGACATTGTTACCCTGCAGGGCGTCACCGGGGGCAACACCTAT
1981 GCTGTGCCTGCACTGCCCCCAGGGGCAGTCGGGGATGGGCCCCCCAGAGTGGATTTCCCT
1648 GCTGTGCCTGCACTGCCCCCAGGGGCAGTCGGGGATGGGCCCCCCAGAGTGGATTTCCCT
2041 CGATCTCGACTCCGCTTCAAGGAGAAGCTTGGCGAGGGCCAGTTTGGGGAGGTGCACCTG
1708 CGATCTCGACTCCGCTTCAAGGAGAAGCTTGGCGAGGGCCAGTTTGGGGAGGTGCACCTG
2101 TGTGAGGTCGACAGCCCTCAAGATCTGGTTAGTCTTGATTTCCCCCTTAATGTGCGTAAG
1768 TGTGAGGTCGACAGCCCTCAAGATCTGGTTAGTCTTGATTTCCCCCTTAATGTGCGTAAG
2161 GGACACCCTTTGCTGGTAGCTGTCAAGATCTTACGGCCAGATGCCACCAAGAATGCCAGG
1828 GGACACCCTTTGCTGGTAGCTGTCAAGATCTTACGGCCAGATGCCACCAAGAATGCCAGG
2221 AATGATTTCCTGAAAGAGGTGAAGATCATGTCGAGGCTCAAGGACCCAAACATCATTCGG
1888 AATGATTTCCTGAAAGAGGTGAAGATCATGTCGAGGCTCAAGGACCCAAACATCATTCGG
2281 CTGCTGGGCGTGTGTGTGCAGGACGACCCCCTCTGCATGATTACTGACTACATGGAGAAC
1948 CTGCTGGGCGTGTGTGTGCAGGACGACCCCCTCTGCATGATTACTGACTACATGGAGAAC
2341 GGCGACCTCAACCAGTTCCTCAGTGCCCACCAGCTGGAGGACAAGGCAGCCGAGGGGGCC
2008 GGCGACCTCAACCAGTTCCTCAGTGCCCACCAGCTGGAGGACAAGGCAGCCGAGGGGGCC
2401 CCTGGGGACGGGCAGGCTGCGCAGGGGCCCACCATCAGCTACCCAATGCTGCTGCATGTG
2068 CCTGGGGACGGGCAGGCTGCGCAGGGGCCCACCATCAGCTACCCAATGCTGCTGCATGTG
2461 GCAGCCCAGATCGCCTCCGGCATGCGCTATCTGGCCACACTCAACTTTGTACATCGGGAC
2128 GCAGCCCAGATCGCCTCCGGCATGCGCTATCTGGCCACACTCAACTTTGTACATCGGGAC
2521 CTGGCCACGCGGAACTGCCTAGTTGGGGAAAATTTCACCATCAAAATCGCAGACTTTGGC
2188 CTGGCCACGCGGAACTGCCTAGTTGGGGAAAATTTCACCATCAAAATCGCAGACTTTGGC
2581 ATGAGCCGGAACCTCTATGCTGGGGACTATTACCGTGTGCAGGGCCGGGCAGTGCTGCCC
2248 ATGAGCCGGAACCTCTATGCTGGGGACTATTACCGTGTGCAGGGCCGGGCAGTGCTGCCC
2641 ATCCGCTGGATGGCCTGGGAGTGCATCCTCATGGGGAAGTTCACGACTGCGAGTGACGTG
2308 ATCCGCTGGATGGCCTGGGAGTGCATCCTCATGGGGAAGTTCACGACTGCGAGTGACGTG
2701 TGGGCCTTTGGTGTGACCCTGTGGGAGGTGCTGATGCTCTGTAGGGCCCAGCCCTTTGGG
2368 TGGGCCTTTGGTGTGACCCTGTGGGAGGTGCTGATGCTCTGTAGGGCCCAGCCCTTTGGG
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2761 CAGCTCACCGACGAGCAGGTCATCGAGAACGCGGGGGAGTTCTTCCGGGACCAGGGCCGG
2428 CAGCTCACCGACGAGCAGGTCATCGAGAACGCGGGGGAGTTCTTCCGGGACCAGGGCCGG
2821 CAGGTGTACCTGTCCCGGCCGCCTGCCTGCCCGCAGGGCCTATATGAGCTGATGCTTCGG
2488 CAGGTGTACCTGTCCCGGCCGCCTGCCTGCCCGCAGGGCCTATATGAGCTGATGCTTCGG
2881 TGCTGGAGCCGGGAGTCTGAGCAGCGACCACCCTTTTCCCAGCTGCATCGGTTCCTGGCA
2548 TGCTGGAGCCGGGAGTCTGAGCAGCGACCACCCTTTTCCCAGCTGCATCGGTTCCTGGCA
2941 GAGGATGCACTCAACACGGTGTGAATCACACATCCAGCTGCCCCTCCCTCAGGGAGCGAT
3001 CCAGGGGAAGCCAGTGACACTAAAACAAGAGGACACAATGGCACCTCTGCCCTTCCCCTC
3061 CCGACAGCCCATCACCTCTAATAGAGGCAGTGAGACTGCAGGTGGGCTGGGCCCACCCAG
3121 GGAGCTGATGCCCCTTCTCCCCTTCCTGGACACACTCTCATGTCCCCTTCCTGTTCTTCC
3181 TTCCTAGAAGCCCCTGTCGCCCACCCAGCTGGTCCTGTGGATGGGATCCTCTCCACCCTC
3241 CTCTAGCCATCCCTTGGGGAAGGGTGGGGAGAAATATAGGATAGACACTGGACATGGCCC
3301 ATTGGAGCACCTGGGCCCCACTGGACAACACTGATTCCTGGAGAGGTGGCTGCGCCCCCA
3361 GCTTCTCTCTCCCTGTCACACACTGGACCCCACTGGCTGAGAATCTGGGGGTGAGGAGGA
3421 CAAGAAGGAGAGGAAAATGTTTCCTTGTGCCTGCTCCTGTACTTGTCCTCAGCTTGGGCT
3481 TCTTCCTCCTCCATCACCTGAAACACTGGACCTGGGGGTAGCCCCGCCCCAGCCCTCAGT
3541 CACCCCCACTTCCCACTTGCAGTCTTGTAGCTAGAACTTCTCTAAGCCTATACGTTTCTG
3601 TGGAGTAAATATTGGGATTGGGGGGAAAGAGGGAGCAACGGCCCATAGCCTTGGGGTTGG
3661 ACATCTCTAGTGTAGCTGCCACATTGATTTTTCTATAATCACTTGGGGTTTGTACATTTT
3721 TGGGGGGAGAGACACAGATTTTTACACTAATATATGGACCTAGCTTGAGGCAATTTTAAT
3781 CCCCTGCACTAGGCAGGTAATAATAAAGGTTGAGTTTTCC
```

The corresponding amino acid sequence is given in ENSEMBL accession no. EP0000365754 and has a sequence as in SEQ ID NO:93

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   1 MGPEALSSLLLLLLVASGDADMKGHFDPAKCRYALGMQDRTIPDSDISASSSWSDSTAAR
  61 HSRLESSDGDGAWCPAGSVFPKEEEYLQVDLQRLHLVALVGTQGRHAGGLGKEFSRSYRL
 121 RYSRDGRRWMGWKDRWGQEVISGNEDPEGVVLKDLGPPMVARLVRFYPRADRVMSVCLRV
 181 ELYGCLWRDGLLSYTAPVGQTMYLSEAVYLNDSTYDGHTVGGLQYGGLGQLADGVVGLDD
 241 FRKSQELRVWPGYDYVGWSNHSFSSGYVEMEFEFDRLRAFQAMQVHCNNMHTLGARLPGG
 301 VECRFRRGPAMAWEGEPMRHNLGGNLGDPRARAVSVPLGGRVARFLQCRFLFAGPWLLFS
 361 EISFISDVVNNSSPALGGTFPPAPWWPPGPPPTNFSSLELEPRGQQPVAKAEGSPTAILI
 421 GCLVAIILLLLLIIALMLWRLHWRRLLSKAERRVLEEELTVHLSVPGDTILINNRPGPRE
 481 PPPYQEPRPRGNPPHSAPCVPNGSAYSGDYMEPEKPGAPLLPPPPQNSVPHYAEADIVTL
 541 QGVTGGNTYAVPALPPGAVGDGPPRVDFPRSRLRFKEKLGEGQFGEVHLCEVDSPQDLVS
 601 LDFPLNVRKGHPLLVAVKILRPDATKNARNDFLKEVKIMSRLKDPNIIRLLGVCVQDDPL
 661 CMITDYMENGDLNQFLSAHQLEDKAAEGAPGDGQAAQGPTISYPMLLHVAAQIASGMRYL
 721 ATLNFVHRDLATRNCLVGENFTIKIADFGMSRNLYAGDYYRVQGRAVLPIRWMAWECILM
 781 GKFTTASDVWAFGVTLWEVLMLCRAQPFGQLTDEQVIENAGEFFRDQGRQVYLSRPPACP
 841 QGLYELMLRCWSRESEQRPPFSQLHRFLAEDALNTV
```

Primers for amplifying the sequence DDR1 can be designed using primer design software such as Oligo Calc and/or Primer 3.

Examples of primer pairs for amplifying DDR1 include those in

Forward SEQ ID NO:94 CATCTCTGCTTCCAGCTCCT
Reverse SEQ ID NO:95 TACTCCTCCTCCTTGGGAAA

Forward SEQ ID NO:96 AGCTACCGGCTGCGTTACT
Reverse SEQ ID NO:97 CTTCAGCACCACTCCCTCAG

Forward SEQ ID NO:98 CGTCTGTCTGCGGGTAGAG
Reverse SEQ ID NO:99 CCGTCATAGGTGGAGTCGTT

Forward SEQ ID NO:100 CAACGACTCCACCTATGACG
Reverse SEQ ID NO:101TGCTCCATCCCACATAGTCA

Forward SEQ ID NO:102 TGACTATGTGGGATGGAGCA
Reverse SEQ ID NO:103 CCAGCGTGTGCATGTTGTTA

Forward SEQ ID NO:104 TGTCTCAGTGCCCCTTGG
Reverse SEQ ID NO:105 GTGCCGGAGAGGAATTGTT

Forward SEQ ID NO:106 ACCTCCCACCAACTTCAGC
Reverse SEQ ID NO:107 CAGCAGGAGCAGGATGATG

Forward SEQ ID NO:108 CATCATCCTGCTCCTGCTG
Reverse SEQ ID NO:109 CCAGGGACAGAGAGGTGAAC

Forward SEQ ID NO:110 ACCGCCCAGGTCCTAGAG
Reverse SEQ ID NO:111 CGGTAGGCTGGATTGGAGA

Forward SEQ ID NO:112 CACCCTTTGCTGGTAGCTGT
Reverse SEQ ID NO:113 CGAATGATGTTTGGGTCCTT

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting DDR1 can be derived from any number of sources depending on the desired use (e.g., using the above described primers and appropriate reagents). Other examples of probes include

SEQ ID NO:114 ACAGCAGGTTGGAGAGCAGT
SEQ ID NO:115 GTCAGGAGGTGATCTCAGGC
SEQ ID NO:116 CTCTATGGCTGCCTCTGGAG
SEQ ID NO:117 GTGGGGCTGGATGACTTTAG
SEQ ID NO:118 AGTTTGAGTTTGACCGGCTG
SEQ ID NO:119 CCCTGGTTACTCTTCAGCGA
SEQ ID NO:120 CTTGGAGCTGGAGCCCAG
SEQ ID NO:121 AGGGTGTTGGAAGAGGAGCT
SEQ ID NO:122 ACTCTGCTCCCTGTGTCCC
SEQ ID NO:123 GCCAGGAATGATTTCCTGAA

A probe used to detect the DDR1 nucleic acid that was used on the microarray has a sequence as in SEQ ID NO:124

ATTGGGATTGGGGGGAAAGAGGGAGCAACGGCCCATAGCCTTGGGGTTGGACAT CTCTAG

Other probes to DDR1 are known in the art and/or can be readily designed by the skilled artisan.

Antibodies against DDR1 include, but are not limited to, Rabbit polyclonal antibody to MCK10 from abcam cat# ab5508 epitope: aa31-47; and Mouse Anti-Human DDR1 Polyclonal Antibody, Unconjugated from abnova cat# H00000780-A01 against full length.

Example 11: EPS8L2

EPS8L2 (EPS8-like 2 also known as AI042819, AW545405, Eps8l2_predicted, Eps8l2 predicted, EPS8R2, FLJ16738, FLJ21935, FLJ22171, MGC126530, MGC3088)

was found to be overexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that EPS8L2 was overexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue and it was surprisingly found that EPS8L2 was overexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the method described in Examples 2-4. Example 5 shows that EPS8L2 can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

The EPS8L2 gene encodes a protein that is related to epidermal growth factor receptor pathway substrate 8 (EPS8), a substrate for the epidermal growth factor receptor. The eps8Ls define a novel family of proteins responsible for functional redundancy in the RTK-activated signaling pathway leading to actin remodeling. Members of this family link growth factor stimulation to actin organization. Members of the eps8 family share a modular organization consisting of a putative PTB domain, a central SH3 domain and a C-terminal effector region. The SH3 domains of eps8Ls display unique binding preferences for peptides containing a proline-X-X-aspartate-tyrosine (pXXDY) consensus and constitute a phylogenetically distinct subfamily within the SH3 domain family. (PMID: 14565974).

Although EPS8L2 function is unknown, gene expression analyses of breast and thyroid cancers identified Eps8, another member of the family, as a novel putative

oncogene and also it was implicated in tumor cell migration in fibrosarcoma cells. (PMID: 16618726) (PMID: 17075124) (PMID: 15289329)

The sequence of an mRNA corresponding to EPS8L2 is given in ENSEMBL accession no. ENST00000318562 and SEQ ID NO:125

ACTCCGCAACCTGTCGCTCAGGTTCCTCCTCTCCCGGCCCCGCCCCGGCCCGGCCCCGCCGAGCGTCCCA
CCCGCCCGCGGGAGACCTGGCGCCCCGGCCGAGGCGCGAACAGACGGACGCACCGGCGAGCGCCGAGGGG
ACAGGCCGAGCGCGGGGCGCCGGAGGCAGGTGTGGGACAGGCACTGGCCTCAGACCGGGGCCACACTGAG
GTCTGCCCTTCTCCCGCTGGCCGCCACCCAAGACACC**ATG**AGCCAGTCCGGGGCCGTGAGCTGCTGCCCG
GGTGCCACCAATGGCAGCCTGGGCCGGTCCGACGGTGTGGCCAAGATGAGCCCCAAGGACCTGTTTGAGC
AGAGGAAGAAGTATTCCAACTCCAACGTCATCATGCACGAGACCTCGCAGTACCACGTCCAGCACCTGGC
CACATTCATCATGGACAAGAGCGAAGCCATCACGTCTGTGGACGACGCCATCCGGAAGCTGGTGCAGCTG
AGCTCCAAGGAGAAGATCTGGACCCAGGAGATGCTGCTGCAGGTGAACGACCAGTCGCTGCGGCTGCTGG
ACATCGAGTCACAGGAGGAGCTGGAAGACTTCCCGCTGCCCACGGTGCAGCGCAGCCAGACGGTCCTCAA
CCAGCTGCGCTACCCGTCTGTGCTGCTGCTCGTGTGCCAGGACTCGGAGCAGAGCAAGCCGGATGTCCAC
TTCTTCCACTGCGATGAGGTGGAGGCAGAGCTGGTGCACGAGGACATCGAGAGCGCGTTGGCCGACTGCC
GGCTGGGCAAGAAGATGCGGCCGCAGACCCTGAAGGGACACCAGGAGAAGATTCGGCAGCGGCAGTCCAT
CCTGCCTCCTCCCCAGGGCCCGGCGCCCATCCCCTTCCAGCACCGCGGCGGGGATTCCCCGGAGGCCAAG
AATCGCGTGGGCCCGCAGGTGCCACTCAGCGAGCCAGGTTTCCGCCGTCGGGAGTCGCAGGAGGAGCCGC
GGGCCGTGCTGGCTCAGAAGATAGAGAAGGAGACGCAAATCCTCAACTGCGCCCTGGACGACATCGAGTG
GTTTGTGGCCCGGCTGCAGAAGGCAGCCGAGGCTTTCAAGCAGCTGAACCAGCGGAAAAAGGGGAAGAAG
AAGGGCAAGAAGGCGCCAGCAGAGGGCGTCCTCACACTGCGGGCACGGCCCCCCTCTGAGGGCGAGTTCA
TCGACTGCTTCCAGAAAATCAAGCTGGCGATTAACTTGCTGGCAAAGCTGCAGAAGCACATCCAGAACCC
CAGCGCCGCGGAGCTCGTGCACTTCCTCTTCGGGCCTCTGGACCTGATCGTCAACACCTGCAGTGGCCCA
GACATCGCACGCTCCGTCTCCTGCCCACTGCTCTCCCGAGATGCCGTGGACTTCCTGCGCGGCCACCTGG
TCCCTAAGGAGATGTCGCTGTGGGAGTCACTGGGAGAGAGCTGGATGCGGCCCCGTTCCGAGTGGCCGCG
GGAGCCACAGGTGCCCCTCTACGTGCCCAAGTTCCACAGCGGCTGGGAGCCTCCTGTGGATGTGCTGCAG
GAGGCCCCCTGGGAGGTGGAGGGGCTGGCGTCTGCCCCCATCGAGGAGGTGAGTCCAGTGAGCCGACAGT
CCATAAGAAACTCCCAGAAGCACAGCCCCACTTCAGAGCCCACCCCCCCGGGGGATGCCCTACCACCAGT
CAGCTCCCCACATACTCACAGGGGCTACCAGCCAACACCAGCCATGGCCAAGTACGTCAAGATCCTGTAT
GACTTCACAGCCCGAAATGCCAACGAGCTATCGGTGCTCAAGGATGAGGTCCTAGAGGTGCTGGAGGACG
GCCGGCAGTGGTGGAAGCTGCGCAGCCGCAGCGGCCAGGCGGGGTACGTGCCCTGCAACATCCTAGGCGA
GGCGCGACCGGAGGACGCCGGCGCCCCGTTCGAGCAGGCCGGTCAGAAGTACTGGGGCCCCGCCAGCCCG
ACCCACAAGCTACCCCCAA**GCTTCCCGGGGAACAAAGACGAGCTCATGCAGCACATGGACGAGGTCAACG**
ACGAGCTCATCCGGAAAATCAGCAACATCAGGGCGCAGCCACAGAGGCACTTCCGCGTGGAGCGCAGCCA
GCCCGTGAGCCAGCCGCTCACCTACGAGTCGGGTCCGGACGAGGTCCGCGCCTGGCTGGAAGCCAAGGCC
TTCAGCCCGCGGATCGTGGAGAACCTGGGCATCCTGACCGGGCCGCAGCTCTTCTCCCTCAACAAGGAGG
AGCTGAAGAAAGTGTGCGGCGAGGAGGGCGTCCGCGTGTACAGCCAGCTCACCATGCAGAAGGCCTTCCT
GGAGAAGCAGCAAAGTGGGTCGGAGCTGGAAGAACTCATGAACAAGTTTCATTCCATGAATCAGAGGAGG
GGGGAGGACAGC**TAG**GCCCAGCTGCCTTGGGCTGGGGCCTGCGGAGGGGAAGCCCACCCACAATGCATGG
AGTATTATTTTTATATGTGTATGTATTTTGTATCAAGGACACGGAGGGGGTGTGGTGCTGGCTAGAGGTC
CCTGCCCCTGTCTGGAGGCACAACGCCCATCCTTAGGCCAAACAGTACCCAAGGCCTCAGCCCACACCAA
GACTAATCTCAGCCAAACCTGCTGCTTGGTGGTGCCAGCCCCTTGTCCACCTTCTCTTGAGGCCACAGAA
CTCCCTGGGGCTGGGGCCTCTTTCTCTGGCCTCCCCTGTGCACCTGGGGGGTCCTGGCCCCTGTGATGCT
CCCCCATCCCCCACCCACTTCTACATCCATCCACACCCCAGGGTGAGCTGGAGCTCCAGGCTGGCCAGGCT
GAACCTCGCACACACGCAGAGTTCTGCTCCCTGAGGGGGGCCCGGGAGGGGCTCCAGCAGGAGGCCGTGG
GTGCCATTCGGGGGAAAGTGGGGGAACGACACACACTTCACCTGCAAGGGCCGACAACGCAGGGGACACC
GTGCCGGCTTCAGACACTCCCAGCGCCCACTCTTACAGGCCCAGGACTGGAGCTTTCTCTGGCCAAGTTT
CAGGCCAATGATCCCCGCATGGTGTTGGGGGTGCTGGTGTGTCTTGGTGCCTGGACTTGAGTCTCACCCT
ACAGATGAGAGGTGGCTGAGGCACCAGGGCTAAGCAATTAAACCAGTTAAGTCTCCCAGGAAAAAAAAAA
AAAAAA

The start and stop codons are indicated in bold as well as the position corresponding to the microarray probe.

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000320828 and has a sequence as in SEQ ID NO:126

MSQSGAVSCCPGATNGSLGRSDGVAKMSPKDLFEQRKKYSNSNV
IMHETSQYHVQHLATFIMDKSEAITSVDDAIRKLVQLSSKEKIWTQEMLLQVNDQSLR
LLDIESQEELEDFPLPTVQRSQTVLNQLRYPSVLLLVCQDSEQSKPDVHFFHCDEVEA
ELVHEDIESALADCRLGKKMRPQTLKGHQEKIRQRQSILPPPQGPAPIPFQHRGGDSP
EAKNRVGPQVPLSEPGFRRRESQEEPRAVLAQKIEKETQILNCALDDIEWFVARLQKA
AEAFKQLNQRKKGKKKGKKAPAEGVLTLRARPPSEGEFIDCFQKIKLAINLLAKLQKH
IQNPSAAELVHFLFGPLDLIVNTCSGPDIARSVSCPLLSRDAVDFLRGHLVPKEMSLW
ESLGESWMRPRSEWPREPQVPLYVPKFHSGWEPPVDVLQEAPWEVEGLASAPIEEVSP
VSRQSIRNSQKHSPTSEPTPPGDALPPVSSPHTHRGYQPTPAMAKYVKILYDFTARNA
NELSVLKDEVLEVLEDGRQWWKLRSRSGQAGYVPCNILGEARPEDAGAPFEQAGQKYW
GPASPTHKLPPSFPGNKDELMQHMDEVNDELIRKISNIRAQPQRHFRVERSQPVSQPL
TYESGPDEVRAWLEAKAFSPRIVENLGILTGPQLFSLNKEELKKVCGEEGVRVYSQLT
MQKAFLEKQQSGSELEELMNKFHSMNQRRGEDS

Primers for amplifying the sequence ENST00000318562 can be designed using primer design software such as Oligo Calc and/or Primer 3. Examples of primer pairs for amplifying EPS8L2 include:

Forward SEQ ID NO:127 GAG ACC TGG CGC CCC GGC (Ex1)
Reverse SEQ ID NO:128 GTG GCC CCG GTC TGA GGC (Ex2)

Forward SEQ ID NO:129 GAG CCA GTC CGG GGC CGT G (Ex2)
Reverse SEQ ID NO:130 CTT GGG GCT CAT CTT GGC (Ex3)

Forward SEQ ID NO:131 CGA CGG TGT GGC CAA GAT GAG (Ex3
Reverse SEQ ID NO:132 CGT GGT ACT GCG AGG TC (Ex4)

Forward SEQ ID NO:133 CTCCAACGTCATCATGCAC (Ex4)
Reverse SEQ ID NO:134 GATGGCGTCGTCCACAGAC (Ex5)

Forward SEQ ID NO:135 CAGTCGCTGCGGCTGCTGG (Ex5)
Reverse SEQ ID NO:136 GGACCGTCTGGCTGCGCTG (Ex6)

Forward SEQ ID NO:137 GATGTCCACTTCTTCCACTGC (Ex6)
Reverse SEQ ID NO:138 CCGAATCTTCTCCTGGTGTC (Ex8)

Forward SEQ ID NO:139 GAGGCCAAGAATCGCGTGGGC (Ex8)
Reverse SEQ ID NO:140 GTCCAGGGCGCAGTTGAGG (Ex10)

Forward SEQ ID NO:141 CGACTGCTTCCAGAAAATC (Ex11)
Reverse SEQ ID NO:142 CGAAGAGGAAGTGCACGAG (Ex12)

Forward SEQ ID NO:143 GATGTCGCTGTGGGAGTCAC (Ex13)
Reverse SEQ ID NO:144 GAGGGGCACCTGTGGCTC (Ex14)

Forward SEQ ID NO:145 GGTGGAGGGGCTGGCGTC (Ex14)

Reverse SEQ ID NO:146 GGCTCTGAAGTG GGGCTGTG (Ex15)

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting EPS8L2 can be derived from any number of sources depending on the desired use (e.g., using the primers described above and the appropriate reagents).

Examples of probes include:

SEQ ID NO:147
GCTTCCCGGGGAACAAAGACGAGCTCATGCAGCACATGGACGAGGTCAACG ACGAGCTCA

SEQ ID NO:148
GCAGAGCTGGTGCACGAGGACATCGAGAGCGCGTTGGCCGACTGCCGG

SEQ ID NO:149
GCCGTCGGGAGTCGCAGGAGGAGCCGCGGGCCGTGCTGGCTCAGAAGATAG

SEQ ID NO:150
GCTCGTGTGCCAGGACTCGGAGCAGAGCAAGCCGGATGTCCAC

SEQ ID NO:151
GTACAGCCAGCTCACCATGCAGAAGGCCTTCCTGGAGAAGCAGCAAAG

Other probes to EPS8L2 are known in the art and/or can be readily designed by the skilled artisan.

Antibodies against EPS8L2 include, but are not limited to, Abnova Cat# H00064787-M01 which is a mouse monoclonal antibody raised against a partial recombinant EPS8L2 (615 a.a. ~ 715 a.a) and Abnova Cat# H00064787-B01which is a mouse polyclonal antibody raised against a full-length human EPS8L2 protein.

Example 12: FASTKD1

FASTKD1 was found to be overexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that FASTKD1 was overexpressed in primary endometrial cancer tissue as compared to normal

endometrial tissue and it was surprisingly found that FASTKD1 was overexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the method described in Examples 2-4. Example 5 shows that FASTKD1 can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

The sequence of an mRNA corresponding to FASTKD1 is given in ENSEMBL accession no. ENST00000260971 and has a sequence as in SEQ ID NO:152

```
   1 ATAAACCCTGAGATATGAGGGTTGGGCGAGACATCCGAGCCTGTTTCGTTCCGTGTTGGG
  61 ACCAGGAATAACCCTGACTTCTGAGCTTTCATAACCCCAGGATCCTCCAGAAAATTTGCG
 121 GCGCGCTGAGGGAAAACCTTGCTGAAGCTGTACATTGGAATGCGTTTACAGTCATTGTAA
 181 TGGAAGCAAAATACATGAAGGAAAAACTGTTATTTGTATCCCTGCTTATTGCACCTGACG
 241 ACTAGTTGCAGATGGTTTTGTTTACCTAAGAAAACTTGTGATATAAATGAAAAAAACACC
 301 TGTTTTCCTAGAGTCATTGGTTACAAATATGCTTCGTCTAAGAGCTATTTGTCCATTCTC
 361 CTGGAGAGTGTTTCAATTTCGACCCATCAGTTGTGAACCACTAATTATTCAGATGAATAA
 421 GTGTACAGATGAGGAGCAAATGTTTGGTTTTATTGAAAGAAACAAAGCCATACTTTCAGA
 481 AAAGCAAGTGGGATGTGCATTTGATATGCTTTGGAAGCTTCAAAAGCAGAAGACCAGCCT
 541 GTTAAAAAATGCTGAGTATGTCAGAGACCATCCTCAATTTCTTACTCTTCATAATTTAGC
 601 TACAAATAAATTCAAATTAATGAATGACGATACCCTGGTGAATGTGTTATACGTCACACA
 661 ACAGTTTGCTGGTGAGGCCCATGACCCGCTAGTTGAAGCACTAGTTACAGAAGCATGGAG
 721 AAGGCTAGAAAGGTTTGATATTAAACTGCTCTCAGAATTTTCCTCTTGCCTAGCAGATCA
 781 GCATTTGTATTTTAGTCCATTAATGGGAAAAATAGCTGATATTGTTCATAGGAACTTGGA
 841 AACCACACAGGACTTAAGTTCCTTGTCTGTCTTGATGGTCAACATATCTTCTTTAATATC
 901 ACGACATTTTCAACAACAACTGGTGAACAAAACAGAACTTCTTTTTGACACCATAGATTC
 961 TTCTGAGGTCAACGTTGCAAAAAGCATAGCAAAGTTTCTTCGAAATGTTAGATATCGTTA
1021 TCAACCACTATTAGAAAGATGTAATAACGTATTTTTAAGTAATGTGGACCACCTTGATTT
1081 GGATTCCATCAGTAAAATACTTAGTGTATACAAATTTCTACAATTTAATAGTTTTGAATT
1141 TATTATAATGGCTAAAAAGAAGCTAACTGAAATGATTCCTCTGTGTAATCATCCTGCTAG
1201 CTTTGTAAAATTGTTTGTAGCATTGGGACCCATTGCAGGACCTGAAGAAAAGAAACAACT
1261 TAAATCAACTATGTTATTGATGTCAGAGGACCTAACTGGCGAGCAAGCCCTGGCAGTGTT
1321 GGGAGCAATGGGAGATATGGAAAGCAGAAACTCATGTCTGATTAAAAGAGTTACTTCAGT
1381 TCTGCATAAACATTTGGATGGCTATAAACCATTAGAGTTGTTGAAGATAACTCAAGAATT
1441 AACTTTTCTGCATTTCCAAAGGAAGGAGTTTTTTGCGAAACTTAGAGAATTACTGCTTAG
1501 TTATTTGAAAAATAGTTTCATACCAACTGAGGTGTCTGTTCTGGTCCGTGCTATTTCCCT
1561 GCTCCCTTCTCCTCACTTGGACGAAGTGGGGATATCCCGAATTGAAGCCGTTTTACCACA
1621 GTGTGACCTAAATAACCTGAGTAGTTTTGCCACATCTGTTTTAAGATGGATTCAGCATGA
1681 TCACATGTATTTGGATAATATGACTGCGAAACAACTGAAACTACTTCAAAAATTAGATCA
1741 CTATGGTCGTCAGAGACTACAACACAGCAACAGTTTGGATCTGTTACGGAAGGAACTTAA
1801 ATCTCTCAAAGGAAACACGTTTCCTGAGTCACTTCTTGAAGAAATGATTGCTACTTTACA
1861 GCATTTCATGGATGATATTAATTACATAAATGTTGGGGAGATTGCATCTTTTATTTCTAG
1921 TACTGATTACCTCAGTACTTTGCTACTAGATAGGATAGCCTCAGTGGCTGTTCAGCAGAT
1981 TGAAAAGATCCATCCTTTTACAATCCCTGCTATTATTCGTCCATTCAGCGTATTGAACTA
2041 TGATCCACCTCAAAGGGATGAATTTTTGGGAACTTGCGTGCAACATCTTAATTCTTACTT
2101 AGGTATATTGGATCCTTTTATATTAGTGTTTCTTGGTTTCTCTTTGGCCACACTTGAATA
2161 TTTTCCAGAAGATCTGCTAAAGGCAATTTTTAACATCAAATTCTTAGCTAGATTGGATTC
2221 TCAACTTGAAAGTATTGGTGGCATGGATGGAACACAACAGCAGATTTTTAAAATGTTAGC
2281 AGAGGTACTAGGAGGAATCAATTGTGTAAAAGCCTCGGTTCTTACGCCTTATTACCACAA
2341 AGTAGATTTTGAGTGTATCTTGGATAAAAGAAAAAAACCTCTTCCGTATGGAAGCCATAA
2401 TATAGCATTGGGACAACTACCAGAAATGCCCTGGGAATCAAATATCGAAATAGTTGGATC
2461 AAGGCTGCCACCAGGGGCTGAAAGGATTGCTTTGGAATTTTTGGATTCAAAAGCACTTTG
2521 TAGAAATATCCCTCACATGAAAGGAAAATCTGCTATGAAAAAACGACATTTGGAAATTCT
2581 GGGGTATCGTGTAATTCAGATTTCCCAGTTTGAATGGAACTCTATGGCACTGTCAACAAA
2641 GGATGCTCGGATGGACTACCTGAGAGAATGTATATTTGGAGAAGTCAAGTCATGTTTGTA
2701 GTTTTTATTTAAAATGAATGTTATCGTGTGTTACATTTGGACCTATTTTAATAAAGTGGC
2761 CTGTCTC
```

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000260971and has a sequence as in SEQ ID NO:153

```
  1 MKKTPVFLESLVTNMLRLRAICPFSWRVFQFRPISCEPLIIQMNKCTDEEQMFGFIERNK
 61 AILSEKQVGCAFDMLWKLQKQKTSLLKNAEYVRDHPQFLTLHNLATNKFKLMNDDTLVNV
121 LYVTQQFAGEAHDPLVEALVTEAWRRLERFDIKLLSEFSSCLADQHLYFSPLMGKIADIV
181 HRNLETTQDLSSLSVLMVNISSLISRHFQQQLVNKTELLFDTIDSSEVNVAKSIAKFLRN
241 VRYRYQPLLERCNNVFLSNVDHLDLDSISKILSVYKFLQFNSFEFIIMAKKKLTEMIPLC
301 NHPASFVKLFVALGPIAGPEEKKQLKSTMLLMSEDLTGEQALAVLGAMGDMESRNSCLIK
361 RVTSVLHKHLDGYKPLELLKITQELTFLHFQRKEFFAKLRELLLSYLKNSFIPTEVSVLV
421 RAISLLPSPHLDEVGISRIEAVLPQCDLNNLSSFATSVLRWIQHDHMYLDNMTAKQLKLL
481 QKLDHYGRQRLQHSNSLDLLRKELKSLKGNTFPESLLEEMIATLQHFMDDINYINVGEIA
541 SFISSTDYLSTLLLDRIASVAVQQIEKIHPFTIPAIIRPFSVLNYDPPQRDEFLGTCVQH
601 LNSYLGILDPFILVFLGFSLATLEYFPEDLLKAIFNIKFLARLDSQLESIGGMDGTQQQI
661 FKMLAEVLGGINCVKASVLTPYYHKVDFECILDKRKKPLPYGSHNIALGQLPEMPWESNI
721 EIVGSRLPPGAERIALEFLDSKALCRNIPHMKGKSAMKKRHLEILGYRVIQISQFEWNSM
781 ALSTKDARMDYLRECIFGEVKSCL
```

Primers for amplifying a FASTKD1 nucleic acid sequence can be designed using primer design software such as Oligo Calc and/or Primer 3.

Examples of primer pairs for amplifying a FASTKD1 nucleic acid include those in

Forward: SEQ ID NO:154 TGAATGACGATACCCTGGTG
Reverse: SEQ ID NO:155 AGCCTTCTCCATGCTTCTGT

Forward: SEQ ID NO:156 CCATGACCCGCTAGTTGAAG
Reverse: SEQ ID NO:157 TGATCTGCTAGGCAAGAGGAA

Forward: SEQ ID NO:158 TTCCTCTTGCCTAGCAGATCA
Reverse: SEQ ID NO:159 TGTTGACCATCAAGACAGACA

Forward: SEQ ID NO:160 TCCTCTGTGTAATCATCCTGCT
Reverse: SEQ ID NO:161 CTCGCCAGTTAGGTCCTCTG

Forward: SEQ ID NO:162 GGAGCAATGGGAGATATGGA
Reverse: SEQ ID NO:163 TTCCTTTGGAAATGCAGAAAA

Forward: SEQ ID NO:164 TGCATTTCCAAAGGAAGGAG
Reverse: SEQ ID NO:165 CAAGTGAGGAGAAGGGAGCA

Forward: SEQ ID NO:166 AAATGTTGGGGAGATTGCAT
Reverse: SEQ ID NO:167 TCAATACGCTGAATGGACGA

Forward: SEQ ID NO:168 GATCCACCTCAAAGGGATGA
Reverse: SEQ ID NO:169 GGCCAAAGAGAAACCAAGAA

Forward: SEQ ID NO:170 GTGTTTCTTGGTTTCTCTTTGG
Reverse: SEQ ID NO:171 CTGTTGTGTTCCATCCATGC

Forward: SEQ ID NO:172 GCATTGGGACAACTACCAGAA
Reverse: SEQ ID NO:173 GTATGGGAGCGCAAAAGAAG

Forward: SEQ ID NO:174 TGTGTTGCTTCATATTTGTACCC
Reverse: SEQ ID NO:175 CATAGCAGATTTTCCTTTCATGTG

Forward: SEQ ID NO:176 TGACCGCTTCTGTCAACAAT
Reverse: SEQ ID NO:177 TGAATCCAAAAATTCCAAAGC

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting FASTKD1 can be derived from any number of sources depending on the desired use (e.g., using the above described primers and appropriate reagents). Other examples of probes include

SEQ ID NO:178 GACCCGCTAGTTGAAGCACT
SEQ ID NO:179 ACAGAAGCATGGAGAAGGCT
SEQ ID NO:180 GAACTTGGAAACCACACAGGA
SEQ ID NO:181 TTGTAGCATTGGGACCCATT
SEQ ID NO:182 TGCATAAACATTTGGATGGC
SEQ ID NO:183 TTCTGGTCCGTGCTATTTCC
SEQ ID NO:184 GTGGCTGTTCAGCAGATTGA
SEQ ID NO:185 GAACTTGCGTGCAACATCTT
SEQ ID NO:186 CCAGAAGATCTGCTAAAGGCA
SEQ ID NO:187 TGCCCTGGGAATCAAATATC
SEQ ID NO:188 GGATTGCTTTGGAATTTTTGG
SEQ ID NO:189 ATGGATGGAACACAACAGCA

A probe for detecting a FASTKD1 nucleic acid that was used on the microarray has a sequence as in SEQ ID NO:190
TGAATGGAACTCTATGGCACTGTCAACAAAGGATGCTCGGATGGACTACCTG AGAGA

Other probes to FASTKD1 are known in the art and/or can be readily designed by the skilled artisan.

Antibodies against FASTKD1 include, but are not limited to, Mouse Anti-Human FLJ21901 Polyclonal Antibody Cat# H00079675-A01 against de N-terminal (from aa 2-100).

Example 13: IKBKE

IKBKE (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase epsilon) also known as IKK-I; IKKE; IKKI; KIAA0151; MGC125294; MGC125295;

MGC125297, was found to be overexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that IKBKE was overexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue and it was surprisingly found that IKBKE was overexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the method described in Example 4. Example 5 shows that IKBKE can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

IKBKE is a member of the large IkB kinase complex capable of phosphorylating IkB. IKK phosphorylates only one of two serine residues in IκBα necessary for ubiquitination and degradation of IκBα. The degradation of IkBα exposes however, the nuclear localization signals on NF-kB, leading to its translocation to the nucleus, where it binds to specific promoters and activates transcription. (PMID: 10882136).

The sequence of an mRNA corresponding to IKBKE is given in ENSEMBL accession no. ENST00000367120 and has a sequence as in SEQ ID NO:191

GAGAGAGCTGAGAGCCAGGACTCAGTGCTGAGCTTGGTGTCCCACCGCCACAAGGAGGCAGGGAAGAAAC
CCACTAGTCCCAGCTCCTGGGGTGGCACAGACATTGCAACTGGCCCTGCCTGTGGGTCCTAGGGGCCCTT
GGCTACCAGGAGGCTAAGAACACTGCTCATGAATGACAGTGAGCCCTGAAAGCTCTGGGGGTGTCACCCA
GTCCCACAAGCCTGCATCCCCTGCAGTGGAGATGGGCTCAGCTCCTGGACGTGCCACAGACAGAAAGCAT
AACATACACTCGCCAGGAAGAGCCTTTGCCTGACTCAGGGCAGCTCAGAGTGTGGGGCAGAAGGTGACCA
GCCAGCTCAGGGCAGGAG**ATG**CAGAGCACAGCCAATTACCTGTGGCACACAGATGACCTGCTGGGGCAGG
GGGCCACTGCCAGTGTGTACAAGGCCCGCAACAAGAAATCCGGAGAGCTGGTTGCTGTGAAGGTCTTCAA
CACTACCAGCTACCTGCGGCCCCGCGAGGTGCAGGTGAGGGAGTTTGAGGTCCTGCGGAAGCTGAACCAC
CAGAACATCGTCAAGCTCTTTGCGGTGGAGGAGACGGGCGGAAGCCGGCAGAAGGTACTGGTGATGGAGT
ACTGCTCCAGTGGGAGCCTGCTGAGTGTGCTGGAGAGCCCTGAGAATGCCTTTGGGCTGCCTGAGGATGA
GTTCCTGGTGGTGCTGCGCTGTGTGGTGGCCGGCATGAACCACCTGCGGGAGAACGGCATTGTGCATCGC
GACATCAAGCCGGGGAACATCATGCGCCTCGTAGGGGAGGAGGGGCAGAGCATCTACAAGCTGACAGACT
TCGGCGCTGCCCGGGAGCTGGATGATGATGAGAAGTTCGTCTCGGTCTATGGGACTGAGGAGTACCTGCA
TCCCGACATGTATGAGCGGGCGGTGCTTCGAAAGCCCCAGCAAAAAGCGTTCGGGGTGACTGTGGATCTC
TGGAGCATTGGAGTGACCTTGTACCATGCAGCCACTGGCAGCCTGCCCTTCATCCCCTTTGGTGGGCCAC
GGCGGAACAAGGAGATCATGTACCGGATCACCACGGAGAAGCCGGCTGGGGCCATTGCAGGTGCCCAGAG
GCGGGAGAACGGGCCCCTGGAGTGGAGCTACACCCTCCCCATCACCTGCCAGCTGTCACTGGGGCTGCAG
AGCCAGCTGGTGCCCATCCTGGCCAACATCCTGGAGGTGGAGCAGGCCAAGTGCTGGGGCTTCGACCAGT
TCTTTGCGGAGACCAGTGACATCCTGCAGCGAGTTGTCGTCCATGTCTTCTCCCTGTCCCAGGCAGTCCT
GCACCACATCTATATCCATGCCCACAACACGATAGCCATTTTCCAGGAGGCCGTGCACAAGCAGACCAGT
GTGGCCCCCCGACACCAGGAGTACCTCTTTGAGGGTCACCTCTGTGTCCTCGAGCCCAGCGTCTCAGCAC
AGCACATCGCCCACACGACGGCAAGCAGCCCCCTGACCCTCTTCAGCACAGCCATCCCTAAGGGGCTGGC
CTTCAGGGACCCTGCTCTGGACGTCCCCAAGTTCGTCCCCAAAGTGGACCTGCAGGCGGATTACAACACT
GCCAAGGGCGTGTTGGGCGCCGGCTACCAGGCCCTGCGGCTGGCACGGGCCCTGCTGGATGGGCAGGAGC
TAATGTTTCGGGGGCTGCACTGGGTCATGGAGGTGCTCCAGGCCACATGCAGACGGACTCTGGAAGTGGC
AAGGACATCCCTCCTCTACCTCAGCAGCAGCCTGGGAACTGAGAGGTTCAGCAGCGTGGCTGGAACGCCT
GAGATCCAGGAACTGAAGGCGGCTGCAGAACTGAGGTCCAGGCTGCGGACTCTAGCGGAGGTCCTCTCCA

GATGCTCCCAAAATATCACGGAGACCCAGGAGAGCCTGAGCAGCCTGAACCGGGAGCTGGTGAAGAGCCG
GGATCAGGTACATGAGGACAGAAGCATCCAGCAGATTCAGTGCTGTTTGGACAAGATGAACTTCATCTAC
AAACAGTTCAAGAAGTCTAGGATGAGGCCAGGGCTTGGCTACAACGAGGAGCAGATTCACAAGCTGGATA
AGGTGAATTTCAGTCATTTAGCCAAAAGACTCCTGCAGGTGTTCCAGGAGGAGTGCGTGCAGAAGTATCA
AGCGTCCTTAGTCACACACGGCAAGAGGATGAGGGTGGTGCACGAGACCAGGAACCACCTGCGCCTGGTT
GGCTGTTCTGTGGCTGCCTGTAACACAGAAGCCCAGGGGGTCCAGGAGAGTCTCAGCAAGCTCCTGGAAG
AGCTATCTCACCAGCTCCTTCAGGACCGAGCAAAGGGGGCTCAGGCCTCGCCGCCTCCCATAGCTCCTTA
CCCCAGCCCTACACGAAAGGACCTGCTTCTCCACATGCAAGAGCTCTGCGAGGGGATGAAGCTGCTGGCA
TCTGACCTCCTGGACAACAACCGCATCATCGAACGGCTAAATAGAGTCCCAGCACCTCCTGATGTC**TGA**G
CTCCATGGGGCACATGAGGCATCCTGAAGCATTAGAATGATTCCAACACTGCTCTTCTGCACCATGAGAC
CAACCCAGGGCAAGATCCCATCCCATCACATCAGCCTACCTCCCTCCTGGCTGCTGGCCAGGATGTCGCC
AGCATTACCTTCCACTGCCTTTCTCCCTGGGAAGCAGCACAGCTGAGACTGGGCACCAGGCCACCTCTGT
TGGGACCCACAGGAAAGAGTGTGGCAGCAACTGCCTGGCTGACCTTTCTATCTTCTCTAGGCTCAGGTAC
TGCTCCTCCATGCCCATGGCTGGGCCGTGGGGAGAAGAAGCTCTCATACGCCTTCCCACTCCCTCTGGTT
TATAGGACTTCACTCCCTAGCCAACAGGAGAGGAGGCCTCCTGGGGTTTCCCCAGGGCAGTAGGTCAAAC
GACCTCATCACAGTCTTCCTTCCTCTTCAAGCGTTTCATGTTGAACACAGCTCTCTCCGCTCCCTTGTGA
TTTCTGAGGGTCACCACTGCCAGCCTCAGGCAACATAGAGAGCCTCCTGTTCTTTCTATGCTTGGTCTGA
CTGAGCCTAAAGTTGAGAAAATGGGTGGCCAAGGCCAGTGCCAGTGTCTTGGGGCCCCTTTGGCTCTCCC
TCACTCTCTGAGGCTCCAGCTGGTCCTGGGACATGCAGCCAGGACTGTGAGTCTGGGCAGGTCCAAGGCC
TGCACCTTCAAGAAGTGGAATAAATGTGGCCTTTGCTTCTGTT

The start and stop codons are indicated in bold.

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000356087 and has a sequence as in SEQ ID NO:192

MQSTANYLWHTDDLLGQGATASVYKARNKKSGELVAVKVFNTTS
YLRPREVQVREFEVLRKLNHQNIVKLFAVEETGGSRQKVLVMEYCSSGSLLSVLESPE
NAFGLPEDEFLVVLRCVVAGMNHLRENGIVHRDIKPGNIMRLVGEEGQSIYKLTDFGA
ARELDDDEKFVSVYGTEEYLHPDMYERAVLRKPQQKAFGVTVDLWSIGVTLYHAATGS
LPFIPFGGPRRNKEIMYRITTEKPAGAIAGAQRRENGPLEWSYTLPITCQLSLGLQSQ
LVPILANILEVEQAKCWGFDQFFAETSDILQRVVVHVFSLSQAVLHHIYIHAHNTIAI
FQEAVHKQTSVAPRHQEYLFEGHLCVLEPSVSAQHIAHTTASSPLTLFSTAIPKGLAF
RDPALDVPKFVPKVDLQADYNTAKGVLGAGYQALRLARALLDGQELMFRGLHWVMEVL
QATCRRTLEVARTSLLYLSSSLGTERFSSVAGTPEIQELKAAAELRSRLRTLAEVLSR
CSQNITETQESLSSLNRELVKSRDQVHEDRSIQQIQCCLDKMNFIYKQFKKSRMRPGL
GYNEEQIHKLDKVNFSHLAKRLLQVFQEECVQKYQASLVTHGKRMRVVHETRNHLRLV
GCSVAACNTEAQGVQESLSKLLEELSHQLLQDRAKGAQASPPPIAPYPSPTRKDLLLH
MQELCEGMKLLASDLLDNNRIIERLNRVPAPPDV

Primers for amplifying the sequence ENST00000367120 can be designed using primer design software such as Oligo Calc and/or Primer 3.

Examples of primer pairs for amplifying IKBKE include:

Forward SEQ ID NO:193 GTGCCACAGACAGAAAGCATAAC (EX2)
Reverse SEQ ID NO:194 GGCTGTGCTCTGCATCTC (ex3)

Foward SEQ ID NO:195 GGGGCCACTGCCAGTGTG (ex3)
Reverse SEQ ID NO:196 GCAGGTAGCTGGTAGTGTTGAAG (ex4)

Forward SEQ ID NO:197 GAGGTCCTGCGGAAGCTGAAC (ex4)

Reverse SEQ ID NO:198 CACTCAGCAGGCTCCCACTG (ex5)

Forward SEQ ID NO:199 CCTGAGGATGAGTTCCTGGTG (ex5)
Reverse SEQ ID NO:200 GTCGCGATGCACAATGCCGTTC (ex6)

Forward SEQ ID NO:201 GGATGATGATGAGAAGTTCGTCTC
Reverse SEQ ID NO:202 GAACGCTTTTTGCTGGGGC (ex7)

Forward SEQ ID NO:203 CATCCCCTTTGGTGGGCCAC (ex7)
Reverse SEQ ID NO:204 CCGTTCTCCCGCCTCTGG (ex8)

Forward SEQ ID NO:205 CCTGGAGTGGAGCTACACC (ex8)
Reverse SEQ ID NO:206 CACTTGGCCTGCTCCACCTC (ex9)

Forward SEQ ID NO:207 GTCCCAGGCAGTCCTGCAC (ex9)
Reverse SEQ ID NO:208 GACGCTGGGCTCGAGGACAC (ex10)

Forward SEQ ID NO:209 GACCCTCTTCAGCACAGCCAT C
Reverse SEQ ID NO:210 GCCGCAGGGCCTGGTAGC (ex12)

Forward SEQ ID NO:211 GATCCAGGAACTGAAGGCGGC (ex14)
Reverse SEQ ID NO:212 CCTGATCCCGGCTCTTCAC (ex15)

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting IKBKE can be derived from any number of sources depending on the desired use (e.g., using the primers described above and the appropriate reagents).

Other examples of probes include:

SEQ ID NO:213
CTCCTGTTCTTTCTATGCTTGGTCTGACTGAGCCTAAAGTTGAGAAAATGGG
TGGCCAAG

SEQ ID NO:214
CATCACCTGCCAGCTGTCACTGGGGCTGCAGAGCC

SEQ ID NO:215
CTATATCCATGCCCACAACACGATAGCCATTTTCC

SEQ ID NO:216
GGACGTCCCCAAGTTCGTCCCCAAAGTGGACCTGCAGGCG

SEQ ID NO:217

GGTCCAGGAGAGTCTCAGCAAGCTCCTGGAAGAGCTATCTCAC

Other probes to IKBKE are known in the art and/or can be readily designed by the skilled artisan.

Antibodies against IKBKE include, but are not limited to, Abcam Cat# ab37596 which is a rabbit polyclonal antibody with an antigen that was a KLH conjugated synthetic peptide selected within a.a. 700-800 of human IKKE; and Abcam Cat# ab12142 which is a mouse monoclonal antibody against a synthetic peptide corresponding to a.a. residues 175-188, 525-540, or 567-580 of human IKK iota/IKK epsilon.

Example 14: PHKG2

PHKG2 was found to be overexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that PHKG2 was overexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue and it was surprisingly found that PHKG2 was overexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the method described in Examples 2-4. Example 5 shows that PHKG2 can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

The sequence of an mRNA corresponding to PHKG2 is given in ENSEMBL accession no. ENST00000328273 and has a sequence as in SEQ ID NO:218

```
   1 AAGGTGAGCGACTGCAGGCAAACCCGGCGACAGCGCAGCTCGCGTCGACCCTGGCTCCTC
  61 TGCCTGCCCCCTCAGGCCCCCGCCTCCTTCAGGATGACGCTGGACGTGGGGCCGGAGGAT
 121 GAGCTGCCCGACTGGGCCGCCGCCAAAGAGTTTTACCAGAAGTACGACCCTAAGGACGTC
 181 ATCGGCAGAGGAGTGAGCTCTGTGGTCCGCCGTTGTGTTCATCGAGCTACTGGCCACGAG
 241 TTTGCGGTGAAGATTATGGAAGTGACAGCTGAGCGGCTGAGTCCTGAGCAGCTGGAGGAG
 301 GTGCGGGAAGCCACACGGCGAGAGACACACATCCTTCGCCAGGTCGCCGGCCACCCCCAC
 361 ATCATCACCCTCATCGATTCCTACGAGTCTTCTAGCTTCATGTTCCTGGTGTTTGACCTG
 421 ATGCGGAAGGGAGAGCTGTTTGACTATCTCACAGAGAAGGTGGCCCTCTCTGAAAAGGAA
 481 ACCAGGTCCATCATGCGGTCTCTGCTGGAAGCAGTGAGCTTTCTCCATGCCAACAACATT
 541 GTGCATCGAGATCTGAAGCCCGAGAATATTCTCCTAGATGACAATATGCAGATCCGACTT
 601 TCAGATTTCGGGTTCTCCTGCCACTTGGAACCTGGCGAGAAGCTTCGAGAGTTGTGTGGG
 661 ACCCCAGGGTATCTAGCGCCAGAGATCCTTAAATGCTCCATGGATGAAACCCACCCAGGC
 721 TATGGCAAGGAGGTCGACCTCTGGGCCTGTGGGGTGATCTTGTTCACACTCCTGGCTGGC
 781 TCGCCACCCTTCTGGCACCGGCGGCAGATCCTGATGTTACGCATGATCATGGAGGGCCAG
 841 TACCAGTTCAGTTCCCCCGAGTGGGATGACCGTTCCAGCACTGTCAAAGACCTGATCTCC
 901 AGGCTGCTGCAGGTGGATCCTGAGGCACGCCTGACAGCTGAGCAGGCCCTACAGCACCCC
 961 TTCTTTGAGCGTTGTGAAGGCAGCCAACCCTGGAACCTCACCCCCCGCCAGCGGTTCCGG
```

```
1021 GTGGCAGTGTGGACAGTGCTGGCTGCTGGACGAGTGGCCCTAAGCACCCATCGTGTACGG
1081 CCACTGACCAAGAATGCACTGTTGAGGGACCCTTATGCGCTGCGGTCAGTGCGGCACCTC
1141 ATCGACAACTGTGCCTTCCGGCTCTACGGGCACTGGGTAAAGAAAGGGGAGCAGCAGAAC
1201 CGGGCGGCTCTCTTTCAGCACCGGCCCCCTGGGCCTTTTCCCATCATGGGCCCTGAAGAG
1261 GAGGGAGACTCTGCTGCTATAACTGAGGATGAGGCCGTGCTTGTGCTGGGCTAGGACCTC
1321 AACCCCAGGGATTCCCAGGAAGCAGAACTCTCCAGAAGAAGGGTTTTGATCATTCCAGCT
1381 CCTCTGGGCTCTGGCCTCTGGCCTCAGGCCCACTAATGATCCTGCTACCCTCTTGAAGAC
1441 CAGCCCGGTACCTCTCTCCCCACTGGCCAGGACTCTGAGATCAGAGCTGGGGTGGAAGGG
1501 AGCCATTCTGAACGCCACGCCTGGCCCGGTCAGTGCTGCATGCACTGCATATGAAATAAA
1561 ATCTGCTACACGCCAGGG
```

The start and stop codons are indicated in bold.

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000329968 and has a sequence as in SEQ ID NO:219

```
1- MTLDVGPEDELPDWAAAKEFYQKYDPKDVIGRGVSSVVRRCVHRATGHEFAVKIMEVTAE
61 RLSPEQLEEVREATRRETHILRQVAGHPHIITLIDSYESSSFMFLVFDLMRKGELFDYLT
121 EKVALSEKETRSIMRSLLEAVSFLHANNIVHRDLKPENILLDDNMQIRLSDFGFSCHLEP
181 GEKLRELCGTPGYLAPEILKCSMDETHPGYGKEVDLWACGVILFTLLAGSPPFWHRRQIL
241 MLRMIMEGQYQFSSPEWDDRSSTVKDLISRLLQVDPEARLTAEQALQHPFFERCEGSQPW
301 NLTPRQRFRVAVWTVLAAGRVALSTHRVRPLTKNALLRDPYALRSVRHLIDNCAFRLYGH
361 WVKKGEQQNRAALFQHRPPGPFPIMGPEEEGDSAAITEDEAVLVLG
```

Primers for amplifying the sequence PHKG2 can be designed using primer design software such as Oligo Calc.

Examples of primer pairs for amplifying PHKG2 include those in

forward SEQ ID NO:220 CCGCCAAAGAGTTTTACCAG
reverse SEQ ID NO:221 TCCATAATCTTCACCGCAAA

forward SEQ ID NO:222 GGCGAGAGACACACATCCTT
reverse SEQ ID NO:223 CAAACACCAGGAACATGAAGC

forward SEQ ID NO:224 GCTTCATGTTCCTGGTGTTTG
reverse SEQ ID NO:225 TTTTCAGAGAGGGCCACCTT

forward SEQ ID NO:226 GGAAGGGAGAGCTGTTTGACT
reverse SEQ ID NO:227 TGTTGTTGGCATGGAGAAAG

forward SEQ ID NO:228 TCAGATTTCGGGTTCTCCTG
reverse SEQ ID NO:229 ATAGCCTGGGTGGGTTTCAT

forward SEQ ID NO:230 ATGAAACCCACCCAGGCTAT
reverse SEQ ID NO:231 TGCGTAACATCAGGATCTGC

forward SEQ ID NO:232 CGTTCCAGCACTGTCAAAGA
reverse: SEQ ID NO:233 CCTTCACAACGCTCAAAGAA

forward SEQ ID NO:234 ACCCCTTCTTTGAGCGTTGT

reverse SEQ ID NO:235 CGTACACGATGGGTGCTTAG

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting PHKG2 can be derived from any number of sources depending on the desired use (e.g., using the above described primers and appropriate reagents). Other examples of probes include

SEQ ID NO:236 CCGTTGTGTTCATCGAGCTA
SEQ ID NO:237 CATCACCCTCATCGATTCCT
SEQ ID NO:238 GGAAGGGAGAGCTGTTTGACT
SEQ ID NO:239 AGGAAACCAGGTCCATCATG
SEQ ID NO:240 CAGGGTATCTAGCGCCAGAG
SEQ ID NO:241 CCTGTGGGGTGATCTTGTTC
SEQ ID NO:242 ACAGCTGAGCAGGCCCTAC
SEQ ID NO:243 GTTGTGGCAGTGTGGACAGT

A probe for detecting a PHKG2 nucleic acid that was used on the microarray has a sequence as in

SEQ ID NO:244
CTCAACCCCAGGGATTCCCAGGAAGCAGAACTCTCCAGAAGAAGGGTTTTGATCA TTCCA

Other probes to PHKG2 are known in the art and/or can be readily designed by the skilled artisan.

Antibodies against PHKG2 include, but are not limited to,Mouse monoclonal antibody Anti-PHKG2 against full length protein Cat# WH0005261M1 from SIGMA; PHKG2 antibody - N-terminal Cat# ab71129 from abcam; and PHKG2 antibody Cat# ab28642 against a region between amino acids 8-57 of human PHKG2 from abcam.

Example 15: P4HB

P4HB was found to be overexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that P4HB was overexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue and it was surprisingly found that P4HB was overexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial

cancer by the method described in Examples 2-4. Example 5 shows that P4HB can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

The sequence of an mRNA corresponding to P4HB is given in ENSEMBL accession no. ENST00000331483 and has a sequence as in SEQ ID NO:245

```
   1 GAGCCTCGAAGTCCGCCGGCCAATCGAAGGCGGGCCCCAGCGGCGCGTGCGCGCCGCGGC
  61 CAGCGCGCGCGGGCGGGGGGGCAGGCGCGCCCCGGACCCAGGATTTATAAAGGCGAGGCC
 121 GGGACCGGCGCGCGCTCTCGTCGCCCCCGCTGTCCCGGCGGCGCCAACCGAAGCGCCCCG
 181 CCTGATCCGTGTCCGACATGCTGCGCCGCGCTCTGCTGTGCCTGGCCGTGGCCGCCCTGG
 241 TGCGCGCCGACGCCCCCGAGGAGGAGGACCACGTCCTGGTGCTGCGGAAAAGCAACTTCG
 301 CGGAGGCGCTGGCGGCCCACAAGTACCTGCTGGTGGAGTTCTATGCCCCTTGGTGTGGCC
 361 ACTGCAAGGCTCTGGCCCCTGAGTATGCCAAAGCCGCTGGGAAGCTGAAGGCAGAAGGTT
 421 CCGAGATCAGGTTGGCCAAGGTGGACGCCACGGAGGAGTCTGACCTGGCCCAGCAGTACG
 481 GCGTGCGCGGCTATCCCACCATCAAGTTCTTCAGGAATGGAGACACGGCTTCCCCCAAGG
 541 AATATACAGCTGGCAGAGAGGCTGATGACATCGTGAACTGGCTGAAGAAGCGCACGGGCC
 601 CGGCTGCCACCACCCTGCCTGACGGCGCAGCTGCAGAGTCCTTGGTGGAGTCCAGCGAGG
 661 TGGCTGTCATCGGCTTCTTCAAGGACGTGGAGTCGGACTCTGCCAAGCAGTTTTTGCAGG
 721 CAGCAGAGGCCATCGATGACATACCATTTGGGATCACTTCCAACAGTGACGTGTTCTCCA
 781 AATACCAGCTCGACAAAGATGGGGTTGTCCTCTTTAAGAAGTTTGATGAAGGCCGGAACA
 841 ACTTTGAAGGGGAGGTCACCAAGGAGAACCTGCTGGACTTTATCAAACACAACCAGCTGC
 901 CCCTTGTCATCGAGTTCACCGAGCAGACAGCCCCGAAGATTTTTGGAGGTGAAATCAAGA
 961 CTCACATCCTGCTGTTCTTGCCCAAGAGTGTGTCTGACTATGACGGCAAACTGAGCAACT
1021 TCAAAACAGCAGCCGAGAGCTTCAAGGGCAAGATCCTGTTCATCTTCATCGACAGCGACC
1081 ACACCGACAACCAGCGCATCCTCGAGTTCTTTGGCCTGAAGAAGGAAGAGTGCCCGGCCG
1141 TGCGCCTCATCACCCTGGAGGAGGAGATGACCAAGTACAAGCCCGAATCGGAGGAGCTGA
1201 CGGCAGAGAGGATCACAGAGTTCTGCCACCGCTTCCTGGAGGGCAAAATCAAGCCCCACC
1261 TGATGAGCCAGGAGCTGCCGGAGGACTGGGACAAGCAGCCTGTCAAGGTGCTTGTTGGGA
1321 AGAACTTTGAAGACGTGGCTTTTGATGAGAAAAAAAACGTCTTTGTGGAGTTCTATGCCC
1381 CATGGTGTGGTCACTGCAAACAGTTGGCTCCCATTTGGGATAAACTGGGAGAGACGTACA
1441 AGGACCATGAGAACATCGTCATCGCCAAGATGGACTCGACTGCCAACGAGGTGGAGGCCG
1501 TCAAAGTGCACAGCTTCCCCACACTCAAGTTCTTTCCTGCCAGTGCCGACAGGACGGTCA
1561 TTGATTACAACGGGGAACGCACGCTGGATGGTTTTAAGAAATTCCTGGAGAGCGGTGGCC
1621 AGGATGGGGCAGGGGATGATGACGATCTCGAGGACCTGGAAGAAGCAGAGGAGCCAGACA
1681 TGGAGGAAGACGATGATCAGAAAGCTGTGAAAGATGAACTGTAATACGCAAAGCCAGACC
1741 CGGGCGCTGCCGAGACCCCTCGGGGGCTGCACACCCAGCAGCAGCGCACGCCTCCGAAGC
1801 CTGCGGCCTCGCTTGAAGGAGGGCGTCGCCGGAAACCCAGGGAACCTCTCTGAAGTGACA
1861 CCTCACCCCTACACACCGTCCGTTCACCCCCGTCTCTTCCTTCTGCTTTTCGGTTTTTGG
1921 AAAGGGATCCATCTCCAGGCAGCCCACCCTGGTGGGGCTTGTTTCCTGAAACCATGATGT
1981 ACTTTTTCATACATGAGTCTGTCCAGAGTGCTTGCTACCGTGTTCGGAGTCTCGCTGCCT
2041 CCCTCCCGCGGGAGGTTTCTCCTCTTTTTGAAAATTCCGTCTGTGGGATTTTTAGACATT
2101 TTTCGACATCAGGGTATTTGTTCCACCTTGGCCAGGCCTCCTCGGAGAAGCTTGTCCCCC
2161 GTGTGGGAGGGACGGAGCCGGACTGGACATGGTCACTCAGTACCGCCTGCAGTGTCGCCA
2221 TGACTGATCATGGCTCTTGCATTTTTGGGTAAATGGAGACTTCCGGATCCTGTCAGGGTG
2281 TCCCCCATGCCTGGAAGAGGAGCTGGTGGCTGCCAGCCCTGGGGCCCGGCACAGGCCTGG
2341 GCCTTCCCCTTCCCTCAAGCCAGGGCTCCTCCTCCTGTCGTGGGCTCATTGTGACCACTG
2401 GCCTCTCTACAGCACGGCCTGTGGCCTGTTCAAGGCAGAACCACGACCCTTGACTCCCGG
2461 GTGGGGAGGTGGCCAAGGATGCTGGAGCTGAATCAGACGCTGACAGTTCTTCAGGCATTT
2521 CTATTTCACAATCGAATTGAACACATTGGCCAAATAAAGTTGAAATTTTACCACCTGT
```

The start and stop codons are indicated in bold as well as the position corresponding to the microarray probe.

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000327801 and has a sequence as in SEQ ID NO:246

```
1 MLRRALLCLAVAALVRADAPEEEDHVLVLRKSNFAEALAAHKYLLVEFYAPWCGHCKALA
61 PEYAKAAGKLKAEGSEIRLAKVDATEESDLAQQYGVRGYPTIKFFRNGDTASPKEYTAGR
121 EADDIVNWLKKRTGPAATTLPDGAAAESLVESSEVAVIGFFKDVESDSAKQFLQAAEAID
181 DIPFGITSNSDVFSKYQLDKDGVVLFKKFDEGRNNFEGEVTKENLLDFIKHNQLPLVIEF
241 TEQTAPKIFGGEIKTHILLFLPKSVSDYDGKLSNFKTAAESFKGKILFIFIDSDHTDNQR
301 ILEFFGLKKEECPAVRLITLEEEMTKYKPESEELTAERITEFCHRFLEGKIKPHLMSQEL
361 PEDWDKQPVKVLVGKNFEDVAFDEKKNVFVEFYAPWCGHCKQLAPIWDKLGETYKDHENI
421 VIAKMDSTANEVEAVKVHSFPTLKFFPASADRTVIDYNGERTLDGFKKFLESGGQDGAGD
481 DDDLEDLEEAEEPDMEEDDDQKAVKDEL
```

Primers for amplifying the sequence P4HB can be designed using primer design software such as Oligo Calc and/or Primer 3.

Examples of primer pairs for amplifying P4HB include those in

Forward SEQ ID NO:247: GCTGCGGAAAAGCAACTTC
Reverse SEQ ID NO:248 CTGATCTCGGAACCTTCTGC

Forward SEQ ID NO:249 GGCTATCCCACCATCAAGTT
Reverse SEQ ID NO:250 TCTTCAGCCAGTTCACGATG

Forward SEQ ID NO:251 GCAGAGTCCTTGGTGGAGTC
Reverse SEQ ID NO:252 TGGAAGTGATCCCAAATGGT

Forward SEQ ID NO:253 ACCATTTGGGATCACTTCCA
Reverse SEQ ID NO:254 GGTGACCTCCCCTTCAAAGT

Forward SEQ ID NO:255 CCCCTTGTCATCGAGTTCAC
Reverse SEQ ID NO:256 TGCTCAGTTTGCCGTCATAG

Forward SEQ ID NO:257 TCACATCCTGCTGTTCTTGC
Reverse SEQ ID NO:258 GTCGCTGTCGATGAAGATGA

Forward SEQ ID NO:259 GACGGCAGAGAGGATCACAG
Reverse SEQ ID NO:260 TTCTTCCCAACAAGCACCTT

Forward SEQ ID NO:261 AGCCTGTCAAGGTGCTTGTT
Reverse SEQ ID NO:262 CAAATGGGAGCCAACTGTTT

Forward SEQ ID NO:263 ACAGCTTCCCCACACTCAAG
Reverse SEQ ID NO:264 CACCGCTCTCCAGGAATTT

Forward SEQ ID NO:265 GCACGCTGGATGGTTTTAAG
Reverse SEQ ID NO:266 TCATCGTCTTCCTCCATGTCT

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting P4HB can be derived from any number of sources depending on the desired use (e.g., using the above described primers and appropriate reagents). Other examples of probes include

SEQ ID NO:267 CACAAGTACCTGCTGGTGGA
SEQ ID NO:268 GGCTTCCCCCAAGGAATATA
SEQ ID NO:269 GCTTCTTCAAGGACGTGGAG
SEQ ID NO:270 CTCGACAAAGATGGGGTTGT
SEQ ID NO:271 TCACATCCTGCTGTTCTTGC
SEQ ID NO:272 CTATGACGGCAAACTGAGCA
SEQ ID NO:273 AAAATCAAGCCCCACCTGAT
SEQ ID NO:274 TGAAGACGTGGCTTTTGATG
SEQ ID NO:275 GGTCATTGATTACAACGGGG
SEQ ID NO:276 ATGACGATCTCGAGGACCTG

A probe for detecting a P4HB nucleic acid that was used on the microarray has a sequence as in

SEQ ID NO:277
GGCATTTCTATTTCACAATCGAATTGAACACATTGGCCAAATAAAGTTGAAATTT TCCCC

Other probes to P4HB are known in the art and/or can be readily designed by the skilled artisan.

Antibodies against P4HB include, but are not limited to, anti P4HB Cat# ab31811 de abcam (rabbit polyclonal) against residues 400 to 500; and PDI (P4HB) Mouse anti-Human Monoclonal Antibody from Lifespan Biosciences Cat# LS-C38385.

Example 16: P2RX4

P2RX4 was found to be overexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that P2RX4 was overexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue as described in Example 2. It was surprisingly found that P2RX4 was overexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the method described in Example 4. Example

5 shows that P2RX4 can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

P2RX4

(also known as P2X4; P2X4R; P2RX4)

P2X purinoceptor 4 (P2X4)(ATP receptor)(Purinergic receptor

ENSG00000135124

The sequence of an mRNA corresponding to P2RX4 is given in ENSEMBL accession no. ENST00000337233 and has a sequence as in SEQ ID NO:278

```
   1 AAGTGCTGGGATGACAGGTGTGAGCCACCGCCCCCGGCCCCTCGCCCGCCTTTTGAAGGA
  61 GCCTTTCGTCCTCAAGGGCGAGGCCACTCCCCCCCCGCGAGTTCCATGCCCCCTAGAGGG
 121 TCATCGTTCCCGACGGGGAGGTGGCGCCCTCCCCCGGGCCCCGGGCCCCGACCGCCCGTG
 181 CTGCCTCCTTCCGGGCCCTCCTCCGCGATGACGGCGCCGCCAGCAGGCCAGGCGGACTGG
 241 GCGGGGCTCCGAGCGGGGACTGGGACCCAGACCGACTAGGGGACTGGGAGCGGGCGGCGC
 301 GGCC[ATG]GCGGGCTGCTGCGCCGCGCTGGCGGCCTTCCTGTTCGAGTACGACACGCCGCG
 361 CATCGTGCTCATCCGCAGCCGCAAAGTGGGGCTCATGAACCGCGCCGTGCAACTGCTCAT
 421 CCTGGCCTACGTCATCGGGTGGGTGTTTGTGTGGGAAAAGGGCTACCAGGAAACTGACTC
 481 CGTGGTCAGCTCCGTTACGACCAAGGTCAAGGGCGTGGCTGTGACCAACACTTCTAAACT
 541 TGGATTCCGGATCTGGGATGTGGCGGATTATGTGATACCAGCTCAGGAGGAAAACTCCCT
 601 CTTCGTCATGACCAACGTGATCCTCACCATGAACCAGACACAGGGCCTGTGCCCCGAGAT
 661 TCCAGATGCGACCACTGTGTGTAAATCAGATGCCAGCTGTACTGCCGGCTCTGCCGGCAC
 721 CCACAGCAACGGAGTCTCAACAGGCAGGTGCGTAGCTTTCAACGGGTCTGTCAAGACGTG
 781 TGAGGTGGCGGCCTGGTGCCCGGTGGAGGATGACACACACGTGCCACAACCTGCTTTTTT
 841 AAAGGCTGCAGAAAACTTCACTCTTTTGGTTAAGAACAACATCTGGTATCCCAAATTTAA
 901 TTTCAGCAAGAGGAATATCCTTCCCAACATCACCACTACTTACCTCAAGTCGTGCATTTA
 961 TGATGCTAAAACAGATCCCTTCTGCCCCATATTCCGTCTTGGCAAAATAGTGGAGAACGC
1021 AGGACACAGTTTCCAGGACATGGCCGTGGAGGGAGGCATCATGGGCATCCAGGTCAACTG
1081 GGACTGCAACCTGGACAGAGCCGCCTCCCTCTGCTTGCCCAGGTACTCCTTCCGCCGCCT
1141 CGATACACGGGACGTTGAGCACAACGTATCTCCTGGCTACAATTTCAGGTTTGCCAAGTA
1201 CTACAGAGACCTGGCTGGCAACGAGCAGCGCACGCTCATCAAGGCCTATGGCATCCGCTT
1261 CGACATCATTGTGTTTGGGAAGGCAGGGAAATTTGACATCATCCCCACTATGATCAACAT
1321 CGGCTCTGGCCTGGCACTGCTAGGCATGGCGACCGTGCTGTGTGACATCATAGTCCTCTA
1381 CTGCATGAAGAAAAGACTCTACTATCGGGAGAAGAAATATAAATATGTGGAAGATTACGA
1441 GCAGGGTCTTGCTAGTGAGCTGGACCAGTGAGGCCTACCCCACACCTGGGCTCTCCACAG
1501 CCCCATCAAAGAACAGAGAGGAGGAGGAGGGAGAAATGGCCACCACATCACCCCAGAGAA
1561 ATTTCTGGAATCTGATTGAGTCTCCACTCCACAAGCACTCAGGGTTCCCCAGCAGCTCCT
1621 GTGTGTTGTGTGCAGGATCTGTTTGCCCACTCGGCCCAGGAGGTCAGCAGTCTGTTCTTG
1681 GCTGGGTCAACTCTGCTTTTCCCGCAACCTGGGGTTGTCGGGGGAGCGCTGGCCCGACGC
1741 AGTGGCACTGCTGTGGCTTTCAGGGCTGGAGCTGGCTTTGCTCAGAAGCCTCCTGTCTCC
1801 AGCTCTCTCCAGGACAGGCCCAGTCCTCTGAGGCACGGCGGCTCTGTTCAAGCACTTTAT
1861 GCGGCAGGGGAGGCCGCCTGGCTGCAGTCACTAGACTTGTAGCAGGCCTGGGCTGCAGGC
1921 TTCCCCCCGACCATTCCCTGCAGCCATGCGGCAGAGCTGGCATTT[CTCCTCAGAGAAGCG
1981 CTGTGCTAAGGTGATCGAGGACCAGACATTAAAGCGTGATTTTCTT]
```

The start and stop codons are indicated in bold as well as the position corresponding to the microarray probe.

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000336607 and has a sequence as in SEQ ID NO:279

```
  1 MAGCCAALAAFLFEYDTPRIVLIRSRKVGLMNRAVQLLILAYVIGWVFVWEKGYQETDSV
 61 VSSVTTKVKGVAVTNTSKLGFRIWDVADYVIPAQEENSLFVMTNVILTMNQTQGLCPEIP
121 DATTVCKSDASCTAGSAGTHSNGVSTGRCVAFNGSVKTCEVAAWCPVEDDTHVPQPAFLK
181 AAENFTLLVKNNIWYPKFNFSKRNILPNITTTYLKSCIYDAKTDPFCPIFRLGKIVENAG
241 HSFQDMAVEGGIMGIQVNWDCNLDRAASLCLPRYSFRRLDTRDVEHNVSPGYNFRFAKYY
301 RDLAGNEQRTLIKAYGIRFDIIVFGKAGKFDIIPTMINIGSGLALLGMATVLCDIIVLYC
361 MKKRLYYREKKYKYVEDYEQGLASELDQ
```

ENST00000359949
ENSP00000353032

SEQ ID NO:280

```
1 MAGCCAALAAFLFEYDTPRIVLIRSRKVGLMNRAVQLLILAYVIGWVFVWEKGYQETDSV
61 VSSVTTKVKGVAVTNTSKLGFRIWDVADYVIPAQEENSLFVMTNVILTMNQTQGLCPEIP
121 DATTVCKSDASCTAGSAGTHSNVVCTLIPAFLKAAENFTLLVKNNIWYPKFNFSKRNILP
181 NITTTYLKSCIYDAKTDPFCPIFRLGKIVENAGHSFQDMAVEGGIMGIQVNWDCNLDRAA
241 SLCLPRYSFRRLDTRDVEHNVSPGYNFRFAKYYRDLAGNEQRTLIKAYGIRFDIIVFGKA
301 GKFDIIPTMINIGSGLALLGMATVLCDIIVLYCMKKRLYYREKKYKYVEDYEQGLASELD
361 Q
```

Examples of primer pairs for amplifying P2RX4 include:

Forward SEQ ID NO:281 AACTGCTCATCCTGGCCTAC
Reverse SEQ ID NO:282 GTCGTAACGGAGCTGACCAC

Forward SEQ ID NO:283 GGATGTGGCGGATTATGTG
Reverse SEQ ID NO:284 CCTGTGTCTGGTTCATGGTG

Forward SEQ ID NO:285 AGATTCCAGATGCGACCACT
Reverse SEQ ID NO:286 CAGACCCGTTGAAAGCTACG

Forward SEQ ID NO:287 TCTGTCAAGACGTGTGAGGTG
Reverse SEQ ID NO:288 CCAAAAGAGTGAAGTTTTCTGC

Forward SEQ ID NO:289 TTTTGGTTAAGAACAACATCTGG
Reverse SEQ ID NO:290 ATATGGGGCAGAAGGGATCT

Forward SEQ ID NO:291 CGCTTCGACATCATTGTGTT
Reverse SEQ ID NO:292 TAGCAGTGCCAGGCCAGAG

Forward SEQ ID NO:293 GAAAAGACTCTACTATCGGGAGAA
Reverse SEQ ID NO:294 CTGTTCTTTGATGGGGCTGT

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting P2RX4 derived from any number of sources depending on the desired use (e.g., using the above described primers and appropriate reagents).

Other examples of probes include:

SEQ ID NO:295 TTGTGTGGGAAAAGGGCTAC
SEQ ID NO:296 TTCGTCATGACCAACGTGAT
SEQ ID NO:297 TCAGATGCCAGCTGTACTGC
SEQ ID NO:298 GTGGAGGATGACACACACGT
SEQ ID NO:299 TCCTTCCCAACATCACCACT
SEQ ID NO:300 GAAGGCAGGGAAATTTGACA
SEQ ID NO:301 GGGTCTTGCTAGTGAGCTGG

A probe for detecting a P2RX4 nucleic acid that was used on the microarray has a sequence as in

SEQ ID NO:302
CTCCTCAGAGAAGCGCTGTGCTAAGGTGATCGAGGACCAGACATTAAAGCGTGA
TTTTCT

Other probes to P2RX4 are known in the art and/or can be readily designed by the skilled artisan.

Antibodies to P2RX4, incluye, but are not limited to, Mouse Anti-Human P2RX4 Maxpab polyclonal, unconjugated from Novus Biologicals, P2RX4 (1 a.a. ~ 388 a.a) full-length human protein, H00005025-B01, and Goat Anti-P2RX4 polyclonal, unconjugated from Novus Biologicals, NBP1-00141, Synthetic peptide, SEQ ID NO:303 YREKKYKYVEDYEQ, representing the C Terminus of the sequence according to NP_002551.2

Example 17: PPFIBP2

PPFIBP2 was found to be overexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that PPFIBP2 was overexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue as described in Example 2. It was surprisingly found that PPFIBP2 was overexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the method described in Example 4. Example 5 shows that PPFIBP2 can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

PPPFIBP2

The sequence of an mRNA corresponding to PPPFIBP2 is given in ENSEMBL accession no. ENST00000299492 and has a sequence as in SEQ ID NO:304

```
   1 GCAGGCTTCTTCGGTGCCCGAGAGGGAGCGGGTGCCCAAGGGGGTGGTCCCTGTGGCAGG
  61 TCCCGGGGTGGGGGCGCGGCGCTCCGGGAAGAGCCTTCCGCAGGTCCCCGCCCCGTCACG
 121 TGGGCGCCGGCCCCGGCCGCTGCGGTCGGTCCGCTGGTTGGTCGGGCGCTTGGTCCGGCA
 181 GTTGGTCGGTGGGCCAGTGGCCCGTCGCTCGCTTCTGGGCTCTCATGTTTGAAGGTGGGA
 241 GGGACACGGGAGCGGCCCGCACACCTGAGCCGCCCGGAGAGGAGCCTCGGCCCCGTACCC
 301 AGTAAGAAGAGGAGGAGGCCAGGCAGGCAAAAGGAGTCATGGCTTCTGATGCTAGTCATG
 361 CGCTGGAAGCTGCCCTGGAGCAAATGGACGGGATCATTGCAGGCACTAAAACAGGTGCAG
 421 ATCTTAGTGATGGTACTTGTGAGCCTGGACTGGCTTCCCCGGCCTCCTACATGAACCCCT
 481 TCCCGGTGCTCCATCTCATCGAGGACTTGAGGCTGGCCTTGGAGATGCTGGAGCTTCCTC
 541 AGGAGAGAGCAGCCCTCCTGAGCCAGATCCCTGGCCCAACAGCTGCCTACATAAAGGAAT
 601 GGTTTGAAGAGAGCTTGTCCCAGGTAAACCACCACAGTGCTGCTAGTAATGAAACCTACC
 661 AGGAACGCTTGGCACGTCTAGAAGGGGATAAGGAGTCCCTCATATTGCAGGTGAGTGTCC
 721 TCACAGACCAAGTAGAAGCCCAGGGAGAAAAGATTCGAGACCTGGAAGTGTGTCTGGAAG
 781 GACACCAGGTGAAACTCAATGCTGCTGAAGAGATGCTTCAACAGGAGCTGCTAAGCCGCA
 841 CATCTCTTGAGACCCAGAAGCTCGATCTGATGACTGAAGTGTCTGAGCTGAAGCTCAAGC
 901 TGGTTGGCATGGAGAAGGAGCAGAGAGAGCAGGAGGAGAAGCAGAGAAAAGCAGAGGAGT
 961 TACTGCAAGAGCTCAGGCACCTCAAAATCAAAGTGGAAGAGTTGGAAAATGAAAGGAATC
1021 AGTATGAATGGAAGCTAAAGGCCACTAAGGCTGAAGTCGCCCAGCTGCAAGAACAGGTGG
1081 CCCTGAAAGATGCAGAAATTGAGCGTCTGCACAGCCAGCTCTCCCGGACAGCAGCTCTCC
1141 ACAGTGAGAGTCACACAGAGAGAGACCAAGAAATTCAACGTCTGAAAATGGGGATGGAAA
1201 CTTTGCTGCTTGCCAATGAAGATAAGGACCGTCGGATAGAGGAGCTTACGGGGCTGTTAA
1261 ACCAGTACCGGAAGGTAAAGGAGATTGTGATGGTCACTCAAGGGCCTTCGGAGAGAACTC
1321 TCTCAATCAATGAAGAAGAACCGGAGGGAGGTTTCAGCAAGTGGAACGCTACAAATAAGG
1381 ACCCTGAAGAATTATTTAAACAAGAGATGCCTCCAAGATGTAGCTCTCCTACAGTGGGGC
1441 CACCTCCATTGCCACAGAAATCACTGGAAACCAGGGCTCAGAAAAAGCTCTCTTGTAGTC
1501 TAGAAGACTTGAGAAGTGAATCTGTGGATAAGTGTATGGATGGGAACCAGCCCTTCCCGG
1561 TGTTAGAACCCAAGGACAGCCCTTTCTTGGCGGAGCACAAATATCCCACTTTACCTGGGA
1621 AGCTTTCAGGAGCCACGCCCAATGGAGAGGCTGCCAAATCTCCTCCCACCATCTGCCAGC
1681 CTGACGCCACGGGGAGCAGCCTGCTGAGGCTGAGAGACACAGAAAGTGGCTGGGACGACA
1741 CTGCTGTGGTCAATGACCTCTCATCCACATCATCGGGCACTGAATCAGGTCCTCAGTCTC
1801 CTCTGACACCAGATGGTAAACGGAATCCCAAAGGCATTAAGAAGTTCTGGGGAAAAATCC
1861 GAAGAACTCAGTCAGGAAATTTCTACACTGACACGCTGGGGATGGCAGAGTTTCGACGAG
1921 GTGGGCTCCGGGCAACCGCAGGGCCAAGACTCTCTAGGACCAGGGACTCCAAGGGACAGA
1981 AAAGTGACGCCAATGCCCCCTTTGCCCAGTGGAGCACAGAGCGTGTGTGTGCATGGCTGG
2041 AGGACTTTGGCCTGGCTCAGTATGTGATCTTTGCCAGGCAGTGGGTATCTTCTGGCCACA
2101 CCTTATTGACAGCCACCCCTCAGGACATGGAAAAGGAGCTAGGAATTAAGCACCCACTCC
2161 ACAGGAAGAAGCTTGTTTTAGCAGTGAAAGCCATCAACACCAAACAGGAGGAGAAGTCTG
2221 CACTGCTAGACCACATTTGGGTGACAAGGTGGCTTGATGATATTGGCTTACCCCAGTACA
2281 AAGACCAGTTTCATGAATCTAGAGTTGACAGACGAATGCTGCAATACCTAACTGTGAACG
2341 ATTTACTCTTCTTAAAAGTCACCAGCCAACTACATCATCTCAGCATCAAATGTGCCATTC
2401 ACGTGCTGCATGTCAACAAGTTCAACCCCCACTGCCTGCACCGGCGGCCAGCTGATGAGA
2461 GTAACCTTTCTCCTTCAGAAGTTGTACAGTGGTCCAACCACAGGGTGATGGAGTGGTTAC
2521 GATCTGTGGACCTGGCAGAGTATGCACCCAATCTTCGAGGGAGTGGAGTCCATGGAGGCC
2581 TCATTATCCTGGAGCCACGCTTCACTGGGGACACCCTGGCTATGCTTCTCAACATCCCCC
2641 CACAAAAGACGCTCCTCAGGCGCCACCTGACCACCAAGTTCAATGCCTTGATTGGTCCGG
2701 AGGCTGAACAGGAGAAGCGAGAGAAAATGGCCTCACCAGCTTACACACCACTGACCACCA
2761 CAGCCAAAGTCCGGCCAAGGAAACTAGGATTTTCACACTTCGGAAACATAAGAAAAAAGA
2821 AGTTCGATGAATCGACGGACTACATTTGCCCAATGGAGCCCAGTGACGGTGTCAGTGATA
2881 GTCACAGGGTCTACAGTGGCTACCGGGGCCTCAGCCCCCTTGATGCCCCTGAACTGGATG
2941 GGCTGGACCAGGTGGGACAGATTAGCTGATGCCCTTGTCACCTGCCCTCTGTGCACCCTG
3001 AGAGCTCACAGTAACACTGTGTGTGTCACCATATAACTGCACCTCACCCCCGCACGTGTG
3061 CATGACTCGCAGAGAATATTCCAGCAATTGTGTACCCCTGGGCCAGTCTCTTTGAACCCT
3121 GAGGGTGGCCAGGATCTGGAGCTGCATCTCTAAGGGGCCAGGCTTTGGGGACCATTGCCA
```

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3181 AAGGTGGACTCAGGAGGAAAGACACTTAAAGACACTTTTACATGTCTAGTAATTCTTGAT
3241 GTTCATCTTCAGCACCAGTGGAAACACATGAACTTCGATGCAGGTCCAGAGACCATGGAC
3301 ACTCCCACGAGGCTCAGCTCTCAGGCACCCCCTACACTTCAGTTGAGGGAAAAGCTCAAG
3361 TGCCTTAGGCCCGTGGACCACAGTCTTGGCTGAGATCAAAGGGATGAGCAACAGGGACTT
3421 CTGCCACAGTGACAATGGAATTGTGTTGTGCCTTACTTCAGAGGTGGTCTCTTCTTTCTT
3481 GTAATAAAAGCAATATTTATGC
```

The start and stop codons are indicated in bold as well as the position corresponding to the microarray probe.

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000299492 and has a sequence as in SEQ ID NO:305

```
   1 MASDASHALEAALEQMDGIIAGTKTGADLSDGTCEPGLASPASYMNPFPVLHLIEDLRLA
  61 LEMLELPQERAALLSQIPGPTAAYIKEWFEESLSQVNHHSAASNETYQERLARLEGDKES
 121 LILQVSVLTDQVEAQGEKIRDLEVCLEGHQVKLNAAEEMLQQELLSRTSLETQKLDLMTE
 181 VSELKLKLVGMEKEQREQEEKQRKAEELLQELRHLKIKVEELENERNQYEWKLKATKAEV
 241 AQLQEQVALKDAEIERLHSQLSRTAALHSESHTERDQEIQRLKMGMETLLLANEDKDRRI
 301 EELTGLLNQYRKVKEIVMVTQGPSERTLSINEEEPEGGFSKWNATNKDPEELFKQEMPPR
 361 CSSPTVGPPPLPQKSLETRAQKKLSCSLEDLRSESVDKCMDGNQPFPVLEPKDSPFLAEH
 421 KYPTLPGKLSGATPNGEAAKSPPTICQPDATGSSLLRLRDTESGWDDTAVVNDLSSTSSG
 481 TESGPQSPLTPDGKRNPKGIKKFWGKIRRTQSGNFYTDTLGMAEFRRGGLRATAGPRLSR
 541 TRDSKGQKSDANAPFAQWSTERVCAWLEDFGLAQYVIFARQWVSSGHTLLTATPQDMEKE
 601 LGIKHPLHRKKLVLAVKAINTKQEEKSALLDHIWVTRWLDDIGLPQYKDQFHESRVDRRM
 661 LQYLTVNDLLFLKVTSQLHHLSIKCAIHVLHVNKFNPHCLHRRPADESNLSPSEVVQWSN
 721 HRVMEWLRSVDLAEYAPNLRGSGVHGGLIILEPRFTGDTLAMLLNIPPQKTLLRRHLTTK
 781 FNALIGPEAEQEKREKMASPAYTPLTTTAKVRPRKLGFSHFGNIRKKKFDESTDYICPME
 841 PSDGVSDSHRVYSGYRGLSPLDAPELDGLDQVGQIS
```

Primers for amplifying the sequence ENST00000299492 can be designed using primer design software such as Oligo Calc and/or Primer 3.

Examples of primer pairs for amplifying PPFIBP2 include:

1) Forward SEQ ID NO:306 GCTAGTCATGCGCTGGAAG
Reverse SEQ ID NO:307 GAAGCTCCAGCATCTCCAAG

2) Forward SEQ ID NO:308 CCCAGGTAAACCACCACAGT
Reverse SEQ ID NO:309 CTGGTGTCCTTCCAGACACA

3) Forward SEQ ID NO:310 TGTGTCTGGAAGGACACCAG
Reverse SEQ ID NO:311 TCCTCCTGCTCTCTCTGCTC

4) Forward SEQ ID NO:312 AAGAGCTCAGGCACCTCAAA
Reverse SEQ ID NO:313 CTCACTGTGGAGAGCTGCTG

5) Forward SEQ ID NO:314 AAACTTTGCTGCTTGCCAAT
Reverse SEQ ID NO:315 TTGAGTGACCATCACAATCTCC

6) Forward SEQ ID NO:316 TCTCTCAATCAATGAAGAAGAACC
Reverse SEQ ID NO:317 TCCAGTGATTTCTGTGGCAAT

7) Forward SEQ ID NO:318 GCCTCCAAGATGTAGCTCTCC
Reverse SEQ ID NO:319 TCCACAGATTCACTTCTCAAGTC

8) Forward SEQ ID NO:320 CGGAGCACAAATATCCCACT
Reverse SEQ ID NO:321 CTTTGGGATTCCGTTTACCA

9) Forward SEQ ID NO:322 TGGTAAACGGAATCCCAAAG
Reverse SEQ ID NO:323 TTGGAGTCCCTGGTCCTAGA

10) Forward SEQ ID NO:324 TCTAGGACCAGGGACTCCAA
Reverse SEQ ID NO:325 GGGTGGCTGTCAATAAGGTG

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting PPFIBP2 derived from any number of sources depending on the desired use (e.g., using the above described primers and appropriate reagents).

Other examples of probes include:

Probe:

SEQ ID NO:326 CAGGCACTAAAACAGGTGCA
SEQ ID NO:327 AGGGGATAAGGAGTCCCTCA
SEQ ID NO:328 TTGAGACCCAGAAGCTCGAT
SEQ ID NO:329 GAAATTGAGCGTCTGCACAG
SEQ ID NO:330 TTACGGGGCTGTTAAACCAG
SEQ ID NO:331 CAGCAAGTGGAACGCTACAA
SEQ ID NO:332 TGCCACAGAAATCACTGGAA
SEQ ID NO:333 ACACAGAAAGTGGCTGGGAC
SEQ ID NO:334 TTCTACACTGACACGCTGGG
SEQ ID NO:335 GGCCTGGCTCAGTATGTGAT

A probe for detecting PPFIBP2 nucleic acid that was used on the microarray has a sequence as in SEQ ID NO:336
AGATCAAAGGGATGAGCAACAGGGACTTCTGCCACAGTGACAATGGAATTGTGTTGTGCC

Other probes to PPP1R16A are known in the art and/or can be readily designed by the skilled artisan.

1) Antibodies:

2) Mouse Anti-Human PPFIBP2 Monoclonal Antibody, Unconjugated, Clone 3A5, Abnova Corporation, PPFIBP2 (NP_003612, 1 a.a. ~ 101 a.a) partial recombinant protein with GST tag. MW of the GST tag alone is 26 KDa.

3) Rabbit Anti-Human PPFIBP2 Purified - MaxPab Polyclonal Antibody, Unconjugated, Abnova Corporation, PPFIBP2 (NP_003612.1, 1 a.a. ~ 876 a.a) full-length human protein.

Example 18: PPP1R16A

PPP1R16A (protein phosphatase 1, regulatory (inhibitor) subunit 16A) also known as MGC14333 and MYPT3 was found to be overexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that PPP1R16A was overexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue as described in Example 2. It was surprisingly found that PPP1R16A was overexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the method described in Example 4. Example 5 shows that PPP1R16A can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

PPP1R16A, also named Myosin phosphatase targeting subunit 3 (MYPT3) is a membrane located protein which having 524 amino acid residues, in which five Ankyrin repeats and a consensus PP1 binding site are located within the N-terminal 300 amino acid residues. The C-terminal region with 224 residues contains two possible Src homology 3 binding sites and a prenylation motif (CaaX). These structural features suggest that R16A could be a scaffold protein regulating protein-protein interactions as well as cellular signalling. (PMID: 18202305)

The sequence of an mRNA corresponding to PPP1R16A is given in ENSEMBL accession no. ENST00000292539 and has a sequence as in SEQ ID NO:337

GTGAAAAGAGGACTCTCAGGGGCTCACAGGGGCTCTCACTGCTGGTTGGCCCTGCCCTCCCTTCCCCCTC
AGCAGGGTGCCCGGAAGCTGGAACCTTGTTATCTGGGTAATTAGTTTCAGACCCTGCACTGAGGCCGGCC
AGGTCTCGGGGCTGCCTCCCATAGGTTGTGCACCCTGACCCCGAGAGGGAGGCGAGGCGCTGCTTGTCGA
CAGCTAGAGGCTGGCCTGGGGAGCAGGTTTGGGGTGCCCTCCCACACTGCCCTCCCTGCCCCGGCCCATG
CCCCCCAGGGCTGCCTGGGCCTGGTTATTGTGTGGGGCCTCCTGACCCAGCCAAGGGCACGAAGCTCTGG
GAAGGGGATGCCCCCGAGGGTGCCAGTCCAGCTAGCTGCCCCACCCCTCAGGCCCAGCCTGGCCCCCAAG
CTCCCCACTCTGGTGCCCCGAGCAGCCCTGTGGGCAAGCAGCCGCCGCC**ATG**GCCGAGCACCTGGAGCTG
CTGGCAGAGATGCCCATGGTGGGCAGGATGAGCACACAGGAGCGGCTGAAGCATGCCCAGAAGCGGCGCG
CCCAGCAGGTGAAGATGTGGGCCCAGGCTGAGAAGGAGGCCCAGGGCAAGAAGGGTCCTGGGGAGCGTCC
CCGGAAGGAGGCAGCCAGCCAAGGGCTCCTGAAGCAGGTCCTCTTCCCTCCCAGTGTTGTCCTTCTGGAG
GCCGCTGCCCGAAATGACCTGGAAGAAGTCCGCCAGTTCCTTGGGAGTGGGGTCAGCCCTGACTTGGCCA
ACGAGGACGGCCTGACGGCCCTGCACCAGTGCTGCATTGATGATTTCCGAGAGATGGTGCAGCAGCTCCT
GGAGGCTGGGGCCAACATCAATGCCTGTGACAGTGAGTGCTGGACGCCTCTGCATGCTGCGGCCACCTGC
GGCCACCTGCACCTGGTGGAGCTGCTCATCGCCAGTGGCGCCAATCTCCTGGCGGTCAACACCGACGGGA
ACATGCCCTATGACCTGTGTGATGATGAGCAGACGCTGGACTGCCTGGAGACTGCCATGGCCGACCGTGG

CATCACCCAGGACAGCATCGAGGCCGCCCGGGCCGTGCCAGAACTGCGCATGCTGGACGACATCCGGAGC
CGGCTGCAGGCCGGGGCAGACCTCCATGCCCCCCTGGACCACGGGGCCACGCTGCTGCACGTCGCAGCCG
CCAACGGGTTCAGCGAGGCGGCTGCCCTGCTGCTGGAACACCGAGCCAGCCTGAGCGCTAAGGACCAAGA
CGGCTGGGAGCCGCTGCACGCCGCGGCCTACTGGGGCCAGGTGCCCCTGGTGGAGCTGCTCGTGGCGCAC
GGGGCCGACCTGAACGCAAAGTCCCTGATGGACGAGACGCCCCTTGATGTGTGCGGGGACGAGGAGGTGC
GGGCCAAGCTGCTGGAGCTGAAGCACAAGCACGACGCCCTCCTGCGCGCCCAGAGCCGCCAGCGCTCCTT
GCTGCGCCGCCGCACCTCCAGCGCCGGCAGCCGCGGGAAGGTGGTGAGGCGGGTGAGCCTAACCCAGCGC
ACCGACCTGTACCGCAAGCAGCACGCCCAGGAGGCCATCGTGTGGCAACAGCCGCCGCCCACCAGCCCGG
AGCCGCCCGAGGACAACGATGACCGCCAGACAGGCGCAGAGCTCAGGCCGCCGCCCCCGGAGGAGGACAA
CCCCGAAGTGGTCAGGCCGCACAATGGCCGAGTAGGGGGCTCCCCAGTGCGGCATCTATACTCCAAGCGA
CTAGACCGGAGTGTCTCCTACCAGCTGAGCCCCCTGGACAGCACCACCCCCCACACCCTGGTCCACGACA
AGGCCCACCACACCCTGGCTGACCTGAAGCGCCAGCGAGCTGCTGCCAAGCTGCAGCGACCCCCACCTGA
GGGGCCCGAGAGCCCTGAGACAGCTGAGCCTGGCCTGCCTGGTGACACGGTGACCCCCCAGCCTGACTGT
GGCTTCAGGGCAGGCGGGGACCCACCCCTGCTCAAGCTCACAGCCCCGGCGGTGGAGGCTCCCGTGGAGA
GGAGGCCGTGCTGCCTGCTCATG**TGA**GGCTGTTGCTCAGCATGCAGGGGCCCTGTCGCGGGCACAGCCCA
AGGCTGCCTCCCCACGGTGCGTGCCCTGGTGCTGCGGGTGCAGCACGGAAACCCCGGCT**TCTACTGTACA**
GGACACTGGCCCCTCTCAGGTCAGAAGACATGCCTGGAGGGATGTCTGGCTGCAAAGACTATTTTTATCC
TGCAACTCTTGATAAAGGGCTGTTTTGCCATGGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAA

The start and stop codons are indicated in bold as well as the position corresponding to the microarray probe.

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000292539 and has a sequence as in SEQ ID NO:338

MAEHLELLAEMPMVGRMSTQERLKHAQKRRAQQVKMWAQAEKEA
QGKKGPGERPRKEAASQGLLKQVLFPPSVVLLEAAARNDLEEVRQFLGSGVSPDLANE
DGLTALHQCCIDDFREMVQQLLEAGANINACDSECWTPLHAAATCGHLHLVELLIASG
ANLLAVNTDGNMPYDLCDDEQTLDCLETAMADRGITQDSIEAARAVPELRMLDDIRSR
LQAGADLHAPLDHGATLLHVAAANGFSEAAALLLEHRASLSAKDQDGWEPLHAAAYWG
QVPLVELLVAHGADLNAKSLMDETPLDVCGDEEVRAKLLELKHKHDALLRAQSRQRSL
LRRRTSSAGSRGKVVRRVSLTQRTDLYRKQHAQEAIVWQQPPPTSPEPPEDNDDRQTG
AELRPPPPEEDNPEVVRPHNGRVGGSPVRHLYSKRLDRSVSYQLSPLDSTTPHTLVHD
KAHHTLADLKRQRAAAKLQRPPPEGPESPETAEPGLPGDTVTPQPDCGFRAGGDPPLL
KLTAPAVEAPVERRPCCLLM

Primers for amplifying the sequence ENST00000292539 can be designed using primer design software such as Oligo Calc and/or Primer 3.

Examples of primer pairs for amplifying PPP1R16A include:

Forward SEQ ID NO:339 GTGTTGTCCTTCTGGAGGCCG (Ex2)
Reverse SEQ ID NO:340 GCCGTCAGGCCGTCCTCGTTG (Ex3)

Forward SEQ ID NO:341 GCTGCCCGAAATGACCTGG (Ex3)
Reverse SEQ ID NO:342 CGGAAATCATCAATGCAGC (Ex5)

Forward SEQ ID NO:343 GACGCCTCTGCATGCTGCGG (Ex5)
Reverse SEQ ID NO:344 CACAGGTCATAGGGCATGTTC (Ex6)

Forward SEQ ID NO:345 GATGAGCAGACGCTGGACTG (Ex6)
Reverse SEQ ID NO:346 CTCCGGATGTCGTCCAGC (Ex7)

Forward SEQ ID NO:347 CAGGCCGGGGCAGACCTC
Reverse SEQ ID NO:348 GGCTCGGTGTTCCAGCAGCAG

Forward SEQ ID NO:349 GGGAGCCGCTGCACGCC
Reverse SEQ ID NO:350 CCCGCACCTCCTCGTCCC

Forward SEQ ID NO:351 CTGCGCGCCCAGAGCCGC
Reverse SEQ ID NO:352 GCGTGCTGCTTGCGGTAC

Forward SEQ ID NO:353 GCCAGACAGGCGCAGAGCTC
Reverse SEQ ID NO:354 CTACTCGGCCATTGTGCG

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting PPP1R16A derived from any number of sources depending on the desired use (e.g., using the above described primers and appropriate reagents).

Other examples of probes include:

SEQ ID NO:355
TCTACTGTACAGGACACTGGCCCCTCTCAGGTCAGAAGACATGCCTGGAGGG
ATGTCTGGCTGCAAAGACTATTTTTATCC

SEQ ID NO:356
CTGACGGCCCTGCACCAGTGCTGCATTGATGATTTCC

SEQ ID NO:357
GACTGCCATGGCCGACCGTGGCATCACCCAG

SEQ ID NO:358
GCTCGTGGCGCACGGGGCCGACCTGAACGC

SEQ ID NO:359
GCGCCGGCAGCCGCGGGAAGGTGGTGAGG

Other probes to PPP1R16A are known in the art and/or can be readily designed by the skilled artisan.

Antibodies against PPP1R16A include, but are not limited to, Abnova Corporation Cat# H00084988-M06 which is a mouse monoclonal antibody raised against a partial

recombinant PPP1R16A: 429 a.a. ~ 529 a.a; and from Abnova Cat# H00084988-B01 which is a mouse polyclonal raised against a full-length human PPP1R16A protein.

Example 19: RASSF7

RASSF7, Ras association (RalGDS/AF-6) domain family (N-terminal) member 7 also known as 2400009B11RIK, AW210608, C11ORF13, HRAS1, HRC1, MGC126069, MGC126070, and RGD1306244 was found to be overexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that RASSF7 was overexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue as described in Example 2. It was surprisingly found that RASSF7 was overexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the method described in Example 4. Example 5 shows that RASSF7 can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

RASSF7 is a member of a new Ras effector family characterise for the presence of a RA domain in their sequence. Although they interact either directly or indirectly with activated Ras, their role in mediating its biological effects remains unclear. What is clear is that they seem to modulate some of the growth inhibitory responses mediated by Ras and may serve as tumour suppressor genes. In fact, it is been described that members of the family are silenced in tumours by methylation of their promoters. (PMID: 17692468).

The sequence of an mRNA corresponding to RASSF7 is given in ENSEMBL accession no. ENST00000344375 and has a sequence as in SEQ ID NO:360

GAATTCGGGGGGAGGGGGCAGTGTCCTCCGAGCCAGGACAGGCATGTTGTTGGGACTGGCGGCCATGGAG
CTGAAGGTGTGGGTGGATGGCATCCAGCGTGTGGTCTGTGGGGTCTCAGAGCAGACCACCTGCCAGGAAG
TGGTCATCGCACTAGCCCAAGCAATAGGCCAGACTGGCCGCTTTGTGCTTGTGCAGCGGCTTCGGGAGAA
GGAGCGGCAGTTGCTGCCACAAGAGTGTCCAGTGGGCGCCCAGGCCACCTGCGGACAGTTTGCCAGCGAT
GTCCAGTTTGTCCTGAGGCGCACAGGGCCCAGCCTAGCTGGGAGGCCCTCCTCAGACAGCTGTCCACCCC
CGGAACGCTGCCTAATTCGTGCCAGCCTCCCTGTAAAGCCACGGGCTGCGCTGGGCTGTGAGCCCCGCAA
AACACTGACCCCCGAGCCAGCCCCCAGCCTCTCACGCCCTGGGCCTGCGGCCCCTGTGACACCCACACCA
GGCTGCTGCACAGACCTGCGGGGCCTGGAGCTCAGGGTGCAGAGGAATGCTGAGGAGCTGGGCCATGAGG
CCTTCTGGGAGCAAGAGCTGCGCCGGGAGCAGGCCCGGGAGCGAGAGGGACAGGCACGCCTGCAGGCACT
AAGTGCGGCCACTGCTGAGCATGCCGCCCGGCTGCAGGCCCTGGACGCTCAGGCCCGTGCCCTGGAGGCT
GAGCTGCAGCTGGCAGCGGAGGCCCCTGGGCCCCCCTCACCTATGGCATCTGCCACTGAGCGCCTGCACC
AGGACCTGGCTGTTCAGGAGCGGCAGAGTGCGGAGGTGCAGGGCAGCCTGGCTCTGGTGAGCCGGGCCCT
GGAGGCAGCAGAGCGAGCCTTGCAGGCTCAGGCTCAGGAGCTGGAGGAGCTGAACCGAGAGCTCCGTCAG

TGCAACCTGCAGCAGTTCATCCAGCAGACCGGGGCTGCGCTGCCACCGCCCCCACGGCCTGACAGGGGCC
CTCCTGGCACTCAGGGCCCTCTGCCTCCAGCCAGAGAGGAGTCCCTCCTGGGCGCTCCCTCTGAGTCCCA
TGCTGGTGCCCAGCCTAGGCCCCGAGGTGGCCCCCATGACGCAGAACTCCTGGAGGTAGCAGCAGCTCCT
GCCCCAGAGTGGTGTCCTCTGGCAGCCCAGCCCCAGGCTCTGTGACAGCCTAGTGAGGGCTGCAAGACCA
TCCTGCCCGGACCACAGAAGGAGAGTTGGCGGTCACAGAGGGCTCCTCTGCCAGGCAGTGGGAAGCCCTG
GGTTTGGCCTCAGGAGCTGGGGGTGCAGTGGGGGACTGCCCTAGTCCTTGCCAGGTCGCCCAGCACCCTG
GAGAAGCATGGGGCGTAGCCAGCTCGGAACTTGCCAGGCCCCAAAGGCCACGACTGCCTGTTGGGGACAG
GAGATGCATGGACAGTGTGCTCAAGCTGTGGGCATGTGCTTGCCTGCGGGAGAGGTCCTTCACTGTGTGT
ACACAGCAAGAGCATGTGTGTGCCACTTCCCCTACCCCAACGTGAAAACCTCAATAAACTGCCCGAAGC

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000344226 and has a sequence as in SEQ ID NO:361

MLLGLAAMELKVWVDGIQRVVCGVSEQTTCQEVVIALAQAIGQTGRFVLVQRLREKERQLLPQECPVGAQ
ATCGQFASDVQFVLRRTGPSLAGRPSSDSCPPPERCLIRASLPVKPRAALGCEPRKTLTPEPAPSLSRPG
PAAPVTPTPGCCTDLRGLELRVQRNAEELGHEAFWEQELRREQARELREGQARLQALSAATAEHAARLQAL
DAQARALEAELQLAAEAPGPPSPMASATERLHQDLAVQERQSAEVQGSLALVSRALEAAERALQAQAQEL
EELNRELRQCNLQQFIQQTGAALPPPPRPDRGPPGTQGPLPPAREESLLGAPSESHAGAQPRPRGGPHDA
ELLEVAAAPAPEWCPLAAQPQAL

Primers for amplifying the sequence ENST00000344375 can be designed using primer design software such as Oligo Calc and/or Primer 3.

Examples of primer pairs for amplifying RASSF7 include:

Forward SEQ ID NO:362 CTGCCAGGAAGTGGTCAT C (Ex1)
Reverse SEQ ID NO:363 GCCGCTGCACAAGCACA (ex2)

Forward SEQ ID NO:364 CATGGAGCTGAAGGTG (ex1)
Reverse SEQ ID NO:365 CTCAGGACAAACTGGAC (ex2)

Forward SEQ ID NO:366 GCCACTGAGCGCCTGC (Ex2)
Reverse SEQ ID NO:367 GTCTGCTGGATGAACTG (EX3)

Forward SEQ ID NO:368 CAG CAG AGC GAG CCT TGC AG
Reverse SEQ ID NO:369 CTG AGT GCC AGG AGG GC (Ex3)

Forward SEQ ID NO:370 CAC GGC CTG ACA GGG GCC (Ex3)
Reverse SEQ ID NO:371 GCC TAG GCT GGG CAC (EX4)

Forward SEQ ID NO:372 CTCTGAGTCCCATGCTGG (EX4)
Reverse SEQ ID NO:373 GACACCACTCTGGGGC (EX5)

Forward SEQ ID NO:374 TGCCCAGCCTAGGCCC (EX4)
Reverse SEQ ID NO:375 GCCAGAGGACACCACTC (EX5)

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting RASSF7 can be derived from any number of sources depending on the desired use (e.g., using the above described primers and appropriate reagents). Other examples of probes include:

SEQ ID NO:376
GAGAGGTCCTTCACTGTGTGTACACAGCAAGAGCATGTGTGTGCCACTTC

SEQ ID NO:377
AGTGTCCTCCGAGCCAGGACAGGCATGTTGTTGGGACTGGCGGCCATGGAG

SEQ ID NO:378
GAGCCGGGCCCTGGAGGCAGCAGAGCGAGCCTTGCAGGCTCAGGCTCAGGA GCTG

SEQ ID NO:379
CGGCCTGACAGGGGCCCTCCTGGCACTCAGGGCCCTCTGCCTCCAGCCAGAG AGGAG

SEQ ID NO:380
GAGGAGCTGGGCCATGAGGCCTTCTGGGAGCAAGAGCTGCGCCGGGAGCAG GCCCGGGAG

Other probes to RASSF7 are known in the art and/or can be readily designed by the skilled artisan.

Antibodies against RASSF7 include, but are not limited to, LifeSpan BioSciences. Cat# LS-C31793-100 which is a rabbit polyclonal antibody; and from Novus Biologivals Cat#NB100-93434 , which is a goat polyclonal anti-RASSF7 against the epitope SEQ ID NO:381 CTDLRGLELRVQRN.

Example 20: RNF183

RNF183 was found to be overexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that RNF183 was overexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue as described in Example 2. It was surprisingly found that RNF183 was overexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the method described in Example 4. Example 5 shows that RNF183 can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

The sequence of an mRNA corresponding to RNF183 is given in ENSEMBL accession no. ENST00000297894 and has a sequence as in SEQ ID NO:382

CGATTCAGGGGAGGGAGCAACTGGAGCCTCAGGCCCTCCAGAGTAGTCTGCCTGACCACCCTGGAGCCCA
CAGAAGCCCAGGACGTCTCCCGCGAAGCCTCCCCGTGTGTGGCTGAGGATGGCTGAGCAGCAGGGCCGGG
AGCTTGAGGCTGAGTGCCCCGTCTGCTGGAACCCCTTCAACAACACGTTCCATACCCCCAAAATGCTGGA
TTGCTGCCACTCCTTCTGCGTGGAATGTCTGGCCCACCTCAGCCTTGTGACTCCAGCCCGGCGCCGCCTG
CTGTGCCCACTCTGTCGCCAGCCCACAGTGCTGGCCTCAGGGCAGCCTGTCACTGACTTGCCCACGGACA
CTGCCATGCTCGCCCTGCTCCGCCTGGAGCCCCACCATGTCATCCTGGAAGGCCATCAGCTGTGCCTCAA
GGACCAGCCCAAGAGCCGCTACTTCCTGCGCCAGCCTCAAGTCTACACGCTGGACCTTGGCCCCCAGCCT
GGGGGCCAGACTGGGCCGCCCCCAGACACGGCCTCTGCCACCGTGTCTACGCCCATCCTCATCCCCAGCC
ACCACTCTTTGAGGGAGTGTTTCCGCAACCCTCAGTTCCGCATCTTTGCCTACCTGATGGCCGTCATCCT
CAGTGTCACTCTGTTGCTCATATTCTCCATCTTTTGGACCAAGCAGTTCCTTTGGGGTGTGGGGTGAGTG
CTGTTCCCAGACAAGAAACCAAACCTTTTTCGGTTGCTGCTGGGTATGGTGACTACGGAGCCTCATTTGG
TATTGTCTTCCTTTGTAGTGTTGTTTATTTTACAATCCAGGGATTGTTCAGGCCATGTGTTTGCTTCTGG
GAACAATTTTAAAAAAAAAACAAAAAAACGAAAAGCTTGAAGGACTGGGAGATGTGGAGCGACCTCCGGGT
GTGAGTGTGGCGTCATGGAAGGGCAGAGAAGCGGTTCTGACCACAGAGCTCCACAGCAAGTTGTGCCAAA
GGGCTGCACAGTGGTATCCAGGAACCTGACTAGCCCAAATAGCAAGTTGCATTTCTCACTGGAGCTGCTT
CAAAATCAGTGCATATTTTTTTGAGTTGCTCTTTTACTATGGGTTGCTAAAAAAAAAAAAAAAAATTGGGA
AGTGAGCTTCAATTCTGTGGGTAAATGTGTGTTTGTTTCTCTTTGAATGTCTTGCCACTGGTTGCAGTAA
AAGTGTTCTGTATTCATTAAAAAAAAAAAAAAAAAAAAAAAAAAA

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000297894 and has a sequence as in SEQ ID NO:383

MAEQQGRELEAECPVCWNPFNNTFHTPKMLDCCHSFCVECLAHLSLVTPARRRLLCPLCRQPTVLASGQPVTDLP
TDTAMLALLRLEPHHVILEGHQLCLKDQPKSRYFLRQPQVYTLDLGPQPGGQTGPPPDTASATVSTPILIPSHHS
LRECFRNPQFRIFAYLMAVILSVTLLLIFSIFWTKQFLWGVG

Primers for amplifying the sequence RNF183 can be designed using primer design software such as Oligo Calc.

Examples of primer pairs for amplifying RNF183 include those in

Forward SEQ ID NO:384 GAGAAGCTGGGCTGGAG (EXON3)
Reverse SEQ ID NO:385 CAGCCACACACGGGGA (EXON4)

Forward SEQ ID NO:386 CAGCTGTGTGCTAAGAACAAAG (EXON3)
Reverse SEQ ID NO:387 GCCCTGCTGCTCAGCCATC (EXON4)

Forward SEQ ID NO:388 GCAGAAGGCAGCGAGGAC (EXON3)
Reverse SEQ ID NO:389 GGCAGCAATCCAGCATTTTG (EXON4)

Forward SEQ ID NO:390 CTGCGTGGAATGTCTGGCC (EXON4)
Reverse SEQ ID NO:391 CAAGTCAGTGACAGGCTGC (EXON4)

Forward SEQ ID NO:392 GTCTACACGCTGGACCTTG (EXON4)
Reverse SEQ ID NO:393 GATGCGGAACTGAGGGTTG (EXON4)

Forward SEQ ID NO:394 CTACCTGATGGCCGTCATC (EXON4)
Reverse SEQ ID NO:395 CCAGCAGCAACCGAAAAAG (EXON4)

Forward SEQ ID NO:396 CATGCGTGCAGGGCTGCA (EXON1)

Reverse SEQ ID NO:397 GTGCTGCTCTCCCAGGG (EXON2)

Forward SEQ ID NO:398 CCG TGGAATCGATTCCCAG (EXON2)
Reverse SEQ ID NO:399 CTGTTTCTCATATGGGTCATTCG (EXON3)

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting RNF183 can be derived from any number of sources depending on the desired use (*e.g.*, using the above described primers and appropriate reagents). Other examples of probes include

SEQ ID NO:400 ATGGCTGAGCAGCAGGGCCGGGAGCTTGAGGCTGAGTGCCC

SEQ ID NO:401 GCCCACGGACACTGCCATGCTCGCCCTGCTCC

SEQ ID NO:402 GGACCAGCCCAAGAGCCGCTACTTCCTGCGCCAGCCT

SEQ ID NO:403 CGCTGGACCTTGGCCCCCAGCCTGGGGGCCAG

SEQ ID NO:404 GTTCCTTTGGGGTGTGGGGTGAGTGCTG

A probe for detecting RNF183 nucleic acid that was used on the microarray has a sequence as in SEQ ID NO:405
CAGTGGTATCCAGGAACCTGACTAGCCCAAATAGCAAGTTGCATTTCTCACT GGAGCTGC

Other probes to RNF183 are known in the art and/or can be readily designed by the skilled artisan.

Example 21: SIRT6

SIRT6 was found to be overexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that SIRT6 was overexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue as described in Example 2. It was surprisingly found that SIRT6 was overexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the method described in Example 4. Example 5 shows that SIRT6 can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

The sequence of an mRNA corresponding to SIRT6 is given in ENSEMBL accession no. ENST00000269860 and has a sequence as in SEQ ID NO:406

```
   1 GCTTCCGGCGGAAGCGGCCTCAACAAGGGAAACTTTATTGTTCCCGTGGGGCAGTCGAGG
  61 ATGTCGGTGAATTACGCGGCGGGGCTGTCGCCGTACGCGGACAAGGGCAAGTGCGGCCTC
 121 CCGGAGATCTTCGACCCCCCGGAGGAGCTGGAGCGGAAGGTGTGGGAACTGGCGAGGCTG
 181 GTCTGGCAGTCTTCCAGTGTGGTGTTCCACACGGGTGCCGGCATCAGCACTGCCTCTGGC
 241 ATCCCCGACTTCAGGGACAAACTGGCAGAGCTCCACGGGAACATGTTTGTGGAAGAATGT
 301 GCCAAGTGTAAGACGCAGTACGTCCGAGACACAGTCGTGGGCACCATGGGCCTGAAGGCC
 361 ACGGGCCGGCTCTGCACCGTGGCTAAGGCAAGGGGGCTGCGAGCCTGCAGGGGAGAGCTG
 421 AGGGACACCATCCTAGACTGGGAGGACTCCCTGCCCGACCGGGACCTGGCACTCGCCGAT
 481 GAGGCCAGCAGATCCGGCCCAGCGGGAACCTGCCGCTGGCTACCAAGCGCCGGGGAGGCC
 541 GCCTGGTCATCGTCAACCTGCAGCCCACCAAGCACGACCGCCATGCTGACCTCCGCATCC
 601 ATGGCTACGTTGACGAGGTCATGACCCGGCTCATGAAGCACCTGGGGCTGGAGATCCCCG
 661 CCTGGGACGGCCCCCGTGTGCTGGAGAGGGCGCTGCCACCCCTGCCCCGCCCGCCCACCC
 721 CCAAGCTGGAGCCCAAGGAGGAATCTCCCACCCGGATCAACGGCTCTATCCCCGCCGGCC
 781 CCAAGCAGGAGCCCTGCGCCCAGCACAACGGCTCAGAGCCCGCCAGCCCCAAACGGGAGC
 841 GGCCCACCAGCCCTGCCCCCCACAGACCCCCCAAAAGGGTGAAGGCCAAGGCGGTCCCCA
 901 GCTGACCAGGGTGCTTGGGGAGGGTGGGGCTTTTTGTAGAAACTGTGGATTCTTTTTCTC
 961 TCGTGGTCTCACTTTGTTACTTGTTTCTGTCCCCGGGAGCCTCAGGGCTCTGAGAGCTGT
1021 GCTCCAGGCCAGGGGTTACACCTGCCCTCCGTGGTCCCTCCCTGGGCTCCAGGGGCCTCT
1081 GGTGCGGTTCCGGGAAGAAGCCACACCCCAGAGGTGACAGGTGAGCCCCTGCCACACCCC
1141 AGCCTCTGACTTGCTGTGTTGTCCAGAGGTGAGGCTGGGCCCTCCCTGGTCTCCAGCTTA
1201 AACAGGAGTGAACTCCCTCTGTCCCCAGGGCCTCCCTTCTGGGCCCCCTACAGCCCACCC
1261 TACCCCTCCTCCATGGGCCCTGCAGGAGGGGAGACCCACCTTGAAGTGGGGGATCAGTAG
1321 AGGCTTGCACTGCCTTTGGGGCTGGAGGGAGACGTGGGTCCACCAGGCTTCTGGAAAAGT
1381 CCTCAATGCAATAAAAACAATTTCTTTCTTGCA
```

The start and stop codons are indicated in bold as well as the position corresponding to the microarray probe.

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000269860 and has a sequence as in SEQ ID NO:407

```
1 MSVNYAAGLSPYADKGKCGLPEIFDPPEELERKVWELARLVWQSSSVVFHTGAGISTASG
61 IPDFRDKLAELHGNMFVEECAKCKTQYVRDTVVGTMGLKATGRLCTVAKARGLRACRGEL
121 RDTILDWEDSLPDRDLALADEASRSGPAGTCRWLPSAGEAAWSSSTCSPPSTTAMLTSAS
181 MATLTRS
```

Primers for amplifying the sequence SIRT6 can be designed using primer design software such as Oligo Calc and/or Primer 3.

Examples of primer pairs for amplifying SIRT6 include those in

Forward SEQ ID NO:408 TTGTGGAAGAATGTGCCAAG
Reverse SEQ ID NO:409CCTTAGCCACGGTGCAGAG

Forward SEQ ID NO:410 TCTTCCAGTGTGGTGTTCCA
Reverse SEQ ID NO:411 TTGGCACATTCTTCCACAAA

Forward SEQ ID NO:412 AGCTGAGGGACACCATCCTA
Reverse SEQ ID NO:413 GCAGGTTGACGATGACCAG

Forward SEQ ID NO:414 GCTTCCTGGTCAGCCAGA
Reverse SEQ ID NO:415 ATGTACCCAGCGTGATGGAC

Forward SEQ ID NO:416 GCTTCCTGGTCAGCCAGA
Reverse SEQ ID NO:417 CTAGGATGGTGTCCCTCAGC

Forward SEQ ID NO:418 GAGAGCTGAGGGACACCATC
Reverse SEQ ID NO:419 GTACCCAGCGTGATGGACAG

Forward SEQ ID NO:420 AGGATGTCGGTGAATTACGC
Reverse SEQ ID NO:421 AAAGGTGGTGTCGAACTTGG

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting SIRT6 can be derived from any number of sources depending on the desired use (e.g., using the above described primers and appropriate reagents). Other examples of probes include

SEQ ID NO:422 TGTAAGACGCAGTACGTCCG
SEQ ID NO:423 GACTTCAGGGACAAACTGGC
SEQ ID NO:424 ACTGGGAGGACTCCCTGC
SEQ ID NO:425 TGTAAGACGCAGTACGTCCG
SEQ ID NO:426 TGTAAGACGCAGTACGTCCG
SEQ ID NO:427 TAGACTGGGAGGACTCCCTG
SEQ ID NO:428 GAGTCTGGACCATGGAGGAG

A probe to detect SIRT6 nucleic acid that was used on the microarray has a sequence as in SEQ ID NO:429
GAAGTGGGGGATCAGTAGAGGCTTGCACTGCCTTTGGGGCTGGAGGGAGA

Other probes to SIRT6 are known in the art and/or can be readily designed by the skilled artisan.

Antibodies against SIRT6 include, but are not limited to, Rabbit polyclonal anti-SIRT6 against de C-terminal Cat# 2590 from Cell Signalling Technology; and Mouse monoclonal antibody raised against a partial recombinant SIRT6 141 a.a. ~ 251 a.a Catalog #:H00051548-M01 from abnova.

Example 22: TJP3

TJP3, tight junction protein 3 (zona occludens 3) also known as MGC119546, ZO-3, ZO3 was found to be overexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that TJP3 was

overexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue as described in Example 2. It was surprisingly found that TJP3 was overexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the method described in Example 4. Example 5 shows that TJP3 can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

TJP3 (ZO-3) was first identified as a 130 kDa protein that coimmunoprecipitates with ZO-1. It is a member of the MAGUK proteins (MEMBRANE-associated guanylate kinase-like homologues). These proteins are implicated in the formation and maintenance of supramolecular complexes at specific areas of the cell surface called tight junctions. Tight junctions locate at the most apical part of lateral membranes of simple epithelial cells, and are considered to be involved in barrier and fence functions.

Cloning and sequencing cDNAs encoding MAGUK proteins showed that all have three PDZ domains (PDZ1 to -3), one SH3 domain, and one guanylate kinase-like (GUK) domain in this order from their NH2 termini (PMID: 10966866). Among these domains, PDZ domains bind to COOH-terminal ends of various proteins, especially integral membrane proteins, most of which end in valine. Thus, MAGUKs can cross-link multiple integral membrane proteins at the cytoplasmic surface of plasma membranes to establish specialized membrane domains. ZO-3 has also been reported to associate with ZO-1, but not with ZO-2, although the domains responsible for ZO-3/ZO-1 interaction remain unidentified. ZO-3 was also shown to directly bind to the cytoplasmic domain of occludin (Haskins et al. 1998).

The sequence of an mRNA corresponding to TJP3 is given in ENSEMBL accession no. ENST00000262968 and has a sequence as in SEQ ID NO:430

ATGAACCTGTGTGGCCTCATGCCCATCTTCCCCGCTCCCCTCGACCAGGTGGCTGACATGGAGGAGCTGA
CCATCTGGGAACAGCACACGGCCACACTGTCCAAGGACCCCCGCCGGGGCTTTGGCATTGCGATCTCTGG
AGGCCGAGACCGGCCCGGTGGATCCATGGTTGTATCTGACGTGGTACCTGGAGGGCCGGCGGAGGGCAGG
CTACAGACAGGCGACCACATCGTCATGGTGAACGGGGTTTCCATGGAGAATGCCACCTCCGCGTTTGCCA
TTCAGATACTCAAGACCTGCACCAAGATGGCCAACATCACAGTGAAACGTCCCCGGAGGATCCACCTGCC
CGCCACCAAAGCCAGCCCCTCCAGCCCAGGGCGCCAGGACTCGGATGAAGACGATGGGCCCCAGCGGGTG
GAGGAGGTGGACCAGGGCCGGGGCTATGACGGCGACTCATCCAGTGGCTCCGGCCGCTCCTGGGACGAGC
GCTCCCGCCGGCCGAGGCCTGGTCGCCGGGGCCGGGCCGGCAGCCATGGGCGTAGGAGCCCAGGTGGTGG
CTCTGAGGCCAACGGGCTGGCCCTGGTGTCCGGCTTTAAGCGGCTGCCACGGCAGGACGTGCAGATGAAG
CCTGTGAAGTCAGTGCTGGTGAAGAGGAGAGACAGCGAAGAGTTTGGCGTCAAGCTGGGCAGTCAGATCT
TCATCAAGCACATTACAGATTCGGGCCTGGCTGCCCGGCACCGTGGGCTGCAGGAAGGAGATCTCATTCT

ACAGATCAACGGGGTGTCTAGCCAGAACCTGTCACTGAACGACACCCGGCGACTGATTGAGAAGTCAGAA
GGGAAGCTAAGCCTGCTGGTGCTGAGAGATCGTGGGCAGTTCCTGGTGAACATTCCGCCTGCTGTCAGTG
ACAGCGACAGCTCGCCATTGGAGGAAGGCGTGACCATGGCTGATGAGATGTCCTCTCCCCCTGCAGACAT
CTCGGACCTCGCCTCGGAGCTATCGCAGGCACCACCATCCCACATCCCACCACCACCCCGGCATGCTCAG
CGGAGCCCCGAGGCCAGCCAGACCGACTCTCCCGTGGAGAGTCCCCGGCTTCGGCGGGAAAGTTCAGTAG
ATTCCAGAACCATCTCGGAACCAGATGAGCAACGGTCAGAGTTGCCCAGGGAAAGCAGCTATGACATCTA
CAGAGTGCCCAGCAGTCAGAGCATGGAGGATCGTGGGTACAGCCCCGACACGCGTGTGGTCCGCTTCCTC
AAGGGCAAGAGCATCGGGCTGCGGCTGGCAGGGGGCAATGACGTGGGCATCTTCGTGTCCGGGGTGCAGG
CGGGCAGCCCGGCCGACGGGCAGGGCATCCAGGAGGGAGATCAGATTCTGCAGGTGAATGACGTGCCATT
CCAGAACCTGACACGGGAGGAGGCAGTGCAGTTCCTGCTGGGGCTGCCACCAGGCGAGGAGATGGAGCTG
GTGACGCAGAGGAAGCAGGACATTTTCTGGAAAATGGTGCAGTCCCGCGTGGGTGACTCCTTCTACATCC
GCACTCACTTTGAGCTGGAGCCCAGTCCACCGTCTGGCCTGGGCTTCACCCGTGGCGACGTCTTCCACGT
GCTGGACACGCTGCACCCCGGCCCCGGGCAGAGCCACGCACGAGGAGGCCACTGGCTGGCGGTGCGCATG
GGTCGTGACCTGCGGGAGCAAGAGCGGGGCATCATTCCCAACCAGAGCAGGGCGGAGCAGCTGGCCAGCC
TGGAAGCTGCCCAGAGGGCCGTGGGAGTCGGGCCCGGCTCCTCCGCGGGCTCCAATGCTCGGGCCGAGTT
CTGGCGGCTGCGGGGTCTTCGTCGAGGAGCCAAGAAGACCACTCAGCGGAGCCGTGAGGACCTCTCAGCT
CTGACCCGACAGGGCCGCTACCCGCCCTACGAACGAGTGGTGTTGCGAGAAGCCAGTTTCAAGCGCCCGG
TAGTGATCCTGGGACCCGTGGCCGACATTGCTATGCAGAAGTTGACTGCTGAGATGCCTGACCAGTTTGA
AATCGCAGAGACTGTGTCCAGGACCGACAGCCCCTCCAAGATCATCAAACTAGACACCGTGCGGGTGATT
GCAGAAAAAGACAAGCATGCGCTCCTGGATGTGACCCCCTCCGCCATCGAGCGCCTCAACTATGTGCAGT
ACTACCCCATTGTGGTCTTCTTCATCCCCGAGAGCCGGCCGGCCCTCAAGGCACTGCGCCAGTGGCTGGC
GCCTGCCTCCCGCCGCAGCACCCGTCGCCTCTACGCACAAGCCCAGAAGCTGCGAAAACACAGCAGCCAC
CTCTTCACAGCCACCATCCCTCTGAATGGCACGAGTGACACCTGGTACCAGGAGCTCAAGGCCATCATTC
GAGAGCAGCAGACGCGGCCCATCTGGACGGCGGAAGATCAGCTGGATGGCTCCTTGGAGGACAACCTAGA
CCTCCCTCACCACGGCCTGGCCGACAGCTCCGCTGACCTCAGCTGCGACAGCCGCGTTAACAGCGACTAC
GAGACGGACGGCGAGGGCGGCGCGTACACGGATGGCGAGGGCTACACAGACGGCGAGGGGGGGCCCTACA
CGGATGTGGATGATGAGCCCCCGGCTCCAGCCCTGGCCCGGTCCTCGGAGCCCGTGCAGGCAGATGAGTC
CCAGAGCCCGAGGGATCGTGGGAGAATCTCGGCTCATCAGGGGGCCCAGGTGGACAGCCGCCACCCCCAG
GGACAGTGGCGACAGGACAGCATGCGAACCTATGAACGGGAAGCCCTGAAGAAAAAGTTTATGCGAGTAC
ATGATGCGGAGTCCTCCGATGAAGACGGCTATGACTGGGGTCCGGCCACTGACCTGTGA

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000262968 and has a sequence as in SEQ ID NO:431

MNLCGLMPIFPAPLDQVADMEELTIWEQHTATLSKDPRRGFGIA
ISGGRDRPGGSMVVSDVVPGGPAEGRLQTGDHIVMVNGVSMENATSAFAIQILKTCTK
MANITVKRPRRIHLPATKASPSSPGRQDSDEDDGPQRVEEVDQGRGYDGDSSSGSGRS
WDERSRRPRPGRRGRAGSHGRRSPGGGSEANGLALVSGFKRLPRQDVQMKPVKSVLVK
RRDSEEFGVKLGSQIFIKHITDSGLAARHRGLQEGDLILQINGVSSQNLSLNDTRRLI
EKSEGKLSLLVLRDRGQFLVNIPPAVSDSDSSPLEEGVTMADEMSSPPADISDLASEL
SQAPPSHIPPPPRHAQRSPEASQTDSPVESPRLRRESSVDSRTISEPDEQRSELPRES
SYDIYRVPSSQSMEDRGYSPDTRVVRFLKGKSIGLRLAGGNDVGIFVSGVQAGSPADG
QGIQEGDQILQVNDVPFQNLTREEAVQFLLGLPPGEEMELVTQRKQDIFWKMVQSRVG
DSFYIRTHFELEPSPPSGLGFTRGDVFHVLDTLHPGPGQSHARGGHWLAVRMGRDLRE
QERGIIPNQSRAEQLASLEAAQRAVGVGPGSSAGSNARAEFWRLRGLRRGAKKTTQRS
REDLSALTRQGRYPPYERVVLREASFKRPVVILGPVADIAMQKLTAEMPDQFEIAETV
SRTDSPSKIIKLDTVRVIAEKDKHALLDVTPSAIERLNYVQYYPIVVFFIPESRPALK
ALRQWLAPASRRSTRRLYAQAQKLRKHSSHLFTATIPLNGTSDTWYQELKAIIREQQT
RPIWTAEDQLDGSLEDNLDLPHHGLADSSADLSCDSRVNSDYETDGEGGAYTDGEGYT
DGEGGPYTDVDDEPPAPALARSSEPVQADESQSPRDRGRISAHQGAQVDSRHPQGQWRQDSMRTYEREALKKKFM
RVHDAESSDEDGYDWGPATDL

Primers for amplifying the sequence ENST00000262968 can be designed using primer design software such as Oligo Calc and/or Primer 3.

Examples of primer pairs for amplifying TJP3 include:

Forward SEQ ID NO:432 CCCTCGACCAGGTGGCTGAC (Exon1)
Reverse SEQ ID NO:433 CCTCCAGAGATCGCAATGC (Exon2)

Forward SEQ ID NO:434 GTATCTGACGTGGTACCTG (Exon2)
Reverse SEQ ID NO:435 GGCAAACGCGGAGGTGGCATT C (Exon3)

Forward SEQ ID NO:436 CGGGGTTTCCATGGAGAATG (Exon3)
Reverse SEQ ID NO:437 GCGGGCAGGTGGATCCTCC (Exon4)

Forward SEQ ID NO:438 GCAGGACGTGCAGATGAAGC (Exon4)
Reverse SEQ ID NO:439 CCCGAATCTGTAATGTGCTTG (Exon5)

Forward SEQ ID NO:440 GTGGGCTGCAGGAAGGAGATC (Exon5)
Reverse SEQ ID NO:441 GAACTGCCCACGATCTCTCAGC (Exon6)

Forward SEQ ID NO:442 GATCGTGGGCAGTTCCTGG (Exon6)
Reverse SEQ ID NO:443 GATGTCTGCAGGGGGAGAGG (Exon7)

Forward SEQ ID NO:444 CACCCCGGCATGCTCAGCG (Exon7)
Reverse SEQ ID NO:445 CCGAGATGGTTCTGGAATC (Exon8)

Forward SEQ ID NO:446 GAGTCCCCGGCTTCGGCGG (Exon8)
Reverse SEQ ID NO:447 CGATCCTCCATGCTCTGACTG (Exon9)

Forward SEQ ID NO:448 GTG CAG GCG GGC AGC CCG (Exon10)
Reverse SEQ ID NO:449 GTC CTG CTT CCT CTG CGT C (Exon11)

Forward SEQ ID NO:450 CGAGAGCAGCAGACGCGGCC
Reverse SEQ ID NO:451 GAGGTCAGCGGAGCTGTCG

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting TJP3 can be derived from any number of sources depending on the desired use (e.g., using the above described primers and appropriate reagents).

Other examples of probes include:

SEQ ID NO:452
CAGGGACAGTGGCGACAGGACAGCATGCGAACCTATGAACGGGAAGCCCTG
AAGAAAAAG

SEQ ID NO:453
GAACAGCACACGGCCACACTGTCCAAGGACCCCCGCCGGGGC

SEQ ID NO:454
ACCAAGATGGCCAACATCACAGTGAAACGTCCCCGGAGGATCCACCTGCCC
GCC

SEQ ID NO:455

CAGTGACAGCGACAGCTCGCCATTGGAGGAAGGCGTGACCATGGCTGATGA
GAT

SEQ ID NO:456
CGAGTGGTGTTGCGAGAAGCCAGTTTCAAGCGCCCGGTAGTGATCCTGGGA
CCC

Other probes to TJP3 are known in the art and/or can be readily designed by the skilled artisan.

Antibodies against include, but are not limited to, TJP3 are commercially available from e.g., Abnova Cat# H00027134-A01 which is a mouse polyclonal antibody raised against a partial recombinant TJP3 having the sequence SEQ ID NO:457 DEPPAPALARSSEPVQADESQSPRDRGRISAHQGAQVDSRHPQGQWRQDS MRTYEREALKKKFMRVHDAESSDEDGYDWGPATDL (NP_055243, 868 a.a. ~ 953 a.a); from LifeSpanBiosciences Cat# LS-C18593 which is a rabbit polyclonal against a synthetic peptide derived from the C-terminus of the human TJP3 (ZO-3) protein; and from LifeSpanBiosciences Cat#LS-C50518 which is a rabbit polyclonal against a synthetic peptide derived from the C-terminus of the human TJP3 (ZO-3) protein.

Example 23: EFEMP2

EFEMP2 also known as FBLN4, MBP1, and UPH1 was found to be underexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that EFEMP2 was underexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue as described in Example 2. It was surprisingly found that EFEMP2 was underexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the method described in Example 4. Example 5 shows that EFEMP2 can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

ENSG00000172638: Just one transcript

The sequence of an mRNA corresponding to EFEMP2 is given in ENSEMBL accession number ENST00000307998 and has a sequence as in SEQ ID NO:458.

GGGGCG

CTTCCTGGGGCCGCGCGTCCAGGGAGCTGTGCCGTCCGCCCGTCCGTCTGCCCGCAGGCATTGCCCGAG
C
CAGCCGAGCCGCCAGAGCCGCGGGCCGCGGGGGTGTCGCGGGCCCAACCCCAGGATGCTCCCCTGCGCC
T
CCTGCCTACCCGGGTCTCTACTGCTCTGGGCGCTGCTACTGTTGCTCTTGGGATCAGCTTCTCCTCAGG
A
TTCTGAAGAGCCCGACAGCTACACGGAATGCACAGATGGCTATGAGTGGGACCCAGACAGCCAGCACTG
C
CGGGATGTCAACGAGTGTCTGACCATCCCTGAGGCCTGCAAGGGGGAAATGAAGTGCATCAACCACTAC
G
GGGGCTACTTGTGCCTGCCCCGCTCCGCTGCCGTCATCAACGACCTACACGGCGAGGGACCCCCGCCAC
C
AGTGCCTCCCGCTCAACACCCCAACCCCTGCCCACCAGGCTATGAGCCCGACGATCAGGACAGCTGTGT
G
GATGTGGACGAGTGTGCCCAGGCCCTGCACGACTGTCGCCCCAGCCAGGACTGCCATAACTTGCCTGGC
T
CCTATCAGTGCACCTGCCCTGATGGTTACCGCAAGATCGGGCCCGAGTGTGTGGACATAGACGAGTGCC
G
CTACCGCTACTGCCAGCACCGCTGCGTGAACCTGCCTGGCTCCTTCCGCTGCCAGTGCGAGCCGGGCTT
C
CAGCTGGGGCCTAACAACCGCTCCTGTGTTGATGTGAACGAGTGTGACATGGGGGCCCCATGCGAGCAG
C
GCTGCTTCAACTCCTATGGGACCTTCCTGTGTCGCTGCCACCAGGGCTATGAGCTGCATCGGGATGGCT
T
CTCCTGCAGTGATATTGATGAGTGTAGCTACTCCAGCTACCTCTGTCAGTACCGCTGCGTCAACGAGCC
A
GGCCGTTTCTCCTGCCACTGCCCACAGGGTTACCAGCTGCTGGCCACACGCCTCTGCCAAGACATTGAT
G
AGTGTGAGTCTGGTGCGCACCAGTGCTCCGAGGCCCAAACCTGTGTCAACTTCCATGGGGGCTACCGCT
G
CGTGGACACCAACCGCTGCGTGGAGCCCTACATCCAGGTCTCTGAGAACCGCTGTCTCTGCCCGGCCTC
C
AACCCTCTATGTCGAGAGCAGCCTTCATCCATTGTGCACCGCTACATGACCATCACCTCGGAGCGGAGC
G
TGCCCGCTGACGTGTTCCAGATCCAGGCGACCTCCGTCTACCCCGGTGCCTACAATGCCTTTCAGATCC
G
TGCTGGAAACTCGCAGGGGGACTTTTACATTAGGCAAATCAACAACGTCAGCGCCATGCTGGTCCTCGC
C
CGGCCGGTGACGGGCCCCCGGGAGTACGTGCTGGACCTGGAGATGGTCACCATGAATTCCCTCATGAGC
T
ACCGGGCCAGCTCTGTACTGAGGCTCACCGTCTTTGTAGGGGCCTACACCTTCTGAGGAGCAGGAGGGA
G
CCACCCTCCCTGCAGCTACCCTAGCTGAGGAGCCTGTTGTGAGGGGCAGAATGAGAAAGGCAATAAAGG
G
AGAAAGAAAGTCCTGGTGGCTGAGGTGGGCGGGTCACACTGCAGGAAGCCTCAGGCTGGGGCAGGGTGG
C
ACTTGGGGGGGCAGGCCAAGTTCACCTAAATGGGGGTCTCTATATGTTCAGGCCCAGGGGCCCCCATTG
A
CAGGAGCTGGGAGCTCTGCACCACGAGCTTCAGTCACCCCGAGAGGAGAGGAGGTAACGAGGAGGGCGG
A
CTCCAGGCCCCGGCCCAGAGATTTGGACTTGGCTGGCTTGCAGGGGTCCTAAGAAACTCCACTCTGGAC
A
GCGCCAGGAGGCCCTGGGTTCCATTCCTAACTCTGCCTCAAACTGTACATTTGGATAAGCCCTAGTAGT
T
CCCTGGGCCTGTTTTTCTATAAAACGAGGCAACTGGACTGTT

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000309953 and has a sequence as in SEQ ID NO:459

MLPCASCLPGSLLLWALLLLLLLGSASPQDSEEPDSYTECTDGYE
WDPDSQHCRDVNECLTIPEACKGEMKCINHYGGYLCLPRSAAVINDLHGEGPPPPVPP
AQHPNPCPPGYEPDDQDSCVDVDECAQALHDCRPSQDCHNLPGSYQCTCPDGYRKIGP
ECVDIDECRYRYCQHRCVNLPGSFRCQCEPGFQLGPNNRSCVDVNECDMGAPCEQRCF
NSYGTFLCRCHQGYELHRDGFSCSDIDECSYSSYLCQYRCVNEPGRFSCHCPQGYQLL
ATRLCQDIDECESGAHQCSEAQTCVNFHGGYRCVDTNRCVEPYIQVSENRCLCPASNP
LCREQPSSIVHRYMTITSERSVPADVFQIQATSVYPGAYNAFQIRAGNSQGDFYIRQI
NNVSAMLVLARPVTGPREYVLDLEMVTMNSLMSYRASSVLRLTVFVGAYTF

Examples of primer pairs for amplifying EFEMP2 include those in

Forward SEQ ID NO:460 TGCTCTTGGGATCAGCTTCT
Reverse SEQ ID NO:461 CCTCAGGGATGGTCAGACAC

Forward SEQ ID NO:462 TGCCCACCAGGCTATGAG
Reverse SEQ ID NO:463 CAGGCAAGTTATGGCAGTCC

Forward SEQ ID NO:464 AACTTGCCTGGCTCCTATCA
Reverse SEQ ID NO:465 GTGCTGGCAGTAGCGGTAG

Forward SEQ ID NO:466 GGCCTAACAACCGCTCCT
Reverse SEQ ID NO:467 CGACACAGGAAGGTCCCATA

Forward SEQ ID NO:468 TATGGGACCTTCCTGTGTCG
Reverse SEQ ID NO:469 GATGCAGCGGTACTGACAGA

Forward SEQ ID NO:470 GTCAGTACCGCTGCATCAAC
Reverse SEQ ID NO:471 CGCACCAGACTCACACTCAT

Forward SEQ ID NO:472 GTGGAGCCCTACATCCAGGT
Reverse SEQ ID NO:473 TCCGAGGTGATGGTCATGTA

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting EFEMP2 can be derived from any number of sources depending on the desired use (e.g., using the above described primers and appropriate reagents). Other examples of probes include

The probe used on the microarray has a sequence as in SEQ ID NO:474
TTCATCCATTGTGCACCGCTACATGACCATCACCTCGGAGCGGAGCGTGC
SEQ ID NO:475 GAAGAGCCCGACAGCTACAC
SEQ ID NO:476 CAGGCAAGTTATGGCAGTCC
SEQ ID NO:477 CCTGATGGTTACCGCAAGAT
SEQ ID NO:478 GTGAACGAGTGTGACATGGG
SEQ ID NO:479 ATGGCTTCTCCTGCAGTGAT
SEQ ID NO:480 ACGCCTCTGCCAAGACATT
SEQ ID NO:481 ATGTCGAGAGCAGCCTTCAT

Antibodies to EFEMP2 include Mouse Anti-Human EFEMP2 MaxPab® Polyclonal Antibody, Unconjugated Cat# H00030008-B01 against full length human EFEMP2; Anti-EFEMP2 Monoclonal Antibody, Unconjugated, Clone 2C8 Cat# H00030008-M01 against a partial protein , 26aa-443aa; and Rabbit Anti-Human EFEMP2 Polyclonal Antibody, Unconjugated Cat# ab74873 against a Synthetic peptide derived from an internal region of human EFEMP2.

Example 24: SOCS2

SOCS2 also known as CIS2, Cish2, SOCS-2, SSI-2, SSI2, and STATI2 was found to be underexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that SOCS2 was underexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue as described in Example 2. It was surprisingly found that SOCS2 was underexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the method described in Example 4. Example 5 shows that SOCS2 can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

The sequence of an mRNA corresponding to SOCS2 is given in ENSEMBL accession number ENST00000340600 and has a sequence as in SEQ ID NO:482

```
   1 AGCCGCGGCCTCAACTAAAAGTGGCCATTGACCTTTCAAGCTTTCGAGCAGTGATGCAAT
  61 AGAATAGTATTTCAAAGAAAAATGCTTATCGAAATTTTGGATCCGGTTTTCCCGTGATTG
 121 TTAAGGGTTTCTTTTAAAAAGTAGGTCACATTTCAAGTAGGTCATATTTCGGGGGCGGGT
 181 GCGCAGACAAGGAGATGAGTTTCCACTAAGGCCAGGGGGCCTCCAACGGGGTTGGAGGTG
 241 AGAATCCCAGGTAGGGTAGAGGTGCCGAGATCCTTCCGAATCCCAGCCCTGGGGCGTCAG
 301 CCCTGCAGGGAATGGCAGAGACACTCTCCGGACTGAGGGAACCGAGGCCAGTCACCAAGC
 361 CCCTTCCGGGCGCGCAGGCGATCAGTGGGTGACCGCGGCTGCGAGGGACTTTGTCATCCG
 421 TCCTCCAGGATCTGGGGAGAAAGAGCCCCATCCCTTCTCTCTCTGCCACCATTTCGGACA
 481 CCCCGCAGGGACTCGTTTTGGGATTCGCACTGACTTCAAGGAAGGACGCGAACCCTTCTC
 541 TGACCCCAGCTCGGGCGGCCACCTGTCTTTGCCGCGGTGACCCTTCTCTC ATG ACCCTGC
 601 GGTGCCTTGAGCCCTCCGGGAATGGCGGGGAAGGGACGCGGAGCCAGTGGGGGACCGCGG
 661 GGTCGGCGGAGGAGCCATCCCCGCAGGCGGCGCGTCTGGCGAAGGCCCTGCGGGAGCTCG
 721 GTCAGACAGGATGGTACTGGGGAAGTATGACTGTTAATGAAGCCAAAGAGAAATTAAAAG
 781 AGGCACCAGAAGGAACTTTCTTGATTAGAGATAGCTCGCATTCAGACTACCTACTAACAA
 841 TATCTGTTAAAACATCAGCTGGACCAACTAATCTTCGAATCGAATACCAAGACGGAAAAT
 901 TCAGATTGGACTCTATCATATGTGTCAAATCCAAGCTTAAACAATTTGACAGTGTGGTTC
 961 ATCTGATCGACTACTATGTTCAGATGTGCAAGGATAAGCGGACAGGTCCAGAAGCCCCCC
1021 GGAACGGCACTGTTCACCTTTATCTGACCAAACCGCTCTACACGTCAGCACCATCTCTGC
1081 AGCATCTCTGTAGGCTCACCATTAACAAATGTACCGGTGCCATCTGGGGACTGCCTTTAC
1141 CAACAAGACTAAAAGATTACTTGGAAGAATATAAATTCCAGGTA TAA ATGTTTCTCTTTT
1201 TTTAAACATGTCTCACATAGAGTATCTCCGAATGCAGCTATGTAAAAGAGAACCAAAACT
1261 TGAGTGCTCTGGATAACTATATGGAATGCTTTCTAAGAACAGCTGAAGCTAATCTAATTT
1321 AAATTTAACAGCTTGAAGAGGTAGCTAGGTGTTTAAAGTTCCTCCAGATACTTTTACCTG
1381 AGTGATGCTTCCCTTCCTAAGGCTGACCAAGACCTGTTGATCCTTTTAGATTAAAAATAA
```

```
1441 AATGTCGCATGTAAAGGCTGAAGTCGCGTTTTATCAGAATGCCTTGCCTTCTTAGGTTCT
1501 TTTCCATTATGTCAAAGGTCCAGGCTCCAGTAGGAGAGAAAGAACTCCTCATAGGAATAC
1561 TGAAGAAGTGGGAAGGAACCAAGCTGACACAGGCCTCACTGCAATTTGATATGCCTGCTG
1621 ATCAGAGTCTCTTGGGCATTTTATATTTTGCATTCTGATGTACCTAGGAGTTTTGTTAAA
1681 CAGATGATGTATGTGAGTATTTATCCCATTTTATGCAATTAACCAAATCAACCAAAAAAA
1741 GTGACCATGAAGTCCTGTATTTGTCTTTTTACTACATGTAGGAACTCTCATGTGAATGAG
1801 TACTGTAGTAATCCATTCTATGGGAGCCTTATTTCAGAAATATTTCAAACTGGTGCAAAT
1861 GGAAAAGACTTTCTCTTTTCCTTTAAAGCTAAAGACAAGAATATCATGCTATACAGGTGC
1921 AACTCAATCCCCGTTAATAAAAACCAATGTAGGTATAGGCATTCTACCCTTTGAAATAGC
1981 TGTGTCCCAACCTGTTGCCATTGATTTTTTGGAAATGGCTTTAGAAATATCCAAGTTGTC
2041 CTTGAATTGTCTAACCATGGACATAAACAGTTGTCTCCCTTCTACTGTGTAGAATACTTT
2101 GACTTAATTTTCTTCCAGATACAGGGGGATACCTGCCTGTTTTTCAAAGTGTTTATTTAC
2161 TGCTGTTACTATTTGATTAGAATGTATTAAATAAAAAAAACCTGATTTCT
```

The start and stop codons are indicated in bold.

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000339428 and has a sequence as in SEQ ID NO:483

```
1 MTLRCLEPSGNGGEGTRSQWGTAGSAEEPSPQAARLAKALRELGQTGWYWGSMTVNEAKE
61 KLKEAPEGTFLIRDSSHSDYLLTISVKTSAGPTNLRIEYQDGKFRLDSIICVKSKLKQFD
121 SVVHLIDYYVQMCKDKRTGPEAPRNGTVHLYLTKPLYTSAPSLQHLCRLTINKCTGAIWG
181 LPLPTRLKDYLEEYKFQV
```

Examples of primer pairs for amplifying SOCS2 include those in

Forward SEQ ID NO:484 AGTCACCAAGCCCCTTCC
Reverse SEQ ID NO:485 GCTCTTTCTCCCCAGATCCT

Forward SEQ ID NO:486 GGGACTGCCTTTACCAACAA
Reverse SEQ ID NO:487 TTTACATAGCTGCATTCGGAGA

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art (e.g., using Oligo Calc and/or Primer 3).

Probes for detecting SOCS2 can be derived from any number of sources depending on the desired use (e.g., using the above described primers and appropriate reagents). Other examples of probes include

The probe used on the microarray has a sequence as in SEQ ID NO:488
AGTGTGGTTCATCTGATCGACTACTATGTTCAGATGTGCAAGGATAAGCGGA
CAGGTCCA
SEQ ID NO:489 GACTTTGTCATCCGTCCTCC
SEQ ID NO:490 ACTTGGAAGAATATAAATTCCAGGT

Antibodies to SOCS2 include, but are not limited to, Mouse Anti-Human SOCS2 Polyclonal Antibody, Unconjugated Cat# H00008835-A01 against a partial protein: 99aa-198aa; Mouse Anti-Human SOCS2 Monoclonal Antibody, Unconjugated, Clone 3E7 Cat# H00008835-M01 againts a partial protein: 99aa-198aa; Rabbit Anti-Human

SOCS2 Polyclonal Antibody, Unconjugated Cat# ab74533 against the C-terminal part of the protein.

Example 25: DCN

DCN also known as CSCD, DSPG2, PG40, PGII, PGS2, and SLRR1B was found to be underexpressed in endometrial cancer primary tissue as compared to normal endometrial tissue by the microarray experiment described in Example 1. Further studies using RT-PCR demonstrated that DCN was underexpressed in primary endometrial cancer tissue as compared to normal endometrial tissue as described in Example 2. It was surprisingly found that DCN was underexpressed in samples obtained from uterine fluid (e.g., aspirates) from patients having endometrial cancer by the method described in Example 4. Example 5 shows that DCN can be combined with other biomarkers to give excellent predictive power for diagnosis of endometrial cancer.

Six transcripts from gene ENSG00000011465 but only 4 of them hybridize with our array probe, the following ones:

The sequence of an mRNA corresponding to DCN is given in ENSEMBL accession number ENST00000052754 and has a sequence as in SEQ ID NO:491

1 GAATCTACAATAAGACAAATTTCAAATCAAGTTGCTCCACTATACTGCATAAGCAGTTTA
61 GAATCTTAAGCAGATGCAAAAAGAATAAAGCAAATGGGAGGAAAAAAAAGGCCGATAAAG
121 TTTCTGGCTACAATACAAGAGACATATCATTACCATATGATCTAATGTGGGTGTCAGCCG
181 GATTGTGTTCATTGAGGGAAACCTTATTT**TTTAACTGTGCTATGGAGTAGAAGCAGGAGG**
241 **TTTTCAACCTAGTCACAGAGCAGCACC**TACCCCCTCCTCCTTTCCACACCTGCAAACTCT
301 TTTACTTGGGCTGAATATTTAGTGTAATTACATCTCAGCTTTGAGGGCTCCTGTGGCAAA
361 TTCCCGGATTAAAAGGTTCCCTGGTTGTGAAAATACATGAGATAAATCATGAAGGCCACT
421 ATCATCCTCCTTCTGCTTGCACAAGTTTCCTGGGCTGGACCGTTTCAACAGAGAGGCTTA
481 TTTGACTTTATGCTAGAAGATGAGGCTTCTGGGATAGGCCCAGAAGTTCCTGATGACCGC
541 GACTTCGAGCCCTCCCTAGGCCCAGTGTGCCCCTTCCGCTGTCAATGCCATCTTCGAGTG
601 GTCCAGTGTTCTGATTTGGGTCTGGACAAAGTGCCAAAGGATCTTCCCCCTGACACAACT
661 CTGCTAGACCTGCAAAACAACAAAATAACCGAAATCAAAGATGGAGACTTTAAGAACCTG
721 AAGAACCTTCACGCATTGATTCTTGTCAACAATAAAATTAGCAAAGTTAGTCCTGGAGCA
781 TTTACACCTTTGGTGAAGTTGGAACGACTTTATCTGTCCAAGAATCAGCTGAAGGAATTG
841 CCAGAAAAAATGCCCAAAACTCTTCAGGAGCTGCGTGCCCATGAGAATGAGATCACCAAA
901 GTGCGAAAAGTTACTTTCAATGGACTGAACCAGATGATTGTCATAGAACTGGGCACCAAT
961 CCGCTGAAGAGCTCAGGAATTGAAAATGGGGCTTTCCAGGGAATGAAGAAGCTCTCCTAC
1021 ATCCGCATTGCTGATACCAATATCACCAGCATTCCTCAAGGTCTTCCTCCTTCCCTTACG
1081 GAATTACATCTTGATGGCAACAAAATCAGCAGAGTTGATGCAGCTAGCCTGAAAGGACTG
1141 AATAATTTGGCTAAGTTGGGATTGAGTTTCAACAGCATCTCTGCTGTTGACAATGGCTCT
1201 CTGGCCAACACGCCTCATCTGAGGGAGCTTCACTTGGACAACAACAAGCTTACCAGAGTA
1261 CCTGGTGGGCTGGCAGAGCATAAGTACATCCAGGTTGTCTACCTTCATAACAACAATATC
1321 TCTGTAGTTGGATCAAGTGACTTCTGCCCACCTGGACACAACACCAAAAAGGCTTCTTAT
1381 TCGGGTGTGAGTCTTTTCAGCAACCCGGTCCAGTACTGGGAGATACAGCCATCCACCTTC
1441 AGATGTGTCTACGTGCGCTCTGCCATTCAACTCGGAAACTATAAG**TAA**TTCTCAAGAAAG
1501 CCCTCATTTTTATAACCTGGCAAAATCTTGTTAATGTCATTGCTAAAAAATAAATAAAAG

1561 CTAGATACTGGAAACCTAACTGCAATGTGGATGTTTTACCCACATGACTTATTATGCATA
1621 AAGCCAAATTTCCAGTTTAAGTAATTGCCTACAATAAAAAGAAATTTTGCCTGCCATTTT
1681 CAGAATCATCTTTTGAAGCTTTCTGTTGATGTTAACTGAGCTACTAGAGATATTCTTATT
1741 TCACTAAATGTAAAATTTGGAGTAAATATATATGTCAATATTTAGTAAAGCTTTTCTTTT
1801 TTAATTTCCAGGAAAAAATAAAAAGAGTATGAGTCTTCTGTAATTCATTGAGCAGTTAGC
1861 TCATTTGAGATAAAGTCAAATGCCAAACACTAGCTCTGTATTAATCCCCATCATTACTGG
1921 TAAAGCCTCATTTGAATGTGTGAATTCAATACAGGCTATGTAAAATTTTTACTAATGTCA
1981 TTATTTTGAAAAAATAAATTTAAAAATACATTCAAAATTACTATTGTATACAAGCTTAAT
2041 TGTTAATATTCCCTAAACACAATTTTATGAAGGGAGAAGACATTGGTTTGTTGACAATAA
2101 CAGTACATCTTTTCAAGTTCTCAGCTATTTCTTCTACCTCTCCCTATCTTACATTTGAGT
2161 ATGGTAACTTATGTCATCTATGTTGAATGTAAGCTTATAAAGCACAAAGCATACATTTCC
2221 TGACTGGTCTAGAGAACTGATGTTTCAATTTACCCCTCTGCTAAATAAATATTAAAACTA
2281 TCATGTG

The stop codon is indicated in bold as well as the position corresponding to the microarray probe.

The corresponding amino acid sequence is given in ENSEMBL accession no. ENSP00000052754 and has a sequence as in SEQ ID NO:492

1 MKATIILLLLAQVSWAGPFQQRGLFDFMLEDEASGIGPEVPDDRDFEPSLGPVCPFRCQC
61 HLRVVQCSDLGLDKVPKDLPPDTTLLDLQNNKITEIKDGDFKNLKNLHALILVNNKISKV
121 SPGAFTPLVKLERLYLSKNQLKELPEKMPKTLQELRAHENEITKVRKVTFNGLNQMIVIE
181 LGTNPLKSSGIENGAFQGMKKLSYIRIADTNITSIPQGLPPSLTELHLDGNKISRVDAAS
241 LKGLNNLAKLGLSFNSISAVDNGSLANTPHLRELHLDNNKLTRVPGGLAEHKYIQVVYLH
301 NNNISVVGSSDFCPPGHNTKKASYSGVSLFSNPVQYWEIQPSTFRCVYVRSAIQLGNYK

Primers for amplifying the sequence DCN can be designed using primer design software such as Oligo Calc and/or Primer 3. Examples of primer pairs for amplifying DCN include those in

Forward SEQ ID NO:493 AGCTTTGAGGGCTCCTGTG
Reverse SEQ ID NO:494 GCAAGCAGAAGGAGGATGAT

Forward SEQ ID NO:495 AATGCCATCTTCGAGTGGTC
Reverse SEQ ID NO:496 TGCAGGTCTAGCAGAGTTGTG

Forward SEQ ID NO:497 AACCGAAATCAAAGATGGAGA
Reverse SEQ ID NO:498 GTCCAGGTGGGCAGAAGTC

Forward SEQ ID NO:499 AATGCCATCTTCGAGTGGTC
Reverse SEQ ID NO:500 CTGCTGATTTTGTTGCCATC

Forward SEQ ID NO:501 TGGCAACAAAATCAGCAGAG
Reverse SEQ ID NO:502 GCCATTGTCAACAGCAGAGA

Forward SEQ ID NO:503 GGGCTGGCAGAGCATAAGTA
Reverse SEQ ID NO:504 GTCCAGGTGGGCAGAAGTC

Forward SEQ ID NO:505 AACCGAAATCAAAGATGGAGA
Reverse SEQ ID NO:506 CCAAAGGTGTAAATGCTCCAG

Forward SEQ ID NO:507 GAGATCACCAAAGTGCGAAA
Reverse SEQ ID NO:508 AAAGCCCCATTTTCAATTCC

Forward SEQ ID NO:509 AATGCCATCTTCGAGTGGTC
Reverse SEQ ID NO:510 AAAGCCCCATTTTCAATTCC

Other sets of primers can be readily designed by the skilled artisan and/or are known in the art.

Probes for detecting DCN can be derived from any number of sources depending on the desired use (e.g., using the above described primers and appropriate reagents). Other examples of probes include

The probe used on the microarray has a sequence as in SEQ ID NO:511
TTTAACTGTGCTATGGAGTAGAAGCAGGAGGTTTTCAACCTAGTCACAGAGCAGC
ACC

SEQ ID NO:512 TTCCCGGATTAAAAGGTTCC
SEQ ID NO:513 AAGTGCCAAAGGATCTTCCC
SEQ ID NO:514 CCTGAAGAACCTTCACGTTG
SEQ ID NO:515 TCCTCCTTCCCTTACGGAAT
SEQ ID NO:516 ATGCAGCTAGCCTGAAAGGA
SEQ ID NO:517 CATCCAGGTTGTCTACCTTCA
SEQ ID NO:518 TGAAGAACCTTCACGCATTG
SEQ ID NO:519 TGTCATAGAACTGGGCACCA
SEQ ID NO:520 GTTCTGATTTGGAACTGGGC

Antibodies to DCN include, but are not limited to, Mouse Anti-Human Decorin Monoclonal Antibody, Unconjugated Cat# ab54728, against recombinant full length protein; and Anti-DCN Monoclonal Antibody, Unconjugated, Clone 2B5-G5 Cat# H00001634-M02, against recombinant full length protein.

Additional primers for the biomarkers of the invention:

ACAA1
SEQ ID NO:521 tcacgggagaagcaggatac
SEQ ID NO:522 cttgctctgggctcttgc

SEQ ID NO:523 ccagagattgcctgattcct
SEQ ID NO:524 cctgcttctcccgtgaaat

SEQ ID NO:525 agctgggggacatctgtgt
SEQ ID NO:526 cactcagaaactgggcgatt

AP1M2
SEQ ID NO:527 cacatcgaagaatgccaatg
SEQ ID NO:528 gctccttgaagtattcgcaga

SEQ ID NO:529 tgctcttcgagctcactgg
SEQ ID NO:530 cacgcactggtggaatttt

SEQ ID NO:531 gttcgctacatcacccagagt
SEQ ID NO:532 gtaaggaagccccgtgttc

CGN
SEQ ID NO:533 gagcttacccgaaaagtgga
SEQ ID NO:534 tctagcttctgccgcttctt

SEQ ID NO:535 ggagatactcgccaggttga
SEQ ID NO:536 ccttaagctcctcctgtgtcc

SEQ ID NO:537 cctctgtgaggaggaaggttag
SEQ ID NO:538 ttagtagaaccagaagaaaccatcac

DDR1
SEQ ID NO:539 tagagagccacccccgta
SEQ ID NO:540 ccatatagtccccactgtaggc

SEQ ID NO:541 ccactctgctccctgtgtc
SEQ ID NO:542 ctggcttctcaggctccata

SEQ ID NO:543 tggggactattaccgtgtgc
SEQ ID NO:544 acgtcactcgcagtcgtg

EPS8L2
SEQ ID NO:545 gcagctcttctccctcaaca
SEQ ID NO:546 cccactttgctgcttctcc

SEQ ID NO:547 caagatgagccccaaggac
SEQ ID NO:548 tgatgacgttggagttggaa

SEQ ID NO:549 caaggatgaggtcctagaggtg
SEQ ID NO:550 gatgttgcagggcacgta

FASTKD1
SEQ ID NO:551 tggaaattctggggtatcgt
SEQ ID NO:552 gcatcctttgttgacagtgc

SEQ ID NO:553 cctgggaatcaaatatcgaaatag
SEQ ID NO:554 ccaaaaattccaaagcaatcc

SEQ ID NO:555 aagaattaacttttctgcatttcca
SEQ ID NO:556 cagaacagacacctcagttggt

GMIP
SEQ ID NO:557 aaccctggccatggagac
SEQ ID NO:558 ccgccacttctcaatctcag

SEQ ID NO:559 cccagcaccacagtaccc
SEQ ID NO:560 ctctgtggagttggaatctcg

SEQ ID NO:561 ctggtggcccatctgttc
SEQ ID NO:562 ggttgttggcagacatcttgt

IKBKE
SEQ ID NO:563 acagttcaagaagtctaggatgagg
SEQ ID NO:564 tggctaaatgactgaaattcacc

SEQ ID NO:565 ggacatccctcctctacctca
SEQ ID NO:566 ggatctcaggcgttccag

SEQ ID NO:567 ctgcctgaggatgagttcct
SEQ ID NO:568 gatgcacaatgccgttctc

P2RX4
SEQ ID NO:569 ccgttacgaccaaggtcaag
SEQ ID NO:570 tgacgaagagggagttttcc

SEQ ID NO:571 tctgtcaagacgtgtgaggtg
SEQ ID NO:572 agtgaagttttctgcagccttta

SEQ ID NO:573 tctcctggctacaatttcagg
SEQ ID NO:574 atgccataggccttgatgag

P4HB
SEQ ID NO:575 gcttcccccaaggaatataca
SEQ ID NO:576 tcttcagccagttcacgatg

SEQ ID NO:577 gcaggggatgatgacgat
SEQ ID NO:578 cgtcttcctccatgtctgg

SEQ ID NO:579 ctggagggcaaaatcaagc
SEQ ID NO:580 ttcttcccaacaagcacctt

PHKG2
SEQ ID NO:581 gcagatccgactttcagatttc
SEQ ID NO:582 ggggtcccacacaactctc

SEQ ID NO:583 ttccagcactgtcaaagacct
SEQ ID NO:584 aaagaaggggtgctgtaggg

SEQ ID NO:585 aggctatggcaaggaggtc
SEQ ID NO:586 tgcgtaacatcaggatctgc

PPFIBP2
SEQ ID NO:587 aggggataaggagtccctca
SEQ ID NO:588 ctggtgtccttccagacaca

SEQ ID NO:589 gaatggaagctaaaggccact
SEQ ID NO:590 atctttcagggccacctgtt

SEQ ID NO:591 aatcttcgagggagtggagtc
SEQ ID NO:592 cagggtgtccccagtgaa

PPP1R16A
SEQ ID NO:593 ccctcccagtgttgtcctt
SEQ ID NO:594 ccccactcccaaggaact

SEQ ID NO:595 gagtgctggacgcctctg
SEQ ID NO:596 ttgaccgccaggagattg

SEQ ID NO:597 atgccctatgacctgtgtgat
SEQ ID NO:598 gatgctgtcctgggtgatg

RASSF7
SEQ ID NO:599 cactagcccaagcaataggc
SEQ ID NO:600 cactcttgtggcagcaactg

SEQ ID NO:601 cagcctggctctggtgag
SEQ ID NO:602 ggagctctcggttcagctc

SEQ ID NO:603 tctgcctccagccagaga
SEQ ID NO:604 ctccaggagttctgcgtcat

RNF183
SEQ ID NO:605 tccagagtagtctgcctgacc
SEQ ID NO:606 catcctcagccacacacg

SEQ ID NO:607 tccagagtagtctgcctgacc
SEQ ID NO:608 tgttgttgaaggggttccag

SEQ ID NO:609 tctgccaccgtgtctacg
SEQ ID NO:610cggaaacactccctcaaaga

SIRT6
SEQ ID NO:611 agctgagggacaccatccta
SEQ ID NO:612 atgtacccagcgtgatggac

SEQ ID NO:613 aggatgtcggtgaattacgc
SEQ ID NO:614 agaccagcctcgccagtt

SEQ ID NO:615 ggtcagccagaacgtgga
SEQ ID NO:616 gtggagctctgccagtttgt

TJP3
SEQ ID NO:617 gtgggcatcttcgtgtcc
SEQ ID NO:618 gaatggcacgtcattcacc

SEQ ID NO:619 atctggacggcggaagat
SEQ ID NO:620 ggtgagggaggtctaggttgt

SEQ ID NO:621 tcatcaagcacattacagattcg
SEQ ID NO:622 ggctagacaccccgttgat

EFEMP2
SEQ ID NO:623 actcgcaggggggacttttac
SEQ ID NO:624 catgagggaattcatggtga

SEQ ID NO:625 atcgggatggcttctcct
SEQ ID NO:626 tgatgcagcggtactgaca

SEQ ID NO:627 agtaccgctgcatcaacga
SEQ ID NO:628 cgcaccagactcacactcat

SOCS2
SEQ ID NO:629 ggagctcggtcagacagg
SEQ ID NO:630 ctaatcaagaaagttccttctggtg

SEQ ID NO:631 cagtcaccaagcccccttc
SEQ ID NO:632 aagggatggggctctttct

SEQ ID NO:633 ggagctcggtcagacagg
SEQ ID NO:634 gttccttctggtgcctctttt

DCN
SEQ ID NO:635 ggagactttaagaacctgaagaacc
SEQ ID NO:636 cgttccaacttcaccaaagg

SEQ ID NO:637 ctgtcaatgccatcttcgag
SEQ ID NO:638 gatcctttggcactttgtcc

SEQ ID NO:639 caatatcaccagcattcctcaag
SEQ ID NO:640 ctgctgattttgttgccatc

All publications and patent applications mentioned in the specification are indicative of the level of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference. The mere mentioning of the publications and patent applications does not necessarily constitute an admission that they are prior art to the instant application.

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

CLAIMS

1. An in vitro diagnostic method for the diagnosis of endometrial cancer comprising (1) detecting the level of from 1 to 17 biomarker(s) chosen from P4HB, GMIP, IKBKE, FASTKD1, DDR1, SIRT6, PHKG2, ACAA1, AP1M2, EPS8L2, P2RX4, PPFIBP2, PPP1R16A, CGN, RASSF7, RNF183, and TJP3 in a sample from a patient wherein an increased level of said from 1 to 17 biomarkers compared to a control value indicates the existence of endometrial cancer and/or (2) detecting the level of from 1 to 3 biomarkers chosen from EFEMP2, SOCS2, and DCN, wherein a decreased level of EFEMP2, SOCS2, and/or DCN compared to a control value indicates the existence of endometrial cancer.

2. The in vitro diagnostic method of claim 1 comprising detecting the level of P4HB.

3. The in vitro diagnostic method of claim 1 comprising detecting the level of EFEMP2.

4. The in vitro method of claim 1 comprising detecting the level of IKBKE.

5. The in vitro diagnostic method of claim 1 comprising detecting the level of GMIP.

6. The in vitro diagnostic method of claim 2 further comprising detecting the level of one or more of GMIP, IKBKE, or EFEMP2.

7. The in vitro diagnostic method of claim 3 further comprising detecting the level of one or more of P4HB, IKBKE, or GMIP.

8. The in vitro diagnostic method of claim 4 further comprising detecting the level of one or more of GMIP, EFEMP2, or P4HB.

9. The in vitro diagnostic method of any one of claims 2 to 8 further comprising detecting the level of FASTKD1.

10. The in vitro diagnostic method of any one of claims 2 to 9 further comprising detecting the level of DDR1.

11. The in vitro diagnostic method of any one of claims 2 to10 further comprising detecting the level of SIRT6.

12. The in vitro diagnostic method of any one of claims 2 to 11 further comprising detecting the level of PHKG2.

13. The in vitro diagnostic method of any one of claims 2 to 12 further comprising detecting the level of from 1 to 12 biomarkers chosen from ACAA1, AP1M2, EPS8L2, P2RX4, PPFIBP2, PPP1R16A, CGN, RASSF7, RNF183, TJP3, SOCS2, and DCN.

14. The in vitro diagnostic of any one of claims 1 to 13 wherein said patient has a risk factor for endometrial cancer or is being screened for endometrial cancer.

15. The in vitro diagnostic method of any one of claims 1 to 14 wherein said sample from said patient is (obtained) from a patient with abnormal uterine bleeding or wherein said patient suffers from abnormal uterine bleeding.

16. The in vitro diagnostic method of any one of claims 1 to 15 wherein said sample from said patient is (obtained) from a patient having an endometrium with increased thickness or wherein said patient has an endometrium with increased thickness.

17. The in vitro diagnostic method of any one of claims 1 to 16 wherein said sample from said patient is (obtained) from a pre-menopausal, peri-menopausal, or post-menopausal patient or wherein said patient is a pre-menopausal, peri-menopausal, or post-menopausal patient.

18. The in vitro diagnostic method of claim 17 wherein said patient is pre-menopausal.

19. The in vitro diagnostic method of claims 17 wherein said patient is peri-menopausal.

20. The in vitro diagnostic method of claim 17 wherein said patient is post-menpausal.

21. The in vitro diagnostic method of any one of claims 1 to 20 wherein said sample is chosen from a tissue sample, blood and/or serum, and uterine fluid.

22. The in vitro diagnostic method of claim 21 wherein said sample is a uterine fluid sample.

23. The in vitro diagnostic method of claim 22 wherein said uterine fluid sample is obtained by aspiration.

24. The in vitro diagnostic method of any one of claims 1 to 23 wherein the level of the biomarkers is determined with an antibody.

25. The in vitro diagnostic method of any one of claims 1 to 23 wherein the level of the biomarker(s) is determined by RT-PCR.

26. The in vitro diagnostic method of any one of claims 1 to 25, wherein said markers are chosen from P4HB, IKBKE, EFEMP2, SOCS2, FASTKD1, GMIP, DDR1, SIRT6, PHKG2, EPS8L2, and PPP1R16A, P2RX4, RASSF7, and TJP3.

27. The in vitro diagnostic method of any one of claims 1 to 26 wherein said marker(s) is chosen from P2RX4, P4HB, PHKG2, PPFIBP2, and SOCS2.

28. The in vitro diagnostic method of any one of claims 1 to 26, wherein said marker(s) is chosen from P4HB, RASSF7, RNF183 and IKBKE.

29. The in vitro diagnostic method of any one of claims 1 to 28 wherein from 2 to 20 markers are detected.

30. The in vitro diagnostic method of any one of claims 1 to 29, wherein a combination of the following markers is detected: P4HB, EFEMP2, SIRT6, GMIP, FASTKD1 and DDR1.

31. The in vitro diagnostic method of any one of claims 1 to 29, wherein a combination of the following markers is detected: P4HB, EFEMP2, SIRT6, GMIP, FASTKD1 and PHKG2.

32. The in vitro diagnostic method of claims 1 to 29, wherein a combination of the following markers is detected: P4HB, EFEMP2, SIRT6, ACAA1, AP1M2, EPS8L2, IKBKE, P2RX4, PPFIBP2 and PPP1R16A.

33. The in vitro diagnostic method of any one of claims 1 to 32 wherein one or more additional biomarkers are detected.

34. The in vitro diagnostic method of claim 33 wherein said one or more additional biomarkers are chosen from differential diagnosis biomarkers, prognostic biomarkers, biomarkers useful for detecting endometrial cancer, biomarkers for classify endometrial cancer and auxiliary biomarkers for detecting endometrial cancer.

35. The in vitro diagnostic method of claim 33 or 34 wherein one or more additional biomarkers are chosen from differential diagnosis biomarkers.

36. The in vitro diagnostic method of claim 33 or 34 wherein one or more auxiliary biomarkers are chosen from prognostic markers.

37. The in vitro diagnostic method of claim 33 or 34 wherein one or more auxiliary biomarkers are chosen from endometrial cancer classification markers.

38. A nucleic acid chosen from
IKBKE mRNA, cDNA, or a complement thereof;
P4HB mRNA, cDNA, or a complement thereof;
SOCS2 mRNA, cDNA, or a complement thereo;f
GMIP mRNA, cDNA, or a complement thereof;
DDR1 mRNA, cDNA, or a complement thereof;
EPS8L2 mRNA, cDNA, or a complement thereof; and
PPP1R16A mRNA, cDNA, or a complement thereof,
for use in diagnosing endometrial cancer.

39. A nucleic acid chosen from
Primers for IKBKE;
Primers for P4HB;
Primers for SOCS2;
Primers for GMIP;
Primers for DDR1;
Primers for EPS8L2; and
Primers for PPP1R16A;
for use in diagnosing endometrial cancer.

40. A nucleic acid chosen from
probe for IKBKE;
probe for P4HB;
probe for SOCS2;
probe for GMIP;
probe for DDR1;
probe for EPS8L2; and
probe for PPP1R16A,
for use in diagnosing endometrial cancer.

41. A kit comprising two or more probes of claim 40, for use in diagnosing endometrial cancer.

42. A kit comprising primers for two or more primers pairs of claim 39 for use in diagnosing endometrial cancer.

43. An antibody chosen from
an antibody to IKBKE;
an antibody to P4HB;
an antibody to SOCS2;
an antibody to GMIP;
an antibody to DDR1;
an antibody to EPS8L2; and
an antibody to PPP1R16A,
for use in diagnosing endometrial cancer.

44. A kit comprising antibodies to two or more antibodies of claim 43 for use in diagnosing endometrial cancer.

45. A kit for obtaining uterine fluid for use in diagnosing endometrial cancer by assessing the levels of from 1-20 biomarkers as defined in claim 1.

46. The in vitro diagnostic method of any one of claim 1 to 37 comprising determining the level of 2 biomarkers.

47. The in vitro diagnostic method of any one of claims 1 to 37 comprising determining the level of 3 biomarkers.

48. The in vitro diagnostic method of any one of claims 1 to 37 comprising determining the level of 4 biomarkers.

49. The in vitro diagnostic method of any one of claims 1 to 37 comprising determining the level of 5 biomarkers.

50. The in vitro diagnostic method of any one of claims 1 to 37 comprising determining the level of 7 biomarkers.

51. The in vitro diagnostic method of any one of claims 1 to 37 comprising determining the level of 10 biomarkers.

52. The in vitro diagnostic method of any one of claims 1 to 37 comprising determining the level of 15 biomarkers.

53. The in vitro diagnostic method of claim any one of claims 1 to 37 comprising determining the level of 20 biomarkers.

54. An in vitro diagnostic method for diagnosing endometrial cancer comprising obtaining a uterine fluid aspirate sample from a patient having a symptom or risk factor for endometrial cancer and determining the level of from 1 to 100 biomarkers markers that are differentially expressed in endometrial cancer as compared to control values representative of individuals not affected by endometrial cancer, wherein (1) if the levels of 1 to 100 biomarkers are upregulated in the endometrial aspirate sample in the patient and in the control value then the patient has an increased likelihood of having endometrial cancer and wherein (2) if the level of the 1 to 100 biomarkers are downregulated in the aspirate sample and then the patient has an increased likelihood of having endometrial cancer.

55. A nucleic acid chosen from
ACAA1 mRNA, cDNA, or a complement thereof;
AP1M2 mRNA, cDNA, or a complement thereof;
CGN mRNA, cDNA, or a complement thereo;f
FASTKD1 mRNA, cDNA, or a complement thereof;
P2RX4 mRNA, cDNA, or a complement thereof;
RASSF7 mRNA, cDNA, or a complement thereof;
RNF183 mRNA, cDNA, or a complement thereof;
PHKG2 mRNA, cDNA, or a complement thereof;
PPFIBP2 mRNA, cDNA, or a complement thereof,

SIRT6 mRNA, cDNA, or a complement thereof,
TJP3 mRNA, cDNA, or a complement thereof;
EFEMP2 mRNA, cDNA, or a complement thereof; and
DCN mRNA, cDNA, or a complement thereof,
for use in diagnosing endometrial cancer.

56. A nucleic acid chosen from
Primers for ACAA1;
Primers for AP1M2;
Primers for CGN;
Primers for FASTKD1;
Primers for P2RX4;
Primers for RASSSF7;
Primers for RNF183;
Primers for SIRT6;
Primers for PPFIBP2;
Primers for PHKG2;
Primers for TJP3;
Primers for EFEMP2;and
Primers for DCN;
for use in diagnosing endometrial cancer.

57. A nucleic acid chosen from
probe for ACAA1;
probe for AP1M2;
probe for CGN;
probe for FASTKD1;
probe for P2RX4;
probe for RASSF7;
probe for RNF183;
probe for SIRT6;
probe for PPFIBP2;
probe for PKHG2;
probe for TJP3;

probe for EFEMP2; and
probe for DCN,
for use in diagnosing endometrial cancer.

58. An antibody chosen from
an antibody to ACAA1;
an antibody to AP1M2;
an antibody to CGN;
an antibody to FASTKD1;
an antibody to P2RX4;
an antibody to RASSF7;
an antibody to RNF183;
an antibody to SIRT6;
an antibody to PPFIBP2;
an antibody to PKHG2;
an antibody to TJP3;
an antibody to EFEMP2; and
an antibody to DCN,
for use in diagnosing endometrial cancer endometrial cancer.

59. An in vitro diagnostic method for diagnosing endometrial cancer comprising providing or obtaining a uterine fluid sample from a human patient having a symptom or risk factor for a gynecological cancer and determining the level of RNA expression of from 2 to 9 biomarkers chosen from P4HB, EFEMP2, GMIP, IKBKE, DDR1, FASTKD1, SIRT6, PKHG2, and SOCS2 by quantitative PCR wherein an increased level of from 1 to 7 biomarkers chosen from P4HB, GMIP, IKBKE, DDR1, FASTKD1, SIRT6, and PKHG2 and/or a decreased level of EFEMP2 or SOCS2 as compared to control indicates the existence of endometrial cancer.

60. The method of claim 59 wherein the gynecological cancer is endometrial cancer.

61. The method of claim 59 or 60 wherein the markers are 2 to 8 biomarkers chosen from P4HB, EFEMP2, GMIP, IKBKE, DDR1, FASTKD1, SIRT6, and PKHG2.

62. The method of claim 59 or 60 wherein the markers are 2 to 8 biomarkers chosen from P4HB, GMIP, IKBKE, DDR1, FASTKD1, SIRT6, PKHG2, and SOCS2.

63. The method of any one of claims 1 to 37, 46 to 54 and 59 to 62, wherein said detecting the level comprises contacting said one or more biomarkers with primers and reagents capable of amplifying specifically said one or more biomarkers and detecting the level of said amplified one or more biomarkers with a probe or probes that hybridize to said amplified biomarker.

64. The method of claim 63, wherein said probe hybrids specifically to said amplified biomarker.

65. The method of any one of claims 1 to 37, 46 to 54 and 59 to 64, wherein P4HB and EFEMP2 are detected.

66. The method of any one of claims 1 to 37, 46 to 54 and 59 to 64, wherein P4HB and IKBKE are detected.

67. The method any one of claims 1 to 37, 46 to 54 and 59 to 64, wherein P4HB and GMIP are detected.

68. The method of any one of claims 1 to 37, 46 to 54 and 59 to 64, wherein EFEMP2 and IKBKE are detected.

69. The method of any one of claims 1 to 37, 46 to 54 and 59 to 64, wherein EFEMP2 and P4HB are detected.

70. The method of any one of claims 1 to 37, 46 to 54 and 59 to 64, wherein P4HB, GMIP, and IKBKE are detected.

71. The method any one of claims 1 to 37, 46 to 54 and 59 to 64, wherein P4HB, GMIP, and IKBKE are detected.

72. The method of any one of claims 1 to 37, 46 to 54 and 59 to 64, wherein a combination of markers is detected wherein said combination comprises IKBKE and P4HB; IKBKE and SOCS2; P4HB and SOCS2; GMIP and IKBKE; GMIP and P4HB; GMIP and SOCS2; GMIP, SOCS2, and IKBKE; GMIP, SOCS2, and P4HB; GMIP, IKBKE, and P4HB; IKBKE,P4HB, and SOCS2; GMIP, IKBKE, P4HB, and SOCS2; GMIP, SOCS2, IKBKE, and EPS8L2; GMIP, SOCS2, P4HB, and EPS8L2; GMIP, IKBKE, P4HB, and EPS8L2; IKBKE, P4HB, SOCS2, and EPS8L2; GMIP, IKBKE, P4HB, SOCS2, and DDR1; GMIP, IKBKE, P4HB, SOCS2, EPS8L2, and PPP1R16A; GMIP, IKBKE, P4HB, SOCS2, PHKG2, and RASSF7; GMIP, IKBKE, P4HB, SOCS2, EPS8L2, and DDR1; GMIP, IKBKE, P4HB, SOCS2, EPS8L2, PPP1R16A, and DDR1; DDR1, EPS8L2, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPP1R16A, RASSF7, SIRT6, TJP3, and SOCS2; or DDR1, EPS8L2, GMIP, IKBKE, P2RX4, P4HB, PHKG2, PPP1R16A, RASSF7, SIRT6, TJP3, RNF183 and SOCS2.

73. The method of any one of claims 1 to 37, 46 to 54 and 59 to 64, wherein a combination of markers is detected wherein said combination comprises GMIP, IKBKE, P4HB, SOCS2 and FASTKD1; GMIP, IKBKE, P4HB, SOCS2 and DDR1; GMIP, IKBKE, P4HB, SOCS2 and PHKG2; GMIP, IKBKE, P4HB, SOCS2 and SIRT6; GMIP, IKBKE, P4HB, SOCS2 and ACAA1; GMIP, IKBKE, P4HB, SOCS2 and EFEMP2; GMIP, IKBKE, P4HB, SOCS2 and EPS8L2; GMIP, IKBKE, P4HB, SOCS2 and P2RX4; GMIP, IKBKE, P4HB, SOCS2 and PPFIBP2; GMIP, IKBKE, P4HB, SOCS2 and PPP1R16A; GMIP, IKBKE, P4HB, SOCS2, ACAA1 and FASTKD1; GMIP, IKBKE, P4HB, SOCS2, PHKG2 and FASTKD1; GMIP, IKBKE, P4HB, SOCS2, SIRT6 and FASTKD1; ACAA1, AP1M2, EPS8L2, IKBKE, P2RX4, P4HB, PPFIBP2, PPP1R16A, SIRT6, and EFEMP2; GMIP, IKBKE, P4HB, and EFEMP2; DDR1, FASTKD1, PHKG2, SIRT6, SOCS2, GMIP, IKBKE, P4HB, and EFEMP2; DDR1, FASTKD1, PHKG2, SIRT6, GMIP,

IKBKE, P4HB, and EFEMP2; or P4HB, EFEMP2, IKBKE, GMIP, and FASTKD1.

74. The method of any one of claims 1 to 37, 46 to 54 and 59 to 64, wherein a combination of markers is detected wherein said combination comprises GMIP, IKBKE, P4HB, EFEMP2 and FASTKD1; GMIP, IKBKE, P4HB, EFEMP2and DDR1; GMIP, IKBKE, P4HB, EFEMP2 and PHKG2; GMIP, IKBKE, P4HB, EFEMP2 and SIRT6; GMIP, IKBKE, P4HB, EFEMP2 and ACAA1; GMIP, IKBKE, P4HB, SOCS2 and EFEMP2; GMIP, IKBKE, P4HB, EFEMP2 and EPS8L2; GMIP, IKBKE, P4HB, EFEMP2 and P2RX4; GMIP, IKBKE, P4HB, EFEMP2 and PPFIBP2; GMIP, IKBKE, P4HB, EFEMP2and PPP1R16A; GMIP, IKBKE, P4HB, EFEMP2, ACAA1 and FASTKD1; GMIP, IKBKE, P4HB, EFEMP2, PHKG2 and FASTKD1; or GMIP, IKBKE, P4HB, EFEMP2, SIRT6 and FASTKD1.

75. The in vitro diagnostic method of any one of claims 1 to 37, 46 to 54 and 59 to 74 comprising providing a uterine fluid sample obtained from a patient with a pipelle device or syringe wherein the patient has a risk factor or symptom of endometrial cancer; contacting said sample with an agent capable of preserving, preventing, or lessening the degradation of RNA in said uterine fluid sample; determining in said sample the expression level of mRNA corresponding to said from 1 to 20 markers and one or more endogenous genes using quantitative PCR; normalizing the expression level of said from 1 to 20 biomarkers with the one or more endogenous genes; comparing the normalized level of the from 1 to 20 biomarkers to a control value wherein differential expression of from1 to 20 of the biomarkers indicates endometrial cancer or an increased likelihood of endometrial cancer.

76. The method of claim 75 wherein said one or more endogenous genes are chosen from POLR2A, B2M, PFN1, HMBS, G6PD, and PABPN1.

FIG 1

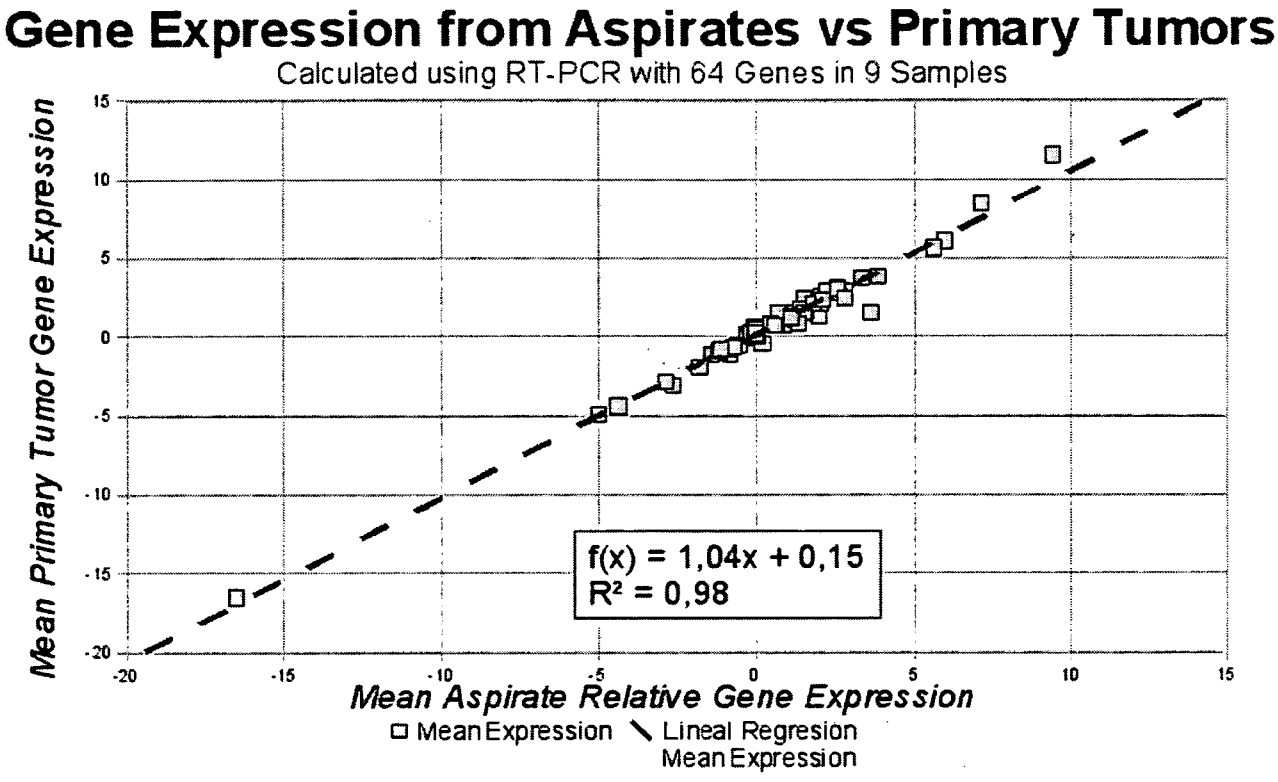

Gene Expression from Aspirates vs Primary Tumors
Calculated using RT-PCR with 64 Genes in 9 Samples
Mean Primary Tumor Gene Expression
15
10
5
0
-5
-10
-15
-20
-20
-15
-10
-5
0
5
10
15
f(x) = 1,04x + 0,15
R² = 0,98
Mean Aspirate Relative Gene Expression
Mean Expression
Lineal Regresion
Mean Expression

FIG 2A

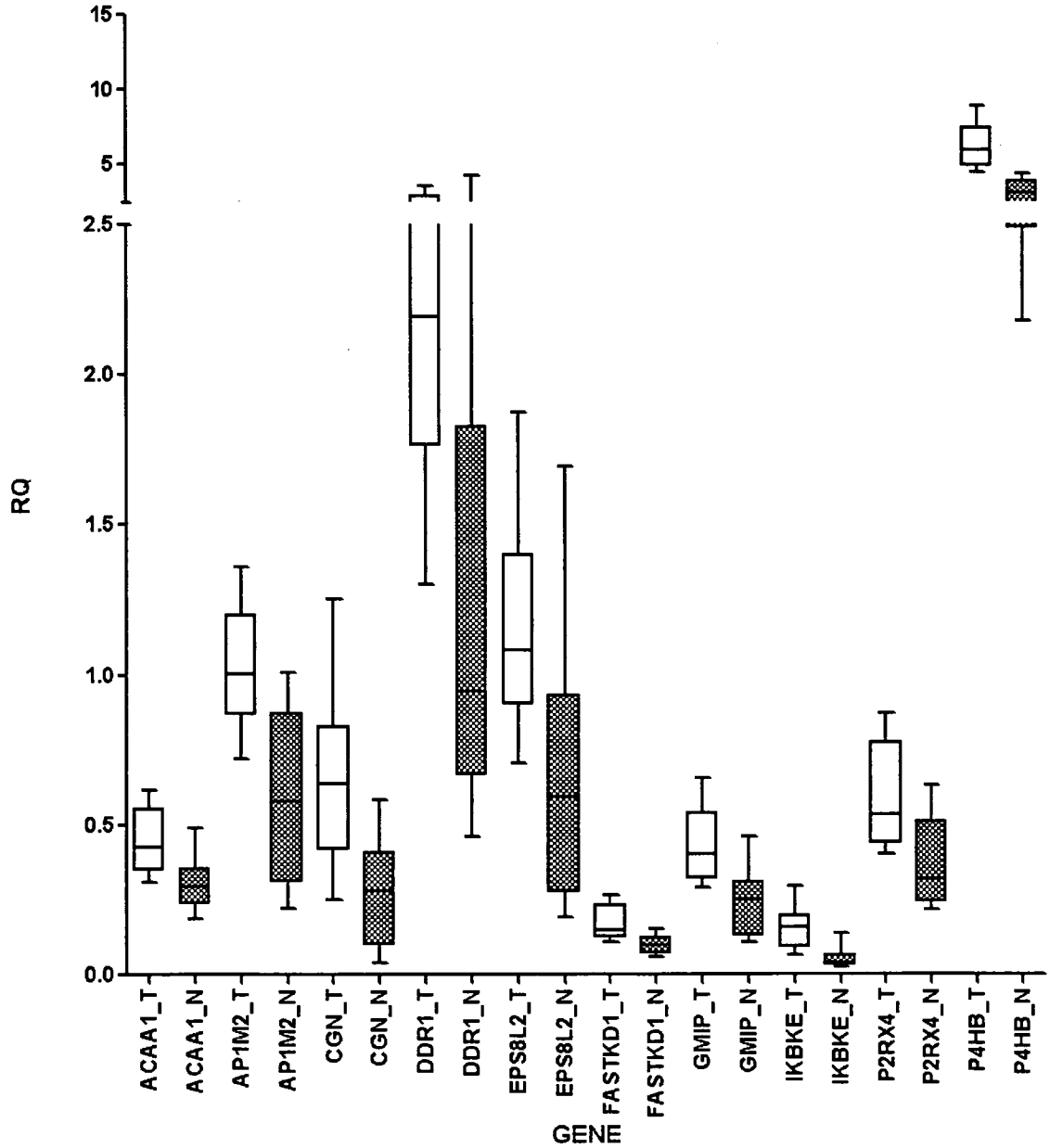

RQ
15
10
5
2.5
2.0
1.5
1.0
0.5
0.0
ACAA1_T
ACAA1_N
AP1M2_T
AP1M2_N
CGN_T
CGN_N
DDR1_T
DDR1_N
EPS8L2_T
EPS8L2_N
FASTKD1_T
FASTKD1_N
GMIP_T
GMIP_N
IKBKE_T
IKBKE_N
P2RX4_T
P2RX4_N
P4HB_T
P4HB_N
GENE

FIG. 2B

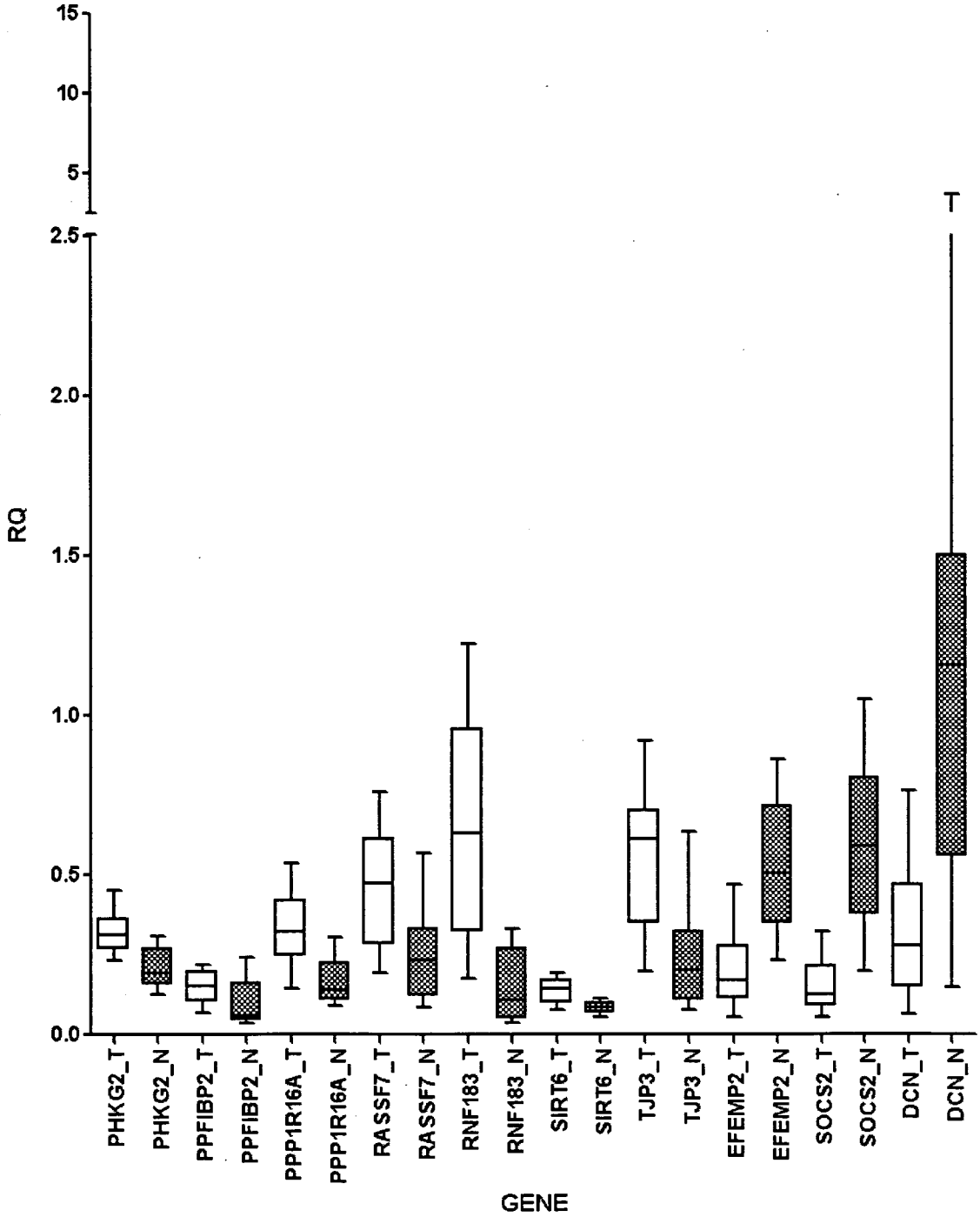

15
10
5
2.5
2.0
1.5
1.0
0.5
0.0
RQ
PHKG2_T
PHKG2_N
PPFIBP2_T
PPFIBP2_N
PPP1R16A_T
PPP1R16A_N
RASSF7_T
RASSF7_N
RNF183_T
RNF183_N
SIRT6_T
SIRT6_N
TJP3_T
TJP3_N
EFEMP2_T
EFEMP2_N
SOCS2_T
SOCS2_N
DCN_T
DCN_N
GENE

FIG. 3 RNF183 data:

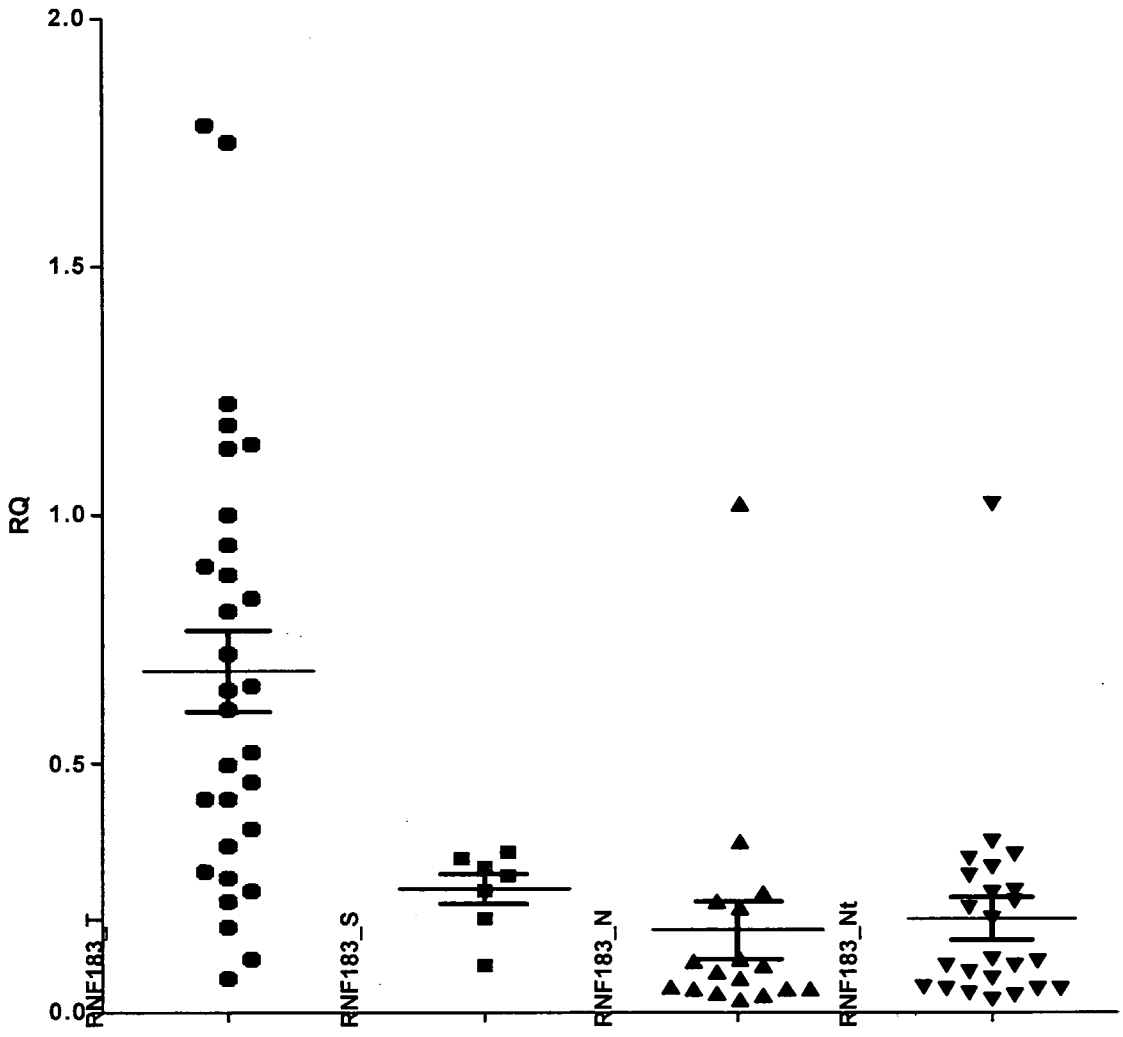


FIG. 4 AP1M2

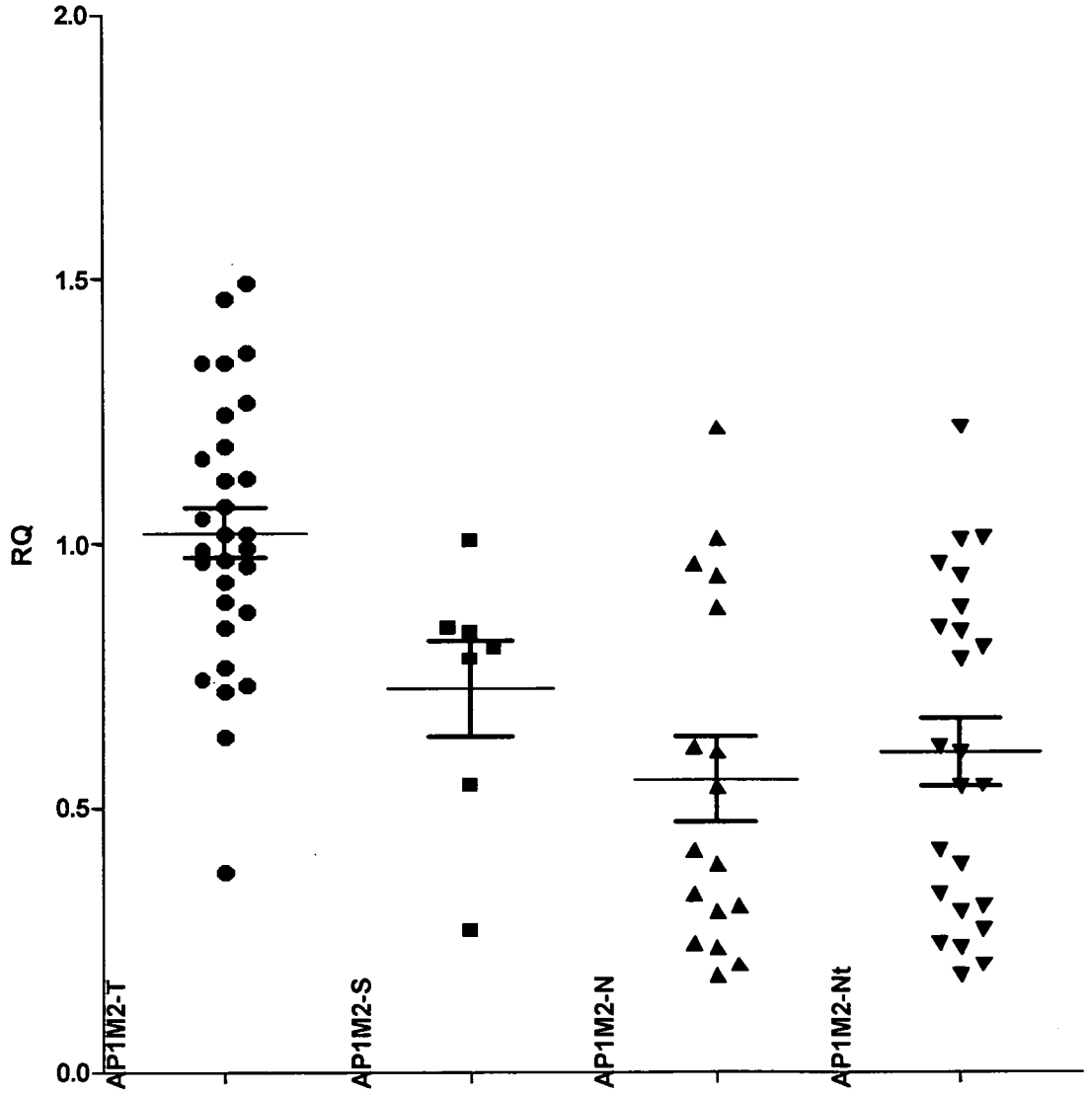


FIG. 5 CGN

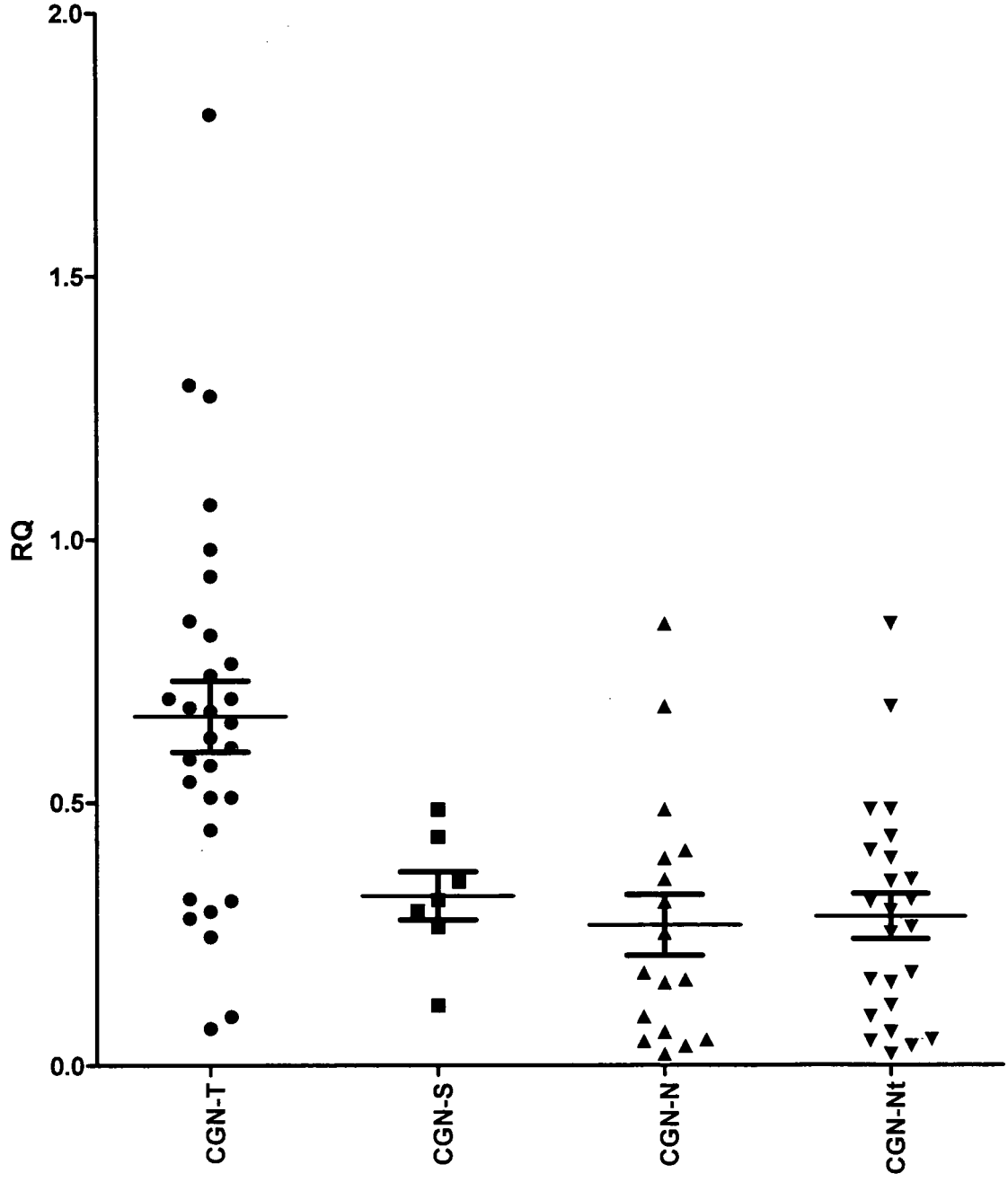


FIG 6. FASTKD1

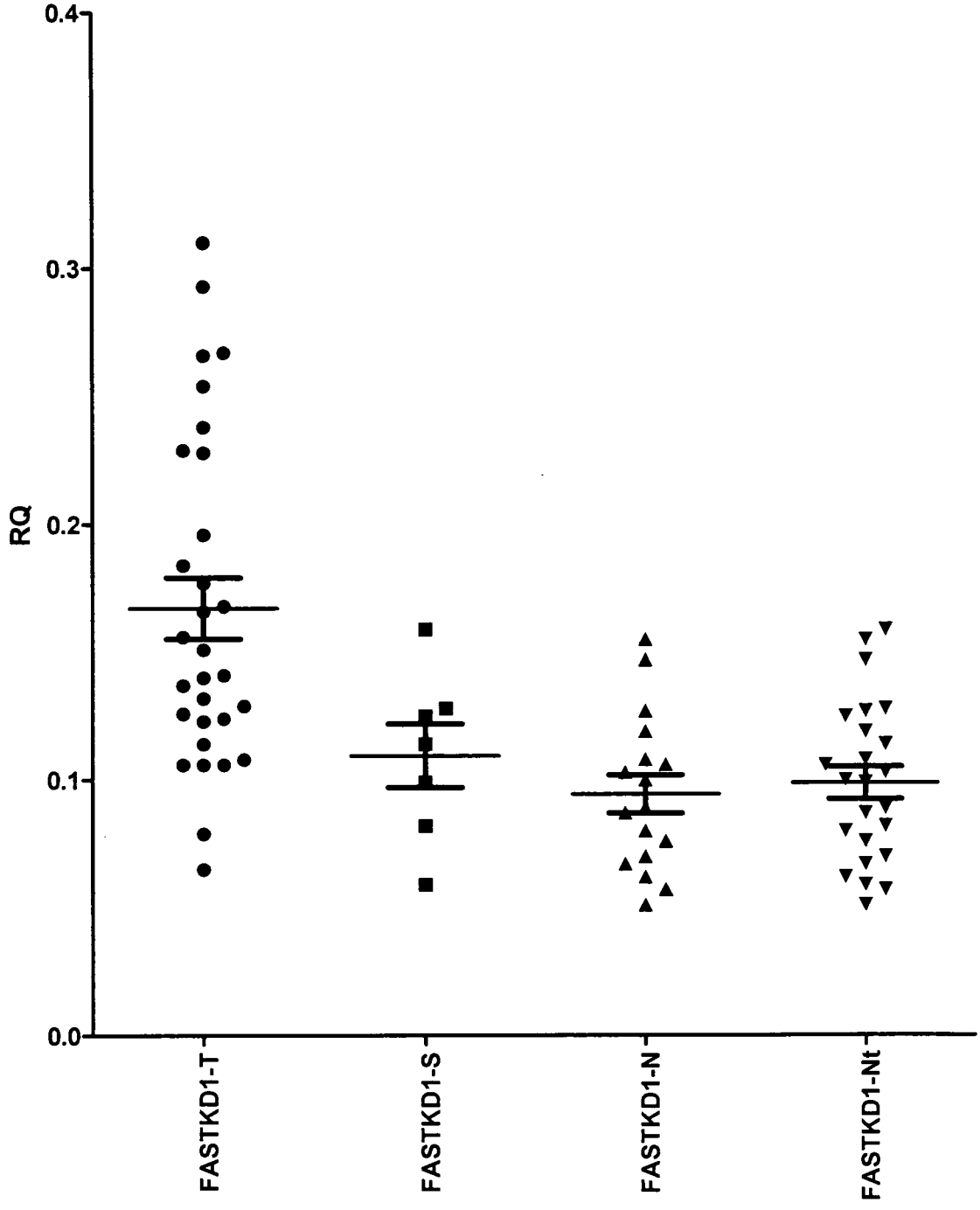


FIG. 7 IKBKE

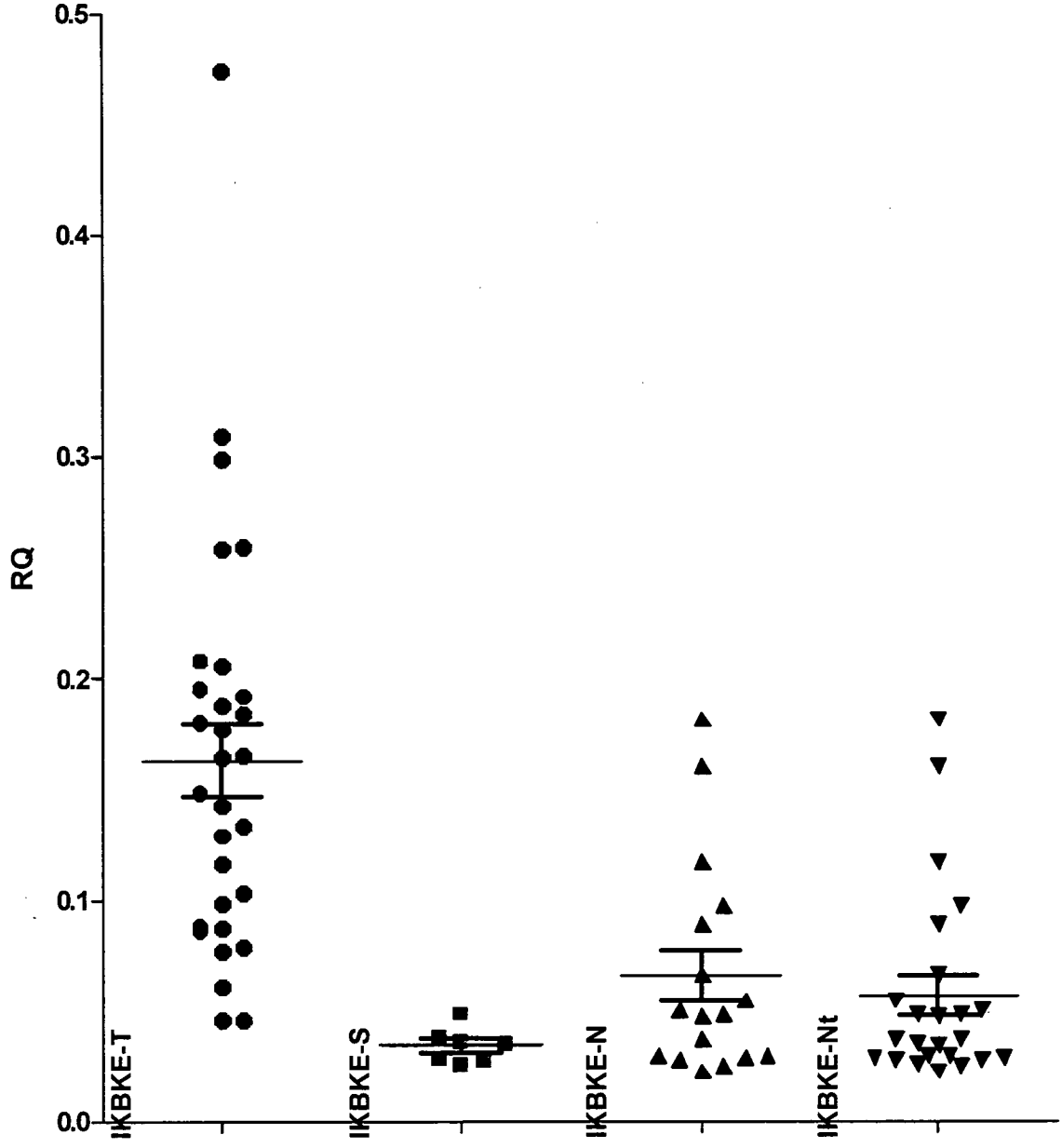


FIG 8. P4HB

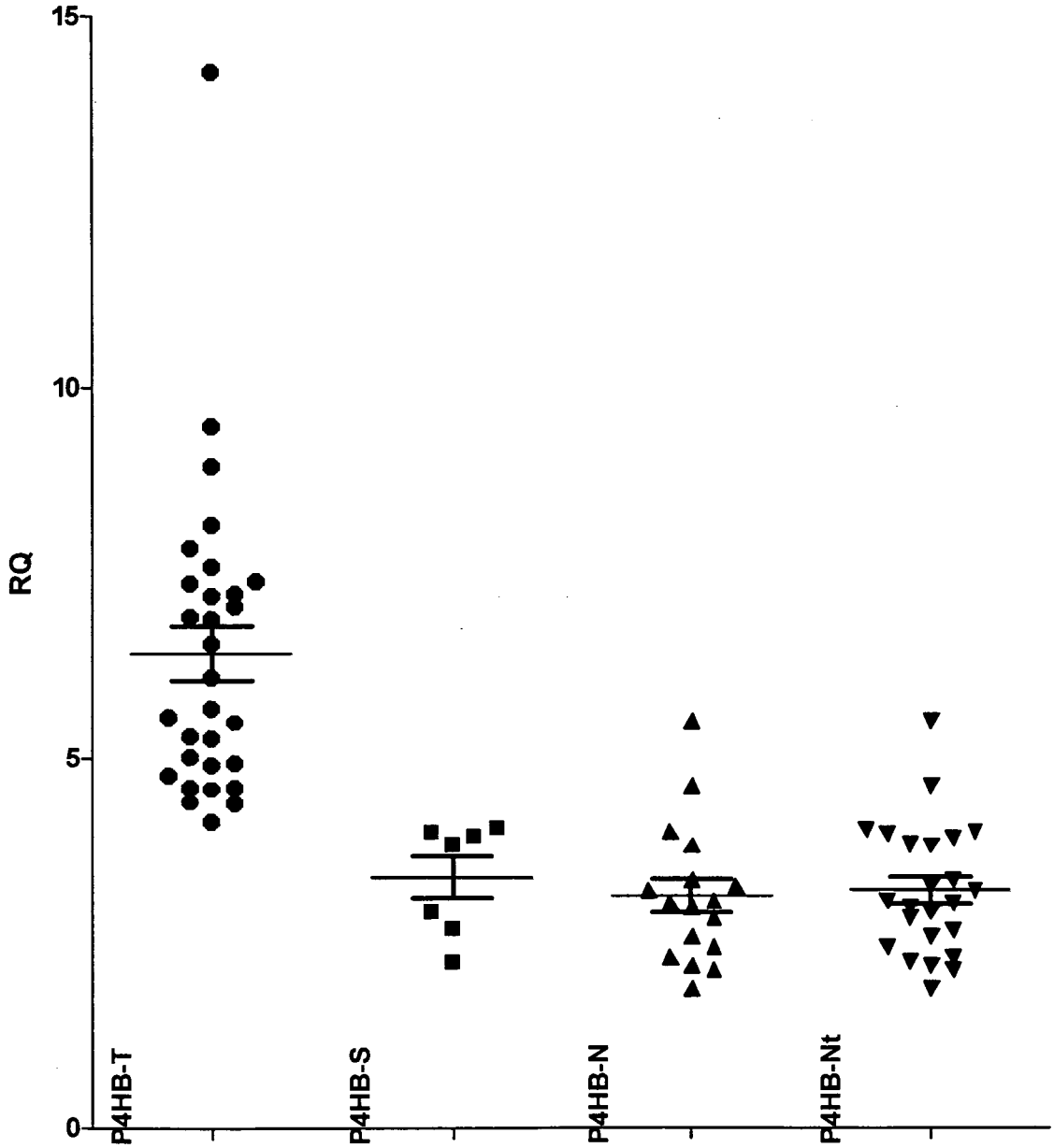


FIG. 9 SOCS2

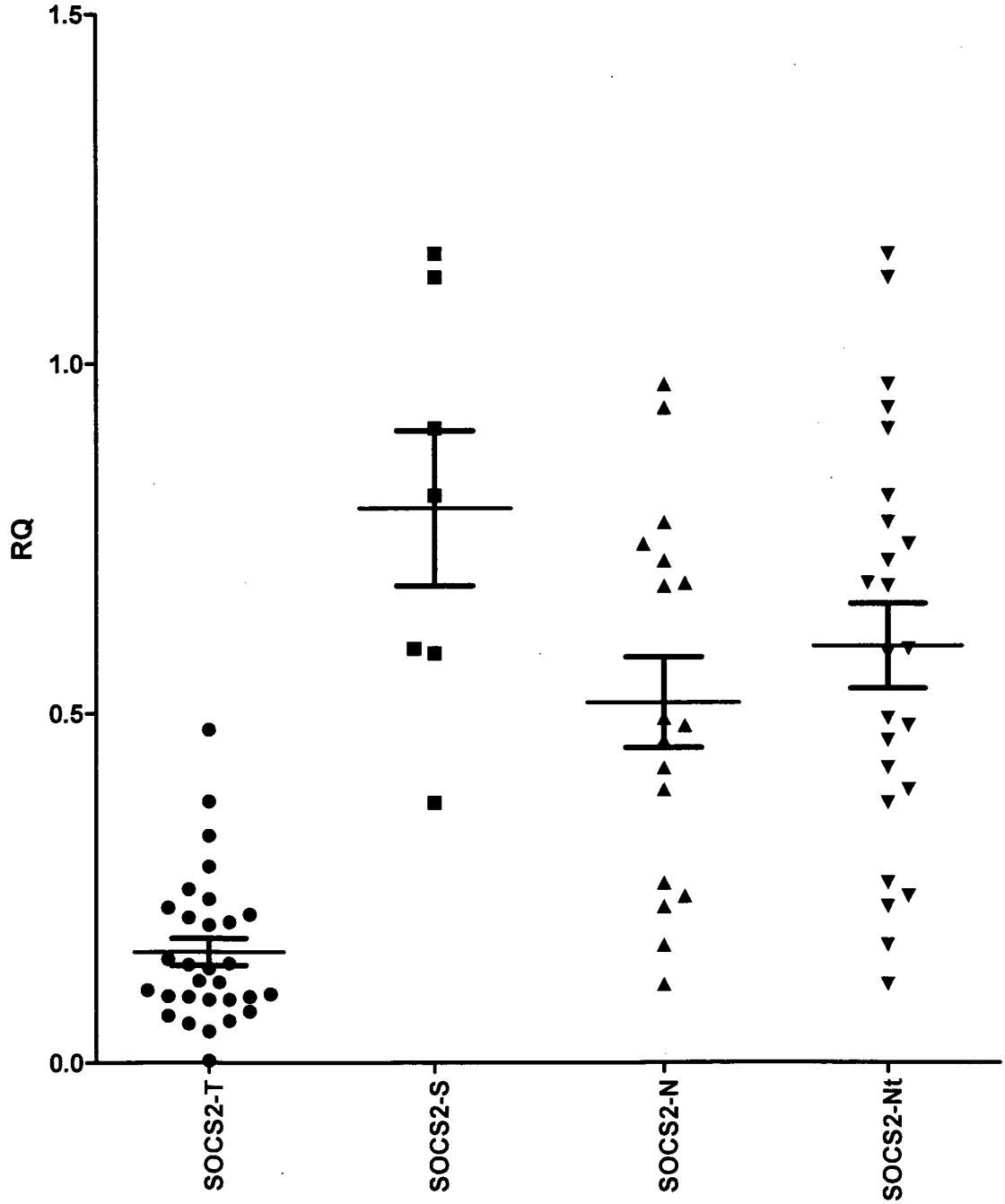


FIG. 10

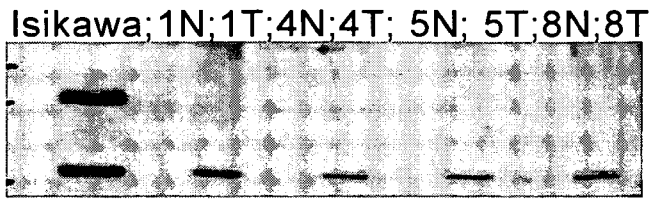


FIG. 11

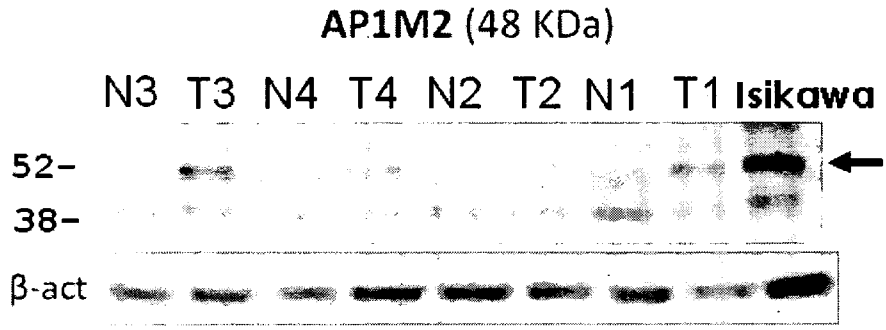


FIG. 12

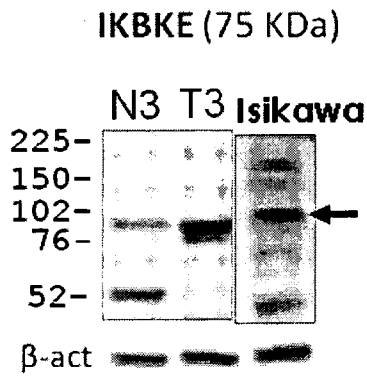


FIG. 13

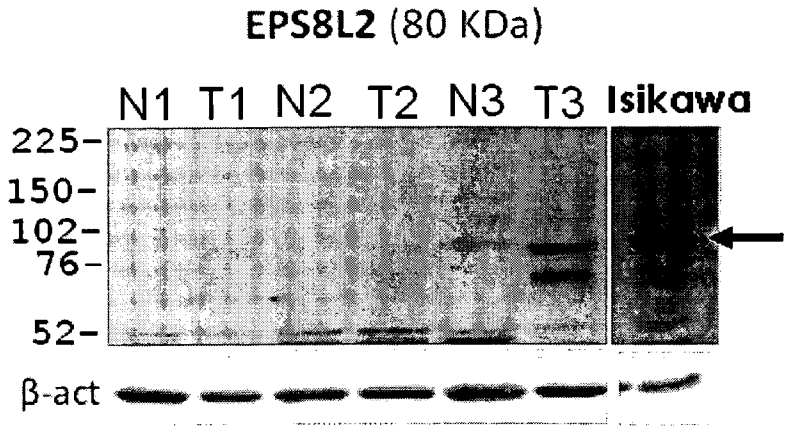


FIG. 14

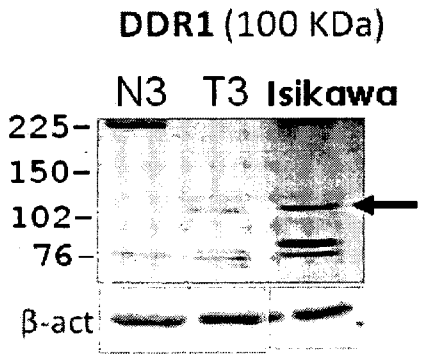


FIG. 15

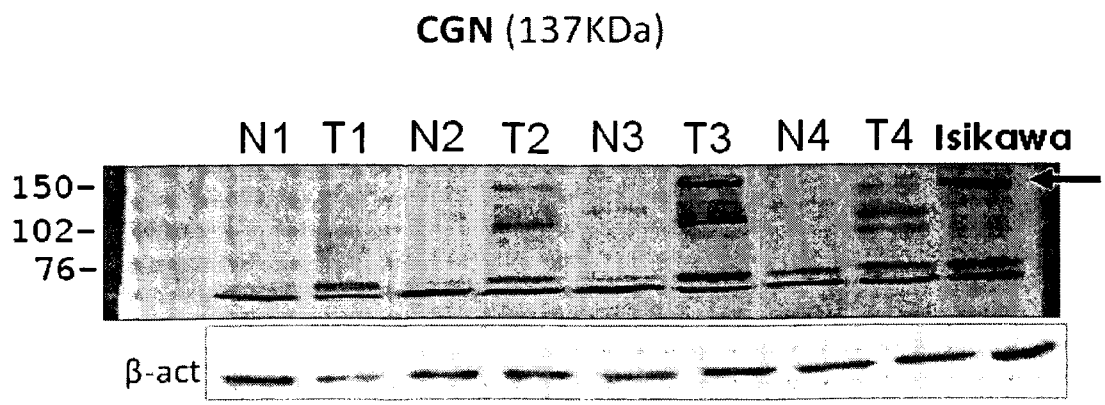


FIG. 16

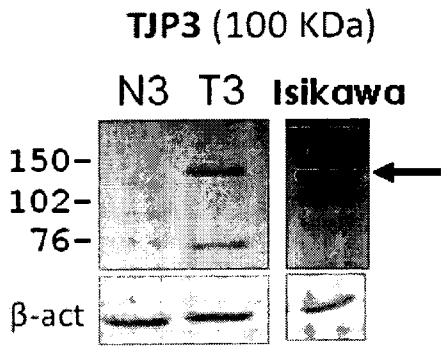

TJP3 (100 KDa)
N3 T3 Isikawa
150-
102-
76-
β-act

FIG. 17

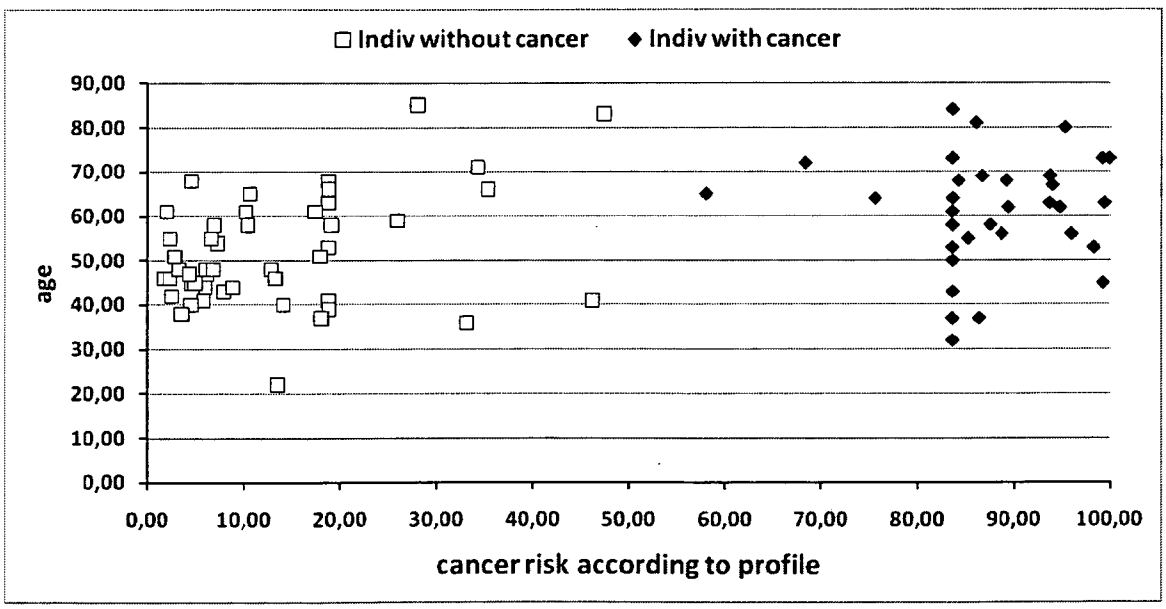

Indiv without cancer
Indiv with cancer
age
90,00
80,00
70,00
60,00
50,00
40,00
30,00
20,00
10,00
0,00
0,00
10,00
20,00
30,00
40,00
50,00
60,00
70,00
80,00
90,00
100,00
cancer risk according to profile

FIG. 18

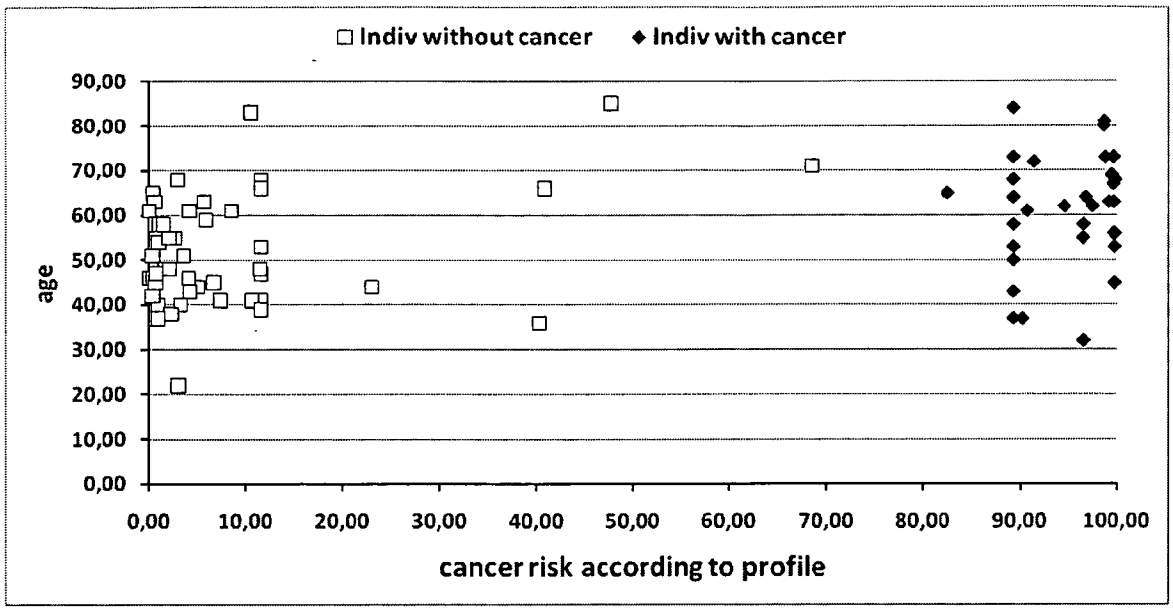
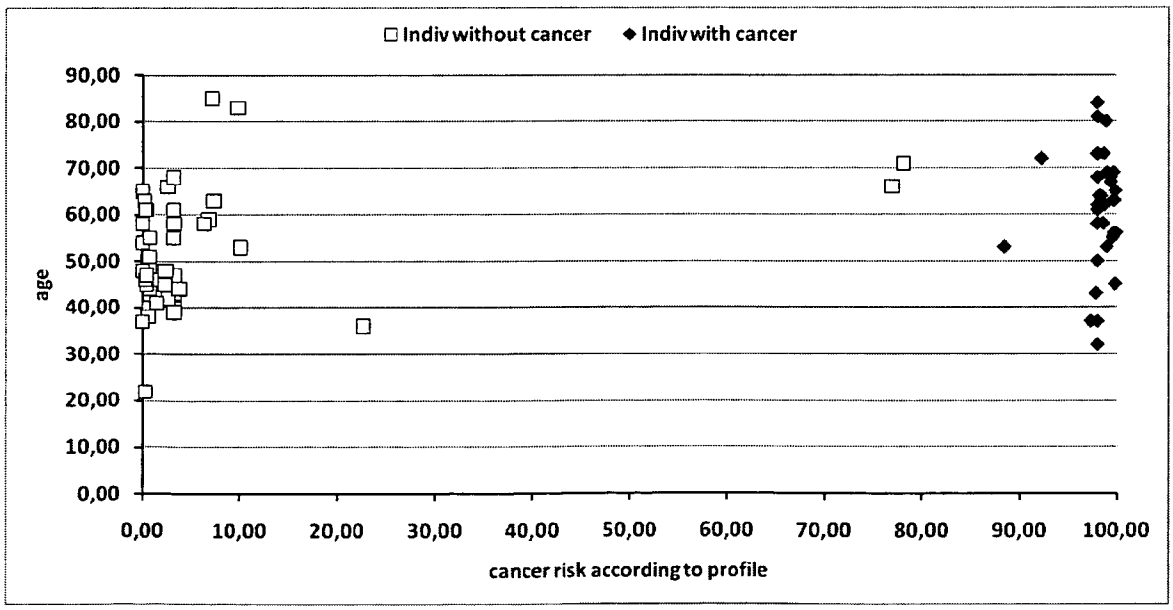

Indiv without cancer
Indiv with cancer
90,00
80,00
70,00
60,00
50,00
40,00
30,00
20,00
10,00
0,00
age
0,00
10,00
20,00
30,00
40,00
50,00
60,00
70,00
80,00
90,00
100,00
cancer risk according to profile

FIG. 19


Indiv without cancer
Indiv with cancer
90,00
80,00
70,00
60,00
50,00
40,00
30,00
20,00
10,00
0,00
age
0,00
10,00
20,00
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50,00
60,00
70,00
80,00
90,00
100,00
cancer risk according to profile